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Circulatory Mass-Transport and Exchange

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Unraveling mysteries of adenosine metabolism and transport

Adenosine is involved in multiple biological actions in the cardiovascular system. Along with its role as a regulator of blood flow, heart rate and myocardial contractility, the cardioprotective effects of adenosine have been observed. However, despite extensive research, the metabolism and transport of adenosine are not now well understood, largely because of its short half-life in biological tissues and the complex compartmentalization of its metabolism (Fig. 1).

To better analyze experimental data, a five-region, axially-distributed model of adenosine metabolism and transport in the heart was developed.[1] The model describes the different biochemical reactions involved in adenosine metabolism, accounts for membrane transport in linear transport terms, and accounts for the effects of convective flow. In the past, this model was calibrated against data from isolated heart and cell experiments, and against data from *in vitro* enzyme activity measurements.

More recently, we used the model to analyze experiments aimed at differentiating between intracellular and extracellular adenosine production, and assessing the direction of the transmembranous concentration gradient.[2] These experiments were conducted on isolated perfused hearts from guinea pigs. A complex set of the specific, powerful inhibitors of enzymes and transporters in cardiac adenosine metabolism was used. We measured the adenosine concentration in the venous effluent perfusate, as well as the accumulation of S-adenosylhomocysteine in the presence of 200 μM L-homocysteine, which serves as a sensitive index of changes of the cytosolic adenosine concentration.[3]

Using the published parameter set,[1] our general modeling strategy was to fit measured venous adenosine concentrations by constraining the flow term using the measurements, and by using adenosine production terms as free parameters. To obtain parameter values that fitted the venous concentrations determined under various experimental conditions equally well, several iterations of parameter adjustment were necessary. Having obtained this parameter set, it was used to fit the SAH contents without further adjustment.

The results of these analyses may be summarized as follows (see also Fig. 2). Under well-oxygenated conditions adenosine is produced in cardiac tissue at a rate exceeding the venous release rate more than 40-fold. The underlying high turnover of adenosine occurs predomi-

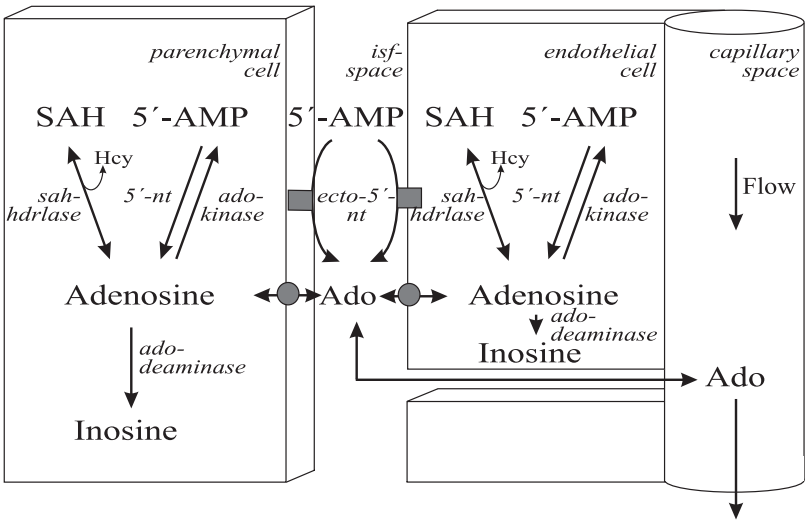

Figure 1. Diagram of cardiac adenosine metabolism and transport. Abbreviations: sah-hdrlase: SAH-hydrolase, 5′-nt: cytosolic 5′-nucleotidase, ecto-5′-nt: ecto-5′-nucleotidase, Hcy: L-homocysteine, Ado: adenosine. The dark circle denotes adenosine facilitative membrane transport, the dark square ecto-5′-nucleotidase facing the interstitial fluid space (isf).

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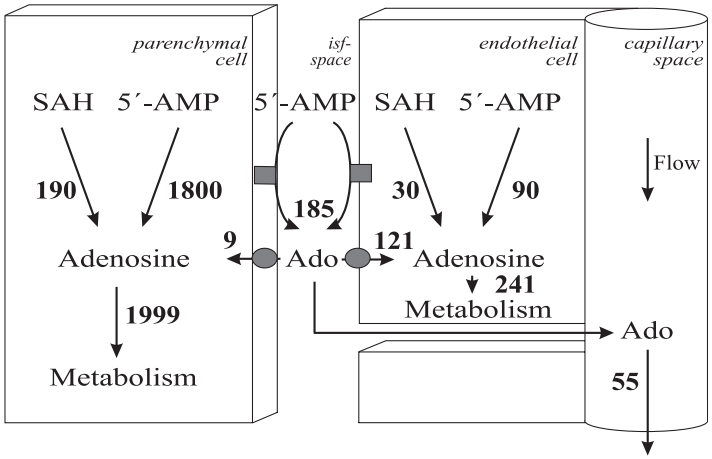

