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**Use of Biodescriptors and
Chemodescriptors in Predictive Toxicology:
A Mathematical / Computational Approach**

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Submitted by:

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II. Manuscripts submitted/published during the current grant cycle

The following peer-reviewed papers, which are currently either published, in press, or submitted, report results of research carried out between March 1, 2002 and August 31, 2002.

2002

Alkane ordering as a criterion for similarity between topological indices: Index J as a "sharpened Wiener index", A.T. Balaban, D. Mills and S.C. Basak, *MATCH (Commun. Math. Comput. Chem.)*, 45, 5-26 (2002).

Quantitative descriptor for SNP related gene sequences, A. Nandy, P. Nandy and S.C. Basak, *Internet Electron. J. Mol. Des.*, 1, 367-373 (2002), <http://www.biochempress.com>.

Structure-water solubility modeling of aliphatic alcohols using the weighted path numbers, D. Amic, S.C. Basak, B. Lučić, S. Nikolić and N. Trinajstić, *SAR QSAR Environ. Res.*, 13, 281-295 (2002).

In press

A comparative study of proteomics maps using graph theoretical biodescriptors, M. Randić and S. C. Basak, *J. Chem. Inf. Comput. Sci.*

Novel matrix invariants for characterization of changes of proteomics maps, M. Randić, J. Zupan, M. Novič, B.D. Gute and S.C. Basak, *SAR QSAR Environ. Res.*

Predicting blood:air partition coefficient of structurally diverse chemicals using theoretical molecular descriptors, S.C. Basak, D.M. Hawkins and D. Mills, in *Advances in Molecular Similarity*, R. Carbo-Dorca, P.G. Mezey, Eds., vol. 5.

Predicting mutagenicity of congeneric and diverse sets of chemicals using computed molecular descriptors: A hierarchical approach, S.C. Basak, D. Mills, B.D. Gute and D.M. Hawkins, in *Quantitative Structure-Activity Relationship (QSAR) Models of Mutagens and Carcinogens*, R. Benigni, Ed., CRC Press, Boca Raton, FL.

Prediction of tissue:air partition coefficients: A comparison of structure-based and property-based methods, S.C. Basak, D. Mills, D.M. Hawkins and H.A. El-Masri, *SAR QSAR Environ. Res.*

Quantitative molecular similarity analysis (QMSA) methods for property estimation: A comparison of property-based, arbitrary, and tailored similarity spaces, S.C. Basak, B.D. Gute and D. Mills, *SAR QSAR Environ. Res.*

Quantitative molecular similarity methods in the property/ toxicity estimation of chemicals: A comparison of arbitrary versus tailored similarity spaces, S.C. Basak, B.D. Gute, D. Mills and D.M. Hawkins, *J. Mol. Struct. THEOCHEM*.

Tailored similarity spaces for the prediction of physicochemical properties, B.D. Gute, S.C. Basak, D. Mills and D.M. Hawkins, *Internet Electron. J. Mol. Des.*, <http://www.biochempress.com/>.

Use of mathematical structural invariants in analysing combinatorial libraries: A case study with Psoralen derivatives, S.C. Basak, D. Mills, B.D. Gute, A.T. Balaban, K. Basak and G.D. Grunwald, In *Some Aspects of Mathematical Chemistry*, Eds. D.K. Sinha, S.C. Basak, R.K. Mohanty and I.N. Basumallick, Visva-Bharati University: Santiniketan, West Bengal, India.

Variable molecular descriptors, M. Randić and S.C. Basak, In *Some Aspects of Mathematical Chemistry*, Eds. D.K. Sinha, S.C. Basak, R.K. Mohanty and I.N. Basumallick, Visva-Bharati University: Santiniketan, West Bengal, India.

Submitted

Assessing model fit by cross-validation, D.M. Hawkins, S.C. Basak and D. Mills, *J. Mol. Graphics and Modelling*.

Chemometrical treatment of proteomic maps, M. Vračko and S.C. Basak, *J. Proteom. Res.*

Distance based molecular shape descriptors, M. Randić, S.C. Basak and D. Mills, *Croat. Chem. Acta*.

Exposure assessment of volatile organic chemicals (VOCs): Predicting blood:air partition coefficients of diverse chemicals using theoretical descriptors, S.C. Basak, H. El-Masri, D.M. Hawkins and D. Mills, *J. Chem. Inf. Comput. Sci.*

Interrelationship of major topological indices, S.C. Basak, A.T. Balaban and B.D. Gute, *J. Chem. Inf. Comput. Sci.*

On canonical labeling of proteins of proteomics maps, M. Randić and S.C. Basak, *J. Chem. Inf. Comput. Sci.*

On numerical characterization of DNA primary sequences, M. Randić, A. Nandy and S.C. Basak, *J. Math. Chem.*

Prediction of cellular toxicity of halocarbons from their computed chemodescriptors: A hierarchical QSAR approach, S.C. Basak, K. Balasubramanian, B.D. Gute, D. Mills, A. Gorczynska and S. Roszak, *J. Chem. Inf. Comput. Sci.*

Prediction of human blood:air partition coefficient: A comparison of structure-based and property-based methods, S.C. Basak, D. Mills, D.M. Hawkins and H. El-Masri, *Risk Analysis*.

Of the 22 papers listed above, copies of three of the manuscripts dealing with the development

of biodescriptors have been attached as Appendices 1.1. The manuscript developed to examine the use of HiQSAR in modeling the toxicity of halocarbons has been attached as Appendix 1.2 and the three manuscripts detailing the development of the tailored similarity method have been attached as Appendix 1.3. Additionally, the four papers dealing with PBPK modeling have been attached as Appendix 1.4. Copies of the remaining manuscripts have been omitted for the sake of brevity.

III. Personnel Supported

Subhash C. Basak, Principal Investigator
Krishnan Balasubramanian, Consultant (Professor; Arizona State Univ., Tempe, AZ)
Brian Gute, Assistant Scientist
Douglas Hawkins, Co-principal Investigator (Professor; Dept. of Applied Statistics; Univ. of Minnesota, St. Paul, MN)
Denise Mills, Senior Laboratory Technician
Milan Randić, Consultant (Distinguished Professor; Drake Univ., Des Moines, IA)
Marjan Vračko, Consultant (Professor; National Institute of Chemistry, Slovenia)

IV. Inventions/Patents/Discoveries

None to report at this time.

V. Collaborators/Consultants

Collaborators

Douglas Hawkins, Ph.D., is a professor and former Chairman of the Department of Applied Statistics at the University of Minnesota Minneapolis campus. He has been involved in the statistical analysis of data for developing QSAR models as part of this project. Specifically, he has worked with our research group in the implementation of new statistical techniques, such as ridge regression (RR) and partial least squares (PLS) in QSAR analysis and in the development of the tailored QMSA method (Basak, Gute, Mills and Hawkins, *J. Mol. Struct. THEOCHEM*, in press; Gute, Basak, Mills and Hawkins, *Internet Electron. J. Mol. Des.*, in press). A recent study with Dr. Hawkins examines the role of cross-validation techniques in QSAR studies, challenging some of the commonly held misconceptions in regards to cross-validation (Hawkins, Basak and Mills, *J. Mol. Graphics and Modelling*, submitted).

Consultants

Krishnan Balasubramanian, Ph.D., is currently a professor at both the University of California Davis and the Lawrence Livermore National Laboratory and Glenn T. Seaborg Center, Lawrence Berkeley National Lab, Berkeley, CA. Dr. Balasubramanian has been pivotal in our implementation of *ab initio* calculations using the *Gaussian98W* software package. He has trained our research team in the use of the software and has served as a resource for further troubleshooting of technical problems. More importantly, he has been advising our group in the selection of quantum chemical basis sets and proper molecular solvation states for calculations based on the electronic nature of the chemicals being studied. Under his guidance we have

expanded our previous analysis of the set of 55 halocarbons to include even higher levels of quantum theoretic calculations including the 6-311G* and cc-pVTZ basis sets, all with geometric optimization (Basak, Balasubramanian, Gute, Mills, Gorczynska and Roszak, *J. Chem. Inf. Comput. Sci.*, submitted). Dr. Balasubramanian is currently working on extremely intensive calculations for a small subset of the 55 halocarbons.

Milan Randić, Ph.D., is the Ellis & Nelle Levitt Professor Emeritus for the Department of Mathematics & Computer Science at Drake University, in Des Moines, Iowa. We have worked closely with Dr. Randić over the past six months to expand on the group of biodescriptors based on proteomics maps developed during the previous project. This effort has been successful and has been well received by the scientific community. Our continuing work on developing novel biodescriptors has been presented at five international conferences to-date and has resulted in 11 manuscripts in varying states of publication to date with several more currently in progress. Appendix 1.5 presents a complete bibliography of proteomics papers developed by our group and our collaborators.

Marjan Vračko, Ph.D., is a senior scientist at the National Institute of Chemistry, in Ljubljana, Slovenia. He has worked with the NRRI team in the development of spectrum-like descriptors for proteomics maps and has contributed to our previous work on the creation of biodescriptors to characterize proteomics maps (Randić, Witzmann, Vračko and Basak, *Med. Chem. Res.*, 2001). A manuscript describing our work to-date on spectrum-like biodescriptors was recently submitted (Vračko and Basak, *J. Proteom. Res.*, submitted).

Frank Witzmann, Ph.D., is a Professor of Cellular & Integrative Physiology and Biochemistry & Molecular Biology, at the Indiana University School of Medicine. Without Dr. Witzmann's assistance and specialized knowledge, this project would not be possible. He has provided proteomics data, in the form of standardized proteomics 'spot' maps and has served as an advisor in the use and interpretation of this data. None of the proteomics related manuscripts listed above would have been possible without the high-quality data that he has made available to our research team. We eagerly await more data from his laboratory.

VI. Honors and Awards

Advisory/Organizational Positions Held by Dr. Basak

1. Co-chair of the Indo-US Workshop in Mathematical Chemistry, an on-going biennial conference series designed to promote an open exchange of scientific ideas between international scholars and with an emphasis on encouraging young Indian and American scientists (since 1997).

Invited Lectures and Seminars Presented by Dr. Basak

1. *Estimation of Toxicological and Ecotoxicological Properties of Chemicals from Structure: A Mathematical-cum-Computational Approach*, presented to the faculty and students of the Toxicology Program of the University of Minnesota, broadcast from Duluth, MN (March 2002).
2. *Numerical Graph Invariants: Development and Applications in Drug Discovery and Risk Assessment of Chemicals*, presented to the Department of Mathematics and Statistics, University of Minnesota Duluth, Duluth, MN (March 2002).

3. *Interrelationship of Major Topological Indices*, co-authored by B.D. Gute and A.T. Balaban, was presented at the Joint Annual Meeting of the Society of Environmental Toxicology and Chemistry (Midwest Chapter) and Society of Toxicology (Northland Chapter) organized at the USEPA Mid- Continental Ecology Division, in Duluth, MN (April 2002).
4. *Development of New Tools for Quantitative Characterization of Proteomics Maps*, at the symposium Development and "Application of Ecogenomics for Water Quality Assessment" organized jointly by the Council of State Governments and the United States Environmental Protection Agency, in Kansas City, MO (May 2002).
5. *Chemodescriptors Versus Biodescriptors in Toxicity Prediction of Halocarbons*, co-authored by B.D. Gute, D. Mills, K. Balasubramanian (UC - Davis), K. Geiss (Wright Patterson Air Force Base, Dayton, OH), D. Hawkins (U of MN, TC Campus), M. Randić (NRRI and National Institute of Chemistry, Ljubljana, Slovenia), F. Witzmann (Indiana University School of Medicine), and M. Vračko (National Institute of Chemistry, Ljubljana, Slovenia), was presented at the QSAR 2002 Conference, May 25-29, Ottawa, Canada.
6. *Predicting Toxicity of Chemicals in the Post-Genomic Era: A Computational Approach*, delivered to the Department of Molecular Biology and Genetics, at the University of Guelph, Guelph, Ontario, Canada (June 2002).
7. *Predicting Bioactivity of Chemicals from Structural and Proteomics-Based Descriptors*, presented at the University of Texas Medical Branch (UTMB) sponsored jointly by UTMB and Department of Marine Sciences, Texas A & M University at Galveston, Galveston, TX (June 2002).
8. Dr. Basak gave the following invited seminar lectures on predictive toxicology, QSAR and Mathematical Chemistry during his recent trip to India:
 - a. *Predicting therapeutic activity, health hazard, and ecotoxicity of chemicals using structural and and proteomics based descriptors: An integrated approach*, July 26, 2002, at the Bose Institute, Kolkata, India;
 - b. A two part lecture on *Predicting bioactivity and toxicity of chemicals from structure and proteomics based descriptors* at the Department of Biochemistry, Calcutta University, Kolkata, August 2, 2002;
 - c. A two part lecture on *Use of discrete mathematics in chemistry, drug design and ecotoxicology*, "Part I: Molecular descriptors and QSAR," August 7, 2002; "Part II: Molecular similarity and integrated QSAR in predictive toxicology," August 8, 2002, at the Sivatosh Mookerjee Science Center, Kolkata, India;
 - d. An invited lecture on *Integration of chemoinformatics and bioinformatics for drug discovery and environmental protection: An integrated approach in the post-genomic era*, at the Indian Institute of Chemical Biology, Kolkata;
 - e. *Use of mathematical invariants in drug discovery and toxicology in the post-genomic era: An in silico approach*.

VII. Key Findings/Results/Accomplishments

1. Biodescriptors

Development and applications of biodescriptors for predictive toxicology by our NRRI team has been expanded to incorporate three major types of biodescriptors: a) global descriptors from invariants of matrices associated with proteomics maps, b) a set of local invariants describing various aspects of each map (instead of one global biodescriptor), and c) spectrum-like descriptors for the characterization of proteomics patterns.

1.1 Global Biodescriptors

Invariants of matrices (e.g. D/D matrix) and their higher power Kronecker products have been used to develop profiles for proteomics patterns for hepatocytes exposed to eight halocarbons (Basak et al, QSAR 2002 Conference, presented). This data was obtained from Dr. Frank Witzmann and is derived from hepatocytes exposed to halocarbons at the WPAFB, Dayton, Ohio, by Frazier, Geiss and coworkers. The profile given in Figure 1 shows that, even for the structurally similar halocarbons, the profiles for the entire set of eigenvalues and their higher powers are non-overlapping. This indicates that these biodescriptors have no degeneracy for the set of eight compounds tested thus far. It would be interesting to see whether this pattern holds when the set of halocarbons is expanded by the future addition of data on an expanded set of halocarbons.

Figure 1. Patterns of the eigenvalues for matrices of eight halocarbons and their Kronecker products.

1.2 Local Biodescriptors

Local biodescriptors are derived from the consideration of a smaller subset of spots than those used in formulating global descriptors. Smaller subsets of m spots are used sequentially instead of using all n spots simultaneously, $m < n$ (Randić, Zupan, Novič, Gute and Basak, *SAR & QSAR Environ. Res.*, accepted). The importance of local

invariants in contrast to global biodescriptors is that the former indices can be used to quantify effects of selected subsets of proteins related to a particular toxicological mode of action, e.g., peroxisome proliferation, apoptosis, etc.

1.3 Spectrum like biodescriptors of proteomics maps

For our purposes a proteomic map is considered as a set of points in 3D space where each point represents a spot in the map. The x and y coordinates determine the position of the spot while the z coordinate corresponds to protein abundance (or intensity). Such a pattern of points in 3D space can be represented with three spectrum-like objects. A representation is constructed in three steps. First, the pattern is projected on the xy, xz, and yz planes, respectively (see Figure 2). In the second step, each projection (or figure) is treated separately. A figure is placed into a circle of arbitrary radius. A projection beam from the center of a circle produces a pattern of points on the circle where each point represents a particular point. In the third step, each point on the circle is taken as a center for a Lorentzian curve of the form:

$$f_i(\varphi_i) = \frac{\rho_i}{(\varphi - \varphi_i)^2 + \sigma_i^2} \quad (1)$$

Here, ρ_i and φ_i are the distances between the origin of the coordinate system and the position of the i -th point and its polar angle, respectively. σ_i is a free parameter, which can be associated with any property given to the point. If we consider only positions of proteomic peaks, the σ_i 's are set to one. The spectrum related to the figure is the sum of all atomic Lorentzians and it is defined in the interval $(0, 2\pi)$. An example of three projections using a pattern comprised of five points is shown in Figure 3. The complete pattern of points in the 3D space is represented with three spectra, each of them associated with the xy, xz, or yz projection, respectively. By selecting k equidistant points on the interval, one figure is represented by a k -dimensional vector. The value of k determines the resolution of the representation. It is obvious that k should be close to the number of points in the proteomic map, otherwise some information is lost. Finally, the three spectrum-like objects are compressed into a single vector $\vec{v}$.

Figure 2. Five arbitrarily selected spots of reference proteomic map. The red, yellow and blue lines are projection lines on xy, xz and yz planes, respectively.

A

B

C

Figure 3: A: xy projection and corresponding 'spectrum-like' object
B: xz projection and corresponding 'spectrum-like' object
C: yz projection

2. Characterization of Macromolecular Structure

It should be mentioned that our work on the development of biodescriptors for proteomics maps is a necessary extension of our research on the characterization of small molecules and biomolecules using discrete mathematics. We have continued our efforts in this area in addition to our work on developing biodescriptors. In the area of DNA sequence characterization, we have developed methods for the characterization of single nucleotide polymorphism (SNP) using numerical sequence descriptors (Nandy, Nandy and Basak, *Internet Electron. J. Mol. Des.*, 2002). This work has great potential for transition in view of the fact that more and more genomics data are being amassed and they need to be compared and stored efficiently by the scientific community.

Continuing this line of effort with the storage and retrieval of proteomics maps, a method for the efficient storage of these maps has been developed based on the partial ordering of the spots of maps and their unique canonical numbering (Randic and Basak, *J. Chem. Inf. Comput. Sci.*, in press).

3. Chemodescriptors and Computational Toxicology

3.1 Mechanism-based HiQSAR for Predictive Toxicology

A successful HiQSAR model has been developed for a set of 55 halocarbons for which cellular level toxicity data is available. It may be noted that this is the "superset" of compounds from which the "subset" of twenty halocarbons, currently being tested by WPAFB and Dr. Witzmann using the DNA microarray and proteomics analysis, was selected. Selection of parameters for the HiQSAR was based on the mechanistic hypothesis that *dissociate electron attachment* and subsequent formation of free radicals, leading to lipid peroxidation, is a major factor in halocarbon toxicity. This conclusion was derived from Dr. Balasubramanian's previous research, based on high-level quantum chemical calculations. If the hypothesis is correct, calculated parameters such as *vertical electron affinity* (VEA) should be strongly related to a chemical's toxicity. Accordingly, we used the following classes of indices in a hierarchical manner to develop QSAR models for the toxicity of 55 halocarbons:

Topostructural (TS), topochemical (TC), geometrical (3-D), semi-empirical quantum chemical (AM1), and calculations using five *ab initio* basis sets (STO-3G, 6-31G(d), 6-311G, 6-311G* and cc-pVTZ).

Results of this analysis are summarized below in Table 1 (Basak, Balasubramanian, Gute, Mills, Gorczynska and Roszak, *J. Chem. Inf. Comput. Sci.*, submitted).

It is evident from these results that only higher level *ab initio* indices (6-311G* and cc-pVTZ) made significant improvement in model quality over topological indices for the prediction of toxicity. The lower level *ab initio* and semi-empirical indices did not make any improvement over the models developed by the topostructural and topochemical indices. It may be noted that even with the addition of these high-level *ab initio* parameters, the easily calculable topological indices outperformed all other types of molecular descriptors in predicting toxicity from structure. This shows the utility and robustness of these simple descriptors.

Table 1. Summary results for the HiQSAR modeling of D₃₇ in *Aspergillus nidulans* for 55 halogenated aliphatic hydrocarbons.

Model	# indep. variables	R^2	R^2_{cv}	s.e.	F
TSI only	2	0.3659	0.2945	1.243	15.00
TCI only	8	0.8623	0.7749	0.6161	36.00
3D only	8	0.8838	0.6496	0.5660	43.72
AM1 only	3	0.4591	0.3008	1.159	14.43
STO-3G only	3	0.3055	0.1624	1.314	7.48
6-31G(d) only	4	0.4111	0.2458	1.222	8.73
6-311G only	4	0.5140	0.3853	1.110	13.22
6-311G* only	4	0.6318	0.5053	0.9663	21.45
cc-pVTZ only	1	0.5099	0.4787	1.083	55.14
TSI + TCI	7	0.8791	0.8074	0.5710	48.83
TSI + TCI + 3D	Same as previous model				
TSI + TCI + AM1	7	0.8840	0.8121	0.5594	51.17
TSI + TCI + STO-3G	7	0.8724	0.7923	0.5866	45.91
TSI + TCI + 6-31G(d)	7	0.8713	0.7926	0.5893	45.45
TSI + TCI + 6-311G	10	0.9015	0.8283	0.5328	40.26
TSI + TCI + 6-311G(d)	8	0.9056	0.8335	0.5100	55.17
TSI + TCI + aug-cc-pVTZ	8	0.9476	0.9236	0.3800	103.98

3.2 Hierarchical QSAR

We have continued our work exploring the various levels of parameters in the development of QSARs for a wide variety of properties (Basak, Mills, Gute and Hawkins, in *Quantitative Structure-Activity Relationship (QSAR) Models of Mutagens and Carcinogens*, in press; Basak, Balasubramanian, Gute, Mills, Gorczynska and Roszak, *J. Chem. Inf. Comput. Sci.*, submitted).

3.3 Estimation of PBPK parameters

Two distinct factors are involved in the causation of toxicity: a) toxicokinetics and b) toxicodynamics. While QSAR for toxicity endpoints can estimate the potential hazard of the pollutant, the extent of exposure determines the bioavailability of the chemical in the biophase and determines the actual risk from the chemical. Physiologically-based pharmacokinetic (PBPK) modeling is used routinely to estimate the availability of chemicals to various biotargets within the organism. These models need a variety of properties as input parameters. Blood:air and tissue:air partition coefficients fall into the category of parameters essential for PBPK modeling. We have developed HiQSARs to estimate blood:air and tissue:air partition coefficients of chemicals using structural parameters which can be calculated directly from the chemical structure without the need for the input of any other experimental data (Basak, Hawkins and Mills, in *Advances in Molecular Similarity*, in press; Basak, Mills, Hawkins and El-Masri, *SAR QSAR Environ. Res.*, in press; Basak, El-Masri, Hawkins and Mills, *J. Chem. Inf. Comput. Sci.*, submitted; Basak, Mills, Hawkins and El-Masri, *Risk Analysis*, submitted). Such models are expected

to be very useful to the PBPK modeling community.

3.4 Tailored Similarity

Our work on developing and refining quantitative molecular similarity analysis (QMSA) methods also continues. One recent addition to the field by our laboratory is the concept of tailored or property-specific QMSA methods (Basak, Gute and Mills, *SAR QSAR Environ. Res.*, in press; Basak, Gute, Mills and Hawkins, *J. Mol. Struct. THEOCHEM*, in press; Gute, Basak, Mills and Hawkins, *Internet Electron. J. Mol. Des.*, in press). Whereas ordinary similarity methods are based on an arbitrary set of descriptors or at best a set of parameters chosen subjectively based on previous experience of the scientist, in tailored QMSA we first choose a subset of indices strongly correlated with the property and then use them to create the n -dimensional space used to measure the structural similarity/dissimilarity of molecules. Results show that tailored QMSA (T-QMSA) outperforms standard (or arbitrary) QMSA methods. It is expected that this novel methodology will find wide applications both in drug design and predictive toxicology and will lead to substantial technology transfer.

3.5 Statistical Methods for QSAR Model Validation

Development of useful quantitative structure-activity/ toxicity relationship (QSAR/QSTR) models has to be based on sound statistical methodology. Our group has been involved in the formulation of methods for the validation of QSAR models (Hawkins, Mills and Basak, submitted). It is expected that such methods will be used widely in pharmaceutical and toxicological QSAR development.

4. Proposed Research Plan for 2002-2003

4.1 Global Biodescriptors

- 4.1.1 The current set of global biodescriptors will be used to characterize an expanded set of halocarbons to be provided by Dr. Witzmann.
- 4.1.2 Now that we have established a set of biodescriptors, we will begin to study the utility of combining chemo- and biodescriptors in HiQSAR for toxicity prediction.

4.2 Local Biodescriptors

- 4.2.1 Local biodescriptors will be used to characterize the toxic effects of peroxisome proliferators on proteomics maps.
- 4.2.2 Local biodescriptors will be used to characterize the toxic effects of halocarbons on proteomics maps.

4.3 Spectrum-like Biodescriptors

- 4.3.1 Local biodescriptors will be used to characterize the toxic effects of peroxisome proliferators on proteomics maps.
- 4.3.2 Local biodescriptors will be used to characterize the toxic effects of halocarbons on proteomics maps.

4.4 Development of Novel Matrix Invariants

- 4.4.1 Novel matrix invariants for the characterization of proteomics maps will be developed based on the 3D-Wiener number.
- 4.4.2 Novel matrix invariants for the characterization of proteomics maps will be

developed based on information theoretic indices.

4.5 Characterization of the Similarity of Proteomics Maps

An n -dimensional biodescriptor space will be developed using global, local, and spectrum-like biodescriptors. Attempts will be made to use standard similarity measures to characterize this space.

4.6 Mechanism-based HiQSAR

- 4.6.1 The greater success of the aug-cc-pVTZ indices indicates that more sophisticated or higher level quantum chemical indices might better reflect the electronic basis of the toxicity of these halocarbons. To this end, we will run *ab initio* calculations at the CCSD(T) level for a subset of the 55 halocarbons, however this can only be a small subset since it is prohibitively time consuming to do so for the entire set. This work will allow us to investigate how far the success of the less expensive parameters can be vindicated using higher level parameters.
- 4.6.2 Calculations on solvated molecules, as opposed to the standard gas phase calculations, will be conducted to see whether such involved calculations give better models or shed some light in the toxic modes of action of halocarbons.

4.7 Tailored Similarity

- 4.7.1 Further work will be done to continue developing the tailored molecular similarity method and to examine its applications for the estimation of toxicologically- and pharmaceutically-relevant properties. In particular we will be examining the usefulness of the method for estimating halocarbon toxicity and for analog selection within a proprietary Astra-Zeneca pharmaceutical database.
- 4.7.2 We will examine the application of the tailored approach to dissimilarity analysis and chemical clustering. Specifically, we will use the JP-8 database as an interesting example for cluster analysis.

4.8 Statistical Method Development

We plan to explore the development and implementation of novel statistical methods for microarray and proteomics analysis.

VIII. Transitions/Technology Transfers

1. Contribution to Computational Toxicology Program

The hierarchical QSAR approach for modeling toxicity (HiQSTR) developed by our research team has been adopted into the curriculum of the Masters coursework for the Predictive Toxicology program of the Environmental Sciences Department of the University of Calcutta, Kolkata, India. In addition, they have incorporated various molecular similarity methods, and just recently as a result of Dr. Basak's most recent visit to India, they have decided to add our recently developed tailored approach to molecular similarity (T-QMSA) into the curriculum as well.

2. Cooperative Work with Astra-Zeneca

We have recently begun a collaborative work with Dr. Indira Ghosh of Astra-Zeneca. We

will be applying our newly developed tailored quantitative molecular similarity analysis (T-QMSA) techniques to a large proprietary drug discovery or pharmaceutical database provided by Astra-Zeneca.

Appendix 1: Publications/Reprints

Appendix 1.1: Manuscripts on the development of biodescriptors for proteomics maps

A comparative study of proteomics maps using graph theoretical biodescriptors, M. Randić and S. C. Basak, *J. Chem. Inf. Comput. Sci.*

Novel matrix invariants for characterization of changes of proteomics maps, M. Randić, J. Zupan, M. Novič, B.D. Gute and S.C. Basak, *SAR QSAR Environ. Res.*

On canonical labeling of proteins of proteomics maps, M. Randić and S.C. Basak, *J. Chem. Inf. Comput. Sci.*

Appendix 1.2: Prediction of cellular toxicity of halocarbons from their computed chemo-descriptors: A hierarchical QSAR approach, S.C. Basak, K. Balasubramanian, B.D. Gute, D. Mills, A. Gorczynska and S. Roszak, *J. Chem. Inf. Comput. Sci.*

Appendix 1.3: Manuscripts on tailored similarity (T-QMSA)

Quantitative molecular similarity analysis (QMSA) methods for property estimation: A comparison of property-based, arbitrary, and tailored similarity spaces, S.C. Basak, B.D. Gute and D. Mills, *SAR QSAR Environ. Res.*

Quantitative molecular similarity methods in the property/ toxicity estimation of chemicals: A comparison of arbitrary versus tailored similarity spaces, S.C. Basak, B.D. Gute, D. Mills and D.M. Hawkins, *J. Mol. Struct. THEOCHEM.*

Tailored similarity spaces for the prediction of physicochemical properties, B.D. Gute, S.C. Basak, D. Mills and D.M. Hawkins, *Internet Electron. J. Mol. Des.*, <http://www.biochempress.com/>.

Appendix 1.4: Manuscripts on PBPK modeling

Predicting blood:air partition coefficient of structurally diverse chemicals using theoretical molecular descriptors, S.C. Basak, D.M. Hawkins and D. Mills, in *Advances in Molecular Similarity*, R. Carbo-Dorca, P.G. Mezey, Eds., vol. 5.

Prediction of tissue:air partition coefficients: A comparison of structure-based and property-based methods, S.C. Basak, D. Mills, D.M. Hawkins and H.A. El-Masri, *SAR QSAR Environ. Res.*

Exposure assessment of volatile organic chemicals (VOCs): Predicting blood:air partition coefficients of diverse chemicals using theoretical descriptors, S.C. Basak, H. El-Masri, D.M. Hawkins and D. Mills, *J. Chem. Inf. Comput. Sci.*

Prediction of human blood:air partition coefficient: A comparison of structure-based and property-based methods, S.C. Basak, D. Mills, D.M. Hawkins and H. El-Masri, *Risk Analysis*.

Appendix 1.5: Bibliography of papers on development of proteomics-based biodescriptors

Appendix 1.1

Manuscripts on the development of biodescriptors for proteomics maps

A Comparative Study of Proteomics Maps Using Graph Theoretical Biodescriptors

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This paper reports the development of new methods for mathematical characterization of effects of different toxic agents on the cellular proteome. We describe numerical characterization of proteomics maps based on mathematical invariants. A graph is first associated with a proteomics map by considering partial ordering of spots on 2-D gels by ordering proteins with respect to the mass and the charge, the two properties by which proteins are separated. The graph is then embedded over the map, and several graph theoretical invariants have been constructed. In particular we consider invariants that can be extracted from the Euclidean distance-adjacency matrix of the embedded graph, in which only Euclidean distances between adjacent vertices of a graph are considered. The approach is illustrated using proteomics patterns of normal liver cells of rats and those derived from liver cells of animals exposed to four peroxisome proliferators. In contrast to direct comparison of spot abundance our approach incorporates information on spots locations. The difference between the two approaches is that in the first case only changes in abundances are considered as a measure of perturbation of the proteome map, but in the second case not only the charge but also the mass of proteins are used for ordering protein spots.

INTRODUCTION

In this paper we have attempted the development of novel numerical descriptors for characterization of proteomics maps, that could facilitate comparison of proteomics data, whether from a single laboratory or from different laboratories. A typical proteomics map may have 2000 and more separated proteins that appear as spots on a 2-D gel in which they are separated by charge (*x*-axis) and mass (*y*-axis). When an experimental animal is exposed to drugs or toxins, the protein content of cells usually change. As a consequence the relative abundance of various proteins that characterize a normal cell is perturbed resulting in an altered proteomics map. To facilitate comparison of such changes we want to characterize individual proteomics maps by a set of map descriptors, which are mathematical invariants, derived from proteomics patterns.

Information contained in a map can be (and often is) represented as a list of coordinates and abundance of individual spots, as illustrated in Table 1 for 20 most intensive spots from the liver of normal rats and those exposed to four toxic chemicals. Figure 1 shows the positions of the 20 most abundant protein spots labeled A–T based on information in the columns listing coordinates *x*, *y* of Table 1. We consider the information in Table 1 as *input* information, and our goal is to arrive at some numerical descriptors that characterize a map as a whole so that they can be used for quantitative comparison of different proteomics maps. What makes our approach different from a direct comparison of spot abundance, as shown in different

Table 1. Gel Coordinates and Abundance for the 20 Most Intensive Protein Spots of Rat Liver Cells of the Normal Cells and the Corresponding Abundance for Rat Liver Cells Exposed to Four Chemicals

#	<i>x</i>	<i>y</i>	control	PFOA	PFDA	clofibrate	DEHP
A	2111.7	2278.6	144357	108713	95028	147081	165886
B	2804.3	903.6	143630	155565	188582	159898	155055
C	1183.9	959.6	136653	113859	150253	163645	8111
D	2182.2	928.8	127195	99160	73071	76642	112096
E	2685.6	1196.1	118581	112790	49769	109856	138795
F	1527.9	825.5	114929	192437	221567	166080	180590
G	1346.0	1352.5	112251	58669	38915	73159	77075
H	2868.5	778.0	108883	26105	50735	45923	116849
I	1406.3	1118.1	98224	91147	82963	84196	92942
J	2450.2	409.2	93601	83172	62934	79870	109381
K	1474.0	665.1	90004	129340	112361	112655	119402
L	2974.9	772.8	86730	70746	78691	105760	116281
M	2068.4	823.1	84842	73814	45482	71911	97444
N	642.2	669.8	82492	73974	74466	84703	88545
O	2860.7	1649.9	81965	16137	16501	60077	148992
P	2032.7	902.8	80015	77314	80072	76027	100836
Q	2752.7	765.6	79847	20782	13103	38816	53830
R	2334.2	982.2	72791	76369	52749	55599	77432
S	1053.6	864.3	72173	77982	60376	46808	78121
T	2519.5	1365.9	69452	37838	16129	57167	71274

columns of Table 1, is that the approach incorporates besides the information on the abundance also the information on spot locations. The difference between the two approaches is that in the first case only changes in abundances are considered as a measure of perturbation of a proteomics map, but in the second case also locations of protein spots, i.e., the charge and mass of proteins, make an influence.

Before continuing with details we need to respond to the question: "Why the 20 most abundant proteins are chosen for analysis?" The answer is that for the development of a mathematical approach neither the number of selected points

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Figure 1. The position of 20 most abundant protein spots of rat liver cells labeled alphabetically.

nor the criteria of selection is essential. Because of the wide variability of experimental data on proteomics in general we focused on the most abundant proteins. Whether 20 most abundant proteins suffice to represent a map as a whole or one should select 50, or 200, remains yet to be better explored. Equally it remains to be seen if the selection of a subset of N proteins rather than all of them could be justified. If N is sufficiently large (and that may be 20, 50, or 200) one hopes that such subsets may capture the most features of a map that may suffice for comparison of different proteomics maps.

A proteomics map invariant is a quantity that is independent of the coordinates and the labels of the proteins in proteomics maps or 2-D gels. Why is it so important for mathematical descriptors to be independent of the adopted protein labels? A quantity independent of the arbitrary labeling of proteins characterizes a system as a *whole* and does not pertain to any of its local features or any particular protein. To be more correct we should say that such characterization pertains to a set of protein spots selected as the basis for numerical characterization of a map. Hence, map invariants are properties of the cell/tissue considered as represented by a group of proteins as a whole and not of any particular protein. This, however, in no way prevents one to compare protein expressions across different samples taken from the same species.

It is obvious that we need many invariants if we are to capture the majority of salient features of information-rich proteomics maps. Thus this paper represents a continuation of our recent efforts¹⁻⁶ to develop mathematical characterization of proteomics maps. In particular, in this article we will consider sets of invariants that can be constructed by a

procedure outlined in ref 4 which can be viewed as part I of this paper, in which an approach is outlined in which one associates an *embedded graph* to a proteomics map through *partial ordering* of spots with respect to their charge and mass.

Because the intensity of a spot in the 2D gel will depend not only on the concentration of proteins but also on the total amount of protein used in running the gel, reliability of experimental data should be known. We used experimental data from a laboratory known for following a rigorous protocol,⁷ and thus we have some confidence that the overall effects of various peroxisome proliferators resulted in reduced overall production or proteins.

PARTIAL ORDERING BASED ON CHARGE AND MASS

Partial ordering has not been widely used in chemistry despite the fact that it offers a useful tool for comparison of objects characterized by sequences. For example, partial ordering allows one to compare properties of isomers,^{8,9} and it can be used to search for pharmacophore in QSAR studies.^{10,11} For a recent review of use of partial orderings in chemistry see the special issue of MATCH.¹² In this paper we will use partial order to generate a *graph* to be associated with a map. Once we have a graph, we can construct various graph matrices, and from such matrices we can construct graph invariants to serve as map descriptors.

To obtain a graph associated with protein spots listed in Table 1, we will *order* the 20 spots of Table 1 with respect to the *charge* and the *mass*. By ordering protein spots with respect to mass we obtain the sequence A, O, T, G, E, I . . . which gives an ordering in which spots appear when we list them as they appear in going from the top of the map to the bottom, beginning with the protein having the greatest mass and ending with the protein having the smallest mass. As we see at the top of Figure 1, the protein spot A has the largest mass and is followed by spot O, the protein with the second largest mass, and so on. When we order the 20 protein spots with respect to the charge we obtain the sequence L, H, O, B, Q, E . . . which reflects the order in which protein spots appear if we go from the right (the largest charge) to the left (the smallest charge). As we see from Figure 1 protein L has the largest charge, followed by protein H, and so on.

Partial ordering is defined as a set of *all* sequential orderings given by subsets of the two sequences, the elements of which maintain the ordering for both sequences. To obtain all sequential orderings preserved in both sequences it is convenient to construct a diagram, as shown in Figure 2, in which the two sequences are listed, one above the other and lines are drawn that connect the same element in both sequences. Any set of noncrossing lines constitutes a subset of partial ordering, the subsequence the relative order of which is present in both sequences. For example, the lines O - O, E - E, R - R, D - D, P - P, F - F, and N - N do not cross giving the subsequence O > E > R > D > P > F > N. In Table 2 we have listed all such fragmentary orderings that start with protein spot A. The totality of all fragmentary orderings makes the partial ordering for the selected 20 proteins of the map of Figure 1.

A complete list of all sequences of partial ordering is neither a necessary nor particularly useful representation of the partial ordering sought. It is customary to represent partial

Figure 2. Ordering of proteins of Figure 1 relative to their mass (the top sequence) and their charge (the bottom sequence). The same labels in both sequences are connected by line to help to identify partial orderings.

Table 2. Fragmentary Orderings of Protein Spots Holding with Respect to Charge and Mass Respectively that Start with Protein A

1	A →	G →	C →	S →	N
2	A →	I →	C →	S →	N
3	A →	M →	K		
4	A →	M →	N		
5	A →	P →	F →	K	
6	A →	P →	F →	N	
7	A →	P →	S →	N	

ordering by a directed graph or a hierarchical diagram shown in Figure 3 in which points at the left *dominate* points to the right. *Dominance* here means that an element at the left in Figure 3 is also at the left in both sequences of Figure 2. Figure 3 facilitates visual inspection of the partial ordering and immediately shows which protein dominates others by mass and charge or is dominated by others. In making Figure 3 one can place vertices (labels) in arbitrary positions as long as the dominance relation is preserved. Nevertheless, one tries to construct partial ordering diagrams that will have, for better visibility, as few crossings of lines as possible.

The next important step in analysis of proteomics map based on partial ordering is to *embed* the partial ordering diagram of Figure 3 directly over the map. This is a critical step that has been for the first time considered in relationship to partial ordering in general and proteomics maps in particular in ref 4. *Embedding* of graphs in 2-D space (plane) or 3-D space in Graph Theory implies that a fixed geometry is assigned to the graph that can no longer be viewed as only giving *adjacency* relationships between vertices but also giving the *distances* between linked elements. While Graph Theory¹³ is usually concerned with *topological* and *combinatorial* properties of mathematical objects, in the case of embedded graphs it is concerned solely with the geometry and the combinatorial properties of the same objects, while topology of objects is no longer of concern. In Figure 4 we have imposed the adjacency relations of Figure 3 directly over the map of Figure 1, and as a result we obtain a partial ordering graph *embedded* on the map. Because the protein spots have definite (x, y) coordinates now proteins at the top dominate those below if connected by lines and proteins at the right dominate those at the left if connected by lines.

Observe an important and interesting feature of the embedded graph of Figure 4 in that all the lines (links) in

the graph have positive slope. This is a consequence of the dominance relation and is a property which can be exploited for a direct construction of embedded graph for a given map, *without* a need for construction of Figure 2, listing the various fragmentary orderings, and depicting the hierarchical diagram of the partial ordering, such as Figure 3. To obtain Figure 4 directly from Figure 1 one can start with the top vertex (spot A in Figure 4) and connect it to the next lower spot to the left of A which is spot G. One can continue the same with vertex G and connect it to the next lower vertex below it and to the left, which is spot C. We continue to connect C to S and finally S to N. By exhausting this particular trail we return to vertex A and repeat the process: we connect A to I and then I to C. In the next step, we connect A to P and finally P to S. By backtracking we connect P to F and F both to K and N, since both K and N are below P and at the left of P. Finally we backtrack again to protein A and we connect it to M, which is connected to K and N. This has exhausted all the fragmentary orders starting with protein spot A, that have been listed in Table 2. The process continues with spot O, then L and H, which completes construction of the embedded graph of partial order for the map considered.

THE EUCLIDEAN-ADJACENCY MATRIX E OF A MAP

The adjacency matrix is a well-known binary matrix of Graph Theory. Its matrix elements are defined as

$$A_{ij} = 1 \quad \text{if vertices } i \text{ and } j \text{ are adjacent}$$

$$A_{ij} = 0 \quad \text{otherwise}$$

The Euclidean-adjacency matrix E is a novel matrix only recently suggested,¹³ that is defined only for *embedded* graphs (because only embedded graph in 2-D or 3-D space have fixed geometry). Its matrix elements are defined by

$$E_{ij} = \text{Euclidean distance} \quad \text{if vertices } i \text{ and } j \text{ are adjacent}$$

$$E_{ij} = 0 \quad \text{otherwise}$$

Hence, the difference between A and E matrices is only in the magnitudes of the nonzero entries, which in the former

Figure 3. Graphical representation of the partial ordering of Figure 1.

Figure 4. The adjacency relationships of Figure 3 embedded upon the proteomics map of Figure 1 that results in embedded graph of the partial order of proteins with respect to mass and charge.

take the value 1 and in the latter assume numerical values determined by the distance between points considered.

The embedded graph of Figure 4 is the starting point for our mathematical characterization of proteomics maps. First, in view of the fact that that x , y coordinates represent

Table 3. Reported Distances, Normalized Distances between Adjacent Spots, as Defined by the Partial Order for the 20 Intensive Protein Spots of Normal Rat Liver Cells, as the Corresponding Matrix Elements of Euclidean-Adjacency Matrix

E_{ij}	line	distance	norm	E_{ij}	line	distance	norm
1, 7	AG	1201.7	1.6207	5, 18	ER	411.4	0.5549
1, 9	AI	1358.1	1.8319	6, 11	FK	169.2	0.2282
1, 13	AM	1456.1	1.9641	6, 14	FN	899.3	1.2130
1, 16	AP	1378.1	1.8588	6, 16	FP	510.7	0.6888
2, 13	BM	740.3	0.9986	7, 20	GT	1173.6	1.5830
2, 15	BO	748.4	1.0095	8, 18	HQ	116.5	0.1571
2, 16	BP	771.6	1.0408	9, 20	IT	1140.4	1.5383
2, 17	BQ	147.3	0.1987	10, 17	JQ	467.5	0.6306
3, 7	CG	425.0	0.5733	10, 20	JT	959.2	1.2938
3, 9	CI	273.1	0.3684	11, 13	KM	615.0	0.8296
3, 18	CR	1150.5	1.5519	11, 17	KQ	1282.6	1.7301
3, 19	CS	161.4	0.2177	12, 17	LQ	222.3	0.2999
4, 13	DM	155.3	0.2095	13, 14	MN	1434.4	1.9348
4, 16	DP	151.7	0.2047	14, 17	NQ	2112.7	2.8497
4, 18	DR	161.1	0.2173	14, 19	NS	455.1	0.6138
5, 9	EI	1281.7	1.7288	15, 20	OT	443.9	0.5988
5, 10	EJ	821.4	1.1079	16, 19	PS	979.9	1.3217
5, 15	EO	486.4	0.6561	18, 20	RT	426.1	0.5748

physically distinct properties and are therefore measured in different units, we will follow a recommendation of Kowalski and Bender¹⁴ and will rescale the coordinate units. However, rather than using the scaling that reduces both coordinate values to an interval $(-1, +1)$, that Kowalski and Bender suggested, we will scale the distances between adjacent spots of Figure 4 so that the average distance becomes 1. The reason for this is that then not only the entries in the Euclidean-adjacency matrix E and the adjacency matrix A are of comparable magnitude but also because their averages are the same, for both matrices the sum of all entries above the main diagonal is the same.^{20,21} In Table 3 in the column "norm" we show the rescaled Euclidean distances between the adjacent vertices of the embedded graph of Figure 4.

Adjacency and the Euclidean-adjacency matrices will generate a number of different topological or topographic indices.¹⁵ As we can see from Table 4, where we have listed the row sums for the adjacency matrix and the Euclidean-

Table 4. Row Sums for the Adjacency Matrix (A) and the Euclidean-Adjacency Matrix (E) of Graph of Figure 4

spot	spot	row sum for A	row sum for E	new label
1	A	4	7.2756	1
2	B	4	3.2476	10
3	C	4	2.7113	14
4	D	3	0.6315	18
5	E	4	4.0477	8
6	F	3	2.1302	17
7	G	3	3.7771	9
8	H	1	0.1571	20
9	I	4	5.4673	6
10	J	3	3.0323	11
11	K	3	2.7880	13
12	L	1	0.2999	29
13	M	5	5.9476	3
14	N	4	6.6114	2
15	O	3	2.2544	25
16	P	5	5.1148	7
17	Q	6	5.8661	5
18	R	4	2.8989	12
19	S	3	2.1533	16
20	T	5	5.887	4

adjacency matrix of the graph of Figure 4, already the two matrices have different row sums and therefore matrix invariants based on them will be distinct. In the case of the adjacency matrix of a graph row sum represents the valence (or the degree) of the vertex, hence, we can interpret the row sums of the Euclidean-adjacency matrix as E as the "distance valences" of vertices of the embedded graph. Vertices that have as neighbors more vertices at larger distances will have a larger value for their "distance valence," while vertices having fewer neighbors and at shorter distances will have lower values of their "distance" valence.

ADDITIONAL MAP MATRICES

An advantage of having a graph (and embedded graph) associated with a map as compared to the case of associating a map with a zigzag curve is that for such a graph we can construct a number of additional matrices, which subsequently will lead to additional alternative characterizations of the same map. We will briefly outline several of such additional matrices associated with the embedded graph of Figure 4 that may be of interest as a source of novel map invariants.

The Geometry Matrix G. In contrast to the adjacency and the Euclidean-adjacency matrices which are sparse matrices (that is matrices having many zero elements)¹⁶ geometrical matrix G is a dense matrix having zero entries only on the main diagonal. Its matrix element (i, j) represents the Euclidean distance between vertex i and vertex j regardless whether i and j are adjacent or not.

D/D Matrix. As is known, the elements of the Graph Theoretical Distance Matrix D express *graph theoretical distances* between a pair of vertices, which are defined by the smallest number of edges that separate two vertices.¹⁷ Once D is constructed, it can be combined with the G matrix for construction of the so-called D/D matrix,¹⁸ the elements of which are given as the quotient of the corresponding elements of D and G matrix.

The Map Connectivity Matrices D_{1k} . These new matrices are reported for the first time in this article. They are based on partitioning of the connectivity index¹⁹ and the higher order connectivity indices²⁰ into contributions arising from paths of length k .

Table 5. Nonzero Matrix Elements of the Map Connectivity Matrix D_{1k}

element		element		element	
1, 7	0.19076	4, 13	0.51599	9, 20	0.17627
1, 9	0.15855	4, 16	0.55642	10, 17	0.23710
1, 13	0.15201	4, 18	0.73909	10, 20	0.23668
1, 16	0.16393	5, 9	0.21257	11, 13	0.24557
2, 13	0.22753	5, 10	0.28544	11, 17	0.24727
2, 15	0.36958	5, 15	0.33104	12, 17	0.75395
2, 16	0.24536	5, 18	0.29193	13, 14	0.15947
2, 17	0.22911	6, 11	0.41034	14, 17	0.16057
3, 7	0.31249	6, 14	0.26647	14, 19	0.26503
3, 9	0.25973	6, 16	0.30295	15, 20	0.27450
3, 18	0.35669	7, 20	0.21207	16, 19	0.30132
3, 19	0.41387	8, 17	1.04169	18, 20	0.24207

Table 6. Nonzero Matrix Elements of the Map Connectivity Matrix D_{2k}

element		element		element	
1, 2	0.06575	3, 4	0.48660	7, 18	0.13858
1, 3	0.22998	3, 5	0.33215	8, 10	0.64853
1, 4	0.45814	3, 14	0.12049	8, 12	2.06227
1, 5	0.08544	3, 16	0.15350	8, 14	0.43921
1, 6	0.10142	3, 20	0.42577	9, 10	0.11265
1, 11	0.09879	4, 5	0.39825	9, 15	0.13033
1, 14	0.06416	4, 6	0.34423	9, 18	0.11519
1, 19	0.00332	4, 11	0.33532	10, 12	0.46939
1, 20	0.16018	4, 14	0.21775	10, 14	0.09997
2, 3	0.12350	4, 19	0.31807	10, 15	0.17500
2, 4	0.22318	4, 20	0.33893	10, 18	0.15467
2, 5	0.14273	5, 17	0.12776	11, 12	0.48952
2, 8	0.45016	5, 20	0.51371	11, 14	0.20789
2, 10	0.10246	6, 13	0.13572	12, 14	0.31789
2, 11	0.23803	6, 17	0.22519	13, 17	0.07145
2, 12	0.32581	6, 19	0.22979	13, 19	0.08143
2, 14	0.30305	7, 9	0.10091	14, 16	0.09830
2, 16	0.20979	7, 10	0.13550	15, 18	0.17898
2, 20	0.12147	7, 15	0.15680		

Table 7. Row Sums of the Map Connectivity Matrix D_{1k} and the Row Sums of the Map Connectivity Matrix D_{2k}

row	sum	row	sum	row	sum	row	sum
1	0.7230	11	0.8422	1	1.2672	11	1.3696
2	1.0381	12	0.7957	2	2.3059	12	3.6645
3	1.2819	13	1.3061	3	1.8720	13	0.2886
4	1.9829	14	0.7401	4	3.1205	14	1.6608
5	1.1822	15	0.9248	5	1.6000	15	0.4661
6	1.0115	16	1.3641	6	1.0363	16	0.4616
7	0.7608	17	1.8465	7	0.5318	17	0.4244
8	1.0993	18	1.7266	8	3.6002	18	0.5874
9	0.8567	19	0.9388	9	0.4591	19	0.6312
10	0.8078	20	1.2358	10	1.7855	20	1.5601

In the case of the first order connectivity index (referred to as the Randić index of order 1 in CODESSA, the computer program of Katritzky, Lobanov, and Kerelson²¹ for computation of molecular descriptors) matrix elements represent contributions of paths of length one (bonds) to the $^1\chi$. In Table 5 we give the nonzero matrix elements for the Map Connectivity Matrix D_{1k} . Similarly, in Table 6 we give the nonzero matrix elements for the Map Connectivity Matrix D_{2k} , which is based on contributions from paths of length two. Finally in Table 7 we have listed the row sums for these two matrices. Tables 4–7 offer new possibilities for construction of additional numerical map descriptors. The situation is similar to that of the construction of novel topological indices from matrices associated with graphs, which produce novel chemodescriptors for QSAR. The difference is that descriptors obtained from matrices associ-

Table 8. Normalized Abundance for the 20 Most Intensive Protein Spots of Rat Liver Cells of the Normal Cells and the Corresponding Abundance for Rat Liver Cells Exposed to Four Chemicals

	control	PFOA	PFDA	clofibrate	DEHP
A	1.44457	1.08788	0.95094	1.47183	1.66001
B	1.43730	1.55673	1.88713	1.60009	1.55162
C	1.36748	1.13938	1.50357	1.63758	0.08116
D	1.27283	0.99229	0.73122	0.76695	1.12174
E	1.18663	1.12868	0.49803	1.09932	1.38891
F	1.15009	1.62550	2.21721	1.66195	1.80715
G	1.12329	0.58710	0.38942	0.73210	0.77128
H	1.08958	0.26123	0.50770	0.45923	1.16930
I	0.98292	0.91210	0.83020	0.19614	0.93006
J	0.93666	0.83230	0.62978	0.79925	1.09457
K	0.90066	1.29430	1.12439	1.12733	1.19485
L	0.86790	0.70795	0.78746	1.05833	1.16362
M	0.84901	0.73865	0.45514	0.71961	0.97512
N	0.82549	0.74025	0.74518	0.84762	0.88606
O	0.82022	0.16148	0.16512	0.60119	1.49095
P	0.80070	0.77368	0.80127	0.76080	1.00906
Q	0.79902	0.20796	0.13112	0.38843	0.53867
R	0.72841	0.76422	0.52786	0.55638	0.77486
S	0.72223	0.78036	0.60418	0.46840	0.78175
T	0.69500	0.37864	0.16140	0.57207	0.71323

ated with proteomics maps serve as potential biodescriptors in an integrated QSAR,²² in which chemodescriptors (topological indices, 3-D descriptors, and quantum chemical indices) are used in combination with invariants of proteomics maps (graph theoretical indices derived from embedded graphs) to predict the bioactivity/toxicity of chemicals. Moreover, any of the new matrices can be algebraically manipulated to produce the so-called "higher order" matrices either by using the Kronecker multiplication of matrices or the standard matrix multiplication.

AUGMENTED MAP MATRICES

So far we have not used information on abundance of proteins as measured by the intensity of gel spots. This information is critical when considering the role of various drugs and xenobiotic agents that perturb the proteome. The information on abundance can be combined in two ways with the information of locations of spots to produce invariants that will characterize altered proteomics maps. One approach would be to introduce the numerical values of experimental abundances as the diagonal entries of the matrix in analogy with differentiation of heteroatoms in construction of variable connectivity indices.²³⁻²⁷ Another way to incorporate the abundance is to view it as the third coordinate to the 2-D map based on the charge and the mass of proteins as separated by electrophoresis and chromatography.² This approach has been outlined in the introductory papers on the mathematical characterization of proteomics maps based on 2-D zigzag pattern of proteomics map and its generalization to 3-D zigzag pattern.² In both cases we will obtain novel matrices for proteomics maps of control cells as well as those derived from cells exposed to different chemicals.

Before one augments a map matrix by either including abundance as the diagonal entries or considers them as the third coordinate, one has to rescale the abundance values so that they are of the same order of magnitude as are the other two coordinates used for construction of the matrix. We have rescaled abundance values so that the average abundance equals one. In Table 8 we listed the rescaled abundance values for the 20 most intense protein spots of normal rat

hepatocytes and the corresponding abundance values for rat hepatocytes exposed to peroxisome proliferators: perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), clofibrate, and diethylhexyl phthalate (DEHP). As is known, the sites of the protein spots for the same protein always occur in the same locations on the gel (the same x , y coordinates), so correspondence can be established without identifying proteins. The 20 most abundant spots of the control group determine the selection of the spots for the remaining four proteomics maps corresponding to PFOA, PFDA, clofibrate, and DEHP. As can be seen in the first numerical column of Table 8, belonging to the control cells, the relative abundance values steadily decrease because spots were ordered by abundance. This, however, need not and is not the case with the remaining four columns, which show considerable oscillations in the relative magnitudes of the abundances when compared to the regular decrease of spots for the control group.

The most abundant spot appears to be the protein having label F for liver cells exposed to PFDA (2.217), and the least abundant is protein C for liver cells exposed to DEHP (0.081). From looking at Table 8, the question to consider is the following: how significant are the changes in abundance and how reproducible would the values in Table 8 be if the experiments were repeated. These are questions directed to *experimentalists* to which we cannot answer, except that we may add that the reproducibility of our numerical analysis is guaranteed once the reliability of the experimental data is established. Our contribution is toward *developing* theoretical methodology for quantitative comparison of proteomics maps, and the questions of reproducibility/error of protein data, which may be a major unanswered question in experimental proteomics, will not affect our *methodology*. In other words, as experimental techniques improve, the proposed numerical analysis will gain more and more reliability, which currently depends solely on the reliability of the experimental data.

In Table 8 we have indicated in bold type abundances of proteins, which show considerable change in rats, treated with peroxisome proliferators. As a threshold we have taken $\pm 50\%$ change in the abundance as compared with that of the control group. It is interesting to observe protein O, which in the case of PFOA and PFDA has *decreased* in abundance considerably; but in the case of DEHP, its abundance has *increased*. In many cases there appear to be considerable change in abundances in comparison with that of the control group even if the change is within the set bounds of $\pm 50\%$. In some cases abundances of proteins increased slightly after exposure to chemicals. Similarly, for some proteins the abundance decreased, although often not evenly (G, I, and Q). Protein N appears to have been the least affected by any of the four chemical agents.

