National Simulation Resource

NSR

University of Washington

Circulatory Mass-Transport and Exchange

Volume 8
Number 1
June, 1999

NSR is funded by NIH grant RR-01243, *Simulation Resource in Circulatory Mass-Transport and Exchange*

A nonstationary, nonlinear oxygen model

A new blood-tissue model for oxygen transport and metabolism differs from the previously published model (Li et al., 1997) in which the background oxygen transport and metabolism are assumed to be at steady state. In this new model, all the parameters, such as blood flow, blood volume and oxygen metabolic rate can be time-varying so that dynamic behavior can be explored with changing physiological conditions.

The model structure is similar to other blood-tissue exchange models developed at NSR. It includes large blood vessels (arteries, arterioles, venules and veins) and capillary-tissue exchange units with multiple pathways to account for flow heterogeneity. The capillary-tissue unit (Fig. 1) is based on the Krogh tissue cylinder geometry that allows for an axial gradient of oxygen concentration along the capillary length. Four-step, nonlinear oxygen binding to hemoglobin in the red blood cells (RBC) is explicitly incorporated into the model. This requires intensive computation but is better suited to studies of fast changing conditions, because there is no assumption of constant equilibrium binding (which is the case in the previous steady-state model). Similarly, one-step oxygen binding to myoglobin is used in the tissue cells. The oxygen consumption in the tissue cells can be either zero-order (constant metabolic rate), or first-order (proportional to local oxygen concentrations), or a combination of the two in the fashion of Michaelis-Menten kinetics.

The model is governed by a set of partial differential equations with respect to time and axial position along the capillary length. The general numeric scheme is a combination of the Lagrangian fluid sliding algorithm for blood convection and a time-splitting method that reduces the model equations to a set of ordinary differential equations (ODE) after the sliding of the blood. In order to handle varied nonstationary and nonlinear situations, four ODE solvers are implemented: a fifth-order Taylor method for linear problems, a variant of back differentiation formulae (LSODES) for nonlinear and sparse problems, an implicit Runge-Kutta method (RADAU) for nonlinear stiff problems, and an adaptive solver that can switch between nonstiff and stiff methods automatically.

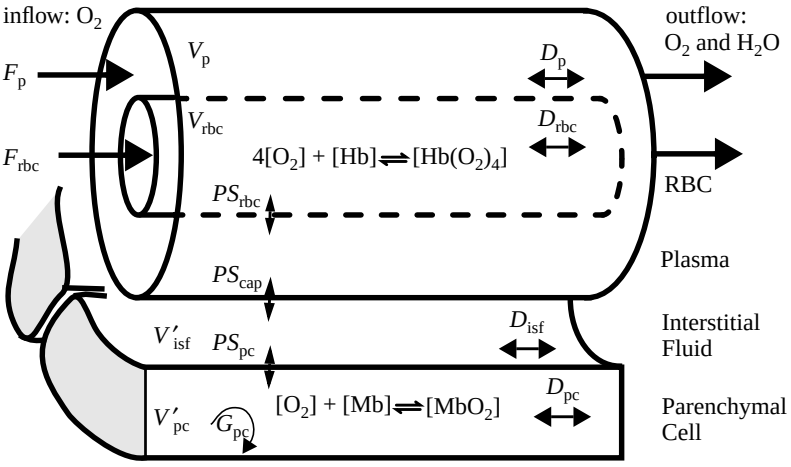

Figure 1. Capillary-tissue model for oxygen transport and metabolism. The four regions are: red blood cells (rbc), plasma (p), interstitial fluid (isf) and parenchymal cells (pc). The symbols used are: *F* for flow, ml min^{-1} g^{-1}; *V* for anatomical volumes and *V'* for virtual volumes of distribution, ml g^{-1}; *PS* for permeability-surface area product, ml min^{-1} g^{-1}; *G* for the consumption rate, ml min^{-1} g^{-1}; and *D* for the axial dispersion coefficient, cm^2 s^{-1}.

This model can also be used for compartmental analysis. Thus, The axially-distributed model can be reduced to a compartmental model in which every region is assumed to be a stirred tank. This provides a convenient way to explore two distinct types of models in varied situations.