Figure 2. Flux rates of adenosine metabolism in guinea pig myocardium. "Metabolism" comprizes flux through the adenosine kinase and adenosine deaminase pathway. Data are given in units of pmol min^{-1} per g wet weight.

nantly in the cytosol. However, a fraction of less than 10% is produced in extracellular regions. In conjunction with the effective intracellular metabolism of adenosine, the extracellular production provides the driving force for net cellular uptake of adenosine during physiological conditions. Therefore, nucleoside transport blockers that induce a bidirectional block of the membrane transport raise the interstitial adenosine concentration under well-oxygenated conditions. The transmembranous concentration gradient from extracellular to intracellular is in contrast to our intuition that there is a concentration gradient from the cytosol to the capillary region, because the largest production site is intracellular.

In conclusion, the combination of mathematical model analysis with sets of detailed experimental data is a promising approach that may further our quantitative understanding of the complex scenario of adenosine metabolism in the heart.

References

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by Andreas Deussen

NSR updates

News

Our director, Professor James B. Bassingthwaighte, was elected to the National Academy of Engineering (NAE) on Feb. 17, 2000, for his contributions to integrative physiology and bioengineering using transport theory and computational methods.

Software update

The graphic simulation interface, XSIM 3.12, has been released for four popular UNIX platforms: SunOS4, Solaris, IRIX and Linux. More models have been added to the XSIM distribution package. The highlighted model is GENTEX, a generalized, whole-organ model for circulatory transport and intra-organ exchange and metabolism. This model allows nonlinear and time-varying model parameters, and, by using a simple switch, can be set up as a axially-distributed model or a compartmental model. The full XSIM package is distributed via the NSR website and CDROM (upon request).

NSR is currently developing JSIM, XSIM's Java-language based successor. Three goals inform JSIM's design: platform independence, dynamic equation-based model assembly, and facilitated collaboration. Sun's Java language and API are platform independent, thus allowing JSIM to be developed simultaneously for Unix, MS-Windows and MacIntosh platforms. JSIM will allow users to dynamically alter existing models, or construct new models, within the simulation environment. In contrast, XSIM models are constructed separately from the simulation environment. JSIM models may be constructed by connecting pre-fabricated pieces using a drag-and-drop GUI, by writing appropriate equations which are parsed and passed to built-in solvers, or by combinations of the two. Equation-based modeling offers great promise for collaboration among research groups by forming a common model description language upon which an inter-group simulation infrastructure can be developed. Additionally, working directly with the underlying mathematical equations lowers the entry barriers to modeling for scientists not well versed in numerical methods. JSIM's architecture is very much in flux during this stage of its development. A more complete picture of JSIM will be described in subsequent newsletters.

New Hardware

We added seven Intel-based PC's running RedHat Linux last year. These new boxes have CPU speeds ranging from 450 MHz to 900 MHz with at least 128M RAM. The average cost per machine is about $1200, a remarkable price compared to other UNIX workstations. PC's running Linux appear to be the best choice for an XSIM analysis machine. We would be happy to provide assistance on installing the Linux system and XSIM.

NSR Web Site (http://nsr.bioeng.washington.edu/)

Visit our new web site!

- New format, easy navigation.
- Up-to-date documentation
- Easy software download and demos.

And much more!

by Zheng Li

A whole-body recirculating model for pharmacokinetic modeling

BODY, a simplified whole-body recirculating model that runs under XSIM, models 1) two injection sites, 2) four arteries and four veins, 3) seven tissues, 4) and a four-chambered heart. Four summing junctions where flow and concentrations recombine are also provided.

1. The first injection site, CIN1, is situated before the right atrium, and the second, CIN2, after the left ventricle.
2. The four arteries and four veins are modeled as vascular operators (VOPB10).
3. The seven tissues are modeled using a re-entrant four-region, distributed blood–tissue exchange module (EBTEX40).
4. The atria and ventricles of the heart are modeled as compartments (ECOMP3)—single compartments for the atria and double compartments in parallel for the ventricles, to simulate incomplete emptying during the ejection phase of contraction.

In the BODY model, there is a point of recirculation, designated **R**, which is before the right atrium. In a computational cycle, recirculating material is added to the material coming from the first injection site, and the calculations proceed, organ-by-organ, around the system, back to the point of recirculation. The concentrations in each organ and vascular segment are solved sequentially, not simultaneously, which allows for faster, smaller computational systems with a cost of small errors in the steady-state concentrations. These small errors can be reduced to any level desired by judiciously choosing as small a time step as is computationally feasible. The amount of material that must re-enter the system during the next computational cycle is outside the system and must be included in the computed mass balance.