Table 9 gives the degree of similarity/dissimilarity for pairwise comparisons of proteomics maps. The values in the table were computed by viewing each column in Table 8 as a 20-component vector. The Euclidean distance (in 20-dimensional vector space) gives the distance between the corresponding end-points of vectors. The smaller is the distance the more similar are vectors (or alternatively the more similar are the corresponding proteomics maps). The first row gives the similarity with the map of the control group, which suggests that among the four peroxisome

Table 9. Similarity/Dissimilarity among Perturbations of Abundances of Proteome Rat Liver Cells for the Control and the Four Peroxisome Proliferators Based on 20-Component Vectors of Table 8

	control	PFOA	PFDA	clofibrate	DEHP
control	0	1.606	2.190	1.499	1.769
PFOA		0	1.217	1.261	2.198
PFDA			0	1.481	2.714
Clofibrate				0	2.224
DEHP					0

proliferators clofibrate is causing the least perturbation in the liver cell proteome. However, such comparisons may obscure important details on how each agent affects individual protein types. Thus, clofibrate may give an overall (average) least perturbation of the map but it introduces the largest change in abundance of protein I, while the other three chemicals hardly change the abundance of the protein I in proteome of liver rat cells exposed to them.

Clearly a single type of descriptor, such as are the components of vectors in 20-D space already mentioned, cannot capture the complexity of variations occurring even for relatively small maps such as a map considered here that is based on information on only 20 proteins. In the next section we will consider 3-D representation of the proteomics maps for control groups, PFOA, PFDA, clofibrate, and DEHP from which we will construct additional map descriptors.

3-D MAP MATRICES

By viewing normalized abundances shown in Table 8 as the third coordinate of a 3-D space, one can combine this information with the data on (x, y) coordinates of Table 3 and compute Euclidean distances for a graph embedded in 3-D space, of which Figure 4 now represents projection on the (x, y) plane. The nonzero matrix elements of the 3-D distance-adjacency graphs are listed in Table 10, where the alphabetic labels indicate line segments of the graph and the numerical labels indicate the corresponding matrix elements for graph considered. A comparison of Tables 3 and 10 for the control group shows some (but not large) changes for corresponding matrix elements. As expected, the new (x, y, z) distances between adjacent spots in 3-D map representation have somewhat increased compared to (x, y) distances of 2-D map when the third dimension is added to the graph. The changes in the abundance between the proteins extracted from control cells and cells treated with the four peroxisome proliferators introduced uneven changes in the matrix elements for the four corresponding matrices.

THE LEADING EIGENVALUE OF MAP MATRICES

In the following we will consider the leading eigenvalues of the 3-D matrices as map descriptors. In Table 11 in the first numerical row we have listed the leading eigenvalue of the 3-D distance-adjacency matrices of proteomics maps for the normal (control) rat liver cells and those treated with the four peroxisome proliferators. To obtain additional map invariants we constructed the "higher order" map matrices, as outlined in ref 4 by considering the Kronecker products of each of the five matrices with itself. The leading eigenvalues of the matrices thus obtained were normalized using the reciprocal factorial $(1/n!)$ as a normalization factor,

Table 10. Nonzero Matrix Elements of the Euclidean Distance-Adjacency Matrix for the 20 Most Intensive Protein Spots of Rat Liver Cells of the Normal Cells (Control) and the Corresponding Abundance for Rat Liver Cells Exposed to Four Chemicals

line		control	PFOA	PFDA	clofibrate	DEHP
AG	1, 7	1.6516	1.6963	1.7152	1.7815	1.8484
AI	1, 9	1.8892	1.8403	1.8359	2.2323	1.9720
AM	1, 13	2.0524	1.9949	2.0257	2.1032	2.0801
AP	1, 16	1.9672	1.8852	1.8648	1.9902	1.9687
BM	2, 13	1.1590	1.2909	1.7458	1.3313	1.1531
BO	2, 15	1.1832	1.7222	1.9961	1.4202	1.0113
BP	2, 16	1.2201	1.3025	1.5041	1.3370	1.1737
BQ	2, 17	0.6685	1.3633	1.7672	1.2278	1.0324
CG	3, 7	0.6231	0.7960	1.2530	1.0717	0.8972
CI	3, 9	0.5325	0.4329	0.7676	1.4878	0.9254
CR	3, 18	1.6783	1.5966	1.8331	1.8914	1.0347
CS	3, 19	0.6810	0.4199	0.9254	1.1893	0.7336
DM	4, 13	0.4728	0.3290	0.3466	0.2148	0.2557
DP	4, 16	0.5146	0.2995	0.2189	0.2048	0.2337
DR	4, 18	0.5862	0.3150	0.2976	0.3026	0.4093
EI	5, 9	1.7408	1.7423	1.7604	1.9505	1.7887
EJ	5, 10	1.1357	1.1469	1.1157	1.1478	1.1463
EO	5, 15	0.7515	1.1687	0.7357	0.8238	0.6640
ER	5, 18	0.7196	0.6639	0.5557	0.7763	0.8276
FK	6, 11	0.3381	0.4022	1.1164	0.5813	0.6534
FN	6, 14	1.2557	1.5017	1.9074	1.4610	1.5231
FP	6, 16	0.7723	1.0955	1.5746	1.1342	1.0542
GT	7, 20	1.6399	1.5967	1.5993	1.5911	1.5841
HQ	8, 17	0.3303	0.1659	0.4080	0.1723	0.6499
IT	9, 20	1.5650	1.6282	1.6774	1.5836	1.5535
JQ	10, 17	0.6454	0.8874	0.8039	0.7526	0.8406
JT	10, 20	1.3162	1.3710	1.3760	1.3136	1.3488
KM	11, 13	0.8312	0.9985	1.0659	0.9334	0.8582
KQ	11, 17	1.7331	2.0429	1.9950	1.8813	1.8504
LQ	12, 17	0.3077	0.5830	0.7216	0.7340	0.6932
MN	13, 14	1.9349	1.9348	1.9564	1.9390	1.9368
NQ	14, 17	2.8498	2.8990	2.9151	2.8865	2.8708
NS	14, 19	0.6224	0.6151	0.6298	0.7215	0.6226
OT	15, 20	0.6118	0.6370	0.5988	0.5995	0.9815
PS	16, 19	1.3240	1.3217	1.3363	1.3537	1.3411
RT	18, 20	0.5758	0.6921	0.6817	0.5750	0.5781

Table 11. Leading Eigenvalue of the Euclidean Distance-Adjacency Matrix E and the Higher Order Matrices Obtained by Kronecker Product of a Matrix E by Itself

power	control	PFOA	PFDA	clofibrate	DEHP
1	5.1421	5.4972	6.0381	5.6998	5.4203
2	5.0141	5.4730	6.0599	5.4770	5.2738
3	4.1788	4.5492	4.8440	4.4267	4.3376
4	2.8409	3.0998	3.2291	3.0112	2.9445
5	1.5887	1.7483	1.8098	1.6985	1.6526
6	0.7486	0.8340	0.8642	0.8093	0.7832
7	0.3037	0.3433	0.3571	0.3323	0.3199
8	0.1080	0.1241	0.1297	0.1197	0.1146
9	0.0342	0.0399	0.0419	0.0384	0.0365
10	0.0097	0.0116	0.0122	0.0111	0.0105

where n is the power to which matrices were raised. The normalized leading eigenvalues listed in Table 11 show a fast convergence. Already when $n = 10$ they practically approach zero. We can view columns in Table 11 as vectors in 10-dimensional vector space. In Table 12 entries above the main diagonal represent the similarity/dissimilarity matrix between the five vectors corresponding to the control and the treated animals. Some similarities and differences can be observed when Table 12 is compared to Table 9 in which the similarity/dissimilarity between the five proteomics maps was based solely on the relative abundances of the leading 20 spots of the control map.

Table 12. Similarity/Dissimilarity Table between the Control Data and Data for the Four Chemicals^a

	control	PFOA	PFDA	clofibrate	DEHP
control	0	0.7586	0.8635	0.8318	0.3671
PFOA	25.88	0	1.5985	0.2591	0.3562
PFDA	85.69	52.86	0	0.8302	1.1705
Clofibrate	44.63	18.83	41.23	0	0.3671
DEHP	19.34	6.56	66.51	25.33	0

^a Entries above the main diagonal: based on the vectors using the leading eigenvalue of the Euclidean distance-adjacency matrix and the higher order matrices obtained by Kronecker product of a matrix. Entries below the main diagonal: based on the vectors using the leading eigenvalue of the distance-adjacency matrix and the higher order matrices obtained by use of the standard product of a matrices.

Table 13. Leading Eigenvalue of the Euclidean-Adjacency Matrix and the Higher Order Matrices Obtained by Use of the Standard Product of a Matrix by Itself

power	control	PFOA	PFDA	clofibrate	DEHP
1	5.1421	5.4972	6.0381	5.6998	5.4203
2	13.2204	15.1094	18.2290	16.2437	14.6897
3	22.6600	27.6864	36.6893	30.8618	26.5409
4	29.1298	38.7149	55.3830	43.9762	35.9647
5	29.9574	41.8326	66.8810	50.1309	38.9878
6	25.6738	38.3268	67.3052	47.6224	35.2209
7	18.8595	30.0984	58.0560	38.7767	27.2724
8	12.1221	20.6820	43.8182	27.6273	18.4780
9	6.9258	12.6325	29.3974	17.4966	11.1285
10	3.5613	6.9433	17.7503	9.9726	6.0319
11	1.6648	3.4704	9.7434	5.1674	2.9723
12	0.7134	1.5898	4.9026	2.4544	1.3425
13	0.2822	0.6722	2.2771	1.0761	0.5598
14	0.1036	0.2640	0.9821	0.4381	0.2167
15	0.0036	0.0967	0.3953	0.2665	0.0783

In addition to the Kronecker product of matrices (with themselves), we have also considered the standard product of matrices (with themselves). In Table 13 we show the leading eigenvalue of the corresponding "higher order" matrices. The first row in both Tables 11 and 13 is the same, but as we raise matrices to the higher powers using the standard matrix product we obtain larger matrix elements and consequently larger leading eigenvalues. We can view the columns of Table 13 as components of vectors in 15-dimensional vector space for which we can calculate the degree of mutual similarity/dissimilarity, which are shown as entries below the main diagonal in Table 12. The leading eigenvalue as well as other Kronecker and standard matrix manipulations were calculated using MATLAB software.²⁸

"FOX TRAIL" APPROACH

The zigzag curve introduced in the seminal work on quantification of proteomics maps¹⁻³ was based on selecting n most abundant spots and ordering them with respect to relative abundance. The resulting zigzag graph besides offering numerous invariants based on the leading eigenvalue of the D/D matrix as discussed in refs 1-3 allows one to construct additional, so-called, "band invariants" that were recently introduced by Randić and Balaban.²⁹ A possible disadvantage of the zigzag curve is that its form may be sensitive to fluctuations in the relative abundance as reported in different maps belonging to the same proteome. This shortcoming has been recently addressed by us⁶ in which we introduced canonical labels for protein spots that are based on 2-D map and do not require information on

Figure 5. The "fox trail", the zigzag curve based on labels derived from two sums of the Euclidean-adjacency matrix E.

abundance. After arriving at canonical labels for protein spots, one simply connects spots using canonical labels as guidance. To differentiate such zigzag curves from the zigzag curve based on relative abundance we referred to the novel zigzag curve as "fox trail", in view of a great similarity of zigzag curves and the experimentally observed paths of a wandering fox recorded at constant time intervals.^{30,31}

We will here outline an alternative "fox trail" associated with the proteomics map of Figure 1 and illustrated in Figure 5. Each time we assign numerical labels to a proteomics map, we can derive a zigzag curve by connecting spots having neighboring labels. The problem is in formulating useful rules that lead toward a *unique* labeling. Advantage of the canonical labels based on the smallest binary code for the embedded graph of the partial ordering is not only that it is unique, but once a set of spots is selected as a basis for quantitative characterization of a map, it offers canonical labels for a map as a whole and allows cataloguing and ordering such maps in a systematic way. A disadvantage of canonical labeling is that it is associated with a nonpolynomial (NP) algorithm, that is, finding canonical labels represent an NP problem,³² which may become computationally intensive and even intractable as the number of spots grows larger.

We propose here to use row sums of the distance-adjacency matrix (listed in Table 4) as the criterion for labeling of vertices of Euclidean-adjacency graphs. In this way we bypassed the difficulties of NP associated with canonical labels and nevertheless obtain a "fox trail" graph that does not require relative abundance of proteomics spots for its construction, except for the *selection* of the 20 (or

whatever number is selected) spots used as a basis of mathematical analysis of proteomics map. In Figure 5 we illustrated the "fox trail" graph for graph of Figure 4.

DISCUSSION

It is of interest to make a closer comparison between the three similarity/dissimilarity tables, Table 9, and both parts of Table 12. First, observe that there is more parallelism between the corresponding entries in Table 12 than those of Table 9, but even here there are a number of important differences. Both tables were based on the leading eigenvalues of the higher order map matrices, the difference being in the kind of matrix multiplication considered. Hence, it appears that computation of the Kronecker product of matrices and use of leading eigenvalues of the higher order Kronecker matrices as map descriptors, (which is simpler and faster), could not replace the standard matrix multiplication for construction of the higher order matrices, which offer somewhat different map descriptors.

The similarity/dissimilarity tables such as in Tables 9 and 12 do show some differences that illustrate the fact, that even though two approaches are based on similar methodologies, they capture somewhat different map information. For example, the smallest entry in Table 9 belongs to the pair (PFOA, PFDA), which is not the case with Table 12 where the smallest entry is associated with the pair (PFOA, clofibrate) and (PFOA, DEHP) for the 10-D and 15-D vectors, respectively. A relatively small value of the Euclidean distance in a similarity/dissimilarity table does not necessarily imply that the corresponding chemicals are the most similar, but it signifies that the effect of those chemicals on the 20 proteome spots of treated cells may be similar. The small amount of data presented may be merely anecdotal, and it would be premature to conclude that because of some parallelism Kronecker multiplication and standard matrix multiplication behave similarly in general. Future applications may clear this point; at this stage we are merely offering a tool for such applications.

Based on the entries in the first row of Table 9 one could conclude that clofibrate makes the least perturbation of the proteome of rat liver cells, but from the first row of Table 12 and the first column of Table 12 we see that DEHP apparently makes the least perturbation of the proteome of rat liver cells. The difference between these approaches is that in the first case, only changes in abundance are considered as a measure of perturbation; but in the other, the location of protein spots i.e., the charge and mass of proteins, makes an influence. Changes in abundance of protein spots which are in the vicinity (i.e., proteins having a similar mass and charge) will be more pronounced in the latter case.

It remains to be seen which graph invariants and what kind of weighting procedure may be more suitable when comparing different proteomics maps. At this stage it is more important to recognize the various possibilities, and it would be premature to suggest or to advocate one scheme over another. We should recollect that here we chose to consider a particular set of invariants, the leading eigenvalues of 3-D matrices as invariants, but other graph invariants ought to be examined. The main reason for the lack of definite conclusions with regard to one set of descriptors relative to

another at this moment is the lack of suitable data for testing. The comparison of similarity/dissimilarity among proteomics maps with similarities/dissimilarities of chemical agents causing perturbations would be facilitated by having data on a set of chemical compounds showing closer structural features. If there is some parallelism between the biological descriptors of proteomics maps and chemodescriptors inducing changes in proteome, one could test the degree to which the paradigm that similar chemical structures induce similar properties, that holds in QSPR and QSAR, also applies to the proteome, even if proteomics data may point to drastic changes of the cell proteome under minor perturbations of biological systems. Another testing ground for the utility of biodescriptors derived from proteomics maps could be the study of perturbations of the cellular proteome induced by a gradual increase of concentrations of chemicals that produce visible perturbations of the proteome. Hopefully, as indicated in ref 22 for the first time, one may use a combination of chemodescriptors and biodescriptors derived from proteomics maps in an effort to arrive at an integrated QSAR.

CONCLUDING REMARKS

Here we have developed two measures of "proteomics similarity" of the chemicals, one based solely on the abundances of the spots and the other based on the Euclidean distance in the eigenvalue space. These two measures give different pictures of the intermolecular similarity of the chemicals analyzed in this paper. This brings us to the well-known problem of similarity methods: Similarity methods are not uniquely defined, they are rather user-defined and context specific.^{33,34} In the area of molecular similarity for relatively small molecules, Basak et al.³⁵⁻³⁷ calculated and used various molecular similarity methods based on graph invariants as well as experimental properties to select analogues, cluster large libraries of chemicals,³⁸ and estimate properties of chemicals from their selected neighbors^{39,40} in the selected spaces. It was concluded that no universal similarity method can handle all situations. It would be interesting to see how far map invariants are able to characterize various aspects of proteomics maps and their perturbation derived from the exposure of organisms/cells to drugs and xenobiotics.

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NOVEL MATRIX INVARIANTS FOR CHARACTERIZATION OF CHANGES OF PROTEOMICS MAPS

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Previous studies on mathematical characterization of proteomics maps by sets of map invariants were based on construction of set of distance-related matrices obtained by matrix multiplication of a single matrix by itself. Here we consider an alternative characterization of proteomics maps based on set of matrices characterizing local features of embedded zigzag curve over the map. It is shown that novel invariants can well characterize proteomics maps. Advantages of the novel approach are discussed.

Keywords: Eigenvalue reduction; Graph spectra; Local matrices; Matrix invariants; Proteomics maps; Quantitative proteomics

INTRODUCTION

Numerical characterization of proteomics maps by invariants to allow for study of quantitative changes in the proteome has been initiated only recently. The first step in such studies is to associate a suitable mathematical object with a proteomics map. In the second stage, the selected mathematical object is represented by various matrices that record distances among various protein spots in 2-D map. In the third step, one constructs various matrix invariants to serve as map descriptors. Finally, one manipulates the matrices mathematically to derive other structurally related matrices, resulting in additional map descriptors. Suitable mathematical objects considered previously included the *zigzag curve*

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that connects spots of neighboring abundance [1-3], the embedded *graph of partial ordering* of protein spots with respect to dominance in mass and the charge [4-6], and embedded *graph depicting clustering* of spots at critical separation [7]. In all previous cases the numerical characterization of proteomics maps was based on the properties of the quotient matrix Q , the elements of which are obtained as the quotient of the direct (Euclidean) distance measured between the spots and the distance between the same spots measured along the lines of the zigzag curve, or along the shortest path of a graph. The leading eigenvalue of the Q matrix was taken as the leading map invariant, to be subsequently augmented by considering the higher order Q^n matrices obtained either by use of the Kronecker (Hadamard) product or by the standard product of matrix Q with itself.

In this contribution we introduce a novel approach to the mathematical characterization of proteomics maps based on *local* features of the zigzag curve used as the mathematical object for the characterization of such maps. As we will see, in this way one can formulate a set of map descriptors that characterize aspects of the structure of proteomics maps not accounted for by descriptors derived from the Q matrix approach.

OUTLINE OF THE APPROACH

We will illustrate the approach on the same proteomics data already considered in some of our earlier work, originating from the Molecular Anatomy Laboratory of F. Witzmann [8]. Table 1 lists the x , y coordinates of the protein spots corresponding to charge and mass, respectively, as separated by electrophoresis and by chromatography. The z coordinate indicates the relative abundance of the proteins. The five columns in Table 1 belong to the control group, i.e. derived from rat liver of healthy animals, and the other four sets of data originating from liver of experimental animals exposed to four peroxisome proliferators: preflorotanoic acid (PFOA), perflourodecanoic acid (PFDA), clofibrate, and di(ethylhexyl)phthalate (DEHP), respectively. The protein spots are ordered according to their control abundance, starting with the most abundant spot and ending with the least abundant one.

The zigzag curve is obtained by connecting the (x, y) coordinates of the most abundant spot with the (x, y) coordinates of the protein spot having the next lower abundance value, which in turn is connected with the spot having the next lower abundance value and so on until all of the 30 selected protein spots listed in Table 1 are connected. Figure 1 illustrates the zigzag curve resulting from the relative abundance of the control group, though the actual zigzag curve is in 3-D space with the abundance as the third coordinate. We use the same (x, y) part of the zigzag curve for the construction of map invariants belonging to the remaining four proteomics maps obtained for the four peroxisome proliferators listed in Table 1. Observe the highly irregular pattern of lines in Figure 1, some of which are overlapping each

other, while others occur at almost perpendicular directions. The pattern of lines depends on the order in which spots are listed and for the same set of 30 spots alternative orderings based on alternative criteria can be considered. Instead of using the relative abundance for ordering spots, for instance, one can order protein spots according their relative charge, or relative mass. In such case one obtains different zigzag curves, seen in Figures 2 and 3, respectively. Hence, the mathematical approach based on the construction

TABLE I The x, y coordinates of the selected proteomics spots. The next five columns give the abundance for proteomics maps of rat liver cells for the control group and the four peroxisome proliferators

<i>SID#</i>	<i>x</i>	<i>y</i>	<i>control</i>	<i>PFOA</i>	<i>PFDA</i>	<i>Clofibrate</i>	<i>DEHP</i>
187	2111.7	2278.6	144,357	108,713	95,028	147,081	165,886
77	2804.3	903.6	143,630	155,565	188,582	159,898	155,055
22	1183.9	959.6	136,653	113,859	150,253	163,645	8,111
52	2182.2	928.8	127,195	99,160	73,071	76,642	112,096
134	2685.6	1196.1	118,581	112,790	49,769	109,856	138,795
20	1527.9	825.5	114,929	192,437	221,567	166,080	180,590
62	1346.0	1352.5	112,251	58,669	38,915	73,159	77,075
67	2868.5	778.0	108,883	26,105	50,735	45,923	116,849
48	1406.3	1118.1	98,224	91,147	82,963	84,196	92,942
96	2450.2	409.2	93,601	83,172	62,934	79,870	109,381
9	1474.0	665.1	90,004	129,340	112,361	112,655	119,402
75	2974.9	772.8	86,730	70,746	78,691	105,760	116,821
36	2068.4	823.1	84,842	73,814	45,482	71,911	97,444
2	642.2	669.8	82,492	73,974	74,466	84,703	88,545
250	2860.7	1649.9	81,965	16,137	16,501	60,077	148,992
44	2032.7	902.8	80,015	77,314	80,072	76,027	100,836
84	2752.7	765.6	79,847	20,782	13,103	38,816	53,830
80	2334.2	982.2	72,791	76,369	52,749	55,599	77,432
15	1053.6	864.3	72,173	77,982	60,376	46,808	78,121
176	2519.5	1365.9	69,452	37,838	16,129	57,167	71,274
309	2552.5	2409.4	67,772	75,767	98,740	135,758	124,008
5	1214.3	620.0	64,684	63,511	38,075	58,364	75,760
126	2651.1	1149.6	61,074	56,365	54,972	85,399	97,303
74	2327.9	677.3	59,294	55,535	32,155	60,155	68,464
45	2094.5	680.5	58,977	142,865	46,225	48,625	146,609
1	1021.7	390.2	58,001	56,547	53,473	60,224	71,654
296	1702.7	2138.3	57,400	51,760	20,272	49,295	52,226
56	2070.4	929.6	55,402	46,146	33,152	59,438	69,031
276	2771.7	1451.0	53,896	22,428	20,155	35,527	62,085
180	2772.8	1326.9	51,347	29,115	40,392	45,713	74,507

FIGURE 1 The zigzag curve based on the relative abundance of the protein spots of the control group.

of a zigzag curve has some flexibility, not only when considering which protein spots should be selected for the analysis of maps, but also when deciding on the criterion of construction for a zigzag curve. For example, in ref. [6] yet another zigzag curve, based on canonical labels for protein spots, was considered.

For the selected 3-D zigzag curve one first has to construct the following distance-related matrices: (1) The Euclidean Distance matrix, ED; (2) The Adjacency Distance Matrix, AD; and (3) The Quotient Matrix, Q. The matrices are briefly outlined below and are illustrated for the first five spots of Table 1 in Table 2.

The Euclidean Distance Matrix ED

The matrix elements (i, j) are given by the Euclidean distance in the 3-D space in which the (x, y) coordinates give the location of the protein spots on the 2-D gel, while the z coordinate gives the abundance of the corresponding spots:

$$[ED]_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

FIGURE 2 The zigzag curve based on the ordering of proteins spots relative to their charge.

FIGURE 3 The zigzag curve based on the ordering of proteins spots relative to their mass.

TABLE II The 5x5 fragment of the Euclidean Distance matrix (ED), the Adjacency Distance matrix (AD) and the Quotient matrix ED/AD

<i>ED</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1702.60	7870.97	17215.14	25805.10
<i>2</i>		0	7162.92	16446.79	25050.99
<i>3</i>			0	9510.59	18135.83
<i>4</i>				0	8632.84
<i>5</i>					0
<i>AD</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1702.60	8865.527	18376.11	27008.95
<i>2</i>		0	7162.92	16673.51	25306.35
<i>3</i>			0	9510.59	18143.43
<i>4</i>				0	8632.84
<i>5</i>					0
<i>ED/AD</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1	0.8879	0.9368	0.9554
<i>2</i>		0	1	0.9864	0.9899
<i>3</i>			0	1	0.9996
<i>4</i>				0	1
<i>5</i>					0

The Adjacency Distance Matrix AD

The matrix elements (i, j) of AD differ from zero only if protein spots i and j are connected. The magnitude of non-zero elements are given by the Euclidean distance in 3-D space between the spots i and j, based on their (x, y, z) coordinates (such as those of Table 1):

$$[AD]_{ij} = \begin{cases} [ED]_{ij} & \text{if } [ED]_{ij} \leq D_x \\ 0 & \text{if } [ED]_{ij} > D_x \end{cases}$$

The Quotient Matrix Q

The matrix elements (i, j) of the quotient matrix Q are given by the quotient of the corresponding elements of the Euclidean distance matrix ED and the adjacency distance matrix AD . The matrix elements for all adjacent pairs of spots are necessarily equal to one, and the matrix elements for the spots which are not adjacent elements are necessarily smaller than one, because three sides of a triangle in general define a triangular inequality $a + b > c$, except if it happens that spots are strictly collinear in which case one would have $a + b = c$, which is highly unlikely for a majority of spots in real proteomics maps.

$$[Q]_{ij} = ED_{ij} / AD_{ij}$$

This matrix was introduced for the first time in ref. [1] and it represents a modification of the D/D matrix considered for embedded molecular graphs [9]. In the case of molecular graphs embedded in 2-D or 3-D spaces, the quotient matrix has been based on the assumption that all bonds have the same length. Thus, the elements of the D/D matrix have been defined as the quotient of the Euclidean distance between vertices (atoms) superimposed on a graphite or diamond grid divided by the graph theoretical distance between vertices, which is given by the number of bonds (edges) between vertices [10]. In the case of linear chains, the leading eigenvalue of the D/D matrix has been interpreted as an index of the degree of bending or foldedness of a system [9].

The Q matrix combines information on the *adjacency* of and the *distances* between the selected spots into a single matrix. Since its elements are less than one (or at most equal to one) the elements of the Q matrix do not require additional normalization. Such normalization is needed when one considers construction of the “higher order” matrices using the Kronecker matrix multiplication in order to ensure a convergence of matrix elements obtained by repeated multiplications. However, in this contribution we will not consider “higher order” quotient matrices. Instead we will consider local matrices and see that local matrices based on shorter segments of a zigzag curve offer a set of invariants that may serve as map descriptors.

In order to illustrate the differences between proteomics maps derived from tissues exposed to different peroxisome proliferators in Table 3 we illustrate the corresponding 5x5 ED/AD quotient matrices obtained for the two to five columns of Table 1 with data on PFOA, PFDA, Clofibrate, and DEHP, respectively. As we can see, quotient matrices of widely different forms have emerged, suggesting that the approach based on local matrices is quite sensitive to changes in proteomics maps. Observe, however, that the changes that we see, as reflected in the magnitudes of the corresponding matrix elements of the quotient matrices belonging to different proliferators, are rather dramatic.

TABLE III The local 5x5 matrices for the first five proteins spots of proteomics maps of rats exposed to PFOA, PFDA, Clofibrate, and DEHP

<i>PFOA</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1	0.0609	0.0934	0.0364
<i>2</i>		0	1	0.9989	0.6101
<i>3</i>			0	1	0.0655
<i>4</i>				0	1
<i>5</i>					0
<i>PFDA</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1	0.4188	0.1052	0.1948
<i>2</i>		0	1	0.9997	0.9997
<i>3</i>			0	1	1.0000
<i>4</i>				0	1
<i>5</i>					0
<i>Clofibrate</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1	0.9794	0.6774	0.2714
<i>2</i>		0	1	0.9140	0.4026
<i>3</i>			0	1	0.4476
<i>4</i>				0	1
<i>5</i>					0
<i>DEHP</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>1</i>	0	1	0.9993	0.2055	0.0940
<i>2</i>		0	1	0.1712	0.0586
<i>3</i>			0	1	1.0000
<i>4</i>				0	1
<i>5</i>					0

TABLE IV The ordered list of eigenvalues of the initial six local 5x5 matrices for the control group (upper part) and six local 5x5 matrices for the animals exposed to PFOA

<i>Control</i>					
<i>1-5</i>	<i>2-6</i>	<i>3-7</i>	<i>4-8</i>	<i>5-9</i>	<i>6-10</i>
3.9033	3.9734	3.9702	3.9260	3.9133	3.9257
-0.8706	-0.9789	-0.9691	-0.9220	-0.9135	-0.9340
-0.9868	-0.9844	-0.9904	-0.9787	-0.9686	-0.9666
-1.0005	-1.0043	-1.0001	-1.0098	-1.0037	-0.9993
-1.0454	-1.0058	-1.0107	-1.0155	-1.0276	-1.0259
<i>PFOA</i>					
<i>1-5</i>	<i>2-6</i>	<i>3-7</i>	<i>4-8</i>	<i>5-9</i>	<i>6-10</i>
2.5764	3.1119	2.7377	2.9094	2.7312	2.9496
0.3272	0.1894	0.1122	0.4724	0.2316	0.2879
-0.0703	-0.4987	-0.0779	-0.9972	-0.3822	-0.9031
-1.3373	-1.2763	-1.3281	-1.0029	-1.2680	-1.0633
-1.4960	-1.5263	-1.4439	-1.3818	-1.3126	-1.2711

FIGURE 4 Plot of the smallest eigenvalue against the leading eigenvalue for the protein spots of the control group.

CHARACTERIZATION OF LOCAL FEATURES OF ZIGZAG CURVE.

We will consider the 5x5 matrix of Table 2 as the first step in the construction of novel *local* map descriptors. The term *local* here does not represent a spatial (geometrical) localization but a *sequential* localization of a *portion* of the lengthy zigzag curve. Thus the zigzag curve is segmented into local groups of five spots, starting with spots 1-5, and continuing with 2-6, 3-7, 4-8, etc. We thus move gradually along the zigzag curve limiting attention each time to a small “window” of five spots for which we will extract local invariants.

Here we will confine our attention to the leading eigenvalues of the 5x5 local matrices and look upon them as the main map invariants. In the upper part of Table 4 we have listed the eigenvalues of the 5x5 quotient matrices for a few initial 5x5 matrices. An inspection of Table 4 shows a limited variation among the eigenvalues of the 5x5 matrices of the control group, which are all close to the values: 4, -1, -1, -1, -1, which are the eigenvalues of K_5 , the complete graph with five vertices. In Table 5 we have listed the leading eigenvalue of all 26 local 5x5 matrices for the control group and local 5x5 matrices belonging to proteomics maps derived from animals exposed to the four peroxisome proliferators. As we see from the column of the “Control,” the leading eigenvalues of the control group show rather limited variation in the magnitude of the leading eigenvalue. In part this is due to the dominant role of protein abundance. In contrast the eigenvalues of the 5x5 matrices belonging to maps of the four treatment groups show considerable variability, reflecting large perturbations of the proteome by the chemicals. If one is interested in a more balanced role of the three variables, charge, mass, and abundance, one should follow a recommendation of Kowalski and Bender [11] and re-scale the proteomics data accordingly. However, as our prime objective is to introduce novel invariants we will continue the analysis based on the non-scaled raw data.

Looking back to Table 4 where we listed all eigenvalues for the local 5x5 matrices we have to decide whether to use the leading eigenvalue or all eigenvalues for the construction of map invariants. In Figure 4 we have presented a plot of the last eigenvalue against the first (leading) eigenvalue for the control group in order to show the extent of correlation between the two. The correlation gave the following statistical parameters: the coefficient of correlation $r = 0.979$; the standard error $s = 0.017$; and the Fisher ratio $F = 546$. Although the residuals of the correlation are not negligible, which indicates that the two extreme eigenvalues do not fully duplicate each other, we decided to consider only the leading eigenvalue as the basic entity for construction of map invariants. Figure 5 presents a plot of the last eigenvalue against the first (leading) eigenvalue in the case of PFOA, which shows a similar overall relationship. The scatter of points in Figure 5, however, is greater, but there is still considerable parallelism between the extreme eigenvalues, as reflected by $r = 0.837$, $s = 0.122$ and $F = 56$.

In view of the observed parallelism between the extreme eigenvalues we will continue using only the *leading eigenvalue* as the basic matrix invariant. In Table 5 we have listed the leading eigenvalues for all five proteomics maps. Each column of Table 5 can be viewed as a 26-component vector characterizing each of the five proteomics maps. Hence, the similarities and dissimilarities among the five proteomics maps will be numerically represented by the differences among the five vectors.

TABLE V The leading eigenvalues of all 26 local 5x5 matrices based on zigzag curve of Fig. 1 for all five proteomics maps considered

	<i>Control</i>	<i>PFOA</i>	<i>PFDA</i>	<i>Clofibrate</i>	<i>DEHP</i>
1	3.9033	2.5764	3.2362	3.1507	2.7307
2	3.9734	3.1119	3.3506	2.8263	3.1429
3	3.9702	2.7377	2.6996	2.5617	3.2769
4	3.9260	2.9094	2.4484	2.8159	2.5997
5	3.9133	2.7312	2.8567	2.7215	2.4564
6	3.9257	2.9496	3.1507	2.9137	2.5042
7	3.9332	3.0236	2.9362	2.9570	2.5989
8	3.9178	2.8880	2.3705	3.3361	2.8545
9	3.8591	2.5483	2.5315	2.9360	3.1889
10	3.8402	2.9634	2.5554	2.8385	3.4237
11	3.5428	3.7656	2.8135	3.0547	3.4209
12	3.2941	2.9645	2.1947	2.4799	2.7120
13	3.1434	2.3630	2.1012	2.4305	2.6499
14	3.4579	1.9752	2.0482	2.4392	2.7158
15	3.6933	2.3875	2.4741	3.1507	3.1717
16	3.6800	2.7153	2.7255	2.4481	2.9840
17	3.6878	2.7506	2.8027	3.0694	3.4465
18	3.6033	2.4135	2.3861	2.6511	2.7437
19	3.7134	2.6168	2.2526	2.4710	2.3154
20	3.7368	3.3156	2.4563	2.2570	2.2612
21	3.8193	3.7526	2.5347	2.7972	2.5245
22	3.8740	2.9867	2.4442	2.5494	2.2715
23	3.5787	2.5714	2.7391	2.6928	2.4788
24	3.2839	3.0777	2.7321	2.0219	2.6027
25	3.3132	3.9721	2.5721	2.3041	2.9137
26	3.6180	3.5496	2.3849	2.3721	2.3774

FIGURE 5 Plot of the smallest eigenvalue against the leading eigenvalue for the protein spots of the PFOA group.

ON THE SIMILARITY/DISSIMILAIRTY OF PROTEOMICS MAPS

We will use the 26-component vectors to represent proteomics maps and the Euclidean distance in the 26-dimensional vector space as a measure of the degree of similarity/dissimilarity among the proteomics maps. Clearly, if two maps are very similar the corresponding 26-dimensional vectors will have similar components and the vector that has as components the difference between the corresponding components of the two vectors will have small magnitude. Consequently, the corresponding entry in the similarity/dissimilarity matrix will be small, close to zero. Conversely, large entries in the similarity/dissimilarity table would indicate vastly different proteomics maps. In Table 6 we show the corresponding values of similarity/dissimilarity for the five maps considered. In the first row of Table 6 are the similarities/dissimilarities with respect to the Control group. As we see all entries in the similarity/dissimilarity table are relatively large. The smallest entry in the first row of the table, which belongs to the PFOA proteomics map, indicates the greatest similarity to the control group. However, all the entries in the first row are of a similar, relatively large magnitude, suggesting little similarity to the control group. Equally, the four proteomics maps among themselves also show little similarity and

considerable differences. Overall, the most similar pairs of are: PDFA and Clofibrate, and Clofibrate and DEHP.

TABLE VI The similarity/dissimilarity table based on map vectors having 26 components

	<i>Control</i>	<i>PFOA</i>	<i>PFDA</i>	<i>Clofibrate</i>	<i>DEHP</i>
<i>Control</i>	0	4.832	5.760	5.265	5.141
<i>PFOA</i>		0	2.984	3.184	3.088
<i>PFDA</i>			0	1.874	2.349
<i>Clofibrate</i>				0	1.877
<i>DEHP</i>					0

Just looking at Table 1 it is difficult to determine the degree of similarity among the different columns of the table. In contrast the columns of Table 5 are more informative. A similar magnitude of the leading eigenvalue in any of the 26 rows points to local similarity of the two maps with respect to the five protein spots considered. For example, in row 11 three of the four proteomics maps show close values for the leading eigenvalue suggesting minor variation in the respective abundance. More important, however, is the fact that the approach outlined here *automatically* gives a lower weight to the contributions of the protein spots that have changed very little by the treatment. This would not be the case if the approach considered a whole 30x30 matrix because the abundances of the spots which are marginally altered would contribute to the averaging of the abundances of the strongly perturbed spots and effectively decrease the signal to noise ratio.

This novel approach has additional flexibility that we will not consider here. This is associated with the liberty of selecting the width of the “window” for building local $n \times n$ matrices. In the case of 5x5 local matrices about half of the matrix entries are variable, while the diagonal zeros and adjacent one always remain constant.

SPECTRAL CHARACTERISTICS OF PROTEOMICS MAPS

In this section we will consider the use of all eigenvalues of local matrices for the characterization of proteomics maps, rather than limiting our attention solely to the leading eigenvalue. The complete set of eigenvalues of a graph is known in Graph Theory [12, 13] as “graph spectra,” so we will refer to characterizations of proteomics maps based on information given by all eigenvalues as “spectral characteristics” of maps.

The extreme form for the 5x5 matrices that can occur corresponds, on the one hand, to the complete graph K_5 and to the chain of length L_5 on the other hand. The 5x5 matrices for both these extreme cases

are shown in Table 7 together with their eigenvalues. Hence, any of the local 5x5 matrices that appear in our analysis (such as those shown in Table 3) can be viewed as representing a *departure* from the two extreme cases. It appears that the leading eigenvalue, which in the case of acyclic graphs has been interpreted by Lovasz and Pelikan [14] as an index of molecular branching, may have a somewhat modified, composite, interpretation. *Branching* is just one aspect of the *departure* of a structure from that of a linear model that has received considerable attention in Chemical Graph Theory [15-20]. The other factor which may influence the graph spectra, which has apparently not attracted attention and has, in fact, only recently been recognized [21], is the *departure* of a graph from the *complete bipartite* graph $K_{1,n}$ in the case of acyclic graphs, or a departure from the *complete graph* K_n for more general graphs. This departure is reflected in the variable magnitudes (in the interval [0,1]) of the matrix elements of the local 5x5 matrices, which are then viewed as the edges of a weighted complete graph [21].

TABLE VII The 5x5 matrices belonging to the complete graph K_5 and the linear chain L_5 with their eigenvalues

	1	2	3	4	5
1	0	1	1	1	1
2		0	1	1	1
3			0	1	1
4				0	1
5					0

Eigenvalues: 4, -1, -1, -1, -1

	1	2	3	4	5
1	0	1	0	0	0
2		0	1	0	0
3			0	1	0
4				0	1
5					0

Eigenvalues: $\sqrt{3}$, 1, 0, -1, $-\sqrt{3}$

That indeed, the eigenvalues of the novel local 5x5 matrices do represent the departure from “linearity” and “completeness” is supported by additional (unpublished) data [21], part of which is presented in Table 8. Here letters A, B, C, D, and E correspond to the control, PFOA, PFDA Clofibrate, and DEHP treatments, respectively, while subscripts 1 – 26 correspond to local 5x5 matrices. Thus the label A_1 represent the local matrix based on spots 1-5 of the zigzag curve of the control group, while the label D_{24} corresponds to zigzag curve of Clofibrate proteomics map using spots 24-28. In Table 8 the labels a_K and a_L represent the coefficients of linear regressions based on the ordered sets of eigenvalues of

the complete graph and eigenvalues of the chain of length five. The labels r , s , and F stand for the correlation coefficient, the standard error, and the Fisher ratio in a correlation of eigenvalues of 5×5 matrices as the independent variable and the eigenvalues of K_5 and L_5 as the dependent variables. Thus the first numerical column abbreviates the regression equation shown below between the eigenvalues of the first local 5×5 matrix and the eigenvectors of the extreme 5×5 matrices of K_5 and L_5 :

$$\begin{bmatrix} 3.9033 \\ -0.8706 \\ -0.9868 \\ -1.0005 \\ -1.0454 \end{bmatrix} = \begin{bmatrix} 4 \\ -1 \\ -1 \\ -1 \\ -1 \end{bmatrix} a_K + \begin{bmatrix} \sqrt{3} \\ 1 \\ 0 \\ -1 \\ -\sqrt{3} \end{bmatrix} a_L$$

Observe that the correlation relates vectors built from all the *five eigenvalues* and that the constant term of the regression was not set to be zero, but was always found to be zero.

TABLE VIII The coefficients of the linear regression of the eigenvalues of a selection of 5×5 local matrices against the eigenvalues of K_5 and L_5 . The statistical parameters r , s , and F are included (r = regression coefficient, s = standard error, F = Fisher ratio)

	A_1	A_2	A_3	A_4	A_5	A_6
K_5	0.95031	0.98856	0.98619	0.96654	0.96046	0.96695
L_5	0.05893	0.01104	0.01470	0.03453	0.04129	0.03346
r	0.99995	1.00000	1.00000	0.99999	1.00000	1.00000
s	0.0308	0.0048	0.0035	0.0149	0.0078	0.0012
F	10072.2	431924.5	9796381.9	43388.5	158533.8	7309534.4

	B_1	B_2	B_3	B_4	B_5	B_6
K_5	0.32416	0.49658	0.40366	0.46155	0.41888	0.50555
L_5	0.73885	0.64987	0.64840	0.61384	0.60952	0.53546
r	0.9926	0.9990	0.9909	0.9834	0.9961	0.9898
s	0.2820	0.1170	0.3215	0.4556	0.2082	0.3545
F	66.8	507.8	54.0	29.3	125.8	48.1

	B_{14}	C_{12}	C_{13}	C_{14}	C_{19}	D_{24}
K_5	0.10779	0.19895	0.15997	0.13907	0.23165	0.12975
L_5	0.89145	0.80763	0.84370	0.86134	0.76559	0.86760
r	0.9895	0.9951	0.9973	0.9964	0.9900	0.9917
s	0.2973	0.2080	0.1513	0.1754	0.2994	0.2638
F	46.7	101.7	186.6	136.5	49.3	59.7

As we can see from the top part of Table 7, the eigenvalues of all 5x5 matrices of the control group show linear combinations dominated by the eigenvalues of K_5 (from about 95% to 99%), with a very small participation of L_5 eigenvalues. On the other hand, from the middle part of Table 8, which corresponds to proteomics maps of PFOA, we see a more balanced mixture of the roles of the eigenvalues of K_5 and L_5 . In fact, in the case of B_6 we see that an almost 50/50 superposition of the eigenvalues of the complete graph and the linear chain give its eigenvalues. In the bottom part of Table 8, we have collected six 5x5 matrices in which the eigenvalues of the linear graph appear to play the dominant role. In the latter cases, the eigenvalues of 5x5 matrices are approximately given as a linear combination of about 85 % of the eigenvalues of the linear model and about 15 % of the eigenvalues of the complete graph K_5 .

TABLE IX The quotients a_i/a_K as a single local map spectral descriptor

L_5/K_5	Control	PFOA	PFDA	Clofibrate	DEHP
1	.0589/.9503	.7389/.3242	.5118/.5875	.4300/.6015	.7306/.3663
2	.0110/.9886	.6499/.4966	.5034/.6196	.6759/.4139	.5786/.5352
3	.0147/.9862	.6484/.4037	.7268/.3602	.7697/.3071	.4691/.6161
4	.0345/.9665	.6138/.4616	.7802/.2743	.7708/.3835	.6786/.3569
5	.0413/.9605	.6095/.4189	.6519/.4319	.6202/.4118	.6875/.3164
6	.0335/.9670	.5355/.5056	.5030/.5699	.5974/.4697	.6652/.3380
7	.0276/.9714	.4840/.5463	.5974/.4754	.5528/.4983	.7641/.3189
8	.0394/.9624	.5730/.4739	.7407/.2719	.3146/.6978	.6465/.4316
9	.0635/.9373	.7137/.3281	.7468/.3095	.5877/.4795	.5652/.5525
10	.0798/.9255	.5936/.4838	.7087/.3320	.6207/.4408	.3469/.7057
11	.2461/.7792	.1165/.8910	.6772/.4101	.5263/.5358	.3940/.6846
12	.3615/.6670	.6329/.4671	.8076/.1990	.6984/.3176	.6880/.3801
13	.3736/.6241	.8749/.2119	.8437/.1600	.7190/.2963	.7102/.3550
14	.2738/.7459	.8915/.1078	.8613/.1391	.7105/.3021	.6508/.3972
15	.4049/.6872	.8837/.2142	.7956/.2740	.7110/.2895	.4644/.5918
16	.1594/.8510	.7789/.3416	.7081/.3730	.6860/.3150	.5071/.5264
17	.1658/.8502	.7741/.3525	.6952/.3996	.6359/.4920	.3059/.7292
18	.1751/.8250	.7868/.2627	.7366/.2762	.7617/.3330	.6588/.4007
19	.1184/.8771	.7121/.3459	.7656/.2317	.7885/.2763	.7969/.2338
20	.1165/.8837	.4161/.6487	.7119/.3058	.8056/.2154	.7840/.2258
21	.0834/.9187	.1952/.8536	.7017/.3298	.7082/.3927	.6542/.3479
22	.0598/.9426	.6330/.4726	.8064/.2619	.7369/.3183	.7883/.2265
23	.2303/.7949	.8272/.2847	.6914/.3854	.7571/.3454	.7823/.2810
24	.3459/.6712	.6274/.4978	.6350/.4080	.8675/.1298	.7529/.3246
25	.3158/.6916	.0206/.9841	.6827/.3474	.7692/.2430	.6456/.4489
26	.1985/.8185	.2565/.7763	.7257/.2820	.7444/.2707	.7335/.2767

NOVEL SPECTRAL INDEX FOR MAPS

The above description of linear regression of local matrices using the eigenvalues of K_5 and L_5 as dependent variables represents an important novelty in the area of topological indices [22-25], and may be of potential use in QSAR (quantitative structure-activity relationship) studies, QSPR (quantitative structure-property relationship) studies, and similarity studies of primary DNA sequences [26-33]. In particular this new way of combining data on eigenvalues among structurally related objects will open new directions in the investigation of eigenvalues as molecular descriptors [34]. Moreover, if one chooses, as we have done here, as extreme structures the linear chain and the complete bipartite graph $K_{1,n}$ (or alternatively K_n) as the two graphs to which others are compared one may consider, in an analogy with Kier's kappa shape indices [35], the coefficients of the linear regression as a new kind of shape descriptors [21]. As we have seen, it is possible to condense information on all eigenvalues of a system into a small number of parameters, such as the coefficients of regression a_K and a_L . Relating the eigenvalues of 5×5 matrices in terms of the eigenvalues of the linear model and the complete graph is a striking novelty in view of the long and continuous interest in the eigenvalues and the eigenvectors of graphs [13]. Besides its important theoretical significance, the results allow us to construct novel map descriptors that condense the information on all five eigenvalues into a single entity! We can take the quotient of the coefficients of the regression (a_K / a_L) or its reciprocal (a_L / a_K), shown in Table 9 for all five proteomics maps, as novel condensed spectra map descriptors. For the data shown in Table 9 the quotients would range in the interval of about (0.1, 10). If we use the quotient (a_K / a_L) we give somewhat greater weight to matrices approaching K_5 , while if we use the quotient (a_L / a_K) the opposite is the case, the matrices approaching K_5 play a somewhat lesser role. The former case corresponds to protein spots that have been less perturbed, while in the latter case we give somewhat larger weight to protein spots that have undergone dramatic changes in their abundance compared to the control group. Both alternatives may be of interest. In the first case, we diminish to some extent the occurrence of observed changes, which may be fitting if one has some doubt in the accuracy of the reported abundance. In the second case, assuming that the reliability of data is satisfactory, we will improve somewhat the signal to noise ratio, as we give less weight to protein spots that have not changed much.

In Table 10 we show the similarity/dissimilarity table for the five proteomics maps based on the 26-component vectors using the quotient (a_L / a_K). Not surprisingly we obtain similar results to those of Table 5 when we used the leading eigenvalues of the 26 local matrices as the components of vectors. The satisfaction is not even in the fact that the alternative approach allows for minor changes in the interpretation between results based on two 26-components vectors. The satisfaction is in the recognition

that we have used all the available spectral information, rather than restricting attention solely to the leading eigenvalues of the quotient matrices.

TABLE X The similarity/dissimilarity table based on vectors having 26 components obtained from spectral quotients a_l/a_k

	<i>Control</i>	<i>PFOA</i>	<i>PFDA</i>	<i>Clofibrate</i>	<i>DEHP</i>
<i>Control</i>	0	11.7959	12.6593	11.3304	9.3268
<i>PFOA</i>		0	6.8121	10.4034	9.9604
<i>PFDA</i>			0	8.1907	7.8770
<i>Clofibrate</i>				0	10.0419
<i>DEHP</i>					0

CONCLUDING REMARKS

We continue our interest in developing biodescriptors for proteomics maps that could facilitate comparisons of proteomics maps from a single source, or even from different laboratories. In this contribution, we have come forward with two important novelties: (1) For the first time we present the concept of local map invariants; and (2) For the first time we have drawn attention to the possibility of a meaningful reduction of map invariants (here the complete spectrum of local 5x5 matrices) without any accompanying loss of essential information. All of these novelties can be combined with the already considered map descriptors based on alternative zigzag curves, embedded graphs based on partial ordering of protein spots, or cluster graphs based on embedded graph connecting spots below selected critical distance. It is expected that the group of local and global proteomics descriptors developed by our group will find applications in the quantitative characterization of proteomic patterns and the assessment of the effects of drugs and toxicants on the cellular proteome.

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ON CANONICAL LABELING OF PROTEINS OF PROTEOMICS MAPS

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We propose a canonical labeling of protein spots in 2-D proteomics maps which will not only facilitate cataloging of 2-D gel maps but also to facilitate comparisons of gel maps originating from different laboratories. The canonical labels are based on labeling of vertices of an embedded graph derived from partial ordering of the protein spots of a 2-D gel that would result in adjacency matrix associated with the smallest binary number obtained by reading the matrix entries from the left to the right and from the top to the bottom.

INTRODUCTION

A 2-D proteomics map summarizes important information regarding a large number of proteins of a particular cell type, tissue or organ, which are separated electrophoretically by charge and by use of chromatography by mass. Typically proteomics gels may have 2000 or more protein spots and provide raw information on the make up of the totality of proteins in a particular cell type, tissue or organ under investigation. Besides a number of experimental challenges, a major challenge in proteomics research, from the theoretical point of view, is the "translation" of the information that proteomics map supplies into some numerical characterization independent of spot labels that would represent map invariants. In analogy with QSAR (quantitative structure-activity relationship) in which chemical structure is characterized by various mathematical graph invariants (topological¹ and topographic² descriptors like various connectivity indices and such³ derived from the representation of molecules by molecular graphs and 3-D models), we would like to characterize proteomics maps by mathematical invariants, to be referred as map invariants or biodescriptors, in view that they characterize a particular biological sample. Advantages of such characterization of proteomics maps are obvious: comparison of maps, instead of being visual, qualitative, and slow, can become computerized, fast, and quantitative. What is not obvious at all is how to accomplish this task.

Recently, however, research on the quantitative characterization of proteomics maps has been initiated,⁴⁻⁸ and has been shown to offer promising novel tools for *quantitative* studies of map

characterization and their perturbations by exposure of cells/tissue to chemical agents that cause of changes in protein patterns.⁹ Construction of biodescriptors for proteomics maps, which are numerical quantities of maps, is clearly of major importance. However, equally important is development of numerical *representations* of maps, which can then allow 2-D maps to be sorted and catalogued. We differentiate here *characterizations* of maps from *representations* of maps, in the former we associate with a map a set of descriptors, in the latter we associate with a map a set of codes (preferably those that can be directly manipulated by computer). Thus with *characterization* is associated some *loss of information* and a map can not be reconstructed from its descriptors, just as molecular structure in general can not be reconstructed from a set of numerical graph invariants (topological indices). In contrast *representations* of maps should lead to reconstruction, at least of the adjacency matrix of a graph associated with a map, if one know and follows the assumed *convention* on labeling of vertices, such as use of canonical labels. A full reconstruction of a map requires information on *embedding* of the graph which can be supplied by matrix the elements of which give the Euclidean distances between connected spots.

In this communication we propose the construction of a *unique* graph to be associated with a map using a particular canonical labeling of vertices of such graph. In this way, as will be seen, we can generate binary or decimal codes for proteomics maps, which can facilitate comparisons of gel maps either within a single laboratory or maps originating from different laboratories. The canonical labels that we have adopted are based on the labeling of vertices of an embedded graph (of the partial ordering) that would result in adjacency matrix associated with the smallest binary number obtained by reading the matrix entries from the left to the right and from the top to the bottom as a single number. Alternatively canonical labels associated with the smallest binary number can be interpreted a sequence of binary or decimal numbers, each corresponding to successive lines of the canonical matrix. We will outline the approach on a smaller hypothetical map that has twenty protein.

PARTIAL ORDERING OF PROTEIN SPOTS OF A 2-D MAP

Partial ordering arises when a set of objects (here proteins of a gel map) are ranked with respect to at least *two* properties, e. g., the charge and the mass, to be considered here. As a results we obtain two sequences, each based on ordering of objects with respect to a single property. Partial ordering is the collection of all subsequences of the two sequences, which maintain the same relative ordering of objects with respect to both properties. If in both sequences element X is ahead of Y, which is ahead of Z, we would say that X dominates Y, which, in turn, dominates Z. The subsequence $X > Y > Z$ is a fragment of

the partial ordering of objects considered. The totality of all such dominance relationships constitute the partial ordering.

We have used letters A – T to label protein spots of the hypothetical proteomics map of Fig. 1 in which we will illustrate our canonical representation of proteomics maps. Proteins are separated by charge along the horizontal axis and are separated by mass along the vertical axis, such that the spots at the top belong to proteins having large mass and those at the bottom of Fig. 1 belongs to proteins having relatively small mass. Hence, the list A, B, C, . . . R, S, T has protein spots already ordered according their mass, A being the most “massive” protein. It is not difficult by a close look at Fig. 1 to find ordering of the spots according to the charge. The sequence starts with the protein L, which is the most right (the highest charged) spot, followed by spot T, which is the next most right spot, an so on.. Hence, the two sequences that will lead to partial ordering are:

A B C D E F G H I J K L M N O P Q R S T
L T D A G K N I S M E B H R J C P Q F O

A comparison of the two sequences reveals several subsets of elements of the two sequences that maintain their relative order in both sequences. For instance, in both sequences: $A > B > C > P > Q$ where we use sign $>$ to indicate the dominance. Similarly $A > E > H > J > O$; or $A > E > F > O$; etc. There is an elegant graphical (pictorial) algorithm which outlines how one finds systematically all such possibilities which has been described in the literature.¹⁰ It is customary instead of listing all partial orderings to represent them pictorially by a *hierarchical diagram* (see ref. 7 for illustration). It is important to be aware that a *hierarchical diagram* does not lead to a unique pictorial representation of a partial ordering. Any diagram in which positioning of vertices from the left to the right preserves the dominance relationship offers an alternative illustration of the particular partial order. This allows one to redraw the diagram by shifting vertices at some length to the left and to the right, and of course, at any length up and down. One tries to construct diagrams with as little as possible crossing of lines merely for better visibility or different dominance relationships. So, a *hierarchical diagram* is essentially a directed graph, with all edges being directed from the left to the right. Clearly graphs and directed graphs have multitude of pictorial representations, hence are to be of limited use for our attempt to arrive at canonical representation of 2-D maps.

EMBEDDING OF PARTIAL ORDERING OF PROTEIN SPOTS OVER A 2-D MAP

The critical step for canonical representation of maps is to arrive at a *unique* mathematical object to serve as the basis for such representation. We follow the procedure outlined in ref. 7 in which among

continuum of alternative representation of the partial ordering of protein spots we select a single such representation which is defined by *embedding* of the partial order on the map. In Fig. 2 this is illustrated for the map of Fig. 1. As one can see from Fig. 2 charge dominance runs from the right to the left and the mass dominance runs from the top to the bottom. Observe an important property of the embedded graph representing the partial ordering: *All line segments have positive slope!* This can be easily understood: only spots linked by positive slope indicate dominance with respect to *both* charge *and* mass. We should also mention because of the *transitivity* of the ordering relationship that only lines connecting spots directly dominating one another are to be drawn. So, if $X > Y$ and $Y > Z$, then transitivity implies also $X > Z$, but we do not inscribe line XZ because dominance of X over Z is depicted by lines indicating the dominance $X > Y$ and $Y > Z$.