Figure 2 presents a simulated experiment of the effect of changes in blood flow on oxy-

Contents

Staff

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

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

William Chan, Software Librarian
wchan@nsr

Eric Lawson, Publications
eric@nsr

Graduate Student:
Michael Kellen, mkellen@nsr

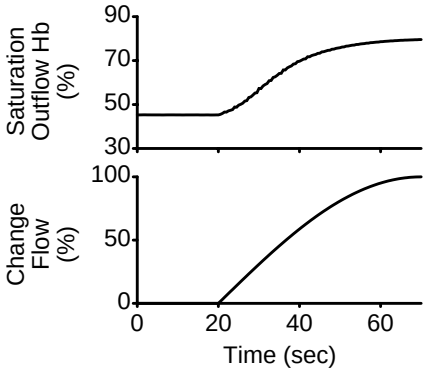

Figure 2. An example of the effect of blood flow change on the outflow hemoglobin saturation. The model used was a single-capillary tissue unit. Starting from 20 seconds the flow was gradually increased by 100%. The metabolic rate was maintained at the same level in this particular case.

gen transport and metabolism. One particular application of this kind of experiment is the brain activation study using either PET imaging of [O-15]oxygen or the BOLD (blood oxygen level dependent) technique with functional MRI.

Reference

Li, Z., T. Yipintsoi, and J. B. Bassingthwaighte. Nonlinear model for capillary-tissue oxygen transport and metabolism. *Ann. Biomed. Eng.* 25:604-619, 1997.

by Zheng Li

Modeling water and nontracer solute fluxes

GENTEX, MMID4, and the other blood-tissue exchange models developed by NSR are specialized for the analysis of multiple indicator dilution data. These data are useful for characterizing the transport properties of solutes across the capillary wall and probing the metabolism of the surrounding cells. The results obtained from indicator dilution studies are necessarily of a purely phenomenological nature; solute movement across barriers is described using the permeability-surface area product, and similar terms describe solute consumption, binding, and diffusion in these models. A key assumption made by all NSR models of indicator-dilution studies is that the experiment occurs at constant organ volume, with no net fluxes of water among cells, interstitium, and capillaries, which is valid when tracer amounts of solute are used in the experiment.

Complementary information can be derived from osmotic transient experiments, when significant quantities of a test solute are introduced into an isolated organ, creating an osmotic driving force for transcapillary water exchange. Both isogravimetric approaches, where vascular pressures are adjusted to keep the organ at constant weight (Pappenheimer, 1948), and weight transient techniques (Vargus and Johnson, 1963) have been used to estimate the transport properties of the capillary wall. In addition to the solute permeability (P), osmotic transient experiments also provide information about the reflection coefficient (σ) and hydraulic conductivity (L_p). Since the assumption of no net water flux can not hold for the osmotic transient experiment, a substantially different sort of model is needed to interpret osmotic transient data.

Such a model soon will be available for distribution from the NSR. Water and solute fluxes are described using the three parameters which comprise the classical phenomenological description of transport across a membrane: P, σ, and L_p. Additionally, this model accounts for volume-variable interstitial and cellular regions, with solute and water loss occurring through both the circulation and lymph. Non-linear tissue compliance and oncotic pressures provide buffering of induced water fluxes. Axial hydrostatic and osmotic pressure gradients in the capillary and interstitium are accounted for, as are interstitial matrix effects on solute exclusion and tissue oncotic pressure.

A goal of the project is to move beyond a phenomenological description of mass transport and develop a mechanistic model of transport across the capillary wall. This would allow a solute's permeability and reflection coefficient to be estimated based on physically measurable properties such as the solute's size and free diffusion coefficient, the number and geometry of the clefts between endothelial cells, and the distribution of water fluxes between trans-endothelial and extracellular pathways. The development of the model as a number of largely independent sub-modules should facilitate comparisons between classical Pore Theory and newer descriptions of the extracellular pathway, such as Fu et al.'s (1994) fiber-matrix model. Additionally, the inclusion of multiple water pathways means that the osmotic reflection coefficient depends not only on interactions between the solute and cleft, but on the distribution of water transport between the paths.

Ultimately, a good model of capillary transport should be able to explain both osmotic transient and indicator dilution data. Reduced versions of the osmotic model and MMID4 give equivalent results for some simple conditions. While the osmotic model will never include all the complexities of specialized indicator-dilution models, the development of some overlap with them will tie the two major experimental approaches for studying mass transport in whole organs together.

by Michael Kellen

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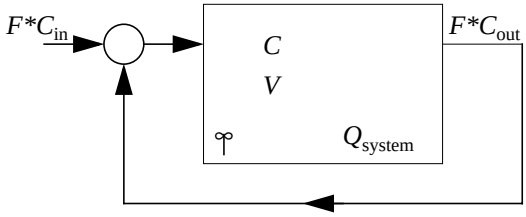
Fu, B.M., S. Weinbaum, R.Y. Tsay, and F.E. Curry. "A junction-orifice-fiber entrance layer model for capillary permeability: Application to frog mesenteric capillaries." *J. Biomech. Eng*. 116:502-513.

