Prepared for Surgical Research (Souba, Wilmore, eds.)
section editor: Lowry
19 February 2000

Mathematical Modeling in Surgical Research

Denise E. Kirschner, Ph.D.
Departments of Microbiology and Immunology
The University of Michigan

Timothy G. Buchman, Ph.D., M.D.
Department of Surgery
Washington University School of Medicine

Correspondence to:
TGB
Buchman@msnotes.wustl.edu
Address on file at Academic Press

DEK's e-mail address:
Kirschne@malthus.micro.med.umich.edu
Contact info:
Dept. of Microbiology & Immunology
6730A MED Sci II
University of Michigan
Ann Arbor, MI 48109
734 647-7722

Mathematical modeling

Surgical research embraces many disciplines ranging from molecular biology to human physiology. Irrespective of the physical scale that characterizes a particular project, most surgical investigators will confront some significant aspect of their research which will benefit from—if not explicitly require--mathematical modeling. In this chapter, we explore fundamental aspects of mathematical modeling to address three questions. Why is mathematical modeling an essential surgical research tool? What is (and what is not) a mathematical model? How is a mathematical model designed and used? Answers to these questions constitute an introduction to mathematical biology and serve to illuminate an interface between that discipline and surgical research.

An important point is that surgeons subconsciously employ models every time a constellation of symptoms is recognized as diagnostic and specific care is delivered. Surgeons extrapolate their accumulated experience to more and more general situations. Such extrapolation to more general situations and to behaviors over time is an hypothesis in its own right, an hypothesis that surgeons routinely verify (and modify) in daily care. Thus testing the extrapolation hypothesis -- "does this particular patient fit the model I use to describe a particular disease process?" -- is clinically routine. Models are merely collections of hypotheses regarding the mechanisms and magnitudes of processes that influence the system under study. This chapter illustrates the way in which mathematics can be used as a language for surgically useful modelling.

Why model?

A formal answer to the "Why model?" question is “to encapsulate knowledge regarding a complicated problem into a simplified representation.” In a familiar example, we surgeons find it much easier to follow the description of a new operation if medical illustrations are provided instead of intraoperative photographs. The medical illustration extracts the critical tissue relationships and allows us to focus on the relevant manipulations. A medical illustration is an excellent example of a static model.

Static Models

Common folklore suggests that the young surgeon initially displays technical skills by "building model airplanes". Demonstrations of dexterity aside, creation of such scaled physical models provide for examination of spatial organization and relationships that are not otherwise discernable. For example, the passenger in seat 15-C of a Boeing 737 is unlikely to appreciate that the length and wingspan of her conveyance are nearly identical; moreover, this similarity is echoed throughout the Boeing line. This systematic examination of physical models can lead to knowledge abstraction: "Boeing builds square airplanes."

Abstracted knowledge about an object that can be embedded into a static model is frequently used in bedside surgical care. For example, water in the adult human is commonly modeled to occupy two compartments, an intracellular space and an extracellular space, where the extracellular space itself consists of two compartments, an interstitial space and an intravascular space. Clinical estimates of the magnitudes of fluid and electrolyte deficits rely on such a static model.

Dynamic Models

The passenger in 15-C is likely less concerned with dimension than with a safe and swift journey. The journey depends on engineering, and the passenger in 15-C is reassured that a professional team has designed systems and subsystems to reliably interact in highly specific and predictable ways. The key phrase is "designed…to interact".

Biomedical engineering excepted, the surgical investigator does not participate in the design of the object under study. In most surgical research projects, the goal is to elucidate the design. The key tool is controlled perturbation of the study object followed by sequential measurement of object parameters. From the measurements—whether the data describe gene expression, bulk flow of blood through the heart, or spread of a particular bacterium through an intensive care unit—surgical investigators make inferences about the relevance of a particular process. The inferences become hypotheses that are experimentally probed, most often by comparing objects that differ in a single feature: the knockout mouse versus its parent; flow at a hematocrit of 20 versus a hematocrit of 40; use of water-based handwashing versus alcohol foam degerming.

Data accumulate much faster than knowledge. The classical, reductionist approach to scientific inquiry requires a full factorial experimental design such that each relevant process ought to be tested across the full range of expected performance in order to understand the effect of that individual process upon the whole experimental system . Organ physiologists a generation ago often performed such systematic studies. Their detailed experiments became the basis for clinically essential models such as cardiac performance as a function of preload, afterload and contractility. Such experiments on the microscale of cells and molecules and on the macroscale of large populations are difficult to design and even more difficult to perform. The usual approach is that a relatively few observations made under arbitrary but strictly controlled conditions in which the object under study has been intentionally "isolated from confounding influences" are extrapolated to more general, analytically more complicated situations. The potential for error is obvious, the realization all too frequent.

