PEERING INSIDE LIVING SYSTEMS: PHYSIOLOGY IN A SUPERCOMPUTER

By

Matthew Witten

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PEERING INSIDE LIVING SYSTEMS: PHYSIOLOGY IN A SUPERCOMPUTER

MATTHEW WITTEN, PH.D.†*

Abstract. Mathematical models of biological systems are often rejected as being biologically oversimplified. This comes as a necessary sideeffect of having to analyze otherwise intractable mathematical equations. Now, for the first time, with the advent of high performance computing, we can readily build ultra-largescale models and simulations of biological processes; thereby leading the way towards a deeper understanding of the complexities of life.

Key words. Supercomputing, life sciences, health sciences, medicine, biology, modeling, simulation, graphics, physiology

Physiology In The Supercomputer?.

Much, if not all, of what we know about living systems has evolved from laboratory experimentation. And, while biological techniques improve and equipment becomes more sophisticated, living systems continue to be investigated within the classical laboratory environment. This is natural as "physiology is the study of function in living matter: it attempts to explain the physical and chemical factors that are responsible for the origin, development, and the progression of life(Guyton[1])". Human physiology attempts to explain these factors as they apply to human beings. Human beings are extremely complex machines; complex systems containing complex subsystems. These subsystems interact with each other in diverse ways. Such complexity and synergism is exceptionally difficult to examine and to understand within the context of a classical experimental laboratory environment.

In the late 1800's the discipline of mathematics began to turn to biology/ecology as a source of intriguing mathematical problems. The very complexity that made life difficult for the experimental physiologists, intrigued the mathematicians. Complex biological systems lead to both simple and complex mathematical models. As a result of this turn of events, the field of *mathematical biology* sprouted into being. The leading edge of technology moved forward and, as computers became more cost effective, simulation modeling became a more widely used means of incorporating the necessary biological complexity into the original, often simplified mathematical models. As an outgrowth of this phase of its growth, mathematical biology added a strong component of computer modeling/simulation to its toolbox.

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*ETA Systems, Computational Biology and Medicine, 1450 Energy Park Drive, St. Paul, MN 55108
†Address correspondence to the author at International BioComputing Technologies, 687 Mount Curve Blvd., St. Paul, MN 55116.

The experimentalists objected. Theoretical analyses were deficient in a variety of areas. The mathematical/computer models were too simple to be useful in clinical and/or practical application. That is, they lacked crucial biological/medical realism. In some cases, the necessary realism was barely understood by the practicing experimental physiologists. *How can we make models of things we don't understand? And, when we understand them, why will we need the models?*(Witten[2–3]). Mathematical modelers bawked at the demands for increased levels of biological complexity. The necessary addition of reality often lead to alterations in the mathematical models; thereby making them intractable to mathematical analysis. Or else , the increased level of realism required extremely complex equations, and such complexity required increased computational memory and ultrahigh computation speeds. In addition, the experimentalists often wanted a level of realism that demanded an understanding of the biological system well beyond known experimental results.

With the advent of the *supercomputer*, biological reality is finally within the grasp of the mathematical/computer modeler. Complexity is not a serious issue, computation speeds are now practical enough to enable large modeling computations to be performed. Large memory is now available. Perhaps, for the first time, we will be able to, paraphrasing Emerson, "model the body electric." With this bit of historical perspective, let us examine some of the areas where *ultra largescale* physiological modeling and simulation have been applied.

Reproductive Ecotoxicology–The Ovaries.

The ovaries are the repository of the female reproductive component, the follicles. Of the approximately 500,000 follicles present in the two ovaries at birth, only about 375 of these follicles will eventually develop into ova. Worldwide, it has been demonstrated that there are increasing levels of infertility in females. This is particularly true in the United States. It is not at all clear what is causing such an increase to occur. As a consequence of this fact, it is of no small amount of importance that the dynamics of the female reproductive cycle be studied in detail. Such models might give insight into how the environment and/or other factors might play into the level of infertility displayed in a particular country or population. In addition, such models can be used to study the dynamics of the aging mammalian reproductive system.

Mathematical models of the development of an egg have been made by a number of groups; Lacker at the Courant Institute for Mathematical Sciences, Gosden et al. in England, and Witten at ETA Systems. These models represent various increasing levels of complexity in the mathematical modeling process. The basic premise of all of these models is that the follicle undergoes a series of stages or steps in its growth. These stages, and the transitions between them, are modeled by differential equations. These compartmental or Markov models can generate systems of equations that can be extremely large. The systems of equations range from fairly simple to fairly complex in their structure. The model system of Witten, for example, involves the solution of anywhere from 50,000 to over 200,000 nonlinear differential equations. These models have been fairly successful in simulating the various known physiological behaviors of the follicular pyramid. However, more needs to be done before they can be used to integrate both the physiological behavior of the female and the impact of the surrounding environment.