Pappenheimer, J.R., and A. Soto-Rivera. "Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hind limbs of cats and dogs." *Am. J. Physiol*., 152:471-491.

Vargus, F., and J.A. Johnson. "Permeability of rabbit heart capillaries to nonelectrolytes." *Am. J. Physiol*. 213:87-93.

Mass balance in recirculation models

A simple one compartment recirculation model is diagrammed below. F is the flow, C_{in} is the input concentration, C_{out} is the outflow concentration of the compartment, C is the concentration in a well-stirred (indicated by the small propeller) tank, and V is the volume. Q_{system} is the amount of tracer material in the tank. The material leaving the compartment is combined with the input concentration and continuously re-enters the system. This simple system is used to illustrate the difference between solving the entire system as a complete set of ordinary differential equations (Case I) and time stepping the solution where the material leaving the tank does not re-enter the system until the next time step (Case II).



The total amount of material entering the system is given by the integral,

$$Q_{integral}(t) = \int_0^t F \cdot C_{in}(t) \cdot dt\,.$$

The equation governing the system in Case I is

$$V\frac{d}{dt}C(t) =$$
$$F \cdot (C_{in}(t) + C_{out}(t)) - F \cdot C_{out}(t) =$$
$$F \cdot C_{in}(t)$$

which is completely equivalent to the first equation. The amount of material in the system is given by the integral, i.e., $Q_{\text{integral}} = Q_{\text{system}}$.

In Case II however, the governing equation is given as

$$V\frac{d}{dt}C(t) =$$
$$F \cdot (C_{in}(t) + C_{out}(t - \Delta t)) - F \cdot C_{out}(t).$$

The small amount of material at each time step, given by

$$F \cdot C_{out}(t - \Delta t) \cdot \Delta t = Q_{recirculation},$$

is outside the system at the end of each time step, and the mass balance is given by

$$Q_{integral} = Q_{system} + Q_{recirculation}\quad .$$

In Case I, the steady state concentration is given by

$$C = Q_{integral}/V$$

and in Case II by

$$C = Q_{integral}/(V + F \cdot \Delta t)\quad .$$

Obviously, unless $F \cdot \Delta t \ll V$, there will be a significant discrepancy in steady state concentrations between Case I and Case II models.

Using a single segment BTEX10 recirculation model (Case II) with C_{in}, a one-second spike of unit amplitude yields the results shown in the table below after 50 seconds when F=0.16666 ml/(g sec), V=0.03 ml/gm, and Δt varies as indicated.

The difference in steady-state concentration C_{out} between a Case I and a Case II model is as expected and given by $V/(V + F \cdot \Delta t)$. In general, one must consider the total volume available to the tracer in comparison to the volume swept out by the total flow during one time step.

There is a trade-off in formulating complex recirculation models. The entire model (multiple arteries, organs, veins) can be formulated as one very large set of differential equations requiring simultaneous solving (Case I), or each subsystem of equations for each artery, organ, and vein can be solved separately for each time step from the point of recirculation (Case II). Case II systems are far simpler to program because each element of the system can be treated separately. The disadvantage of Case II systems is that they always contain some error--the amount of material about to re-enter the system during the next time step. By requiring

$$Q_{recirculation}/Q_{system} \ll \varepsilon$$

by a judicious choice of time-step, Case II numerical error can be minimized to an acceptable level. Recirculation models implemented by NSR are usually Case II. $Q_{integral}$, Q_{system}, and $Q_{recirculation}$ are made available for checking.

by Gary Raymond

Δt (sec)	Q_{integral}/V *BTEX10*	C_{out} BTEX10	$Q_{\text{integral}}/(V + F \cdot \Delta t)$ BTEX10	$Q_{\text{recirculation}}/Q_{\text{system}}$
1.000	5.5556	0.8475	0.8475	5.5556
0.100	5.5556	3.5714	3.5714	0.5556
0.010	5.6111	5.3150	5.3158	0.0556
0.001	5.5612	5.5274	5.5304	0.0056

I4: An open four-dimensional biomedical image processing system

I4 grew out of the need for an open system capable of dealing with three- and four-dimensional image files. Several open-design public-domain packages deal with two-dimensional image manipulation, most admirably Jef Poskanzer's PBM and PBMPLUS, a set of utilities for two-dimensional imaging whose great usefulness is due to

- simple, intelligent, portable file specifications;
- a base set of simple, portable tools;
- a reasonable framework for adding tools; and
- a pipeline design that facilitates combining old and new tools.

