NEW FUNDAMENTAL RESULT IN TWO DIMENSIONAL MULTIPLE MINIMA

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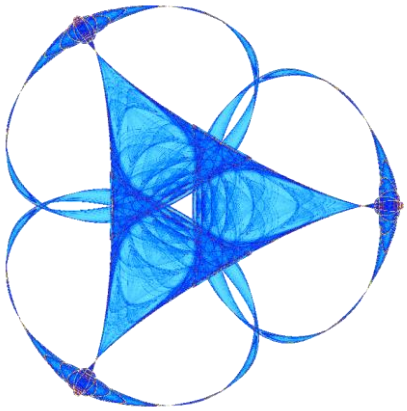


INSTITUTE FOR MATHEMATICS AND ITS APPLICATIONS
UNIVERSITY OF MINNESOTA
400 Lind Hall
207 Church Street S.E.
Minneapolis, Minnesota 55455-0436
Phone: 612-624-6066 Fax: 612-626-7370
URL: http://www.ima.umn.edu

New Fundamental Result in Two Dimensional Multiple Minima

by

Ezio Marchi*

Abstract

In this paper we introduce a novel method, solving the rather complicate problem of the multiple minima in two dimension.

This method concernes with the fact that the two dimension problem is attacked and solving with the parametrization among the multiple minima one direction and then moving in the other direction again to fund the multiple minima. In this way we obtain a solution . We use Kakutani´s fixed theorem for the correctness.

From an intuive point of view we have all the frameworks for applying the just kmown algorithm or to perform new ones. We believe that the present method, provides a better insight.

This method provide a big insight to attack and solve the problem in an arbitrary number for the dimension we consider it in a further publication. We believe that it is possible to have for the infinite dimension space as an analogous approach in Hilber space.

Descriptive Introduction

The study and comparison of sequences of characters from a finite alphabet is relevant to various areas of science, notably molecular biology. The measurement of sequence similarity involves the consideration of the different possible sequence alignments in order to find an optimal one for which the “distance” between sequences is minimum. By associating a path in a lattice to each alignment, a geometric insight can be brought into the problem of finding an optimal alignment. This problem can then be solved by applying a dynamic programming

* ***Emeritus Professor National University of San Luis (UNSL)***
San Luis, Argentina.Founder and First Director of the Insituto de MatemáticaAplicada San Luis (IMASL)
(ex) Superior Resercher CONICET. Email: emarchi1940@gmail.com

algorithm. However, the computational effort grows rapidly with the number N of sequences to be compared.

It is proved here that knowledge of the measure of an arbitrarily chosen alignment can be used in combination with information from the pairwise alignments to considerably restrict the size of the region of the lattice in consideration. This reduction implies fewer computations and less memory space needed to carry out the dynamic programming optimization process. The observations also suggest new variants of the multiple alignment problem.[1]

The Chemistry Monte Carlo-minimization approach to the multiple-minima problem in protein folding has been studied in many aspects. One representative is the following study. [2]

A Monte Carlo-minimization method has been developed to overcome the multiple-minima problem. The Metropolis Monte Carlo sampling, assisted by energy minimization, surmounts intervening barriers in moving through successive discrete local minima in the multidimensional energy surface. The method has located the lowest-energy minimum thus far reported for the brain pentapeptide [Met5]enkephalin in the absence of water. Presumably it is the global minimum energy structure. This supports the concept that protein folding may be a Markov process. In the presence of water, the molecules appear to exist as an ensemble of different conformations. Optimization procedures are required for an ultimate understanding as to how interatomic interactions lead to the folded, most-stable conformation of a protein from existence of many local minima in the multidimensional energy surface: the multipleminima problem. This problem exists even for a system as small as a terminally blocked amino acid and becomes aggravated as the size of the system increases. Whereas algorithms are available for minimizing a function of many variables, none exist for passing from one local minimum, over an intervening barrier, to the next local minimum-and ultimately to the global minimum-in a many-dimensional space. Several procedures have been developed to overcome this problem; these include the "buildup" method, optimization of electrostatics, relaxation of dimensionality, adaptive importance sampling Monte Carlo, pattern recognition based on factor analysis of protein data, use of distance constraints, and use of short-, medium-, and long-range interactions. Most of these procedures have been tested so far on short oligopeptides (up to 20 residues, in some cases), and their possible extension to proteins containing of the order of 100 residues would be of great interest. In our continual search for procedures to overcome this problem.