The Heart of Supercomputing—Cardiac Dynamics.

The cardiovascular system is fundamental to the life support of the human. Pivotal in this system is the four chambered muscle called the heart. Arthur Winfree, a MacArthur Foundation Fellow at the University of Arizona, is involved in the mathematical modeling and computer simulation of nonlinear waves in excitable media. One particular example of an excitable medium is the heart muscle. Winfree has been studying circulating, vortex–like excitation(re-entrant tachycardia) in the heart as it is related to the onset of fibrillation; when the heart suddenly loses the rhythmic movement that allows it to pump blood. Within the context of his theory and simulations, Winfree has been able to show that normal healthy heart muscle is an excitable medium within the sense of his mathematical framework. Additionally, he has been able to show that 2 and 3 dimensional vortices arise in excitable media such as heart muscle and that they do so in ways that are predicted by the theory. Finally, in dog heart, Winfree has been able to show that these vortices do represent the first stages of fibrillation(Winfree[4–6]).

At the University of Calgary, Wayne Giles heads a research team that is investigating the electrical energy of the heart and its affect upon the organ's natural rhythm. He is particularly interested in how such a model could be utilized to study the interaction of cardiac function and cardiac drugs(Murphey et al.[7–8]). Dr. Peter Backx, Dr. H. terKeurs of the University of Calgary and Dr. S. Goldman of the University of Guelph have been involved in studying the property of propagated after–contractions in cardiac preparations. Their mathematical model, involving up to 40,000 coupled ordinary differential equations, is numerically integrated to study the dynamics of calcium mediated contractile waves in cardiac prepartions(Backx et al.[9], Schouten et al.[10]).

M.H. Lambert and T.R. Chay[11], at the University 0f Pittsburgh, are involved in studying the dynamical relationship between cellular and sub-cellular behavior, and its affect at the physiological level. In particular, they are studing a mathematical model of cardiac cells which incorporates membrane potential and the dynamics of intracellular calcium transport. They show that simple dynamics, such as entrainment, is observed in systems of two cardiac pacemaker cells. In addition, they simulate the propagation of cardiac membrane potential and intracellular calcium concentration through a cellular sheet. The simulation shows a behavior suggestive of cardiac tachycardia.

Charles Peskin, at the Courant Institute for Mathematical Sciences, is actively involved in cardiac modeling from a different perspective. He has been doing 2 and now 3 dimensional modeling of the heart, including valves, ventricles, and is now involved in adding atria and other vessels. This working model beats and moves the blood through the chambers of the heart. The model is a complex one involving a coupled system of equations modeling the wall, the blood, and the valve motion(Peskin[12], Peskin et al.[13], McQueen and Peskin[14], Peskin and McQueen[15]).

The purpose of the Peskin research project is to develop a model that will allow for the design of artifical valves and their subsequent testing. In addition, he wishes to be able to study the affect of heart function on the valve design(D.M. McQueen and C.S. Peskin[16]).

Peskin points out that such a model can be used for a number of other investigatory questions. For example, looking at the timing between the atrial and ventricular contraction; a clinically important facet of cardiac function, as sophisticated pacemakers can now separately pace the chambers. Using their model they have, in fact, studied this question and have shown how it relates to the optimal delay for ventricular filling(Meisner et al.[17]).

Finally, Peskin points out that such a model can be used to study heart disease and its affect on cardiac dynamics. He was able to use his model to show weakened capillary muscles in the valve lead to valve prolapse.

Deborah Sulsky at the University of New Mexico has been extending the work of Peskin to account for clot formation. She has been examining 2 dimensional models(and is now extending her work to 3 dimensional models) of blood flow in which she includes platelets and red blood cells as particles in the fluid.

The Nervous System.

The nervous system(along with the endocrine system) provides the control functions for the human body. "In general, the nervous system is responsible for the rapid activities of the body; muscular contraction, rapidly changing visceral events, and even the rates of secretion of some of the endocrine glands(Guyton[1])." The nervous system is a unique system in that it can control and perform a vast complex of actions. The human brain is estimated to contain approximately 10^{12} neurons. Many of these neurons are connected to 10,000 other neurons. Thus, in many ways, the brain is itself a sophisticated supercomputer(Koshland[18], Sejnowksi et al.[19]).