One novel feature of the BODY model is that tissue components and vascular operators may be "turned off" by specifying either zero flow or zero volume. For zero flow, no material enters or exits a given tissue component or vascular operator. For zero volume, any material that enters immediately exits. Hence it is possible to run the BODY model with a reduced number of parallel circulating systems. Recirculation can also be halted in this model by giving some of the tissues or vascular operators very large volumes, so they become sinks in the system. BODY is available from the "Software" section of the NSR website (see logo on the first page for the URL). The individual components used to construct the model, EBTEX40, VOPB10, and ECOMP3 are available from the NSR library.

by Gary M. Raymond

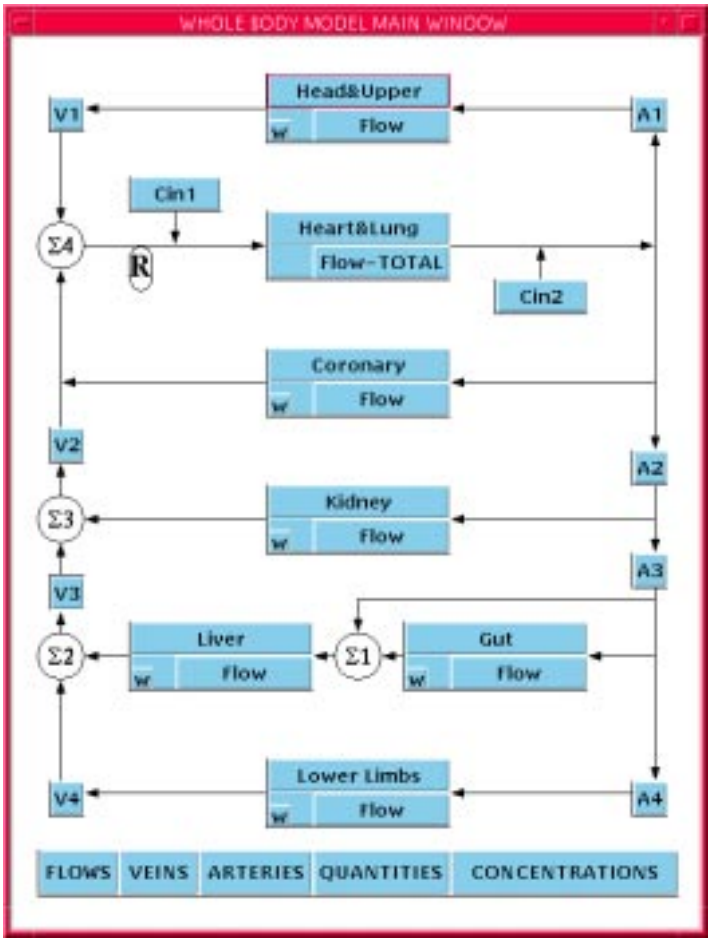


Figure 1. Diagram of the BODY model. Arteries are A1-4; Veins, V1-4. In the tissue models, "w" stands for tissue weight.

Tracer contents

Development of BODY, the simplified whole-body recirculating model described in the article above, caused us to reconsider mass balance in the vascular operator and compartment models. Calculating the outflow from these operators as the average outflow over the time step is necessary for correct mass balance.

Consider a one-compartment model with a steady flow and a constant infusion of material given by the following equation, $V(dC/dt) = \mathrm{FC_{in}} - \mathrm{FC_{out}}$, where $C_{\mathrm{out}} = C$ and $C(0) = 0.0$. Let $\tau = V/F$. The solution to this differential equation is given by

$$C(t) = C_{\mathrm{in}} \cdot \left[1 - \exp\left(-\frac{t}{\tau}\right)\right].$$

The contents of the compartment at the end of each time step is given by

$$\begin{aligned} Q_{\mathrm{analytic}}(n\Delta t) &= \int_0^{n\Delta t} F \cdot [C_{\mathrm{in}} - C(t)]dt \\ &= V \cdot C_{\mathrm{in}} \cdot \left[1 - \exp\left(-\frac{n\Delta t}{\tau}\right)\right] \end{aligned}$$

but is usually calculated by

$$\begin{aligned} Q_{\mathrm{numeric}}(n\Delta t) &= \sum_{i=1}^{n} F \cdot [C_{\mathrm{in}} - C(i\Delta t)] \cdot \Delta t \\ &= V \cdot C_{\mathrm{in}} \cdot \frac{\Delta t}{\tau} \cdot \left[\frac{\exp\left(\frac{\Delta t}{\tau}\right) - \exp\left(\frac{-n\Delta t}{\tau}\right)}{\exp\left(\frac{\Delta t}{\tau}\right) - 1}\right]. \end{aligned}$$

The answers can be quite different depending on the time step. The figure (at right) shows the ratio of $Q_{\text{numeric}}/Q_{\text{analytic}}$. At the end of the first time step (thin line), the answer is off by a factor of 2, even for small time steps. At steady state (thick line), the answer is better for small, and worse for large, time steps.