It has been developed an approach that appears to work very efficiently on the pentapeptide [Met5]enkephalin (H-Tyr-Gly-Gly-Phe-Met-OH) and hopefully can be extended to larger

structures. The application of this procedure to enkephalin is reported here. The multiple-minima problem is not unique to protein folding but arises in many other fields of biology, chemistry, and physics whenever complexity appears (e.g., for intrinsically heterogeneous systems with a large number of strongly coupled degrees of freedom). A protein, composed of chemically distinct amino acids in a unique sequence, is a heterogeneous system that is fundamentally different from a homopolymer, and its many degrees of freedom contribute to the formidable difficulty of the multiple-minima problem. From a computational point of view, the multiple-minima problem is reminiscent of the NP (nondeterministic polynomial time) problem, in that the total number of possible conformations is an exponential function of the total number of degrees of freedom. The approach taken here combines the power of conventional energy minimization to find local minima and that of the Metropolis Monte Carlo method in global combinatorial optimization. When implemented, it generates a Markov walk on the hyperlattice of all (discrete) energy minima, with Boltzmann transition probabilities. The working hypothesis ("Markovian hypothesis") underlying this method is (i) protein folding is a Markov process with Boltzmann transition probabilities and (ii) for a natural biologically active protein, such a Markov process leads to a unique absorbing state(one in which equilibrium is reached after a sufficiently long time and in which the stationary probability of occurrence approaches unity), corresponding to the native structure of a protein. The method has been tested extensively on [Met5]enkephalin, with interaction energies computed by the ECEPP/2 (empirical conformational energy program for peptides) algorithm. In the absence of water, the Monte Carlo-minimization procedure converges consistently to the same global minimum (a type II' p-bend structure, the central two residues of which are Gly-Phe) for as many as 12 random starting conformations (and an additional one selected to have a different,-bend structure). In the presence of water, the molecule undergoes considerable structural fluctuations, with no unique stable structure, suggesting that a large ensemble of distinct conformations coexist at equilibrium.

THE MONTE CARLO-MINIMIZATION METHOD

Motivation. Experimental studies have demonstrated that a protein is not a static structure but instead undergoes fluctuations. Based on photodissociation studies of carbon monoxide bound to myoglobin, it has been suggested that a protein can exist in a large number of conformational substates separated by barriers, with transitions among substates constituting equilibrium fluctuations. A recent molecular dynamics study of myoglobin reported the existence of many minima in the vicinity of the native protein; these corresponded to relative reorientations of the a-helices coupled with rearrangements of the side chains, as a

consequence of the internal dynamics of the protein. It follows, as a necessary condition that a structure be stable, that the native conformation of a protein must be stable not only against small disturbances but also against larger-scale thermal fluctuations; i.e., the native structure must be able to recover from any thermal impulse, even though the latter may (temporarily) lead to a different local minimum-energy .

A structure determined by energy minimization alone, which is stable only against small distortions, is very likely to be thermally unstable and hence cannot be admitted as a candidate for the native structure. These considerations suggest that thermal fluctuations play an indispensable role in selecting the native structure. The fact that a protein in a thermodynamic environment can fold into its native structure within a time scale of milliseconds to seconds implies that, if it can reproduce the natural processes theoretically or at least simulate their essential and most relevant features (mainly thermal fluctuations and energetic processes), we may be able to devise a sufficiently efficient method to fold a protein. Since a Metropolis Monte Carlo method simulates natural thermal processes, by taking into account both random fluctuations and energetic considerations, it might be applicable to protein folding. The successful application of the simulated annealing method, which is essentially a Metropolis Monte Carlo simulation technique with an artificial "temperature," to the computationally difficult "traveling-salesman problem" is very similar to the multiple-minima problem, in that the total number of possible solutions is a nonpolynomial function of the number of cities. A straightforward application of the Metropolis Monte Carlo method to polypeptides, however, has proven to be very inefficient, or even impossible, because we have to search a high-dimensional conformational space rather than discrete states. Conventional Metropolis Monte Carlo samples the whole space by making small increments in each step. The large energy barriers in the conformational space of a protein make such a method impractical because, for most of the time, the sampling is confined to a very restricted region of the whole conformational space. A different type of Monte Carlo algorithm is an alternative approach to this problem. To overcome these difficulties, it has developed the Monte Carlo-minimization method, which randomly samples only the discrete set of energy minima instead of the whole conformational space. Implementation. The method consists of three components. [3]

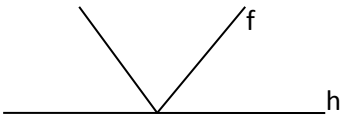
All this material has been obtained from the important contributions quoted in the bibliography.

