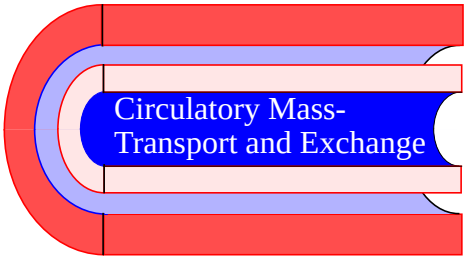
National Simulation Resource

NSR

University of Washington



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Keith Kroll, Ph.D.

Associate Director, NSR
Associate Professor, Bioengineering
University of Washington

Born December 9, 1948, died July 15, 1997.

Dr. Keith Kroll, Associate Professor in the Department of Bioengineering, and Adjunct Associate Professor of Physiology and Biophysics at the University of Washington died July 15, 1997, within four months of diagnosis of gastric adenocarcinoma.

Born in Seattle, Dr. Kroll received his BA in Biological Sciences at Stanford. He began his research early, publishing physiological papers while working in Leiden as a research assistant. His fifth published paper examined adenosine's role in coronary regulation, the field where he contributed so much.

At the University of Washington he completed his Ph.D. in Physiology in 1983 with Eric Feigl, showing that adenosine was not a major regulator of coronary flow under normal conditions, but was clearly influential during hypoxia.

His postdoctoral period in Dusseldorf was the beginning of a long series of collaborations with Juergen Schrader, Andreas Deussen and others. While there he showed that endothelial adenosine transport and accumulation was a dominating influence on the kinetics of adenosine exchange and a strong modulator of its vasoactive effects.

Appointed to the Department of Bioengineering at the University of Washington in 1987, he worked with James Bassingthwaighte on endothelial purine exchange processes, and independently developed a wide range of collaborative programs in quantitative, model-based analyses of purine nucleoside and nucleotide kinetics in the normal heart and during hypoxia and ischemia. He became recognized as the leader nationally and internationally in providing an integrated picture of the ATP and phosphocreatine energetics in ischemia and their relationship to interstitial adenosine release.

As the Associate Director of the Simulation Resource in Circulatory Mass-Transport and Exchange at the University of Washington, he provided analysis techniques and advice to many investigators around the world, very often getting involved directly in their research. His devotion to the quality of his scientific studies was evident in all he did, and created an ambience appealing to students and colleagues. His leadership in metabolic aspects of cardiac bioengineering was expressed in his organization of symposia at BMES and Experimental Biology.

Above all, Keith was the best of teachers, the most patient of advisors and friends, and the kindest of persons. His wife Marie shared his love of the outdoors, of music and of the arts, and supported his love of science. He leaves Marie, his son Aaron and his sisters and parents and his extensive circle of close friends with loving memories of a kind, considerate, multi-talented and highly accomplished man.

Marguerita Jensen and
James Bassingthwaighte

Newly Released: *Whole Organ Approaches to Cellular Metabolism*

Permeation, Cellular Uptake and Product Formation. Editors: James B. Bassingthwaighte, Carl A. Goresky and John H. Linehan. Springer Verlag, New York, 1998: 575 pp.

This book, off the press in time for the Experimental Biology 1998 meeting in San Francisco, contains material closely related to the focus of effort of NSR. Four sections follow an introduction giving the general principles used in studies of biological transport. The first of the four sections is five chapters on the mechanisms of endothelial transport, exchange and regulation common to all organs and tissues. The remaining three sections deal with processes in muscle (heart and skeletal), in liver, and in lung. Twenty-two chapters summarize the approaches and views of twenty-five leaders in the field. The book includes the last writings of Keith Kroll and of Carl Goresky, to whom the book is dedicated.

Contents

Staff

Jim Bassingthwaighte, Director
jbb@nsr.bioeng.washington.edu

Rita Jensen, Administration
jensen@nsr

Rick King, Assoc. Dir., Software
rick@nsr

Zheng Li, Assoc. Dir., Modeling
zhengli@nsr

Hong Qian, Assoc. Dir., Mathematics
hongq@nsr

Gary Raymond, Applications
garyr@nsr

Erik Butterworth, XSIM
butterw@nsr

Steve Bangs, System Mgmt.
steve@nsr

William Chan, Software Librarian
wchan@nsr

Eric Lawson, Publications
eric@nsr

Postdoctoral Fellows:
Jons Rijcken, jons@nsr
Lori Gustafson, lorig@nsr

Graduate Students:
Michael Kellen, mkellen@nsr
Melissa Lambeth, mlambeth@nsr

NSR News Briefs

- Zheng Li was promoted to Research Assistant Professor in the University of Washington's Bioengineering Department, and was appointed as Associate Director, Modeling, at NSR.
- Hong Qian joined NSR as Associate Director, Mathematics.