At the single neuron level, Steve Young and Mark Ellisman, at the Laboratory for Neurocytology at UC San Diego, are using the supercomputer to reconstruct single neurons. The neurons are frozen, sliced into sections $0.25 - 5.0\mu m$ thick, and photographed through a high voltage electron microscope. The computer is then used to reconstruct the slices and to subsequently view them on a graphics workstation. Ultimately such techniques can be integrated with advanced simulation modeling to allow the scientist to investigate and to simulate tissue activities and structure/function relationships. For the moment, the work of Young and Ellisman will have impact in other areas. Alzheimer's disease, which plays havoc with the aged in our population, will be able to be viewed at the single cell level. Perhaps, with these more sophisticated techniques, we will begin to understand how the disease progresses and how it might be treated(Maisel[20]).

T.R. Chay, at the University of Pittsburgh has been studying the dynamics of excitable cells.In particular, he and his group have been trying to understand the behavior of channel gating in patch clamp data(Chay[21–23]). From the single cell, we move to the nerve. T.D. Lagerlund of the Mayo clinic has examined the effects of axial diffusion on oxygen delivery in the peripheral nerve. It is known that victims of diabetes often suffer changes in their system of blood vessels. These changes reduce the supply of oxygen and nutrients to the tissue and subsequently damage the kidneys, retinas, and nerves. The work of Lagerlund has been in examining the mechanism of tissue damage in diabetes and how nutrients reach the cells. His work has been primarily concerned with diffusion of various nutrient and other substances through nerve tissue. A deeper understanding of these mechanisms could well lead to a deeper understanding of and a subsequent treatment for a variety of nerve diseases caused by diabetes and other conditions(Lagerlund[24–25]).

At a higher level of neural organization, we reach the brain itself. Lagerlund[26–28] has developed computer models for modeling various features of the electroencephalogram or EEG as recorded by scalp electrodes. Their model has been an attempt to understand the mechanisms that are responsible for the generation of the rhythmic fluctuations in potential. Further, they wished to assess how the characteristic frequences seen in scalp EEG recordings might be determined by characteristics of local neuronal circuits.

Computing the Kidney.

The body fluids are extremely important to the basic physiology of the human being. The kidneys perform two major functions: (1) they excrete most of the end–products of bodily metabolism and, (2) they control the concentrations of most of the constituents of the bodily fluids. Loss of kidney function can lead to death. Don Marsh, University of Southern California School of Medicine, is leading a group of investigators in large scale mathematical modeling and simulation of the kidney. He and his group have looked at two problems: (1) the concentrating mechanism of the inner medulla of the kidney and, (2) the oscillation in tubular pressure initiated by the kidney's nonlinear control mechanism. The concentrating mechanism was modeled using a 3D model of the kidney structure. It included longitudingal symmetry, tubules, and blood vessels. The group was able to demonstrate that the longitudinal symmetry played no part in the concentrating mechanism of the kidney. In their study of the oscillation in tubular pressure, Marsh's group is using a sophisticated system of partial differential equation models to describe the physiological control of the kidney tubular pressure. They have been able to show the existence of what appears to be a chaotic attractor in the system and that there is a period doubling bifurcation in the development of hypertension.

Layton[29] and Pitman and Layton[30] have studied urea transport in a dynamic model for the mammalian nephron. These models make use of what are called evolution equations; these equations modeling salt and urea concentrations and fluid flux in the nephron. The results of their analysis suggest that a small increase in single nephron glomerular filtration rate produces a large increase in the salt concentration of tubular fluid. Secondly, they observed that the nephron acts as a low-pass filter . Finally, they noted that as a consequence of the long time delay in the tubuloglomerular feedback loop, some perturbations in afferent arteriolar blood pressure induce sustained periodic oscillations. These oscillations are similar to those observed in recent kidney experiments.

Modeling the Dynamics of the Body.

Mathematical/computer models of limb motion are of importance in a number of areas, from robotics to biomechanics. Karl Newell, University of Illinois Urbana–Champaign simulates limb movements using spring–mass models. Such models are currently used as a metaphor for the neuromuscular organization of limb motion. The result of such models is a simulation of limb motion in space and in time. Other investigators, at the Illinois Institute of Technology, are looking at modeling the biomechanics of the skeleton. Such models can then be used to study how collision forces are distributed through the skeletal structure. Hopefully, such understanding will lead to better ways to design sports equipment and other protective outerwear. In addition, such models can better aid in the design of prothestics and bioimplants.