Embedded graph of Fig. 2 represents a unique schematic diagram that captures some of the relationships for protein spots of the map. Observe that for the construction of this graph we only used the information on charge and mass and *have not used information on abundance*. Thus all maps that have the same set of proteins (which always come with the same (x, y) coordinates, that is all maps originating from the same type of cell/tissue/organ/species) will have the same graphical representation by the same embedded graph. One way to differentiate such maps is to associate with individual protein spots canonical labels, in this case the labels 1 – 20, and then list individual abundance. We will come later to this point but at this stage we want to introduce canonical labels so that maps belonging to different cell types will introduce different embedded graphs are associated with different binary matrices.

CANONICAL LABELS

Canonical labels have been used in chemical documentation and computer manipulations with chemical structures to resolve the isomorphism problem for graphs,^{11, 12} the automorphism problem,¹³⁻¹⁵ and have also been used for an *ordered* construction of graphs.¹⁶ There are different schemes for deriving distinct canonical labels. Historically one of the earliest such scheme was due to Morgan,¹⁷ known as Morgan algorithm. In Morgan algorithm one considers extended connectivity which is obtained by adding in an iterative way valence of neighbors to replace valence of each vertex. Although computationally simple (or elegant) the algorithm may lead to oscillatory behavior and occasionally may not yielded the answer.¹⁸

We decided to opt for another approach, which is conceptually elegant but computationally is more involved and may occasionally require considerable computational time, particularly in the case of graphs in which all vertices are of the same degree. One should recall that graph isomorphism is inherently a NP problem,¹⁹ that is, a problem for which computational time increases exponentially with

time. We will outline the approach on the embedded graph of the hypothetical proteomics map of Fig. 1, the graph of Fig. 2, and will show that in the case of proteomics maps canonical labels for protein spots can be found quite fast. The rule for canonical labels for graphs that we adopt has been described previously.^{12,14} We will choose a canonical labeling of vertices in a graph such that the accompanying **adjacency matrix represents the smallest binary number when its rows are read from the left to the right and from the top to the bottom as a single number.** What that means is that the smallest labels have adjacent the largest *possible* labels because then the corresponding row of the adjacency matrix will be the smallest possible number (subject to compliance with the assignments of smaller labels already used).

In order to better see how we find canonical labels we will outline the search for canonical labels for the embedded graph of Fig. 2. Observe that spots Q and T are the only terminal vertices in this case. Hence we have to explore two possibilities: either assigning label 1 to spot Q or to spot T. If we assign label 1 to spot Q that spot P, which is adjacent, has to have label 20 because only then the first row of the adjacency matrix will be

0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1

which is the smallest possible number for a 20 x 20 binary matrix. The same first row will also occur if we assign label 1 to spot T and label 20 to L, which is adjacent to T. Hence, we have to explore two alternatives for placing the labels 1 and 2 illustrated in Fig. 3. Next we search for the location of the next smallest label, label 3, which should have as *few neighbors as possible*, because that would assure the *smallest entry for the second row* of the adjacency matrix. Examination of Fig. 3 shows that there are two vertices that have only two neighbors: protein spots D and S. This leads to the total of four possibilities illustrated in Fig. 4. We have assigned to the nearest neighbors of spot 3 labels 18/17 and those of label 4 as 16/15, because at this stage we know for sure that 3 has neighbors 18 and 17 and 4 has neighbors 16 and 15, but we cannot be sure which spots take labels 18 and 16 and which take labels 17 and 15. We will see later that this ambiguity will be resolved satisfactorily without a need at this stage to multiplying all unresolved possibilities. Next we have to find location for label 5. After little of reflection we find that there are only two sites that 5 can take the sites of spots A and K respectively (Fig. 5). These are the only two sites in which there is only one neighbor spot that need assignment, leading to neighbors (18, 17 and 14) for protein A and neighbors (18, 16, 14) for protein K. Any other spot will require at least two new labels, involving thus label 13, which would result in a larger binary number for the fifth row. Comparing neighbor labels for the sites A and K we see that A gives a smaller binary number, thus A takes number 5 as label. We still cannot assign 18 and 17 between spots E and G, because A is adjacent to both A and G. At this point there are only two sites, which have three neighbors of which two have already, labels. These are: K with neighbors (18/17, 16/15) and C with neighbors (19,

14). Clearly spot K is to be preferred as its smallest number for neighbor (16/15) is larger than the smaller number of spot C (which is 14). By assigning label 6 to spot K (Fig. 6) we can get the smallest number in row six of the adjacency matrix if we assign to its neighbors labels 18 and 16 (rather than 17 and 15).

We continue with assigning label 7 to protein spot C, which leaves only four spots : H, J, O, and R yet to be assigned labels from 8 to 11. Label 8 immediately can be assigned to spot R, which is the only sport that has already two neighbors assigned. Hence we introduce label 11 to spot H; leaving only spots J and O for labels 9 and 10. It is not difficult to see that if we assign label 9 to spot O that makes the binary number smaller than the opposite assignment. Selecting spot J for label 10 completes the assignment. In Table 1 we listed the unique adjacency matrix for the graph of Fig. 2 as induced by the canonical labels. The canonical labels for all twenty vertices are shown in Fig. 7 and are listed below:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Q	T	D	S	A	K	C	R	O	J	H	F	M	B	I	N	E	G	L	P

DISCUSSION

By arriving at the canonical adjacency matrix we in fact not only established unique labels for protein spots but also have arrived at unique label for the proteomics map. Instead of using a single binary number for label we can consider a sequence of 20 binary numbers, each representing one row of the adjacency matrix. The binary numbers representing each row of the adjacency matrix of Table 1, when translated into decimal numbers, yield the sequence:

1, 2, 12, 48, 76, 148, 321, 656, 1424, 2593, 5196, ...

that is unique to the cell type of the considered proteomics map. Different maps will be represented by different sequences as it is unlikely that in different cells/tissues/organs/ species the same proteins will appear and be among those with the highest abundance.

Observe that the canonical labeling here proposed offers a relatively simple cataloguing of proteomics maps that can be ordered lexicographically. First we consider the leading number of the canonical sequence and order maps accordingly. If the leading number is the same we compare the next numbers in the sequence, and continue until we come upon two entries that are different, which then determines the ordering of maps.

It is possible, though it does not appear likely, that two different proteomics maps which will have different embedded graph nevertheless result the same graph when embedding is not considered. Such case would lead to the same canonical labeling for vertices of the graph and produce the same

canonical adjacency matrix. For example, if in Fig. 1 we move the spot A a little up or a little right and do not by such "move" change the dominance relationship with the neighboring protein spots we will obtain different map but the same canonical labeling will hold. If such situation arises one would need to incorporate in the procedure *additional* information on maps, such as actual (suitably normalized) *distances* between connected vertices of embedded graphs.

MAP SPECIFIC FACTORS

As we have seen the process of arriving at canonical labels does not includes information of abundance. Thus the proteomics map of a healthy rat liver cell, the column indicated as A_0 in Table 2 and corresponding to the control group) as well as liver cells of mice exposed to various toxic substances will necessarily have *the same* canonical adjacency matrix. We believe that this is an *advantage* of the present scheme, rather than disadvantage, because it allows maps associated with *the same* species, *the same* organ, and *the same* tissue to be immediately grouped into the same *class*, under *the same* canonical label. We can nevertheless differentiate maps belonging to the same class by constructing a vector that has as components the abundance. Alternatively the abundance can be inserted as the diagonal elements of the *augmented* binary adjacency matrices.

A question to consider is how the canonical labeling of maps depends on the number of protein spots considered in constructing the partial ordering and how increase in the number of spots affect construction of the partial ordering. It is not difficult to recognize that canonical labeling of vertices of a graph is affected with addition of vertices or deletion of vertices. Because of this we have *in advance* to select the number of vertices to be used for construction of canonical labels for maps. For instance we can start with $n = 20$, that is select the twenty most abundant spots, as has been assumed in our hypothetical proteomics map of Fig. 1. If this is found somewhat restrictive we can increase n to 50, 100 or 250. It is not very likely that among 2,000 to 10,000 that typically cells may contain the same twenty proteins will be among the most abundant. If this would happen there is not difficulty to increase the size of the graph of partial ordering to include 50, 100 or 250 proteins, thus eliminating chance for fortuitous coincidence in protein distribution in different cells of different species and different organs.

The other question raised, that of construction of the partial ordering for maps that include larger number of spots, has been considered in the literature.⁷ In Fig. 8 we show embedded graph for the partial ordering of 70 most abundant protein spots (out of 1570 that have been given in a list supplied by the laboratory of Frank Witzmann²⁰) corresponding to cells of normal rat liver. Observe that an increase in the number of protein spots from 20 to 70 has not been accompanied with a dramatic increase in the

complexity of the embedded graph of the partial ordering. This need not be surprising, because partial ordering of protein spots is sensitive to *local* features of a map, and locally proteomics map having 20, 200 or 2000 spots will be similar!

Finally, we may mention that the canonical labels introduced here can be combined with the approach that uses zigzag curve for arriving at D/D matrices and set of invariants extracted from these matrices. Instead of using abundance as a “tool” for construction of zigzag curve we can use canonical labels and construct the zigzag curve by connecting spots having adjacent labels. In Fig. 9 we show so constructed zigzag curve for the hypothetical proteomics map of Fig. 1. What makes this construction rather interesting and “foxy” is that we have obtained zigzag curve without explicit reference to *abundance* of spots (which in the case of Fig. 1 have not even been specified). The basis of the quantitative characterization of protein maps reported in the literature has been use of abundance data to *order* spots and assigns them sequential labels. Here we may use abundance to *select* spots to be considered for analysis, but not to order them. Moreover, one can select spots using different criteria, besides abundance, such as functional role of proteins (if known). In order not to confuse this approach with the already established approach based on zigzag curve we may refer to curve of Fig. 9 as “fox trail.” Indeed derived zigzag curves resemble very much the fox trail as reported by Siniff and Jessen,²¹ and depicted in a paper by George Hall²² on mathematical modeling in chemistry.

ILLUSTRATION

We will illustrate the outlined approach on the five proteomics maps listed in Table 2 where x (charge) and y (mass) give location of separated protein spots for the rat liver cells as reported by the Molecular Anatomy Laboratory of F. Witzmann.²⁰ The first column gives the canonical labels, while the last column gives arbitrary labels used to identify individual protein spots. The abundance of the protein spots of the control group (A_0) are shown in **bold**, while the abundance of the corresponding protein spots for four peroxisome proliferators (A_x) are given, following Anderson and collaborators²³ as quotient A_x/A_0 . There is some advantage of such practice as we will see later when we consider map vectors (ordered sequence of proteins and their abundance).

Partial ordering

The first step in our analysis of proteomics map for documentation is to select the number (N) of spots to be considered. We have taken data in Table 2 as reported in an article on characterization of proteomics maps and chemically induced changes in proteome using matrix invariants.⁶ This table includes data on

$N = 29$ protein spots selected as those spots having the largest abundance. The (x, y) coordinates of these spots allow us to depict the locations of proteins (Fig. 10). We now proceed to find partial ordering of the 29 spots, recalling that the pictorial representation of the partial ordering as an *embedded* graph require all line segments (edges) in the embedded graph to have *positive* slope. For most pairs of spots inspection of Fig. 10 allows one to draw line connecting such spots, but one should first consider spots in the same neighborhood and only later connect spots at greater separation in order to avoid introducing redundant lines. For example, we can start at the top of the figure and connect spot 62 to spot 41, then 48 to 35 and 41, both 41 and 35 to spots 22 and 39, and so on. In few instances it may not be clearly visible from the Fig. 10 if two spots should be connected or not, as is the case with spots 15, 30, 29 and 39 or spots 36, 46 and 19 and 24. Each such case can be resolved by inspecting the (x, y) coordinates of Table 2. For instance the spots 15 and 30 should not be connected because the corresponding coordinates (1053.6, 864.3) and (1122.7, 863.0), respectively, show non-comparability: protein 15 has larger mass but protein 30 has larger charge. In contrast spots 29 and 39, having coordinates (1170.0, 862.2) and (1278.8, 981.6) respectively should be connected because 39 has larger charge and larger mass than 29, thus establishing the dominance in both properties. In Fig. 11 we show the graph of partial ordering *embedded* over the proteomics map of Table 2 with labels as shown in the last column of the Table 2.

Canonical Labels

Fig. 12 we show again the graph of partial ordering, however graph is no longer embedded over the map but is somewhat modified for better illustration of adjacency of connected protein spots. This is a graph for which we will seek canonical labels. Although it is not essential how we represent the graph, nevertheless we have drawn graph in a form that still preserves pictorial similarity with Fig. 11 in order to facilitate comparisons between the new and the old labels. In order to appreciate not only the complexity of the task but also a surprising efficiency of the algorithm associated with the smallest binary labels let us point out that we are searching for a unique labeling of 29 vertices of a graph which is one in $29!$ possibilities, a number between $10^{30} - 10^{31}$. It took less than dozen trials to arrive at labels shown in Fig. 13. In fact since we have some experience with canonical labeling, that we previously considered as a tool for graph isomorphism problem, ordered construction of graphs, and determining symmetry properties of transitive graphs^{13-15, 23-30} in this particular case we used only four templates of the graph to find canonical labels! We should add that search for canonical labels for transitive graphs is generally a more involved task, especially when degree of vertices of graph is higher, in view that all vertices have the same degree. Readers may consult this literature and test their skills in trying to reproduce some of the canonical labeling of graphs reported in the literature. We should also mention that Brandt and Scholley

to represent unique coding of chemical reactions.³¹ also used canonical labels based on the smallest binary number

Graph of Fig. 12, however, has vertices of different degree, which allows focusing attention first to vertices of the lowest degree to which one assigns the smallest labels. Clearly location of labels 1 and 2 (which also determines location for labels 29 and 28) are easy to find, because there is but a single terminal vertex and of the seven vertices of degree two only one site requires a *single* new label (label 28), all the other possibilities would demand *two* new labels (28 and 27) which correspond to a large binary number for row 2.

When considering alternatives the guiding rule is to prefer locations which at each step introduce the *smallest number of novel labels* not previously introduced. Consider, for instance, the remaining six vertices of degree two, which received labels 3, 4, 5, 6, 7, and 10 in Fig. 13, which shows canonical labels. Where should we put label 3 and to it adjacent spots labels 27 and 26? We can immediately recognize that the three locations at the bottom left part of the graph should be preferred to other locations because if we assign to one of the three spots label 3 and to adjacent spots 27 and 26 in the next step we can assign label 4 *without* introducing novel labels, and again the same hold for label 5.

There is here an apparent novelty in assigning labels 3, 4, and 5 in that *any* of six possible alternative placing would result in the *same adjacency matrix* for the graph. This means that the three sites are *equivalent* (with respect to adjacency) and that graph has some symmetry. The same again happens with labels 19 and 20, which can be interchanged without changing the form of the adjacency matrix. Hence, the order of the automorphism group of the graph of Fig. 12 is $(3!) \times (2!) = 12$. That is, there are twelve *different* ways of placing labels (any labels, canonical or not) on a graph which produce the same adjacency matrix (and in the case of canonical labels all the twelve alternatives will give the same canonical matrix). Since we are interested in unique labels for protein spots of proteomics map we can resolve the ambiguities associated with automorphism group of a graph (which disappears when graph is embedded over the proteomics map) by giving preference to spots of proteins having a larger mass. Thus in our case we assigned labels 3, 4, 5 to spots 18, 14 and 12 respectively, and labels 19 and 20 to spots 57 and 44 respectively.

We have to decide on positions of labels 26 and 27. It is not difficult to see that the cut point vertex should have label 27 because in this way we will get smaller binary rows for vertices adjacent to the cut vertex (vertices 9, 11, and 13). The cut point vertex is defined in graph theory as a vertex which when deleted separates a graph into two or more disjoint fragments). Assignment of vertices 6 and seven requires some testing but it is not difficult to select the proper sites (shown in Fig. 13) as the case shown is optimally placing labels 25 and 24 to produce for subsequent labels minimal row binary numbers. In fact after assignment of 6 and to it adjacent 25 and 24 the locations of all subsequent labels is unique!

Hence we are not continuing with describing justifications for the rest of labels, which readers can not only find by themselves but can find search for canonical labels even somewhat entertaining.

Fox trail diagram

We will end this section with construction of a zigzag curve based on the canonical labels to which we have referred as fox trail diagram (to differentiate this zigzag curve from zigzag curves based on ordering of spots as dictated by their relative abundance). In Fig. 14 we show fox trail diagram with canonical labels given for most spots (for clarity not all the canonical labels are shown). The fox trail diagram can be used in the same manner that zigzag curves based on the abundance have been used in building D/D matrices and construction of map invariants. An advantage of the fox trail diagram is that it does not utilize information on abundance, except in selecting the initial N spots, if not selected otherwise. This may in some circumstances allow construction of fox trail diagrams for proteomics maps of unknown origin if set of N proteins that will form a basis for analysis has been identified. Proteins can be selected if they are identified or if a list of coordinates for a set of "standard" proteins for comparative studies is composed.

CANONICAL LABELS FOR PEROXISOME PROLIFERATORS

In order to arrive at canonical representation of proteomics map we have first to get canonical labels for set of N pre-selected protein spots. In the procedure outlined here we selected 29 most abundant spots in the proteomics map for the control group of rat liver cells. The derived canonical labels lead to unique adjacency matrix which is the same for all proteomics maps derived for liver cells of rats, whether exposed to different chemicals, different diseases, possibly different diet, and so on. In Table 3 we show the first dozen rows of the adjacency matrix corresponding to the canonical labels found here. The corresponding decimal sequence is:

1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...

The occurrence of repetitions of a number in the sequence indicates the presence of symmetry equivalent vertices in the graph. Observe that the above sequence of numbers equally belong to all the five proteomics data (maps) of Table 2 because they differ only in relative abundance of individual spots, but protein spots (at least under the same experimental conditions) always appear at the same location. If we want to differentiate maps associated with different peroxisome proliferators we ought to incorporate information on abundance, because that is the only parameter that will vary when same cell types or the same tissue is considered. A way to do is to assign abundance values to the diagonal elements of the map

graph or construct N-component vector in which components are ordered according to the given canonical labels of spots with components representing abundance. For the five cases of Table 2 this is illustrated in Table 4.

We will refer to the common code for all five maps based on decimal interpretation of the rows of the canonical matrix as *class code*. Thus class code becomes a code for specific type of cell/organ/species. Within the class we differentiate individual maps by canonical abundance vectors. We define the lead map and the map of unperturbed cell/tissue/organ and such map will have numerical values of abundance explicitly given (preferably in some standardized unit scale). The rest map vectors (ordered sequence of proteins and their abundance) of maps belonging to the same cell/tissue/organ (that is to the same class) will have as entries quotients of relative abundance. In this way, when examining considers one can immediately distinguish the lead map from other maps of the same class.

CONCLUDING REMARKS

We have outlined a procedure for associating with proteomics maps a single binary code, which for convenience can be represented as numerical sequence based on decimal interpretation of individual rows of canonical adjacency matrix. The approach assigns to individual proteins unique labels, which may facilitate comparison of maps that may originate with different laboratories. Partial ordering is not very sensitive to minor variations between maps, as can happen with the maps made at somewhat different experimental conditions.

Alternative canonical scheme can be proposed. One such approach, elaborated by Hendrickson,²⁵ represents a modification of our canonical scheme for molecules in that instead of searching for the minimal binary code for the adjacency matrix one is seeking the maximal possible binary number. Hendrickson and Toczko²⁵ claimed that the maximal adjacency code is easier to find. We are skeptical about this claim that has not been substantiated at any great length, because one can construct graphs for which the smallest codes can be easily found, just as one can construct graphs for which the opposite is the case. In the case of graphs such as discussed here it is not difficult to see that finding the smallest binary matrix may be easier than finding the largest binary matrix. In the case of the smallest binary matrix one initiate labeling by looking for vertices with the smallest valence, while in the case of the largest binary matrix one initiate labeling by looking for vertices with the largest valence in order to have the largest possible entry in the first row of the adjacency matrix. In the case of the embedded graph of Fig. 1 vertices Q and T were given label 1 and 2 and to their neighbors we could immediately assign labels 20 and 19 respectively. Were we to follow Hendrickson and Toczko and search for the maximal

binary numbers we would have to consider protein spots M and N, each having six neighbors as candidates for labels 1 and 2 respectively. But to complete the assignment for the neighbors of each of the two vertices we would have to consider $6!$ possibilities, that is 720^2 possibilities or over half a million possibilities!

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Figure Captions

- Fig. 1 Hypothetical proteomics map with twenty protein spots used to illustrate partial ordering of protein spots.
- Fig. 2 The graph of partial ordering superimposed over the proteomics map. Observe that slopes of all line segments are positive.
- Fig. 3 Initiation of the search for canonical labels: Assignment of labels 1 and 2 to terminal vertices.
- Fig. 4 Four possible placement of labels 3 and 4 to divalent vertices D and S.
- Fig. 5 The unique site for label 5 at spot A forces labels 18/17 for spots E and G and eliminates Fig. 4b and Fig. 4d from further considerations.
- Fig. 6 The unique site for the label 6 at the spot K forces label 18 for spot G and label 16 for spot N.
- Fig. 7 Complete canonical labels for embedded graph of Fig. 2.
- Fig. 8 Separation of 70 most abundant protein spots obtained by electrophoresis and chromatography of homogenized rat liver cells.
- Fig. 9 Embedded graph of partial ordering for 70 protein spots of Fig. 8 showing that limited complexity of such graphs.
- Fig. 10 The x, y locations of 29 protein spots of Table 2.
- Fig. 11 Embedded graph of the partial ordering for 29 protein spots of Table 2.
- Fig. 12 A pictorial representation of the graph of the partial ordering for 29 protein spots of Table 2 (observe that no longer lines representing edges have to have positive slope)
- Fig. 13 The canonical labeling of vertices for the graph of Fig. 12.
- Fig. 14 The "fox trail" diagram based on the canonical labels for the proteomics maps of Fig. 11

Table 1 Canonical Adjacency matrix of the Partial Ordering of the graph of Fig. 1

[illegible]

Table 2 The x, y coordinates and the abundance for the control rat liver cells and when the animals were exposed to the four peroxisome proliferators.

Canonical labels	x	y	A ₀	A ₁ /A ₀	A ₂ /A ₀	A ₃ /A ₀	A ₄ /A ₀	Old labels
8				0.8332	1.0995	1.1975	0.0712	22
12				0.7796	0.5745	0.6026	0.8813	52
14				1.6744	1.9279	1.4451	1.5713	20
1				0.5214	0.3467	0.6517	0.6866	62
2				0.9280	0.8446	0.8572	0.9462	48
16				1.4370	1.2484	1.2517	1.3266	9
18				0.8700	0.5361	0.8476	1.1485	36
24				0.8967	0.9027	1.0268	1.0734	2
20				0.9662	1.0007	0.9502	1.2602	44
7				1.0805	0.8365	0.6486	1.0824	15
27				0.9819	0.5886	0.9023	1.1712	5
17				2.4224	0.7838	0.8245	2.4859	45
26				0.9749	0.9219	1.0383	1.2354	1
10				0.8329	0.5984	1.0728	1.2460	56
28				0.8670	1.0634	0.9394	1.4118	35
11				1.6631	2.7300	1.3186	1.3471	19
21				0.8389	0.5016	0.9884	1.0873	47
4				1.1466	1.8036	1.0756	1.3869	14
15				1.4749	2.2973	1.9544	0.0938	26
29				0.8410	0.8676	0.9267	1.2267	41
9				0.8833	0.6073	0.8086	0.9181	39
13				1.3537	1.3300	1.3637	2.2165	24
22				0.9748	1.0090	0.8673	1.2393	29
25				1.0263	1.3494	1.3382	0.9409	33
3				0.9628	1.5907	0.8044	0.8859	18
5				0.8985	0.6803	0.8041	1.2152	12
23				1.1912	1.5306	2.0926	1.9225	40
6				1.4279	0.8306	0.7795	0.8687	30
19								57

Table 3 Part of the canonical adjacency matrix for graph of Fig. 12

		14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
1	. .	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	. .	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
3	. .	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
4	. .	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
5	. .	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
6	. .	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
7	. .	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0
8	. .	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1
9	. .	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	1
10	. .	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
11	. .	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0
12	. .	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0
13	. .	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0
14	. .	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0

Table 4

1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...

Control	1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...
PFOA	1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...
	0.521, 0.928, 0.963, 1.147, 1.428, 1.081, 0.833, 0.883, 0.833, 1.663, 0.780, ...
PFDA	1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...
	0.347, 0.845, 1.591, 1.804, 0.680, 0.831, 0.837, 1.100; 0.607, 0.598, 2.730, ...
Clofibrate	1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...
	0.652, 0.857, 0.804, 1.076, 0.804, 0.780, 0.649, 1.198, 0.809, 1.073, 1.319, ...
DEHP	1, 3, 12, 12, 12, 48, 80, 144, 391, 1536, 4098, 7680, ...
	0.687, 0.687, 0.886, 1.387, 1.215, 0.869, 1.082, 0.071, 0.918, 1.246, 1.347, ...

Appendix 1.2

*Prediction of cellular toxicity of halocarbons from their
computed chemodescriptors: A hierarchical QSAR approach*

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PREDICTION OF CELLULAR TOXICITY OF HALOCARBONS FROM COMPUTED CHEMODESCRIPTORS: A HIERARCHICAL QSAR APPROACH

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A hierarchical quantitative structure-activity relationship (HiQSAR) approach was used to estimate toxicity and genetic toxicity for a set of 55 halocarbons using computed chemodescriptors. The descriptors consisted of topostructural (TS), topochemical (TS), geometrical, semi-empirical (AM1) quantum chemical, and *ab initio* (STO-3G, 6-31G(d), 6-311G, 6-311G(d), and aug-cc-pVTZ) quantum chemical indices. For the two toxicity endpoints investigated, ARR and D₃₇, the TC indices gave the best cross-validated R² values. The 3-D indices also performed either as well as, or slightly superior to the TC indices. For the four categories of quantum chemical indices used for the development of predictive models, the AM1 parameters gave the worst performance and the most advanced *ab initio* (B3LYP/aug-CC-pVTZ) parameters gave the best results when used alone. This was also the case when the quantum chemical indices were used in the hierarchical QSAR approach for both of the toxicity endpoints, ARR and D₃₇. The models resulting from HiQSAR are of sufficiently good quality to estimate toxicity of halocarbons from structure.

1. INTRODUCTION

An important objective of contemporary computational toxicology is the prediction of the potential toxic effects of chemicals from their computed molecular descriptors.¹⁻²⁰ Thousands of chemicals are already in the marketplace and their numbers are growing at an ever increasing rate. The TSCA Inventory of USEPA currently has over 81,000 entries and the list is increasing yearly.²¹ Most of these chemicals have none of the experimental data necessary for the estimation of their effects on human and environmental health.²² In the areas of chemical ecotoxicity and genotoxicity, the availability of data is even more appalling. Only 15% of TSCA chemicals have genotoxicity data; less than 6% have chronic toxicity or ecotoxicity data.²² Only a few hundred of the many thousands of candidate chemicals have

been tested in the National Toxicology Program (NTP) for carcinogenicity in the two-year rodent bioassay program.

It is clear from the above that, in the foreseeable future, hazard assessment of chemicals must be carried out in a data-poor situation, while the number of candidate chemicals is increasing at a rate much faster than the availability of experimental physicochemical and toxicity data prerequisite to the proper hazard estimation of all these substances. A viable solution to this quagmire is the use of quantitative structure-activity relationship (QSAR) models which use algorithmically derived properties, *i.e.*, properties which can be calculated directly from chemical structure without the input of any further experimental data.

Halocarbons constitute an important class of chemicals as solvents and useful intermediates in various synthetic processes. So, the potential of their release to the environment worldwide is substantial.²³⁻²⁵ Therefore, it was of interest to develop QSARs of halocarbons using descriptors that can be calculated from structure. Crebelli *et al.* determined various toxicity endpoints for a set of 55 halocarbons.²⁶ They formulated QSAR models using a mixture of calculated and experimental properties, *viz.*, molecular refractivity (MR), octanol / water partition coefficient ($\log P$), and quantum chemical indices such as HOMO energy, LUMO energy and the difference between HOMO and LUMO energies calculated by *ab initio* methods. While MR characterized the generalized shape and size of molecules, the quantum chemical indices quantify the electrophilic nature of the molecules. In our hierarchical QSAR (HiQSAR) approach, we have used a combination of chemodescriptors, calculated directly from molecular structure, for the formulation of QSARs to predict various toxicity endpoints.^{5-8, 11-13, 27-31} The HiQSAR method begins model building with parameters which can be computed most easily; parameters demanding more computational resources are added only if the easily calculable indices do not give satisfactory results. We have routinely used topostructural (TS), topochemical (TC), geometrical, and semi-empirical quantum chemical indices for the development of QSARs for toxicity estimation. Previous results with halocarbons by Crebelli *et al* showed that they achieved moderately good results in QSAR development using a combination calculated descriptors.²⁶ So, in the current study we have attempted to develop QSARs for the set of 55 halocarbons using a combination of topological, geometrical, and quantum chemical indices using the HiQSAR approach.

2. METHODS AND MATERIALS

2.1. Halogenated Aliphatic Hydrocarbon Database. The database of halogenated aliphatic hydrocarbons used in this study was taken from the work of Crebelli *et al.*²⁶ Crebelli and his co-workers present test data for mitotic chromosome malsegregation and lipid peroxidation tested in *Aspergillus nidulans* diploid strain P1. Results presented for mitotic chromosome malsegregation include lowest effective concentration affecting chromosome distribution (LEC), lowest concentration for arresting

conidial development (ARR), and lowest concentration inducing one lethal hit per cell (D_{37}). Lipid peroxidation study results were presented as lowest effective concentration resulting in lipid peroxidation (LEC_{LP}), however not all of the chemicals were tested for lipid peroxidation. For the purposes of this study, we chose to model the two continuous biological endpoints (ARR and D_{37}) that were available for all 55 chemicals. It should be noted that LEC data was available for all of the chemicals in the set as well, however, activity values were only available for twenty-four of the fifty-five chemicals, the remaining thirty-one chemicals tested negative. Chemical names and activity data (ARR and D_{37}) are presented in Table 1. Figure 1 shows the optimized geometries of all 55 neutral halocarbons in the Crebelli set that we considered in this study. These geometries were optimized using the high-level cc-pVTZ basis set using the DFT/B3LYP method. The basis set and the technique are considered quite reliable for the geometry optimization. Subsequent to the geometry optimization of the neutral halocarbons we computed the energies of the anions at the optimized neutral geometries. The vertical electron affinities are taken as the difference of the geometries of the anion and neutral species at the optimized neutral geometries. For further details of the testing regimens, please refer to the original work of Crebelli and his co-workers.²⁶

^{32, 33}

2.2 Calculation of Topological Indices. The topological indices (TIs) used in this study were calculated using three main software programs: POLLY 2.3,³⁴ MolConn-Z 3.50,³⁵ and Triplet.³⁶ Included in the suite of 192 topological indices used in this study are: Wiener number,³⁷ molecular connectivity indices as calculated by Randić³⁸ and Kier and Hall,³⁹ frequency of path lengths of varying size, information theoretic indices defined on distance matrices of graphs using the methods of Bonchev and Trinajstić⁴⁰ as well as those of Raychaudhury *et al.*,⁴¹ parameters defined on the neighborhood complexity of vertices in hydrogen-filled molecular graphs,⁴²⁻⁴⁴ Balaban's J indices,⁴⁵⁻⁴⁷ local orthogonal vertex invariants,³⁶ and the electrotopological indices of Kier and Hall.⁴⁸ More information on the topological indices calculated by POLLY has been reported in earlier studies.^{4, 10, 13, 49}

2.3. Calculation of Geometrical Indices. The geometrical indices include van der Waals volume,⁵⁰ the three-dimensional Wiener numbers for both the hydrogen-filled and hydrogen-suppressed molecular structures,⁵¹ and the Kappa shape descriptors of Kier and Hall.^{52, 53} Van der Waals volume, V_w , was calculated using SYBYL 6.4 from Tripos Associates, Inc.⁵⁴ The 3-D Wiener numbers were calculated in the SYBYL interface using an SPL (Sybyl Programming Language) program developed in our lab. Calculation of 3-D Wiener numbers consists of the sum entries in the upper triangular submatrix of the topographic Euclidean distance matrix for a molecule. The 3-D coordinates for the atoms were determined using CONCORD 3.2.1.⁵⁵ Finally, the Kappa shape descriptors were calculated using MolConn-Z 3.50.³⁵

2.4. Quantum Chemical Parameters. Semi-empirical quantum chemical parameters were calculated using the Austin Model version one (AM1) Hamiltonian. These parameters were calculated using

MOPAC 6.00 in the SYBYL interface.⁵⁶ *Ab initio* quantum chemical calculations were performed applying the second order Møller-Plesset perturbation theory⁵⁷ for the sequence of standard Pople's atomic basis sets: STO-3G,^{58, 59} 6-31G(d),⁶⁰⁻⁶⁵ 6-311G,^{66, 67} 6-311G(d), and aug-cc-pVTZ.⁶⁸⁻⁷² Additional calculations were done within the density functional theory (DFT) approach.⁷³ The DFT calculations utilized Becke's three-parameter functional⁷⁴ with Vosco *et al.*'s⁷⁵ local correlation part and Lee *et al.*'s⁷⁶ nonlocal part (abbreviated as B3LYP). DFT studies were done applying extended aug-cc-pVTZ basis set.^{57, 73-76} This basis set consists of a set of diffuse functions to account for the negative electronic charge distribution on anions. The density functional theory has been shown as a reliable method for reproducing electron affinity properties.⁷⁷

The calculations in the MP2/STO-3G approach were utilized as the lowest-level *ab initio* scheme, similar to semi-empirical quantum chemical approaches. All calculations applying Pople's basis sets were done at the MP2 level of theory and are denoted in the text by the name of the atomic basis sets. The DFT calculations are referred to as B3LYP/aug-cc-pVTZ. The results from the *ab initio* calculations are presented in Tables 2-5. Table 5 provides additionally experimental dipole moments¹⁷ for the assessment of the quality of the charge distribution. All *ab initio* quantum chemical calculations were conducted using Gaussian98W.⁷⁸

2.5. Statistical Analysis. Initially, the majority of topological indices were transformed by the natural logarithm of the index plus one. This was done to scale the indices, since some may be several orders of magnitude greater than others, while other indices may equal zero. The geometric indices were transformed by the natural logarithm of the index for consistency, the addition of one was unnecessary. Other indices, including the majority of the quantum chemical indices were also transformed using natural logarithm, however, constants were chosen on a case-by-case basis to bring the minimal value for the descriptor above zero. Finally, the *ab initio* values for $\text{Gap}_{\text{HOMO-LUMO}}$ and VEA were not scaled since their values were already distributed between negative one and one.

The set of 192 topological indices was then partitioned into the two distinct sets: topostructural indices (eighty-six) and topochemical indices (106). Each of the sets were then divided into subsets, or principal components (PCs), using the SAS principal components analysis (PCA) procedure (PRINCOMP)⁷⁹ to further reduce the number of independent variables for use in model construction. This procedure results in the creation of a new set of completely orthogonal PCs derived from linear combinations of all indices. Only PCs with eigenvalues greater than or equal to one have been retained for this study. A more detailed explanation of this approach has been provided in a previous study by Basak *et al.*⁴⁹. After the PCA, a correlation analysis was conducted on the PCs to determine which TIs were most highly correlated with each of the PCs. The TI most-highly correlated with each PC was then selected for modeling, resulting in a greatly reduced set of indices. The PCA and selection of indices was performed independently for both

the topostructural and topochemical indices and resulted in a set of five topostructural indices and a set of twelve topochemical indices.

As is well known, the smaller the data set, the greater the chance of spurious error when using a large number of independent variables (descriptors), so reducing the number of independent variables is crucial when modeling of data set of this size. Topliss and Edwards⁸⁰ have thoroughly studied this issue of chance correlations. For a set with between fifty and sixty dependent variables (observations), to keep the probability of chance correlations less than 0.01, at most about forty-five independent variables may be used (if a correlation coefficient of $R^2 \geq 0.9$ is achieved). This number is dependent on the actual correlation achieved in the modeling process, a higher correlation results in a better chance of using more variables with the same limited probability of chance correlations. In this study we are well below the cut-off of forty-five independent variables. In fact, the total number of descriptors which will be considered for all models and estimation is twenty-three (this includes the topostructural, topochemical and geometrical indices), well within the bounds of the Topliss and Edwards criteria.⁸⁰ Addition of all quantum chemical indices employed in hierarchical modeling takes the total up to sixty, beyond the allowable bounds of the Topliss and Edwards criteria. However, we consider the descriptors on the quantum chemical level to be exclusive, in other words we never use parameters from the four different quantum chemical approaches at the same time. So for any HiQSAR including quantum chemical parameters, the total number of indices considered in modeling never exceeds thirty, again well within the bounds of the Topliss and Edwards criteria.

Regression modeling was accomplished using the SAS procedure REG⁷⁹ on nine distinct sets of indices. These sets were constructed as part of the HiQSAR approach to model development. The hierarchy begins with the simplest parameters, the TSIs. After using the TSIs to model the activity, the next level of parameters of higher complexity are added. To the indices included in the best TSI model, we add all of the TCIs and proceed to model the activity using these parameters. Likewise, the indices included in the best model from this procedure are combined with the indices from the next complexity level, the geometrical indices and modeling is conducted once again. Finally, the best model utilizing TSIs, TCIs and geometrical indices is combined with the various quantum chemical parameters to develop the highest level models in the hierarchy.

3. RESULTS

The PCA of the topostructural indices resulted in the retention of five PCs with eigenvalues greater than or equal to 1.0. These five PCs are presented in Table 6 in terms of their eigenvalues, the amount of data variance incorporated into each of the PCs, and the one topostructural index most-highly correlated with each of the PCs. The topostructural index most-highly correlated with each PC was chosen for use in

HiQSAR modeling. Similarly, the PCA on the topochemical indices resulted in twelve PCs with eigenvalues greater than or equal to zero. These PCs and their attendant most-highly correlated topochemical index are presented in Table 7.

3.1. Results for Modeling ARR. For modeling ARR, all-subsets regression on the set of five topostructural indices resulted in the selection of a three-parameter model. This model used $^4\chi_{PC}$, W and DS1₃, in a poor regression with a regression coefficient (R^2) of 0.3661, a cross-validated regression coefficient (R^2_{cv}) of 0.2213, and a standard error (*s.e.*) of 1.27. These three indices were then included in modeling with the topochemical indices, creating a beginning set of fifteen topological indices. Again, all-subsets regression was used and resulted in the selection of an eight-parameter model. This model retained W and DS1₃ and added the following topochemical indices: $^1\chi^v$, AZV₃, H_{MIN}, SssssC, SdCH₂, and SdsCH. This model showed great improvement ($R^2 = 0.8606$, $R^2_{cv} = 0.7637$, *s.e.* = 0.63) over the topostructural model. The addition of the six geometrical indices to this set of eight topological indices result in further improvement in modeling ARR ($R^2 = 0.9014$, $R^2_{cv} = 0.8345$, *s.e.* = 0.52). The model selected eliminated all topostructural indices and two topochemical indices and added four geometrical parameters resulting in the following seven-parameter model: H_{MIN}, SssssC, SdCH₂, City_H, V_w, Ka₃, and Kp₃. Next, the addition of AM1, STO-3G, 6-31G(d) and 6-311G parameters to the topochemical and geometrical indices did not lead to any improvement in modeling. Modeling with the 6-311G(d) basis set resulted marginal improvement with an eight parameter model, showing a slight increase over the topochemical and geometrical model while using one more index. This model added the energy of the second-lowest unoccupied molecular orbital (E_{LUMO+1}) to the existing hierarchical model. The model statistics are as follows: $R^2 = 0.9065$, $R^2_{cv} = 0.8340$, and *s.e.* = 0.51. Finally, the B3LYP/aug-cc-pVTZ parameters were combined with the topochemical and geometrical parameters, resulting in the selection of an eight-parameter model incorporating the following indices: H_{MIN}, SssssC, SdCH₂, City_H, V_w, Ka₃, Kp₃, and E_{LUMO} . This model showed some improvement over the topochemical and geometrical model ($R^2 = 0.9120$, $R^2_{cv} = 0.8511$, and *s.e.* = 0.50). For the purposes of completeness, models were created using each of the levels of the hierarchy singly. These results, along with the results for the rest of the models can be found in Table 8.

3.2. Results for Modeling D₃₇. All-subsets regression on the set of five topostructural indices using the SAS procedure REG⁷⁹ resulted in the selection of a two-parameter model. This model incorporated W and DS1₃, demonstrating a poor regression with a regression coefficient (R^2) of 0.3659, a cross-validated regression coefficient (R^2_{cv}) of 0.2945, and a standard error (*s.e.*) of 1.24. These two indices were then included in modeling with the topochemical indices, creating a beginning set of fourteen topological indices. Again, all-subsets regression was used and resulted in the selection of a seven-parameter model. This model retained the Weiner index, W, and added the following topochemical indices: AZV₃, $^2\chi^b$, Q_v, SdCH₂, H_{MIN}, and SsF. This model was much more satisfactory in terms of R^2 and *s.e.* ($R^2 = 0.8791$, $R^2_{cv} =$

0.8074, *s.e.* = 0.57). The addition of geometrical indices did not result in any improvement to modeling D_{37} . The model selected during all-subsets regression was identical to the one selected during the previous step in modeling hierarchy. Next, the set of seven topostructural and topochemical parameters was supplemented with the various quantum chemical parameters. The use of AM1 semi-empirical descriptors led to the selection of a seven-parameter model showing slight improvement in both R^2 and *s.e.* ($R^2 = 0.8840$, $R^2_{cv} = 0.8121$, *s.e.* = 0.56). This model replaced the Triplet parameter, AZV_3 , with the energy of the second-lowest unoccupied molecular orbital (E_{LUMO+1}). The addition of STO-3G and 6-31G(d) parameters to the topostructural and topochemical indices did not lead to any improvement in modeling. Next, the addition of 6-311G parameters to the seven topostructural and topochemical indices led to some improvement in modeling. A ten-parameter model, adding the energies of the lowest occupied (E_{LUMO}) and second-lowest occupied (E_{LUMO+1}) molecular orbitals and vertical electron affinity (VEA), was selected through all-subsets regression showing a reasonable increase in model performance over the topological model. This model resulted in an $R^2 = 0.9015$, a cross-validated $R^2 = 0.8283$, and *s.e.* = 0.53. While this is a noticeable increase in the regression coefficient and the standard error, it is somewhat of a sacrifice with the inclusion of three additional indices. Modeling with the slightly higher 6-311G(d) basis set resulted in a more acceptable eight parameter model, showing a slight increase over the 6-311G model while using two fewer indices. This model removed W, but retained all five of the topochemical indices remaining at this point and added three *ab initio* parameters: E_{HOMO} , E_{LUMO} , and E_{LUMO+1} . The model statistics are as follows: $R^2 = 0.9056$, $R^2_{cv} = 0.8335$, and *s.e.* = 0.51. Finally, the B3LYP/aug-cc-pVTZ parameters were combined with the topostructural and topochemical parameters, resulting in the selection of an eight-parameter model incorporating the following indices: W, AZV_3 , χ^b , Q_v , $SdCH_2$, H_{MIN} , SsF, and E_{LUMO} . This model was by far superior to all of the previous models ($R^2 = 0.9476$, $R^2_{cv} = 0.9236$, and *s.e.* = 0.38). For the purposes of completeness, we created models using each of the levels of the hierarchy alone. These results, along with the results for the rest of the models can be found in Table 9.

4. DISCUSSION

The major objective of this study was to develop high quality QSAR models for the prediction of the toxicity of halocarbons from chemodescriptors calculated directly from their structure. To, this end we have developed HiQSARs for two toxicity endpoints, viz. ARR and D_{37} , for which data was available for the entire set of 55 compounds.

It is clear from the HiQSAR models presented in Tables 8 and 9 that the simplest topostructural indices do not give very good predictive results. This is not surprising considering the fact that halocarbons are believed to act through a mechanism dominated by electron transfer to the molecule. The topostructural indices, being derived from the skeletal graphs of the molecule quantify the connectedness (adjacency and

topological distances) of the atoms in the molecular structure. However, they are insensitive to such features as bonding pattern and atom type. The topochemical indices, on the other hand, contribute significantly to the predictive power of the models for both toxicity endpoints. These indices quantify both the topological and chemical aspects of atoms in the molecule, simultaneously being able to characterize the shape and size of molecules. It is interesting to note that Crebelli *et al*²⁶ found MR to be well correlated with both ARR and D₃₇ toxicity values for this set of halocarbons. MR is not only a shape and size descriptor, but it also encodes information about the electronic nature of the molecule.

The 3-D (geometrical) indices also performed surprisingly well for both properties, though more so in modeling ARR. This should be expected in the light of the fact that both the topochemical indices and MR did well in predicting these toxicity endpoints.

In the realm of quantum chemical indices we used both semi-empirical (AM1) and *ab initio* (STO-3G, 6-31G(d), 6-311G, 6-311G(d) and B3LYP/aug-cc-pVTZ) indices. In our model development using the HiQSAR method, we used each of these six classes of quantum chemical indices alone and in the hierarchical modeling with one type of quantum chemical indices being used at a time. As is clear from Table 8, there is little noticeable model improvement for ARR with the addition of quantum chemical parameters of any of the levels included in this study. Even at the high B3LYP/aug-cc-pVTZ level, there is only minor improvement over the existing topochemical and geometrical model. However, as can be seen in Table 9, there is significant improvement in the modeling of D₃₇ with the addition of the B3LYP/aug-cc-pVTZ parameters.

It is interesting to note that of the six classes of quantum chemical indices, the high level B3LYP/aug-cc-pVTZ indices were most useful in toxicity prediction either alone or as independent variables in the HiQSAR scheme. This vindicates the belief that the critical step in the toxic mode of action of halocarbons is the attachment of the electron to the halocarbon moiety. The best models after the full hierarchical modeling process yielded the following high quality QSARs:

$$\begin{aligned}\text{Ln(ARR)} &= 39.902 + 0.898(\text{H}_{\text{MIN}}) - 0.551(\text{SssssC}) - 0.623(\text{SdCH}_2) + 1.859(\text{City}_\text{H}) \\ &\quad - 10.726(\text{V}_\text{w}) + 7.417(\text{Ka}_3) - 8.097(\text{Kp}_3) + 0.582(\text{E}_{\text{LUMO}}) \\ R^2 &= 0.9120, R^2_{\text{c.v.}} = 0.8511, n = 55, s.e. = 0.50, F = 59.59\end{aligned}$$

$$\begin{aligned}\text{Ln(D}_{37}\text{)} &= 4.016 - 5.282(\text{W}) + 10.771(\text{AZV}_3) + 2.010(\chi^b) - 0.745(\text{Q}_\text{v}) \\ &\quad - 0.546(\text{SdCH}_2) + 0.926(\text{H}_{\text{MIN}}) + 0.547(\text{SsF}) + 1.329(\text{E}_{\text{LUMO}}) \\ R^2 &= 0.9476, R^2_{\text{c.v.}} = 0.9236, n = 55, s.e. = 0.38, F = 103.98\end{aligned}$$

For comparative purposes, we examined the models initially developed by Crebelli *et al.*²⁶ The following equations represent our re-analysis of the Crebelli models (using MR, logP, and STO-3G *ab initio* parameters) to calculate cross-validated regression coefficients:

$$\begin{aligned}\text{Ln}(1/\text{ARR}) &= -0.085 + 0.186(\text{MR}) - 10.962(\text{Gap}_{\text{LUMO-HOMO}}) \\ R^2 &= 0.6154, R^2_{\text{cv}} = 0.5298, n = 55, s.e. = 0.98, F = 41.60\end{aligned}$$

$$\begin{aligned}\text{Ln}(1/D_{37}) &= -0.330 + 0.203(\text{MR}) - 11.249(\text{Gap}_{\text{LUMO-HOMO}}) \\ R^2 &= 0.7284, R^2_{\text{cv}} = 0.6726, n = 55, s.e. = 0.81, F = 69.73\end{aligned}$$

The greater success of the B3LYP/aug-cc-pVTZ indices as compared to the STO-3G, 6-31G(d), 6-311G, 6-311G(d), and AM1 parameters in predicting toxicity indicates that more sophisticated or higher level QC indices might better reflect the electronic basis of the toxicity of these halocarbons. To this end, we are currently calculating VEA for a subset of halocarbons at the CCSD(T) level, however only a small subset will be calculated at this level since it is prohibitively time consuming to do so for the entire set. We would like to investigate how far the success of the less expensive parameters can be vindicated using the higher level of parameters. Also, we will be doing calculations on solvated molecules as opposed to gas phase calculations to see whether such involved calculations give better models or shed some light in the toxic modes of action of halocarbons. Such studies are in progress and will be reported subsequently.

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Figure Caption:

Figure 1. The optimized ground state geometries of 55 neutral halocarbons in the Crebelli set. The geometries were optimized at the cc-pVTZ/DFT/B3LYP level.

Table 1. The 55 halocarbons and their experimental and estimated toxicity values for ARR and D₃₇ in *Aspergillus nidulans* diploid strain P1.

	Chemical Name	D ₃₇	Est. D ₃₇ ^a	ARR	Est. ARR ^b
1	Dichloromethane	93.6	124.3	135.7	158.9
2	Chloroform	24.8	22.9	23.5	18.1
3	Carbon tetrachloride	3.1	1.9	2.9	2.5
4	1,1-Dichloroethane	47.6	47.9	38.1	37.2
5	1,2-Dichloroethane	50.8	32.7	44.4	33.4
6	1,1,1-Trichloroethane	10	8.4	11	10.1
7	1,1,2-Trichloroethane	10.7	9.9	11.8	7.5
8	1,1,1,2-Tetrachloroethane	2.8	2.9	2.4	2.5
9	1,1,2,2-Tetrachloroethane	2.8	4.3	3.3	5.0
10	Pentachloroethane	1.7	1.6	1.2	4.9
11	Hexachloroethane	0.8	1.5	16.9	4.8
12	1,1,2-Trichloroethylene	11.1	8.6	10.6	7.9
13	Tetrachloroethylene	1.2	1.6	1.5	1.8
14	1,2-Dichloroethylene	29.9	25.9	25.5	34.5
15	1,1-Dichloroethylene	25	17.8	21.9	14.4
16	1,2-Dichloropropane	15.4	15.2	17.4	12.6
17	2,2-Dichloropropane	19.2	17.6	17.2	20.5
18	1,3-Dichloropropane	10.5	8.9	13.7	13.4
19	1,2,3-Trichloropropane	9.4	4.2	6.7	7.3
20	1-Chlorobutane	14.4	13.4	12.4	16.1
21	2-Chlorobutane	18.9	22.2	25.5	14.9
22	1,3-Dichlorobutane	8.8	6.5	8.3	8.3
23	2,3-Dichlorobutane	8.7	8.7	10.5	8.3
24	1-Chloro-2-methylpropane	14.3	20.7	14.3	13.2
25	2-Chloro-2-methylpropane	18.4	23.8	23.9	29.8
26	1-Chloropentane	5	5.1	5	5.0
27	1-Chlorohexane	1.5	2.3	1	2.1
28	1-Chlorooctane	1.5	0.7	1	0.5
29	1,1-Dichloropropene	6.6	11.6	5	11.1
30	2,3-Dichloro-1-propene	2.7	4.7	2.7	5.3
31	1,3-Dichloropropene	5.3	6.7	7.8	10.9
32	1,1,3-Trichloropropene	2.4	2.8	1.7	2.6
33	3-Chloro-2-chloromethyl propene	2.7	2.3	2.6	3.5
34	1-Chloro-2-methylpropene	12.7	17.4	9.7	16.4
35	3-Chloro-2-methylpropene	7.6	7.2	10.1	5.8
36	Chlorodibromofluoromethane	3.1	3.1	2.6	2.7
37	Bromoform	5.2	2.4	5.5	2.0
38	Bromochloromethane	61.6	56.0	69.3	74.8
39	Bromotrichloromethane	0.8	0.8	1	0.6

40	Bromodichloromethane	10.6	10.5	11.1	8.0
41	Chlorodibromomethane	2.9	5.1	3.3	3.4
42	1-Bromo-2-chloroethane	24	16.2	20.4	16.6
43	1-Bromobutane	5.6	8.5	4.9	9.6
44	2-Bromobutane	11.5	14.4	9.8	10.1
45	1-Bromo-3-chloropropane	7.5	5.2	8.1	7.2
46	2-Bromo-1-chloropropane	9.8	9.6	8.3	8.2
47	1-Bromo-2-methylpropane	18.4	12.8	14.7	9.0
48	2-Bromo-2-methylpropane	26	14.8	26	13.8
49	1-Bromo-4-chlorobutane	3.3	2.7	3.4	2.6
50	1-Bromo-3-methylbutane	3.1	4.9	3.6	2.9
51	Dibromodichloromethane	0.2	0.3	0.1	0.2
52	Dibromomethane	21.4	26.0	25.7	36.8
53	Tetrabromomethane	0.01	0.0	0.01	0.0
54	1,1,2,2-Tetrabromoethane	0.4	0.6	0.7	1.1
55	1,2-Dibromoethylene	9.1	10.0	9.2	9.5

^aEstimated values for D_{37} are derived from the HiQSAR model combining topostructural, topochemical and aug-cc-pVTZ *ab initio* parameters.

^bEstimated values for ARR are derived from the HiQSAR model combining topostructural, topochemical, geometrical and aug-cc-pVTZ *ab initio* parameters.

Table 2. *Ab initio* parameters calculated using the MP2/ 6-31G(d) level of theory. Energies in eV, dipole moments in debye.

	$E_{\text{HOMO-1}}$	E_{HOMO}	E_{LUMO}	$E_{\text{LUMO+1}}$	$\text{GAP}_{\text{L-H}}$	VEA	μ
1	-12.2280	-12.1594	4.1663	5.7209	16.3257	-2.9518	2.0604
2	-12.7148	-12.3504	3.2414	4.9435	15.5919	-1.9258	1.4484
3	-12.6291	-12.6291	2.5086	4.2164	15.1377	-1.0713	0.0003
4	-12.0587	-11.9823	4.3136	5.5887	16.2958	-2.9718	2.3255
5	-12.1567	-12.0038	4.8406	5.1389	16.8444	-3.2024	0.0000
6	-12.4813	-12.1474	3.4172	4.8216	15.5646	-1.9919	2.0236
7	-12.3050	-12.1526	4.0262	4.5742	16.1788	-2.6031	1.7334
8	-12.4209	-12.3200	3.2115	4.0412	15.5314	-1.7687	1.8895
9	-12.4367	-11.9959	3.8632	3.9612	15.8591	-2.1399	0.0000
10	-12.5632	-12.1853	3.1073	3.7010	15.2925	-1.6118	1.3176
11	-12.5632	-12.1853	3.1073	3.7010	15.2925	-1.6118	1.3176
12	-12.5624	-9.9637	3.2572	4.3721	13.2209	-2.1823	1.2378
13	-12.3197	-9.9539	2.8583	4.1413	12.8122	-1.7918	0.0000
14	-12.6713	-9.9466	3.6452	4.9087	13.5918	-2.5886	0.0000
15	-12.3945	-10.1033	3.7138	4.5941	13.8171	-2.6501	1.6788
16	-11.8087	-11.7485	4.7356	5.5639	16.4841	-3.2712	3.4002
17	-11.9793	-11.7795	4.4077	5.2970	16.1872	-2.9447	2.4800

18	-11.9273	-11.6914	4.3119	6.0426	16.0033	-2.8340	2.1247
19	-12.0546	-11.9638	3.9726	5.0763	15.9364	-2.4362	3.4644
20	-11.6367	-11.5469	5.3481	6.2355	16.8950	-4.0458	2.4272
21	-11.5485	-11.5393	5.4801	6.2110	17.0194	-4.0190	2.1906
22	-11.7423	-11.7151	4.8738	5.5582	16.5889	-3.3023	3.4267
23	-11.9463	-11.6574	4.7223	5.3606	16.3796	-2.9426	0.0000
24	-11.6087	-11.5646	5.2649	6.4597	16.8294	-4.0238	2.2074
25	-11.4971	-11.4971	5.2695	5.9215	16.7666	-3.8193	2.2666
26	-11.6269	-11.5080	5.3655	6.1269	16.8735	-4.0381	2.4338
27	-11.6220	-11.4721	5.3680	6.0529	16.8400	-4.0292	2.4983
28	-11.6171	-11.4160	5.3753	6.0262	16.7913	-4.0248	2.5311
29	-12.2576	-9.6622	3.8523	4.7541	13.5145	-2.7223	2.1433
30	-11.9746	-9.9256	3.7633	4.6836	13.6890	-2.6546	3.0483
31	-12.1474	-10.0152	3.6918	4.4934	13.7069	-2.5717	1.9498
32	-12.2666	-10.1284	3.3603	4.1857	13.4887	-2.1945	0.5262
33	-11.9126	-10.1811	4.2885	4.4395	14.4697	-3.0517	2.1328
34	-11.9850	-9.1711	4.2406	5.8777	13.4117	-3.1091	2.2321
35	-11.8236	-9.6293	4.4357	5.3745	14.0650	-3.2574	1.6584
36	-11.8359	-11.4397	1.8868	3.8216	13.3265	-0.6251	0.5398
37	-11.3975	-10.9855	2.0438	4.0852	13.0294	-0.7113	1.1128
38	-11.3140	-11.2995	3.4681	5.3696	14.7676	-2.2490	1.9306
39	-11.7725	-11.7725	1.9647	3.6363	13.7371	-0.7056	0.2805
40	-11.7224	-11.5365	2.6490	4.4643	14.1856	-1.3901	1.3435
41	-11.6285	-11.1629	2.3132	3.9908	13.4762	-1.0163	1.2314
42	-11.1934	-11.1659	3.9840	5.0202	15.1499	-2.6013	0.0935
43	-10.6331	-10.6092	4.5201	6.0986	15.1293	-3.1173	2.4445
44	-10.5877	-10.5520	4.5462	6.1351	15.0982	-3.0473	2.2093
45	-10.9684	-10.9292	3.7416	5.8377	14.6708	-2.4781	2.0906
46	-10.9191	-10.8065	4.0803	5.2396	14.8868	-2.7061	3.3259
47	-10.6367	-10.6122	4.4994	6.1852	15.1116	-3.1047	2.2147
48	-10.5074	-10.5074	4.3655	5.8319	14.8729	-2.8626	2.3084
49	-10.8693	-10.8467	4.2406	5.0619	15.0874	-2.8356	0.0168
50	-10.6209	-10.5795	4.4529	6.0589	15.0324	-3.0402	2.4962
51	-11.6503	-11.3526	1.6577	3.2542	13.0103	-0.3403	0.3071
52	-11.2127	-10.9167	3.0928	4.7481	14.0095	-1.8362	1.8031
53	-11.1809	-11.1809	1.1878	3.4833	12.3687	-0.2475	0.0002
54	-11.4187	-10.5292	2.6512	2.9663	13.1804	-0.9331	0.0000
55	-11.5749	-9.6502	3.4948	3.6953	13.1450	-2.2764	0.0000

Table 3. *Ab initio* parameters generated within the MP2/ 6-311G computational scheme. Energy in eV, dipole moments in debye.

