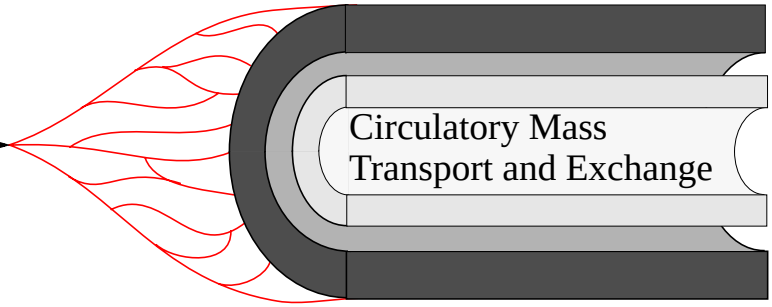
National Simulation Resource

NSR

University of Washington

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## Nonlinear BTEX models

*Introduction*

In axially distributed two-region blood–tissue exchange units such as in Figure 1, the transport and exchange of solute is represented by a set of partial differential equations like

$$\left\{\begin{aligned} \frac{\partial C_1}{\partial t} + \frac{FL}{V_1}\frac{\partial C_1}{\partial x} &= -\frac{PS_{1-2} + G_1}{V_1}C_1 \\ &\quad + \frac{PS_{2-1}}{V_1}C_2 + D_1\frac{\partial^2 C_1}{\partial x^2} \\ \frac{\partial C_2}{\partial t} &= +\frac{PS_{1-2}}{V_2}C_1 \\ &\quad - \frac{PS_{2-1} + G_2}{V_2}C_2 + D_2\frac{\partial^2 C_2}{\partial x^2} \end{aligned}\right.$$

In previous models, the permeability-surface area products (PS) and the gulosities (G) were assumed to be constant. However, such linear models fail to provide an adequate tool for the

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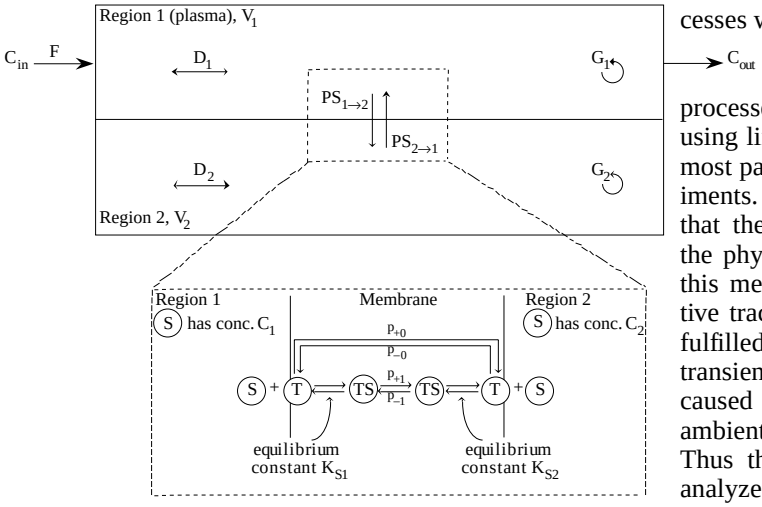


Figure 1. Schematic representation of the nonlinear, two-region BTEX model and its facilitated transporter model.

## Biology and nonlinearity

Can one do biology without being aware of the fundamental nonlinearity of the systems? If asked this question point blank, one would automatically say that would be impossible; just think of the biochemical reactions, the components of the action potential, the actions of receptors, and the quantal nature of synaptic transmission. Yet, as physiologists and medical investigators, our texts and teachings on regulation and control in the body are all based on linear systems analysis. An example is the baroreceptor: at first we are taught that when the pressure in the carotid artery goes up there is proportional firing of C-fibers that leads through central neural sites that result in heart rate reduction; next we learn that there is also baroreceptor firing that is proportional to the derivative or rate of change of pressure. Next we are taught that the firing rate is proportional to the difference between ambient pressure and some "set point" in pressure.