The Hidden Hypothesis

The passenger in 15-C is flying in an airplane whose behavior over time was predicted on the basis of an explicit design. The surgical investigator pursues the "inverse problem". The design of the object under study is to be extracted from its behavior over time subject to a host of noisome experimental constraints. We have already alluded to the limit of the number of data that may be collected. Biologic objects also limit the types of data that can be collected. The precision of the data obtained from biological objects is typically less than that obtained from physical objects. And so on. The extrapolation to the more general situation and to behaviors over time is an hypothesis in its own right, an hypothesis that is subject to verification by experiment. Testing this "extrapolation hypothesis" drives modeling such that behaviors are predicted and then experimentally tested. As stated in the introductory paragraphs, models themselves are merely collections of hypotheses regarding the mechanisms and magnitudes of processes that influence the object under study. [1]

What is (and what is not) a mathematical model?

[1] As a collection of hypotheses which itself is an hypothesis, models can never be proven "correct". Their greatest investigational value lies in illuminating what is "missing" or "wrong".

A mathematical model is a tool with that an investigator encapsulates hypotheses concerning the mechanisms and relationships that underlie the behavior of a system over time. Equations are used to describe the relationships. It is important that surgeons understand that once the relationships are described as mathematical equations, solutions to those equations are often readily obtained by desktop computers.

Mathematical models are ubiquitous in surgical care. Some are expressed as informal "rules", such as the "three-for-one rule" (which states that three volumes of a balanced salt infusion are required to compensate for each volume of acute blood loss). The 3:1 rule originates from experiments showing that water and small ions readily equilibrate across blood vessel walls into the interstitial compartment, and a model that envisions the interstitial compartment to be twice as large as the intravascular compartment.

Other mathematical models are more formal, such as the pharmacokinetic models that guide administration of aminoglycoside antibiotics. The nomograms that surgical residents use to make dose adjustments are simply graphic representations of models of the aqueous compartments and the predicted clearance rate of the drug. Each patient is viewed as an individual experiment, with the model offering continuous predictions about plasma concentrations. Measuring the patient's plasma level of the drug at a particular time is a test of the model, not of the patient. An accurate prediction merely indicated that the dose may be left unchanged. An inaccurate prediction does something more--it not only indicates to the surgeon that the dose must be changed but also suggests that the model contains relations that are inaccurate or incomplete. Indeed, unexpectedly high levels may suggest that there is incipient renal insufficiency whereas unexpectedly low levels may suggest that the patient has a larger-than-normal volume of distribution.

However useful they may be, memorable "rules" and nomograms are no more than representations of someone else's model. The surgical investigator must ultimately venture into building his own model if he is to make and test hypotheses concerning the design of the object being studied. He must ultimately propose relationships that govern the measurable parameters, make predictions, perturb the object, and observe the fidelity with which his model describes the behavior of his system. Simply stating the anticipated

change in a parameter ("I predict drug D will cause parameter P to decrease") is not a model. It may well be an event predicted by a model, but the prediction is not the model.

Model Building: An Example

To illustrate one way that modeling illuminates a problem to focus attention on particular aspects of that problem, consider this familiar and vexing scenario.

Review during rounds of a postoperative patient shows two abnormalities. First, the urine output is decreasing. Second, the serum creatinine concentration is rising. The patient has received appropriate volumes of fluid. The inescapable conclusion is that the patient has acute renal insufficiency. The apparent cause of the kidney failure is identified and reversed. The next day, the serum creatinine level has climbed again. Has the true cause of the renal insufficiency been identified? Why has the serum creatinine level risen? Is there another cause for the problem? When will the creatinine concentration peak and begin returning towards normal? These gnawing questions have cost every surgeon anxious moments.

To apply mathematical modeling to this (or any other) problem, the universe of the problem must be explicitly defined along with the hypothesized relationships among the components of the experimental system. In the case of the patient with renal insufficiency, it is enough to define the universe to include a source of creatinine (muscle breakdown), a reservoir in which the creatinine is accumulated (in total body water), and sinks into which the creatinine flows (urine).