	$E_{\text{HOMO-1}}$	E_{HOMO}	E_{LUMO}	$E_{\text{LUMO+1}}$	$\text{GAP}_{\text{L-H}}$	VEA	μ
1	-12.5910	-12.4228	2.6191	4.0907	15.0419	-1.6695	2.5911
2	-13.0432	-12.8117	1.6863	3.5100	14.4980	-0.6978	1.7400
3	-13.1605	-13.1605	0.7396	2.8879	13.9001	0.2161	0.0001
4	-12.4253	-12.1442	2.9089	3.9206	15.0531	-1.7708	3.1867
5	-12.3932	-12.2955	2.8455	3.5427	15.1410	-1.5355	0.0000
6	-12.7151	-12.5390	1.9004	3.4289	14.4395	-0.7912	2.7738
7	-12.6626	-12.4718	2.3108	2.9456	14.7826	-1.2098	1.9151
8	-12.7747	-12.6911	1.6362	2.2107	14.3273	-0.5188	2.1691
9	-13.0465	-12.4302	1.9402	2.1437	14.3703	-0.6789	0.0000
10	-13.0296	-12.6495	1.4999	1.8044	14.1494	-0.3770	1.4106
11	-13.0296	-12.6495	1.4999	1.8044	14.1494	-0.3770	1.4106
12	-12.8770	-10.8157	2.5954	2.6308	13.4111	-1.7504	1.5650
13	-12.7953	-10.9107	2.2931	2.3051	13.2038	-0.8162	0.0000
14	-12.9630	-10.6927	2.9296	2.9413	13.6223	-2.1632	0.0000
15	-12.5728	-10.7292	3.0488	3.0841	13.7779	-2.2704	2.6089
16	-12.0484	-11.8944	3.1492	3.6999	15.0435	-2.2592	4.5327
17	-12.2898	-11.8868	3.0719	3.7734	14.9586	-1.7795	3.5658
18	-12.1491	-11.9406	2.6058	3.9435	14.5464	-1.4407	2.9276
19	-12.2979	-12.2566	2.2999	3.2752	14.5565	-1.1058	4.3320
20	-11.7393	-11.6503	3.6246	4.2148	15.2748	-2.6772	3.4043
21	-11.6016	-11.5760	3.9282	4.1203	15.5042	-2.7246	3.3348
22	-11.9907	-11.8576	3.3326	3.6561	15.1902	-2.3150	4.6201
23	-12.1439	-11.9597	2.8760	3.9076	14.8357	-1.3815	0.0000
24	-11.7055	-11.6721	3.5560	4.5868	15.2280	-2.6541	3.2249
25	-11.4846	-11.4846	3.7495	3.9435	15.2340	-2.5521	3.5189
26	-11.7319	-11.6179	3.6510	4.1797	15.2689	-2.6827	3.4369
27	-11.7287	-11.5855	3.6602	4.0959	15.2457	-2.6678	3.4930
28	-11.7254	-11.5276	3.6635	4.1089	15.1910	-2.6620	3.5340
29	-12.4065	-10.2737	3.2686	3.2983	13.5423	-2.2046	3.2482
30	-12.0813	-10.4481	3.0142	3.0768	13.4623	-2.2311	4.2274
31	-12.3768	-10.5972	2.8077	2.9543	13.4049	-2.0280	2.6591
32	-12.5368	-10.8560	2.6860	2.7070	13.5420	-1.7526	0.6535
33	-12.1474	-10.5180	2.7007	3.4605	13.2188	-1.5870	2.1876
34	-12.0536	-9.6100	3.6847	3.8896	13.2947	-2.8000	3.2391
35	-11.9374	-9.8750	3.6803	3.7367	13.5554	-2.7111	2.5016
36	-12.3134	-11.9932	0.6884	2.7807	12.6816	0.1121	1.6765
37	-11.5964	-11.3169	1.0501	3.1154	12.3670	-0.2161	1.2637
38	-11.6734	-11.5616	2.2743	3.9726	13.8359	-1.4049	2.3641
39	-12.3273	-12.3273	0.5287	2.5927	12.8560	0.3396	0.9380

40	-12.1284	-11.9959	1.3951	3.2964	13.3910	-0.4991	1.7694
41	-11.9439	-11.5847	1.2011	3.1070	12.7858	-0.3453	1.6190
42	-11.4506	-11.4304	2.6213	3.5059	14.0517	-1.5996	0.6559
43	-10.7567	-10.7216	3.3971	4.1429	14.1186	-2.3824	2.8839
44	-10.6644	-10.6367	3.6099	4.0276	14.2465	-2.3921	2.8693
45	-11.1842	-11.1447	2.4498	3.9633	13.5945	-1.5114	2.7197
46	-11.1131	-10.9953	2.9976	3.4907	13.9929	-2.0144	4.1308
47	-10.7379	-10.7295	3.3492	4.4428	14.0786	-2.3666	2.7335
48	-10.5635	-10.5635	3.4754	3.8578	14.0389	-2.2455	3.0377
49	-11.0642	-11.0334	3.0790	3.4052	14.1124	-2.0769	0.5658
50	-10.7428	-10.6900	3.3666	4.2017	14.0566	-2.3266	2.9363
51	-12.1306	-11.8941	0.3867	2.4213	12.2808	0.4507	1.0603
52	-11.4152	-11.1382	2.0504	3.7835	13.1885	-1.2116	1.9915
53	-11.5205	-11.5205	0.1867	2.4474	11.7072	0.6307	0.0000
54	-11.6111	-10.8511	1.5491	1.9266	12.4002	-0.4372	0.0000
55	-11.7436	-10.0015	2.5298	3.0479	12.5314	-1.3099	0.0000

Table 4. *Ab initio* parameters calculated within the MP2/ 6-311G(d) computational scheme. Energy in eV, dipole moments in debye.

	$E_{\text{HOMO-1}}$	E_{HOMO}	E_{LUMO}	$E_{\text{LUMO+1}}$	$\text{GAP}_{\text{L-H}}$	VEA	μ
1	-12.3145	-12.2432	3.4207	4.6330	15.6640	-2.3414	2.0169
2	-12.7956	-12.4231	2.8926	4.1829	15.3157	-1.5352	1.3567
3	-12.6887	-12.6887	2.2653	3.8349	14.9540	-0.7347	0.0001
4	-12.1385	-12.0661	3.7021	4.3296	15.7682	-2.4713	2.4314
5	-12.2302	-12.0838	3.8188	4.2888	15.9026	-2.9407	0.0000
6	-12.5657	-12.2117	3.1511	4.3239	15.3627	-1.6131	2.1200
7	-12.3874	-12.2332	3.5424	3.9187	15.7755	-2.1506	1.5217
8	-12.4955	-12.3910	2.9533	3.6512	15.3442	-1.4192	1.6950
9	-12.5200	-12.0775	3.4711	3.4975	15.5486	-2.0442	0.0000
10	-12.6274	-12.2568	2.8523	3.3462	15.1091	-1.2735	1.1031
11	-12.6274	-12.2568	2.8523	3.3462	15.1091	-1.2735	1.1031
12	-12.6626	-10.0435	2.9856	3.9369	13.0291	-1.7801	1.1322
13	-12.4125	-10.0258	2.6376	3.7209	12.6634	-1.4436	0.0000
14	-12.7662	-10.0375	3.3184	4.3429	13.3559	-2.1237	0.0000
15	-12.4966	-10.1877	3.3606	4.1446	13.5483	-2.1711	1.8006
16	-11.8868	-11.8220	3.6137	4.4736	15.4357	-2.6913	3.4763
17	-12.0555	-11.8557	4.0178	4.0945	15.8735	-3.1157	2.6737
18	-12.0062	-11.7602	3.3176	4.5394	15.0778	-2.2346	2.2087
19	-12.1287	-12.0408	3.1805	4.0020	15.2212	-1.9873	3.3222
20	-11.7134	-11.6122	3.9114	4.4325	15.5236	-2.9907	2.5987

21	-11.6269	-11.6125	4.0580	4.6912	15.6705	-3.2163	2.4815
22	-11.8168	-11.7869	3.7554	4.3220	15.5423	-2.8571	3.5707
23	-12.0285	-11.7453	4.1182	4.2931	15.8634	-3.1047	0.0000
24	-11.6832	-11.6345	3.8469	4.8156	15.4814	-2.8920	2.4380
25	-11.5746	-11.5746	3.9233	4.5941	15.4980	-3.0902	2.5560
26	-11.7031	-11.5722	3.9263	4.3598	15.4985	-2.9807	2.6117
27	-11.6979	-11.5352	3.9440	4.2550	15.4792	-2.9678	2.6700
28	-11.6927	-11.4772	3.9478	4.2352	15.4251	-2.9546	2.7021
29	-12.3621	-9.7439	3.5671	4.0940	13.3110	-2.2915	2.3368
30	-12.0800	-10.0149	3.3361	3.8175	13.3510	-2.1309	3.0929
31	-12.2310	-10.1158	3.3032	3.6088	13.4190	-2.0721	1.9999
32	-12.3472	-10.2130	3.0795	3.8314	13.2925	-1.7774	0.5362
33	-12.0029	-10.3014	3.4194	3.7636	13.7208	-2.3659	1.6886
34	-12.0840	-9.2619	3.8948	4.0393	13.1567	-2.6302	2.3583
35	-11.9055	-9.7262	3.9584	3.9870	13.6846	-2.6881	1.8311
36	-11.9551	-11.5774	1.5924	3.3530	13.1698	-0.3506	0.7990
37	-11.5439	-11.1159	1.6629	3.6354	12.7787	-0.3872	1.1055
38	-11.4448	-11.4405	2.8890	4.4638	14.3295	-1.7754	1.9010
39	-11.8979	-11.8979	1.6849	3.3168	13.5828	-0.4090	0.2674
40	-11.8644	-11.6726	2.2882	4.0276	13.9608	-1.0451	1.2847
41	-11.7640	-11.3140	1.9402	3.5884	13.2541	-0.6800	1.2019
42	-11.3175	-11.2884	3.3957	4.0131	14.6841	-2.1363	0.1331
43	-10.7575	-10.7289	3.6711	4.2638	14.4000	-2.5361	2.5767
44	-10.7123	-10.6832	3.9274	4.1799	14.6106	-2.5691	2.5058
45	-11.0935	-11.0481	3.0338	4.2959	14.0819	-1.8860	2.1666
46	-11.0533	-10.9490	3.4722	3.8814	14.4212	-2.2523	3.3920
47	-10.7537	-10.7363	3.6041	4.6839	14.3404	-2.5200	2.4247
48	-10.6426	-10.6426	3.8412	3.9372	14.4838	-2.3910	2.6109
49	-10.9956	-10.9686	3.4158	3.8692	14.3845	-2.2843	0.0534
50	-10.7455	-10.6976	3.6319	4.3527	14.3295	-2.4794	2.6193
51	-11.7635	-11.4955	1.3701	2.8852	12.8655	-0.0607	0.2977
52	-11.3052	-11.0712	2.5380	4.3027	13.6092	-1.3889	1.7767
53	-11.2925	-11.2925	0.9064	3.0265	12.1989	0.4890	0.0000
54	-11.5360	-10.6658	2.3195	2.5034	12.9853	-0.6484	0.0000
55	-11.6851	-9.7292	3.1854	3.2874	12.9145	-1.9003	0.0000

Table 5. *Ab initio* parameters calculated using within the b3lyp/aug-cc-pVTZ approach. Energies in eV and dipole moment in debye. Experimental dipole moment values^a are given in parenthesis.

	E_{HOMO}	E_{LUMO}	VEA	μ
1	-8.556	-0.872	0.383	1.677(1.60)
2	-8.685	-1.492	0.263	1.085(1.04)
3	-8.880	-2.125	-0.252	0.000
4	-8.420	-0.676	0.404	2.163(2.06)
5	-8.507	-0.619	0.442	0.000
6	-8.486	-1.373	0.247	1.878(1.755)
7	-8.599	-0.986	0.422	1.252
8	-8.662	-1.549	0.171	1.405
9	-8.245	-1.153	0.422	0.000
10	-8.563	-1.618	0.117	0.869
11	-8.461	-1.675	-0.091	0.000
12	-7.260	-1.159	0.453	0.859
13	-7.230	-1.339	0.560	0.000
14	7.260	-0.998	0.537	0.000
15	-7.462	-1.000	0.452	1.373(1.34)
16	-8.207	-0.583	0.296	3.115
17	-8.223	-0.618	0.354	2.422
18	-8.225	-0.832	0.255	1.958(2.08)
19	-8.429	-1.005	0.186	2.880
20	-8.058	-0.408	0.369	2.415
21	-8.017	-0.357	0.383	2.307
22	-8.179	-0.496	0.296	3.194
23	-8.184	-0.602	0.435	0.000
24	-8.060	-0.444	0.359	2.237
25	-7.984	-0.431	0.354	2.415
26	-8.038	-0.417	0.341	2.432
27	-8.020	-0.408	0.326	2.497
28	-7.997	-0.441	0.289	2.535
29	-7.048	-0.692	0.379	1.935
30	-7.295	-0.960	0.326	2.596
31	-7.369	-0.968	0.354	1.787
32	-7.448	-1.104	0.369	0.640
33	-7.472	-0.695	0.341	1.900
34	-6.336	-0.377	0.379	2.049
35	-7.102	-0.467	0.392	1.537
36	-8.264	-2.551	-0.654	0.435
37	-7.924	-2.369	-0.403	0.865(0.99)
38	-8.132	-1.326	0.256	1.580
39	-8.427	-2.498	-0.632	0.083

40	-8.281	-1.915	-0.043	1.013
41	-8.067	-2.169	-0.327	0.939
42	-8.039	-1.086	0.381	0.082
43	-7.562	-0.598	0.339	2.456
44	-7.500	-0.515	0.358	2.403
45	-7.850	-1.148	0.159	1.923
46	-7.729	-0.823	0.279	3.077
47	-7.547	-0.649	0.313	2.292
48	-7.457	-0.677	0.315	2.540
49	-7.785	-0.789	0.270	0.022
50	-7.544	-0.621	0.307	2.485
51	-8.174	-2.726	-0.900	0.102
52	-9.970	-1.592	0.099	1.479(1.43)
53	-8.044	-3.058	-1.305	0.000
54	-7.583	-1.997	-0.409	0.000
55	-7.117	-1.229	0.297	0.000

Table 6. Five principal components retained from the PCA of eighty-six topostructural indices.

PC	Eigenvalue	Proportion of Variance	Cumulative Variance	Most-highly Correlated TCI
1	54.2983	0.6314	0.6314	W
2	21.2275	0.2468	0.8782	DS1 ₃
3	5.4819	0.0637	0.9420	⁴ χ _{PC}
4	2.2830	0.0265	0.9685	⁶ χ _C
5	1.1342	0.0132	0.9817	⁵ χ _{PC}

Table 7. Twelve principal components retained from the PCA of 106 topochemical indices.

PC	Eigenvalue	Proportion of Variance	Cumulative Variance	Most-highly Correlated TCI
1	37.9045	0.3384	0.3384	AZV ₃
2	20.7565	0.1853	0.5238	² χ ^b
3	13.1183	0.1171	0.6409	Q _v
4	9.7944	0.0875	0.7283	¹ χ ^v
5	6.7769	0.0605	0.7888	⁴ χ ^v _{PC}
6	4.9909	0.0446	0.8334	SdssC

7	3.6443	0.0325	0.8659	SdsCH
8	2.4341	0.0217	0.8877	SdCH ₂
9	2.1676	0.0194	0.9070	⁵ χ _{PC} ^v
10	1.6602	0.0148	0.9219	SssssC
11	1.4927	0.0133	0.9352	H _{MIN}
12	1.3051	0.0117	0.9468	SsF

Table 8. Summary results for the HiQSAR modeling of ARR in *Aspergillus nidulans* for 55 halogenated aliphatic hydrocarbons.

Model	# indep. variables	R ²	R ² _{cv}	s.e.	F
TSI only	3	0.3661	0.2213	1.273	9.82
TCI only	8	0.8370	0.7272	0.6795	29.54
3D only	4	0.8326	0.7683	0.6605	62.19
AM1 only	3	0.4285	0.2671	1.208	12.75
STO-3G only	4	0.4240	0.2673	1.225	9.20
6-31G(d) only	4	0.3645	0.1899	1.287	7.17
6-311G only	4	0.4328	0.2790	1.216	9.54
6-311G* only	4	0.5802	0.4337	1.046	17.28
cc-pVTZ only	1	0.4880	0.4504	1.122	50.51
TSI + TCI	8	0.8606	0.7637	0.6285	35.50
TSI + TCI + 3D	7	0.9014	0.8345	0.5228	61.41
TSI + TCI + 3D + AM1	Same as previous model				
TSI + TCI + 3D + STO-3G	Same as previous model				
TSI + TCI + 3D + 6-31G(d)	Same as previous model				
TSI + TCI + 3D + 6-311G	Same as previous model				
TSI + TCI + 3D + 6-311G(d)	8	0.9065	0.8340	0.5146	55.77
TSI + TCI + 3D + aug-cc-pVTZ	8	0.9120	0.8511	0.4994	59.59

Table 9. Summary results for the HiQSAR modeling of D_{37} in *Aspergillus nidulans* for 55 halogenated aliphatic hydrocarbons.

Model	# indep. variables	R^2	R^2_{cv}	s.e.	F
TSI only	2	0.3659	0.2945	1.243	15.00
TCI only	8	0.8623	0.7749	0.6161	36.00
3D only	8	0.8838	0.6496	0.5660	43.72
AM1 only	3	0.4591	0.3008	1.159	14.43
STO-3G only	3	0.3055	0.1624	1.314	7.48
6-31G(d) only	4	0.4111	0.2458	1.222	8.73
6-311G only	4	0.5140	0.3853	1.110	13.22
6-311G* only	4	0.6318	0.5053	0.9663	21.45
cc-pVTZ only	1	0.5099	0.4787	1.083	55.14
TSI + TCI	7	0.8791	0.8074	0.5710	48.83
TSI + TCI + 3D	<i>Same as previous model</i>				
TSI + TCI + AM1	7	0.8840	0.8121	0.5594	51.17
TSI + TCI + STO-3G	7	0.8724	0.7923	0.5866	45.91
TSI + TCI + 6-31G(d)	7	0.8713	0.7926	0.5893	45.45
TSI + TCI + 6-311G	10	0.9015	0.8283	0.5328	40.26
TSI + TCI + 6-311G(d)	8	0.9056	0.8335	0.5100	55.17
TSI + TCI + aug-cc-pVTZ	8	0.9476	0.9236	0.3800	103.98

Appendix 1.3

Manuscripts on tailored similarity (T-QMSA)

QUANTITATIVE MOLECULAR SIMILARITY ANALYSIS (QMSA) METHODS FOR PROPERTY ESTIMATION: A COMPARISON OF PROPERTY-BASED, ARBITRARY, AND TAILORED SIMILARITY SPACES

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Three classes of arbitrary QMSA methods have been computed using atom pairs, topological indices, and physicochemical properties. Tailored QMSA models have been developed using selected number of TIs chosen by ridge regression. The methods have been applied to the k nearest neighbor (KNN) based estimation of log*P* of two sets of chemicals. Results show that the property-based and tailored QMSA methods are superior to the arbitrary similarity methods in estimating log*P* of both sets of chemicals

Keywords: Quantitative molecular similarity analysis (QMSA); Arbitrary QMSA method; Tailored QMSA method; Atom pairs; Topological indices; Physicochemical properties

INTRODUCTION

Quantitative molecular similarity analysis (QMSA) and quantitative structure-activity relationship (QSAR) models are important tools in modern drug design and the hazard assessment of chemicals [1-8]. QSARs attempt to develop relationships to estimate the physicochemical properties, biological activities, or toxicities of specific classes of chemicals from their experimentally-based properties or calculated molecular descriptors. The problem with the use of QSAR is that these models usually apply only to specific, narrowly defined structural classes of molecules. In many practical cases of hazard estimation an arbitrary candidate chemical cannot be unambiguously

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categorized into a particular class. For example, a molecule with five or ten different functional groups cannot be classified as belonging to any one particular structural class. QSARs based on experimental data, e.g., linear free / solvation energy related (LFER/ LSER) methods, suffer from the additional problem that such data are available for only a small fraction of candidate chemicals [9, 10].

When the applicability of QSAR is in doubt, the method of choice for property/activity/ toxicity estimation is molecular similarity. The tacit assumption underlying the use of molecular similarity is that "similar" molecules usually behave similarly in terms of physicochemical, biomedical, and toxicological processes. Similarity is also an intuitively understood concept so that given a set of chemicals one can pick the most similar pair of them based on one's own criteria of similarity. The problem with such intuitive criteria is that they are ill defined and can vary from time to time; for sets of very complex molecules they will be difficult to come up with. For the analysis of large databases such intuitive methods will either be inadequate or so slow as to be completely impractical.

Various molecular similarity methods have been formulated based on parameters computed directly from molecular structure. Quantum chemical indices [11], substructures, and topological indices [1, 4, 5, 12-30] have frequently been used for this purpose.

Most of the QMSA methods mentioned above can be considered arbitrary similarity methods because they are based on structure spaces, the elements of which are selected without having any necessary relationship with the property of interest. Designers of QMSA methods seem to fall into two major categories. Some have an intuitive notion of the structural attributes that will be useful for the property of interest, while others take a wide variety of structural attributes representing important and diverse aspects of molecular structure. In the latter case, because these arbitrary structural descriptors encompass such a broad range of important structural features, they are expected to be useful in estimating the property of interest through the selection of proper analogs.

To correct the arbitrariness in the QMSA methodology, we recently developed the idea of tailored similarity [14, 30]. In this scheme we begin by selecting the elements of the structure space based on a specific property. The structure space thus created is then used for the selection of analogs and estimation of properties of chemicals from their analogs. It has been found that both for physicochemical and toxicological properties tailored similarity spaces outperformed arbitrary QMSA models.

As an expansion on a previously published study [29], in this paper we have compared three classes of QMSA methods: a) arbitrary QMSA methods based on calculated topological indices

(TIs) and substructures called atom pairs (APs), b) arbitrary QMSA methods based on physicochemical properties, and c) tailored similarity methods based on calculated TIs. These methods have been studied for two sets of chemicals: 1) a relatively homogeneous set of 166 hydrocarbons which are identified as constituents of the jet fuel JP-8 and 2) a structurally diverse subset of 76 chemicals.

MATERIALS AND METHODS

Databases

In this study, we are expanding on a study previously reported in this journal [29], using the same data sets as the original study. One is a set of 166 hydrocarbons, a subset of the constituents of JP-8 identified by GC/MS [31]. Of the 228 identified components, this subset represents the total group for which boiling point, vapor pressure, heat of vaporization, water solubility, adsorption coefficient, and logP were available from the USEPA ASTER (ASsessment Tools for the Evaluation of Risk) system [32]. However, most of the data values available from ASTER were calculated, not experimental values.

The second set is a group of seventy-six diverse compounds that has been used in several earlier studies [17, 28, 29], we will refer to this set as the TSCA set hence forth. This set represents the intersection of a set of about 10,000 chemicals from the TSCA (Toxic Substances Control Act) Inventory [9], physicochemical property data available from ASTER [32], and a database of solvatochromic parameters provided through personal communication with M. Kamlet

The chemical names and physicochemical property data for both sets has been reported previously in this journal [29] and thus will be omitted from the current report.

Calculation of Molecular Descriptors

The molecular descriptors used in this study were calculated using POLLY v.2.3 [33] and Molconn-Z v.3.50 [34]. These descriptors include Wiener number [35], the molecular connectivity (χ) indices as calculated by Randić [36, 37] and Kier and Hall [38], information theoretic indices defined on distance matrices of graphs using the methods of Bonchev and Trinajstić [39] as well as those of Raychaudhury *et al.* [40], parameters defined on the neighborhood complexity of vertices in hydrogen-filled molecular graphs [41-43], Balaban's *J* indices [44-46], the local orthogonal vertex

invariants (LOVIs) [47], kappa shape descriptors [48, 49], and the electrotopological indices of Kier and Hall [50]. More information on the set of molecular descriptors calculated by POLLY has been reported in earlier studies [25, 51, 52]. The two models using atom pairs were developed in our earlier work [29]. More details of the atom pair methodology can be found in that report and others [4, 5, 51].

STATISTICAL METHODS AND COMPUTATION OF INTERMOLECULAR SIMILARITY

Data Reduction

Initially, all TIs were transformed by the natural logarithm of the index plus a constant. For all indices with minimum values greater than negative one, the constant used was one. In all other indices, the constant was determined on a case-by-case basis and was just large enough to make the minimum greater than zero. This rescaling was done since there may be several orders of magnitude difference between some of the molecular descriptors. After this step is completed, we begin data reduction. At this stage any descriptors with zero values for all compounds in the data set, or that are completely correlated with another descriptor, are removed from the descriptor set.

The primary purpose of this study was to compare several methods for selecting descriptors. To this end we have used both the original, limited set of topological indices from the first study and in the current study we have expanded the set to include the LOVI indices and molecular descriptors calculated using Molconn-Z. POLLY v2.3 alone calculates 102 molecular descriptors, far more descriptors than the number of dimensions we want in a similarity space. With the addition of the LOVI and Molconn-Z descriptor sets, our initial set of indices begins with 362 descriptors. Thus, some method is needed to reduce the number of descriptors available for modeling. In this study we make use of two such methods. The arbitrary similarity spaces make use of principal component analysis (PCA) for purposes of data reduction and selection of a small set of topological indices. The tailored similarity approach uses the ridge regression (RR) technique to select an "optimal" set of descriptors. Both of these approaches and their application to descriptor selection are described below.

Principal component analysis (PCA), conducted using the SAS PRINCOMP procedure [53], takes a large set of non-orthogonal variables (descriptors) and transforms them into a like number of completely orthogonal principal components. Each principal component is a linear combination of

the complete set of initial variables. In this manner, we create a set of orthogonal descriptors for use a dimensions within a similarity space. Generally, only a small subset of the PCs is retained for modeling. Eigenvalues are reported for each of the PCs. The first PC explains the greatest amount of the variance in the data and has the largest eigenvalue. Each subsequent PC explains a smaller portion of the remaining data variance and has a likewise reduced eigenvalue. Routinely those PCs with eigenvalues greater than or equal to one are retained, leaving us with a small number of completely orthogonal descriptors that explain the bulk of the variance in our original descriptor set.

This technique can also be used for the selection of a small set of topological indices. In this approach, after construction of the set of PCs, a correlation analysis is used to determine which descriptors are most correlated with each of the principal components. In this manner, one or more descriptors are chosen for each PC with an eigenvalue greater than or equal to one. Reducing our set of hundreds of descriptors to a more manageable set of ten or fifteen. Both of these techniques were used in this study. For a more detailed explanation of this approach, please see a previous study by Basak *et al* [1].

As was mentioned previously, the tailored similarity method makes use of ridge regression (RR) for descriptor selection. RR is a method wherein modeling is conducted using the entire set of descriptors retained after initial data reduction as opposed to subset or principal component regression. This regression method is useful in cases where the descriptors are highly multicollinear and where the number of descriptors is substantially larger than the number of observations [54]. Conceptually, RR can be thought of as recasting the regression as one using the principal components of the predictor variables as new predictors. It differs in that in principal component regression the leading components are retained and used just as in ordinary least squares regression while the trailing components are dropped. RR retains all components, but weights each of them in accordance with the component's eigenvalue and the 'ridging constant' k . More details on the RR method can be found in some of our other papers [14, 55, 56].

One of the by-products of the RR is a ranking of the contribution of the descriptors. The absolute values of this ranking score were used to select the descriptors for development of the tailored similarity spaces. Separate RR studies were conducted for both the set of POLLY indices alone and the combined full set of descriptors for both data sets.

Similarity Measures

Intermolecular similarity was measured using three methods. The first method used Euclidean distance (*ED*) within an *n*-dimensional space to measure intermolecular similarity. *ED* between molecules *i* and *j* is defined as:

$$ED_{ij} = \left[\sum_{k=1}^n (D_{ik} - D_{jk})^2 \right]^{1/2} \quad (1)$$

where *n* equals the number of dimensions (descriptors) used. *D_{ik}* and *D_{jk}* are the data values of the *kth* dimension for molecules *i* and *j*, respectively. This technique for measuring intermolecular similarity was used to develop similarity spaces from the PCs, the sets of descriptors selected from the PCs, and the sets of descriptors selected using RR. The same technique was used for the development of the physicochemical property spaces as has been described previously [29]. The similarity spaces derived from atom pairs uses an associative measure described also described in detail in the previous study.

Analog / K-Nearest Neighbor Selection

Following the quantification of intermolecular similarity of the molecules, analogs or nearest neighbors are determined on the basis of *ED* or the similarity score (*S*) described previously. The *ED* method measures the distance between molecules in the space, thus the lower the value of *ED* the greater the similarity between two molecules. In the case of the AP method, two molecules are considered identical if *S*=1, while they have no atom pairs in common if *S*=0.

Property Estimation

Property estimation was carried out using the *K*-nearest neighbor (KNN) method. For each probe (or query) compound a number (*K*) of similar chemicals, ranging from 1 to 25, are selected and the property of interest is estimated based on the values of these nearest neighbors. In estimating the log*P* of the probe compound, the mean of the log*P* of the *K*-nearest neighbors was used as the estimate.

TABLE I Principal component analysis results for POLLY TIs and the expanded set of descriptors for the 166 JP-8 constituents

<i>POLLY Topological Indices only</i>					
<i>PC</i>	<i>Eigenvalue</i>	<i>% data var. explained</i>	<i>Cumulative % var. explained</i>	<i>Most highly correlated index</i>	
1	31.4795	0.342	0.342	P ₁	0.9433
2	19.3298	0.210	0.552	⁵ χ ^b _{PC}	0.8311
3	11.9527	0.130	0.682	CIC ₀	0.8942
4	8.5428	0.093	0.775	I _{ORB}	0.6179
5	6.2243	0.068	0.843	⁶ χ ^b _{Ch}	0.7149
6	3.8318	0.042	0.884	⁵ χ ^v _C	0.5831
7	2.4620	0.027	0.911	³ χ _{Ch}	0.4797
8	1.7081	0.019	0.930	P ₉	0.4306
9	1.2922	0.014	0.944	P ₁₀	0.3508
10	1.0024	0.011	0.955	O _{ORB}	0.4648
<i>Expanded set of Topological Indices</i>					
<i>PC</i>	<i>Eigenvalue</i>	<i>% data var. explained</i>	<i>Cumulative % var. explained</i>	<i>Most highly correlated index</i>	
1	93.3837	0.421	0.421	DN ² N ₄	0.9935
2	45.8446	0.207	0.627	Phia	-0.9796
3	26.2411	0.118	0.745	² χ ^b	0.8424
4	12.7416	0.057	0.803	IC ₃	0.7474
5	9.3209	0.042	0.845	J ^B	-0.6415
6	6.3087	0.028	0.873	¹⁰ χ	0.5502
7	4.7517	0.021	0.895	SdsCH	0.5365
8	3.9706	0.018	0.912	⁵ χ ^b _C	0.4954
9	2.6602	0.012	0.924	³ χ _{Ch}	-0.5075
10	2.3647	0.011	0.935	⁹ χ ^v _{Ch}	-0.6410
11	1.9136	0.009	0.944	³ χ _{Ch}	0.3557
12	1.6762	0.008	0.951	SHvin	-0.3997
13	1.3773	0.006	0.958	O	0.3681
14	1.1548	0.005	0.963	¹⁰ χ ^v	0.4065
15	1.0759	0.005	0.968	⁶ χ ^b	0.3111

RESULTS

Development of QMSA Models for JP-8

Initial data reduction on the set of POLLY TIs, resulted in the removal of ten TIs, leaving a set of ninety-two descriptors for the JP-8 set. These ninety-two TIs were then subjected to PCA and ten PCs were retained with eigenvalues greater than or equal to one. These PCs (and the index most highly correlated with each PC) are summarized in Table 1. This PCA and the correlation analysis of the PCs with the set of ninety-two TIs gave us two of the three descriptor sets using only the POLLY indices to be used in this study.

The tailored similarity model using only the ninety-two POLLY descriptors was developed using RR. The entire set of descriptors was run through RR and since we had ten PCs, we selected the ten descriptors that contributed the most to the RR based on their t values. The t -values, indicated in Table 2, are model coefficients extracted from the RR procedure and used to rank the TIs from most to least influential based on the absolute value of the regression coefficient.

TABLE II Topological indices used in creating similarity spaces for the 166 JP-8 chemicals

TI	TIs selected from Polly RR		TIs selected from Expanded RR	
	(t-values)		(t-values)	
1	${}^0\chi^b$	(9.23)	${}^0\chi^b$	(16.47)
2	${}^0\chi^v$	(9.05)	${}^0\chi^v$	(16.42)
3	P_1	(-4.17)	Fw	(14.77)
4	I^D	(-4.07)	AZS ₁	(14.22)
5	SIC ₀	(3.55)	W	(14.03)
6	J^B	(3.53)	ANS ₃	(14.00)
7	${}^0\chi$	(3.24)	AZS ₃	(13.31)
8	J	(-3.15)	ANS ₁	(12.19)
9	${}^3\chi^b$	(3.10)	${}^0\chi$	(11.71)
10	I_D^W	(-3.00)	Ka ₁	(11.42)
11			I_D^W	(11.31)
12			ANN ₃	(11.31)
13			DN ² S ₃	(11.29)
14			ANN ₅	(11.14)
15			Q _v	(11.08)

Data reduction on the expanded set of 369 descriptors resulted in the removal of 147 descriptors, leaving a set of 222. PCA on this set resulted in the retention of fifteen PCs and the one TI most correlated with each of the PCs (see Table 1). Following our protocol, a set of the fifteen descriptors with the highest *t*-values were selected by RR (Table 2). Additionally, to examine the importance of the size of the descriptor set versus the utility of the tailoring method, we decided to use the top ten TIs as determined by RR to see how this space would differ from the space using fifteen descriptors. Details of the atom pair and physicochemical modeling were already presented in the earlier study.

FIGURE 1 Plot of KNN estimation of $\log P$ for the JP-8 constituents demonstrating the variation in correlation between the nine methods over values of *K* ranging from 1 to 25.

K-Nearest Neighbor Property Estimation for JP-8

Each similarity space developed above was used in K-nearest neighbor based property estimation for *K* = 1-10, 15, 20, and 25. Correlation analyses were conducted on the property estimates to determine the strength of each of the similarity spaces in estimating $\log P$. Figure 1 presents a plot of the correlation coefficients (*r*) as they vary with *K* for all nine models. Correlation coefficients and standard errors for the POLLY-based spaces are presented in Table 3 and results for the expanded descriptor set models are summarized in Table 4.

TABLE III K-Nearest Neighbor results for estimation of JP-8 logP for the models using only POLLY indices

<i>K</i>	<i>PC Method</i>		<i>TI method</i>		<i>RR method</i>	
	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>
1	0.8219	0.442	0.8330	0.425	0.9305	0.278
2	0.8718	0.374	0.8726	0.372	0.9220	0.296
3	0.8527	0.401	0.8542	0.401	0.9270	0.291
4	0.8488	0.408	0.8622	0.399	0.9279	0.294
5	0.8639	0.393	0.8655	0.400	0.9269	0.298
6	0.8708	0.388	0.8588	0.409	0.9213	0.310
7	0.8789	0.383	0.8641	0.409	0.9219	0.314
8	0.8801	0.384	0.8671	0.411	0.9203	0.321
9	0.8799	0.389	0.8622	0.421	0.9180	0.328
10	0.8800	0.395	0.8587	0.429	0.9104	0.343
15	0.8697	0.427	0.8576	0.464	0.9001	0.369
20	0.8639	0.447	0.8642	0.486	0.8929	0.388
25	0.8662	0.456	0.8629	0.508	0.8831	0.412

TABLE IV K-Nearest Neighbor results for estimation of JP-8 logP for the models using the expanded set of indices

<i>K</i>	<i>PC Method</i>		<i>TI method</i>		<i>RR method</i>	
	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>
1	0.8058	0.459	0.8798	0.361	0.9497	0.238
2	0.8578	0.393	0.8717	0.376	0.9504	0.239
3	0.8575	0.399	0.8638	0.392	0.9438	0.255
4	0.8513	0.409	0.8850	0.371	0.9441	0.260
5	0.8573	0.403	0.8762	0.383	0.9419	0.268
6	0.8632	0.401	0.8600	0.403	0.9420	0.271
7	0.8628	0.404	0.8487	0.419	0.9379	0.278
8	0.8625	0.408	0.8458	0.422	0.9358	0.284
9	0.8578	0.413	0.8511	0.419	0.9356	0.285
10	0.8598	0.413	0.8494	0.423	0.9340	0.290
15	0.8448	0.436	0.8320	0.447	0.9208	0.325
20	0.8272	0.461	0.8247	0.463	0.9230	0.341
25	0.8184	0.479	0.8204	0.478	0.9272	0.360

TABLE V Topological indices used in creating similarity spaces for the 76 industrial chemicals

<i>POLLY Topological Indices only</i>					
<i>PC</i>	<i>Eigenvalue</i>	<i>% data var. explained</i>	<i>Cumulative % var. explained</i>	<i>Most highly correlated index</i>	
1	41.7583	0.469	0.469	$^1\chi$	0.9759
2	14.0440	0.158	0.627	SIC ₃	0.9673
3	9.0400	0.102	0.729	CIC ₁	-0.7444
4	6.2892	0.071	0.799	J	0.8637
5	3.8182	0.043	0.842	$^4\chi_C$	0.7100
6	2.9551	0.033	0.875	P ₈	0.3656
<i>Expanded set of Topological Indices</i>					
<i>PC</i>	<i>Eigenvalue</i>	<i>% data var. explained</i>	<i>Cumulative % var. explained</i>	<i>Most highly correlated index</i>	
1	115.7516	0.469	0.469	DN ² Z ₄	0.9937
2	30.3616	0.123	0.592	ASN ₂	0.9080
3	17.9402	0.073	0.664	J	0.7789
4	16.0951	0.065	0.729	SIC ₁	0.8642
5	9.9801	0.040	0.770	$^8\chi^v$	0.6077
6	7.5558	0.031	0.800	$^4\chi_C$	0.6248
7	5.4580	0.022	0.822	SdO	-0.6203
8	4.7299	0.019	0.842	SsCH ₃	0.6015
9	3.8975	0.016	0.857	$^5\chi_{Ch}$	0.3578
10	3.8378	0.016	0.873	$^5\chi^b_{Ch}$	0.6295
11	3.2325	0.013	0.886	H _{MAX}	-0.3854
12	2.6013	0.011	0.897	SHsNH ₂	0.7109
13	2.4524	0.010	0.907	SHCsatu	-0.5985
14	2.3494	0.010	0.916	SdssC	-0.6674
15	1.9808	0.008	0.924	SsssN	0.3948
16	1.7841	0.007	0.931	SsssCH	-0.4659
17	1.7385	0.007	0.938	StsC	0.3934
18	1.6391	0.007	0.945	SsBr	0.6731
19	1.4685	0.006	0.951	$^{10}\chi_{Ch}$	-0.3286
20	1.3449	0.005	0.956	SHssNH	-0.5603
21	1.2352	0.005	0.961	SaaN	0.6947
22	1.1406	0.005	0.966	SddsN	0.4028

TABLE VI Topological indices used in creating similarity spaces for the 76 industrial chemicals

<i>TI</i>	<i>TIs selected from Polly RR</i>		<i>TIs selected from Expanded RR</i>	
	<i>(t-values)</i>		<i>(t-values)</i>	
1	${}^0\chi^v$	(8.82)	Fw	(13.92)
2	${}^1\chi^v$	(6.73)	AZV ₄	(13.49)
3	${}^2\chi^v$	(6.51)	${}^0\chi^v$	(12.52)
4	${}^3\chi^v$	(5.76)	ANZ ₁	(12.12)
5	${}^3\chi^v_c$	(5.37)	Ka ₁	(11.04)
6	IC ₁	(-5.15)	DN ² 1 ₄	(10.33)
7			W	(10.22)
8			DN ² N ₄	(9.89)
9			G _{max}	(-9.70)
10			SsCl	(9.47)
11			ANS ₁	(9.20)
12			AS1 ₄	(9.14)
13			DN ² Z ₃	(9.14)
14			DN ² S ₃	(8.98)
15			AS1 ₁	(-8.71)
16			P ₀	(8.51)
17			ANN ₃	(8.42)
18			AN1 ₃	(8.39)
19			DN ² S ₁	(8.29)
20			AS1 ₅	(-8.27)
21			DN ² S ₅	(8.08)
22			P ₁	(8.07)

Development of QMSA Models for the TSCA Chemicals

Initial data reduction on the set of POLLY TIs, resulted in the removal of nine TIs, leaving a set of ninety-three descriptors for the TSCA set. PCA on these ninety-three TIs left us with six PCs. These PCs (and the index most highly correlated with each PC) are summarized in Table 5. The six most influential indices from RR were also selected (Table 6).

Data reduction on the expanded set of 369 descriptors resulted in the removal of 122 descriptors, leaving a set of 247. In part, this demonstrates the greater diversity of this set vis-à-vis the JP-8 set. Many of the additional descriptors retained in this analysis were atom-type electrotopological indices that can be viewed as being similar to structural indicator variables. Since many of these structural features were not present in the JP-8 set, the descriptors were discarded.

PCA on this set resulted in the retention of twenty-three PCs and the one TI most correlated with each of the PCs (see Table 5). Unfortunately, the twenty-third PC could not be meaningfully characterized as distinct from the other twenty-two through correlation with the TIs (the first five most correlated TIs were all the first most correlated with one of the other PCs) so it was dropped and we used only the first twenty-two. Following our protocol, a set of the twenty-two descriptors with the highest t -values were selected by RR. These indices and their t -values are presented in Table 6. Additionally, to examine the importance of the size of the descriptor set versus the utility of the tailoring method, we used the top six TIs as determined by RR to see how this space would differ from the space using twenty-two descriptors. Again, details of the atom pair and physicochemical modeling were already presented in the earlier study.

FIGURE 2 Plot of KNN estimation of $\log P$ for the TSCA chemicals demonstrating the variation in correlation between the nine methods over values of K ranging from 1 to 15.

K-Nearest Neighbor Property Estimation for the TSCA Set

Each similarity space developed above was used in K-nearest neighbor based property estimation for $K = 1$ -10, and 15. Due to the smaller size of the set, it was not deemed useful to examine K-nearest neighbors greater than fifteen. Correlation analyses were conducted on the property estimates to determine the strength of each of the similarity spaces in estimating $\log P$. Figure 2 presents a plot of the correlation coefficients (r) as they vary with K for all nine models. Results for

the POLLY only models are summarized in Table 7 and results for the expanded descriptor set models are summarized in Table 8.

TABLE VII *K*-Nearest Neighbor results for estimation of TSCA log*P* for the models using only POLLY indices

<i>K</i>	<i>PC Method</i>		<i>TI method</i>		<i>RR method</i>	
	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>
1	0.7877	0.887	0.6840	1.066	0.8100	0.828
2	0.8213	0.790	0.6846	1.012	0.8358	0.754
3	0.8139	0.804	0.7102	0.962	0.8561	0.704
4	0.8460	0.747	0.7151	0.949	0.8682	0.675
5	0.8451	0.757	0.7148	0.948	0.8813	0.641
6	0.8653	0.734	0.7056	0.961	0.8765	0.653
7	0.8675	0.746	0.6832	0.990	0.8868	0.627
8	0.8596	0.775	0.7125	0.953	0.8907	0.617
9	0.8493	0.822	0.7191	0.944	0.9019	0.592
10	0.8458	0.840	0.7135	0.954	0.9012	0.595
15	0.8278	0.946	0.7336	0.939	0.9055	0.603

TABLE VIII *K*-Nearest Neighbor results for estimation of TSCA log*P* for the models using the expanded set of indices

<i>K</i>	<i>PC Method</i>		<i>TI method</i>		<i>RR method</i>	
	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>	<i>r</i>	<i>se</i>
1	0.8254	0.789	0.7865	0.846	0.9198	0.543
2	0.8411	0.737	0.8413	0.736	0.9185	0.536
3	0.8349	0.746	0.8091	0.803	0.9147	0.548
4	0.8342	0.749	0.8025	0.820	0.9203	0.530
5	0.8515	0.720	0.7985	0.824	0.9279	0.510
6	0.8765	0.687	0.7847	0.846	0.9307	0.509
7	0.8758	0.701	0.7644	0.879	0.9243	0.540
8	0.8704	0.732	0.7573	0.887	0.9206	0.564
9	0.8807	0.740	0.7711	0.867	0.9184	0.579
10	0.8824	0.768	0.7727	0.877	0.9181	0.590
15	0.8359	0.953	0.6641	1.053	0.9279	0.605

FIGURE 3 A closer examination of the overlap in the arbitrary similarity spaces for estimation of $\log P$ for JP-8 in terms of correlation coefficients.

DISCUSSION

The objective of this study was to evaluate the relative effectiveness of tailored versus arbitrary similarity methods in the estimation of properties of chemicals from their selected neighbors.

For the set of 166 JP-8 chemicals, we selected K ($K=1-25$) nearest neighbors by nine different similarity methods used in this paper (Figure 1 and Tables 3 and 4) and used the K -nearest neighbor (KNN) approach to estimate $\log P$. While the method based on atom pairs used the largest number of independent variables, that based on properties has the least number of such variables. Yet it is interesting to note that the AP method gives the weakest estimation of $\log P$ while the property method uses only five independent variables and gives the best estimates. This is probably because of the fact that many atom pair descriptors might not have any significant relationship with the property and their inclusion in the estimation method increases noise instead of information. On the other hand, one of the properties, viz., water solubility, is known to have strong relationship with hydrophobicity [57] while others may be indirectly related. When PCs are used to create the structure spaces, PCs derived from POLLY are lower in number (10) as compared to those derived

from the expanded set of descriptors (15). Yet Figures 1 and 3 show that the KNN $\log P$ estimations based on these two structure spaces are almost identical. This shows that the addition of more independent variables in the model does not necessarily increase the quality of the model. The same is true of the models developed from ten TIs selected from the POLLY indices versus the fifteen chosen from the expanded set.

FIGURE 4 A closer examination of the overlap in the tailored and physicochemical property-derived similarity spaces for estimation of $\log P$ for JP-8 in terms of correlation coefficients.

The situation is different with the similarity spaces tailored to the $\log P$ using the RR method (Figures 1 and 4). The parameter space developed from ten selected POLLY indices outperforms the methods based on APs, PCs derived from POLLY, and the expanded set of indices. When we selected ten indices from the expanded set of independent variables selected by RR, there was not much improvement in model quality. However, an increase in the number of independent variables to fifteen for the expanded made significant improvement. In fact, the last model and the QMSA estimates using the experimental property data are of similar quality.

A perusal of results derived for the seventy-six diverse chemicals (Figure 2 and Tables 7 and 8) shows that QMSA models based on six PCs and TIs from POLLY, PCs and TIs from the expanded set of indices and APs do not perform as well as the tailored similarity methods. A comparison of

estimates using six TIs in the arbitrary method and the RR method (Figure 5) shows that even at this level the RR method outperforms the arbitrary method substantially. The quality of the tailored method using the same number of TIs (6) goes up substantially when the indices are selected from the expanded set of independent variables. Presumably this is because the RR method selects the most relevant six indices related to the property. An increase in the number of independent variables from six to twenty-two descriptors makes another improvement in model quality (Figures 4 and 6). In fact, this model is almost as good as the property-based one. Using the same number of parameters (22) in the arbitrary QMSA techniques, the estimated $\log P$ values were inferior to the tailored similarity method.

FIGURE 5 A closer examination of the overlap in the similarity spaces using a limited number of TIs and the property-based and atom pair based spaces for estimation of $\log P$ for TSCA chemicals in terms of correlation coefficients.

In conclusion, the results reported in this paper for one relatively homogeneous and one structurally diverse set of chemicals show that of the two classes of similarity methods, *viz.*, arbitrary and tailored QMSA methods, the latter generally outperforms the former. Somewhat surprisingly, the tailored similarity spaces perform nearly as well as physicochemical spaces, results that until now have not been seen using molecular descriptors in the creation of similarity spaces.

Further studies of the relative utility of these techniques are needed to determine their relative utility in property/ activity/ toxicity estimation and analog selection.

FIGURE 6 A closer examination of the overlap in the similarity spaces using the expanded set of TIs compared to the property-based and atom pair based spaces for estimation of $\log P$ for TSCA chemicals in terms of correlation coefficients.

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QUANTITATIVE MOLECULAR SIMILARITY METHODS IN THE PROPERTY/ TOXICITY ESTIMATION OF CHEMICALS: A COMPARISON OF ARBITRARY VERSUS TAILORED SIMILARITY SPACES

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Quantitative molecular similarity analysis (QMSA) methods based on structure spaces using a variety of calculated molecular descriptors and experimental properties have been used for selection of analogs and estimation of a variety of properties pertaining to chemistry, drug discovery, and environmental toxicology. The set of descriptors, orthogonalized or not, have been selected either arbitrarily or based on some intuitive notion of their association to the property of interest. In this study we have developed a method of 'tailoring' the QMSA method to a particular property of interest through the use of indices which are strongly correlated with the property instead of using an arbitrary set of parameters. Comparative studies of the tailored vis-à-vis two non-tailored (arbitrary) similarity spaces based on principal components (PCs) derived from topological indices show that the tailored method outperforms the two non-tailored techniques in the QMSA based estimation of hydrophobicity (logP, octanol/water) for a set of 213 compounds and Ames' mutagenicity of a group of 95 aromatic and heteroaromatic amines.

Keywords: Quantitative molecular similarity analysis (QMSA); Tailored QMSA method; Arbitrary QMSA method; Hydrophobicity; Mutagenicity

INTRODUCTION

The modern drug discovery process and the regulation of chemicals for the assessment of their potential deleterious effects on human and environmental health are both heavily dependent on the availability of a number of physicochemical, biochemical, and toxicological properties for the candidate chemicals. A partial list of such properties is presented in Table 1. Ideally, experimental data on bioactivity, various toxic effects, metabolic profile, environmental fate, and distribution should be available for all chemicals. However, such data are available only for a fraction of the candidate chemicals. In the area of

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ecotoxicology, the Toxic Substances Control Act (TSCA) Inventory currently includes over 81,000 chemicals and the list is growing by about 3,000 new submissions per year via the premanufacture notification (PMN) process. Few of the existing TSCA chemicals have any experimental toxicity, ecotoxicity, environmental fate, or physicochemical data necessary for hazard assessment. This data is also missing for many of the PMN chemicals. No physicochemical property data whatsoever is available for at least 50% of the chemicals currently listed in the TSCA Inventory. And, of the other 50% of the Inventory chemicals that do have some available data, fewer than 15% have available mutagenicity data, just over 12,000 out of 81,000 chemicals. And only about 6% of these chemicals, less than 5,000, have ecotoxicological and environmental fate data [1]. In the realm of drug discovery, after a lead chemical is identified, large numbers of analogs are synthesized in order to find a compound with an acceptable therapeutic profile and few, if any, undesirable side effects. As a result, modern combinatorial chemistry is producing large real and virtual combinatorial libraries of chemicals, most of which do not contain any experimental data for their evaluation.

TABLE I Partial list of properties necessary for risk assessment of chemical

Physicochemical	Biological
Molar Volume	Receptor Binding (K_D)
Boiling Point	Michaelis Constant (K_m)
Melting Point	Inhibitor Constant (K_i)
Vapor Pressure	Biodegradation
Aqueous Solubility	Bioconcentration
Dissociation Constant (pKa)	Alkylation Profile
Reactivity (Electrophile)	Metabolic Profile
Partition Coefficient	Mutagenicity
Octanol-Water, Air-Water, Sediment-Water,	Carcinogenicity
Tissue-Air, Blood-Air	Chronic Toxicity
	Acute Toxicity
	LD ₅₀ , LC ₅₀ , EC ₅₀

A perusal of the above conditions indicates that in the foreseeable future the regulation of chemicals for human and environmental health, as well as evaluation of chemicals for the discovery of life saving drugs, will need to be carried out with little or none of the experimental data necessary. A valid alternative under these circumstances has been the use of estimated property/ bioactivity/ toxicity values that are computed using parameters calculated directly from the chemical's structure. These theoretical descriptors of molecular structure can be used in both quantitative structure activity relationship (QSAR) and quantitative molecular similarity relationship (QMSA) models.

QSAR is based on the idea that the structure of a molecule is the principal determinant of its physicochemical, toxicological, and biomedical properties [2-4]. Various types of calculated parameters, viz., topological [5-7], substructural [8, 9], geometrical [10], and quantum chemical parameters [11-16], have been used in the development of QSARs. Linear free energy related (LFER) and linear solvation energy related (LSER) parameters, as well as physicochemical properties such as the various types of partition coefficients, have been used in QSARs pertaining to drug discovery and environmental toxicology [2, 17]. The problem with the use of LFER and LSER parameters and experimental physicochemical properties in QSARs for toxicity estimation is that such properties are not available for many chemicals. Another problem with the use of QSARs is that these models usually work most effectively for sets of molecules which are 'congeneric,' i.e., belong to a narrow class either by structural analogy or having the same biochemical mechanism of action. The United States Environmental Protection Agency (USEPA) currently has over 300 class-specific QSARs for various subsets of the TSCA Inventory [18]. But these models cover only a small fraction of the 81,000 substances in the Inventory.

Often it is difficult to unambiguously classify a molecule into a particular structural class. This happens when a molecule possesses a complex structure, e.g., contains many functional groups. In such circumstances, one practical alternative for hazard assessment of a chemical is to select a subset of chemicals that are structurally analogous to the candidate chemical and use the properties of these selected analogs in assessing the hazard posed by the chemical of interest. This can be done either intuitively, based on the subjective experience of the risk assessor, or it can be carried out using computational methods that are fast and objective. The intuitive selection of chemical analogs is generally based on a set of rules or unspoken notions developed through the practitioner's experience of structural attributes that have been found to be associated with some kind of activity or toxicity. On the other hand, the evaluation of a large number of chemicals through the use of their selected analogs necessitates the use of methods where the descriptors used in analog selection are rapidly computed directly from the molecular structure in an unambiguous manner.

Our research group has been involved in the development of QMSA methods based on computed theoretical molecular descriptors for the past two decades. These methods have used topological indices, atom pairs, and physicochemical properties in the creation of structure spaces and the selection of analogs. Specifically, we have used two major approaches to quantifying molecular similarity. The first method uses Euclidean distance (ED) within an n -dimensional space. For these studies we have used smaller sets of topological indices selected through methods such as variable clustering (VC) or principal component analysis (PCA). In using VC to select a set of indices we have taken the one TI most correlated with each cluster, while in using PCA for index selection we have taken the one TI most

correlated with each principal component (PC) having an eigenvalue greater than or equal to zero [19-22]. Additionally, the clusters from VC method and the PCs from PCA can be used as new descriptors within a ED space. In this way we avoid some of the issues of intercorrelation between the individual TIs by creating completely orthogonal (PCs) [22-34] or nearly orthogonal (VCs) [19-21] descriptors derived from the TIs. ED has also been used in the construction of physicochemical property-based similarity spaces [32, 34, 35]. The second method employs a Tanimoto-type association coefficient to compare the atom pairs within two molecules as a measure of their similarity/dissimilarity [19-22, 24-27, 29, 31, 32, 34, 36, 37]. We have carried out comparative studies on the relative utility of experimental property-based and molecular descriptor-based similarity spaces in the selection of analogs [25, 32] and the estimation of properties of chemicals from their selected analogs in these spaces [32, 34, 35]. The theoretical spaces have been found to behave in a manner analogous to those derived from experimental properties in some limited number of cases. The advantage of theoretical structure spaces is that they can be used for any arbitrary database of chemicals including libraries comprised of molecules that have never been synthesized.