A View of the Physiome

The Physiome Project is the successor to the Genome Project. The Genome Project, which will finish sequencing the human genome by about the year 2002, has greatly enhanced our understanding of biology, fostering new qualitative and quantitative approaches in the biological sciences. Yet phenotypic responses can seldom be predicted from genomic interventions.

Changes in protein expression are not the same as pharmaceutical intervention. The identification of each gene and the amino acid sequence of its associated protein forces us to recognize that we don't understand how these proteins function as parts of organized cells, tissues and organisms. What we need is the physiological phenotyping of organisms with knockouts or insertions. This follows from protein structuring and characterization, if a bottom up approach is taken. However, a lesson from the geneticists is that most of the genes identified so far have been pinpointed from the top down, identifying the locus by association with other genes and with expressed sequence tags.

A large role for direct genomic intervention in therapy does not yet exist, although industrial production of human proteins by yeast and E. coli is increasing. Pharmaceutical intervention, like genomic intervention, is not highly predictable: side effects abound and interactions with other drugs put patients at risk. Accurate prediction will require a comprehensive grasp of the workings of cells, tissues and whole intact organisms and information about short and long term regulation of physiology from gross system behavior (e.g., blood pressure) to modulation of protein expression.

Physiome: The word "physiome" is coined from "physio", meaning 'life' or 'nature', and "ome", meaning 'as a whole entity', or as an abbreviation of "physionome", where 'nome' means the nominal identification or description of normal function (Bassingthwaighte, 1992, Marmarelis et al., 1994). The definition of physiome is the quantitative description of the physiological dynamics or functions of the intact organism. The name fits into this sequence: genome, morphome (including proteome), physiome. [Perhaps the "phenome" or phenotype lies between morphome and physiome, in recognition of the importance of the qualitative identification of form and function derived from the gene, though lacking in the quantitative, integrative identification.]

The Physiome Project: Undertaking the Physiome Project is an immense task (Bassingthwaighte, 1995). This project is many times more complex than the genome project. Its goal is to systematize current and future biophysical, biochemical, and physiological knowledge into a framework where it can be used for prediction. Capability for prediction is of high economic benefit: a few million dollars a year put into predictors of intervention could within the decade start saving hundreds of millions per year by improved drug design, target specificity in pharmaceutical and genomic therapies, and eventually in disease prevention.

The Project consists of the databasing of biological information for rapid retrieval, and the systematic organization of that information into descriptive schema and computational models of integrated systems.

Networking is central to the success of the Project. Databases on biochemical and cellular systems, tissue properties, organ functions, and functions of the composite organism (blood pressure regulation, ambulation) must be publicly and freely accessible and searchable via the Internet. Likewise, functional models should be Internet-accessible; furthermore they should be designed so that they can be explored with or without being downloaded by the exploring investigator.

Models come in different forms. Useful simple forms are diagrams of relationships; they exhibit functional connections or perhaps merely associations, and encourage the investigator to figure out the nature and importance of the relationship. They provide cartoons of systems that convey in a glance an overview of a system, but are not predictive. A second, more explicit level of modeling is provided, for example, by chemical reaction schema: the model here is translatable to chemical rate equations, but may lack specific values for parameters, and at the schematic stage still does not allow quantitative prediction. The third stage would be the set of differential equations for those chemical reactions: given the rate constants, this model now can be used to predict outcomes in the form of product fluxes.

Since highly complex systems are not intuitively understandable, the comprehensive mathematical models should be designed so that an explorer can begin with a simple version, and use it as the entry into the deeper, more complete and complex versions. Imagine a model of the heart: How does it respond to the constriction of a specific coronary artery, to the compression of the aorta, or to a sympathetic nerve stimulation?

Only a very comprehensive model can give correct responses to all of these. Supposing the model is adequate to such tasks, the explorer might be yet more demanding, asking for not only the short term acute responses, but also the long-term responses. Guyton's model of the cardiovascular-renal regulation of blood pressure (Guyton, 1972) exhibits both short and long-term regulation in its more modern versions.