Unfortunately, dealing with higher dimensional image sets within the confines of a two-dimensional package becomes an arduous collation problem, rather like doing numeric integration on a 4 function pocket calculator. Existing commercial packages for handling higher dimensional image sets are uniformly expensive and closed in their design, making them problematic and of limited usefulness for ongoing research projects.

I4 attempts to be the PBM of biomedical imaging by extending its design properties to the four-dimensional imaging requirements of modern imaging technologies such as Positron-Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). I4 is an "open" software system whose internal features are easily accessible and modifiable. NSR distributes the I4 system source code free of charge for purposes of education and research and encourages correspondence that may result in joint research projects involving I4. Source code is available, as are pre-built versions for SunOS 4 & 5, Irix, and the Cygwin-32 Unix-like system running over Windows-NT. I4 has been built on Linux, and a binary distribution is expected this year.

Key I4 system features include:

•Support for XYZT Pixel images, regions of interest (ROIs), cardiac "bull's-eye" images, and time activity curves;

•A host of well documented, simple utilities for routine image processing tasks such as ROI sampling, decay correction, tomograph correction, image arithmetic, etc.;

•An efficient and powerful scripting language for image processing functions that allows researchers to add additional utilities with minimal effort;

•A pipelining methodology for combining base system and user-written utilities

•A scripting methodology for the same thing, but performing more quickly;

•Support for set-theoretic ROI operations, allowing complex sampling strategies;

• Intelligent, uncluttered, and open file specifications with documented access libraries allowing researchers to write additional programs without "reinventing the wheel";

• An interactive image viewing query program supporting image overlay, custom color scales and point-and-click 3-D ROI editing;

• Artificial intelligence utilities for automatic definition of ROIs in image sets (article in preparation); and

• Interfaces to modeling programs for functional imaging.

This enables researchers to add modules specific to their own research that will work cooperatively with the base functionality of the system.

For further details see http://nsr.bioeng.washington.edu/NSR/NSRinfo/avsoftware/I4.

by Erik Butterworth

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.

HXSIM: A simulation and data analysis program for protein hydrogen exchange

XSIM, the computer simulation interface program developed at NSR, is useful in quickly building a variety of user-friendly computational models for biological research. The models calculate experimentally relevant data, and can be parameterized and optimized against laboratory measurements. Although the developmental thrust behind XSIM aims toward modeling circulatory mass-transport and exchange with tissues in physiology, we have recently applied the program to other biological problems.

A computational program for proton hydrogen exchange (HX) in proteins based on the two-process, two-stage model of Qian and Chan (1998, manuscript to be published) is now available for testing. This model, HXSIM, is a further development of the augmented two-process model proposed by Loh et al. [1].

The main display for the HXSIM model is shown in Figure 1. We consider a given amide proton in a protein in terms of four states: F_c, F_o, U_c, and U_o. They stand for the globally folded (F) and unfolded (U) states, with the possibilities of the local amide proton being open (o) and closed (c). Hence, F_o can represent local unfolding in the globally folded protein, and U_c can represent the residual structure in the unfolded protein, as shown by the two big boxes for

"Native State" and "Denatured State". Within each box, there is rapid equilibrium with respect to folding and unfolding rates, k_{gf} and k_{gu}, as well as the intrinsic hydrogen exchange rate k_x. This choice, which greatly reduces the complexity of the kinetic model, is based on many recent experimental observations.

Clicking the k_x button (Figure 2a), reveals that it contains the acid, base and water catalysis given by Bai et al. [2]. Similarly, clicking on the other rate and equilibrium constants (Figure 2b), reveals their denaturant dependence. The model is capable of simulating either the equilibrium HX, by specifying the pH and denaturant concentration (clicking the "Solvent Conditions" button on the lower-right produces a dialog box that allows a pH and denaturant to be specified), or the transient pulse-labeling HX experiment by giving a schedule for changing solvent (clicking the "Pulse-Labeling" button evokes the window shown in Figure 3).

After giving appropriate initial conditions, the model can be run and the time course for HX obtained, such as might be gotten from an NMR tube. The results (available through the "Results" menu) can be displayed in various forms. Furthermore, parameters in the model can be specified, the calculation fitted to a real experimental curve (using the "Optimize" menu), and the optimal values from the best fit obtained. These functions are a standard feature of the XSIM program.

HXSIM provides researchers studying HX with an important quantitative tool. Using HXSIM, researchers no longer need to make kinetic assumptions, such as EX1 and EX2, in the course of data interpretation. Information on local fluctuation can be obtained equally well by doing experiments under EX1, and then fitting the data to the model to obtain $K_{loc,n}$. This will greatly ease the constraints on the solvent conditions experimentalists have had to struggle with in the past. The goal is to obtain a full set of $K_{loc,n}$'s, which can give more detailed energetic information about the folded state of proteins. Such information is crucial in ultimately solving the protein folding problem [3].