In our earlier QMSA studies, we represented a molecule by a set of n calculated descriptors, viz, topological indices and atom pairs. A chemical is then represented as an object in the n -dimensional vector space. The pair-wise similarity/ dissimilarity of molecule is then quantified using some kind of distance function or association coefficient. These approaches have yielded reasonable results in the selection of analogs and prediction of properties of chemicals from their selected neighbors using the k -nearest neighbor (KNN) approach. In many of these approaches it is possible that the elements of the vector (the descriptors) are mutually correlated to some extent so that we are using redundant information. One approach to correct this problem has been to extract a set of orthogonal or minimally correlated variables derived from the set of original predictors using techniques such as principal component analysis or variable clustering. Such variables are orthogonal, or nearly so, but have no intrinsic relationship with the property that we are interested in estimating using the particular QMSA method. Such similarity spaces may be termed "arbitrary" similarity spaces. One may use the broadest category of descriptors in creating such spaces and the descriptors may be related to the property only by chance or intuitive association. On the other hand, our major interest in the selection of analogs is the prediction of properties.

In this paper we have developed a method for the design of similarity spaces from molecular descriptors which are "tailored" to a particular property. We have created such tailored spaces for two sets of molecules: a) a group of 213 compounds for which we are interested in estimating $\log P$ (octanol/water partition coefficient) and b) a collection of ninety-five aromatic and heteroaromatic amines for which the interest was to predict Ames' mutagenicity. In this paper we have presented the utility of our newly

developed tailored QMSA method vis-à-vis arbitrary QMSA methods in the similarity-based estimation of log P and mutagenicity.

MATERIALS AND METHODS

Log P Database

The log P set consists of 213 diverse compounds used in several earlier studies [33, 38]. Measured values of log P were obtained from CLOGP [39], as this set is a subset of the STARLIST chemical database. In this study, as in the earlier studies, we have used only chemicals where HB₁ was equal to zero (HB₁ is a measure of the hydrogen bonding potential of a chemical). Therefore, none of the chemicals have available hydrogen bonding centers, creating a more homogeneous group of chemicals and a more densely packed similarity space. Also, the chemicals were selected such that their log P values fall within the range of -2 to 5.5, since actual measurements for log P beyond this range have been shown to be problematic [40]. It should be noted that six compounds included in the earliest study have been excluded from this study. All six of these compounds were excluded because they consist of only two non-hydrogen atoms and the triplet indices cannot be calculated for molecules with fewer than three non-hydrogen atoms. The chemicals used in this study and their log P values from CLOGP are reported in Table 2.

Mutagenicity Database

The mutagenicity data set, a set of 95 aromatic and heteroaromatic amines, was previously collected from the literature by Debnath *et al.* [41], and has been used to study mutagenic potency in a number of our earlier studies [13, 20, 21, 42, 43]. The mutagenic activities of these compounds in *S. typhimurium* TA98 + S9 microsomal preparation are expressed as the mutation rate, ln(R), in natural logarithm (revertants/nmol). Table 3 lists the compounds included in this study and their experimentally measured mutation rates.

Calculation of Molecular Descriptors

The first set of 102 TIs used in this study include the Wiener number [44], molecular connectivity indices as calculated by Randić [45] and Kier and Hall [5, 46], frequency of path lengths of varying size, information theoretic indices defined on distance matrices of graphs using the methods of Bonchev and Trinajstić [47] as well as those of Raychaudhury *et al.* [48], parameters defined on the neighborhood

TABLE II List of the 213 STARLIST chemicals included in this study and their experimental and estimated values for $\log P$

ID#	Compound name	LogP (exp.)	Estimated logP		
			PC ($k = 3$)	TI/PC ($k = 8$)	TI/RR ($k = 2$)
1	1,4-dimethylnaphthalene	4.37	4.35	4.41	4.32
2	cyclopropane	1.72	2.75	2.57	1.61
3	3,4-dimethylchlorobenzene	3.82	3.65	3.50	3.60
4	2,2-diphenyl-1,1,1-trichloroethane	4.87	5.13	3.85	5.45
5	2,6-dimethylnaphthalene	4.31	4.38	4.41	4.42
6	hexafluoroethane	2.00	3.06	2.26	3.10
7	1-iodoheptane	4.70	4.38	3.17	4.47
8	allylbromide	1.79	2.14	2.85	2.50
9	1,5-dimethylnaphthalene	4.38	4.34	4.41	4.32
10	1,8-dimethylnaphthalene	4.26	4.38	4.42	4.38
11	1,2,3-trichlorobenzene	4.05	4.39	4.13	4.09
12	2-ethylthiophene	2.87	2.50	2.62	2.91
14	γ -phenylpropylfluoride	2.95	3.59	3.35	3.69
15	iodobenzene	3.25	3.55	3.28	2.93
16	1-methylpentachlorocyclohexane	4.04	3.73	3.14	3.63
18	2,3'-pcb	5.02	5.19	5.08	5.13
19	cyclopentane	3.00	2.81	2.75	2.15
20	ethylchloride	1.43	1.88	2.04	1.33
21	2-phenylthiophene	3.74	2.92	2.57	3.87
22	trichlorofluoromethane	2.53	1.89	2.40	2.80
23	fluoroform	0.64	1.13	1.37	0.92
24	dimethyldisulfide	1.77	2.11	2.35	2.03
25	propane	2.36	2.36	2.25	1.67
26	hexamethylbenzene	5.11	4.22	3.98	4.79
27	butanethiol	2.28	2.40	2.40	3.07
28	diethylsulfide	1.95	2.68	2.44	2.03
29	cyclohexane	3.44	2.66	3.50	2.60
30	diphenyldisulfide	4.41	4.46	4.84	4.12
31	<i>m</i> -fluorobenzylchloride	2.77	3.02	3.42	2.63
32	1-chloropropane	2.04	2.41	2.05	1.85
33	2,4-dichlorobenzylchloride	3.82	3.77	3.29	3.25
34	<i>m</i> -chlorotoluene	3.28	3.66	3.59	3.38
35	butane	2.89	3.09	2.35	2.10
36	1,2,3-trimethylbenzene	3.66	4.02	3.78	3.60
37	1,1-difluoroethylene	1.24	0.82	2.70	2.17
38	1-chlorobutane	2.64	2.32	2.31	2.29
39	2,3-dibromothiophene	3.53	2.64	3.08	3.23
40	pentafluorethylbenzene	3.36	2.61	2.82	3.85
41	1,2,4,5-tetrabromobenzene	5.13	3.98	3.49	4.87
42	<i>o</i> -dichlorobenzene	3.38	3.50	3.41	3.51
43	1,2,3,4-tetrachlorobenzene	4.64	4.71	4.26	4.87
44	tribromoethene	3.20	3.06	3.60	2.79
45	pentane	3.39	3.13	2.37	2.52

TABLE II (Continued)

ID#	Compound name	LogP (exp.)	Estimated logP		
			PC (k = 3)	TI/PC (k = 8)	TI/RR (k = 2)
46	isobutane	2.76	2.88	3.18	2.24
47	mirex	5.28	4.52	4.78	5.15
48	1,3-dichlorobenzene	3.60	3.42	3.38	3.45
49	1,2-dimethylnaphthalene	4.31	4.24	4.41	4.40
50	2-ethylnaphthalene	4.38	4.06	4.34	4.36
51	cycloheptatriene	2.63	2.66	2.88	2.50
52	3-chlorobiphenyl	4.58	4.70	4.82	4.50
53	3-ethylthiophene	2.82	2.51	2.63	2.93
54	1,3,5-tribromobenzene	4.51	4.19	3.56	4.09
55	β -phenylethylchloride	2.95	2.86	3.40	3.46
56	acenaphthene	3.92	3.91	3.92	4.32
57	<i>m</i> -dibromobenzene	3.75	3.18	3.66	3.72
58	dichlorodifluoromethane	2.16	2.01	2.47	2.20
59	toluene	2.73	3.16	3.36	2.68
60	anthracene	4.45	4.28	4.03	4.36
61	hexachlorocyclopentadiene	5.04	4.78	4.32	4.87
62	3-phenyl-1-chloropropane	3.55	3.39	3.50	3.39
63	bibenzyl	4.79	4.49	3.97	4.96
64	1-chloroheptane	4.15	3.50	3.23	2.86
65	2,4-dichlorotoluene	4.24	3.66	3.47	4.22
66	1,1-dichloroethane	1.79	2.00	2.09	1.94
67	(β)-benzothiophene	3.12	3.49	2.85	3.05
68	2-bromothiophene	2.75	2.90	2.72	2.58
69	chlorodifluoromethane	1.08	0.98	1.31	1.15
70	pentachlorobenzene	5.17	4.54	4.62	4.80
71	9,10-dihydroanthracene	4.25	4.64	4.07	4.46
72	1,3-(bis-chloromethyl)benzene	2.72	2.93	3.43	3.39
73	chlorobenzene	2.84	3.08	3.26	2.63
74	1,2,4-trichlorobenzene	4.02	4.71	4.14	4.10
75	2,2',6-pcb	5.48	5.30	5.16	5.39
76	2-butyne	1.46	3.17	2.60	2.20
77	azulene	3.20	3.33	3.82	3.16
78	trifluoromethylthiobenzene	3.57	3.09	3.34	4.06
79	2,5-pcb	5.16	5.15	5.07	4.96
80	1,2,3-trichlorocyclohexene(34)	2.84	3.56	3.06	2.77
81	biphenyl	4.09	4.02	4.78	4.35
82	<i>p</i> -xylene	3.15	3.25	3.58	3.27
84	thiophenol	2.52	2.91	2.88	2.79
85	bromotrifluoromethane	1.86	2.11	2.41	2.35
86	9-methylantracene	5.07	4.37	4.25	4.95
87	trichloroethylene	2.42	2.05	1.89	2.29
88	1,4-dimethyltetrachlorocyclohexane	4.40	3.61	3.02	4.01
89	propylene	1.77	2.37	2.42	1.91
90	cyclohexene	2.86	2.64	2.62	2.96

TABLE II (Continued)

ID#	Compound name	LogP (exp.)	Estimated logP		
			PC (k = 3)	TI/PC (k = 8)	TI/RR (k = 2)
91	methylthiobenzene	2.74	3.30	3.38	3.06
93	γ -phenylpropyl iodide	3.90	3.89	3.51	3.99
94	2,3,4'-pcb	5.42	5.24	5.17	5.39
95	fluoropentachlorocyclohexane	3.19	3.77	3.34	3.66
96	1,2,3,5-tetrachlorobenzene	4.92	4.62	4.23	4.73
97	2,2'-pcb	4.90	5.19	5.24	5.05
98	1-butene	2.40	2.62	3.10	2.18
99	1,3-dimethylnaphthalene	4.42	4.20	4.40	4.38
100	1,7-dimethylnaphthalene	4.44	4.37	4.40	4.37
101	1-methylnaphthalene	3.87	4.18	4.40	3.80
102	2,6-pcb	4.93	5.18	5.23	5.03
103	α -bromotoluene	2.92	3.28	3.59	3.56
104	2,2',3'-trichlorobiphenyl	5.31	5.31	5.19	5.48
105	hexafluorobenzene	2.22	3.00	4.48	3.47
106	3-bromothiophene	2.62	2.94	2.73	2.65
107	1,2,3,5-tetramethylbenzene	4.17	4.11	4.09	4.06
108	halothane	2.30	2.33	2.58	2.36
109	2,4,6-pcb	5.47	5.17	5.17	5.40
110	1,1-dichloroethylene	2.13	1.89	3.11	2.55
111	<i>o</i> -dibromobenzene	3.64	4.02	3.67	3.77
112	1,2,4,5-tetramethylbenzene	4.00	3.56	4.11	4.14
113	1-hexene	3.39	3.65	3.83	3.61
114	neopentane	3.11	3.02	3.23	2.51
115	chloroform	1.97	1.75	1.43	1.67
116	1-fluorobutane	2.58	2.34	2.32	2.32
117	pyrene	4.88	4.66	4.12	5.28
118	1,1-dichloro-2,2-diphenylethane	4.51	4.84	3.52	5.15
119	isobutylene	2.34	2.14	3.16	2.45
120	diphenylmethane	4.14	4.56	4.00	4.60
121	isopropylbenzene	3.66	3.48	3.47	3.63
122	naphthalene	3.30	4.33	3.81	3.11
123	1-heptene	3.99	4.37	3.88	3.48
124	2,2-dimethylbutane	3.82	3.69	3.29	3.63
125	1-fluoropentane	2.33	3.12	2.53	2.85
126	<i>o</i> -xylene	3.12	3.34	3.53	3.31
127	ethylbenzene	3.15	3.37	3.44	3.16
128	trichloromethylthiobenzene	3.78	4.21	4.42	4.81
129	thiophene	1.81	2.40	2.75	2.74
130	bromochloromethane	1.41	1.48	1.44	1.34
131	1,2-dichlorotetrafluoroethane	2.82	2.55	2.35	2.69
132	2-chlorobiphenyl	4.38	4.76	4.97	4.60
133	2,4'-dichlorobiphenyl	5.10	5.17	4.98	5.09
134	1,3,5-trichlorobenzene	4.15	3.91	4.12	4.04
135	1-octene	4.57	4.18	3.81	4.53

TABLE II (Continued)

ID#	Compound name	LogP (exp.)	Estimated logP		
			PC (k = 3)	TI/PC (k = 8)	TI/RR (k = 2)
137	phenylethylsulfide	3.20	3.40	3.52	3.26
138	1-ethyl-2-methylbenzene	3.53	3.75	3.53	3.54
139	propylbenzene	3.72	3.69	3.42	3.45
140	indane	3.18	3.67	3.55	3.02
141	2-chloropropane	1.90	2.17	2.37	1.92
142	phenylazide	2.59	2.90	3.51	3.48
143	2,4-dibromotetrachlorocyclohexane	3.98	3.75	3.46	4.22
144	tetrachloroethylene	3.40	4.00	4.07	3.84
145	1-nonene	5.15	3.98	3.60	4.31
146	2,3-dimethylbutane	3.85	3.01	3.09	3.61
147	dichlorofluoromethane	1.55	1.27	1.48	1.73
148	1,1,2,2-tetrachloroethane	2.39	1.97	2.14	2.32
149	1,2,4-trimethylbenzene	3.78	3.79	3.76	3.54
150	fluorobenzene	2.27	2.99	3.33	2.68
151	butylbenzene	4.26	3.64	3.33	3.81
152	ethylbromide	1.61	1.69	2.06	1.79
153	tetrafluoromethane	1.18	1.89	2.28	1.91
154	<i>p</i> -cymene	4.10	3.83	3.44	4.06
155	<i>p</i> -chlorotoluene	3.33	3.80	3.45	3.40
156	1-bromopropane	2.10	2.72	2.86	2.34
157	bromocyclohexane	3.20	3.00	3.55	3.04
158	2-methylthiophene	2.33	2.68	2.69	2.44
159	diphenylsulfide	4.45	4.21	4.77	4.10
160	1,2,4,5-tetrachlorobenzene	4.82	4.10	4.24	4.78
161	1,1,1-trichloroethane	2.49	2.82	2.66	2.68
162	<i>p</i> -dichlorobenzene	3.52	4.12	3.39	3.47
163	1-bromobutane	2.75	3.09	3.16	2.84
164	<i>p</i> -chlorobiphenyl	4.61	4.62	4.82	4.48
165	cyclopropylbenzene	3.27	2.98	3.40	3.05
166	2,6-dichlorotoluene	4.29	3.80	3.34	4.15
167	allene	1.45	2.03	2.59	2.07
168	β -phenylethylbromide	3.09	3.45	3.23	3.69
169	1,3-butadiene	1.99	2.61	2.45	1.93
170	2-chlorothiophene	2.54	2.57	2.66	2.34
171	1-bromopentane	3.37	3.64	3.21	3.40
172	γ -phenylpropylbromide	3.72	3.42	3.15	4.08
173	1,3-cyclohexadiene	2.47	2.70	2.67	2.58
174	pentamethylbenzene	4.56	3.98	4.04	5.11
175	<i>p</i> -dibromobenzene	3.79	3.97	3.65	3.70
176	1,4-pentadiene	2.48	2.59	2.70	2.84
178	1,1-difluoroethane	0.75	1.09	1.71	1.32
179	1-bromohexane	3.80	4.21	3.39	3.89
180	<i>m</i> -xylene	3.20	3.31	3.57	3.14
181	dibenzothiophene	4.38	3.74	2.93	4.28

TABLE II (Continued)

ID#	Compound name	LogP (exp.)	Estimated logP		
			PC (k = 3)	TI/PC (k = 8)	TI/RR (k = 2)
182	ethyl iodide	2.00	1.71	2.68	1.59
183	trifluoromethylbenzene	3.01	3.13	3.26	4.11
184	2,3,6-trimethylnaphthalene	4.73	4.39	4.36	4.48
185	difluoromethane	0.20	1.03	1.27	1.34
186	1,2,4-trifluorobenzene	2.52	2.68	3.45	3.13
187	bromobenzene	2.99	3.44	3.58	2.85
188	hexachloro-1,3-butadiene	4.78	4.40	4.44	5.00
189	vinylbromide	1.57	1.60	2.38	1.99
190	<i>o</i> -chlorotoluene	3.42	3.78	3.57	3.33
191	α -chlorotoluene	2.30	3.29	3.14	2.86
192	1,4-cyclohexadiene	2.30	2.76	2.69	2.67
193	1-bromoheptane	4.36	4.02	3.39	4.64
194	styrene	2.95	3.04	2.82	3.16
195	chlorotrifluoromethane	1.65	2.18	2.32	2.01
196	(dimethyl)phenylphosphine	2.57	3.35	3.36	4.20
197	cycloocta-1,5-diene	3.16	2.54	2.72	3.24
198	tetrachlorocyclohexane	2.82	4.14	2.85	2.78
199	1-bromooctane	4.89	3.84	3.50	4.53
200	2-methylnaphthalene	3.86	4.22	4.40	3.81
201	3-methylthiophene	2.34	2.67	2.69	2.44
202	methylenechloride	1.25	1.44	1.39	1.42
203	hexachlorobenzene	5.31	4.33	4.28	5.14
204	indene	2.92	3.49	2.76	3.15
205	tert-butylbenzene	4.11	3.85	3.41	4.05
206	1,2-dichloroethane	1.48	2.00	1.49	1.76
207	1,3,5-trimethylbenzene	3.42	3.42	3.81	3.72
208	phenanthrene	4.46	4.27	4.03	4.35
209	benzene	2.13	3.32	2.88	2.39
210	3,3,3-trifluoropropylbenzene	3.31	3.18	3.53	4.48
211	α -(2,2,2-trichloroethyl)styrene	4.56	3.96	3.59	4.92
212	2,3-dimethylnaphthalene	4.40	4.35	4.40	4.43
213	1,3-dichloropropane	2.00	2.05	2.02	2.50
214	1,2,3,4-tetramethylbenzene	4.11	4.13	4.10	4.09
215	stilbene-t	4.81	4.34	3.57	4.95
216	fluorene	4.18	3.83	3.90	4.38
217	2-fluoro-3-bromotetrachlorocyclohexane	3.28	3.74	3.37	3.62
218	allylbenzene	3.23	3.05	3.02	3.16
219	carbontetrachloride	2.83	2.71	3.27	2.51

TABLE III Observed and estimated mutagenic potency [Ln(revertants/nmol)] for ninety-five aromatic and heteroaromatic amines

ID#	Compound	Ln(R)(exp.)	Estimated Ln(R)		
			PC (<i>k</i> = 4)	TI/PC (<i>k</i> = 4)	TI/RR (<i>k</i> = 3)
1	2-bromo-7-aminofluorene	2.62	2.09	0.17	0.59
2	2-methoxy-5-methylaniline (<i>p</i> -cresidine)	-2.05	-2.11	-1.54	-2.35
3	5-aminoquinoline	-2.00	-1.89	-1.74	-2.32
4	4-ethoxyaniline (<i>p</i> -phenetidine)	-2.30	-1.95	-1.48	-2.34
5	1-aminonaphthalene	-0.60	1.93	1.93	-1.03
6	4-aminofluorene	1.13	2.70	2.01	1.08
7	2-aminoanthracene	2.62	2.60	2.07	2.47
8	7-aminofluoranthene	2.88	3.34	2.95	3.46
9	8-aminoquinoline	-1.14	-2.10	-1.96	-2.60
10	1,7-diaminophenazine	0.75	0.45	0.44	1.14
11	2-aminonaphthalene	-0.67	0.10	-1.98	-1.00
12	4-aminopyrene	3.16	1.83	2.13	2.97
13	3-amino-3'-nitrobiphenyl	-0.55	0.78	-0.38	-0.94
14	2,4,5-trimethylaniline	-1.32	-1.81	-1.81	-1.74
15	3-aminofluorene	0.89	1.33	1.35	1.16
16	3,3'-dichlorobenzidine	0.81	-0.49	-0.14	0.30
17	2,4-dimethylaniline (2,4-xylidine)	-2.22	-1.59	-1.59	-1.73
18	2,7-diaminofluorene	0.48	0.96	0.47	0.35
19	3-aminofluoranthene	3.31	2.09	2.09	2.92
20	2-aminofluorene	1.93	1.07	1.09	0.82
21	2-amino-4'-nitrobiphenyl	-0.62	0.22	0.22	-0.79
22	4-aminobiphenyl	-0.14	-0.33	-0.55	-0.27
23	3-methoxy-4-methylaniline (<i>o</i> -cresidine)	-1.96	-1.95	-1.65	-2.38
24	2-aminocarbazole	0.60	1.00	1.42	1.19
25	2-amino-5-nitrophenol	-2.52	-1.45	-1.54	-2.44
26	2,2'-diaminobiphenyl	-1.52	0.62	0.86	-0.89
27	2-hydroxy-7-aminofluorene	0.41	1.04	0.52	1.32
28	1-aminophenanthrene	2.38	1.96	0.98	3.07
29	2,5-dimethylaniline (2,5-xylidine)	-2.40	-1.54	-1.54	-1.34
30	4-amino-2'-nitrobiphenyl	-0.92	-0.12	-0.24	-0.94
31	2-amino-4-methylphenol	-2.10	-2.40	-2.30	-2.58
32	2-aminophenazine	0.55	1.56	-1.74	1.26
33	4-aminophenylsulfide	0.31	0.12	0.32	0.15
34	2,4-dinitroaniline	-2.00	-0.61	-1.62	-1.49
35	2,4-diaminoisopropylbenzene	-3.00	-1.94	-1.30	-2.41
36	2,4-difluoroaniline	-2.70	-1.71	-2.31	-2.70
37	4,4'-methylenedianiline	-1.60	-0.37	-0.65	-1.53
38	3,3'-dimethylbenzidine	0.01	-1.42	-1.55	1.45
39	2-aminofluoranthene	3.23	3.25	2.90	3.34
40	2-amino-3'-nitrobiphenyl	-0.89	-0.13	0.36	-0.92
41	1-aminofluoranthene	3.35	3.22	2.84	3.30
42	4,4'-ethylenebis (aniline)	-2.15	-0.69	-1.05	-1.35
43	4-chloroaniline	-2.52	-2.29	-2.41	-3.01

TABLE III (Continued)

ID#	Compound	Ln(R)(exp.)	Estimated Ln(R)		
			PC (<i>k</i> = 4)	TI/PC (<i>k</i> = 4)	TI/RR (<i>k</i> = 3)
44	2-aminophenanthrene	2.46	2.64	2.11	2.52
45	4-fluoroaniline	-3.32	-2.21	-2.21	-2.74
46	9-aminophenanthrene	2.98	2.51	2.07	2.47
47	3,3'-diaminobiphenyl	-1.30	-0.60	-0.73	-0.79
48	2-aminopyrene	3.50	1.78	2.84	2.82
49	2,6-dichloro-1,4-phenylenediamine	-0.69	-2.06	-1.23	-1.33
50	2-amino-7-acetamidofluorene	1.18	0.83	-0.69	1.26
51	2,8-diaminophenazine	1.12	1.19	1.09	0.24
52	6-aminoquinoline	-2.67	-1.72	-1.43	-2.09
53	4-methoxy-2-methylaniline (<i>m</i> -Cresidine)	-3.00	-1.87	-1.30	-2.04
54	3-amino-2'-nitrobiphenyl	-1.30	-0.03	-0.09	-0.79
55	2,4'-diamino-biphenyl	-0.92	-0.87	-0.82	-0.30
56	1,6-diaminophenazine	0.20	0.96	1.14	0.55
57	4-aminophenyldisulfide	-1.03	-0.71	-0.75	-1.63
58	2-bromo-4,6-dinitroaniline	-0.54	-1.23	-0.84	-2.09
59	2,4-diamino- <i>n</i> -butylbenzene	-2.70	-1.32	-1.46	-2.68
60	4-aminophenylether	-1.14	-0.14	-0.73	-1.59
61	2-aminobiphenyl	-1.49	0.90	2.51	0.15
62	1,9-diaminophenazine	0.04	1.32	0.60	0.60
63	1-aminofluorene	0.43	2.88	2.19	1.32
64	8-aminofluoranthene	3.80	3.11	2.76	3.15
65	2-chloroaniline	-3.00	-1.58	-2.29	-1.90
66	2-amino-aaa-trifluorotoluene	-0.80	-0.45	-1.85	-2.35
67	2-amino-1-nitronaphthalene	-1.17	0.29	-0.85	-1.33
68	3-amino-4'-nitrobiphenyl	0.69	0.06	-0.03	0.47
69	4-bromoaniline	-2.70	-1.56	-1.28	-2.95
70	2-amino-4-chlorophenol	-3.00	-2.07	-1.05	-2.34
71	3,3'-dimethoxybenzidine	0.15	-0.98	-0.37	1.40
72	4-cyclohexylaniline	-1.24	-1.04	-0.66	-0.61
73	4-phenoxyaniline	0.38	-0.23	-2.12	-0.44
74	4,4'-methylenebis (<i>o</i> -ethylaniline)	-0.99	-1.59	-0.78	-0.55
75	2-amino-7-nitrofluorene	3.00	0.82	-0.12	0.96
76	Benzidine	-0.39	-0.79	-0.95	-0.91
77	1-amino-4-nitronaphthalene	-1.77	-0.39	-1.34	-1.12
78	4-amino-3'-nitrobiphenyl	1.02	-0.02	-0.12	0.36
79	4-amino-4'-nitrobiphenyl	1.04	-0.18	-0.12	-0.24
80	1-aminophenazine	-0.01	2.03	-1.60	0.70
81	4,4'-methylenebis (<i>o</i> -fluoroaniline)	0.23	-0.75	-0.47	0.28
82	4-chloro-2-nitroaniline	-2.22	-1.60	-1.52	-2.54
83	3-aminoquinoline	-3.14	-1.60	-1.46	-1.94
84	3-aminocarbazole	-0.48	1.03	-1.17	-0.62
85	4-chloro-1,2-phenylenediamine	-0.49	-1.75	-1.48	-1.97
86	3-aminophenanthrene	3.77	2.31	1.87	2.09

TABLE III (Continued)

ID#	Compound	Ln(R)(exp.)	Estimated Ln(R)		
			PC ($k = 4$)	TI/PC ($k = 4$)	TI/RR ($k = 3$)
87	3,4'-diaminobiphenyl	0.20	-0.12	-0.88	-0.68
88	1-aminoanthracene	1.18	2.96	2.43	2.95
89	1-aminocarbazole	-1.04	1.17	-1.03	-0.43
90	9-aminoanthracene	0.87	2.86	2.60	2.26
91	4-aminocarbazole	-1.42	1.27	-0.94	-0.31
92	6-aminochrysene	1.83	2.34	2.99	2.67
93	1-aminopyrene	1.43	2.37	3.35	3.30
94	4-4'-methylenebis (<i>o</i> -isopropyl-aniline)	-1.77	-1.40	-0.59	0.39
95	2,7-diaminophenazine	3.97	0.34	0.47	0.13

complexity of vertices defined by Basak and co-workers for hydrogen-filled molecular graphs [49-51], and Balaban's J indices [52-54]. Ninety-eight of the TIs were calculated using POLLY 2.3 [55], while the remaining four J indices were calculated using other in-house software. More information on the set of topological indices calculated by POLLY has been reported in earlier studies [22, 30, 56]. One hundred additional indices, the real-number local vertex invariants (LOVIs) [33, 57, 58], were added to this set of topological indices. The triplet indices, developed by Balaban and coworkers [57] result from a matrix, a main diagonal column vector, and a free term column vector, converting the matrix into a system of linear equations whose solutions are the local vertex invariants. The notation used to represent the vectors and matrices is as follows:

A = Adjacency matrix

V = Vertex degree

S = Distance sum

N = Total number of vertices in the graph

Z = Atomic number

D = Distance matrix

1 = Unity matrix.

After the system of N linear equations is solved, the local vertex invariants, x_i , are assembled into a triplet descriptor based on one of the following operations:

Summation, $\sum_i x_i$

Summation of squares, $\sum_i x_i^2$

Summation of square roots, $\sum_i x_i^{1/2}$

Sum of inverse square root of cross-product over edges ij , $\sum_{ij} (x_i x_j)^{-1/2}$

Product, $N(\sum_i x_i)^{1/N}$

TABLE IV Symbols and definitions of topological indices

Topostructural Indices	
I_D^W	Information index for the magnitudes of distances between all possible pairs of vertices of a graph
$\bar{I}_D^W$	Mean information index for the magnitude of distance
W	Wiener index = half-sum of the off-diagonal elements of the distance matrix of a graph
I^D	Degree complexity
H^V	Graph vertex complexity
H^D	Graph distance complexity
IC	Information content of the distance matrix partitioned by frequency of occurrences of distance h
M_1	A Zagreb group parameter = sum of square of degree over all vertices
M_2	A Zagreb group parameter = sum of cross-product of degrees over all neighboring (connected) vertices
$^h\chi$	Path connectivity index of order h = 0-6
$^h\chi_C$	Cluster connectivity index of order h = 3-6
$^h\chi_{Ch}$	Chain connectivity index of order h = 3-6
$^h\chi_{PC}$	Path-cluster connectivity index of order h = 4-6
P_h	Number of paths of length h = 0-10
J	Balaban's J index based on distance
Nrings	Number of rings in a graph
Ncirc	Number of circuits in a graph
DN^2S_y	Triplet index from distance matrix, square of graph order (# of non-H atoms), and distance sum; operation y = 1-5
DN^21_y	Triplet index from distance matrix, square of graph order, and number 1; operation y = 1-5
$AS1_y$	Triplet index from adjacency matrix, distance sum, and number 1; operation y = 1-5
$DS1_y$	Triplet index from distance matrix, distance sum, and number 1; operation y = 1-5
ASN_y	Triplet index from adjacency matrix, distance sum, and graph order; operation y = 1-5
DSN_y	Triplet index from distance matrix, distance sum, and graph order; operation y = 1-5
DN^2N_y	Triplet index from distance matrix, square of graph order, and graph order; operation y = 1-5
ANS_y	Triplet index from adjacency matrix, graph order, and distance sum; operation y = 1-5
$AN1_y$	Triplet index from adjacency matrix, graph order, and number 1; operation y = 1-5
ANN_y	Triplet index from adjacency matrix, graph order, and graph order again; operation y = 1-5
ASV_y	Triplet index from adjacency matrix, distance sum, and vertex degree; operation y = 1-5
DSV_y	Triplet index from distance matrix, distance sum, and vertex degree; operation y = 1-5
ANV_y	Triplet index from adjacency matrix, graph order, and vertex degree; operation y = 1-5
Topochemical Indices	
I_{ORB}	Information content or complexity of the hydrogen-suppressed graph at its maximum neighborhood of vertices
O	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-filled graph
O_{ORB}	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-suppressed graph

TABLE IV (Continued)

IC_r	Mean information content or complexity of a graph based on the r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
SIC_r	Structural information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
CIC_r	Complementary information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
${}^h\chi^b$	Bond path connectivity index of order $h = 0-6$
${}^h\chi_C^b$	Bond cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^b$	Bond chain connectivity index of order $h = 3-6$
${}^h\chi_{PC}^b$	Bond path-cluster connectivity index of order $h = 4-6$
${}^h\chi^v$	Valence path connectivity index of order $h = 0-6$
${}^h\chi_C^v$	Valence cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^v$	Valence chain connectivity index of order $h = 3-6$
${}^h\chi_{PC}^v$	Valence path-cluster connectivity index of order $h = 4-6$
J^B	Balaban's J index based on bond types
J^X	Balaban's J index based on relative electronegativities
J^Y	Balaban's J index based on relative covalent radii
AZV_y	Triplet index from adjacency matrix, atomic number, and vertex degree; operation $y = 1-5$
AZS_y	Triplet index from adjacency matrix, atomic number, and distance sum; operation $y = 1-5$
ASZ_y	Triplet index from adjacency matrix, distance sum, and atomic number; operation $y = 1-5$
AZN_y	Triplet index from adjacency matrix, atomic number, and graph order; operation $y = 1-5$
ANZ_y	Triplet index from adjacency matrix, graph order, and atomic number; operation $y = 1-5$
DSZ_y	Triplet index from distance matrix, distance sum, and atomic number; operation $y = 1-5$
DN^2Z_y	Triplet index from distance matrix, square of graph order, and atomic number; operation $y = 1-5$
Nvx	Number of non-hydrogen atoms in a molecule
$Nelem$	Number of elements in a molecule
Fw	Molecular weight
${}^h\chi^v$	Valence path connectivity index of order $h = 7-10$
${}^h\chi_{Ch}^v$	Valence chain connectivity index of order $h = 7-10$
Si	Shannon information index
$Totop$	Total Topological Index t
$SumI$	Sum of the intrinsic state values I
$SumdelI$	Sum of delta- I values
$Tets2$	Total topological state index based on electrotopological state indices
$Phia$	Flexibility index ($kp1 * kp2/nvx$)
I_C^D	Bonchev-Trinajstic mean information index
I_C^D	Bonchev-Trinajstic information index
Wp	Wiener p
Pf	Platt f
Wt	Total Wiener number
$Knotp$	Difference of chi-cluster-3 and path/cluster-4
$Knotpv$	Valence difference of chi-cluster-3 and path/cluster-4
$Nclass$	Number of classes of topologically (symmetry) equivalent graph vertices
$NumHBd$	Number of hydrogen bond donors
$NumHBa$	Number of hydrogen bond acceptors

TABLE IV (Continued)

SHCsats	E-State of C sp^3 bonded to other saturated C atoms
SHCsatu	E-State of C sp^3 bonded to unsaturated C atoms
Shvin	E-State of C atoms in the vinyl group, =CH-
Shvin	E-State of C atoms in the terminal vinyl group, =CH ₂
Shavin	E-State of C atoms in the vinyl group, =CH-, bonded to an aromatic C
Sharom	E-State of C sp^2 which are part of an aromatic system
SHHBd	Hydrogen bond donor index, sum of Hydrogen E-State values for -OH, =NH, -NH ₂ , -NH-, -SH, and #CH
SHwHBd	Weak hydrogen bond donor index, sum of C-H Hydrogen E-State values for hydrogen atoms on a C to which a F and/or Cl are also bonded
SHHBa	Hydrogen bond acceptor index, sum of the E-State values for -OH, =NH, -NH ₂ , -NH-, >N-, -O-, -S-, along with -F and -Cl
Qv	General Polarity descriptor
NHBint _y	Count of potential internal hydrogen bonders (y = 2-10)
SHBint _y	E-State descriptors of potential internal hydrogen bond strength (y = 2-10)
	Electrotopological State index values for atoms types:
	SHsOH, SHdNH, SHsSH, SHsNH ₂ , SHssNH, SHtCH, Shother, SHCHnX, Hmax Gmax, Hmin, Gmin, Hmaxpos, Hminneg, SsLi, SssBe, SssssBem, SssBH, SssssB, SssssBm, SsCH ₃ , SdCH ₂ , SssCH ₂ , StCH, SdsCH, SaaCH, SssCH, SddC, StsC, SdssC, SaasC, SaaaC, SssssC, SsNH ₃ p, SsNH ₂ , SssNH ₂ p, SdNH, SssNH, SaaNH, StN, SssssNHp, SdsN, SaaN, SssN, SddsN, SaasN, SssssNp, SsOH, SdO, SssO, SaaO, SsF, SsSiH ₃ , SssSiH ₂ , SssSiH, SssssSi, SsPH ₂ , SssPH, SssP, SdssP, SssssP, SssSH, SdS, SssS, SaaS, SdssS, SddssS, SssssS, SsCl, SsGeH ₃ , SssGeH ₂ , SssGeH, SssssGe, SsAsH ₂ , SssAsH, SssAs, SdssAs, SssssAs, SsSeH, SdSe, SssSe, SaaSe, SdssSe, SddssSe, SsBr, SsSnH ₃ , SssSnH ₂ , SssSnH, SssssSn, SsI, SsPbH ₃ , SssPbH ₂ , SssPbH, SssssPb
kp0	Kappa zero
kp1-kp3	Kappa simple indices
ka1-ka3	Kappa alpha indices

The triplet indices were calculated using in-house software. Finally, Molconn-Z v3.50 [59] was used to calculate an additional 167 topological and electrotopological indices. This brought the total number of indices used in this study to 369. These sets of topological indices have recently been analyzed in detail to provide an overview of their utility [31, 60]. Table 4 presents a comprehensive list of the topological indices included in this study.

Data Reduction

Initially, almost all of the TIs were transformed by the natural logarithm of the index plus one. Some TIs may be several orders of magnitude greater than others, so the scaling is conducted to minimize the effect of scale. However, minimal values for some of the Molconn-Z parameters were much less than zero. These indices were logarithmically scaled on a case by case basis. This was done using the natural logarithm of the index plus x , where x was an integer large enough to make the minimal value of the

index greater than zero. Next, correlation analysis was conducted on the indices. In all cases of a perfect correlation between several indices, only one of the indices was retained within the descriptor set.

Statistical Analysis (PCA and Ridge Regression)

Principal component analysis (PCA) was used on the transformed indices to minimize the intercorrelation of indices. The PCA was conducted using the SAS procedure PRINCOMP [61]. Only PCs with eigenvalues greater than or equal to one have been retained for this study. A more detailed explanation of this approach has been provided in a previous study by Basak *et al* [23]. These PCs were subsequently used as independent variables (in place of the TIs) to determine similarity scores in the Euclidean distance method described below. After the PCA, a correlation analysis was conducted on the PCs to determine which TIs were most highly correlated with each of the PCs. This not only allows us to select a small set of TIs for the creation of similarity spaces instead of using the PCs, but it can also provide some insight into the general nature of the principal components, i.e., what aspects of molecular structure are explained by the PCs [22, 62, 63].

Additionally, ridge regression (RR) [64], a method wherein the entire set of descriptors is retained as opposed to subset regression was conducted on the sets of indices retained after the data reduction step. This regression method is useful in cases where the descriptors are highly multicollinear and where the number of descriptors is substantially larger than the number of observations [65]. Conceptually, RR can be thought of as recasting the regression as one using the principal components of the predictor variables as new predictors. It differs in that in principal component regression the leading components are retained and used just as in ordinary least squares regression while the trailing components are dropped. RR retains all components, but downweights each of them in accordance with the component's eigenvalue and the 'ridging constant' k .

The ridge parameter k controls the amount of smoothing in ridge regression. If k is large, then all regression coefficients are 'shrunk' towards zero. Smaller k values shrink the directions of small eigenvalue substantially, but the directions with large eigenvalue less so. A suitable value for k needs to be found when performing ridge regression. In the current study, the k value was chosen to minimize the prediction sum of squares (PRESS), a cross-validation measure. As in jack-knifing, each compound in turn is temporarily omitted from the data set and the RR fitted to the remaining compounds. The resulting model is used to predict the compound that was held back. PRESS is the sum of squares of the differences between the actual values and these holdout predictions. The cross-validated R^2 is defined in terms of PRESS and provides an honest measure of the predictive power of the modeling approach.

Quantification of Molecular Similarity

Intermolecular similarity was measured using Euclidean distance (*ED*) within an *n*-dimensional space derived from TIs or PCs. The *ED* between two molecules, *i* and *j*, is defined as:

$$ED_{ij} = \left[\sum_{k=1}^n (D_{ik} - D_{jk})^2 \right]^{1/2} \quad \text{Eq. 1}$$

where *n* equals the number of dimensions utilized, whether those dimensions are derived from TIs or PCs. *D_{ik}* and *D_{jk}* are the data values of the *kth* dimension for molecules *i* and *j*, respectively.

Property Estimation

Property estimation was carried out using the *k*-nearest neighbor (KNN) method. For each compound, a number of similar chemicals (*k* = 1-10, 15, 20, 25) are selected and the property of interest is estimated based on the values of these nearest neighbors. For instance, in estimating the log*P* of the probe compound, the mean log*P* for the *k*-nearest neighbors was used as the estimate. KNN estimation was carried out for all chemicals in both of the data sets, resulting in a full cross-validation. Thus the correlation coefficients reported are the cross-validated correlation coefficients.

FIGURE 1 Pattern of correlation for the three similarity methods on the STARLIST set.

FIGURE 2 Pattern of standard error for the three similarity methods on the STARLIST set.

RESULTS AND DISCUSSION

The principal objective of this paper was to determine whether similarity spaces tailored to a specific property could be more useful in the prediction of that property from selected analogs, as compared to spaces which are constructed from orthogonal, or a minimally correlated subset of, descriptors derived from an arbitrary collection of indices. To this end, we used three spaces, viz., a principal component space, a topological index space based on the indices most highly correlated with each PC, and a topological index space based on the weighting of the indices as determined through ridge regression analysis.

For the STARLIST logP set, consisting of a group of 213 diverse structures, we selected analogs using three distinct similarity methods. These methods all began using the set of 252 calculated molecular descriptors (TIs) remaining after data reduction. PCA resulted in the selection of the first twenty-four principal components, all of which had eigenvalues greater than or equal to one (see Table 5). Also indicated on Table 5 are the two TIs most correlated with each of the PCs. Next, RR was carried out on the set of 252 TIs. Model coefficients were extracted and used to rank the TIs from most to least influential based on the absolute value of the regression coefficient. In this manner, a set of twenty-four topological indices were selected for creation of the "tailored" similarity space (see Table 6). Finally, three Euclidean distance-based similarity spaces were constructed based on: 1) twenty-four PCs derived from the set of 252 calculated TIs, b) twenty-four TIs, each one being the most correlated with one of the

first twenty-four PCs, and c) the set of the twenty-four TIs having the most significant contribution (t value) in modeling $\log P$ using the RR method. To compare the methods, the k -nearest neighbors ($k = 1-10, 15, 20, 25$) for each chemical were chosen using each of the QMSA methods and the arithmetic mean of the $\log P$ values for the selected analogs was taken as the estimated $\log P$ of the compound under investigation. It is clear from the results (see Figures 1 & 2) that the tailored similarity space based on the indices selected by the RR method gives a much better estimate of $\log P$ as compared to the two non-tailored methods.

TABLE V Summary of the first twenty-four principal components derived from a set of 252 topological indices calculated for a set of 213 STARLIST chemicals

PC	Eigenvalue	Proportion of Variance Explained	Cumulative Variance Explained	First Most Correlated TI		Second Most Correlated TI	
1	121.74	0.483	0.483	DN ² N ₃	0.993	P ₀	0.993
2	25.31	0.100	0.583	SssssC	-0.748	³ χ ^b _C	0.719
3	17.23	0.068	0.651	IC ₀	0.849	CIC ₃	-0.822
4	14.37	0.057	0.708	J	-0.667	⁵ χ ^v _{Ch}	0.598
5	11.29	0.045	0.753	Phia	0.875	Ka ₂	0.745
6	7.38	0.029	0.782	J ^x	-0.532	¹⁰ χ _{PC}	0.494
7	6.55	0.026	0.808	Gmin	0.552	SsF	-0.533
8	4.69	0.019	0.827	SHwHBd	-0.590	SHCHnX	-0.585
9	4.03	0.016	0.843	SsCH ₃	0.681	Qv	0.391
10	3.22	0.013	0.856	NumHBd	-0.589	SsSH	-0.589
11	2.98	0.012	0.868	SHsSH	0.724	SsSH	0.723
12	2.60	0.010	0.878	Shvin	0.543	SdsCH	0.542
13	2.50	0.010	0.888	¹⁰ χ _{Ch}	-0.390	¹⁰ χ ^v _{Ch}	-0.379
14	2.14	0.008	0.896	⁹ χ ^v _{Ch}	0.672	⁹ χ _{Ch}	0.660
15	1.91	0.008	0.904	¹⁰ χ ^v _{Ch}	-0.382	¹⁰ χ _{Ch}	-0.380
16	1.81	0.007	0.911	³ χ _{Ch}	-0.545	⁴ χ _{Ch}	-0.390
17	1.67	0.007	0.918	SsBr	0.375	SsCl	-0.355
18	1.49	0.006	0.924	⁸ χ _{Ch}	0.569	⁸ χ ^v _{Ch}	0.509
19	1.42	0.006	0.930	SsI	-0.298	SdssC	0.283
20	1.23	0.005	0.935	SaaS	0.340	SaasC	-0.355
21	1.15	0.005	0.940	SHCsatu	-0.394	SddC	0.265
22	1.11	0.004	0.944	SdssC	0.583	SsssP	-0.372
23	1.08	0.004	0.948	StsC	-0.521	SsI	0.489
24	1.02	0.004	0.952	SsssP	-0.598	SssNH ₂ P	0.568

TABLE VI Twenty-four TIs selected by PCA and RR for the 213 STARLIST chemicals. Bold typeface has been used to highlight the indices common to both sets of TIs

PC	TIs from PCA	TIs from RR (t-value)
1	DN²N₃	ka ₁ (12.41)
2	SssssC	W (11.95)
3	IC ₀	⁰ χ ^v (11.62)
4	J	P ₀ (11.32)
5	Phia	ANN ₃ (11.31)
6	J ^x	DN ² S ₃ (11.12)
7	Gmin	SHwHBd (-10.87)
8	SHwHBd	ANS ₁ (10.66)
9	SsCH ₃	ANN ₁ (10.55)
10	NumHBd	AN ₁₃ (10.47)
11	SHsSH	ANN ₅ (10.39)
12	Shvin	⁰ χ (10.14)
13	¹⁰ χ _{Ch}	DN ² I ₄ (9.92)
14	⁹ χ ^v _{Ch}	SHCHnX (-9.92)
15	¹⁰ χ ^v _{Ch}	⁰ χ ^b (9.65)
16	³ χ _{Ch}	AS ₁₄ (9.32)
17	SsBr	DN ² S ₁ (9.16)
18	⁸ χ _{Ch}	DN ² N ₄ (9.09)
19	SsI	DN²N₃ (9.00)
20	SaaS	DN ² S ₅ (8.89)
21	SHCsatu	SssS (-8.74)
22	SdssC	ANN ₂ (8.33)
23	StsC	SaasC (8.16)
24	SsssP	SsssP (-8.14)

An analogous situation is found with the set of ninety-five aromatic and heteroaromatic amines. 267 indices were retained after data reduction for this data set. PCA resulted in twenty principal components with eigenvalues greater than or equal to one (see Table 7). As with the STARLIST log P set, Table 7 also indicates the two TIs most correlated with each of the principal components. Table 8 lists the TIs selected from the RR analysis. As before, the number of TIs selected by RR (twenty) was selected to match the number of PCs with eigenvalues greater than or equal to one for creation of the "tailored" similarity space. Finally, the three Euclidean distance-based similarity spaces were constructed based on: 1) twenty PCs derived from the set of 267 calculated TIs, b) the twenty TIs most correlated with the first twenty PCs, and c) the set of the twenty TIs having the most significant contribution (t value) in modeling mutagenicity using the RR method. Here, the similarity method based on indices chosen by the RR method also gives a better estimate of mutagenicity as compared to the methods based either on the PCs or indices most correlated with the first twenty PCs with eigenvalues greater than or equal to one. (Figures 3 & 4).

FIGURE 3 Pattern of correlation for the three similarity methods on the set of ninety-five aromatic and heteroaromatic amines.

FIGURE 4 Pattern of standard error for the three similarity methods on the set of ninety-five aromatic and heteroaromatic amines.

TABLE VII Summary of the first twenty principal components derived from a set of 267 TIs calculated for a set of 95 aromatic and heteroaromatic amines

PC	Eigenvalue	Proportion of Variance Explained	Cumulative Variance Explained	First Most Correlated TI		Second Most Correlated TI	
1	141.47	0.532	0.532	AZV ₃	0.994	AZV ₁	0.993
2	34.28	0.129	0.661	ASN ₂	0.887	ka ₃	-0.879
3	17.04	0.064	0.725	SumdelI	0.799	SHHBa	0.746
4	10.41	0.039	0.764	Knotpv	-0.539	¹⁰ χ _{PC}	0.528
5	8.69	0.033	0.797	Phia	0.560	Nvx	-0.556
6	8.34	0.031	0.828	Hmin	-0.666	IC ₂	0.645
7	6.06	0.023	0.851	ANZ ₁	0.497	SsCH ₃	-0.476
8	4.95	0.019	0.869	SHHBd	0.602	NumHBd	0.553
9	3.85	0.015	0.884	⁴ χ _C	-0.649	SsF	-0.638
10	3.11	0.012	0.896	ShsOH	0.487	SsOH	0.487
11	2.76	0.010	0.906	SaaN	0.379	IC ₁	0.340
12	2.34	0.009	0.915	SHssNH	-0.374	SaaNH	-0.332
13	2.10	0.008	0.923	SsOH	-0.408	ShsOH	-0.408
14	1.82	0.007	0.929	NHBint ₈	0.480	SssNH	0.398
15	1.79	0.007	0.936	SsBr	0.427	SssS	-0.384
16	1.64	0.006	0.942	SssNH	0.510	NHBint ₉	-0.389
17	1.56	0.006	0.948	SssO	-0.633	NHBint ₇	0.487
18	1.38	0.005	0.953	NHBint ₈	0.385	SssS	0.367
19	1.21	0.005	0.958	SdsCH	-0.582	SssS	0.391
20	1.12	0.004	0.962	NHBint ₆	0.342	NHBint ₇	-0.336

A comparison of the list of the twenty-four TIs most correlated with the twenty-four PCs and the twenty-four most important TIs necessary for the correlation of Log*P* for the STARLIST set of 213 chemicals (Table 6) shows that they have only three TIs, viz., DN²N₃, SHwHBd, and SsssP, in common. This shows that the set of minimally correlated TIs selected by the PCA process and the group of twenty-four TIs selected by the RR method are quite different. It is interesting to note that the group of twenty TIs chosen by the PCA procedure and those selected by the RR method for the data set of ninety-five aromatic amines have no TIs in common (Table 8).

It is interesting to note that for both types of QMSA methods, tailored and non-tailored, the value of *k* = 3–8 gives the best estimate of the properties, viz., log*P* and mutagenicity. This is in line with our earlier observation with various QMSA methods pertaining to different properties and diverse databases [19-37, 62]. It should also be noted that variable clustering was considered as a means of selecting indices or creating nearly orthogonal descriptors for the construction of ED spaces. However, this notion was discarded when we first attempted to cluster the sets of 250+ descriptors. Unfortunately the implementation of variable clustering that we attempted to use required constant monitoring and had not finished clustering the variables even after two hours had elapsed. By comparison, the PCA took only a few seconds and produced a new set of descriptors that were completely orthogonal.

TABLE VIII Twenty topological indices selected by PCA and RR for the ninety-five aromatic and heteroaromatic amines. There are no common TIs between the two descriptor sets

PC	TIs from PCA	TIs from RR	t value
1	AZV ₃	P ₂	5.18
2	ASN ₂	M ₁	4.82
3	SumdelI	M ₂	4.72
4	Knotpv	NHBint ₉	4.39
5	Phia	IC ₁	-4.20
6	Hmin	SIC ₂	-4.17
7	ANZ ₁	AZN ₄	3.97
8	SHHBd	SIC ₁	-3.88
9	⁴ χ _C	P ₅	3.86
10	ShsOH	P ₆	3.84
11	SaaN	IC ₂	-3.77
12	SHssNH	⁶ χ	3.74
13	SsOH	⁹ χ _{PC}	3.65
14	NHBint ₈	I _{ORB}	3.62
15	SsBr	SaaNH	-3.55
16	SssNH	CIC ₂	3.52
17	SssO	ANS ₄	3.49
18	SssS	AZV ₂	3.42
19	SdsCH	CIC ₃	3.36
20	NHBint ₆	IC ₅	3.19

In conclusion, we have reported for the first time in this paper that one can construct appropriately tailored similarity spaces using adequately selected molecular descriptors. Such tailored spaces perform better in property/toxicity estimation than spaces constructed from an arbitrary collection of descriptors. We hope the idea of tailored similarity space will find application in analog selection, property/ toxicity estimation as well as in the property-specific clustering of databases for predictive toxicology research and drug design.

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Tailored Similarity Spaces for the Prediction of Physicochemical Properties

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Tailored Similarity Spaces for the Prediction of Physicochemical Properties[#]

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Abstract

Motivation. In the past, molecular similarity spaces have been developed from arbitrary sets of molecular properties or theoretical descriptors and the results of property estimation based on these methods have always been inferior to SAR and QSAR models. Tailored QMSA methods attempt to create similarity spaces specific for a property of interest, rather than being purely arbitrary spaces characterizing the general aspects of all chemicals within the space or intuitively selected structure spaces whose elements are chosen subjectively. To this end, we have created three similarity spaces, two tailored and one non-tailored, for a set of 166 chemicals for which we have both log *P* and normal boiling point (BP) data. The tailored spaces were each tailored to one of the properties, while the other similarity space was developed using standard QMSA methods.

Method. Ridge regression was used to determine which of the available molecular descriptors were most useful in modeling each of the available properties. Fifteen topological descriptors were selected for use as dimensions within each the tailored similarity spaces. The same number of principal components were developed using principal component analysis for the arbitrary similarity space.

Results. The log *P* tailored similarity space was superior to both the arbitrary structure space and the BP tailored space for the estimation of log *P*. Also, the BP tailored similarity space was superior to the arbitrary structure space for the estimation of BP. Interestingly, the space tailored to model log *P* performed as well at modeling BP as did the BP tailored space. This unexpected result is explained by the degree of overlap between the indices used in both of the tailored spaces and in the presence of connectivity indices related to BP in the log *P* model.

Conclusions. The tailored similarity method presents a promising approach to creating property specific similarity spaces derived from structural descriptors based on the results of this study and from a previous study. Further work is necessary to determine to true utility of this method with large, diverse data sets.

Keywords. Quantitative molecular similarity analysis (QMSA); tailored QMSA; arbitrary QMSA; topological indices; lipophilicity; normal boiling point.

Abbreviations and notations

ASTER, Assessment Tools for the Evaluation of Risk	QMSA, quantitative molecular similarity analysis
BP, normal boiling point	QSAR, quantitative structure–activity relationship
ED, Euclidean distance	<i>R</i> , regression coefficient
JP–8, jet propellant formulation #8	RR, Ridge regression
KNN, <i>K</i> -nearest neighbor	<i>s.e.</i> , standard error
log <i>P</i> , lipophilicity	TI, topological index
PCs, principal components	USEPA, United States Environmental Protection Agency
PCA, principal components analysis	

[#] Dedicated to Professor Milan Randić on the occasion of the 70th birthday.

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1 INTRODUCTION

Quantitative molecular similarity analysis (QMSA) is an important computational tool both for the hazard assessment of environmental pollutants and pharmaceutical drug design. In the area of the hazard estimation of chemicals, QMSA methods are routinely used to assess the potential hazard of a chemical based on the toxicity profiles of analogous chemicals when little or no experimental toxicity data and toxicologically relevant property data are available for the chemical of interest [1–4]. This course of action is generally followed when the structure of the chemical is complex enough that it cannot be unambiguously classified into a particular structural category. If it could be categorized into a specific chemical class, class-specific quantitative structure–activity relationship (QSAR) models would instead be used for hazard assessment. In the area of drug discovery, QMSA techniques are useful for determining whether interesting lead compounds have structural analogs with similar pharmacological and toxicological profiles. The other side of similarity is dissimilarity. Dissimilarity-based clustering of large libraries of real or *in silico* (virtual libraries) of chemicals has been successfully used [5] and suggested [6] as possible methods in the management of combinatorial explosions in various drug design scenarios.

QMSA methods are based on the basic assumption that similar molecular structures usually have similar properties [7]. Two chemicals, X1 and X2, are said to be similar if they resemble each other with respect to some user-defined set of properties or structural attributes, or both. Substructural descriptors [8–17], experimental properties [12,17–19], and theoretical structural invariants [6,7,11–17,19–32] have been widely used in the formulation of QMSA methods and ranking of chemical databases via such techniques.

Our research group has been involved in the development of novel QMSA techniques and their applications in analog selection and the *k*-nearest neighbor (KNN) based estimation of properties, as well as the use of similarity spaces in the clustering of chemical databases. Our experience has shown that increasing the intrinsic dimensionality of similarity spaces by the progressive use of more diverse and mutually uncorrelated (or minimally correlated) indices leads to better analog selection as is evident from both a visual inspection of their structures and the predictive power of the selected analogs in property estimation for query chemicals using the KNN method.

The stepwise use of increasingly higher dimensional structure spaces, derived from collections of progressively more diverse and comprehensive indices, suffers from the fact that elements of the enhanced spaces do not have any intrinsic relationship to the property of interest that we are attempting to estimate from the chosen analogs. Rather, these spaces are simply a reflection of the chemical diversity within the selected data set. If there is an improvement in the usefulness of analogs selected, that is only by chance, not by design. This is why we have developed the idea of tailored QMSA methods where the structure space is constructed from parameters that are strongly associated with the property of interest [32]. The advantage of such directed spaces over blind or

arbitrary spaces is that analogs selected by the former will be relevant with respect to the property to which they are tailored.

In a previous study, we reported for the first time the development of structure spaces tailored towards two properties, *viz.*, $\log P$ (octanol/water) and Ames mutagenicity, based on calculated topological indices. We also showed that the analogs selected from the tailored similarity spaces gave much better results in KNN-based estimation for both of the properties studied, as compared to our previous results using arbitrary similarity spaces. In the current study, we have used a set of 166 chemicals which represent a subset of the known constituents of jet propellant #8 (JP-8), a jet fuel currently in use by the United States Armed Forces. This set of chemicals was of interest for this study since we have data for two physicochemical properties, $\log P$ and normal boiling point, for this set of chemicals. Three similarity spaces have been constructed for this study. Two of the similarity spaces are tailored spaces, one tailored towards $\log P$ and the other towards normal boiling point (hereafter simply referred to as BP). The third similarity space is a standard, arbitrary similarity space developed from the set of available molecular descriptors.