A fully constructed model is to the explorer just like the real system; the reasons for its behavior are not immediately identified. Consider the "cardiome" (Bassingthwaighte, 1997). Is it the decrease in pH that leads to the dissociation between cardiac excitation and contraction several seconds after coronary obstruction? Exploring a model has the advantage that any of the variables may be revealed without going to the laboratory. The explorer can ask, "What is the intracellular pH?" and be provided the value or the time course. The cause and effect relationship can be explored within the model, if it is constructed to allow "experimental" intervention by the explorer. Such models are predictors of responses and are therefore testable and refutable by experiment; in this way they serve also as the vehicle for the design of the critical experiment, the one that will disprove the inferences of the model.

Models are merely "working hypotheses" expressed in a quantitative and therefore refutable fashion. Through disproof and invention of a replacement hypothesis the science is advanced. As T. H. Huxley recommended when discoursing on Darwin's theory of evolution, maintain your "staetige Skepsis" or "active doubt", a phrase he took from Goethe. Active doubt means not bland acceptance, but careful consideration and persistent conscious skepticism with respect to any model. Models are all wrong, inexact or incomplete, and will probably be so forever.

The models need to be usable by learners and teachers. It is difficult to design model systems and displays that are useful by everyone from high-schoolers to advanced investigators. Most models will be constructed so that they cover very few hierarchical levels; one comprehensive model covering genome to physiome is currently impossible. Predicting organism level adaptive behavior without bringing all the pieces together will be difficult, so strategies will have to be developed by which the behavior of pieces of the system can be represented at the higher levels, even while maintaining capability to adjust those pieces at their deeper levels.

An overall strategy is to begin where there are beginnings: there are many levels, from genome to integrated system, where both databases and quantitative analysis are well underway. Since it is impossible to build up total organisms from the genome itself, or even from the subset of proteins transcribed without taking the environment for development into account, it is essential to start at points where the accumulated knowledge is sufficiently advanced to allow conjectures about how the parts fit into the whole. When the systemization is complete enough to allow prediction, then it is clear that the whole is greater than the sum of the parts. Many biophysical and physiological target areas are now well enough known to serve as exemplary foci of effort, because further development of knowledge about these areas will prove useful, not merely for demonstrating that databasing and systematizing are helpful in advancing the science, but potentially also for aid in diagnosis and in the design of therapy.

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James B. Bassingthwaighte

Anonymous ftp at NSR

You may get files from NSR by using anonymous ftp. If you are using a UNIX system, use the following steps to get the "Readme" file, then read it carefully for detailed instructions. The "Readme" file is a text file that can be read with your usual text editor or word processing application. Macintosh and PC users may use similar procedures specific to their system and communication software.

1. Enter `ftp nsr.bioeng.washington.edu` at the system prompt.
2. Enter `anonymous` at the resulting `Name` prompt.
3. Enter a complete electronic mail address at the `Password` prompt.
4. Enter `get Readme` at the `ftp` prompt.
5. Enter `quit` to return to your system.

Fractal Generation and Analysis Programs from the NSR Web Site

Program packages are available for the generation of synthetic one-dimensional signals that are fractional Gaussian noise (fGn) or fractional Brownian motion (fBm) and analysis programs for determining the fractal dimension D or the related Hurst coefficient H, $H = 2 - D$ from a fractal one-dimensional signal.

Each package includes the source code for the product, its test program, and all subprograms upon which they depend, a README file with notes about the files, a manual page (plain text and UNIX troff source versions), a Makefile to create and run the test program, and the auxiliary files required by the test program.

These software packages can be transferred using anonymous ftp by clicking on the name of the package desired, or by using the procedure described in the sidebar "Anonymous ftp at NSR" on page 3 of this newsletter. Transferred files are compressed tar archives which, if automatically uncompressed by a helper application in your browser, may be extracted using the UNIX `tar` command. If the files are not automatically uncompressed during transfer, uncompress the transferred files with the UNIX `compress` command before extracting the files with the `tar` command. Files extracted from the archive will be placed in a new subdirectory with the same name as the program.

Signal generating programs include:

fgp: Generates a fractional (fractal) Gaussian process 1-dimensional series at evenly spaced intervals using the Davies-Harte method. This is the recommended generating algorithm. It has the correct autocorrelation; the falloff in power spectral density with frequency follows a power law only at very low frequencies, deviating greatly from those at high frequencies. (Caccia, et al., 1997).

ssm: Generates an fGn or fBm 1-dimensional series at evenly spaced intervals using the spectral synthesis method. This is the standard spectral synthesis method, widely reported and used, but it is not correct. It has power law diminution in power spectral density, but the autocorrelation is incorrect (the correlation between the first and seconds points is the same as between the first and last). Error is reduced by generating a signal of at least 2N, preferably 8N, and then taking any segment of length N out of the results.

sra: Generates a one-dimensional fGn or fBm series at evenly spaced intervals using the successive random addition method. Notes: Like the SSM method, the successive random addition method is also inaccurate, but we have not yet well characterized its inadequacies.