Proportional, .... derivative, ..... set points, ..... this is the traditional view, and is nicely established in our literature. Naturally, this isn't really the way it is. There are no set points, for there is no known way by which the body can "memorize" a reference state in pressure, or concentration, or whatever. The real systems aren't linear, despite all our successes with linear systems analysis.

In our modeling analyses of blood–tissue exchange processes we have gotten away with using linear models because, for the most part, we analyzed tracer experiments. The definition of "tracer" is that the marker should not change the physiological/biochemical state; this meant in practice that radioactive tracers of high specific activity fulfilled the requirement, and that transients in tracer concentration caused no significant change in the ambient chemical concentrations. Thus the tracer transient could be analyzed correctly with linear mod-

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analysis of experimental data when the transport of substrate across the capillary wall and/or its metabolism are strongly nonlinear. For these situations the dependence of PS and/or G on the local concentration values must be taken into account, transforming the set of linear model equations into a set of nonlinear equations.

Nonlinearity, however, often gives rise to serious numerical difficulties. To overcome these difficulties, specialized numerical techniques have been investigated. The best methods have been chosen to provide SIMCON users with powerful, nonlinear BTEX models. Their main features are outlined below.

*I. Nonlinear transporter and reaction kinetics*

The nonlinear blood–tissue exchange units assume that the transport of the substrate across the capillary wall is facilitated. Expressions for the PS's take the form

$$PS_{i \to j} = \frac{a_i + b_i C_j}{\alpha_1 + \alpha_2 C_2 + C_1 (\alpha_3 + \alpha_4 C_2)} ,$$

where a, b and α's are constants dependent on the parameters of the transporter model.

The new models also let SIMCON users choose between first-order reactions ($G_i = G_{maxi}$) and first-order enzymatic processes ($G_i = G_{maxi} / (K_{mi} + C_i)$).

*II. Numerical algorithms*

Codes for the nonlinear BTEX model have been implemented for random choice and explicit Euler-Lagrange numerical techniques. The decision to implement these two numerical techniques was motivated by a recent study[1] in which different numerical techniques particularly well suited for the solution of problems dominated by convection and nonlinear processes were compared. A *good* method was expected to be not only accurate but also fast. To obtain a quantitative measure of the quality of each method, we ran several severe test problems for which analytical solutions existed. Thus, it was possible to associate each numerical solution with an error estimate. The latter was then plotted versus the computational time while the number, $N_{seg}$, of axial segments dividing the capillary cylinder was increased and the ratio $\Delta t / N_{seg}$ was kept constant. A typical error versus CPU time plot is displayed in Figure 2. As expected, both the accuracy and the computational time of each method increase as $N_{seg}$ becomes bigger. The best methods should lie in the lower left corner. Figure 2 shows that the explicit Euler-Lagrange and the random choice methods offer a particularly reasonable trade-off between speed and accuracy.