At the cellular level, Cy Frank and Raj Rangayyan at the University of Calgary, are examining ligament injuries and methods of treatment. Collagen fibrils, the basic building block of normal healthy ligament, are in nearly parallel arrangement when the ligament is healthy. In injured tissue, the arrangement is highly random. These investigators have been able to demonstrate that the randomness of the distribution depends upon the nature of the injury sustained and the stage of healing. As the tissues heal, the collagen fibrils realign in a process called collagen remodeling. Using the supercomputer for sophisticated and intense image processing, these investigators are attempting to interpret the realignment stages and to use such knowledge to more accurately treat trauma to the limbs(Chaudhuri et al.[31]).

When considering body dynamics, one does not need to consider only peripheral limb motion, arms and legs. Motion of joints is also important. One of the greatests dental healthcare costs in TMJ(Temporal Mandibular Joint) Syndrome. ETA Systems, in collaboration with the School of Dentistry at the University of Texas Health Science Center San Antonio, is developing a neuromuscular joint model, in an effort to study TMJ Syndrome. The model involves, not only the use of sophisticated mathematical equations but also patient based data input for the joint/bone structures. Thus, the models will be based upon real patient data rather than hypothesized dental structures(Weiss[32]). Such models require the supercomputer to be used not only as a computation engine for model simulation, but as an image processing system to facilitate the handling of patient–based image data(CAT, NMR, PET). This is a subject area in and of itself. And, as such, is beyond the scope of our present discussion(Garwood et al.[33], Centofanti[34]).

Second only to the problem of TMJ Syndrome is the problem of periodontal disease.

This complex interplay between the bacterial ecology of the patient's mouth and the basic physiology of the patient is not very well understood. In a newly instigated and embarked project between the University of Texas Health Science Center, the University–Industrial Consortium, and ETA Systems, an ultralargescale simulation of the mouth and its bacterial environment is being developed. The purpose of this simulation is to better understand how periodontal disease occurs, what factors can influence the progression of the disease, and how can it be better treated.

Patient–Based Physiological Simulation.

Patient–based physiological modeling has come of age. More and more computer systems are being marketed to take patient image data and to reconstruct it so that a physician can view/review in 3–D a patient's x–ray, CAT, PET, NMR, or other data. Computerized surgery systems are currently in place at the Washington University of St. Louis Mallincrodt Institute and at the Mayo Clinic(Robb[35]). Facial reconstruction and surgical simulation are no longer a pipe dream. They are a practiced reality. The day of the computer enhanced mathematical scalpel has arrived(Spitzer and Whitlock[36]).

Such workstation–based and mainframe based systems allow one to dream of the kind of ultra largescale patient based physiological simulations that could be performed with a high performance computing engine. At the VA Medical Center Minneapolis, T.K. Johnson and R.L. Vessella([37–39]) are developing a patient based simulation of radioactive decay in the organs of the body. Such a problem is intensive in that it requires the mapping of the three dimensional spatial distribution of radiolabeled compounds. In addition, the difficulty of the problem is enhanced by the fact that the radiation may travel a distance before it interacts with matter, and the irregular shapes of the organs do not lend themselves to simple dose–distance relationships. Alternate models for calculating dose distributions in materials, when they are irradiated by fast neutron beams, are discussed in Moyers et al.[40].

Project DaVinci, at the University of Illinois, is attempting to build a 3–D simulation of the human body. At International BioComputing Technologies, we are looking at the problem of ultralargescale simulation of cellular systems and the interaction between aging cellular systems and cancerous ones. The increased graying of the US population and the increased evidence of age–related cancer points to the fact that there will be increased healthcare costs to be born by the healthcare system. Understanding of the dynamics of such acomplex biological system will allow us to better understand how to treat cancer in an individual of advanced years(Witten[41–42]).

Project Human.

Beyond the complexity of such ultra-largescale simulations and models is the no longer unreasonable goal of an ultralargescale simulation of a human. Such a simulation would be based upon the patients image data, non–invasive measurements of his physiological functions, and assorted clinical tests. Based upon such models, one can begin to hypothesis scenarios in which chemotherapy can be simulated in a patient, before the therapy is performed. Radical and new drug treatments can be simulated and the results can be examined and evaluated, not based upon an idealized mathematical model but rather, as based upon an integrated model and patient system. Eventually, one can envision the possibility of actually testing newly designed drugs(now designed in computers) in computer–based large scale simulations. While it will be a long time before such a complex simulation/modeling system can be put into place, it is no longer a pipedream to imagine its existence. Project Human is slowly becoming a practical reality.

Apologetica and Acknowledgements.

Many investigators were contacted and many others were not reached. To those to whom I spoke, thank you for your willingness to discuss your research. To those whom I was unable to reach, I apologize. I invite anyone working in supercomputing in the life sciences to contact me about his/her research.

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