Signal analysis programs include:

disp: Perform dispersion analysis on a fractal time series. Notes: Dispersion analysis is for the analysis of an fGn and is not suitable for analyzing fBm (Bassingthwaighte et al, 1995; Caccia, et al., 1997).

hurst: Perform Hurst rescaled range (R/S) analysis on a fractal time series, an fGn, not an fBm. The rescaled range analysis is included for historical perspective and in recognition of the marvellous insights of Harold Edwin Hurst into the analysis of natural time series. The method is, however, seriously flawed and gives biased results even if trend correction is used (Bassingthwaighte et al., 1994).

flowrect: Perform relative dispersion (fractal) and correlation analysis of flow distributions. Flowrect reads coordinates and flow values for voxels of a 3-dimensional organ, calculates the relative dispersion (RD) of flow for ever-larger groupings of adjacent voxels, and estimates the slope of the graph of log(RD) versus log(volume). For the same data, the correlation statistic (r) for pairs of flows as a function of distance is also calculated.

Four beta test programs are available and are undergoing final testing. The first three are versions of scaled windowed variance analysis (Cannon, et al., 1996) and are described elsewhere in this newsletter.

swv: Estimate the Hurst coefficient of a time series using scaled windowed variance analysis.

bdswv: Estimate the Hurst coefficient of a time series using bridge detrended scaled windowed variance analysis.

ldswv: Estimate the Hurst coefficient of a time series using linearly detrended scaled windowed variance analysis.

acf: Calculate the autocorrelation function and Hurst coefficient.

Cannon, M.J., Percival, D.B., Caccia, D.C., Raymond, G.M., and Bassingthwaighte, J.B. Evaluating scaled windowed variance methods for estimating the Hurst coefficient of time series. Physica A 241, 3-4, 606-26, 1997.

Gary M. Raymond

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Now available, the XSIM *MMID4 User Guide*

MMID4 stands for Multiple path, Multiple Indicator Dilution, 4 region model. MMID4 is used to model the blood–tissue exchange of three tracers—one that remains in the vasculature, one that leaves the capillaries but does not enter cells, and a permeable tracer that enters cells. Using MMID4, the effects of exchange and flow heterogeneity on tracer delay, dispersion and uptake may be examined.

The *MMID4 User Guide* for SIMCON has now been rewritten for XSIM. New XSIM users interested in modeling transport phenomenon with MMID4 will find that the extensive tutorial section of the *Guide* is an excellent set of exercises and reference. Much of the tutorial material is now applicable to more complex models, as well as MMID4. Those who have not used XSIM models and who would like to run a more complex model, such as GenTex, will find the XSIM MMID4 tutorial a useful introduction to the XSIM interface and the concepts of multi-region blood–tissue exchange modeling. Experienced XSIM users will find the tutorial is an effective way to learn about the MMID4 model.

The tutorial presents a series of interactive exercises which the user can run under XSIM. At the start of each exercise the user configures the MMID4 parameters by loading a new parameter file into XSIM, then manipulates the parameters as he or she progresses through the exercise. The content of the exercises is essentially the same as in the SIMCON version of the tutorial.

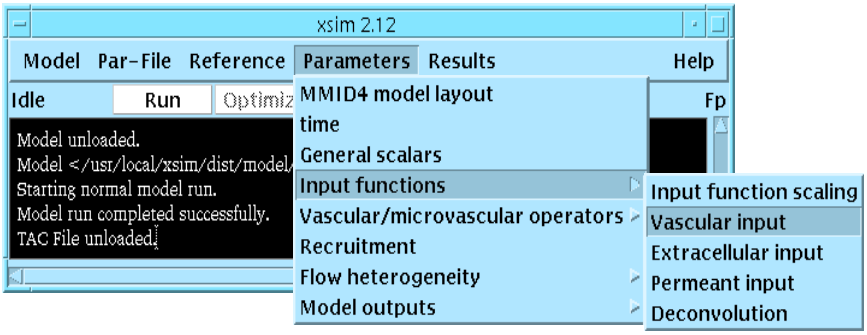

Figure 1. Opening the vascular input window from the main window

An MMID4 reference manual is included in the guide. The reference section provides detailed discussions of model capabilities such as heterogeneity, deconvolution, vascular and BTEX operators, as well as descriptive lists of model parameters.