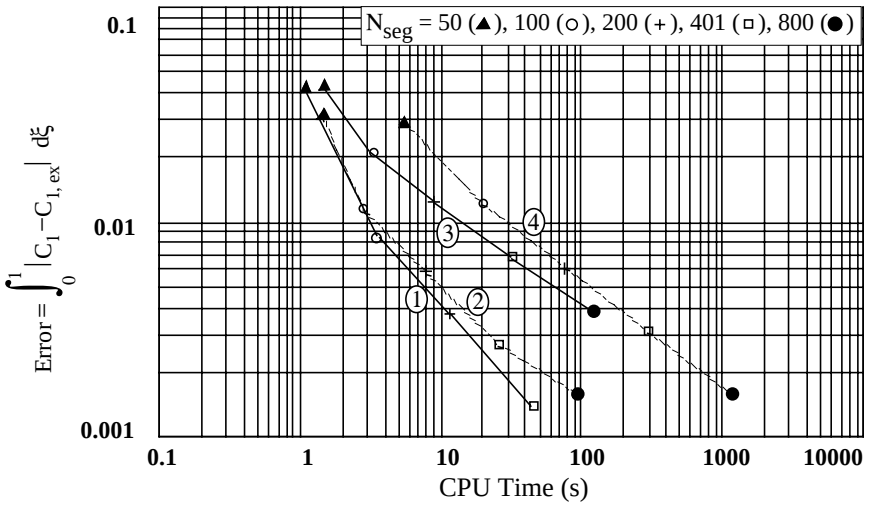



Figure 2. Error vs. computational time for the injection of a square pulse when $D_1 = D_2 = 0$, $G_1 = G_2 = 0$, $PS_{1\to2} = k_1 (C^s - C_2)$, $PS_{2\to1} = k_2$ and $PS_{1\to2} C_1 = PS_{2\to1} C_2$. The upstream finite difference method (curve 3) provides good speed but low accuracy. On the contrary, the third-order Essentially Non-Oscillatory method (curve 4) gives good accuracy but is slow. Euler-Lagrange (curve 1) and random choice (curve 2) methods offer a better trade-off. (Note: for the Euler-Lagrange method $N_{seg}$ is the initial number of segments).

The random choice method first solves the convection equation using Riemann solvers. This provides a fast and accurate intermediate solution on which any exchange, reaction or diffusion effects are superimposed. Because a random variable is introduced to solve the Riemann problems, the solution at a given time has slight uncertainties, but on average it is correct.

The Euler-Lagrange method also starts by treating the convection equation. Then any other effects are added. The convection part of the problem is solved exactly by the method of characteristics. Thus, the grid in the plasma region moves in time. Cubic spline interpolation is used to permit evaluation of the exchange terms between fixed and moving regions.

For both methods, the choice of a proper time step is important. If the time step is too big the solution will grow unstable and the program might crash. To provide SIMCON users with a reliable package, the nonlinear BTEX routines use an internal time step chosen to provide a stable solution in the smallest computational time possible.

*Conclusion*

Code for the nonlinear BTEX models outlined above will soon be delivered to the Simulation Resource so it can be made available to all SIMCON users.

*— Christophe Poulain*

1. C. Poulain and B. A. Finlayson, "A comparison of numerical methods applied to nonlinear adsorption problems" (*Int. j. numer. methods. fluids*, submitted Nov. 1992).

# Modeling blood flow heterogeneity in tissues

Organs are known to be heterogeneous in many of their physical properties including regional blood flow. The regional flows in an organ can be described by a probability density function (PDF) of relative flows.[1] Each flow path is described by a relative flow, $f_i$, and its probability of occurrence, $wd_i$ (equal to the mass fraction of the organ with flow $f_i$).

Blood flow heterogeneity affects the shape of outflow and residue curves measured in indicator dilution experiments. Comparing the outflow curve from a multipath (heterogeneous flow) model to that from a single path (homogeneous flow) model, differences include: (1) shortened appearance time (caused by the presence of paths with flows greater than the mean), (2) decreased peak height and increased dispersion (caused by distributing the total flow among paths with different flows), and (3) an elevated tail of the curve (caused by paths with flows lower than the mean).

A procedure for specifying the parameters of flow heterogeneity in multipath models has been developed. The goals of the procedure are to allow several choices for selecting a PDF that represents the distribution of flows in the tissue being modeled, allow flexibility in selecting the flows used for the pathways, and select weights for these flows that faithfully represent the selected PDF. The flowchart at right outlines the procedure. In Phase 1 a PDF that characterizes the tissue being modeled is specified. Relative flows that best represent the data being analyzed, and weights for each path, are selected in Phase 2.