The numeric value for tracer contents can be corrected by using the average value of $C(t)$ over the time step,

$$C_{\text{avg}}(n\Delta t) = \frac{1}{\Delta t}\cdot\int_{(n-1)\Delta t}^{n\Delta t} C(t)dt\,,$$

and then calculating

$$Q_{\text{numeric}}(n\Delta t) = \sum_{i=1}^{n} F\cdot[C_{\text{in}} - C_{\text{avg}}(i\Delta t)]\cdot\Delta t$$

$$= V\cdot C_{\text{in}}\cdot\left[1-\exp\left(\frac{-n\Delta t}{\tau}\right)\right]$$

which gives the same result as the analytic solution.

For multiple compartments, the formulas are more complicated, but the principle remains the same. Using the averaged value of the outflow from a compartment yields a correct calculation of the tracer contents. The average value of the outflow can be calculated numerically. Using the value of the outflow at the end of the time step yields a result which is dependent on the size of the time step employed.

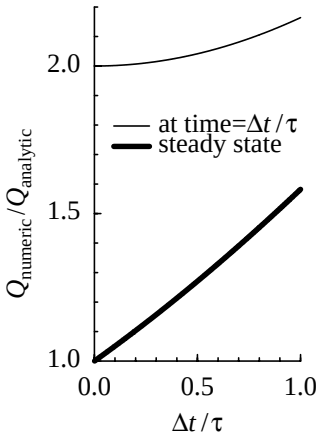


Figure. The ratio of $Q_{\text{numeric}}/Q_{\text{analytic}}$ as a function of $\Delta t/\tau$ initially at time equals $\Delta t/\tau$ (thin line) and at steady state (thick line).

The blood–tissue exchange operators return the average outflow. We have recently added a new routine to the libraries, ECOMP3, for 1, 2 and 3 compartment models, which calculates the averaged outflow over a time step instead of outflow at the end of the time step. The vascular operator, VASOP, is being replaced by VOPB10, a vascular operator based on EBTEX10, which also returns average outflow over the time step.

by Gary M. Raymond

NSR development for web-based learning

The staff at NSR recently began to expand the scope of the NSR website. One of the goals of the effort is to develop online resources for teaching basic concepts in biological mass transport. These resources will serve as companions to courses offered at the NSR and the University of Washington, and will also serve as stand-alone references for individual learning.

A premise of the NSR website development effort is that interacting with models will permit students to develop greater insight into and understanding of the physical processes than they would develop by simply reading about a concept. To this end, we have recently developed the ability to run our simulation interface, XSIM, and several of our models, via browsers on the web.

The models implemented for use via the web fall into two broad categories: 1) fully developed research models designed to describe actual experimental data, and 2) simpler teaching models that serve primarily to illustrate basic mechanisms important in physiology.

One example of the second category, the teaching models, is *compos* (see Fig. 1). *Compos* is a simple two-compartment model that describes the coupled flux of solute and solvent across a membrane. Web pages that provide descriptions of the equations and parameters used to build the model can be viewed at ~mkellen/example.html (from the NSR base URL). Additionally, several simulation runs are presented as examples, with commentary describing the physical process being modeled. Students may follow along with the examples by running the model via their web browser, then further explore the model behavior by modifying the basic sets of parameter values. A good understanding of the simple model will provide a foundation for successfully using and developing more sophisticated models.

Comments about NSR's website development are particularly useful at this stage. I encourage readers to visit our site and send us their thoughts regarding this effort. Because user platforms and browser mechanisms vary, please let us know if any feature fails or does not work as expected. After completely developing a few sample projects, we will be able to focus on adding additional models.