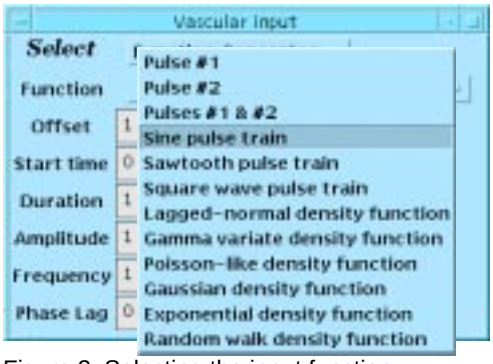

Figure 2. Selecting the input function option sine pulse train.

The new MMID4 tutorial is accessible via the NSR WWW page,

http://nsr.bioeng.washington.edu/

under “Publications ...”, then “MMID4 Guide”.

Jim Ploger

Fractals: Scaled Windowed Variance Analysis for fBm Signals

Scaled windowed variance (SWV) analysis of fractional Brownian motion signals computes the means of the standard deviations (SD's) at different scale lengths to obtain an estimate of the Hurst coefficient H, or the fractal dimension D, where $H = 2 - D$. Given a series of N points, the data is partitioned into non-overlapping windows of size 2, 4, ...N/2, N. The SD of each window is calculated, and all the standard deviations of a particular window size are averaged together. The averaged SD's are found to follow a simple scaling law, $\overline{SD_m}/\overline{SD_n} = (m/n)^H$, where m and n are window sizes and H is the Hurst coefficient. H is the slope of the linear regression of the logarithms, $H = [\log(\overline{SD_m}) - \log(\overline{SD_n})]/[\log(m) - \log(n)]$. Practically, the largest and smallest windows yield estimates of the averaged SD that diverge from this simple equation. Cannon et al. (1997) give advice on window sizes best omitted from the calculation based on the length of the series analyzed.

Two variants of SWV have also been investigated. Linearly detrended SWV (LDSWV) subtracts the linear regression line of the data in each window from the points before computing the standard deviation. Bridge detrended SWV (BDSWV) subtracts the line connecting the first and last points in each window before computing the standard deviation.

The analysis programs SWV, BDSWV and LDSWV are available as beta test software from nsr.bioeng.washington.edu by anonymous ftp in the directory pub/FRACTAL/SWV, pub/FRACTAL/LDSWV, and pub/FRACTAL/BDSWV. They can also be downloaded from

http://nsr.bioeng.washington.edu/

by clicking on, first, “Available Software”, then “Fractal Analysis Programs” (under the heading “Other Analysis Programs” at the bottom of the page), then clicking the name of the desired package.

Gary M. Raymond

Reference

M.J. Cannon, D.B. Percival, D.C. Caccia, G.M. Raymond, and J.B. Bassingthwaighte. Evaluating scaled windowed variance methods for estimating the Hurst coefficient of time series. Physica A 241:606-626 1997. Reprints are available from NSR.

Generalized Nonlinear Modeling of Blood-Tissue Exchange and Metabolism

A new multi-pathway, multi-species, nonlinear blood-tissue exchange model (GENTEX) has been developed and implemented under XSIM. The multi-pathway structure of GENTEX is similar to MMID4 and MSID4. The capillary-tissue exchange unit uses a "tissue cylinder" consisting of 6 concentric regions of equal length (Fig. 1). The two convective regions representing RBCs and plasma can have different velocities. Exchanges between RBCs and plasma and chemical reactions in blood are incorporated in the large vessel operators for arteries, arterioles, venules and veins. Nonlinear features of the model include competitive membrane transporters with instantaneous surface binding, competitive slow on-and-off binding within each region, and enzyme binding and reaction sequences within each region. The model accounts for both nontracer and tracer substances of up to 5 species. The nonlinear features are dependent solely on the nontracer concentrations. The definition of tracer in this model is a tiny amount of species that is chemically insignificant and follows exactly the same behavior of the mother substance. Interactions among species are allowed via chemical reactions (first-order, Michaelis-Menten type or enzyme binding & reaction).