Now we are going to consider a more theoretical aspect which is concerned from the more mathematical consideration.

2. Some important preliminary facts

In a previous paper Marchi [4] we are concerned with the fact that the convex envelope reaches the minimum and equals the minimum of the function under consideration, this in the case of in any dimension. Moreover, this is regarding as a difficult and important problem of the multiple minima

There is an aspect which is of importance. The fact that is important in the problem of one dimension, and it is going to be important for the study of two dimensions, is that in one dimension if the function is “sharp” at the minimum as is illustrated in the figure 1, the “separation” hyperplane to the



m

fig 1

set formed by all the points(x,y) whose y is greater or equal to f (x) and to the corresponding envelope: one to be stressed is that the point m is an interior and not in the boundary. Here we do draw the partial “slide” envelope since it depends en the whole range or domain.

A second consideration that you have to take into account is when the case is geometrically given in the fig 2.

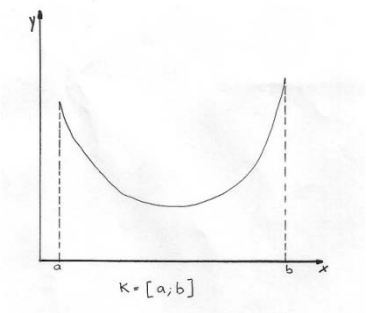


Fig 2

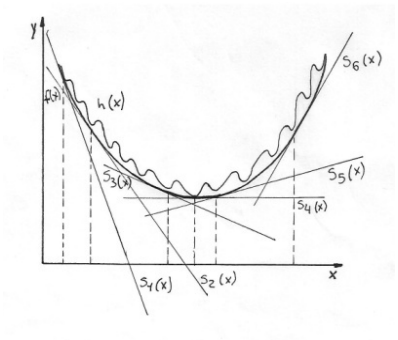


Fig 3

Then in all case we have a separation g hyperplane in a horizontal way and parallel to the axis. It is important to keep in mind that the slide function is similar to the one expressed in the previous case of only one dimension.

3. <u>The main results</u>

Without any less of generality we might consider a real continuous function f (x, y) ϵR defined on the unit square I=[0,1]x[0,1], with the property that the minimum it is reach in the interior

Ĭ = (0,1) x (0,1).

Then here we are going to study in very good way its minimum.

Now let is take the slides function for any fixed $\bar{y} \in [0,1]$

$$f_{\bar{y}}\,(x,\bar{y}) : [0,1] \longrightarrow R$$

$$: x1 \longrightarrow f_{\bar{y}}(x,\bar{y})$$

and on the other direction

$$f_{\bar{x}}\,(\,\bar{x},y) : [0,1] \longrightarrow R$$

$$: y\,1 \longrightarrow f\,(\bar{x},y)$$

Then the convex envelope of a real function in a open interval can be constructed in two ways namely: by taking the supreme or maximum of all convex function from below. The second

method is taking all the straight lives. In one dimension they provide the same convex curve: the envelope.

On the other hand, let $C_{.,\bar{y}}$ be the convex envelope at the place ȳ and let be $C_{\bar{x}},.$ at the place in the other remain coordinate: clearly both of then are continues. Since the f is continuous then both, $C_{.,\bar{y}}$ and $C_{\bar{x}},.$ are continuous and convex,

The sets of the minimum are non-empty convex and compact

$$m_{\bar{x}},. = \left\{y \in [0,1]: C_{\bar{x}},.(y) = \min_{z} C_{\overline{x_{,.}}}(z)\right\}$$

$$m_{.,\bar{y}} = \left\{x \in [0,1]: C_{.,\bar{y}}(x) = \min_{z} C_{.,\bar{y}}(z)\right\}$$

Therefore the graph of both functions

$G., = \{(x,y): [x,y] \epsilon\ I\ y \epsilon\ m_x,.\}$

$G,. = \left\{(x,y): [x,y] \epsilon\ I\ x \epsilon\ m_{.,y}\right\}$

Are closed.