2 MATERIALS AND METHODS

Physicochemical property data used in this study represent property values extracted from the ASTER [33] system of the USEPA. These data are predominantly calculated values, rather than experimental values, reflecting the difficulty of obtaining simple physicochemical experimental data for common compounds.

2.1 Chemical Data

The set of chemicals used in this study represents a subset of the known constituents of JP-8 identified through GC/MS [34], a set of 166 hydrocarbons. This subset consisted of all of the chemicals in the full set of 228 chemicals for which $\log P$ and normal boiling point (BP) were both available from the ASTER database. However, even for the reduced set of 166 chemicals, most of the data values available from ASTER were calculated, not experimental values. This set of chemicals and the data obtained from ASTER are reported in Table 1.

2.2 Calculation of Molecular Descriptors

The topological indices (TIs) used in this study were calculated using three main software programs: POLLY 2.3 [35], MolConn-Z 3.50 [36], and Triplet [37]. Included in the suite of more than 220 indices in this study are: Wiener number [38], molecular connectivity indices as calculated by Randić [39] and Kier and Hall [40], frequency of path lengths of varying size, information theoretic indices defined on distance matrices of graphs using the methods of Bonchev and Trinajstić [41] as well as those of Raychaudhury *et al.* [42], parameters defined on the

neighborhood complexity of vertices in hydrogen-filled molecular graphs [43–45], Balaban's *J* indices [46–48], local orthogonal vertex invariants [37], kappa shape descriptors [49,50], and the electrotopological indices of Kier and Hall [51]. More information on the topological indices calculated by POLLY has been reported in earlier studies [15,20,27,31].

Table 1. Chemicals and Their Physicochemical Property Data for the 166 Identified Components of JP-8

No	Name	logP	BP	No	Name	logP	BP
1	ISTD (d10-anthracene)	4.49	300	50	3,3-dimethylheptane	5.2	137
2	2,2,3-trimethylbutane	4.01	81	51	2,4-dimethyl-3-ethylpentane	5.07	137
3	2,3,3-trimethyl-1-butene	3.46	78	52	2,3,4-trimethylhexane	5.07	139
4	3,3-dimethylpentane	4.14	86	53	2,2,3,3-tetramethylpentane	4.94	140
5	Benzene	2.14	80	54	2,3,3,4-tetramethylpentane	4.94	142
6	2-methylhexane	4.27	90	55	2,3-dimethylheptane	5.2	141
7	3-ethylpentane	4.27	93.5	56	3,4-dimethylheptane	5.2	141
8	<i>t</i> -1,3-dimethylcyclopentane	3.83	91	57	4-ethylheptane	5.33	141
9	Iso-octane	4.54	99	58	Ethylbenzene	3.32	136
10	1-heptene	3.85	94	59	4-methyloctane	5.33	141
11	3-heptene	3.85	92.7	60	<i>m</i> -xylene	3.44	139
12	<i>n</i> -heptane	4.4	98	61	3-methyloctane	5.33	143
13	2,2-dimethylhexane	4.67	106	62	<i>c</i> -1,2,3-trimethylcyclohexane	4.91	144
14	1,1,3-trimethylcyclopentane	4.35	105	63	3,3-diethylpentane	5.2	146
15	2,3,3-trimethyl-1,4-pentadiene	3.45	125	64	1,2,4-trimethylcyclohexane	4.91	142
16	2,4,4-trimethyl-2-pentene	3.99	105	65	<i>c,c,t</i> -1,3,5-trimethylcyclohexane	4.91	144
17	2,5-dimethylhexane	4.67	109	66	1-nonene	4.91	147
18	2,4-dimethylhexane	4.67	110	67	<i>o</i> -xylene	3.44	144
19	3,3-dimethylhexane	4.67	112	68	4-nonene	4.91	145
20	4-methylcyclohexene	3.33	103	69	<i>n</i> -nonane	5.46	151
21	<i>c,t,c</i> -1,2,3-trimethylcyclopentane	4.35	123	70	<i>c,c,t</i> -1,2,3-trimethylcyclohexane	4.91	144
22	2,3,4-trimethylpentane	4.54	114	71	3,3,5-trimethylheptane	5.59	156
23	2,3,3-trimethylpentane	4.54	115	72	1-ethyl-1-methylcyclohexane	4.92	144
24	<i>t</i> -3,4,4-trimethyl-2-pentene	3.99	119	73	1,3,5,5-tetramethyl-1,3-cyclohexadiene	4.52	173
25	1,1,3,3-tetramethylcyclopentane	4.87	114	74	<i>t</i> -1,1,3,5-tetramethylcyclohexane	5.43	166
26	2-methylheptane	4.8	118	75	Isopropylcyclohexane	4.8	155
27	4-methylheptane	4.8	118	76	3,5-dimethyloctane	5.72	160
28	Toluene	2.79	111	77	Isopropylbenzene	3.72	152
29	3,4-dimethylhexane	4.67	118	78	2,7-dimethyloctane	5.72	160
30	2,2,4,4-tetramethylpentane	4.94	122	79	<i>n</i> -propylcyclohexane	4.93	157
31	3-methylheptane	4.8	119	80	2,6-dimethyloctane	5.72	155
32	3-ethylhexane	4.8	119	81	3,4-diethylhexane	5.72	162
33	<i>t</i> -1,1,3,4-tetramethylcyclopentane	4.87	144	82	3,6-dimethyloctane	5.72	160
34	2-ethyl-1-hexene	4.25	120	83	3-ethyl-2-methylheptane	5.72	166
35	2,2,4-trimethylhexane	5.07	127	84	3,4,5-trimethylheptane	5.59	164
36	1-ethyl-1-methylcyclopentane	4.36	122	85	Propylbenzene	3.85	159
37	<i>n</i> -octane	4.93	126	86	2,3-dimethyloctane	5.72	164
38	2,4,4-trimethylhexane	5.07	131	87	4-ethyloctane	5.85	168
39	2,4-dimethylheptane	5.2	134	88	5-methylnonane	5.85	165
40	2,2,3-trimethylhexane	5.07	134	89	4-methylnonane	5.85	165
41	4,4-dimethylheptane	5.2	135	90	1-ethyl-3-methylbenzene	3.97	161
42	3,3,5-trimethylcyclohexene	4.37	145	91	1-ethyl-4-methylbenzene	3.97	162
43	2,2,5,5-tetramethylhexane	5.46	137	92	3-ethyloctane	5.85	168
44	2,6-dimethylheptane	5.2	135	93	1,3,5-trimethylbenzene	4.09	165
45	<i>c,c,c</i> -1,3,5-trimethylcyclohexane	4.91	144	94	3-methylnonane	5.85	167
46	Propylcyclopentane	4.37	131	95	1-isopropyl-4-methylcyclohexane	5.32	169
47	1,3,5-trimethylcyclohexane	4.91	144	96	1-ethyl-2-methylbenzene	3.97	165
48	3,5,5-trimethylcyclohexene	4.37	145	97	2,2,4,6,6-pentamethylheptane	6.39	205
49	Ethylcyclohexane	4.4	132	98	<i>t</i> -butylbenzene	4.12	169

Table 1. (Continued)

No	Name	logP	BP	No	Name	logP	BP
99	1,2,4-trimethylbenzene	4.09	169	133	1,2-dimethyl-3-ethylbenzene	4.62	194
100	<i>n</i> -decane	5.98	174	134	1,2,4,5-tetramethylbenzene	4.74	197
101	Isobutylbenzene	4.25	173	135	(2-methylbutyl)-benzene	4.78	205
102	<i>sec</i> -butylbenzene	4.25	174	136	1,2,3,5-tetramethylbenzene	4.74	198
103	3,7,7-trimethylbicyclo(4.1.0)-3-heptene	4.12	170	137	(3-methylbutyl)-benzene	4.78	199
104	1-isopropyl-3-methylbenzene	4.37	175	138	1,2-diisopropylbenzene	5.3	204
105	1,2,3-trimethylbenzene	4.09	176	139	1,2,3,4-tetramethylbenzene	4.74	205
106	1-ethyl-2,5-dimethylbenzene	4.62	187	140	<i>n</i> -pentylbenzene	4.91	205
107	Dicyclopentadiene	3.44	175	141	1,4-diisopropylbenzene	5.3	203
108	Butylcyclohexane	5.46	181	142	1- <i>t</i> -butyl-3,5-dimethylbenzene	5.42	204
109	Indane (2,3-dihydro-1H-indene)	3.46	176	143	Naphthalene	3.32	218
110	1-isopropyl-2-methylbenzene	4.37	178	144	1-dodecene	6.5	213
111	1,3-diethylbenzene	4.5	181	145	1,3,5-triethylbenzene	5.68	215
112	1-propyl-4-methylbenzene	4.5	183	146	<i>n</i> -hexylbenzene	5.44	226
113	1,4-diethylbenzene	4.5	183	147	(1,1-diethylpropyl)-benzene	5.71	243
114	Butylbenzene	4.38	183	148	2-methylnaphthalene	3.97	241
115	1-ethyl-3,5-dimethylbenzene	4.62	184	149	1-methylnaphthalene	3.97	245
116	4-methyldecane	6.38	185	150	Cyclohexylbenzene	4.91	235
117	1,2-diethylbenzene	4.5	183	151	1- <i>t</i> -butyl-3,4,5-trimethylbenzene	6.07	243
118	2-methyldecane	6.38	185	152	1,1,6-trimethyltetralin	5.7	247
119	Neopentylbenzene	4.65	186	153	<i>n</i> -heptylbenzene	5.97	245
120	1-propyl-2-methylbenzene	4.5	185	154	1,1'-biphenyl	4.03	254
121	3-methyldecane	6.38	185	155	2-ethylnaphthalene	4.49	258
122	1-isopropyl-4-methylbenzene	4.37	177	156	1-ethylnaphthalene	4.49	259
123	1-ethyl-2,4-dimethylbenzene	4.62	188	157	2,6-dimethylnaphthalene	4.61	262
124	(1,2-dimethylpropyl)-benzene	4.65	188	158	2,3-dimethylnaphthalene	4.61	268
125	1-ethyl-3,4-dimethylbenzene	4.62	190	159	1,4-dimethylnaphthalene	4.61	268
126	1- <i>t</i> -butyl-3-methylbenzene	4.77	189	160	1,5-dimethylnaphthalene	4.61	265
127	(1-ethylpropyl)-benzene	4.78	191	161	1,2-dimethylnaphthalene	4.61	266
128	1-undecene	5.97	193	162	<i>n</i> -octylbenzene	6.49	262
129	2-ethyl-1,3-dimethylbenzene	4.62	190	163	1,8-dimethylnaphthalene	4.61	270
130	<i>n</i> -undecane	6.51	196	164	Fluorene	4.23	293
131	1-ethyl-3-isopropylbenzene	4.9	192	165	2,5-dimethylheptane	5.2	136
132	<i>sec</i> -pentylbenzene	4.78	193	166	<i>p</i> -xylene	3.44	138

2.2.1 Data reduction

Initially, the TIs were transformed by the natural logarithm of the index plus one. Since the magnitude of some TIs is several orders greater than that of others, re-scaling is conducted to minimize the effect of scale. However, minimal values for some of the Molconn-Z parameters were much less than zero. These indices were logarithmically scaled on a case-by-case basis using the natural logarithm of the index plus x , where x was an integer large enough to make the minimal value of the index greater than zero. Next, correlation analysis was conducted on the indices. In all cases of a perfect correlation between several indices, only one of the indices was retained within the descriptor set. Additionally, a number of indices encoding features not present in the data set (having zero values for all compounds) were discarded.

2.2.2 Statistical analysis software

Two statistical software packages were used for the construction of similarity spaces used in this study. For the development of the arbitrary similarity space, SAS [52] was used to conduct a principal component analysis (PCA) on the transformed indices to minimize the intercorrelation of indices. This was done using the SAS procedure PRINCOMP. For the tailored spaces, an in-house ridge regression (RR) [53] program was used to select a small set of descriptors for the development of each of the spaces.

2.2.3 Construction of arbitrary similarity spaces

A traditional (arbitrary) molecular similarity space was constructed for the set of 166 JP-8 constituents using the principal components created using the SAS PRINCOMP procedure. Only PCs with eigenvalues greater than or equal to one have been retained for this study. A more detailed explanation of this approach has been provided in a previous study by Basak *et al.* [20]. These PCs were subsequently used as independent variables (in place of the TIs) to determine similarity scores in the Euclidean distance method described later. After the PCA, a correlation analysis was conducted on the PCs to determine which TIs were most highly correlated with each of the PCs. This allows for the creation of similarity spaces based on a small set of TIs (as has been done previously), and also provides some insight into the general nature of the principal components, *i.e.*, which aspects of molecular structure are explained by each of the PCs [6,54,55].

2.2.4 Construction of tailored similarity spaces

Two tailored similarity spaces were constructed for use in this study. One of the spaces was tailored specifically to log *P* and the other for BP. As was mentioned earlier, the RR method was used in the development of these spaces. RR is a method wherein modeling is conducted using the entire set of descriptors retained after the data reduction step as opposed to subset regression. This regression method is useful in cases where the descriptors are highly multicollinear and where the number of descriptors is substantially larger than the number of observations [56]. Conceptually, RR can be thought of as recasting the regression as one using the principal components of the predictor variables as new predictors. It differs in that in principal component regression the leading components are retained and used just as in ordinary least squares regression while the trailing components are dropped. RR retains all components, but weights each of them in accordance with the component's eigenvalue and the 'ridging constant' *k*. More details on the RR method can be found in some of our previous papers [32,57–58].

One of the by-products of the RR is a ranking of the contribution of the indices. The absolute values of this ranking score were used to select the descriptors for use in the development of tailored similarity spaces. Separate RR studies were conducted for log *P* and BP, resulting in a selection of optimal descriptors for use in constructing the tailored similarity spaces.

Table 2. Summary of the First Fifteen Principal Components Derived from a set of 222 Topological Indices Calculated for a Set of 166 JP–8 Constituents

PC	Eigenvalue	Proportion of Explained Variance	Cumulative Explained Variance	First Most Correlated TI	Second Most Correlated TI
1	93.38	0.421	0.421	DN ² N ₄	DN ² I ₄
2	45.84	0.206	0.627	Phia	ASN ₂
3	26.24	0.118	0.745	² χ ^b	² χ ^v
4	12.74	0.057	0.802	IC ₃	IC ₄
5	9.32	0.042	0.844	J ^B	⁴ χ ^b
6	6.31	0.029	0.873	¹⁰ χ	⁹ χ ^v
7	4.75	0.021	0.894	SdsCH	Shvin
8	3.97	0.018	0.912	⁵ χ ^b C	⁵ χ ^v C
9	2.66	0.012	0.924	³ χ ^b Ch	G _{MAX}
10	2.36	0.011	0.935	⁹ χ ^v Ch	⁹ χ ^b Ch
11	1.91	0.009	0.944	J ^B	⁸ χ ^b Ch
12	1.68	0.008	0.952	Shvin	SdsCH
13	1.38	0.006	0.958	O _{ORB}	O
14	1.15	0.005	0.963	¹⁰ χ ^v	SdsCH
15	1.07	0.005	0.968	⁶ χ ^b	⁶ χ ^v

Table 3. Fifteen TIs Selected by RR for the 166 JP–8 Chemicals. Indices Common to both RR Sets are Indicated in Bold

PC	TIs from RR for log <i>P</i> (t-value)		TIs from RR for BP (t-value)	
1	⁰ χ ^b	(16.47)	ANN ₅	(16.77)
2	⁰ χ ^v	(16.42)	ANN ₃	(16.10)
3	Fw	(14.77)	ANL ₃	(15.81)
4	AZS ₁	(14.22)	ANN ₁	(15.51)
5	W	(14.03)	W	(15.30)
6	ANS ₃	(14.00)	P ₀	(15.07)
7	AZS ₃	(13.31)	ANS ₃	(14.74)
8	ANS ₁	(12.19)	I ^W _D	(14.58)
9	⁰ χ	(11.71)	DN ² I ₄	(14.10)
10	ka ₁	(11.42)	AZS ₃	(13.93)
11	I ^W _D	(11.31)	AZN ₃	(13.88)
12	ANN ₃	(11.31)	AZN ₅	(13.13)
13	DN ² S ₃	(11.29)	AZN ₁	(12.81)
14	ANN ₅	(11.14)	Fw	(12.65)
15	Q _v	(11.08)	DN ² N ₃	(12.46)

2.3 Quantification of Intermolecular Similarity

Once the similarity spaces were constructed, it was possible to calculate similarity scores based on the intermolecular distances within the arbitrary and tailored molecular similarity spaces. Intermolecular similarity was measured using Euclidean distance (ED) within an *n*-dimensional space derived from TIs or PCs. The ED between two molecules, *i* and *j*, is defined as:

$$ED_{ij} = \left[\sum_{k=1}^n (D_{ik} - D_{jk})^2 \right]^{1/2} \quad (1)$$

where *n* is equal to the number dimensions (descriptors) used to define the similarity space, whether

those dimensions are derived from TIs or PCs. D_{ik} and D_{jk} are the data values of the k^{th} dimension for molecules i and j , respectively.

Once distances between all molecules within the molecular similarity space have been calculated, these distance “scores” can then be used for analog selection or in KNN-based property estimation. This type of quantifiable analog selection can be a powerful tool for finding chemicals that are similar to a chemical of interest, replacing the need for subjective assessment of molecular similarity. More often than not, we are interested in predicting a property of interest. In this case, KNN-based similarity offers an alternative to standard linear regression approaches that works well for large, diverse data sets.

KNN-based property estimation is carried out by selecting the k -nearest neighbors for each compound and using the average of the neighbor's properties as an estimate of the property of our chemical of interest. A number of similar chemicals ($k = 1-10, 15, 20, 25$) are selected and the property of interest is estimated based on the values of these nearest neighbors. For instance, in estimating the $\log P$ of the probe compound, the mean $\log P$ for the k -nearest neighbors was used as the estimate. KNN estimation was carried out for all chemicals in all three of the similarity spaces, resulting in a full cross-validation. Thus the correlation coefficients reported are the cross-validated correlation coefficients.

3 RESULTS AND DISCUSSION

The principal objective of this paper was to illustrate the utility of tailoring similarity spaces to a specific property as opposed to the standard method of constructing similarity spaces that are property independent. To this end, we used three spaces, *viz.*, an arbitrary principal component space that would be used for the KNN-based estimation of both $\log P$ and BP, a topological index space based on the RR weighting of the indices for $\log P$, and a topological index space based on the RR weighting of the indices for BP.

From the initial set of 369 topological indices, 222 were retained for inclusion in the PCA and RR procedures after data reduction. From this set of 222 indices, 15 PCs were extracted with eigenvalues greater than or equal to one, resulting in the construction of a 15-dimensional arbitrary similarity space. Table 2 presents a summary of the two TIs most-highly correlated with each of the 15 PCs. For the sake of consistency, it was determined that we would then use the fifteen TIs with the highest rankings from the RR procedure. Table 3 presents the TIs selected for use in developing the similarity spaces tailored for $\log P$ and BP.

The t -values, indicated in Table 3, are model coefficients extracted from the RR procedure and used to rank the TIs from most to least influential based on the absolute value of the regression coefficient. On close examination of tables 2 and 3 we find that none of the TIs selected by RR are

well represented in the PCs. Only one of the indices chosen for the tailored BP model, DN^21_4 , shows up as the second most-correlated TI in PC_1 . Otherwise, the tailored sets have little in common with the TIs selected by RR. Further analysis shows that, of the five TIs most correlated with each of the fifteen PCs, DN^21_4 , is still the only TI shared in common between the arbitrary similarity space and either of the tailored spaces. A much higher degree of overlap exists between the two tailored sets. These sets share a total of seven of the fifteen TIs in common (indicated in bold face in Table 3).

Interestingly, beyond the seven shared indices, each of the tailored sets show a marked difference in the types of indices selected. The set developed for modeling $\log P$ is skewed towards zero-order chi indices, while the BP set shows a strong tendency towards the AZN triplets. While there is significant overlap between the two tailored sets of descriptors, it is encouraging to see that they show distinct differences as well. It is also encouraging to see the low-degree of overlap between the indices prevalent in the arbitrary set versus those present in the tailored sets. The arbitrary set should be a general characterization of the structural diversity within the data set and while this is useful for property estimation, there is no intrinsic link to any particular property. The tailored sets are geared towards the prediction of a specific property and, as such, should be geared more strongly towards defining the property of interest than simply characterizing the structural diversity of the structure space.

Figure 1. Plot of regression coefficient, R , for KNN-based estimation of $\log P$ in arbitrary and tailored similarity spaces at varying levels of K ($k = 1-10, 15, 20$ and 25).

Three Euclidean distance-based molecular similarity spaces were constructed from the PCs and TIs indicated in Tables 2 and 3: (a) an arbitrary molecular structure space using the fifteen PCs indicated in Table 2, (b) a space tailored for $\log P$ estimation based on the fifteen TIs presented in the second column of Table 3, and (c) a space tailored for BP estimation based on the TIs presented

in the third column of Table 3.

Figure 2. Plot of standard error, *s.e.*, for KNN-based estimation of log *P* in arbitrary and tailored similarity spaces at varying levels of *K* (*k* = 1–10, 15, 20 and 25).

Figure 3. Plot of regression coefficient, *R*, for KNN-based estimation of BP in arbitrary and tailored similarity spaces at varying levels of *K* (*k* = 1–10, 15, 20 and 25).

Finally, KNN-based property estimation was carried out on the three similarity spaces. First we examined the ability of each of the three spaces to estimate log *P*. In part this was done to verify that the tailored spaces are indeed fitted to the property of interest rather than simply another nonspecific structure space. The results of this analysis are depicted in Figures 1 and 2. Figure 1 presents the correlation coefficients for log *P* estimation in each of the similarity spaces for *K* = 1–10, 15, 20 and 25. Likewise, Figure 2 presents the standard error of log *P* estimation for each of the similarity spaces. As can be seen from these figures, the space tailored to log *P* definitely outperforms both of the other spaces for the purposes of estimating log *P*. As might be expected, the

arbitrary structure space outperforms the BP tailored space in estimating $\log P$ except for when using the one and two nearest neighbors. So, for the purposes of $\log P$ prediction, our tailored similarity space meets our expectations in its performance versus the performance of other spaces.

The examination of these structure spaces for the estimation of BP was carried out in a manner identical to that for the estimation of $\log P$. Each of the three similarity spaces was used in KNN-based estimation of BP for the complete set of 166 chemicals. These results are summarized in Figures 3 and 4. Figure 3 presents the correlation coefficients for BP estimation in each of the similarity spaces for $K = 1-10, 15, 20$ and 25 . Likewise, Figure 4 presents the standard error of BP estimation for each of the similarity spaces. As can be seen from these figures, the space tailored to BP definitely outperforms the arbitrary structure space, though, somewhat surprisingly, the space tailored to $\log P$ performs about as well as the BP tailored space. The BP tailored space just slightly outperforms the $\log P$ tailored space through $K = 1-6$. However, at higher values of K , the $\log P$ space actually outperforms the BP tailored space for the estimation of BP. While this is interesting, not too much weight should be given to the model's performance at higher values for K . As was shown in a recent study [30], loss of data variance is a real concern at the higher values of K . Thus we ideally want a model that has a high correlation, R , and low standard error, *s.e.*, using a minimal number of neighbors. Taking this into consideration, the two tailored similarity spaces are still essentially identical with regards to the prediction of BP for this particular set of 166 JP-8 components.

Figure 4. Plot of standard error, *s.e.*, for KNN-based estimation of BP in arbitrary and tailored similarity spaces at varying levels of K ($k = 1-10, 15, 20$ and 25).

It should be noted that while none of the molecular connectivity indices (chi indices) were selected by the RR method for modeling BP, they have been shown to be related to the modeling of normal boiling point in a number of studies [60–62]. Bearing this mind, we should not be terribly

surprised by the performance of the log P tailored space in the estimation of BP. After all, seven of the fifteen indices were shared in common between the two tailored sets, and then if we consider the chi indices as also related to BP, we now see that ten of the fifteen parameters in the log P set are also important for the prediction of BP.

4 CONCLUSIONS

As can be seen from the results presented in this study, tailored similarity spaces show definite promise in the development of property-specific similarity spaces, as opposed to standard structure-based similarity spaces. Further studies are needed to verify the general utility of this approach, specifically we need to examine the utility of spaces constructed from smaller “training sets” of chemicals when applied to large, diverse data sets. If these methods can be applied successfully to increase the predictive power of similarity measures for large, diverse data sets, this will become a powerful tool for both risk assessment and pharmaceutical design.

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Appendix 1.4

Manuscripts on PBPK modeling

PREDICTING BLOOD:AIR PARTITION COEFFICIENT OF STRUCTURALLY DIVERSE CHEMICALS USING THEORETICAL MOLECULAR DESCRIPTORS

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Quantitative structure-property relationship (QSPR) models for the estimation of rat blood:air partition coefficient were developed using ridge regression (RR), principal components regression (PCR), and partial least squares (PLS). A set of 24 compounds was analyzed, including 14 haloalkanes, 7 aromatic hydrocarbons, and 3 alkanes. Four classes of mathematical structural descriptors, viz., topostructural indices (TSI), topochemical indices (TCI), geometrical/shape indices (3DI), and quantum chemical indices (QCI), were used in the development of hierarchical and single-class models. The models developed using RR were superior to those developed using either PCR or PLS. The results indicate that the easily calculated TC descriptors give the best model.

Keywords: Blood:air partition coefficient; PBPK modeling; Mathematical molecular descriptors; Hierarchical QSPR; Ridge regression

INTRODUCTION

Partition coefficients of volatile organic chemicals are routinely used in the assessment of their hazard. In particular, partition coefficients are used in estimating uptake, distribution, metabolism and elimination of chemicals as well as the potential risk posed by such chemicals to human health as a result of exposure to them [1]. Therefore, there is an interest in estimating realistic blood:air and tissue:air partition coefficient (P) values of chemicals to which we are frequently exposed.

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Gargas et al. [1] determined various liquid:air and tissue:air partition coefficients for 0.9% saline, olive oil, blood, liver, muscle and fat tissue. Then they used regression models to predict the partition coefficient in one pair of media from the data for another pair. For example, human blood:air partition coefficient was estimated from the corresponding rat blood:air value; P for blood:air, liver:air, and muscle:air pairs were estimated from the P values of olive oil:air for various subsets of volatile organic chemicals (VOCs).

The blood:air partition coefficient (P , blood:air) is an important factor in determining the pulmonary uptake of VOCs through the inhalation route. P is routinely used in building physiologically based pharmacokinetic (PBPK) models for exposure assessment. Solubility of VOCs in blood is determined by two major factors: a) composition including the content of neutral lipid, phospholipid and water, and b) the extent of binding of these chemicals to specific blood components such as plasma proteins, hemoglobin, etc. Such physicochemical considerations have been used to develop physicochemically based estimation methods for blood:air P values of chemicals [2].

Methods for the estimation of P described above are essentially property-property correlations, which depend on the availability of relevant experimental and tissue composition data. In practical situations of hazard assessment of chemicals, the majority of them have very little or no available physicochemical data [3]. A viable alternative in such cases is the use of theoretical molecular descriptors, which can be calculated directly from molecular structure for the estimation of P . Quantitative structure-property/activity/toxicity relationships (QSPRs/ QSARs/QSTRs) based on such descriptors have been found to be useful in the estimation of diverse properties including boiling point [4-11], vapor pressure [12-17], octanol/water partition coefficient [7, 18], mutagenicity [19-23], aquatic toxicity [24-32], complement inhibitory activity [33], penetration through the blood-brain barrier [34], skin penetration [35], and toxic modes of action [36], to name just a few. In a recent paper, we found that computed molecular descriptors correlate well with blood:air partition coefficient of a congeneric set of 13 chlorocarbons [37]. In this paper, we have extended our study to estimate the blood:air P values for a large and structurally more diverse set of VOCs.

METHODS

Database

In a 1996 study, Poulin and Krishnan presented a table containing experimental blood:air partition coefficients for a set of 27 compounds including alkanes, haloalkanes, and aromatic hydrocarbons [2]; with the experimental values having been obtained from an earlier study performed by Gargas et al. using a modified version of the vial-equilibration technique [1]. Three of the 27 compounds were not included

in the present study, as it was not possible to calculate all descriptors for one of these compounds, and two of the compounds were cis/trans isomers which are not distinguishable in terms of their descriptors. The 24 compounds used in the current study, along with their experimental blood:air partition coefficient values, are provided in Table I.

TABLE I Experimental rat blood:air partition coefficients (P, blood:air) for the set of 24 compounds

<i>Chemicals</i>	<i>Experimental P^a</i>
Alkanes	
<i>n</i> -Hexane	2.29 ± 0.11
Cyclohexane	1.39 ± 0.09
<i>n</i> -Heptane	4.75 ± 0.15
Haloalkanes	
Dichloromethane	19.4 ± 0.8
Chloroform	20.8 ± 0.1
Carbon tetrachloride	4.52 ± 0.35
Bromochloromethane	41.5 ± 0.9
1,1-Dichloroethane	11.2 ± 0.1
1,2-Dichloroethane	30.4 ± 1.2
1,1,1-Trichloroethane	5.76 ± 0.5
1,1,2-Trichloroethane	58.0 ± 1.1
1,1,1,2-Tetrachloroethane	41.7 ± 1.0
1,1,2,2,-Tetrachloroethane	142 ± 6
Pentachloroethane	104 ± 3
1,2-Dichloropropane	18.7 ± 0.5
Trichloroethylene	21.9 ± 1.4
Tetrachloroethylene	18.9 ± 1.1
Aromatic hydrocarbons	
Benzene	17.8 ± 0.3
Chlorobenzene	59.4 ± 1.0
Toluene	18.0 ± 1.0
Styrene	40.2 ± 3.7
<i>o</i> -Xylene	44.3 ± 2.0
<i>m</i> -Xylene	46.0 ± 1.5
<i>p</i> -Xylene	41.3 ± 3.5

^a Values represent means ± standard error.

Calculation of Molecular Descriptors

A complete list of the 378 mathematical molecular descriptors calculated for use in the current study is provided in Table II. These parameters are partitioned into classes that are ordered hierarchically based on their level of complexity. At the lowest level of the hierarchy are the topostructural indices (TSI) which encode information strictly about the adjacency and topological distances of atoms in molecular structures. The topochemical indices (TCI) are more complex, encoding information not only about the topology but also chemical properties of the molecular structures. The geometrical indices (3DI) are more complex still, encoding information about the shape and 3-dimensional aspects of the structure. Finally,

the quantum chemical indices (QCI) are at the upper end of the hierarchy, encoding electronic information. The software programs used for the calculation of these descriptors include POLLY [38], Triplet [39, 40], Molconn-Z [41], Sybyl [42], and MOPAC [43]. Together, POLLY and Triplet calculate a large number of topological, i.e. topostructural and topochemical, descriptors. Molconn-Z provides additional topological descriptors as well as a small set of molecular shape indices. Sybyl and MOPAC calculate relatively small sets of 3-dimensional and quantum chemical descriptors, respectively.

TABLE II Descriptors calculated for use in the current study, along with brief descriptions and hierarchical classification

<i>Topostructural (TS)</i>	
I_D^W	Information index for the magnitudes of distances between all possible pairs of vertices of a graph
$\overline{I}_D^W$	Mean information index for the magnitude of distance
W	Wiener index = half-sum of the off-diagonal elements of the distance matrix of a graph
I^D	Degree complexity
H^V	Graph vertex complexity
H^D	Graph distance complexity
$\overline{IC}$	Information content of the distance matrix partitioned by frequency of occurrences of distance h
M_1	A Zagreb group parameter = sum of square of degree over all vertices
M_2	A Zagreb group parameter = sum of cross-product of degrees over all neighboring (connected) vertices
${}^h\chi$	Path connectivity index of order $h = 0-10$
${}^h\chi_C$	Cluster connectivity index of order $h = 3-6$
${}^h\chi_{PC}$	Path-cluster connectivity index of order $h = 4-6$
${}^h\chi_{Ch}$	Chain connectivity index of order $h = 3-10$
P_h	Number of paths of length $h = 0-10$
J	Balaban's J index based on topological distance
n_{rings}	Number of rings in a graph
n_{circ}	Number of circuits in a graph
DN^2S_y	Triplet index of distance matrix, square of graph order (# of non-H atoms), and distance sum; operation $y = 1-5$
DN^21_y	Triplet index of distance matrix, square of graph order, and number 1; operation $y = 1-5$
$AS1_y$	Triplet index of adjacency matrix, distance sum, and number 1; operation $y = 1-5$
$DS1_y$	Triplet index of distance matrix, distance sum, and number 1; operation $y = 1-5$
ASN_y	Triplet index of adjacency matrix, distance sum, and graph order; operation $y = 1-5$
DSN_y	Triplet index of distance matrix, distance sum, and graph order; operation $y = 1-5$
DN^2N_y	Triplet index of distance matrix, square of graph order, and graph order; operation $y = 1-5$
ANS_y	Triplet index of adjacency matrix, graph order, and distance sum; operation $y = 1-5$
$AN1_y$	Triplet index of adjacency matrix, graph order, and number 1; operation $y = 1-5$
ANN_y	Triplet index of adjacency matrix, graph order, and graph order again; operation $y = 1-5$
ASV_y	Triplet index of adjacency matrix, distance sum, and vertex degree; operation $y = 1-5$
DSV_y	Triplet index of distance matrix, distance sum, and vertex degree; operation $y = 1-5$
ANV_y	Triplet index of adjacency matrix, graph order, and vertex degree; operation $y = 1-5$

TABLE II (Continued)

<i>Topochemical (TC)</i>	
O	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-filled graph
O_{orb}	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-suppressed graph
I_{orb}	Information content or complexity of the hydrogen-suppressed graph at its maximum neighborhood of vertices
IC_r	Mean information content or complexity of a graph based on the r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
SIC_r	Structural information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
CIC_r	Complementary information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
${}^h\chi^b$	Bond path connectivity index of order $h = 0-6$
${}^h\chi_C^b$	Bond cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^b$	Bond chain connectivity index of order $h = 3-6$
${}^h\chi_{PC}^b$	Bond path-cluster connectivity index of order $h = 4-6$
${}^h\chi^v$	Valence path connectivity index of order $h = 0-10$
${}^h\chi_C^v$	Valence cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^v$	Valence chain connectivity index of order $h = 3-10$
${}^h\chi_{PC}^v$	Valence path-cluster connectivity index of order $h = 4-6$
J^B	Balaban's J index based on bond types
J^X	Balaban's J index based on relative electronegativities
J^Y	Balaban's J index based on relative covalent radii
AZV_y	Triplet index of adjacency matrix, atomic number, and vertex degree; operation $y = 1-5$
AZS_y	Triplet index of adjacency matrix, atomic number, and distance sum; operation $y = 1-5$
ASZ_y	Triplet index of adjacency matrix, distance sum, and atomic number; operation $y = 1-5$
AZN_y	Triplet index of adjacency matrix, atomic number, and graph order; operation $y = 1-5$
ANZ_y	Triplet index of adjacency matrix, graph order, and atomic number; operation $y = 1-5$
DSZ_y	Triplet index of distance matrix, distance sum, and atomic number; operation $y = 1-5$
DN^2Z_y	Triplet index of distance matrix, square of graph order, and atomic number; operation $y = 1-5$
nvx	Number of non-hydrogen atoms in a molecule
$nelem$	Number of elements in a molecule
fw	Molecular weight
${}^h\chi^v$	Valence path connectivity index of order $h = 7-10$
${}^h\chi_{Ch}^v$	Valence chain connectivity index of order $h = 7-10$
si	Shannon information index
$totop$	Total Topological Index t
$sumI$	Sum of the intrinsic state values I
$sumdelI$	Sum of delta- I values
$tets2$	Total topological state index based on electrotopological state indices
$phia$	Flexibility index ($kp1 * kp2/nvx$)
$IdCbar$	Bonchev-Trinajstić information index
IdC	Bonchev-Trinajstić information index
Wp	Wienerp
Pf	Plattf

TABLE II (Continued)

Wt	Total Wiener number
knotp	Difference of chi-cluster-3 and path/cluster-4
knotpv	Valence difference of chi-cluster-3 and path/cluster-4
nclass	Number of classes of topologically (symmetry) equivalent graph vertices
numHBd	Number of hydrogen bond donors
numwHBd	Number of weak hydrogen bond donors
numHBa	Number of hydrogen bond acceptors
SHCsats	E-State of C sp ³ bonded to other saturated C atoms
SHCsatu	E-State of C sp ³ bonded to unsaturated C atoms
SHvin	E-State of C atoms in the vinyl group, =CH-
SHtvn	E-State of C atoms in the terminal vinyl group, =CH ₂
SHavin	E-State of C atoms in the vinyl group, =CH-, bonded to an aromatic C
SHarom	E-State of C sp ² which are part of an aromatic system
SHHBd	Hydrogen bond donor index, sum of Hydrogen E-State values for -OH, =NH, -NH ₂ , -NH-, -SH, and #CH
SHwHBd	Weak hydrogen bond donor index, sum of C-H Hydrogen E-State values for hydrogen atoms on a C to which a F and/or Cl are also bonded
SHHBa	Hydrogen bond acceptor index, sum of the E-State values for -OH, =NH, -NH ₂ , -NH-, >N-, -O-, -S-, along with -F and -Cl
Qv	General Polarity descriptor
NHBint _y	Count of potential internal hydrogen bonders (y = 2-10)
SHBint _y	E-State descriptors of potential internal hydrogen bond strength (y = 2-10)
	Electrotopological State index values for atoms types: SHsOH, SHdNH, SHsSH, SHsNH ₂ , SHssNH, SHtCH, SHother, SHCHnX, Hmax Gmax, Hmin, Gmin, Hmaxpos, Hminneg, SsLi, SssBe, SssssBem, SssBH, SssB, SssssBm, SsCH ₃ , SdCH ₂ , SssCH ₂ , StCH, SdsCH, SaaCH, SssCH, SddC, StsC, SdssC, SaasC, SaaaC, SssssC, SsNH ₃ p, SsNH ₂ , SssNH ₂ p, SdNH, SssNH, SaaNH, StN, SssNHp, SdsN, SaaN, SssN, SddsN, SaasN, SssssNp, SsOH, SdO, SssO, SaaO, SsF, SsSiH ₃ , SssSiH ₂ , SssssSiH, SssssSi, SsPH ₂ , SssPH, SssP, SssssP, SssssP, SsSH, SdS, SssS, SaaS, SdssS, SddssS, SssssssS, SsCl, SsGeH ₂ , SssGeH ₂ , SssssGeH, SssssGe, SsAsH ₂ , SssAsH, SssAs, SdssAs, SssssAs, SsSeH, SdSe, SssSe, SaaSe, SdssSe, SddssSe, SsBr, SsSnH ₃ , SssSnH ₂ , SssssSnH, SssssSn, SsI, SsPbH ₃ , SssPbH ₂ , SssPbH, SssssPb
<i>Geometrical / Shape (3D)</i>	
kp0	Kappa zero
kp1-kp3	Kappa simple indices
ka1-ka3	Kappa alpha indices
V _w	Van der Waals volume
^{3D} W _H	3D Wiener number based on the hydrogen-filled geometric distance matrix
^{3D} W	3D Wiener number based on the hydrogen-suppressed geometric distance matrix
<i>Quantum Chemical (QC)</i>	
E _{HOMO}	Energy of the highest occupied molecular orbital
E _{HOMO-1}	Energy of the second highest occupied molecular orbital
E _{LUMO}	Energy of the lowest unoccupied molecular orbital
E _{LUMO+1}	Energy of the second lowest unoccupied molecular orbital
ΔH _f	Heat of formation
μ	Dipole moment

Statistical Analysis

Prior to performing regression analysis, the number of independent variables was reduced as follows: (1) descriptors that had a value of 0 for all 24 compounds were eliminated, (2) descriptors which could not be calculated for all 24 compounds were eliminated, (3) perfectly correlated descriptors were eliminated. In the latter case, the CORR procedure of the SAS statistical package [44] was used to identify pairs of perfectly correlated descriptors, and only one of each of the correlated pairs was retained for use in the subsequent analysis. At this point, 219 descriptors remained. The independent variables were scaled by the natural logarithm prior to analysis, as their ranges differed in some cases by several orders of magnitude. A small constant was added prior to the transformation in order to allow for log scaling of descriptors with values less than or equal to zero. Likewise, the values of the dependent variable differed by more than one order of magnitude and therefore were also log scaled.

Three forms of regression analyses were used to analyze the data, namely, ridge regression (RR) [45], principal component regression (PCR) [46], and partial least squares (PLS) [47], all of which are methods wherein the entire set of descriptors is utilized in modeling as opposed to subset regression. These regression methods are also useful in cases where the number of descriptors is substantially larger than the number of observations [45]. Hierarchical models and single-class models were developed utilizing the TSI, TCI, 3DI, and QCI in order to illuminate the roles played by the various classes of descriptors. Statistical parameters reported include the following: 1) the ridging constant, k , which controls the amount of smoothing in ridge regression, 2) cross-validated R^2 , which is obtained by temporarily removing each compound in turn from the data set and fitting the regression to the remaining $n-1$ compounds, and 3) the PRESS statistic, which is an accurate measure of model predictability.

TABLE III Summary statistics for ridge (RR), principal components (PCR), and partial least squares (PLS) regression models, $n = 24$.

Model Type	RR			PCR		PLS	
	$R^2_{c.v.}$	k	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
TS	0.2975	11.44	21.391	0.2166	23.854	-0.1100	33.797
TS+TC	0.6878	5.22	9.5059	0.6104	11.863	0.4480	16.809
TS+TC+3D	0.6758	6.88	9.8708	0.6090	11.905	0.4168	17.759
TS+TC+3D+QC	0.7095	2.95	8.8467	0.6331	11.172	0.4812	15.795
TS	0.2975	11.44	21.391	0.2166	23.854	-0.1100	33.797
TC	0.7732	0.1E-02	6.9065	0.6905	9.4246	0.5345	14.175
3D	0.0812	0.522	27.976	-0.1567	35.219	-0.4600	44.456
QC	0.2612	6.96	22.495	-1.1381	65.103	0.0472	29.013

TABLE IV Summary statistics for topological ridge regression models, $n = 23$

Model Type	RR		
	$R^2_{c.v.}$	k	PRESS
TS	0.458	10.04	12.372
TC	0.888	0.112E-02	2.565
TS+TC	0.885	0.888	2.6343

TABLE V Fitted ridge regression for the TC model, $n = 23$.

Descriptor	Coeff.	s.e.	t	$ t $	Descriptor	Coeff.	s.e.	t	$ t $
SHarom	0.094	0.016	5.870	5.870	$^2\chi^v$	-0.116	0.108	-1.080	1.080
Wt	0.033	0.006	5.760	5.760	Gmin	0.048	0.045	1.080	1.080
totop	0.042	0.008	5.600	5.600	AZN ₃	0.025	0.024	1.070	1.070
SaaCH	0.070	0.013	5.550	5.550	SIC ₄	-0.222	0.211	-1.050	1.050
$^6\chi^b_{Ch}$	5.411	1.007	5.380	5.380	SIC ₂	-0.446	0.429	-1.040	1.040
AZV ₃	0.085	0.020	4.380	4.380	IdC	0.017	0.017	1.020	1.020
SsCH3	-0.165	0.044	-3.770	3.770	SIC ₀	0.231	0.230	1.010	1.010
$^3\chi^v_C$	-0.124	0.034	-3.670	3.670	$^5\chi^v_{PC}$	0.276	0.275	1.000	1.000
numwHBd	0.281	0.078	3.590	3.590	$^4\chi^b_{PC}$	0.164	0.166	0.990	0.990
$^3\chi^b_C$	-0.141	0.042	-3.340	3.340	$^4\chi^v_C$	-0.366	0.373	-0.980	0.980
AZV ₁	0.097	0.031	3.160	3.160	$^4\chi^v_{PC}$	0.133	0.146	0.910	0.910
$^3\chi^v$	0.213	0.072	2.980	2.980	J ^X	-0.128	0.149	-0.850	0.850
DN ₂ Z ₄	0.041	0.014	2.910	2.910	Hmax	0.193	0.228	0.850	0.850
SHwHBd	0.253	0.091	2.780	2.780	CIC ₂	0.188	0.238	0.790	0.790
ASZ ₁	0.031	0.013	2.410	2.410	CIC ₃	0.132	0.168	0.790	0.790
$^3\chi^b$	0.188	0.081	2.320	2.320	SssssC	0.047	0.063	0.750	0.750
IC ₀	0.809	0.354	2.290	2.290	AZN ₁	0.020	0.028	0.710	0.710
nelem	0.662	0.298	2.220	2.220	CIC ₄	0.079	0.124	0.630	0.630
Qv	-0.421	0.199	-2.110	2.110	SHother	0.020	0.033	0.610	0.610
fw	0.181	0.087	2.070	2.070	SHvin	-0.136	0.225	-0.610	0.610
$^0\chi^b$	-0.158	0.077	-2.060	2.060	AZS ₃	0.010	0.017	0.590	0.590
AZN ₄	0.814	0.397	2.050	2.050	IC ₂	-0.056	0.118	-0.480	0.480
ANZ ₂	0.017	0.008	2.020	2.020	AZS ₂	-0.011	0.027	-0.410	0.410
SsBr	0.356	0.177	2.020	2.020	$^0\chi^v$	-0.032	0.079	-0.400	0.400
$^2\chi^b$	-0.182	0.092	-1.990	1.990	AZN ₂	0.013	0.033	0.400	0.400
AZV ₅	0.058	0.030	1.960	1.960	CIC ₁	0.031	0.083	0.370	0.370
SssCH2	-0.169	0.087	-1.950	1.950	O _{orb}	-0.089	0.253	-0.350	0.350
$^1\chi^v$	0.277	0.143	1.940	1.940	AZN ₅	0.009	0.026	0.340	0.340
sumdelI	0.116	0.060	1.920	1.920	IdCbar	0.085	0.250	0.340	0.340
$^6\chi^v$	1.907	1.006	1.890	1.890	tets2	0.024	0.080	0.290	0.290
SHCHnX	0.357	0.189	1.890	1.890	Hmin	0.086	0.307	0.280	0.280
Gmax	0.367	0.200	1.840	1.840	O	-0.030	0.112	-0.270	0.270
IC ₁	0.515	0.283	1.820	1.820	$^5\chi^b$	-0.128	0.551	-0.230	0.230
J ^Y	-0.234	0.130	-1.810	1.810	DN ₂ Z ₃	-0.041	0.182	-0.230	0.230
$^6\chi^b$	1.844	1.032	1.790	1.790	SIC ₁	0.070	0.334	0.210	0.210
DN ₂ Z ₂	0.055	0.032	1.700	1.700	$^5\chi^v$	-0.114	0.544	-0.210	0.210
SHHBA	0.028	0.017	1.700	1.700	SdssC	0.280	1.335	0.210	0.210

TABLE V (Continued)

knotp	-0.248	0.154	-1.610	1.610	I_{orb}	0.030	0.170	0.180	0.180
J^B	-0.217	0.143	-1.520	1.520	CIC_0	-0.013	0.071	-0.180	0.180
AZV ₄	0.155	0.102	1.520	1.520	IC_3	-0.017	0.108	-0.160	0.160
$^5\chi^v_c$	0.243	0.166	1.470	1.470	$^4\chi^v$	0.038	0.270	0.140	0.140
SaasC	0.113	0.080	1.420	1.420	SdsCH	-0.020	0.152	-0.130	0.130
DSZ ₂	0.052	0.038	1.380	1.380	$^4\chi^b$	0.031	0.264	0.120	0.120
phia	-0.106	0.078	-1.360	1.360	AZV ₂	0.020	0.164	0.120	0.120
DN ₂ Z ₁	0.030	0.023	1.350	1.350	$^1\chi^b$	0.012	0.104	0.110	0.110
SdCH2	0.203	0.151	1.350	1.350	SHCsatu	0.019	0.212	0.090	0.090
SsssCH	-0.389	0.291	-1.340	1.340	AZS ₅	0.002	0.020	0.080	0.080
$^6\chi^b_{PC}$	0.398	0.302	1.320	1.320	IC_4	0.006	0.080	0.070	0.070
ANZ ₁	0.051	0.039	1.320	1.320	ASZ ₂	0.001	0.022	0.050	0.050
SIC ₃	-0.313	0.240	-1.300	1.300	AZS ₄	0.003	0.063	0.040	0.040
$^5\chi^b_c$	0.300	0.230	1.300	1.300	AZS ₁	0.001	0.022	0.030	0.030
$^6\chi^v_{PC}$	0.425	0.327	1.300	1.300	$^7\chi^v$	-0.336	10.007	-0.030	0.030
knotpv	-0.168	0.134	-1.250	1.250	SHCsats	0.003	0.085	0.030	0.030
DN ₂ Z ₅	-0.182	0.146	-1.240	1.240	DSZ ₁	0.001	0.035	0.020	0.020
sumI	0.097	0.078	1.240	1.240	nclass	-0.002	0.127	-0.010	0.010
$^5\chi^b_{PC}$	0.432	0.373	1.160	1.160	CONSTANT	-3.275			
numHBa	0.020	0.018	1.110	1.110

Figure 1 Experimental vs predicted log P (blood:air) using the TC model, $n = 23$.

TABLE VI Experimental and predicted log P (blood:air) using the TC model, $n = 23$

<i>Chemicals</i>	<i>Experimental log P</i>	<i>Predicted log P</i>	<i>Residual</i>
Alkanes			
<i>n</i> -Hexane	0.82911	0.82855	-0.00056
<i>n</i> -Heptane	1.55812	1.55814	2E-05
Haloalkanes			
Dichloromethane	2.96563	2.96527	-0.00036
Chloroform	3.03587	3.03495	-0.00092
Carbon tetrachloride	1.50834	1.50851	0.00017
Bromochloromethane	3.72546	3.72569	0.00023
1,1-Dichloroethane	2.41493	2.41591	0.00098
1,2-Dichloroethane	3.4137	3.41444	0.00074
1,1,1-Trichloroethane	1.75148	1.75094	-0.00054
1,1,2-Trichloroethane	3.8954	4.06044	0.16504
1,1,1,2-Tetrachloroethane	3.8954	3.7305	-0.1649
1,1,2,2-Tetrachloroethane	4.95521	4.95583	0.00062
Pentachloroethane	4.6445	4.64439	-0.00011
1,2-Dichloropropane	2.92902	2.92852	-0.0005
Trichloroethylene	3.08672	3.08649	-0.00023
Tetrachloroethylene	2.93929	2.93916	-0.00013
Aromatic hydrocarbons			
Benzene	2.87916	2.8792	4E-05
Chlorobenzene	4.084	4.08429	0.00029
Toluene	2.89058	2.89037	-0.00021
Styrene	3.69372	3.69387	0.00015
<i>o</i> -Xylene	3.79113	3.79098	-0.00015
<i>m</i> -Xylene	3.82812	3.82864	0.00052
<i>p</i> -Xylene	3.72109	3.72086	-0.00023

RESULTS

Summary statistics for the models developed in this study based on the set of 24 structurally diverse compounds are provided in Table III. Overall, models developed using RR were superior to those developed using PCR or PLS. Therefore, the subsequent discussion will focus on RR results. Examining the hierarchically developed models, a significant increase in model quality is obtained upon the addition of TCI to the TSI set. The addition of 3DI and QCI yields little or no improvement in model quality. Of the single-class models, the TC is significantly better than any other descriptor class in modeling blood:air partition coefficient.

Further investigation showed that one compound in the set of 24, viz., cyclohexane, was an influential outlier. This is not altogether unexpected, as cyclohexane is the only cyclic non-aromatic compound in

the data set. The omission of cyclohexane led to significant model improvement. Table IV provides summary results utilizing the data set with cyclohexane removed. Although cyclohexane was an outlier for all but one of the models developed in this study, i.e. the QC model, Table IV includes models developed with topological indices only.

Table V provides the fitted ridge regression for the TC model developed using the data set with cyclohexane omitted and includes the coefficient, standard error, and t value for each of the descriptors in the model. The t value is obtained by dividing the coefficient by the standard error. A large $|t|$ value indicates that the associated descriptor is important in the model; however, the reverse is not necessarily so. A plot of the experimental vs predicted log P (blood:air) using the TC model is shown in Figure 1. The values of the log-scaled experimental and predicted log P values plotted in Figure 1 are provided in Table VI.

DISCUSSION

The goal of this study was to investigate the utility of four classes of calculated molecular descriptors, viz., topostructural indices, topochemical indices, 3-D descriptors, and quantum chemical indices, in estimating blood:air P values of a set of structurally diverse VOCs comprising alkanes, various haloalkanes and aromatics. In an earlier paper, Basak et al. [37] reported QSPRs for a congeneric subset of this set of compounds, viz., 13 chlorocarbons. A summary of the regression results from that study is provided in Table VII. Again, we find that the TC model obtained by ridge regression is superior to all other models developed. The TC model for the subset of chlorocarbons is nearly as good as the TC model developed for the set of 23 diverse compounds in terms of the cross-validated R^2 and the PRESS statistic. In many previous studies, we have found that either TSI or TSI+TCI provide acceptable QSAR models for both congeneric and diverse data sets [13, 21, 23, 31, 37, 48].

TABLE VII Summary statistics for ridge (RR), principal components (PCR), and partial least squares (PLS) regression models for the subset of 13 chlorocarbons.

Model Type	RR			PCR		PLS	
	$R^2_{c.v.}$	k	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
TS	0.452	9.212	6.60	-1.300	27.71	0.252	8.89
TS+TC	0.886	0.10E-02	1.37	0.790	2.53	0.807	2.33
TS+TC+3D	0.876	0.721	1.50	0.806	2.34	0.808	2.31
TS+TC+3D+QC	0.883	0.43E-01	1.40	0.819	2.18	0.821	2.16
TS	0.452	9.212	6.60	-1.300	27.71	0.262	8.89
TC	0.916	0.10E-02	1.02	0.843	1.89	0.848	1.83
3D	0.480	0.71E-01	6.27	-0.124	15.54	-0.205	14.52
QC	0.095	0.323	10.91	-0.250	15.06	-1.446	29.46

TABLE VIII Ten model descriptors with highest $|t|$ values for the diverse data set and the chlorocarbon subset.

<i>Diverse data set (n = 23)</i>					<i>Chlorocarbons (n = 13)</i>				
<i>Descriptor</i>	<i>Coeff.</i>	<i>s.e.</i>	<i>t</i>	$ t $	<i>Descriptor</i>	<i>Coeff.</i>	<i>s.e.</i>	<i>t</i>	$ t $
SHarom	0.094	0.016	5.870	5.870	AZV ₃	0.130	0.022	6.010	6.01
Wt	0.033	0.006	5.760	5.760	NoCl	0.027	0.005	4.990	4.99
totop	0.042	0.008	5.600	5.600	numHBa	0.080	0.021	3.910	3.91
SaaCH	0.070	0.013	5.550	5.550	SsssCH	-0.280	0.080	-3.510	3.51
$^6\chi^b_{Ch}$	5.411	1.007	5.380	5.380	SHHBa	0.061	0.018	3.340	3.34
AZV ₃	0.085	0.020	4.380	4.380	$^3\chi^v_C$	-0.062	0.019	-3.300	3.30
SsCH3	-0.165	0.044	-3.770	3.770	SsCH3	-0.124	0.038	-3.280	3.28
$^3\chi^v_C$	-0.124	0.034	-3.670	3.670	$^3\chi^b_C$	-0.073	0.023	-3.170	3.17
numwHBd	0.281	0.078	3.590	3.590	AZS ₄	-0.268	0.090	-2.970	2.97
$^3\chi^b_C$	-0.141	0.042	-3.340	3.340	SHother	-0.349	0.118	-2.960	2.96

It was of interest to examine which descriptors in the TC model developed in the current study had the greatest $|t|$ values, and thus held the greatest importance in the model. Comparing these with the important TC descriptors in the previous study involving only chlorocarbons (Table VIII) tells us something about which descriptors are important for the different sets of compounds. In doing so, we find that some descriptors are important for both data sets, including AZV₃, $^3\chi^v_C$ and SsCH3. The hydrogen bond acceptor descriptors which were important in the chlorocarbon model, i.e. numHBa and SHHBa, have been replaced by the hydrogen donor index, numwHBd. Other descriptors important in the current model which were not important in the chlorocarbon model include totop, Wt, and SHarom, the latter of which is an E-state descriptor associated with aromatic systems. It is well known that QSPR models work best with homogeneous data sets, which represent some structural or mechanistic class. On the other hand, Basak et al. argued that a collection of diverse molecular descriptors should be able to predict properties of structurally diverse sets [26]. A comparison of QSPRs of the set of 23 diverse compounds and the congeneric set of 13 chlorocarbons (Table IV and Table VII) supports this notion. Further studies with different properties of various congeneric and structurally diverse sets and properties are needed to test the validity of this hypothesis.