by Michael Kellen

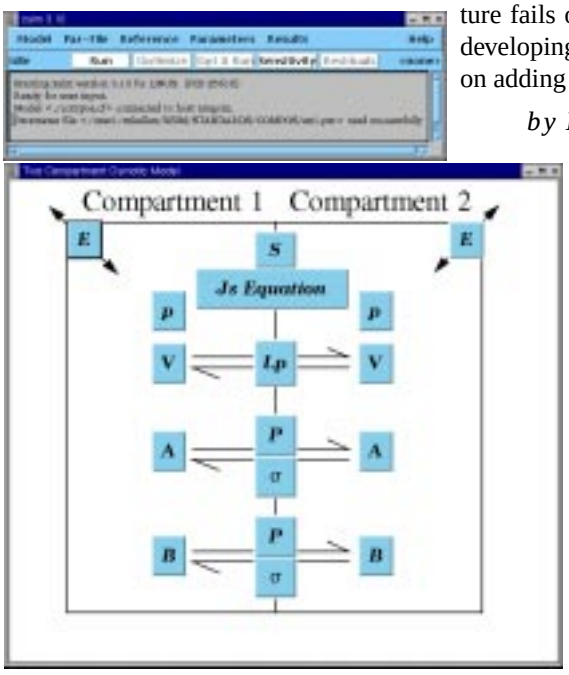
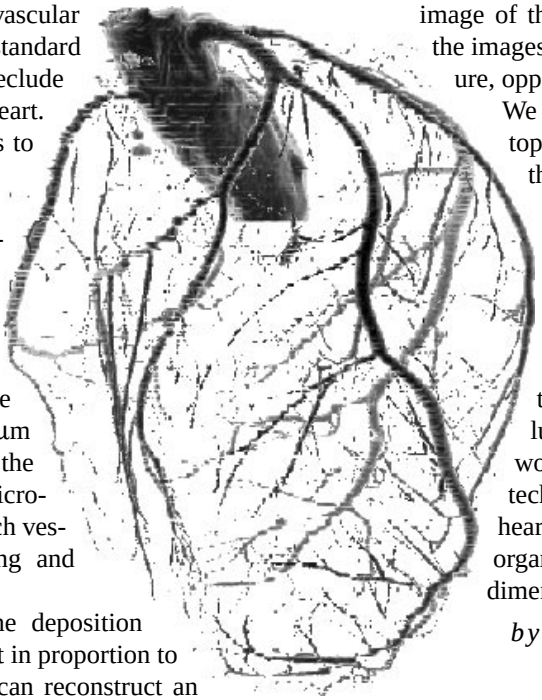


Figure 1. The model *compos* is a simple model of coupled exchange of solute and solvent between two compartments. After setting initial values for the volumes, pressures, and concentrations of each solute for each compartment, the model solves a system of ordinary differential equations to calculate the time course of solute and solvent fluxes between compartments. Users can modify the permeability, hydraulic conductivity, and selectivity of the membrane, virial coefficients of the solutes, and mechanical compliance of the compartments. Additionally, the ability to switch between the Kedem and Katchalsky and the non-linear Patlak solute flux equations allows these two models to be compared under different conditions. Detailed description of the model's governing equations and parameters is given via html help pages accessible at the NSR website.

Three-dimensional arterial cast reconstruction



The correlation of regional flow rates with vascular anatomy has not yet been done, because standard techniques used to measure one variable preclude the measurement of the other in the same heart. The long-term goal of our ongoing study is to develop a technique to compare local flows calculated from microsphere depositions with flows calculated from networks reconstructed from arterial castings.

Fluorescent 15 μm microspheres and then fluorescent polymer are injected into the coronary arteries of isolated, Krebs-Ringer perfused rabbit hearts. The hearts are then embedded, frozen, and sliced at 15 μm intervals. For each slice, digital images of the heart are taken, recording separately the microsphere positions and the section through each vessel. The images are enhanced by filtering and deconvolution.

Regional flows are determined from the deposition densities of the microspheres, which deposit in proportion to flow. Preliminary results indicate that we can reconstruct an image of the tree in three dimensions by stacking the images of the vessel cross-sections (see the figure, opposite, for one such image).

We are also trying to determine the tree's topology by using a computer to examine the continuity of the fluorescent pixels from slice to slice. Segment lengths are defined as the distance between bifurcation points, and we are attempting to estimate diameters from those topologically defined lengths.

A lot of work is needed to make this technique reliable and improve the resolution down to pre-capillary vessels. It is worth the effort because, although this technique is being developed with rabbit hearts, it can be easily applied to other organs and will yield a complete three-dimensional arterial data set.

by Marc Lacoin

Recent developments in the Physiome Project

FUNDING. The advancement of the Physiome Project is accelerating, but is not yet rapid. The efforts so far have been mostly on a volunteer basis or with funds coming from a variety of normal project grants. This remains generally true even though federal agencies have announced programs of support. Some, pointers to whose websites can be found on ours, are:

A. NIH/NCRR: The National Center for Research Resources has for years supported Resource Facilities for simulation, computational biology, for supercomputing for biomedical applications, for databasing and analyzing genomic information.
B. NIH/NIGMS: Program Announcement 98004 was the first announced, and others have been announced since. These will support multiuniversity collaborations related to integrative and computational biology and the development of tools to foster interdisciplinary research in complex systems.
C. NSF: Programs in complex systems analysis and in Biomedical Engineering. The NSF/ITR (Innovative Technology Research) program is especially designed to promote multiuniversity collaboration.
D. Whitaker Foundation: Special Opportunity Awards and individual awards can be sought.
E. NASA/NSBRI: The National Space Biomedical Research Institute, NASA's research arm, is now establishing a set of 12 space-related programs concerning human functioning in space. One such program is Integrated Human Function.
F. DARPA: Complex systems and large scale systems.

MEETINGS. NSR investigators have contributed to events in the following list of meetings where the Physiome Project and the Virtual Human Project were featured. Most of the meetings in the list were simply regular scientific meetings, but a few that I will mention were planning sessions pulled together by particular agencies.