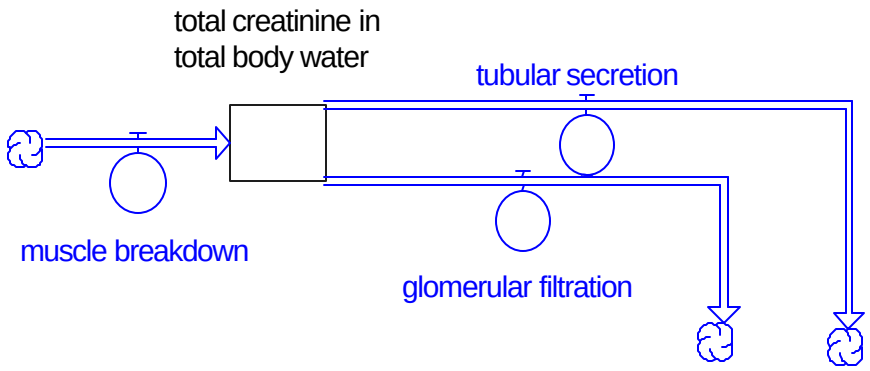

Figure 1. Schematic representation of production and elimination of creatinine. Tubular secretion and glomerular filtration are independent processes which occur in the kidneys and deliver creatinine into the urine.

This graphic representation encapsulates not only the universe but also the relationships represented in what will become a "conservation of mass"relationship. The graphic emphasizes that we are not particularly interested in the exact source of the creatinine, only that the source continues to pour creatinine into the reservoir by the process of myolysis. The graphic also recognizes that the kidney has two distinct mechanisms by which it removes creatinine from plasma (and, by extension, from total body water): filtration by the glomerulus and secretion into the renal tubule. Although both mechanisms deliver creatinine into the urine, we can and will treat them as distinct processes. The conservation of mass relationship can be "read" as follows.

> "The rate of change in the total amount of creatinine (where the total amount is equal to the concentration of creatinine multiplied by the volume in which the creatinine is distributed) must equal the difference in the rates at which creatinine is being delivered and creatinine is being disposed. Creatinine is delivered by a single process (muscle breakdown). Creatinine is disposed by two processes, tubular secretion and glomerular filtration. The rate of glomerular filtration depends on the local creatinine concentration."

A conservation of mass equation containing these relationships might read:

$$\frac{d([Cr]*V_{Cr})}{dt} = \dot{R} - (\dot{S} + \dot{g}[Cr]) \qquad (1)$$

where [Cr] is the concentration of creatinine in body water, V_{Cr} is the volume of that body water, $\dot{R}$ is the rate of creatinine released by muscle breakdown, $\dot{S}$ is the rate at which creatinine is secreted by the renal tubules, and $\dot{g}$ is the glomerular filtration rate. The instantaneous rate of change is denoted by the derivative, *d/dt.*

Two data series are immediately available to the clinician at the bedside. One is the series of concentrations of creatinine [Cr]. Surgeons mentally calculate Δ[Cr] as the data are being examined ("The creatinine went up 1 mg/dl since yesterday!") The other series, typically ignored on patient rounds, is the series of time intervals (Δt) at which the [Cr] determinations

were made. What (if anything) can be inferred from relationships between the incremental change in creatinine, $\Delta[Cr]/\Delta t$ and the average value of [Cr] during the change?

The following simple expansion comes from elementary calculus. If m and n are both functions of the variable t, then

$$\frac{d(mn)}{dt} = m\frac{dn}{dt} + n\frac{dm}{dt}$$

Rearrangement of terms in equation (1) yields

$$\frac{d[Cr]}{dt} = \frac{1}{V_{Cr}}(\dot{R} - \dot{S}) - \frac{1}{V_{Cr}}(\dot{g} + \frac{dV_{Cr}}{dt})[Cr] \qquad (2)$$

Inspection shows that so long as V_{Cr}, $\dot{R}$ and $\dot{S}$ are constant, the slope of a d[Cr]/dt vs. [Cr] plot will be a linear function of $\dot{g}$. [2] In other words, the slope of the d[Cr]/dt vs. [Cr] plot--which some refer to as a phase plot or phase portrait--represents the glomerular filtration rate as long as the volume of distribution is more or less constant.

Few of us—surgeons or mathematicians—have the intuition or experience to relate clinical data to this rather unfriendly-looking equation. Fortunately, neither are necessary. Desktop microcomputers with appropriate modeling software substitute nicely. The next several sections illustrate how equation (2) might be analyzed using a couple of popular modeling software packages.