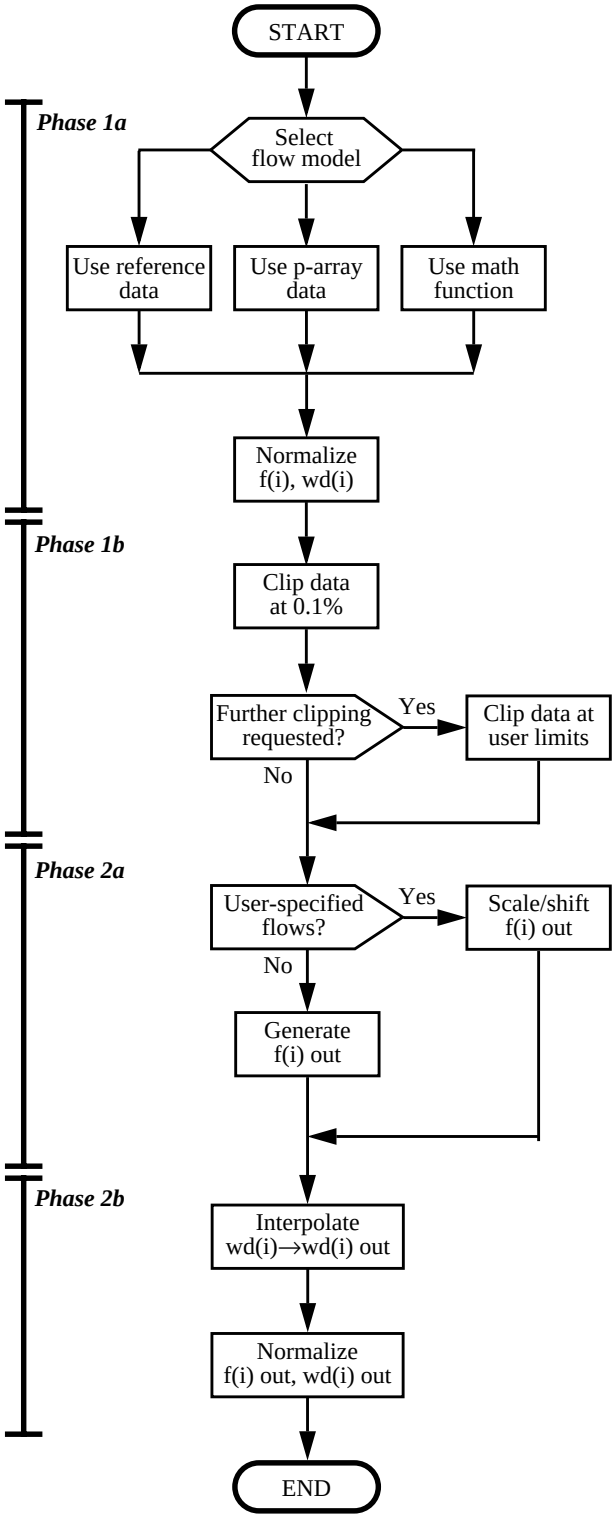
Four choices are available in Phase 1a: (1) the PDF for a particular experiment can be loaded from the reference data, (2) a PDF can be taken from the parameter array, or (3) a mathematical distribution can be used. Two mathematical distributions are available: a lagged normal density curve (LNDC) or a random walk (RANWOK). The LNDC is used for distributions with moderate skewness and RANWOK is used when the skewness exceeds three times the relative dispersion. In Phase 1b, the high and low ends of the PDF are clipped to eliminate paths with very small probabilities (default $wd_i < 0.1\%$). The user may specify additional clipping.

In Phase 2a the relative flows that will be used by the model, $f_i out$, are selected. These flows can be specified by the user or generated by a mathematical algorithm that selects flows equally spaced in either the flow or the transit time domains, or at some point intermediate between those limits. If the flows are specified by the user, they may be scaled and shifted to bring them into the range of flows spanned by the PDF. In Phase 2b, the PDF is interpolated to obtain the weighting factors for the paths, $wd_i out$. Finally $f_i out$ and $wd_i out$ are normalized to ensure that mass is conserved in the model. See the NSR Newsletter of March, 1992 for exemplary distributions.