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PREDICTION OF TISSUE:AIR PARTITION COEFFICIENTS: A COMPARISON OF STRUCTURE-BASED AND PROPERTY-BASED METHODS

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Three linear regression methods were used to develop models for the prediction of rat tissue:air partition coefficient (P). In general, ridge regression (RR) was found to be superior to principal component regression (PCR) and partial least squares (PLS). A set of 46 diverse low molecular-weight volatile chemicals was used to model fat:air, liver:air, and muscle:air partition coefficients for male Fischer 344 rats. Comparisons were made between models developed using descriptors based solely on molecular structure and those developed using experimental properties, including saline:air and olive oil:air partition coefficients, as independent variables, indicating that the structure-property correlations are comparable to the property-property correlations. Multiple structure-based models were developed utilizing various classes of structural descriptors based on level of complexity, i.e., topostructural (TS), topochemical (TC), 3-dimensional (3D), and calculated octanol:water partition coefficient. In most cases, the structure-based models developed using only the TC descriptors were found to be superior to those developed using other structural descriptor classes. Haloalkane subgroups were modeled separately for comparative purposes, and although models based on the congeneric compounds were superior, the models developed on the complete sets of diverse compounds were acceptable. Comparisons were also made with respect to the types of descriptors important for partitioning across the various media.

Key Words: Tissue:air partition coefficient; PBPK model; Theoretical molecular descriptors; Ridge regression; Hierarchical QSAR (HiQSAR)

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INTRODUCTION

Blood:air and tissue:air partition coefficients of volatile organic chemicals (VOCs) are important for their hazard assessment and estimation of bioavailability of such chemicals at the various tissues. Such properties are routinely used in the physiologically based pharmacokinetic (PBPK) models pertaining to risk assessment of chemicals and also extrapolation of toxicity of a chemical from one species to another.

Gargas *et al.*[1] determined blood:air and tissue:air partition coefficients for various tissues including fat, muscle and liver. While experimental determination of blood:fat, blood:liver, and blood:muscle partition coefficients could be complicated and time consuming, these quantities can be computed as the ratio of blood:air and the various tissue:air partition coefficients. Such blood:tissue partition coefficients can be convenient input variables in PBPK models for hazard estimation.

In the practical hazard assessment of chemicals by regulatory agencies such as the United States Environmental Protection Agency (USEPA), Agency for Toxic Substances and Disease Registry (ATSDR), one must carry out rapid toxicity estimation of many chemicals. The Toxic Substances Control Act (TSCA) Inventory currently has over 75,000 chemicals [2]; the list of high production volume (HPV) chemicals contains over 2,800 substances [3]; and the 2001 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) priority list [4] contains 275 substances, many of which are VOCs, that are most commonly found at facilities on the National Priorities List (NPL) and have been determined to pose the most significant threat to human health based on toxicity and potential exposure at the NPL sites. Experimental determination of the various blood:tissue partition coefficients of all these chemicals for hazard assessment and PBPK modeling could be a daunting task. The list would become considerably larger if we also include the probable metabolites of the VOCs under study. A viable alternative to this quagmire is the computation of these properties from molecular descriptors that can be computed directly from chemical structure without any further input of experimental data.

In one of our earlier studies, Basak *et al.*[5] used computed structural parameters to develop successful predictive models for the estimation of blood:air partition coefficient of VOCs. Calculated descriptors have also been used by us in the estimation of lipophilicity [6-9], vapor pressure [10, 11], boiling point [12, 13], toxicity including mutagenicity [14-17], and toxic modes of actions of various congeneric and structurally diverse groups of chemicals[18]. In this paper, we have used calculated structural descriptors to formulate models for the estimation of fat:air, liver:air and muscle:air partition coefficients for a set of 46 structurally diverse VOCs.

METHODS

Database

Liquid:air and tissue:air partition coefficients were experimentally determined by Gargas *et al.* [1] using a modified version of the gas-phase vial equilibrium technique [19] and tissue homogenates prepared in 0.9% saline solution [20] for a set of low molecular-weight volatile chemicals. Table I includes experimentally determined male Fischer 344 rat tissue:air partition coefficients, including fat, liver, and muscle tissues, for a set of 46 chemicals including 26 haloalkanes, 2 nitroalkanes, 6 haloalkenes, 9 aromatics, and 3 additional compounds. Saline:air and olive oil:air partition coefficients, determined by Gargas *et al.*, are also listed in Table I. All experimental values were obtained at 37 °C.

It should be noted that the data used in the current study represent a subset of that reported by Gargas *et al.* [1]. Two cis/trans isomers were eliminated because they are indistinguishable in terms of their calculated molecular descriptors based on SMILES input. Methyl chloride was also removed from the data set as it is not possible to calculate our entire set of theoretic descriptors on two-atom compounds. In addition, three compounds were reported without discrete values for 0.9% saline:air P, all of which were aliphatic hydrocarbons. Preliminary studies indicated that the remaining three aliphatic hydrocarbons were outliers thus the decision was made to eliminate those, as well.

TABLE I Experimental liquid:air, calculated logP_{OW}, and experimental rat tissue:air partition coefficient data^a

No.	Chemical	0.9% saline:air	Olive oil:air	LogP _{OW}	Fat:air	Liver:air	Muscle:air
Haloalkanes							
1	Dichloromethane	5.96 ± 0.71	131 ± 7	1.16	120 ± 6	14.2 ± 1.2	7.92 ± 1.77
2	Chloroform	3.38 ± 0.09	402 ± 12	1.86	203 ± 5	21.1 ± 1.5	13.9 ± 1.9
3	Carbon tetrachloride	0.35 ± 0.03	374 ± 11	3	359 ± 11	14.2 ± 1.0	4.57 ± 0.59
4	Difluoromethane	1.31 ± 0.05	4.76 ± 0.75	0.56	1.43 ± 0.31	2.75 ± 0.39	1.44 ± 0.25
5	Fluorochloromethane	3.08 ± 0.07	22.3 ± 1.4	0.68	15.4 ± 1.0	3.44 ± 0.27	2.46 ± 0.52
6	Bromochloromethane	8.65 ± 0.28	361 ± 9	1.45	325 ± 3	29.2 ± 0.5	11.1 ± 1.8
7	Dibromomethane	14.4 ± 0.4	957 ± 39	1.95	792 ± 14	68.1 ± 1.4	40.5 ± 2.0
8	Chlorodibromomethane	7.34 ± 0.42	2683 ± 152	1.77	1917 ± 165	126 ± 7.1	55.6 ± 0.7
9	Chloroethane	1.09 ± 0.06	38.9 ± 3.1	1.47	38.6 ± 0.7	3.61 ± 0.32	3.22 ± 0.68
10	1,1-Dichloroethane	2.45 ± 0.04	186 ± 7	1.86	164 ± 4	10.8 ± 0.5	5.12 ± 0.48
11	1,2-Dichloroethane	11.4 ± 0.1	366 ± 8	1.6	344 ± 5	35.7 ± 1.6	23.4 ± 1.4
12	1,1,1-Trichloroethane	0.75 ± 0.07	295 ± 22	2.26	263 ± 12	8.6 ± 0.6	3.15 ± 0.33
13	1,1,2-Trichloroethane	13.3 ± 0.3	1776 ± 26	2.08	1438 ± 58	73.1 ± 0.8	22.9 ± 0.8
14	1,1,1,2-Tetrachloroethane	3.53 ± 0.23	2686 ± 51	2.64	2148 ± 82	88.2 ± 1.8	39.5 ± 2.5
15	1,1,2,2-Tetrachloroethane	23.4 ± 2.0	6358 ± 402	2.51	3767 ± 93	196 ± 12	101 ± 10
16	Pentachloroethane	2.32 ± 0.35	6689 ± 471	3.07	4118 ± 209	260 ± 11	72.4 ± 2.9
17	Hexachloroethane	0.66 ± 0.21	5015 ± 318	4.24	3321 ± 193	369 ± 17.5	75 ± 0.9
18	1,2-Dibromoethane	17.3 ± 0.8	1267 ± 91	2.13	1219 ± 50	119 ± 4	45.6 ± 3.3
19	1-Bromo-2-chloroethane	8.91 ± 0.56	569 ± 23	1.73	959 ± 39	42.8 ± 3.3	25.4 ± 3.1

TABLE I (Continued)

20	1,1,1-Trifluoro-2-chloroethane	0.42 ± 0.04	24.0 ± 2.5	1.7	21.2 ± 0.6	1.84 ± 0.14	1.23 ± 0.14
21	1,1,1-Trifluoro-2-bromo-2-chloroethane	0.50 ± 0.05	198 ± 4	2.44	182 ± 5	7.62 ± 1.20	4.46 ± 0.29
22	1-Chloropropane	1.04 ± 0.01	105 ± 2	1.95	118 ± 2	5.18 ± 0.38	2.08 ± 0.66
23	2-Chloropropane	0.82 ± 0.09	69.9 ± 3.5	1.81	68.4 ± 2.0	3.15 ± 0.24	2.04 ± 0.48
24	1,2-Dichloropropane	2.75 ± 0.11	428 ± 30	2.18	499 ± 30	24.8 ± 2.4	12.0 ± 1.1
25	n-Propyl bromide	1.44 ± 0.12	272 ± 8	2.13	236 ± 6	8.17 ± 0.62	4.21 ± 0.32
26	Isopropyl bromide	1.08 ± 0.04	164 ± 5	1.63	158 ± 5	4.41 ± 0.34	4.12 ± 0.35
Nitroalkanes							
27	1-Nitropropane	127 ± 4	1062 ± 21	0.8	506 ± 33	153 ± 17	28.9 ± 6.1
28	2-Nitropropane	98.3 ± 5.4	640 ± 16	0.61	155 ± 4	62.4 ± 1.4	29.1 ± 3.3
Haloalkenes							
29	Vinyl chloride	0.43 ± 0.04	24.4 ± 3.7	1.37	20.0 ± 0.7	1.60 ± 0.17	2.10 ± 0.45
30	1,1-Dichloroethylene	0.35 ± 0.06	64.3 ± 3.4	2.03	68.6 ± 2.1	4.42 ± 0.30	2.05 ± 0.31
31	Trichloroethylene	0.83 ± 0.30	553 ± 46	2.36	554 ± 21	27.2 ± 3.4	10.1 ± 2.7
32	Tetrachloroethylene	0.79 ± 0.06	2134 ± 159	3.47	1638 ± 91	70.3 ± 9.0	20.0 ± 2.5
33	Vinyl bromide	0.44 ± 0.06	56.0 ± 1.5	1.61	49.2 ± 1.3	3.33 ± 0.38	2.26 ± 0.13
34	Allyl chloride	2.75 ± 0.10	465 ± 5	2.04	101 ± 2	38.9 ± 4.5	11.0 ± 0.2
Aromatics							
35	Benzene	2.81 ± 0.07	2188 ± 41	2.64	499 ± 12	17.0 ± 1.3	10.3 ± 0.9
36	Chlorobenzene	1.75 ± 0.13	1056 ± 38	2.66	1277 ± 43	86.1 ± 3.0	34.0 ± 3.9
37	Toluene	1.41 ± 0.47	3548 ± 269	3.01	1021 ± 11	83.6 ± 5.8	27.7 ± 4.0
38	Styrene	1.97 ± 0.28	14706 ± 665	3.73	3476 ± 73	139 ± 7	46.7 ± 3.9
39	m-Methylstyrene	2.11 ± 0.30	13942 ± 567	3.75	11951 ± 692	327 ± 23	182 ± 10
40	p-Methylstyrene	2.65 ± 0.08	3534 ± 208	3.15	11281 ± 972	324 ± 17	183 ± 8
41	o-Xylene	1.92 ± 0.12	3245 ± 116	3.21	1877 ± 132	108 ± 7	51.5 ± 6.7
42	m-Xylene	1.77 ± 0.07	3319 ± 96	3.2	1859 ± 93	90.9 ± 4.4	41.9 ± 5.7
43	p-Xylene	11.4 ± 0.4	55.6 ± 1.4	1.13	1748 ± 65	90.0 ± 4.3	38.4 ± 4.1
Other							
44	Diethyl ether	0.56 ± 0.04	78.9 ± 9.1	2.45	47.7 ± 3.9	6.82 ± 0.54	5.28 ± 0.54
45	Isoflurane	2.06 ± 0.01	109 ± 5	1.99	98.1 ± 4.6	4.07 ± 0.20	1.60 ± 0.34
46	Isoprene	0.21 ± 0.02	8.81 ± 0.15	2.6	72.0 ± 2.4	3.12 ± 0.87	2.04 ± 0.27

^a Values represent mean ± standard error.

Molecular Descriptors

Theoretical molecular descriptors may be divided into hierarchical classes based upon level of complexity and demand for computational resources for their calculation. Topostructural (TS) descriptors, which encode information strictly on the adjacency and connectedness of atoms within a molecule, are the simplest of the hierarchical classes. Topochemical (TC) descriptors encode information related to both molecular topology and the chemical nature atoms and bonds within a molecule, such as atomic valence and bond type. The 3-dimensional or shape descriptors (3D) are still more complex, encoding information about the 3-dimensional aspects of molecular structure. The topostructural and topochemical descriptors are collectively referred to as topological descriptors. With the hierarchical QSAR (HiQSAR) method, multiple models are developed, each time including an additional class of descriptors which are more

complex and computationally demanding. Comparing the statistical parameters of the hierarchically developed models, we are able to see the relative contribution of each descriptor class.

Descriptors used in the present study were derived from molecular structure using software packages including POLLY [21], Triplet [22, 23], and Molconn-Z [24]. From POLLY and associated software developed by the authors, a set of 102 topological descriptors is available, including a large group of connectivity indices [25-28], path-length descriptors [25], Balaban's J indices [29-31], and information theoretic [32, 33] and neighborhood complexity indices [33]. The Triplet program calculates a set of 100 topological parameters which are derived from a matrix, a main diagonal column vector, and a free term column vector, converting the matrix into a system of linear equations whose solutions are the local vertex invariants. These local vertex invariants are then used in the following mathematical operations in order to obtain the triplet descriptors:

1. Summation, $E_i x_i$
2. Summation of squares, $E_i x_i^2$
3. Summation of square roots, $E_i x_i^{1/2}$
4. Sum of inverse square root of cross-product over edges ij , $E_{ij}(x_i x_j)^{-1/2}$
5. Product, $N(E_i x_i)^{1/N}$

We have also included 167 descriptors from Molconn-Z, including an extended set of connectivity indices, electrotopological indices [34, 35] and hydrogen bonding descriptors, as well as a small set of molecular shape descriptors.

H-Bond, a software program developed by Basak [36], was used to calculate HB_1 , a measure of hydrogen bonding potential. *n*-octanol:water partition coefficients were calculated by the LogP program [37] and are included in Table I.

A brief description of the set of theoretical molecular descriptors used in the current study is provided in Table II. For the sake of brevity, the calculated values for these descriptors are not provided, though they may be obtained from the authors upon request.

Statistical Analysis

Independent and dependent variables were scaled by the natural logarithm, as their respective ranges differed by several orders of magnitude. The CORR procedure of the SAS statistical package [38] was used to identify perfectly correlated descriptors, i.e. $r = 1.0$. In each case, only one descriptor of a perfectly correlated pair was retained for use in the subsequent analysis. Any descriptor that either had a value of zero for all compounds in the data set or could not be calculated for all compounds in the data set was removed.

TABLE II Symbols, definitions and classification of calculated molecular descriptors

<i>Topostructural (TS)</i>	
I_D^W	Information index for the magnitudes of distances between all possible pairs of vertices of a graph
$\overline{I_D^W}$	Mean information index for the magnitude of distance
W	Wiener index = half-sum of the off-diagonal elements of the distance matrix of a graph
I^D	Degree complexity
H^V	Graph vertex complexity
H^D	Graph distance complexity
$\overline{IC}$	Information content of the distance matrix partitioned by frequency of occurrences of distance h
M_1	A Zagreb group parameter = sum of square of degree over all vertices
M_2	A Zagreb group parameter = sum of cross-product of degrees over all neighboring (connected) vertices
${}^h\chi$	Path connectivity index of order h = 0-10
${}^h\chi_C$	Cluster connectivity index of order h = 3-6
${}^h\chi_{PC}$	Path-cluster connectivity index of order h = 4-6
${}^h\chi_{Ch}$	Chain connectivity index of order h = 3-10
P_h	Number of paths of length h = 0-10
J	Balaban's J index based on topological distance
nrings	Number of rings in a graph
ncirc	Number of circuits in a graph
DN^2S_y	Triplet index of distance matrix, square of graph order (# of non-H atoms), and distance sum; operation y = 1-5
DN^21_y	Triplet index of distance matrix, square of graph order, and number 1; operation y = 1-5
$AS1_y$	Triplet index of adjacency matrix, distance sum, and number 1; operation y = 1-5
$DS1_y$	Triplet index of distance matrix, distance sum, and number 1; operation y = 1-5
ASN_y	Triplet index of adjacency matrix, distance sum, and graph order; operation y = 1-5
DSN_y	Triplet index of distance matrix, distance sum, and graph order; operation y = 1-5
DN^2N_y	Triplet index of distance matrix, square of graph order, and graph order; operation y = 1-5
ANS_y	Triplet index of adjacency matrix, graph order, and distance sum; operation y = 1-5
$AN1_y$	Triplet index of adjacency matrix, graph order, and number 1; operation y = 1-5
ANN_y	Triplet index of adjacency matrix, graph order, and graph order again; operation y = 1-5
ASV_y	Triplet index of adjacency matrix, distance sum, and vertex degree; operation y = 1-5
DSV_y	Triplet index of distance matrix, distance sum, and vertex degree; operation y = 1-5
ANV_y	Triplet index of adjacency matrix, graph order, and vertex degree; operation y = 1-5
<i>Topochemical (TC)</i>	
O	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-filled graph
O_{orb}	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-suppressed graph
I_{orb}	Information content or complexity of the hydrogen-suppressed graph at its maximum neighborhood of vertices
IC_r	Mean information content or complexity of a graph based on the r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
SIC_r	Structural information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph

TABLE II (Continued)

CIC_r	Complementary information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
${}^h\chi^b$	Bond path connectivity index of order $h = 0-6$
${}^h\chi_C^b$	Bond cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^b$	Bond chain connectivity index of order $h = 3-6$
${}^h\chi_{PC}^b$	Bond path-cluster connectivity index of order $h = 4-6$
${}^h\chi^v$	Valence path connectivity index of order $h = 0-10$
${}^h\chi_C^v$	Valence cluster connectivity index of order $h = 3-6$
${}^h\chi_{Ch}^v$	Valence chain connectivity index of order $h = 3-10$
${}^h\chi_{PC}^v$	Valence path-cluster connectivity index of order $h = 4-6$
J^B	Balaban's J index based on bond types
J^X	Balaban's J index based on relative electronegativities
J^Y	Balaban's J index based on relative covalent radii
HB_1	Hydrogen bonding parameter
AZV_y	Triplet index of adjacency matrix, atomic number, and vertex degree; operation $y = 1-5$
AZS_y	Triplet index of adjacency matrix, atomic number, and distance sum; operation $y = 1-5$
ASZ_y	Triplet index of adjacency matrix, distance sum, and atomic number; operation $y = 1-5$
AZN_y	Triplet index of adjacency matrix, atomic number, and graph order; operation $y = 1-5$
ANZ_y	Triplet index of adjacency matrix, graph order, and atomic number; operation $y = 1-5$
DSZ_y	Triplet index of distance matrix, distance sum, and atomic number; operation $y = 1-5$
DN^2Z_y	Triplet index of distance matrix, square of graph order, and atomic number; operation $y = 1-5$
nvx	Number of non-hydrogen atoms in a molecule
$nelem$	Number of elements in a molecule
fw	Molecular weight
si	Shannon information index
$totop$	Total Topological Index t
$sumI$	Sum of the intrinsic state values I
$sumdelI$	Sum of delta- I values
$tets2$	Total topological state index based on electrotopological state indices
$phia$	Flexibility index ($kp1 * kp2/nvx$)
$IdCbar$	Bonchev-Trinajstić information index
IdC	Bonchev-Trinajstić information index
Wp	Wienerp
Pf	Plattf
Wt	Total Wiener number
$knotp$	Difference of chi-cluster-3 and path/cluster-4
$knotpv$	Valence difference of chi-cluster-3 and path/cluster-4
$nclass$	Number of classes of topologically (symmetry) equivalent graph vertices
$numHBd$	Number of hydrogen bond donors
$numwHBd$	Number of weak hydrogen bond donors
$numHBa$	Number of hydrogen bond acceptors
$SHCsats$	E-State of C sp^3 bonded to other saturated C atoms
$SHCsatu$	E-State of C sp^3 bonded to unsaturated C atoms
$SHvin$	E-State of C atoms in the vinyl group, $=CH-$
$SHtvn$	E-State of C atoms in the terminal vinyl group, $=CH_2$

TABLE II (Continued)

SHavin	E-State of C atoms in the vinyl group, =CH-, bonded to an aromatic C
SHarom	E-State of C sp ² which are part of an aromatic system
SHHBd	Hydrogen bond donor index, sum of Hydrogen E-State values for -OH, =NH, -NH ₂ , -NH-, -SH, and #CH
SHwHBd	Weak hydrogen bond donor index, sum of C-H Hydrogen E-State values for hydrogen atoms on a C to which a F and/or Cl are also bonded
SHHBa	Hydrogen bond acceptor index, sum of the E-State values for -OH, =NH, -NH ₂ , -NH-, >N-, -O-, -S-, along with -F and -Cl
Qv	General Polarity descriptor
NHBint _y	Count of potential internal hydrogen bonders (y = 2-10)
SHBint _y	E-State descriptors of potential internal hydrogen bond strength (y =2-10)
	Electrotopological State index values for atoms types: SHsOH, SHdNH, SHsSH, SHsNH ₂ , SHssNH, SHtCH, SHother, SHCHnX, Hmax Gmax, Hmin, Gmin, Hmaxpos, Hminneg, SsLi, SssBe, SssssBem, SssBH, SsssB, SssssBm, SsCH ₃ , SdCH ₂ , SssCH ₂ , StCH, SdsCH, SaaCH, SsssCH, SddC, StsC, SdssC, SaasC, SaaaC, SssssC, SsNH ₃ p, SsNH ₂ , SssNH ₂ p, SdNH, SssNH, SaaNH, StN, SssNHp, SdsN, SaaN, SssN, SddsN, SaasN, SssssNp, SsOH, SdO, SssO, SaaO, SsF, SsSiH ₃ , SssSiH ₂ , SssssSi, SssPH ₂ , SssPH, SssssP, SdssssP, SssssP, SsSH, SdS, SssS, SaaS, SdssS, SddssS, SssssssS, SsCl, SsGeH ₃ , SssGeH ₂ , SssssGeH, SssssGe, SsAsH ₂ , SssAsH, SssssAs, SdssssAs, SssssssAs, SsSeH, SdSe, SssSe, SaaSe, SdssSe, SddssSe, SsBr, SsSnH ₃ , SssSnH ₂ , SssssSnH, SssssSn, SsI, SsPbH ₃ , SssPbH ₂ , SssssPbH, SssssPb
<i>Geometrical / Shape (3D)</i>	
kp0	Kappa zero
kp1-kp3	Kappa simple indices
ka1-ka3	Kappa alpha indices

Models were developed using ridge regression (RR) [39], principal components regression (PCR) [40], and partial least squares (PLS) regression [41-43] methodologies, utilizing molecular descriptors in a hierarchical fashion. In addition, each class of descriptors was used independently to obtain single-class models. RR, PCR, and PLS are useful in cases wherein the number of descriptors is much greater than the number of observations, as well as in cases where the independent variables are highly intercorrelated. In addition, these regression methods make use of all independent variables as opposed to subset regression wherein it is possible that important parameters may be eliminated from the study. Statistical parameters reported include the cross-validated R² value, which is obtained by removing each compound in turn from the data set and fitting the regression to the remaining *n*-1 compounds, and the PRESS statistic which is a reliable measure of model predictability. In addition, the *t* values (coefficient estimate/std. err) can be examined in order to identify significant descriptors. Although a descriptor with a large $|t|$ indicates that the associated descriptor is important in the model, it should be cautioned that the reverse is not necessarily true.

Honest assessment of the quality of a prediction model is seldom straightforward, but is particularly challenging in a situation such as this where the number of independent variables far exceeds the number of observations [44, 45]. In these cases, conventional regression measures such as R^2 are useless. The measure we use is the cross-validation (or jack-knife) sum of squares. For this measure, each compound in turn is omitted from the data set, and the coefficients of the regression model (RR, PLS or PCR) computed using the remaining $n-1$ cases. These coefficients are used to predict the hold-out case. The overall quality of the fit is measured by the prediction sum of squares PRESS – the sum of squares of the difference between the actual observed activity and that predicted from the regression. A cross-validation R^2 can be defined by:

$$R_{cv}^2 = 1 - \frac{PRESS}{SSTotal}$$

Unlike R^2 , this R_{cv}^2 does not increase if irrelevant predictors are added to the model; rather it tends to decrease. And where R^2 is necessarily non-negative, R_{cv}^2 may be negative. This non-uncommon situation is an indication that the model fitted is poor – worse, in fact, than making predictions by ignoring the predictors and using the mean activity as the prediction in all circumstances.

R_{cv}^2 mimics the results of applying the final regression to predicting a future case; large values can be interpreted unequivocally and without regard to either the number of cases or predictors as indicating that the fitted regression will accurately predict the activity of future compounds of the same chemical type as those used to calibrate the regression.

In an attempt to gain further insight into the types of descriptors that are important in the partitioning of chemicals across the various tissues, variable clustering was performed using the VARCLUS procedure of the SAS statistical package [38]. This procedure divides the set of descriptors into disjoint clusters such that each cluster is essentially uni-dimensional. Interpretation of the descriptors, in terms of what aspects of chemical structure they represent, may be aided by examining other descriptors that fall within the same cluster.

RESULTS

Studies were done on the complete set of 46 diverse compounds as well as the structurally homogeneous subset of 26 haloalkanes for the prediction of rat fat:air, liver:air, and muscle:air partition coefficients, the results of which are provided in Tables III-V, respectively. It was of interest to compare our models developed with theoretical structural descriptors to models developed with experimental properties used by Gargas *et al.* [1] as independent variables, namely, $\log P_{\text{olive oil:air}}$ and $\log P_{\text{saline:air}}$. The results of these

property-property correlations are also included in Tables III-V. It is important to note that the statistical results reported for the property-property correlations were not taken directly from the Gargas study. Rather, property data were taken from the Gargas study for the same sets of compounds utilized in the current study, and linear models were developed by our team using the SAS statistical package [38]. In general, the RR methodology outperformed either PCR or PLS, and either the TC or the TS+TC models were superior to those developed using other descriptor classes. It is not surprising that, for each type of partition coefficient, the model developed for the set of 26 haloalkanes is superior to the model developed for the more diverse set of 46 compounds. However, models developed for the larger, more diverse set are reasonable.

TABLE III Summary statistics of predictive models for rat fat:air partition coefficient based on experimental properties and theoretical structural descriptors

<i>A. 46 DIVERSE CHEMICALS</i>								
<i>Independent Variables</i>	<i>RR</i>		<i>PCR</i>		<i>PLS</i>		<i>LR</i>	
	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>
<i>Structural descriptors</i>								
TS	0.325	106	0.239	119	0.328	106		
TS+TC	0.947	8.35	0.701	46.8	0.886	17.8		
TS+TC+3D	0.943	9.00	0.710	45.5	0.888	17.6		
TS+TC+3D+logP	0.941	9.23	0.708	45.9	0.892	17.0		
TS	0.325	106	0.239	119	0.328	106		
TC	0.939	9.49	0.565	68.2	0.843	24.7		
3D	0.253	117	0.015	154	-0.023	160		
<i>Properties</i>								
logP _{olive oil:air}							0.927	11.5
logP _{olive oil:air} + logP _{saline:air}							0.932	10.6
<i>B. 26 HALOALKANES</i>								
<i>Independent Variables</i>	<i>RR</i>		<i>PCR</i>		<i>PLS</i>		<i>LR</i>	
	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>	$R^2_{c.v.}$	<i>PRESS</i>
<i>Structural descriptors</i>								
TS	0.143	74.6	-0.432	125	-0.112	96.8		
TS+TC	0.971	2.54	-0.917	7.23	0.941	5.16		
TS+TC+3D	0.969	2.68	0.894	9.21	0.930	6.06		
TS+TC+3D+logP	0.969	2.74	0.898	8.91	0.930	6.09		
TS	0.143	74.6	-0.432	125	-0.112	96.8		
TC	0.972	2.46	0.952	4.19	0.945	4.81		
3D	0.926	6.41	0.918	7.14	0.927	6.38		
<i>Properties</i>								
logP _{olive oil:air}							0.960	3.48
logP _{olive oil:air} + logP _{saline:air}							0.958	3.69

TABLE IV Summary statistics of predictive models for rat liver:air partition coefficient based on experimental properties and theoretical structural descriptors.

A. 46 DIVERSE CHEMICALS								
Independent Variables	RR		PCR		PLS		LR	
	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
Structural descriptors								
TS	0.226	88.6	-0.058	121	0.242	86.8		
TS+TC	0.917	9.48	0.250	85.9	0.678	36.9		
TS+TC+3D	0.916	9.56	0.259	84.9	0.746	29.1		
TS+TC+3D+logP	0.920	9.20	0.243	86.7	0.743	29.4		
TS	0.226	88.6	-0.058	121	0.242	86.8		
TC	0.942	6.62	0.064	107	0.678	36.8		
3D	0.165	95.6	0.055	108	0.035	110		
Properties								
logP _{olive oil:air} + logP _{saline:air}							0.894	12.1
B. 26 HALOALKANES								
Independent Variables	RR		PCR		PLS		LR	
	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
Structural descriptors								
TS	0.029	57.8	-0.845	110	-0.262	75.2		
TS+TC	0.954	2.76	0.884	6.93	0.837	9.69		
TS+TC+3D	0.950	2.95	0.870	7.74	0.779	13.1		
TS+TC+3D+logP	0.957	2.54	0.871	7.70	0.813	11.1		
TS	0.029	57.8	-0.845	110	-0.262	75.2		
TC	0.964	2.16	0.896	6.17	0.837	9.70		
3D	0.826	10.4	0.808	11.4	0.803	11.7		
Properties								
logP _{olive oil:air} + logP _{saline:air}							0.851	8.89

Ridge regression models developed using the TC or TS+TC theoretical descriptors were comparable or superior to models developed using experimental properties, i.e. logP_{olive oil:air} and/or logP_{saline:air} (Tables III-V). For example, the cross-validated R^2 and PRESS statistic for the rat muscle:air partition coefficient are 0.863 and 12.2, respectively, for the TC model, based on the set of 46 diverse compounds and developed using theoretical descriptors; while the same statistical measures are 0.891 and 9.70, respectively for the model based on experimental logP_{olive oil:air} and logP_{saline:air} (Table V). When the same study is done on the set of 26 haloalkanes, the cross-validated R^2 and PRESS are 0.906 and 4.30, respectively, for the TC model using theoretical descriptors; while the same statistical measures are 0.876 and 5.67 for the model based on experimental logP_{olive oil:air} and logP_{saline:air} (Table V). As would be expected, the PRESS statistic increases as the structurally different chemicals are added to the haloalkane subsets.

Tables VI-VIII provide ridge regression coefficients, standard errors, and cluster membership for the top 20 descriptors based on $|t|$ values for the TC rat fat:air, liver:air, and muscle:air models, respectively, based on the set of 46 diverse chemicals. Examining only the 20 descriptors with highest $|t|$ values, descriptors from clusters 10 and 20 are present in both the muscle:air and liver:air models and are absent from the fat:air model. Cluster 10 is composed of descriptors representing polarity and hydrogen bonding and includes E-state descriptors for O and N atom types as well as a hydrogen bonding parameter. The descriptors from cluster 20 that are important here include Balaban's J indices, J^B , J^X , and J^Y . Descriptors from clusters 14 and 18 are present in all studies, the former including low-order valence connectivity indices and molecular weight, and the latter including descriptors of cyclicity and aromaticity.

TABLE V Summary statistics of predictive models for rat muscle:air partition coefficient based on experimental properties and theoretical structural descriptors

A. 46 DIVERSE CHEMICALS								
Independent Variables	RR		PCR		PLS		LR	
	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
Structural descriptors								
TS	0.203	70.8	0.004	88.7	0.169	73.8		
TS+TC	0.849	13.4	0.222	69.0	0.624	33.4		
TS+TC+3D	0.855	12.9	0.232	68.2	0.589	36.4		
TS+TC+3D+logP	0.855	12.9	0.216	69.6	0.599	35.6		
TS	0.203	70.8	0.004	88.7	0.169	73.8		
TC	0.863	12.2	-0.010	89.7	0.576	37.6		
3D	0.089	80.9	-0.061	94.2	-0.079	95.8		
Properties								
$\log P_{\text{olive oil:air}} + \log P_{\text{saline:air}}$							0.891	9.70
B. 26 HALOALKANES								
Independent Variables	RR		PCR		PLS		LR	
	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS	$R^2_{c.v.}$	PRESS
Structural descriptors								
TS	-0.014	46.5	-1.265	104	-0.248	57.2		
TS+TC	0.902	4.49	0.855	6.65	0.870	5.98		
TS+TC+3D	0.900	4.60	0.855	6.64	0.826	7.96		
TS+TC+3D+logP	0.899	4.63	0.855	6.64	0.826	7.99		
TS	-0.014	46.5	-1.265	104	-0.248	57.2		
TC	0.906	4.30	0.871	5.91	0.848	6.98		
3D	0.820	8.27	0.792	9.56	0.800	9.18		
Properties								
$\log P_{\text{olive oil:air}} + \log P_{\text{saline:air}}$							0.876	5.67

DISCUSSION

The objective of the study reported in this paper was two-fold: a) estimation of fat:air, muscle:air, and liver:air partition coefficients of VOCs from their chemical structure and b) a comparative analysis of structure-based and property based descriptors in the estimation of tissue:air partition coefficients.

To this end, we developed HiQSAR models for a set of 46 diverse chemicals as well as a subset of 26 halocarbons for all three tissue:air partition coefficients. A perusal of the regression models presented in Table III shows that for the fat:air partition coefficient, either the TC indices or the combination of TS&TC indices gave the best predictive models. The ridge regression method resulted in superior models compared to PLS and PCR techniques, in line with our earlier observations [5, 17, 46-48] It is interesting to note that attempts to estimate fat:air partition coefficients of the VOCs by property-property correlation using either olive oil:air or the combination of olive oil:air and saline:air partition coefficients resulted in models of comparable quality.

Models developed with the congeneric set of 26 haloalkanes for tissue:air partition coefficient show a similar trend. There is improvement in model quality for this smaller subset as compared to the total set of 46 VOCs. Here again either the TC or the TS plus TC indices gave the best result; these models also outperformed the property-property correlation models based on either olive oil:air partition coefficient or a combination of olive oil:air and saline:air partition coefficients.

Data depicted in Tables IV and V, dealing with regression models of liver:air and muscle:air partition coefficients, respectively, show the same trend as observed for the fat:air partition coefficient, viz., in the HiQSAR scheme, either the TC or TS+TC models performed the best; structure-based descriptors and experimental olive oil:air and saline:air partition coefficients resulted in QSARs of comparable quality; there was some improvement in the predictive models for the subset of 26 haloalkanes vis-a-vis the diverse set of 46 chemicals.

It is interesting to note the profile of molecular descriptors which play important role in the prediction of the three tissue:air partition coefficients. The RR routine provides as output the t values of the individual indices which can be used to order the TIs according to their relative importance in estimating the property under investigation. The 20 TIs in the TC models with highest $|t|$ values are given in Tables VI-VIII for fat:air, liver:air, and muscle:air partition coefficients, respectively. A perusal of the data in Tabel VI for fat:air partition coefficient shows that the connectivity and triplet indices dominate the set of parameters. On the other hand, hydrogen-bonding parameters such as HB_1 do not appear in the list of most important twenty indices. This makes sense in view of the fact that fatty tissues contain more hydrophobic materials such as triglycerides through which lipophilic chemicals will cross by passive

transport mechanism, and this will be governed mainly by general shape, size, branching, etc, associate with the molecular architecture.

TABLE VI Cluster membership, ridge regression coefficient, and standard error for each of the top 20 descriptors, ranked by $|t|$, in the topochemical rat fat:air partition coefficient model, $n = 46$

Cluster #	Descriptor	RR coeff	s.e.	t
14	$^1\chi^v$	1.223	0.073	16.66
14	$^0\chi^v$	0.816	0.054	15.05
14	AZV ₄	0.421	0.029	14.44
6	AZV ₁	0.227	0.025	8.97
14	AZN ₄	1.377	0.161	8.54
6	AZV ₃	0.172	0.021	8.14
14	$^2\chi^v$	0.528	0.066	7.98
13	SsF	-0.200	0.027	-7.32
6	AZS ₅	0.073	0.010	6.95
18	SaaCH	0.090	0.013	6.77
18	$^6\chi^v_{ch}$	7.925	1.186	6.68
6	AZS ₃	0.086	0.013	6.65
18	SHarom	0.121	0.018	6.65
13	Gmin	0.432	0.066	6.59
1	$^1\chi^b$	0.407	0.063	6.5
17	ANZ ₁	0.202	0.033	6.22
6	Wt	0.063	0.010	6.09
10	SdO	0.157	0.027	5.76
14	fw	0.381	0.068	5.6
18	phia	0.447	0.080	5.58

A perusal of the TIs most important for the QSARs for muscle:air and liver:air partition coefficients (Tables VII and VIII) shows that parameters such as HB₁, SdO and SddsN play an important role in predicting the property. The liver and muscle tissues, particularly their membranous components (which play a dominant role in the partitioning and uptake of chemicals) will contain higher amounts of polar lipids such as phospholipids, gangliosides, sulfolipids, etc. as compared to the fatty tissues. This may be the reason why parameters encoding information about hydrogen bonding and polarity assume dominant roles in the partitioning of chemicals between muscle/liver:air as opposed to fat:air. Independent variables belonging to clusters 14 and 18 are important in modeling all of the tissue:air partition coefficients. These two clusters contain the following parameters:

Cluster #14: $^0\chi^v$, $^1\chi^v$, $^2\chi^v$, AZV₄, AZN₄, fw, ka1

Cluster #18: $^6\chi_{ch}$, $^6\chi^v_{ch}$, nrings, ncirc, phia, SHother, SaaCH, Sharom

TABLE VII Cluster membership, ridge regression coefficient, and standard error for each of the top 20 descriptors, ranked by $|t|$, in the topochemical rat liver:air partition coefficient model, $n = 46$

Cluster #	Descriptor	RR coeff	s.e.	t
10	SdO	0.381	0.004	90.29
20	J ^B	-1.628	0.022	-75.08
20	J ^Y	-1.620	0.022	-73.83
14	fw	1.372	0.022	63.6
20	J ^X	-1.683	0.031	-54.93
10	HB ₁	0.456	0.009	53.35
18	⁶ χ _{ch} ^v	19.137	0.432	44.26
18	SHarom	0.309	0.007	43.3
10	SddsN	-2.341	0.055	-42.72
12	SdsCH	0.615	0.015	42.42
6	AZN ₁	-0.149	0.004	-41.07
11	AZS ₄	-0.843	0.021	-39.22
16	nelem	-1.999	0.051	-39.21
17	ASZ ₂	-0.146	0.004	-39.13
6	totop	-0.174	0.004	-39.06
18	SaaCH	0.224	0.006	38.39
6	AZN ₅	-0.129	0.004	-35.05
7	⁴ χ _{pc} ^v	0.707	0.020	35.01
14	² χ ^v	0.499	0.015	33.94
14	AZV ₄	0.501	0.015	33.5

Clusters 14 and 18 have descriptors which encode information regarding general structural features; cluster 14 (e.g., ⁰χ^v, ¹χ^v, ²χ^v, fw) quantifying molecular size, and cluster 18 (e.g., ⁶χ_{ch}, ⁶χ_{ch}^v, nrings, ncirc, SHarom) containing information about cyclicity. It is important to note that 9 of the 46 compounds (Table I) analyzed in this paper are cyclic/aromatic, and cluster 18 represents information about molecular cyclicity/aromaticity. Therefore, it is clear that molecular features such as general shape and size, as well as special structural attributes of the particular set chosen (e.g., cyclicity) have dominant roles in determining the partitioning of the chemicals between air and nonpolar fatty tissue.

The picture is, however, quite different in the cases of liver:air and muscle:air partition coefficients. Whereas parameters belonging to clusters 14 and 18 play a less important but essential role, the dominant role is played by parameters belonging to clusters 10 and 20. The latter two clusters contain the following independent variables:

Cluster #10: SddsN, SdO, HB₁

Cluster #20: M₁, M₂, ⁰χ, ²χ, ⁰χ^b, P₂, J^B, J^X, J^Y, AZV₂, DN²S₄, AS₁₃, ASN₁, ASN₃, ASN₅, DSN₃, ANV₄, AN₁₁, AN₁₄, ANN₂, ANN₄, Pf

TABLE VIII Cluster membership, ridge regression coefficient, and standard error for each of the top 20 descriptors, ranked by $|t|$, in the topochemical rat muscle:air partition coefficient model, $n = 46$

Cluster #	Descriptor	RR coeff	s.e.	t
10	SdO	0.294	0.046	6.34
10	SddsN	-2.320	0.382	-6.07
10	HB ₁	0.375	0.069	5.41
14	$^1\chi^v$	0.961	0.191	5.02
20	J ^Y	-0.920	0.192	-4.79
2	SHCsatu	1.380	0.323	4.27
18	SHarom	0.156	0.037	4.24
20	J ^B	-0.908	0.221	-4.1
14	fw	0.640	0.163	3.94
18	SaaCH	0.108	0.027	3.94
18	$^6\chi^v_{ch}$	9.052	2.387	3.79
20	J ^X	-0.980	0.262	-3.74
14	AZV ₄	0.224	0.061	3.65
14	$^2\chi^v$	0.563	0.165	3.41
9	IC ₂	-0.611	0.182	-3.35
21	$^6\chi^b_{pc}$	-0.714	0.216	-3.31
4	SIC ₂	-1.581	0.501	-3.16
16	IC ₀	1.403	0.473	2.97
7	$^4\chi^v_{pc}$	0.487	0.164	2.97
16	SIC ₀	1.010	0.346	2.92

Whereas cluster 10 contains HB₁, an explicit hydrogen-bonding parameter, as well as descriptors encoding information about nitrogen and oxygen atoms which are strong hydrogen bond acceptors, cluster 20 contains indices which are either TS parameters encoding molecular size or TC indices which quantify information both about size/shape and polarity of molecular structure. It is tempting to speculate that partitioning of chemicals between air and more polar tissues, viz., muscle and liver, are governed by: a) general size and shape, b) strength of hydrogen bonding, and c) dipolarity /polarizability. Such a conclusion is supported by Kamlet *et al.* [49] and our earlier studies on the prediction of logP_{octanol:water} from molecular descriptors [9, 50, 51].

In conclusion, results reported in this paper show that HiQSAR based on theoretical molecular descriptors can be useful in the estimation of tissue:air partition coefficients of VOCs. The theoretically based models are comparable or superior to those developed using experimental properties including olive oil:air and/or saline:air partition coefficients. The dominant parameters needed to develop the QSARs lead to some interpretation of the different biological situations involved in the partitioning of chemicals in the different types of tissues.

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EXPOSURE ASSESSMENT OF VOLATILE ORGANIC CHEMICALS (VOCS): PREDICTING BLOOD:AIR PARTITION COEFFICIENTS OF DIVERSE CHEMICALS USING THEORETICAL DESCRIPTORS

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Three regression methods, namely ridge regression (RR), partial least squares (PLS), and principal components regression (PCR), were used to develop models for the prediction of rat blood:air partition coefficient for increasingly diverse data sets. Initially, modeling was performed for a set of 13 chlorocarbons. To this set, 10 additional hydrophobic compounds were added, including aromatic and non-aromatic hydrocarbons. A set of 16 hydrophilic compounds was also modeled. Finally, all 39 compounds were combined into one data set for which comprehensive models were developed. A large set of diverse, theoretical molecular descriptors, including topostructural (TS), topochemical (TC), and geometrical or 3-dimensional (3D) indices were used both hierarchically and independently in model development. In most cases, RR outperformed PLS and PCR, and the models developed using TC indices were superior to those developed using other combinations of descriptors.

1. INTRODUCTION

The quality of modern life is dependent upon the use of a multitude of man-made and natural chemicals. Collectively, we are exposed to thousands of these chemicals from their routine use as well as accidental spill to the environment. Risk assessment (RA) of chemicals is an important activity pertinent to sustainable human and ecological health. Important aspects of RA are: a) hazard identification, b) dose-response assessment, c) exposure assessment, and d) risk characterization¹.

Health risk assessment of human exposure to environmental chemicals is usually based on experimental findings performed on test animals for single chemicals. Current assessment methods include two issues that are constantly debated in the scientific community. First, the use of these findings to estimate health risks to humans is routinely done by the use of default uncertainty factors, the purpose

which is to extrapolate between experimental settings and real life situations among different doses, animal species and exposure scenarios. The acceptance of these uncertainty factors by the scientific community reflects the lack of understanding of physiological, and biochemical mechanisms underlying the toxicity of environmental chemicals. Secondly, in most cases, risks are only estimated for exposures to single chemicals in the environment. This also is an oversimplification of real world situations where people are exposed to multiple chemicals concurrently. Biologically based computational models can address both issues by linking tissue levels, pharmacokinetically, or mechanisms of actions, pharmacodynamically, with exposure levels. This linkage provides a numerical procedure which can be used to investigate the role of physiological (e.g., body weight, cardiac output), or biochemical factors (such as metabolism, or protein binding etc.) in determining risk estimates among different species, and exposure scenarios. Whenever possible, mechanisms of interactions, such as metabolic inhibitions or competition for protein binding sites, can also be introduced into the models to address the effect of combined chemicals exposure to human health.

Pharmacokinetics (PK) involves the study of the rates of absorption, distribution, excretion, and biotransformation of chemicals and their metabolites. PK models can be used to reconstruct extensive data sets based on a small number of kinetic parameters². These models can be used to generate hypotheses, predict the results of new experiments, and integrate studies on kinetics, disposition and metabolism in various animal species³. In physiologically based pharmacokinetic (PBPK) models, compartments correspond more closely to actual anatomical structures, defined with respect to their volumes, blood flows, chemical binding (partitioning) characteristics, and the ability to metabolize or excrete the compounds of interest. Because the kinetic parameters of these models reflect tissue blood flows, and partitioning and other biochemical constants, these models are more readily scaled from one animal species to another⁴. Quantitative applications of PBPK models in risk assessment date from the development of a number of such models for methylene chloride in the mid 1980s⁵. The use of PBPK models in toxicology research and chemical risk assessment situations today is primarily related to their ability to make more accurate predictions of target tissue dose for different exposure situations in different animal species, including humans. Such models constitute an important tool in improving the degree of accuracy of human health risk assessment for toxic substances in the environment⁶. One of the disadvantages of PBPK modeling is its heavy reliance on often experimentally determined parameters. However, advances in computational and mathematical chemistry can provide a methodology which in many cases is used to estimate model parameters such as tissue:air partition coefficients

Tissue-air partition coefficient values of volatile organic chemicals (VOCs) are used to estimate the uptake, distribution, metabolism, and elimination as well as potential hazard of xenobiotics to humans⁷. Gargas et al.⁷ experimentally determined various liquid solvent:air and tissue:air partition coefficients (P)

for .9% saline, olive oil, blood, liver, muscle, and fat tissue. Subsequently, they studied the relationship among the various partition coefficients using regression models. For example, P values for blood:air, liver:air and muscle:air pairs were found to be strongly correlated with P values for olive oil:air for various subsets of volatile organic chemicals (VOCs).

The blood:air partition coefficient (P, blood:air) is an important determinant of the pulmonary uptake of VOCs via the inhalation route. Solubility of VOCs in blood is primarily determined by two factors: a) tissue composition including the content of neutral lipid, phospholipid, and water, and b) the degree of binding of these chemicals to specific components of blood, e.g., hemoglobin, plasma proteins, etc. Such physiological considerations have been utilized by Poulin and Krishnan⁸ to estimate blood:air P values of different subsets of chemicals.

Attempts have been made by various authors to estimate PBPK parameters of chemicals from their physicochemical and calculated properties. de Jongh et al.⁹ estimated tissue: blood partition coefficients of a diverse set of chemicals from their octanol:water (P, octanol:water) partition coefficient. Poulin and Krishnan⁸, on the other hand, attempted to estimate tissue:air P values for hydrophobic and hydrophilic classes of chemicals separately. To this end, they developed an algorithm based the ratio of blood solubility to air solubility (saturable vapor concentration).

The estimation of various tissue:blood P values from other experimental properties (e.g. olive oil:water by Gargas et al.⁷ or calculated octanol:water P value by de Jongh et al.⁹) are examples of property-property correlations where one property is used to estimate another property of interest. The basic paradigm of quantitative structure-activity relationship is that any property of a molecule can be estimated from the pertinent aspects of molecular structure which constitute the molecular and submolecular basis of that property¹⁰. Following that paradigm, attempts have been made to predict various properties, e.g., boiling point,¹¹⁻¹⁷ vapor pressure,¹⁸⁻²³ logP (octanol:water),^{15, 24-26} carcinogenicity,^{27, 28} mutagenicity,²⁸⁻³⁷ blood-brain barrier transport,³⁸ and skin penetration of chemicals³⁸. Theoretical descriptors have been used to predict the so-called modes of actions (MOAs) of chemicals from their calculated theoretical descriptors.³⁹ So, it is reasonable to attempt to estimate tissue:air P values of chemicals from their structure. Such an effort is also supported by the fact that calculated octanol:water P is primarily a structural parameter being calculated from fragment values of the molecule with some empirical corrections for structural peculiarities not accounted for by the fragmental constant^{40 41}. The finding of de Jongh et al.⁹ that tissue:air P can be estimated from octanol:water P values is also an impetus for attempting to estimate blood:air P values directly from structural parameters.

In our previous studies, we first found a successful correlation between theoretical structural invariants and blood:air P values for a congeneric set of chlorocarbons⁴². Subsequently, we added a few non-chlorocarbon hydrophobic chemicals to the set of chlorocarbons and found a satisfactory relationship

between the P values of the combined set and the calculated descriptors. A comparison of the models for the two data sets demonstrated that the best model for the combined set included parameters that reflected the structural diversity of the data set. This supports the belief that a diverse range of descriptors is required in order to model a diverse data set⁴³. In this paper, we have attempted to predict P (blood:air) values of a larger set of chemicals comprised of hydrophobic and hydrophilic molecules using a set of purely calculated molecular descriptors.

2. METHODS

2.1 Database. Rat blood:air partition coefficient data for set of 41 compounds was obtained from the literature^{7, 44, 45} by Poulin and Krishnan⁸, who divided the data into two subsets: a relatively hydrophobic set consisting of alkanes, haloalkanes, and aromatic hydrocarbons, and a set of relatively hydrophilic compounds made up of ketones, alcohols, acetate esters, and one ether. Four compounds included in the data set analyzed by Poulin and Krishnan are not included here, two of which were cis/trans isomers and therefore have identical values for theoretical descriptors based on SMILES input, and two for which it was not possible to calculate the entire set of descriptors used in the current study. The experimental blood:air partition coefficients are provided in Table 1.

2.2 Molecular Descriptors. The calculated molecular descriptors can be categorized into hierarchical groups based on level of complexity. At the lowest end of the hierarchy are the topostructural (TS) descriptors which encode information strictly on the adjacency and connectedness of atoms within a molecule. The topochemical (TC) descriptors also take into account the chemical nature of a molecule including bond type. The 3-dimensional or shape (3D) descriptors are even more complex, encoding information about the 3-dimensional aspects of a molecule. The topostructural and topochemical descriptors are known collectively as topological descriptors.

All descriptors used in the present study were derived strictly from molecular structure using software packages including POLLY,⁴⁶ Triplet,^{47, 48} and Molconn-Z.⁴⁹ From POLLY, we obtain a set of topological descriptors, including a large group of connectivity indices,⁵⁰⁻⁵² information theoretic^{53, 54} and neighborhood complexity indices.⁵⁴ The Triplet descriptors also constitute a large group of topological parameters. They are derived from a matrix, a main diagonal column vector, and a free term column vector, converting the matrix into a system of linear equations whose solutions are the local vertex invariants. These local vertex invariants are then used various mathematical operations in order to obtain the triplet descriptors. Molconn-Z provides additional topological descriptors, including an extended set

of connectivity indices, electrotopological indices,^{55, 56} hydrogen bonding descriptors, as well as a small number of molecular shape descriptors.

For the analysis of one of the data sets analyzed in this study, namely the set of chlorocarbons, three additional 3-dimensional descriptors were obtained from Sybyl.⁵⁷ These descriptors were not available for use at the time that the remaining data sets were analyzed. Also unique to the chlorocarbon analysis was a descriptor representing the number of chloride atoms.

A brief description of the complete set of molecular descriptors used in the current study is provided in Table 2.

2.3 Statistical Analysis. Prior to performing regression analysis, the descriptors were scaled by the natural logarithm as their scales differed by several orders of magnitude. The values of the dependent variable differed by more than one order of magnitude and therefore were also log scaled. The original set of independent variables was reduced by eliminating: a) descriptors which had a value of 0 for the entire set of compounds, b) descriptors which could not be calculated for all compounds in the data set, and c) all but one of a given set of perfectly correlated descriptors, i.e. $r = 1.0$, as determined by the CORR procedure of the SAS statistical package.⁵⁸ This procedure was performed independently for each of the following analyses:

1. A set of 13 chlorocarbons (a subset of the $N = 24$ hydrophobic data set)
2. A set of 24 hydrophobic compounds
3. A set of 17 hydrophilic compounds
4. A set of 41 hydrophobic + hydrophilic compounds

Ridge regression (RR),⁵⁹ principal components regression (PCR)⁶⁰, and partial least squares (PLS) regression⁶¹⁻⁶³ models were developed using molecular descriptors in a hierarchical fashion. In addition, each class of descriptors was used independently to obtain single-class models. Each of these regression methods is useful in studies wherein the number of descriptors is much greater than the number of observations, as well as in cases where the independent variables are highly intercorrelated; and they make use of all independent variables as opposed to subset regression wherein it is possible that important parameters may be eliminated. Statistical parameters reported include the cross-validated R^2 value, which is obtained by removing each compound in turn from the data set and fitting the regression to the remaining $n-1$ compounds, and the PRESS statistic which is a reliable measure of model predictability. In addition, the t values can be examined in order to identify significant descriptors. Although a descriptor

with a large $|t|$ indicates that the associated descriptor is important in the model, it should be cautioned that the reverse is not necessarily so.

3. RESULTS

A summary of the regression results for the various data sets analyzed in the present study are provided in Tables 3-6. The three statistical methods, viz., PCR, PLS and RR, were used for model development. Three classes of calculated descriptors, viz., topostructural (TS) indices, topochemical (TC) indices, and geometrical or 3-dimensional (3D) molecular descriptors, were used either alone or in various combinations for model building (Tables 3-6). Of the three statistical techniques, the RR method generally gave superior $R^2_{c.v.}$ and PRESS values as compared to those derived by PCR or PLS methods. In addition, models derived either from TC descriptors alone or TS+TC descriptors were superior to those involving other combinations of descriptor classes. In some of our earlier studies involving the development of QSARs using TS, TC, 3D and quantum chemical (QC) indices, we found that the TS+TC combination explained most of the variance in the data and the addition of 3D or QC indices made only marginal or no improvement in the model quality.^{18, 22, 23, 34, 35, 37, 64-66} A reasonable model with a cross-validated R^2 value 0.866 and a PRESS of 1.61 was obtained for the set of 13 chlorocarbons⁴², which may not be surprising in light of the homogenous nature of the data set (Table 3). When additional hydrophobic compounds are added to this set, we find that cyclohexane is an influential outlier. Cyclohexane is the only cyclic non-aromatic in the data set. With this compound removed, a cross-validated R^2 of 0.873 is obtained with a PRESS of 2.90 (Table 4). The set of hydrophilic compounds is also well modeled, with a cross-validated R^2 of 0.964 and a PRESS of 0.92. In this analysis, diethyl ether was found to be an outlier, which is not surprising since this compound is the only ether in the set (Table 5). A significant finding is the fact that when the data set is further diversified by combining the hydrophobic and hydrophilic compounds, an acceptable model is obtained, with a cross-validated R^2 of 0.944 and a PRESS of 5.57. In the combined data set, we find that cyclohexane and bromochloromethane are influential outliers (Table 6).

For each of the four data sets analyzed, the descriptors in the TC ridge regression model were ordered according to their respective $|t|$ values. Approximately, the top 10% of the descriptors, based on $|t|$ values, are listed in Tables 7-10 for the four sets of chemicals for which models are developed in Tables 3-6, viz., chlorocarbons, hydrophobic chemicals, hydrophilic chemicals, and the union of all three sets, along with the descriptor coefficient, standard error, and t value.

Table 11 provides the predicted logP (blood:air) values and residuals for the TC ridge regression model developed for the combined set of hydrophobic and hydrophilic descriptors. The predicted values and residuals obtained by the solubility algorithm of Poulin and Krishnan⁸ are included for comparative purposes. A scatterplot of the experimental vs the predicted values given in Table 11 is shown in Figure 1.

4. DISCUSSION

The question we wanted to investigate in this study was three fold: a) Can we use theoretical structural descriptors instead of experimental physicochemical data to predict properties relevant to PBPK modelling, b) Is it possible to predict relevant properties of not only congeneric sets, but also structurally diverse collections of molecules, and c) Can we interpret the resulting QSAR models for the congeneric vis-a-vis diverse sets in order to understand the basis of the roles of various types of descriptors in the predictive models?