[2] Mathematically inclined readers may wish to examine this equation in several special cases. First, if coefficients are constant then an analytic solution is possible. In this case, $\Delta[Cr]/\Delta t$ can be calculated precisely, and the difference between the measurable and the infinitessimal d[Cr]/dt can be estimated. Second, behaviors during an acute change in g (step, ramp and so on) display characteristic plots of d[Cr]/dt vs. [Cr]. Third, and perhaps most important, the effect of sequential acute changes in g (two steps) give characteristic behaviors in the plot.

STELLA

STELLA (High Performance Systems, Hanover NH) is the most intuitive modeling system used in surgical laboratories. The simple, graphical approach to defining relationships among elements in the modeling universe and carefully selected defaults invites even the novice to begin modeling within the first hour working with this package. Indeed, STELLA is used in secondary schools and college courses to introduce scientists and nonscientists to systems thinking.

The STELLA workspace is deceptively simple. It is never necessary to actually write an equation. Rather, the equations are "written" as the modeler defines flows among the elements of the model system. The specifications can take many forms including equations, numerical arrays and even hand-drawn curves. To set up the clinical problem in STELLA, we used this model

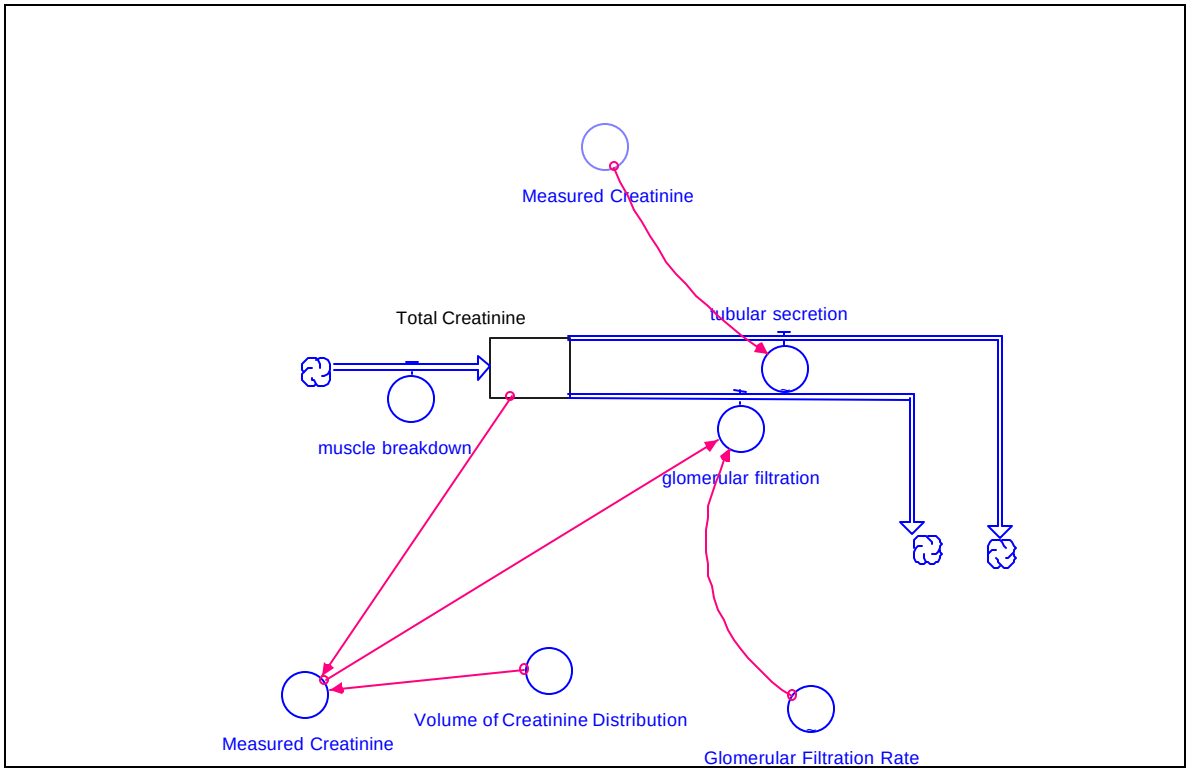

Figure 2. STELLA model of creatinine production and elimination. See text for further details.