*NOTE:* Code modules that implement this procedure have been developed and tested. These will be used in the next revision of the MMID4 model (Version 2.1) that is scheduled for release in early May. A new MMID4 User Guide will accompany this release.

*— Gary Raymond*

1. Bassingthwaighte, J. B. Calculation of transorgan transport functions for a multipath capillary-tissue system: Multipath transorgan transport. Report PB82-2295 35 (UW/BIOENG-82/1) National Technical Information Services: Springfield, VA 22161, 1982.

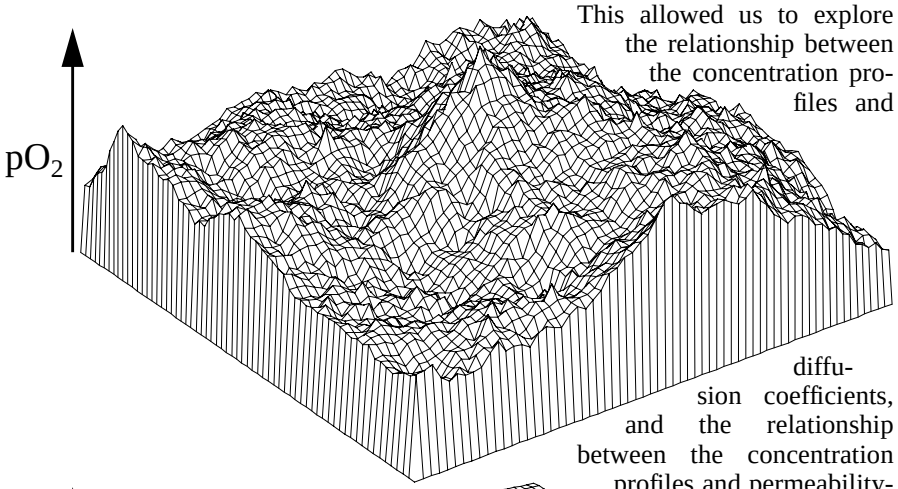


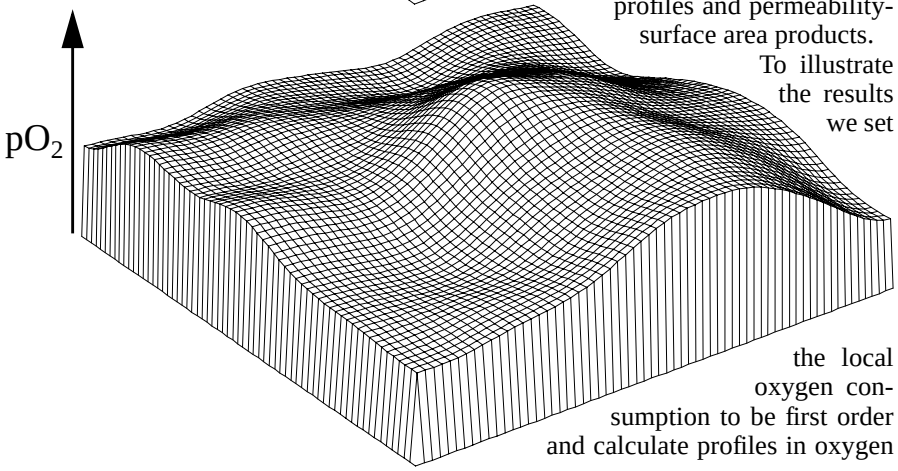
# Fractal flows and oxygen concentration profiles in a two-dimensional matrix of flows

Flow distributions in the heart and lung are heterogeneous but not random. The fractal characterization is a statement that the system is nonrandom and that it shows correlation. Near neighbors have higher correlations than distant neighbors. When adjacent capillary–tissue exchange units are exactly alike, then no net exchange of solutes across the intervening boundary takes place. If neighbors are dissimilar in flow, permeability, or solute consumption, then concentration gradients arise and result in net transfer by diffusion. The net flux between unlike neighbors is greater for highly diffusive, lipid soluble gasses than for hydrophilic solutes. Here we begin an exploration of the effects of diffusion in smoothing out local oxygen tension variation. The fluxes are naturally less for a fractal flow distribution than for a random flow distribution since gradients are smaller.