Nonlinear trans-membrane transport is one of the highlights of GENTEX and is used here to illustrate the potential application of the model in terms of experimental design and data analysis. Shown in Fig. 2. is a nonlinear transporter. Substrate (S) binds to the transporters (T) at one side of the membrane; the transporter-substrate complex (TS) undergoes conformational change to face the other side of the membrane, and then releases the substrate. The binding is governed by equilibrium dissociation constant K_d and is assumed to be instantaneous. The conformational change is assumed to be first-order with rate constants, P_T and P_{TS}, for T and TS, respectively. The apparent unidirectional PS from region 1 to region 2, for example, is $PS_{12} = \text{Flux}_{12} / C_1 = C_{TS1} P_{TS} / C_1$, where C_{TS1} is related to C_2 via conformational change and binding. Therefore, PS_{12} is generally dependent on the concentrations of free substrate in both regions, C_1 and C_2. Michaelis-Menten transport is a special case under the conditions: (1) symmetric conformational change, (2) $K_{d1} = K_{d2}, = K_d$, and (3) zero capacitance, i.e., no receptor. In this case, $PS_{12} = V_{max} / (C_1 + K_m)$, where $V_{max} = T_{tot} P_T P_{TS} / (P_T + P_{TS})$, $K_m = 2K_d P_T / (P_T + P_{TS})$ and T_{tot} is the transporter density, mmol g^{-1}.

Shown in Fig. 3 is a simulation of a bolus sweep experiment in which a bolus of tracer and nontracer substance is injected in order to characterize nonlinear trans-membrane transport. To focus on the nonlinear behavior of the membrane transport, the simulation used single-pathway, single-species, and two regions (plasma and endothelial cells) with high consumption in the cells. Two cases were tested: Michaelis-Menten transport and nonlinear transport with capacitance. Model parameters used are the same for both cases. In both cases, the mean value of PS from plasma to endothelial cells, $\overline{PS}_{ecl1}$, was reduced in presence of nontracer in the capillary (bottom panels), resulting in lower instantaneous extraction (middle panels). This phenomenon was more pronounced when the center of the bolus passed through the capillary and when the amount of nontracer substance in the bolus was increased by tenfold. Furthermore, there is marked difference in kinetics for these two types of transporters. A membrane transporter with capacitance also served as two surface receptors and is equivalent to a Michaelis-Menten transporter with equilibrium binding sites in plasma and endothelial cells in this particular case. The result was prolonged retention of substrate (notice the extraction ratio never returned to unity), which was less obvious when

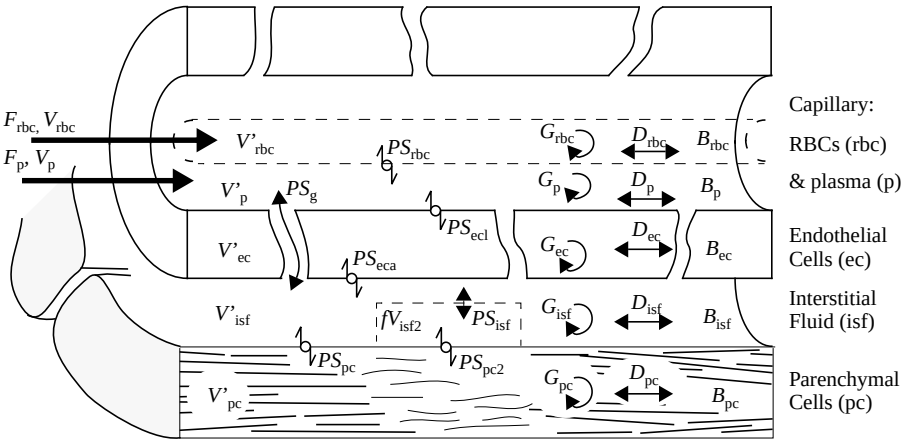

Figure 1. Model diagram for capillary-tissue unit. Model parameters are subscribed by region names: rbc for red blood cells, p for plasma, ec for endothelial cells, isf for interstitial fluid and pc for parenchymal cells. *F* is flow in ml min^{-1} g^{-1}. *V* and *V'* are real volumes and volumes of distribution in ml g^{-1}. *PS* is the effective permeability-surface area product (ml min^{-1} g^{-1}) representing linear or nonlinear trans-membrane transport including linear pathways through the endothelial clefts and between the 2 ISF regions. *G* is consumption, ml min^{-1} g^{-1}. The kinetics of binding sites (*B*'s) can be fast or slow, competitive or non-competitive. *D* is the axial dispersion coefficient (cm^2 s^{-1}). fV_{isf2} is the fraction of total ISF region distant from capillary.

more nontracer was injected because the transporter/receptor was saturated faster. With bolus-sweep experiment, more insight can be gained with a single injection because the nonlinear transporter kinetics can be explored over a wide range of substrate concentration. Fig. 4 shows the *PS*-concentration relationship: the effective PS_{ecl1} decreased from nearly 10 to about 2.5 ml min^{-1} g^{-1} when nontracer concentrations increased from 0 to 2.5 μM. Note in this case, the total amount of nontracer injected was 2.4μmol, K_d = 0.7 μM, and T_{tot} = 0.11 nmol g^{-1}.With high consumption in the last experiment, endothelial cells served as a sink resulting in return flux from endothelial cells. Backflux was observed using lower G_{ec}, e.g., 2 ml min^{-1} g^{-1}.