The general perspective is that as one approaches the identification of the genes in the genome, it is increasing obvious that the functions of the organism are not easily predicted from the genome. Even the prediction of the proteins built by transcription is complex, for the human may have about 10 proteins per gene, and post-transcriptional modification is partly dependent upon the environment of the cell.

1. The German and Dutch Respiratory Physiology Societies met in January, 1999. I presented the keynote address on the role of the Physiome Project in contributing to the understanding of chaos and fractals in pulmonary structure and function. The conference was attended by 48 physiologists, clinicians and biomathematicians. Discussions concerned how data would be entered the databases, who would curate and update databases, whose models would be anointed as representing the prevailing view, and how corrections would be made (because it is tacitly assumed that all models are wrong and are therefore to be regarded as works in progress rather than finished works).
2. Netherlands Biophysical Society Meeting, March 29–30, 1999. I gave the keynote address: "The Physiome Project". The highly sympathetic audience of about 100 biophysicists and physiologists interested in quantitative studies will probably lead the Dutch components of the project.
3. Experimental Biology, Washington DC, April 21, 1999: Symposium on the Cardiome Project chaired by Peter Hunter with

about 150 attendees. Speakers were Hunter, McCulloch, myself, and others.

Discussion focused on mechanisms of collaboration and on the freedom to release the models for public use; there is not yet adequate web-based modeling, except for some models supported by Meryl Wastney's efforts at Georgetown (http://gopher.dml.georgetown.edu/model/), so the method of distribution of the technology is mainly through downloading to other users. While web-based modeling can be done for some of the transport models from NSR (http://nsr.bioeng.washington.edu/) by users with X-windows interfaces, this is not generally the case at modeling websites.

4. "Biomathematics and the Physiome Project" was my keynote presentation at the Italian Society for Biomathematics, Trento, Italy, May 10, 1999. The meeting was excellent, with the greatest focus of effort being on the modeling of glucose-insulin systems; there were several centers involved in carbohydrate metabolism and diabetes, with good collaboration between clinical and analytical efforts.

5. FEPS, June 30 to July 4, 1999: Symposium on the Physiome Project at the meeting of the Federation of European Physiological Societies in Prague, Czech Republic. Chair: Bernard Swynghedouw, incoming FEPS President. Speaker: myself, "The Physiome Project: Capturing Information on Integrative Physiology in Databases and Models". Discussion 1.5 hours. Much scepticism from a few people whose view centered on the concept that this was merely "good physiology" which physiologists would undertake in any case. The importance of databasing and information retrieval was not universally appreciated. Some of the naysayers really felt that modeling was not useful. It is clear that a more persuasive presentation would have to include demonstration that new insight or new strategies were fostered by the approach.

6. My lecture as part of Physiology Day, July 8, 1999 at the University of Maastricht, NL, was "Abnormalities of cardiac pacing induce gene expression and changes in substrate metabolism". This summarized my sabbatical effort over 6 months in Maastricht with Drs. Reneman, Slaaf, van der Vusse, Arts, and Prinzen. Other papers concerned the whole range of cardiac and microvascular physiology; Marc Van Bilsen illustrated changes in expression in lipid metabolism. Discussion of the Physiome Project showed support for the principles, and it was envisaged that this work would be facilitated by bioengineering students in the joint Eindthoven/Maastricht program begun in 1997. These students start research late in 1999.

7. ORNL: By September, Clay Easterly and David Reichle and others at Oak Ridge National Labs (ORNL) had begun the "Virtual Human" Project. Basically this project has the same computational modeling objectives as the Human Physiome Project, but the Virtual Human Project lacks a database component. However, ORNL's targeted missions are different, being more closely attuned to the needs of DoD (Defense) and DoE (Energy) and therefore allied to the effects of injury. The Physiome Project is more attuned to the "reverse engineering" of human physiology and pathophysiology, i.e., to the discovery of biological processes and their regulation, and to finding the best means of pursuing interventional therapy.

8. A Symposium/Workshop, "Integrated Biology of the Heart", was held at the University of Washington, Seattle, Sept. 8-11. It is reported elsewhere in this issue.

9. BMES/EMBS meeting, Atlanta GA, October 12-16. This meeting included a series of scientific sessions on Integrated Modeling of the Heart and of the Lung. These were packed sessions, overflowing the rooms. The final session of the meeting on Saturday afternoon was a panel discussion entitled "Challenges, Opportunities and the Future of Computer-Aided Engineering of Drugs, Molecules, Cells, Tissues and Organs: A Roundtable Discussion between Academics, Industry, National Laboratories and Funding Agencies", organized by John Halter (Baylor, Neuroscience). Shankar Subramanian (UCSD) led a lively discussion on all aspects of the physiome ideas, from basic research to industrial application in process control and protein production, all the way through to therapeutic intervention (pharmaceutical and genomic). The panelists (Bernhard Palsson, James Bassingthwaighte, Rai Winslow (Johns Hopkins), Forbes Dewey (MIT), Cynthia Stokes (Entelos Corp), Peter Katona (Whitaker Foundation), and Andrew McCulloch (UCSD)) approached the issues not only of the scientific methods for experimentation and analysis and the databasing, but also the marketing of the concepts, the return to quantitative experimentation and analysis, the training of young scientists, and the role of Federal agencies, private foundations, and universities in the funding of these programs.