We used the Successive Random Additions with midpoint and endpoint additions algorithm[1] to generate a fractal two-dimensional matrix of flows.

From this flow matrix we computed the concentration profiles with a simple blood–tissue exchange model, and allowed diffusional exchanges between neighboring capillaries. This allowed us to explore the relationship between the concentration profiles and diffusion coefficients, and the relationship between the concentration profiles and permeability-surface area products. To illustrate the results we set the local oxygen consumption to be first order and calculate profiles in oxygen concentration over the matrix in two situations, one with no diffusion, and one with diffusion $D = 10^{-5}$ $cm^2/s$. The smoothing is rather dramatic because we considered the diameter of the functional microvascular unit to be 50 microns. The approach suggests that one might use such profiles to actually help define the dimensions of the functional units.




*— Joseph Chan*

1. Peitgen, H.-O., and Saupe, D., editors. *The Science of Fractal Images*. Springer-Verlag, New York, 1988.

# Selected NSR publications on fractals

Bassingthwaighte, J. B. Physiological heterogeneity: Fractals link determinism and randomness in structures and functions. *News Physiol. Sci.* 3:5-10, 1988.

Bassingthwaighte, J. B., and J. H. G. M. van Beek. Lightning and the heart: Fractal behavior in cardiac function. *Proc. IEEE* 76:693-699, 1988.

Bassingthwaighte, J. B., R. B. King, and S. A. Roger. Fractal nature of regional myocardial blood flow heterogeneity. *Circ. Res.* 65:578-590, 1989.

van Beek, J. H. G. M., S. A. Roger, and J. B. Bassingthwaighte. Regional myocardial flow heterogeneity explained with fractal networks. *Am. J. Physiol.* 257 (Heart. Circ. Physiol. 26):H1670-H1680, 1989.

King, R. B., L. J. Weissman, and J. B. Bassingthwaighte. Fractal descriptions for spatial statistics. *Ann. Biomed. Eng.* 18:111-121, 1990.

Wang, C. Y., and J. B. Bassingthwaighte. Area-filling distributive network model. *Mathl. Comput. Modelling* 13:27-33, 1990.

Glenny, R., H. T. Robertson, S. Yamashiro, and J. B. Bassingthwaighte. Applications of fractal analysis to physiology. *J. Appl. Physiol.* 70:2351-2367, 1991.

Bassingthwaighte, J. B., and R. P. Beyer. Fractal correlation in heterogeneous systems. *Physica D* 53:71-84, 1991.

Wang, C. Y., L. J. Weissman, and J. B. Bassingthwaighte. Bifurcating Distributive System using Monte Carlo method. *Mathl. Comput. Modelling* 16:91-98, 1992.

Schepers, H. E., J. H. G. M. van Beek, and J. B. Bassingthwaighte. Comparison of four methods to estimate the fractal dimension from self-affine signals. *IEEE Eng. Med. Biol.* 11:57-64x71, 1992.

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els even when the system was actually nonlinear. The results portrayed the system behavior as a snapshot of the state at a particular time, whatever the ambient concentrations were at that moment. To probe cellular reaction kinetics, and to unearth the behavior under a variety of conditions, one needs therefore to try to change the ambient conditions to a new steady state and then to perform the linear, tracer-based analysis under several such different steady states. The problem with this approach is that having, for example, a continuously high concentration of a stimulator or agonist often causes such a change in the physiological state that the data are not relevant any longer to the state existent at the lower, naturally ambient concentration. There are situations where the kinetics of reaction can be revealed correctly by a sequence of tracer experiments in different steady states, e.g., those by Malcorps et al. (1984), but these are probably the exception rather than the rule.