In summary, GENTEX can be used for experimental design, such as varying dosage and flows in appropriate ranges, to explore tracer kinetics related to underlying mechanisms of nonlinear membrane transport and cell metabolism, and for modeling analysis to gain physiological insights from the experimental data. The GENTEX model is conceptually general but its numeric algorithm is well designed so that specific or simpler applications can be set up with high computational efficiency. The model is widely applicable for studies of receptor binding, enzyme kinetics and membrane transport.

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Zheng Li

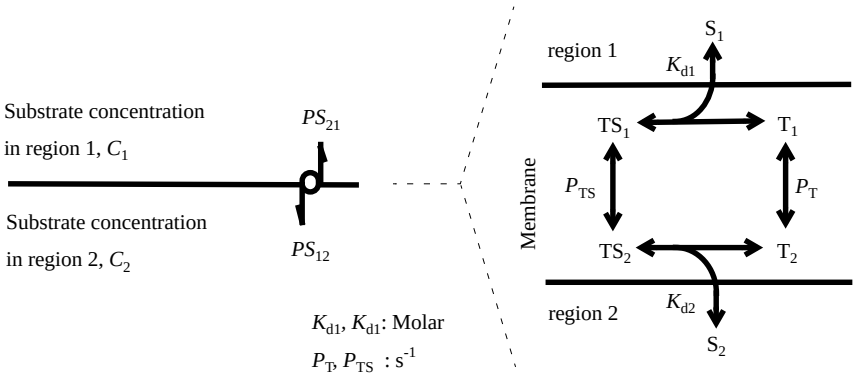

Figure 2. Model diagram for nonlinear transporter. There are 4 forms of transporters (mmol g^{-1}) in the 2-sided membrane: free transporter facing side 1 (T_1) and side 2 (T_2), and transporter-substrate complex facing side 1 (TS_1) and side 2 (TS_2).

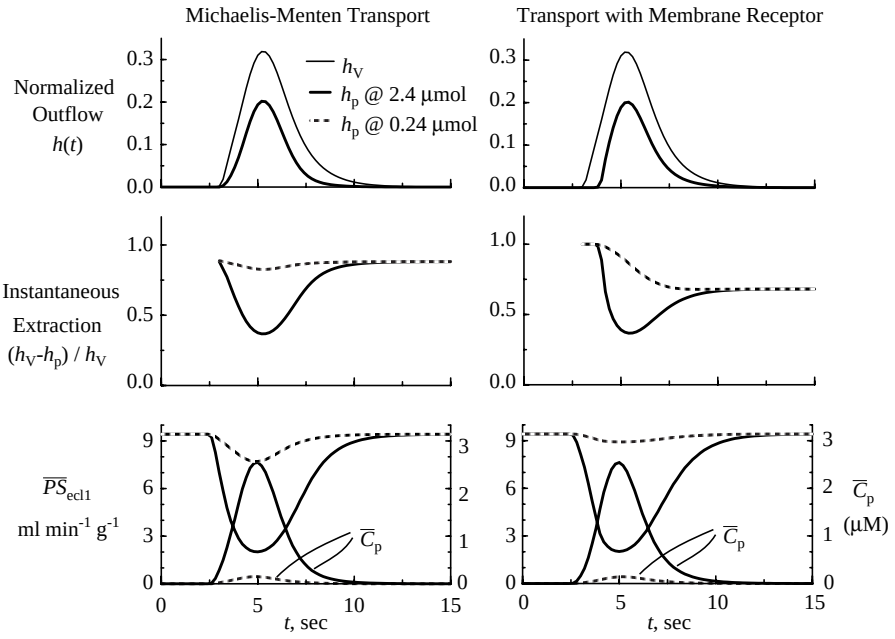

Figure 3. Simulation results from a bolus-sweep experiment through a 2-region, 1-barrier model. Left panels: Michaelis-Menten transport. Right panels: nonlinear transport with capacitance. F_p = 4 ml min^{-1} g^{-1}, V_p = V'_p = 0.035 ml g^{-1}, V'_{ec} = 0.05 ml g^{-1}. G_{ec} = 100 ml min^{-1} g^{-1}, T_{tot} = 0.11 nmol g^{-1}, K_d = 0.7 μM, and P_T = P_{TS} = 2 s^{-1}.