The core of the picture is identical to Figure 1. Several variables have been added to the model so that flows can be more precisely specified. For example, glomerular filtration is the product of the glomerular filtration rate and the concentration of creatinine ("measured creatinine") in the plasma. This "measured creatinine" is the ratio of the total creatinine to the total volume of creatinine distribution. The process of tubular secretion is known to be both saturable by and dependent on the concentration of creatinine, so a "ghost" of the measured creatinine is inserted to influence the tubular secretion process.

Exploration of the model requires rational selection of starting parameter values. Knowledge of "starting" values comes from clinical experience or direct experimental measurement. We chose to begin with an archetypal 70 kg patient, a young man with normal renal function. We suggested that with a normal diet, exercise and muscle mass, he would deliver 1.6 gm (1600 mg) to the circulation each 24 hour day. About 60% of his body mass is water, so that the initial volume of distribution of this small molecule is about 42 liters (420 deciliters or dl). Since a normal creatinine concentration is about 1.0 mg/dl, we set the total creatinine to 420 mg. We set his initial glomerular filtration rate at 80 ml/min (1150 dl/day). We set his initial secretion rate at 150 mg/day. All of these values are normals retrievable from phsiology and medical textbooks.

Table 1. Model Parameters

Parameter	Initial Value	Comment
Body Mass	70 kg	archetype
Total Body Water	42 L = 420 dL	60% body mass; may wish to change to a variable in next iteration of the model
Total Body Creatinine	420 mg	1 mg/dl distributed in 420 dl
Creatinine Production Rate	1600 mg/day	typical for young male, normal diet
Glomerular Filtration Rate	80 ml/min = 1150 dl/day	Low-normal value
Creatinine Secretion Rate	150 mg day	Low-normal value

Second, we check to make sure that these normal values yield a stable profile over time. By definition, normal physiologic values should represent an equilibrium point.

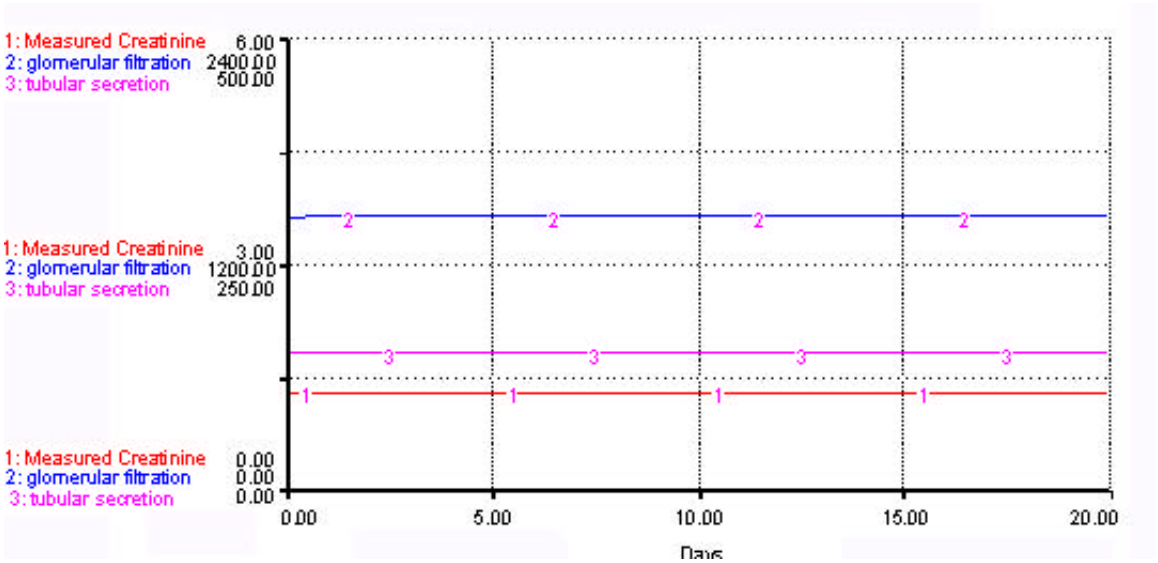

Figure 3 . Time plot of stable renal function. The red line shows a stable creatine concentration. The blue line shows a stable glomerular filtration. The purple line shows a stable tubular secretion. The scale shows that tubular secretion normally represents <20% of total creatinine clearance.

Since the creatinine is stable, a phase plot of its first derivative versus the creatinine concentration is just a point.