The more efficient experimental strategy for characterizing nonlinear systems is to determine the parameters of the nonlinear model. The pioneering work in studies of the nonlinear transport and reaction in intact organs has been done principally in two laboratories, those of Goresky and colleagues at McGill University in Mont-

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## SIMCON status

The names and titles of the currently outstanding bugs and enhancement requests are listed in the table below. Users can get more details about them by reading the Software Trouble Reports which are stored in the directory ~simcon/STR. Bug reports and enhancement requests are in separate sub-directories, BUGS and ENHANCEMENTS respectively, and the files are named with the STR number. The STR's are also available as a compressed tar archive by anonymous ftp from nsr.bioeng.washington.edu. The file to transfer is pub/SIMCON/STR.tar.Z.

A new SIMCON release (Version 2.8.1) is scheduled in May 1993. This release will address most of the outstanding bugs and enhancement requests E15, E16, and E17 and others. This will be the last release in the SIMCON 2.N.N series. We will then focus on Release 3.0.0 which will separate the interface and model into two separate tasks and will make it possible to maintain the interface and models separately.

*— Rick King*

| No. | Title |
|---|---|
| **Enhancements** | |
| E11 | Standardize function letters in submenus |
| E12 | Run number should appear on plot |
| E13 | Ability to do log-log plots |
| E14 | Weighting of sensitivity functions |
| E15 | Additional optimizer |
| E16 | Add function generator |
| E17 | Show tabular results for residuals |
| E18 | Sensitivity and residuals should be available from submenus |

Outstanding SIMCON Software Trouble Reports (STR's)

| **Bugs** | |
|---|---|
| B09 | A help screen cannot be just a title |
| B10 | The data read switch, p(120), and the axes switch, p(143), interact |
| B21 | Long lines in tabular output are not handled gracefully |
| B29 | There are incorrect entries in the parameter help screens |
| B33 | A model will run when no output is selected |
| B35 | There is an error in scrolling help output |
| B37 | Stderr is assumed to be unit 0 |
| B40 | The configuration control menu has the wrong title |
| B41 | The database menu uses incorrect terminology |
| B42 | The simnlist program does not know about installed names files |
| B43 | User Guide Section 4.3 does not discuss referencing parameter files by name |
| B44 | Cannot access help from the data index menu |
| B45 | Program hangs when a run is killed then saved |
| B46 | Note 15 is missing from the control parameter reference card |
| B47 | Program crashes on sensitivity calculation |
| B48 | Model manual pages specify the incorrect source location |
| B50 | Program crashes in CV calculation when two data points have the same x value |
| B51 | Sensitivities not calculated when run immediately after starting a session |
| B52 | Inconsistency between names in names file and help file for simbt40 |
| B53 | Optimization with curve index, p(196), of 0 causes crash |
| B54 | CV calculation is incorrect when scalar, p(119), is not 1. |
| B55 | Incorrect loop increment label on plot hard copies |
| B56 | Model crashes after kill signal |
| B57 | Model crashes on 0 divided in CV calculation |
| B58 | Reference data scaled incorrectly on log plot |

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real, e.g., Goresky, Gordon and Bach (1983), and of Linehan and Dawson in Milwaukee (Marquette University and Medical College of Wisconsin), e.g., Bronikowski et al. (1982) The "bolus sweep" experimental technique of Linehan, Dawson, et al. (1987) is particularly nice: instead of using a pure high specific activity tracer in the injectate for a multiple indicator dilution study, they lower the specific activity of the tracer by adding amounts of nontracer mother substance that can result in intravascular concentrations that approach or exceed the levels of the apparent Michaelis constant for the transporter or enzyme. As the bolus passes through the capillary–tissue unit the nontracer concentrations sweep upward from the pre-injection level (ambient or near zero) toward the level in the injectate. Since tracer binding by the saturable transporters and enzymes is inhibited by competition with nontracer in a graded fashion during the several seconds during which the bolus passes, the effective permeability-surface area products or consumption rates can be assessed over the whole range of concentrations swept through. Thus in one shot one can get measures that would otherwise take a good many steady state experiments, and do it without there being the time for big physiological changes to occur. This strategy won't work if the "big" changes are exceedingly fast, but normally can reduce strikingly the number of studies, and reduce the usage of experimental animals. The corollary is that one needs the fancier, slower, nonlinear models and probably more time in the analysis.