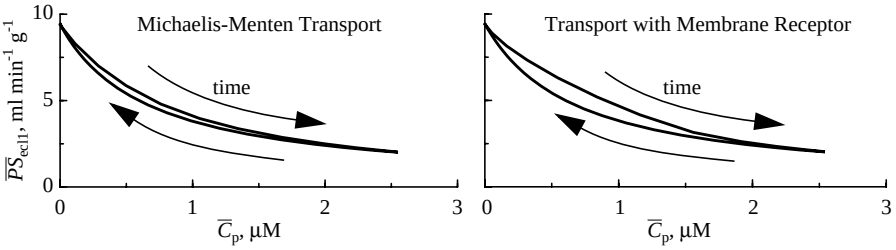

Figure 4. Plot of effective PS vs. nontracer concentration from the bottom panels of Fig. when injected nontracer amount is 2.4 μmol. Left panel: Michaelis-Menten transport. Right panel: nonlinear transport with capacitance. The hysteresis loop in the left panel was the artifact of averaging *PS* and C_p over the length of the capillary. The buffer effect of the receptor exaggerated the hysteresis loop in the right panel.

NSR at Experimental Biology 98

NSR was part of the "Computers in Research and Training" demonstration at Experimental Biology 98 in San Francisco's Moscone Center, April 18th through April 22.

We displayed XSIM, our easy-to-use Xwindow-based simulation program. Using XSIM and a simple two-compartment model, we demonstrated "Model Behavioral Analysis", an XSIM feature that automatically generates contour plots of an output variable as different parameters are varied over a range of values.

We also demonstrated GENTEX, a generalized tissue exchange model for nonlinear transport processes (facilitation, inhibition, competition, and capacitance in the membrane) and chemical reactions (fast and slow binding, Michaelis-Menten kinetics, and enzyme binding and reaction).

Our exhibit showed I4, a four-dimensional biomedical imaging system, with automated myocardial left ventrical (LV) region-of-interest definition, and its use in conjunction with XSIM running a metabolic model to yield parametric images of blood flow and ^{11}C-MHED uptake in the LV mapped onto a parabolic cone.

Our exhibit and demonstrations proved interesting to many. Professors from many institutions want to use XSIM and our metabolic models for their physiological simulation courses. Representatives from pharmaceutical companies were excited about our metabolic models. We talked with many researchers about using XSIM to model diverse processes, including transport and exchange in skeletal muscle, ischemic reperfusion, injured organs, pulmonary microcirculation, Ca++ flux, counter-current exchange, pharmacokinetics, bone remodeling, and nutrition modeling.

Gary R. Raymond

NSR Simulation Analysis Workshop: Modeling and Imaging

This workshop will help investigators learn to use computer simulation and modeling as aids in understanding biological systems, and as tools for analyzing data. Two foci contribute to those objectives: 1) general principles governing intravascular convection, membrane transport, and metabolic reactions in studies of whole organs; 2) analysis of time-course data from outflow dilution dynamic imaging studies.

"Hands-on" computer work during the workshop will use XSIM, a graphical user interface for simulation control and analysis developed by NSR. Participants may bring problems and data from their own research to be considered during the course.

Areas to be covered

- Membrane transport and receptor kinetics
- Heterogeneity
- Cellular metabolism and enzyme kinetics
- Functional imaging with kinetic models
- Fitting models to data
- Computer implementation techniques

General information

Dates: 13–15 September, 1998
Enrollment: limited to 18
Tuition: $300
Accommodation: Available in local hotels/motels
Travel: Participants to make their own arrangements

Questions and registration

For answers, contact Rita Jensen, jensen@nsr.bioeng.washington.edu (206-685-2005) or Rick King, rick@nsr.bioeng.washington.edu (206-685-2007). To register, use the form enclosed with this newsletter, or register online by visiting NSR's website at http://nsr.bioeng.washington.edu/, then clicking "What's New?" followed by "Modeling and Imaging".

Eric Lawson, Publications
Bioengineering, Box 357962
University of Washington
Seattle, WA 98195-7962