10. Dept.of Energy/National Academy of Sciences meeting on Oct. 28, 1999. The meeting concerned the development of support for the Virtual Human Project. Introduced by Dennis Chamot of NAS, outlined by Alvin Trivelpiece, Director, ORNL, the first session was a survey of the scientific outlook chaired and given an overview by Charles DeLisi (Boston U). Speakers were myself (UW), Clay Easterly (DoE/ORNL), Bob Berwick (MIT), Ken Lutchen (Boston U), James Schafer (Alabama), and Evgeni Selkov (Argonne Nat'l Laboratory).

The second session, overviewed and chaired by William Raub (Dept. Health Human Services) provided responses from the various agencies: James Preston (Marine Corps, DoD) focussed on its value in the assessment of the potential for nonlethal weapons in this modern day when "peace-keeping" also means "saving the village without destroying it or its people". Ari Patrinos (Director, DoE), the last of the leaders of the federal agencies to speak, strongly supported the notion that this was a project which needed to go forward in collaboration with all the principal agencies, and made the point that some "turf" would need to be sacrificed here and there to make progress. The discussion suggested that competition even between Institutes within NIH had hampered collaboration, but new programs, especially the BECON (Bioengineering Consortium) effort, were helping to bridge the gaps.

DeLisi then led a purposeful discussion of whether or not it would be useful to ask for a review of the "Virtual Human/Human Physiome" project with respect to its possible designation as a "Grand Challenge" effort, as was the High Performance Supercomputing Project and the Genome Project. The mechanism is for one or more agencies to request such a review by NAS, to obtain a response from NAS outlining what they propose to be the scope of the review and its cost, then for the requesting agencies to determine if they like the NAS proposal and if they will fund the NAS

effort. Finally then, given resources and the approval of the NAS plan by the funding agencies, NAS would get on with the job. The anticipated time would be about 18 months.

The decision was that a request would be forwarded by DoE, quite possibly with NHLBI participation. Participation from NIH might be at the Director's level, rather than individual institutes.

11. DoE staff met with consultants and advisors at DoE offices in Rockville Pike, MD, on 8–9 Nov., 1999, to focus on the Virtual Human effort as a means toward the development of understanding human function and its responses to environmental and other insults. The program started with a detailed summary of DoE's Virtual Human effort (given by Clay Easterley), followed by Bassingthwaighte's view of the Physiome Project. The Virtual Human focuses on the human and begins with the whole body. The Physiome Project is not only to define the Physiome (the quantitative description of the integrated behavior of the physiologically functioning intact organism and its components at all levels) for ALL ORGANISMS from bacteria to man, from genome to intact organism and its responses to environment, but also to support this effort with massive databases. Focusing on the Virtual Human is a narrower, more directed and more appealing goal. However, much basic information must inevitably come from studies of simpler animals. Breakout groups planned for how to develop the varied aspects of the Project.

12. NASA/NSBRI Program Directors Meeting, 17–18 Nov., 1999 on New NSBRI Directions: This meeting centered on defining the next program directions and formulating descriptions of the Requests For Applications for the new NSBRI initiatives. The focus is on physiological and psychological aspects of long space flights, where microgravity and long confinement are major influences on human function. Martin Kushmerick and Jim Bassingthwaighte of the University of Washington have been appointed as team co-leaders for a new program on Integrated Human Function within which the large-scale modeling of physiological systems will be centered. Other teams focus on calcium and bone loss, on muscle alterations and atrophy, neurovestibular adaptation, technology development, nutrition and fitness, smart medical systems, radiation effects, cardioavascular adaptations, and neurobehavioral and psychosocial performance. Modeling analysis is a critical component of most of these. See the NSBRI website.

13. Meeting of the Association of Chairs of Physiology Departments. Indian Wells, CA, 2–5 Dec., 1999. I presented a keynote address on Genomics to the Physiome, and emphasized the need for training biomedical scientist in ways differing from the current style. Organized by the President of the Association, John Solaro, the idea behind the meeting was to challenge the chairs to consider what the needs for revisions in the training of modern physiologists should be. Is there acceptance of the idea that training in the physical, chemical, and mathematical sciences is greatly needed by physiologists? Physiologists of the younger generation have had almost no quantitative training, in instrumentation, analysis, systems analysis, modeling, control systems, etc., so that it is stimulating to see that numbers of molecular biologists are moving in this direction.