Another potential advantage in this approach is that one may be able to obtain estimates of the individual association and dissociation rate constants, if these are appropriately described in the model. This approach would be desirable when on and off rates are slow compared to the rates of change of tracer concentrations, since under these conditions the normal assumption of equilibrium is invalid. Since the indicator dilution approach provides high temporal resolution of the free tracer, it may provide the critical data. Using this approach, one would not model the Michaelis-Menten parameters of Km and Vmax, but rather the underlying rate constants.

We began the use of nonlinear models in our laboratory some time ago (Bassingthwaighte et al., 1985), putting transporters of quite general form on all the membranes of a four-region (capillary, endothelial cell, ISF, parenchymal cell) model and putting first order Michaelis-Menten reactions in all regions. This was nice in its generality, but when put in multicapillary form to handle the flow heterogeneity was very slow to compute, and optimizing model fits to experimental data was impractical. This seriously impeded our use of these models. Now, no longer able to postpone the inevitable, we must move to such models, and make them usable. Computational speed is the key, and going always to somebody's Cray over the network wasn't the answer. The answer, as is most often the case, is better algorithms which run faster, and yet have adequate accuracy. In our lead article, by Christophe Poulain, is the outline of the strategy that he and Bruce Finlayson have devised. The approach comes out of the extensive numerical developments recently published by Finlayson (1992), and holds much promise for future efficiencies.



*— Jim Bassingthwaighte*

Bassingthwaighte, J. B., C. Y. Wang, M. Gorman, D. DeWitt, I. S. Chan, and H. V. Sparks. Endothelial regulation of agonist and metabolite concentrations in the interstitium. In: *Carrier-Mediated Transport of Solutes from Blood to Tissue*, edited by D. L. Yudilevich and G. E. Mann. New York: Longman, 1985, pp. 191-203.

Bassingthwaighte, J. B., L. Noodleman, R. T. Eakin, and R. B. King. Integrated phenomenology of transport, permeation, and metabolic reactions in the heart. In: *Activation, Metabolism and Perfusion of the Heart. Simulation and Experimental Models*, edited by S. Sideman and R. Beyar. Dordrecht: Martinus Nijhoff, 1987, pp. 621-642.

Bronikowski, T. A., C. A. Dawson, J. H. Linehan, and D. A. Rickaby. A mathematical model of indicator extraction by the pulmonary endothelium via saturation kinetics. *Math. Biosci.* 61:237-266, 1982.

Finlayson, B. A. *Numerical Methods for Problems with Moving Fronts*. Seattle: Ravenna Park Publishing, 1992, 605 pp.

Goresky, C. A., E. R. Gordon, and G. G. Bach. Uptake of monohydric alcohols by liver: demonstration of a shared enzymic space. *Am. J. Physiol.* 244:G198-G214, 1983.

Linehan, J. H., T. A. Bronikowski, and C. A. Dawson. Kinetics of uptake and metabolism by endothelial cell from indicator dilution data. *Ann. Biomed. Eng.* 15:201-215, 1987.

Malcorps, C. M., C. A. Dawson, J. H. Linehan, T. A. Bronikowski, D. A. Rickaby, A. G. Herman, and J. A. Will. Lung serotonin uptake kinetics from indicator-dilution and constant-infusion methods. *J. Appl. Physiol.* 57 (Respirat):720-730, 1984.

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