HXSIM can now run under X-windows on a SUN workstation, and will soon be ready to run on an SGI. For more information contact hongq@nsr.bioeng.washington.edu.

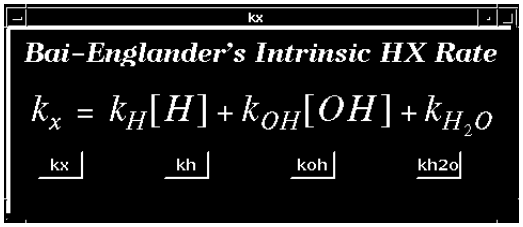


Figure 2a. Contents of the k_x button..

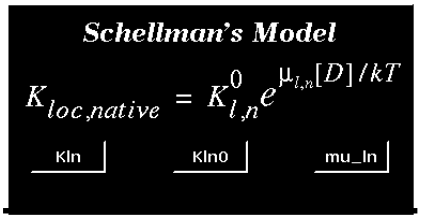


Figure 2b. Example of the contents of other constants buttons' denaturant dependence.

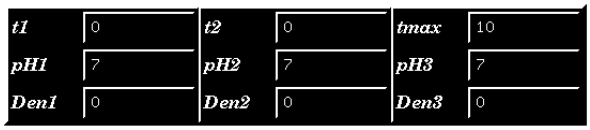


Figure 3. Result of clicking "Pulse Labeling" button.

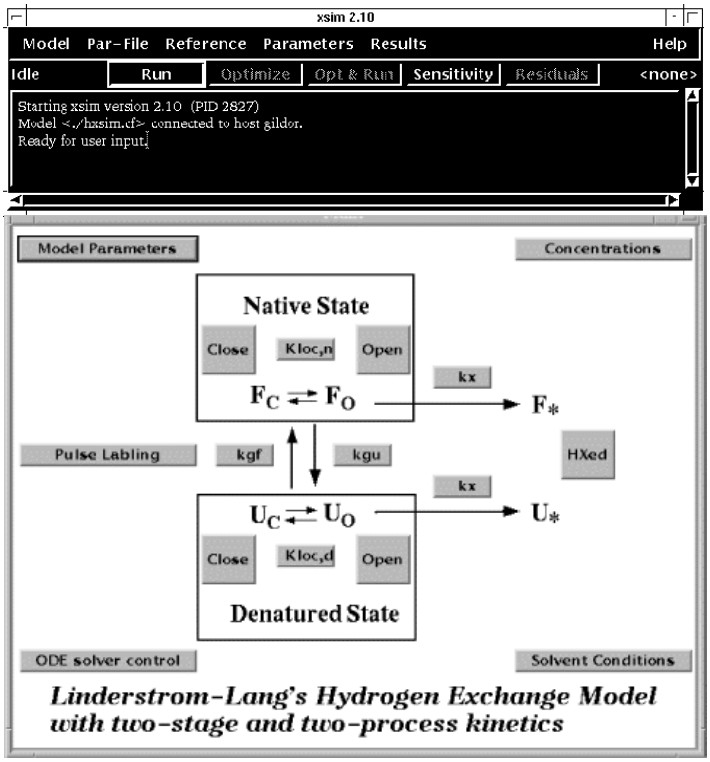


Figure 1. Main display of HXSIM. (To see a larger version go to http://amath.washington.edu/~qian/hxsim.gif.)

References

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by Hong Qian

NSR simulation analysis workshop

The National Simulation Resource in Circulatory Mass-Transport & Exchange is offering its annual course in the use of modeling to analyze flow, transport, and metabolism in cells and organs. The course will be held September 13–15, 1999 at the University of Washington, Seattle, Washington.

This course is designed to train investigators in the use of computer simulation and modeling as aids in understanding biological systems and as tools for analyzing data. There will be two foci: (i) general principles governing intravascular convection, membrane transport, and cellular metabolism in *in vitro* studies and whole organs studies and (ii) analysis of time-course data, including parameter estimation and error analysis. Topics to be covered include general enzyme kinetics, membrane transport and receptor kinetics, blood flow heterogeneity, cellular metabolism, functional imaging with kinetic models, fitting models to data and computer implementation techniques.

There will be considerable "hands on" computer work during the workshop using 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 workshop.

Brochures and additional information can be obtained from Dr. Zheng Li, 206-685-2840, (zhengli@nsr.bioeng.washington.edu) or from

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

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