14. Cold Spring Harbor Laboratory meeting on 9–12 Dec., 1999, "Physiological Genomics and Rat Models", organized by Howard Jacob (MCW) and Doug Vollrath (Stanford). The meeting focussed on genomics, bioinformatics, expression profiling, complex trait analysis, model systems (meaning a variety of topics from heart disease to autoimmunity and cancer), transgenics, and pharmacogenomics and risk assessment.

15. Computational Modeling of Biological Systems: From Gene to Organ" on 23–26 Feb., 2000, at Hilton Head, SC. Robert Nerem and Aleksander Popel were the meeting organizers. Michael Savageau and myself were the keynote speakers. There were 33 speakers and 29 poster presentations plus a workshop discussion with NSF officials concerning NSF funding for programs in integrated biology, complexity, modeling systems, and databasing. The range of topics included regulation of gene expression, metabolic control analysis in cycling and bifurcating systems, emergent behavior in integrated systems, regulatory motifs and engineering principles in cellular circuitry, the generation of testable hypotheses in silico from bacterial metabolic models, receptor signaling pathways, and predictive computational models of asthma. The meeting fostered the development of a number of collaborations among groups. The funding outlook is increasingly encouraging.

FORTHCOMING MEETINGS. Biomedical Engineering Society meeting 12–14 Oct., 2000, in Seattle WA. There will be 6 symposia on the physiome. Another 6 will be on metabolic engineering, and yet another six on pharmacokinetics and the estimation of the parameters governing drug distribution and its effects from the studies of subject populations.

Biomedical Engineering Education Summit (BEES), 8–10 Dec., 2000, Lansdowne VA, is a meeting sponsored by the Whitaker Foundation for the purposes of advancing the methods and enhancing the contents of bioengineering educational programs.

by James B. Bassingthwaighte

Physiome Workshop: Integrated biology of the heart

Sept. 8–11, 1999, the NSR hosted a symposium/workshop: "Integrated Biology of the Heart" at the University of Washington, Seattle. It was organized by Zheng Li (UW) with a committee composed of John H. Linehan (Whitaker Foundation), Andrew McCulloch (UCSD), and Rob Reneman (Univ. of Maastricht). The sponsors were NSR, with special grants from the Whitaker Foundation, the National Center for Research Resources, the Biome Resource at UCSD, and the UW School of Medicine.

Eighty people from fourteen countries participated. A subset of the thirty papers presented, after peer review, will be published in a special issue of the *Annals of Biomedical Engineering*, as position papers combining original research, review of the particular fields, and recommendations for future developments. The papers are mainly cardiovascular (from molecular bases for contraction, electrophysiology, metabolism and energetics, to intact organ contraction, and microcirculatory exchanges), but also reflect two sessions on strategies for physiome developments in the lung and

kidney. The discussions were searching, enthusiastic, provocative and forward-looking.

A central question for the participants was how to foster progress toward the development of the Computational Heart and the requisite databasing of physiological information. This is the Cardiome Project. An early goal is the development of the "Virtual Heart", a model of the functioning beating heart. Much work toward this end has been accomplished by the groups of Peter Hunter (Auckland, NZ), Dennis Noble (Oxford, UK), Rai Winslow (Johns Hopkins) and Andrew McCulloch (UCSD): the composite model accounts for the spread of excitation and the resultant contraction and deformation of an anatomically highly realistic finite-element model of the heart. Ghassan Kassab (USCD) leads a group providing the anatomy of the coronary system. Jim Bassingthwaighte's group (UW) has developed models for coronary flows, solute transport and exchange, and with Martin Kushmerick (also UW) and others they are working on the systems for ATP synthesis and utilization. Yoram Rudy's models for the ionic currents and calcium cycling play a central role. Many others are developing quantitative models for components of the system.

Databasing is a major issue. The attempts to parameterize the models from physiological information are frustrated by a dearth of precise, well-documented data. This becomes more evident as the models are pieced together. Published data are often contradictory, leading to the question of how to make the databases reliable: how will they be curated and maintained, yet be up-to-date and immediately available over the Internet? Forbes Dewey's review on databasing techniques and problems illustrated that emphasis should be placed on using a set of standard technologies and standardized semantics in order to facilitate the collaborative efforts toward databasing and modeling.

Other Physiome-related Projects were presented. The Microcirculatory Physiome, led by Aleksander Popel (Johns Hopkins), Axel Pries (Berlin), and Andrew Greene (Med. Coll. Wisc., Milwaukee) is advancing well. Projects in pulmonary physiology were presented by Chris Dawson (Med. Coll. Wisc.), and Tom Robertson and Michael Hlastala at UW. The renal efforts were stimulated by James Schafer (Alabama) and Melvin Silverman (Toronto).

This meeting gathered a strong group of the key workers in the fields, so one expects the enthusiasm generated by such a gathering to spill over into effective working collaborations. Because even the short-term goals can only be achieved with several years work, more such meetings will be important to pull these efforts together.

by James B. Bassingthwaighte