Now consider the multivalued function

φ: I => I

(x,y) => φ(x,y)

defined by

$\varphi(x,y)=m_{x.,}$ x $m_{.,\bar{y}}$

This is a multivalued function defined on I where the image is non-empty, convex and compact, then we apply Kakutani's fixed pewit theorem, which says:

Theorem 1 (Kakutani)

Led K c R^n be an non-empty and convex in compact and consider a multivalued function L: K=>K, such that the set L(x)≠ ∅ , is convex and compact and the graph is closed them there exists fixed pewit $\bar{x} \epsilon L(\bar{x})$.

Using this important result to our function under consideration, there exists a fixed point, namely:

$(\bar{x},\bar{y}) \in \varphi\ (\bar{x},\bar{y})$

From where, it means

$\bar{x} \in m_{.,\bar{y}}$ and $\bar{y} \in m_{\bar{x},}$.

$C_{.,\bar{y}}(\bar{x}) = \min_{z} \ C^{(z)}_{.,\bar{y}}$

$C_{\overline{\bar{x},.}}(\bar{y}) = \min_{z} \ C_{\bar{x},.}$; (z)

Now we will prove that at such point we reach the minimum off defined an the entire I. For this consider the convex envelope from below, now by the following there simple and important results proved by J Martinez Legaz[5], that says that in any dimension the envelope from below reaches the same minimum as the function and to a same point. Moreover, there is a tangent separation hyperplane parallel to the plane of the orthant or of constant value whose axis are x,y, reaching the minimum of the function f under consideration. The minimum is reached in a point part of the graph of f and the separation plane just mentioned.

Theorem 2 (Martin Legaz): let X be a vector topological space, C ⊆ X is a men- empty convex set, f:C →R is a teal function.

Which reaches the minimum in $\bar{x} \epsilon C$ and conv f is the convex envelope of: f: C → R, then $\bar{x}$ is also minimum of conv f.

Proof : Since the constant function of value f($\bar{x}$) is a convex minorant, then it holds $f\ (\bar{x}) \leq$ conv f, therefore

$f\ (\bar{x}) \leq \inf_{x \epsilon C}$ (conv f) (x) ≤ (conv f) ($\bar{x}$) ≤ $f(\bar{x})$

From here we obtain that

$\inf_{x \epsilon C}$ (conv f) (x) = (conv f) ($\bar{x}$)

q.e.d.

One has that there is a point ($\bar{x}$, ȳ) such that the hyperplane H minorant is parallel to the orthant x,y and moreover the value of H at the point ($\bar{x}$, ȳ) it is the name as f ($\bar{x}$, ȳ).

On the other hand H is generated by the two perpendicular straight lives $h_{\bar{x}}$ and $h_{\bar{y}}$ which intersect at point ($\bar{x}$, ȳ) and they generated H.

Thus we have proved in a general way that this new method of perpendicular contraction of the minimum: Clearly it is interesting to set what is the method with the best algorithm from a point of view of complexity and saving rime of real computation.
A new theory for linear programming is given by Marchi-Matons[]

NOTE: We have used Kakutani's fixed point theorem. However for higher dimension we are going to use it again. But we indicate for the future study of the subject that another strong result is the fixed point theorem by Eilenberg and Montgomery that instead of having convexity in the text of Kakutani's, is change for contractible.

We remaind that a set M is contractible if there exist a continuous function

$$\alpha: [0,1] x\, M \ \rightarrow M$$

$$\alpha\,(0, m) = \ m_0 \ \in M$$

$$\alpha\,(1, m) = m$$

The theorem says that under general conditions there exist a fixed point.

It is my intuition that this theorem will be of great importance when one apply and study Morse theory, related to biotechnology.

More over a further generalization of Eilenberg Montgomery it is possible to find a fixed point theorem with more general topological conditions: Beagle's theorem.

Finally we would to say that might a mathematical tool to used in more sophisticate set up or related with this is the non-cooperative game theory and the Morse theory. For this reason we incorporate some specific bibliography.

As an addendum, we would lied to say that our method of face projection and the construction of the envelope, would be an important feature. Since in the future will probably be possible to construct the envelope then we include various papers regarding the envelope.

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