Regarding the first point above, it is clear from results presented in Tables 3-6 that either the topochemical indices alone or the combination of TS+TC indices gave reasonable regression equations for chlorocarbons, hydrophobics (chlorocarbons plus hydrocarbons), hydrophilics, and finally, a combined set of hydrophobic and hydrophilic compounds. There were some outliers which influenced the results for the smaller subsets as well as the final combined set. Such compounds, namely diethyl ether, cyclohexane and bromochloromethane, are but lone examples of their respective structural classes, which is probably the reason why the models could not account for them. It is interesting to note that of the three methods of modeling attempted, viz., PCR, PLS and RR, the ridge regression method gave the best predictive models in most cases. In an earlier paper,⁶⁷ we showed with four different sets of physicochemical and toxicological properties that RR is superior to multiple linear regression (MLR) or PLS in the development of QSAR models.

There is some degradation of the PRESS statistic, an important measure of model quality, when we compare the class-specific models (Tables 4 & 5) with those derived from the combined set (Table 6) using the RR method. However, the difference between the measure for the combined set and the sum of those for the individual sets is not as large as one might expect, and the combined model is a reasonable one. This may be due to the large number of descriptors utilized, capable of characterizing many different structural features. Table 11 gives results of the relative effectiveness of our current approach, using the TC model developed with the ridge regression method for the combined set of hydrophobic and hydrophilic compounds, vis-a-vis a physicochemically-based approach derived by Poulin and Krishnan⁸

from mechanistic considerations in the prediction of blood:air partition coefficients of the VOCs analyzed in this paper.

It is instructive to look at the most important descriptors (in terms of $|t|$ values in the RR models) for the various subsets of chemicals. Some important indices for the subset of chlorocarbons are: the triplet indices AZV_3 and AZS_4 , $NoCl$ (the number of chlorine atoms), E-state indices encoding information about the electronic states of atoms ($SHCsats$ and $SsssCH$), and both first and third order connectivity indices, the latter of which represents third order cluster subgraphs occurring frequently in the hydrogen-suppressed graphs of the halocarbons.

The addition of the aromatic and nonaromatic hydrocarbons to the set of chlorocarbons results in an interesting change. It is clear from Table 8 that parameters such as $SHarom$ (E-state aromatic indices) and sixth order cyclic connectivity index⁶⁸ have become important in the regression equation. This is clearly a shift towards aromaticity and cyclicity, which are inherent structural features of the subset of compounds added to the group of chlorocarbons.

The predictors important for the hydrophilic subset (Table 9) show the importance of hydrogen bonding ($SHHBd$, $numHBd$) parameters, as well as indices related to atomic heterogeneity and symmetry, viz., $nclass$, $SHCsatu$, and molecular weight (representing molecular size). Kamlet et al.⁶⁹ showed in their research with linear solvated energy related studies that molecular size, dipolarity, and hydrogen bonding are three important determinants of properties including water solubility, partition coefficients, etc.

Finally, in the RR model developed from the mixed set of chlorocarbons, aromatics and hydrophilics, we find that the following factors are important: a) Molecular size, encoded by zero order connectivity index ($^0\chi^v$),⁵⁰ b) Hydrogen bonding represented by $numHBd$, $SHHBd$, $SHHBa$, and HB_1 , and c) Polarity (Q_v). Results derived from the combined set clearly vindicate the proposition of Kamlet et al.⁶⁹ that molecular size, dipolarity/polarizability, hydrogen bond donor acidity, and hydrogen bond acceptor basicity are the major determining factors for partitioning properties such as hydrophobicity. The importance of structural factors such as $^0\chi^v$ and van der Waals' volume (encoding molecular size), IC_0 , CIC_1 , CIC_2 , and CIC_3 (representing atomic neighborhood heterogeneity), and HB_1 (representing hydrogen bonding) in predicting octanol-water partition coefficient ($\log P$, octanol-water) was also evident in our previous studies of smaller subsets of 219¹⁵, 139 and 382 compounds^{70,71}, as well as larger diverse $\log P$ sets of 4,111 and 4,000 chemicals.²⁴

In conclusion, results presented in this paper show that data relevant to toxicological and PBPK modeling of VOCs can be more accurately predicted using RR method and calculated molecular descriptors than by using the mechanistic approaches based on physicochemical and biological considerations. The wide spectrum of molecular descriptors considered in this paper afforded us the ability to model not only the particular structural types but also the combined set of different structural

asses of chemicals without significant degradation in the model quality as compared to class-specific QSARs. Inspection of the parameters that play important roles in class-specific QSARs as well as the corresponding models for the combined set showed that parameters assuming important roles in the different predictive models reflect the nature and diversity of the chemicals under consideration. Further studies on the comparative QSARs of congeneric vis-a-vis structurally diverse sets using theoretical structural indices are needed to validate the utility of the approach outlined in this paper.

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Table 1. Experimental rat blood:air partition coefficients (P, blood:air)

Chemicals	Experimental P ^a
Alkanes ^b	
1. <i>n</i> -Hexane	2.29 ± 0.11
2. Cyclohexane	1.39 ± 0.09
3. <i>n</i> -Heptane	4.75 ± 0.15
Haloalkanes ^b	
4. Dichloromethane	19.4 ± 0.8
5. Chloroform	20.8 ± 0.1
6. Carbon tetrachloride	4.52 ± 0.35
7. Bromochloromethane	41.5 ± 0.9
8. 1,1-Dichloroethane	11.2 ± 0.1
9. 1,2-Dichloroethane	30.4 ± 1.2
10. 1,1,1-Trichloroethane	5.76 ± 0.5
11. 1,1,2-Trichloroethane	58.0 ± 1.1
12. 1,1,1,2-Tetrachloroethane	41.7 ± 1.0
13. 1,1,2,2-Tetrachloroethane	142 ± 6
14. Pentachloroethane	104 ± 3
15. 1,2-Dichloropropane	18.7 ± 0.5
16. Trichloroethylene	21.9 ± 1.4
17. Tetrachloroethylene	18.9 ± 1.1
Aromatic hydrocarbons ^b	
18. Benzene	17.8 ± 0.3
19. Chlorobenzene	59.4 ± 1.0
20. Toluene	18.0 ± 1.0
21. Styrene	40.2 ± 3.7
22. <i>o</i> -Xylene	44.3 ± 2.0
23. <i>m</i> -Xylene	46.0 ± 1.5
24. <i>p</i> -Xylene	41.3 ± 3.5
Ketones ^c	
25. Dimethyl ketone	208 ± 4
26. Methyl ethyl ketone	191 ± 2
27. Methyl propyl ketone	127 ± 3
28. Methyl isobutyl ketone	79 ± 6
29. Methyl pentyl ketone	225 ± 30
Alcohols ^c	
30. Ethyl alcohol	2140 ± 80
31. <i>n</i> -Propyl alcohol	1340 ± 24
32. Isopropyl alcohol	1290 ± 21
33. <i>n</i> -Butyl alcohol	1160 ± 17
34. <i>n</i> -Pentyl alcohol	829 ± 25
Acetate esters ^c	
35. Methyl acetate ester	100 ± 2
36. Ethyl acetate ester	81.7 ± 2.1
37. <i>n</i> -Propyl acetate ester	76.2 ± 2.1
38. Isopropyl acetate ester	35.1 ± 1.3
39. <i>n</i> -Butyl acetate ester	89.4 ± 2.5
40. Isopentyl acetate ester	64.7 ± 2.0
Ether ^c	
41. Diethyl ether	12.2 ± 0.4

^a Values represent means ± standard error.^b Relatively hydrophobic compounds⁸^c Relatively hydrophilic compounds⁸

Table 2. Symbols, definitions and classification of calculated molecular descriptors

<i>Topostructural (TS)</i>	
I_D^W	Information index for the magnitudes of distances between all possible pairs of vertices of a graph
$\overline{I_D^W}$	Mean information index for the magnitude of distance
W	Wiener index = half-sum of the off-diagonal elements of the distance matrix of a graph
I^D	Degree complexity
H^V	Graph vertex complexity
H^D	Graph distance complexity
IC	Information content of the distance matrix partitioned by frequency of occurrences of distance h
M_1	A Zagreb group parameter = sum of square of degree over all vertices
M_2	A Zagreb group parameter = sum of cross-product of degrees over all neighboring (connected) vertices
${}^h\chi$	Path connectivity index of order $h = 0-10$
${}^h\chi_C$	Cluster connectivity index of order $h = 3-6$
${}^h\chi_{PC}$	Path-cluster connectivity index of order $h = 4-6$
${}^h\chi_{Ch}$	Chain connectivity index of order $h = 3-10$
P_h	Number of paths of length $h = 0-10$
J	Balaban's J index based on topological distance
nrings	Number of rings in a graph
ncirc	Number of circuits in a graph
DN^2S_y	Triplet index from distance matrix, square of graph order (# of non-H atoms), and distance sum; operation $y = 1-5$
DN^21_y	Triplet index from distance matrix, square of graph order, and number 1; operation $y = 1-5$
$AS1_y$	Triplet index from adjacency matrix, distance sum, and number 1; operation $y = 1-5$
$DS1_y$	Triplet index from distance matrix, distance sum, and number 1; operation $y = 1-5$
ASN_y	Triplet index from adjacency matrix, distance sum, and graph order; operation $y = 1-5$
DSN_y	Triplet index from distance matrix, distance sum, and graph order; operation $y = 1-5$
DN^2N_y	Triplet index from distance matrix, square of graph order, and graph order; operation $y = 1-5$
ANS_y	Triplet index from adjacency matrix, graph order, and distance sum; operation $y = 1-5$
$AN1_y$	Triplet index from adjacency matrix, graph order, and number 1; operation $y = 1-5$
ANN_y	Triplet index from adjacency matrix, graph order, and graph order again; operation $y = 1-5$
ASV_y	Triplet index from adjacency matrix, distance sum, and vertex degree; operation $y = 1-5$
DSV_y	Triplet index from distance matrix, distance sum, and vertex degree; operation $y = 1-5$
ANV_y	Triplet index from adjacency matrix, graph order, and vertex degree; operation $y = 1-5$
<i>Topochemical (TC)</i>	
NoCl	Number of chlorine atoms
HB_1	Hydrogen bonding parameter
O	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-filled graph
O_{orb}	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-suppressed graph
I_{orb}	Information content or complexity of the hydrogen-suppressed graph at its maximum neighborhood of vertices
IC_r	Mean information content or complexity of a graph based on the r^{th} ($r = 0-6$) order

	neighborhood of vertices in a hydrogen-filled graph
SIC _r	Structural information content for r th (r = 0-6) order neighborhood of vertices in a hydrogen-filled graph
CIC _r	Complementary information content for r th (r = 0-6) order neighborhood of vertices in a hydrogen-filled graph
χ^b_h	Bond path connectivity index of order h = 0-6
χ^b_C	Bond cluster connectivity index of order h = 3-6
χ^b_{Ch}	Bond chain connectivity index of order h = 3-6
χ^b_{PC}	Bond path-cluster connectivity index of order h = 4-6
χ^v_h	Valence path connectivity index of order h = 0-10
χ^v_C	Valence cluster connectivity index of order h = 3-6
χ^v_{Ch}	Valence chain connectivity index of order h = 3-10
χ^v_{PC}	Valence path-cluster connectivity index of order h = 4-6
J ^B	Balaban's J index based on bond types
J ^X	Balaban's J index based on relative electronegativities
J ^Y	Balaban's J index based on relative covalent radii
AZV _y	Triplet index from adjacency matrix, atomic number, and vertex degree; operation y = 1-5
AZS _y	Triplet index from adjacency matrix, atomic number, and distance sum; operation y = 1-5
ASZ _y	Triplet index from adjacency matrix, distance sum, and atomic number; operation y = 1-5
AZN _y	Triplet index from adjacency matrix, atomic number, and graph order; operation y = 1-5
ANZ _y	Triplet index from adjacency matrix, graph order, and atomic number; operation y = 1-5
DSZ _y	Triplet index from distance matrix, distance sum, and atomic number; operation y = 1-5
DN ² Z _y	Triplet index from distance matrix, square of graph order, and atomic number; operation y = 1-5
nvx	Number of non-hydrogen atoms in a molecule
nelem	Number of elements in a molecule
fw	Molecular weight
χ^v_h	Valence path connectivity index of order h = 7-10
χ^v_{Ch}	Valence chain connectivity index of order h = 7-10
si	Shannon information index
totop	Total Topological Index t
sumI	Sum of the intrinsic state values I
sumdelI	Sum of delta-I values
tets2	Total topological state index based on electrotopological state indices
phia	Flexibility index (kp1 * kp2/nvx)
IdCbar	Bonchev-Trinajstić information index
IdC	Bonchev-Trinajstić information index
Wp	Wienerp
Pf	Plattf
Wt	Total Wiener number
knotp	Difference of chi-cluster-3 and path/cluster-4
knotpv	Valence difference of chi-cluster-3 and path/cluster-4
nclasse	Number of classes of topologically (symmetry) equivalent graph vertices
numHBd	Number of hydrogen bond donors
numwHBd	Number of weak hydrogen bond donors
numHBa	Number of hydrogen bond acceptors
SHCsats	E-State of C sp ³ bonded to other saturated C atoms
SHCsatu	E-State of C sp ³ bonded to unsaturated C atoms
SHvin	E-State of C atoms in the vinyl group, =CH-
SHtvn	E-State of C atoms in the terminal vinyl group, =CH ₂
SHavin	E-State of C atoms in the vinyl group, =CH-, bonded to an aromatic C
SHarom	E-State of C sp ² which are part of an aromatic system
SHHBd	Hydrogen bond donor index, sum of Hydrogen E-State values for -OH, =NH, -NH ₂ , -NH-, -SH, and #CH

SHwHBd	Weak hydrogen bond donor index, sum of C-H Hydrogen E-State values for hydrogen atoms on a C to which a F and/or Cl are also bonded
SHHBa	Hydrogen bond acceptor index, sum of the E-State values for -OH, =NH, -NH ₂ , -NH-, >N-, -O-, -S-, along with -F and -Cl
Qv	General Polarity descriptor
NHBint _y	Count of potential internal hydrogen bonders (y = 2-10)
SHBint _y	E-State descriptors of potential internal hydrogen bond strength (y = 2-10)
	Electrotopological State index values for atoms types: SHsOH, SHdNH, SHsSH, SHsNH ₂ , SHssNH, SHtCH, SHother, SHCHnX, Hmax Gmax, Hmin, Gmin, Hmaxpos, Hminneg, SsLi, SssBe, SssssBem, SssBH, SssB, SssssBm, SsCH ₃ , SdCH ₂ , SssCH ₂ , StCH, SdsCH, SaaCH, SssCH, SddC, StsC, SdssC, SaasC, SaaaC, SssssC, SsNH ₃ p, SsNH ₂ , SssNH ₂ p, SdNH, SssNH, SaaNH, StN, SssNHp, SdsN, SaaN, SssN, SddsN, SaasN, SssssNp, SsOH, SdO, SssO, SaaO, SsF, SsSiH ₃ , SssSiH ₂ , SssssSiH, SssssSi, SsPH ₂ , SssPH, SssP, SdssP, SssssP, SsSH, SdS, SssS, SaaS, SdssS, SddssS, SssssS, SsCl, SsGeH ₃ , SssGeH ₂ , SssssGeH, SssssGe, SsAsH ₂ , SssAsH, SssAs, SdssAs, SssssAs, SsSeH, SdSe, SssSe, SaaSe, SdssSe, SddssSe, SsBr, SsSnH ₃ , SssSnH ₂ , SssssSnH, SssssSn, SsI, SsPbH ₃ , SssPbH ₂ , SssPbH, SssssPb
<i>Geometrical / Shape (3D)^a</i>	
kp0	Kappa zero
kp1-kp3	Kappa simple indices
ka1-ka3	Kappa alpha indices
V _w	Van der Waals volume
^{3D} W _H	3D Wiener number based on the hydrogen-filled geometric distance matrix
^{3D} W	3D Wiener number based on the hydrogen-suppressed geometric distance matrix
^a V _w , ^{3D} W _H , and ^{3D} W used in chlorocarbon analysis only. These descriptors were unavailable for subsequent analyses.	

Table 3. Summary of regression results for the set of chlorocarbons^a

Model Type	RR		PCR		PLS	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
TS	0.436	6.79	-0.259	15.2	-0.172	9.97
TS+TC	0.835	1.99	0.716	3.42	0.697	3.65
TS+TC+3D	0.827	2.08	0.762	2.87	0.726	3.31
TS	0.436	6.79	-0.259	15.2	-0.172	9.97
TC	0.866	1.61	0.732	3.23	0.800	2.41
3D	0.584	5.01	0.444	6.70	0.179	9.88

^a Subset of hydrophobic compounds (N = 13)**Table 4.** Summary of regression results for the set of hydrophobic compounds^a

Model Type	RR		PCR		PLS	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
TS	0.424	12.7	0.403	13.6	0.393	13.8
TS+TC	0.873	2.90	0.768	5.28	0.749	5.72
TS+TC+3D	0.870	2.98	0.768	5.30	0.717	6.45
TS	0.424	12.7	0.403	13.6	0.393	13.8
TC	0.856	3.30	0.757	5.54	0.708	6.68
3D	0.264	16.8	0.239	17.4	-0.268	28.9

^a Cyclohexane removed from data set (N = 23)

Table 5. Summary of regression results for the set of hydrophilic compounds^a

Model Type	RR		PCR		PLS	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
TS	0.543	11.8	-0.355	35.0	0.168	21.5
TS+TC	0.948	1.34	0.922	2.02	0.913	2.25
TS+TC+3D	0.945	1.42	0.917	2.15	0.906	2.43
TS	0.543	11.8	-0.355	35.0	0.168	21.5
TC	0.964	0.92	0.924	1.95	0.919	2.10
3D	0.743	6.64	-0.747	45.2	-0.562	40.4

^a Diethyl ether removed from data set (N = 16)**Table 6.** Summary of regression results for the set of hydrophobic + hydrophilic compounds^a

Model Type	RR		PCR		PLS	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
TS	-0.053	105	-0.210	120	-0.228	122
TS+TC	0.938	6.11	0.358	63.8	0.941	5.82
TS+TC+3D	0.939	6.06	0.349	64.6	0.943	5.69
TS	-0.053	105	-0.210	120	-0.228	122
TC	0.944	5.57	0.396	60.0	0.942	5.80
3D	0.066	92.7	-0.020	101	0.013	98.0

^a Cyclohexane and bromochloromethane removed from data set (N = 39).**Table 7.** Most significant ~10% of TC model parameters based on $|t|$ value for the chlorocarbon data set^a

Descriptor	Descriptor type	Coeff.	s.e.	t	$ t $
AZV ₃	Triplet	0.12127	0.01249	9.71	9.71
NoCl	No. Cl atoms	0.03012	0.00359	8.39	8.39
numHBa	H-bond acceptor	0.11561	0.01487	7.78	7.78
SHCsats	Atom type E-state	0.25081	0.03253	7.71	7.71
¹ χ^b	1 st order bond path connectivity	0.29577	0.03846	7.69	7.69
AZS ₄	Triplet	-0.30389	0.03962	-7.67	7.67
¹ χ^v	1 st order valence path connectivity	0.30732	0.04019	7.65	7.65
phia	Flexibility	0.43651	0.05868	7.44	7.44
SHHBa	H-bond acceptor	0.09488	0.01280	7.41	7.41
SsssCH	Atom type E-state	-0.30596	0.04188	-7.31	7.31
³ χ^b	3 rd order bond cluster connectivity	-0.08884	0.01237	-7.18	7.18
idCbar	Information	0.27432	0.03828	7.17	7.17

^a Subset of hydrophobic compounds (N = 13)

Table 8. Most significant ~10% of TC model parameters based on $|t|$ value for the hydrophobic data set^a

Descriptor	Descriptor type	Coeff.	s.e.	t	$ t $
Wt	Total Wiener number	0.03421	0.00316	10.84	10.84
AZV ₃	Triplet	0.08093	0.00857	9.45	9.45
SaaCH	Atom type E-state	0.06459	0.00714	9.05	9.05
SHarom	E-state, aromatic system	0.08534	0.00958	8.90	8.90
$^6\chi^v_{Ch}$	6 th order valence cyclic connectivity	5.01933	0.59190	8.48	8.48
totop	Total topological index	0.03811	0.00464	8.21	8.21
AZV ₁	Triplet	0.09593	0.01175	8.17	8.17
Qv	Polarity	-0.48399	0.06541	-7.40	7.40
AZN ₄	Triplet	0.92923	0.12848	7.23	7.23
$^3\chi^v$	3 rd order valence path connectivity	0.23300	0.03329	7.00	7.00
SsCH3	Atom type E-state	-0.19602	0.03003	-6.53	6.53
numwHBd	Hydrogen bond donor	0.23978	0.03677	6.52	6.52

^a Cyclohexane removed from data set (N = 23)**Table 9.** Most significant ~10% of TC model parameters based on $|t|$ value for the hydrophilic data set^a

Descriptor	Descriptor type	Coeff.	s.e.	t	$ t $
totop	Total topological index	-0.094	0.003	-30.47	30.47
SumI	Sum of intrinsic state values	-0.152	0.006	-24.44	24.44
ANZ ₃	Triplet	-0.117	0.005	-23.80	23.80
NumHBd	Hydrogen bond donor	0.238	0.012	20.30	20.30
SHHBd	Hydrogen bond donor	0.139	0.007	20.11	20.11
Hmax	Atom type E-state	0.228	0.011	20.07	20.07
SdO	Atom type E-state	-0.068	0.004	-18.76	18.76
SHCsatu	E-state, sp ³ bonded to unsaturated C	-0.252	0.019	-13.10	13.10
DN ² Z ₄	Triplet	-0.017	0.001	-12.31	12.31
AZV ₄	Triplet	-0.050	0.004	-11.67	11.67
Fw	Molecular weight	-0.041	0.004	-11.34	11.34
nclass	No. classes of topologically equivalent graph vertices	-0.079	0.007	-10.53	10.53

^a Diethyl ether removed from data set (N = 16)**Table 10.** Most significant ~10% of TC model parameters based on $|t|$ value for the hydrophobic + hydrophilic data set^a

Descriptor	Descriptor type	Coeff.	s.e.	t	$ t $
numHBd	Hydrogen bond donor	1.09032	0.04716	23.12	23.12
SHHBd	Hydrogen bond donor	0.63524	0.02806	22.64	22.64
SsOH	Atom type E-state	0.34518	0.01661	20.78	20.78
Hmax	Atom type E-state	0.71396	0.05969	11.96	11.96
HB ₁	Hydrogen bonding	0.33321	0.02804	11.88	11.88
sumI	Sum of intrinsic state values	0.56713	0.05096	11.13	11.13
Qv	General polarity	-1.50364	0.13949	-10.78	10.78
Gmax	Atom type E-state	0.42754	0.04274	10.00	10.00
$^0\chi^v$	Zero order valence connectivity	-0.38320	0.03854	-9.94	9.94
sumDELI	Sum of delta-I values	0.30960	0.03158	9.80	9.80
SHHBa	Hydrogen bond acceptor	0.09410	0.01089	8.64	8.64
ASZ ₁	Triplet	-0.12561	0.01498	-8.39	8.39

^a Cyclohexane and bromochloromethane removed from data set (N = 39)

Table 11. Log scaled experimental and predicted rat blood:air partition coefficients (P, blood:air), as well as residuals, for the current study and the solubility algorithm derived by Poulin and Krishnan⁸

Chemicals	Exp. log P ^a	Current study ^b		Solubility algorithm		
		Pred. log P	Residual	Pred. log P ^c	Residual	
Alkanes						
1. <i>n</i> -Hexane	0.828	0.999	-0.170	-1.204	2.032	
2. Cyclohexane	0.329	--	--	-0.511	0.840	
3. <i>n</i> -Heptane	1.558	1.518	0.040	-0.105	1.663	
Haloalkanes						
4. Dichloromethane	2.965	2.983	-0.018	1.609	1.356	
5. Chloroform	3.035	3.136	-0.101	1.386	1.649	
6. Carbon tetrachloride	1.508	1.513	-0.005	0.000	1.508	
7. Bromochloromethane	3.726	--	--	2.079	1.647	
8. 1,1-Dichloroethane	2.416	2.528	-0.112	0.693	1.723	
9. 1,2-Dichloroethane	3.414	3.390	0.024	2.303	1.111	
10. 1,1,1-Trichloroethane	1.751	1.799	-0.048	0.000	1.751	
11. 1,1,2-Trichloroethane	4.060	3.749	0.312	2.708	1.352	
12. 1,1,1,2-Tetrachloroethane	3.730	3.692	0.038	2.079	1.651	
13. 1,1,2,2-Tetrachloroethane	4.956	4.935	0.021	3.466	1.490	
14. Pentachloroethane	4.644	4.640	0.005	2.708	1.936	
15. 1,2-Dichloropropane	2.928	3.076	-0.147	1.099	1.829	
16. Trichloroethylene	3.086	3.179	-0.092	0.693	2.393	
17. Tetrachloroethylene	2.939	2.918	0.021	1.609	1.330	
Aromatic hydrocarbons						
18. Benzene	2.879	2.837	0.042	1.099	1.780	
19. Chlorobenzene	4.084	4.120	-0.036	1.946	2.138	
20. Toluene	2.890	3.088	-0.198	1.386	1.504	
21. Styrene	3.694	3.655	0.039	2.079	1.615	
22. <i>o</i> -Xylene	3.791	3.815	-0.024	2.197	1.594	
23. <i>m</i> -Xylene	3.829	3.672	0.157	2.079	1.750	
24. <i>p</i> -Xylene	3.721	3.698	0.023	2.079	1.642	
Ketones						
25. Dimethyl ketone	5.337	5.233	0.104	5.215	0.123	
26. Methyl ethyl ketone	5.252	5.269	-0.016	5.170	0.082	
27. Methyl propyl ketone	4.844	4.856	-0.012	4.575	0.269	
28. Methyl isobutyl ketone	4.369	4.372	-0.002	3.989	0.380	
29. Methyl pentyl ketone	5.416	5.300	0.117	5.193	0.223	
Alcohols						
30. Ethyl alcohol	7.669	7.585	0.084	7.493	0.175	
31. <i>n</i> -Propyl alcohol	7.200	7.334	-0.134	7.348	-0.148	
32. <i>Isopropyl</i> alcohol	7.162	6.993	0.169	7.138	0.024	
33. <i>n</i> -Butyl alcohol	7.056	6.965	0.091	6.909	0.147	
34. <i>n</i> -Pentyl alcohol	6.720	6.725	-0.005	6.812	-0.092	
Acetate esters						
35. Methyl acetate ester	4.605	4.691	-0.085	4.511	0.094	
36. Ethyl acetate ester	4.403	4.255	0.148	4.094	0.309	
37. <i>n</i> -Propyl acetate ester	4.333	4.230	0.103	3.807	0.527	
38. <i>Isopropyl</i> acetate ester	3.558	3.743	-0.185	3.367	0.191	
39. <i>n</i> -Butyl acetate ester	4.493	4.486	0.007	3.434	1.059	
40. <i>Isopentyl</i> acetate ester	4.170	4.271	-0.101	3.219	0.951	
Ether						
41. Diethyl ether	2.501	2.557	-0.055	2.303	0.199	

^a Values represent log of mean PC^b TC model developed on combined hydrophobic and hydrophilic compounds using ridge regression^c Values have been log scaled for ease of comparison

Figure 1. Scatterplot of the experimental vs predicted log P (blood:air) values using the TC model developed with the ridge regression method for the combined set of hydrophobic and hydrophilic compounds ($N = 39$).

PREDICTION OF HUMAN BLOOD:AIR PARTITION COEFFICIENT: A COMPARISON OF STRUCTURE-BASED AND PROPERTY-BASED METHODS

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In recent years, there has been increased interest in the development and use of quantitative structure activity/property relationship (QSAR/QSPR) models. For the most part, this is due to the fact that experimental data is sparse and obtaining such data is costly, while theoretical structural descriptors can be obtained quickly and inexpensively. In this study, three linear regression methods, viz. principal component regression (PCR), partial least squares (PLS), and ridge regression (RR), were used to develop QSPR models for the estimation of human blood:air partition coefficient ($\log P_{\text{blood:air}}$) for a group of 31 diverse low-molecular weight volatile chemicals from their computed molecular descriptors. In general, RR was found to be superior to PCR or PLS. Comparisons were made between models developed using parameters based solely on molecular structure and linear regression (LR) models developed using experimental properties, including saline:air partition coefficient ($\log P_{\text{saline:air}}$) and olive oil:air partition coefficient ($\log P_{\text{olive oil:air}}$), as independent variables, indicating that the structure-property correlations are comparable to the property-property correlations. The best models, however, were those which used rat $\log P_{\text{blood:air}}$ as the independent variable. Haloalkane subgroups were modeled separately for comparative purposes, and although models based on the congeneric compounds were superior, the models developed on the complete set of diverse compounds were of acceptable quality. The structural descriptors were placed into one of three classes based on level of complexity: Topostructural (TS), topochemical (TC), or 3-dimensional / geometrical (3D). Modeling was performed using the structural descriptor classes both in a hierarchical fashion and separately. The results indicate that the highest quality structure-based models, in terms of descriptor classes, were those derived using TC or TS+TC descriptors.

Key Words: Blood:air partition coefficient; PBPK model; theoretical molecular descriptors; ridge regression; quantitative structure-property relationship (QSPR) model.

1. INTRODUCTION

Modern lifestyle worldwide is based on the use of a large number of chemicals. Natural and synthetic chemicals are used as drugs, pesticides, herbicides, components of diagnostic tools, ingredients and solvents in industrial processes, to name just a few. The Toxic Substances Control Act (TSCA) Inventory maintained by the United States Environmental Protection Agency (USEPA) currently has over 81,000 entries and the list is growing every year.⁽¹⁾ Many of these chemicals are used for various purposes and have the potential to be released in the environment. Therefore, it is natural that we need to carry out risk assessment of the TSCA chemicals, particularly for those that are used frequently and in large quantities. Volatile organic chemicals (VOCs) constitute a class of chemicals that are frequently used in various industrial processes. Therefore, there is an interest to predict the potential adverse effects of these chemicals on human and environmental health. The overall risk of a chemical is determined primarily by its intrinsic toxicity (hazard) and exposure potential.

The blood:air partition coefficient of VOCs is an important determinant of pulmonary uptake of such chemicals from inhaled air. Such parameters are routinely used in building physiologically-based pharmacokinetic (PBPK) models for exposure assessment of such chemicals. Solubility of VOCs in blood is determined by its composition including the content of neutral lipid, phospholipid, and water, as well as the extent of binding of these chemicals to specific components such as plasma proteins and hemoglobin.⁽²⁾ Such physicochemical considerations can be used to come up with physicochemically-based methods for the estimation of partition coefficient values of chemicals. The other possibility is the use of molecular descriptors to estimate partition coefficient of chemicals directly from their structure. Such quantitative structure-activity/property relationship (QSAR/QSPR) methods derived using theoretical descriptors are based on the idea that observable physicochemical and biological properties of chemicals are determined by their molecular structure. In particular, QSPRs have been found to be useful in the estimation of physicochemical properties such as octanol:water partition coefficient of various groups of chemicals,^(3,4) as well as the degree of transport through the blood-brain barrier⁽⁵⁾ and skin,⁽⁶⁾ of various congeneric and diverse sets.

While some quantitative models use experimental data per se as independent variables, it is important to note that experimental data does not exist for the majority of compounds, and obtaining such data is costly in terms of time and monetary resources. Computational modeling involving algorithmically calculated parameters based solely on molecular structure is an inexpensive alternative. In this paper, we have attempted to develop QSPR models to estimate human blood:air partition coefficients for a set of 31 VOCs using molecular descriptors which can be computed directly from molecular structure.

2. METHODS

2.1 Database. Liquid:air partition coefficients were experimentally determined by Gargas *et al.*⁽⁷⁾ using a modified version of the gas-phase vial equilibrium technique⁽⁸⁾ for a set of low molecular-weight volatile chemicals. Table I includes experimentally determined human and male Fischer 344 rat blood:air partition coefficient data for a set of 31 chemicals including 18 haloalkanes, 2 nitroalkanes, 2 aliphatic hydrocarbons, 4 haloalkenes, and 5 aromatics compounds. The human blood:air partition coefficient values were determined on blood pretreated with diethyl maleate to inhibit an observed glutathione transferase reaction. Experimental saline:air and olive oil:air partition coefficients, determined by Gargas *et al.*, are also listed in Table I. All experimental values were obtained at 37 °C.

It should be noted that the data used in the current study are a subset of that reported by Gargas *et al.*⁽⁷⁾ Two *cis/trans* isomers were eliminated because they are indistinguishable in terms of their calculated molecular descriptors based on SMILES input. Methyl chloride was also removed from the data set as it is not possible to calculate our entire set of theoretic descriptors on two-atom compounds. In addition, two compounds were reported without discrete values for 0.9% saline:air partition coefficient and thus were not included in this study.

2.2 Theoretical Molecular Descriptors. Theoretical molecular descriptors may be divided into hierarchical classes based upon level of complexity. Topostructural (TS) descriptors, which encode information strictly on the adjacency and connectedness of atoms within a molecule, make up the simplest of the hierarchical classes. Topochemical (TC) descriptors encode information related to the chemical nature of a molecule including bond type. The 3-dimensional or shape descriptors (3D) are still more complex, encoding information about the 3-dimensional aspects of a molecule. Calculated $\log P_{n\text{-octanol:water}}$ descriptors⁽⁹⁾ were included at the final stage of hierarchical model development. The topostructural and topochemical descriptors are collectively referred to as topological descriptors.

Descriptors used in the present study were derived from molecular structure using software packages including POLLY,⁽¹⁰⁾ Triplet,^(11, 12) and Molconn-Z.⁽¹³⁾ From POLLY, a set of topological descriptors is available, including a large group of connectivity indices,⁽¹⁴⁻¹⁷⁾ path-length descriptors,⁽¹⁴⁾ and information theoretic^(18, 19) and neighborhood complexity indices.⁽¹⁹⁾ The Triplet descriptors also constitute a large group of topological parameters. They are derived from a matrix, a main diagonal column vector, and a free term column vector, converting the matrix into a system of linear equations whose solutions are the local vertex invariants. These local vertex invariants are then used in the following mathematical operations in order to obtain the triplet descriptors:

1. Summation, $E_i x_i$
2. Summation of squares, $E_i x_i^2$
3. Summation of square roots, $E_i x_i^{1/2}$
4. Sum of inverse square root of cross-product over edges ij , $E_{ij}(x_i x_j)^{-1/2}$
5. Product, $N(E_i x_i)^{1/N}$

Molconn-Z provides additional topological descriptors, including an extended set of connectivity indices, electrotopological indices,^(20, 21) and hydrogen bonding descriptors, as well as a small set of molecular shape descriptors.

H-Bond, a software program developed by Basak,⁽²²⁾ was used to calculate HB_1 , a measure of hydrogen bonding potential. Balaban's J indices were also calculated by software developed by the authors.⁽²³⁻²⁵⁾

$\text{LogP}_{n\text{-octanol:water}}$ values were calculated by the LogP program⁽⁹⁾ and are included in Table I. Table II provides a brief description of all other theoretical molecular descriptors used in the current study, though the calculated values for these descriptors are not included for the sake of brevity.

2.3 Statistical Analysis. Independent and dependent variables were scaled by the natural logarithm, as their respective ranges differed by several orders of magnitude. The CORR procedure of the SAS statistical package⁽²⁶⁾ was used to identify perfectly correlated descriptors, i.e. $r = 1.0$. In each case, only one descriptor of a perfectly correlated pair was retained for use in the subsequent analysis. Any descriptor that either had a value of zero for all compounds in the data set or could not be calculated for all compounds in the data set was removed.

The structure-property models were developed using ridge regression (RR),⁽²⁷⁾ principal components regression (PCR),⁽²⁸⁾ and partial least squares (PLS) regression⁽²⁹⁻³¹⁾ methodologies, utilizing molecular descriptors in a hierarchical fashion. In addition, each class of descriptors was used independently to obtain single-class models. RR, PCR, and PLS are useful in cases wherein the number of descriptors is much greater than the number of observations, as well as in cases where the independent variables are highly intercorrelated. In addition, these regression methods make use of all independent variables as opposed to subset regression wherein it is possible that important parameters may be eliminated from the study. Linear regression (LR) was used to obtain the property-property models, which involve 1-2 independent variables. Statistical parameters reported include the cross-validated R^2 value and the PRESS statistic which are reliable measures of model predictability. In addition, the t values can be examined in

or t to identify significant descriptors. Although a descriptor with a large $|t|$ indicates that the associated descriptor is important in the model, it should be cautioned that the reverse is not necessarily true.

Honest assessment of the quality of a prediction model is seldom straightforward, but is particularly challenging in a situation such as this where the number of independent variables far exceeds the number of observations.^(32, 33) In these cases, conventional regression measures such as R^2 are useless. The measure we use is the cross-validation (or jack-knife) sum of squares. For this measure, each compound in turn is omitted from the data set, and the coefficients of the regression model (RR, PLS or PCR) computed using the remaining $n-1$ cases. These coefficients are used to predict the hold-out case. The overall quality of the fit is measured by the prediction sum of squares PRESS – the sum of squares of the difference between the actual observed activity and that predicted from the regression. A cross-validation R^2 can be defined by

$$R_{cv}^2 = 1 - \frac{PRESS}{SSTotal}$$

Unlike R^2 , this R_{cv}^2 does not increase if irrelevant predictors are added to the model; rather it tends to decrease. And where R^2 is necessarily non-negative, R_{cv}^2 may be negative. This non-uncommon situation is an indication that the model fitted is poor – worse, in fact, than making predictions by ignoring the predictors and using the mean activity as the prediction in all circumstances.

R_{cv}^2 mimics the results of applying the final regression to predicting a future case; large values can be interpreted unequivocally and without regard to either the number of cases or predictors as indicating that the fitted regression will accurately predict the activity of future compounds of the same chemical type as those used to calibrate the regression.

3. RESULTS AND DISCUSSION

Table III provides results of studies done on the complete set of 31 diverse compounds as well as the subset of 18 haloalkanes for the prediction of human $\log P_{\text{blood:air}}$. Examining the models developed using structural descriptors, we find that the RR methodology is generally superior to both PCR and PLS. This is supported by our earlier studies with various congeneric and diverse sets of chemicals.⁽³⁴⁻³⁶⁾ The model developed using TC descriptors as independent variables was superior to those developed with other structural descriptor classes in the analysis of the 31 diverse compounds, while the TS+TC model was superior in the analysis of the 18 haloalkanes.

The results of QSPRs reported in this paper show that structure-property correlations are comparable or superior to property-property correlations involving experimental saline:air and olive oil:air partition coefficients in the prediction of human blood:air partition coefficient. For the set of 31 diverse chemicals, a cross-validated R^2 of 0.874 and a PRESS of 7.79 is obtained for the TC model, while the property-property model utilizing $\log P_{\text{saline:air}}$ and $\log P_{\text{olive:oil air}}$ yields a cross-validated R^2 of 0.889 with a PRESS of 6.19 (Table III). For the set of 18 haloalkanes, the TS+TC models yields a cross-validated R^2 of 0.897 with a PRESS of 3.02, while the property-property model utilizing $\log P_{\text{saline:air}}$ and $\log P_{\text{olive:oil air}}$ yields a cross-validated R^2 of 0.846 with a PRESS of 4.50. However, property-property models in which rat $\log P_{\text{blood:air}}$ is used to predict human $\log P_{\text{blood:air}}$ are superior to those in which either $\log P_{\text{saline:air}}$ and $\log P_{\text{olive:oil air}}$ or structural parameters are used as predictors; with a cross-validated R^2 of 0.963 and PRESS of 2.25 for the full set of 31 compounds, and a cross-validated R^2 of 0.961 and PRESS of 1.16 for the subset of 18 haloalkanes.

It is clear from the results presented in Table III that experimental rat blood:air partition coefficient is the best predictor of human blood:air partition coefficient. Acquiring these data, however, is time consuming and requires laboratory testing resources along with the sacrifice of animals. Experimental determination of rat blood:air partition coefficient of hundreds or thousands of candidate chemicals would be a daunting task. The theoretical descriptor-based models, on the other hand, can provide reasonable estimates very quickly and at a low cost.

Ridge regression coefficients and standard errors for the top 10 descriptors based on $|t|$ values for the human $\log P_{\text{blood:air}}$ TC model based on the set of 31 diverse chemicals are provided in Table IV. The indices most important for the prediction of human $\log P_{\text{blood:air}}$ include: a) molecular weight (fw), quantifying molecular size, b) triplet indices (AZV_y), encoding information about the nature of atoms, c) electrotopological state indices (SdO, SddSN, SSB_r), which are numerical descriptors of the electronic states of atoms, d) valence and bonding connectivity indices ($^1\chi^b$, $^1\chi^v$), which quantify structural information regarding molecular size and shape, and e) a hydrogen bonding parameter (HB₁). The important role of molecular factors such as size, electronic interactions, and hydrogen bonding in determining partition coefficients of chemicals is evident from our earlier studies^(3, 37) and those of Kamlet et al.⁽³⁸⁾

It is important to reiterate that model predictability is best judged, not with a fitted model, but with a cross-validated model wherein each of the compounds, in turn, is omitted from the data set and its value then determined by the coefficients of the remaining $n-1$ compounds. In this way, we have an accurate, if not conservative, indication of how well the model will predict property values of new compounds which are similar to those used to create the model. Figure 1 illustrates the relationship between the fitted and experimental human $\log P_{\text{blood:air}}$ values using the TC model for the set of 31 diverse compounds. All

statistical values reported in this paper, however, are based on cross-validated results. Accordingly, Figure 2 illustrates the relationship between the cross-validated predicted and experimental human $\log P_{\text{blood:air}}$ values using the TC model for the set of 31 diverse compounds.

In conclusion, the models based on rat $\log P_{\text{blood:air}}$ are superior to any of the structure-based models. It is important to note, however, that experimental data are not currently available for the majority of compounds; and obtaining this data is costly in terms of time and monetary resources. In contrast, we are able to obtain reasonably good models using structural descriptors that can be calculated very quickly and inexpensively for both existing and unsynthesized chemicals. Modeling based on structural descriptors also promotes an understanding of the theoretical basis of properties and reduces the need for animal research, an area to which a growing aversion exists in our society.

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Table I. Experimental liquid:air partition coefficients^a and calculated logP_{n-octanol:water}

		Experimental			Calculated	
No.	Chemical	P(0.9%saline:air)	P(olive oil:air)	Rat P(blood:air)	Human P(blood:air)	LogP (<i>n</i> -octanol:water)
Haloalkanes						
1	Dichloromethane	5.96 ± 0.71	131 ± 7	19.4 ± 0.8	8.94 ± 0.13	1.16
2	Chloroform	3.38 ± 0.09	402 ± 12	20.8 ± 0.1	6.85 ± 0.51	1.86
3	Carbon tetrachloride	0.35 ± 0.03	374 ± 11	4.52 ± 0.35	2.73 ± 0.23	3
4	Chlorodibromomethane	7.34 ± 0.42	2683 ± 152	116 ± 4	52.7 ± 1.2	1.77
5	Chloroethane	1.09 ± 0.06	38.9 ± 3.1	4.08 ± 0.39	2.69 ± 0.20	1.47
6	1,1-Dichloroethane	2.45 ± 0.04	186 ± 7	11.2 ± 0.1	4.94 ± 0.24	1.86
7	1,2-Dichloroethane	11.4 ± 0.1	366 ± 8	30.4 ± 1.2	19.5 ± 0.7	1.6
8	1,1,1-Trichloroethane	0.75 ± 0.07	295 ± 22	5.76 ± 0.50	2.53 ± 0.13	2.26
9	1,1,2-Trichloroethane	13.3 ± 0.3	1776 ± 26	58.0 ± 1.1	35.7 ± 0.4	2.08
10	1,1,1,2-Tetrachloroethane	3.53 ± 0.23	2686 ± 51	41.7 ± 1.0	30.2 ± 1.3	2.64
11	1,1,2,2-Tetrachloroethane	23.4 ± 2.0	6358 ± 402	142 ± 6	116 ± 6	2.51
12	Hexachloroethane	0.66 ± 0.21	5015 ± 318	62.7 ± 2.1	52.4 ± 1.4	4.24
13	1-Bromo-2-chloroethane	8.91 ± 0.56	569 ± 23	52.7 ± 3.5	29.2 ± 2.1	1.73
14	1-Chloropropane	1.04 ± 0.01	105 ± 2	5.21 ± 0.06	2.85 ± 0.06	1.95
15	2-Chloropropane	0.82 ± 0.09	69.9 ± 3.5	3.10 ± 0.17	1.39 ± 0.29	1.81
16	1,2-Dichloropropane	2.75 ± 0.11	428 ± 30	18.7 ± 0.5	8.75 ± 0.50	2.18
17	<i>n</i> -Propyl bromide	1.44 ± 0.12	272 ± 8	11.7 ± 0.4	7.08 ± 0.40	2.13
18	Isopropyl bromide	1.08 ± 0.04	164 ± 5	5.95 ± 0.14	2.57 ± 0.15	1.63
19	1-Nitropropane	127 ± 4	1062 ± 21	223 ± 10	187 ± 6	0.8
20	2-Nitropropane	98.3 ± 5.4	640 ± 16	183 ± 12	154 ± 17	0.61
21	<i>n</i> -Heptane	0.18 ± 0.10	405 ± 3	4.75 ± 0.15	8.19 ± 0.10	4.31
22	JP-10 (tricyclo[5.2.1.0 ^{2,6}]-decane)	0.21 ± 0.07	12970 ± 420	62 ± 4	52.5 ± 3.7	3.75
23	Vinyl chloride	0.43 ± 0.04	24.4 ± 3.7	1.68 ± 0.18	1.16 ± 0.08	1.37
24	Trichloroethylene	0.83 ± 0.30	553 ± 46	21.9 ± 1.4	8.11 ± 0.17	2.36
25	Tetrachloroethylene	0.79 ± 0.06	2134 ± 159	18.9 ± 1.1	10.3 ± 1.1	3.47
26	Vinyl bromide	0.44 ± 0.06	56.0 ± 1.5	4.05 ± 0.16	2.27 ± 0.16	1.61
27	Benzene	2.75 ± 0.10	465 ± 5	17.8 ± 0.3	8.19 ± 0.10	2.04
28	Chlorobenzene	2.81 ± 0.07	2188 ± 41	59.4 ± 1.0	30.0 ± 0.3	2.64
29	<i>o</i> -Xylene	2.65 ± 0.08	3534 ± 208	44.3 ± 2.0	34.9 ± 1.7	3.15
30	<i>m</i> -Xylene	1.92 ± 0.12	3245 ± 116	46.0 ± 1.5	32.5 ± 1.6	3.21
31	<i>p</i> -Xylene	1.77 ± 0.07	3319 ± 96	41.3 ± 3.5	44.7 ± 1.9	3.20

^a Values represent mean ± standard error

Table II. Symbols, definitions and classification of calculated molecular descriptors

<i>Topostructural (TS)</i>	
I_D^W	Information index for the magnitudes of distances between all possible pairs of vertices of a graph
$\bar{I}_D^W$	Mean information index for the magnitude of distance
W	Wiener index = half-sum of the off-diagonal elements of the distance matrix of a graph
I^D	Degree complexity
H^V	Graph vertex complexity
H^D	Graph distance complexity
IC	Information content of the distance matrix partitioned by frequency of occurrences of distance h
M_1	A Zagreb group parameter = sum of square of degree over all vertices
M_2	A Zagreb group parameter = sum of cross-product of degrees over all neighboring (connected) vertices
${}^h\chi$	Path connectivity index of order $h = 0-10$
${}^h\chi_C$	Cluster connectivity index of order $h = 3-6$
${}^h\chi_{PC}$	Path-cluster connectivity index of order $h = 4-6$
${}^h\chi_{Ch}$	Chain connectivity index of order $h = 3-10$
P_h	Number of paths of length $h = 0-10$
J	Balaban's J index based on topological distance
nrings	Number of rings in a graph
ncirc	Number of circuits in a graph
DN^2S_y	Triplet index from distance matrix, square of graph order (# of non-H atoms), and distance sum; operation $y = 1-5$
DN^2I_y	Triplet index from distance matrix, square of graph order, and number 1; operation $y = 1-5$
$AS1_y$	Triplet index from adjacency matrix, distance sum, and number 1; operation $y = 1-5$
$DS1_y$	Triplet index from distance matrix, distance sum, and number 1; operation $y = 1-5$
ASN_y	Triplet index from adjacency matrix, distance sum, and graph order; operation $y = 1-5$
DSN_y	Triplet index from distance matrix, distance sum, and graph order; operation $y = 1-5$
DN^2N_y	Triplet index from distance matrix, square of graph order, and graph order; operation $y = 1-5$
ANS_y	Triplet index from adjacency matrix, graph order, and distance sum; operation $y = 1-5$
$AN1_y$	Triplet index from adjacency matrix, graph order, and number 1; operation $y = 1-5$
ANN_y	Triplet index from adjacency matrix, graph order, and graph order again; operation $y = 1-5$
ASV_y	Triplet index from adjacency matrix, distance sum, and vertex degree; operation $y = 1-5$
DSV_y	Triplet index from distance matrix, distance sum, and vertex degree; operation $y = 1-5$
ANV_y	Triplet index from adjacency matrix, graph order, and vertex degree; operation $y = 1-5$
<i>Topochemical (TC)</i>	
O	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-filled graph
O_{orb}	Order of neighborhood when IC_r reaches its maximum value for the hydrogen-suppressed graph
I_{orb}	Information content or complexity of the hydrogen-suppressed graph at its maximum neighborhood of vertices
IC_r	Mean information content or complexity of a graph based on the r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-filled graph
SIC_r	Structural information content for r^{th} ($r = 0-6$) order neighborhood of vertices in a hydrogen-

	filled graph
CIC _r	Complementary information content for r th (r = 0-6) order neighborhood of vertices in a hydrogen-filled graph
χ^b_h	Bond path connectivity index of order h = 0-6
χ^b_c	Bond cluster connectivity index of order h = 3-6
χ^b_{ch}	Bond chain connectivity index of order h = 3-6
χ^b_{pc}	Bond path-cluster connectivity index of order h = 4-6
χ^v_h	Valence path connectivity index of order h = 0-10
χ^v_c	Valence cluster connectivity index of order h = 3-6
χ^v_{ch}	Valence chain connectivity index of order h = 3-10
χ^v_{pc}	Valence path-cluster connectivity index of order h = 4-6
J ^B	Balaban's J index based on bond types
J ^X	Balaban's J index based on relative electronegativities
J ^Y	Balaban's J index based on relative covalent radii
HB ₁	Hydrogen bonding parameter
AZV _y	Triplet index from adjacency matrix, atomic number, and vertex degree; operation y = 1-5
AZS _y	Triplet index from adjacency matrix, atomic number, and distance sum; operation y = 1-5
ASZ _y	Triplet index from adjacency matrix, distance sum, and atomic number; operation y = 1-5
AZN _y	Triplet index from adjacency matrix, atomic number, and graph order; operation y = 1-5
ANZ _y	Triplet index from adjacency matrix, graph order, and atomic number; operation y = 1-5
DSZ _y	Triplet index from distance matrix, distance sum, and atomic number; operation y = 1-5
DN ² Z _y	Triplet index from distance matrix, square of graph order, and atomic number; operation y = 1-5
nvx	Number of non-hydrogen atoms in a molecule
nelem	Number of elements in a molecule
fw	Molecular weight
si	Shannon information index
totop	Total Topological Index t
sumI	Sum of the intrinsic state values I
sumdell	Sum of delta-I values
tets2	Total topological state index based on electrotopological state indices
phia	Flexibility index (kp1* kp2/nvx)
IdCbar	Bonchev-Trinajsti information index
IdC	Bonchev-Trinajsti information index
Wp	Wienerp
Pf	Plattf
Wt	Total Wiener number
knotp	Difference of chi-cluster-3 and path/cluster-4
knotpv	Valence difference of chi-cluster-3 and path/cluster-4
nclass	Number of classes of topologically (symmetry) equivalent graph vertices
numHBd	Number of hydrogen bond donors
numwHBd	Number of weak hydrogen bond donors
numHBa	Number of hydrogen bond acceptors
SHCsats	E-State of C sp ³ bonded to other saturated C atoms
SHCsatu	E-State of C sp ³ bonded to unsaturated C atoms
SHvin	E-State of C atoms in the vinyl group, =CH-
SHTvin	E-State of C atoms in the terminal vinyl group, =CH ₂
SHavin	E-State of C atoms in the vinyl group, =CH-, bonded to an aromatic C
SHarom	E-State of C sp ² which are part of an aromatic system
SHHBd	Hydrogen bond donor index, sum of Hydrogen E-State values for -OH, =NH, -NH ₂ , -NH-, -SH, and #CH
SHwHBd	Weak hydrogen bond donor index, sum of C-H Hydrogen E-State values for hydrogen atoms on a C to which a F and/or Cl are also bonded
SHHBa	Hydrogen bond acceptor index, sum of the E-State values for -OH, =NH,

Qv	-NH ₂ , -NH-, >N-, -O-, -S-, along with -F and -Cl
NHBint,	General Polarity descriptor
SHBint,	Count of potential internal hydrogen bonders (y = 2-10)
	E-State descriptors of potential internal hydrogen bond strength (y =2-10)
	Electrotopological State index values for atoms types:
	SHsOH, SHdNH, SHsSH, SHsNH ₂ , SHssNH, SHtCH, SHother, SHCHnX, Hmax Gmax, Hmin, Gmin, Hmaxpos, Hminneg, SsLi, SssBe, SssssBem, SssBH, SsssB, SssssBm, SsCH ₃ , SdCH ₂ , SssCH ₂ , StCH, SdsCH, SaaCH, SsssCH, SddC, StsC, SdssC, SaasC, SaaaC, SssssC, SsNH ₃ p, SsNH ₂ , SssNH ₂ p, SdNH, SssNH, SaaNH, StN, SssNHp, SdsN, SaaN, SssN, SddsN, SaasN, SssssNp, SsOH, SdO, SssO, SaaO, SsF, SsSiH ₃ , SssSiH ₂ , SssSiH, SssssSi, SsPH ₂ , SssPH, SsssP, SdsssP, SssssP, SsSH, SdS, SssS, SaaS, SdssS, SddssS, SssssssS, SsCl, SsGeH ₃ , SssGeH ₂ , SssssGeH, SssssGe, SsAsH ₂ , SssAsH, SssAs, SdssAs, SssssAs, SsSeH, SdSe, SssSe, SaaSe, SdssSe, SddssSe, SsBr, SsSnH ₃ , SssSnH ₂ , SssSnH, SssssSn, SsI, SsPbH ₃ , SssPbH ₂ , SssPbH, SssssPb
<i>Geometrical / Shape (3D)</i>	
kp0	Kappa zero
kp1-kp3	Kappa simple indices
ka1-ka3	Kappa alpha indices

Table III. Summary statistics of predictive models for human $\log P_{\text{blood:air}}$ based on experimental properties and theoretical structural descriptors.

A. 31 DIVERSE CHEMICALS								
Independent Variables	RR		PCR		PLS		LR	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
<u>Structural descriptors</u>								
TS	0.257	45.8	-0.451	89.4	0.052	58.4		
TS+TC	0.846	9.48	0.165	51.4	0.677	19.9		
TS+TC+3D	0.827	10.6	0.140	53.0	0.620	23.4		
TS+TC+3D+logP ^a	0.835	10.2	0.112	54.7	0.652	21.4		
TS	0.257	45.8	-0.451	89.4	0.052	58.4		
TC	0.874	7.79	0.403	36.8	0.709	17.9		
3D	0.147	52.6	-0.013	62.4	-0.256	77.4		
<u>Properties</u>								
LogP _{olive oil:air} + LogP _{saline:air}							0.899	6.19
Rat logP _{blood:air}							0.963	2.25
B. 18 HALOALKANES								
Independent Variables	RR		PCR		PLS		LR	
	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS	R ² _{c.v.}	PRESS
<u>Structural descriptors</u>								
TS	0.252	22.0	-1.53	74.3	-0.815	53.2		
TS+TC	0.897	3.02	0.825	5.14	0.678	9.45		
TS+TC+3D	0.892	3.16	0.856	4.22	0.702	8.74		
TS+TC+3D+logP ^a	0.892	3.18	0.856	4.23	0.704	8.69		
TS	0.252	22.0	-1.53	74.3	-0.815	53.2		
TC	0.891	3.21	0.853	4.32	0.616	11.3		
3D	0.753	7.24	0.593	11.9	0.562	12.9		
<u>Properties</u>								
LogP _{olive oil:air} + LogP _{saline:air}							0.846	4.50
Rat logP _{blood:air}							0.961	1.16

^aCalculated $\log P_{n\text{-octanol:water}}$; values included in Table I.

Table IV. Ridge regression coefficient and standard error for each of the top 10 descriptors, ranked by $|t|$, in the topochemical model for the prediction of human $\log P_{\text{blood:air}}$, $n = 31$.

Descriptor	RR coeff	s.e.	t
SdO	0.227	0.021	10.690
HB ₁	0.340	0.032	10.660
SddsN	-1.694	0.159	-10.640
AZV ₃	0.130	0.016	8.000
$^1\chi^v$	0.345	0.052	6.670
AZV ₄	0.224	0.034	6.580
AZV ₁	0.133	0.024	5.640
SsBr	0.238	0.044	5.390
fw	0.287	0.054	5.310
$^1\chi^b$	0.139	0.028	5.060

FIGURE CAPTIONS

Figure 1. Experimental vs fitted human $\log P_{\text{blood:air}}$ using the topochemical (TC) ridge regression (RR) model for the set of 31 diverse compounds

Figure 2. Experimental vs cross-validated predicted human $\log P_{\text{blood:air}}$ using the topochemical (TC) ridge regression (RR) model for the set of 31 diverse compounds

Figure 1.

Figure 2.

Bibliography of papers on development of proteomics-based biodescriptors

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