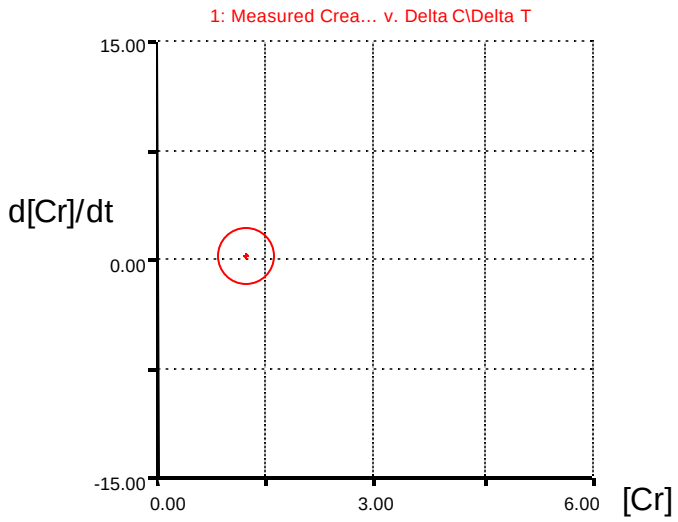

Figure 4 . The phase plot of the first derivative versus creatinine concentration is a single point. This is not only stable over time (d[Cr]/dt is zero) but also this is a true equilibrium point for this system. In a perfectly compensated physiologic system, creatinine does not change.

Consider the same patient with two modifications. First, the glomerular filtration rate changes with time

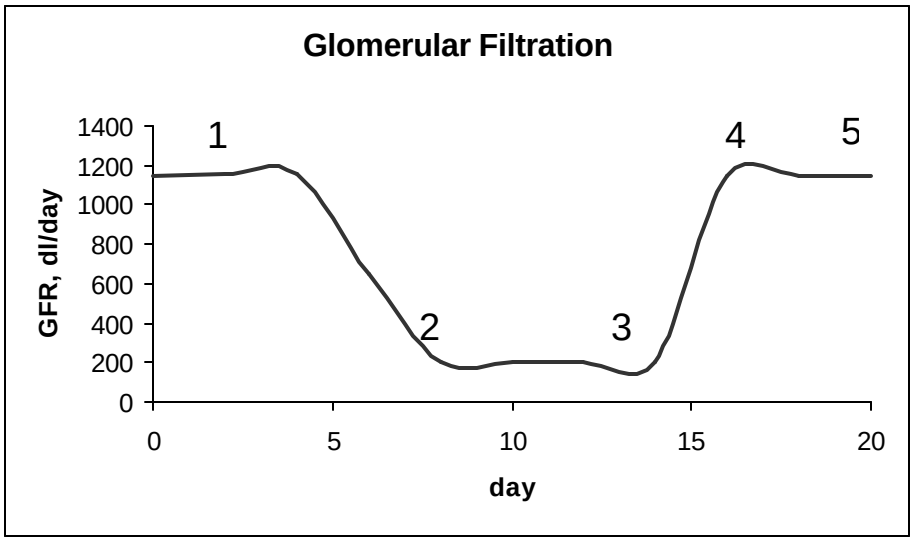

Figure 5. In this scenario, the patient receives a nephrotoxic drug for several days, after which the toxicity is recognized and the drug removed. Kidney function recovers spontaneously. Numbers on curve refer to regions of curve that will be inferred from Figure 8.

Second, the tubular secretion is a saturable process.

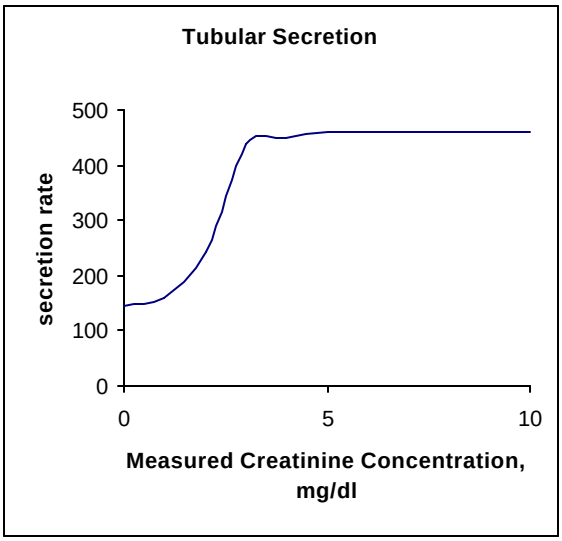

Figure 6 . Tubular secretion can partially compensate for the loss of glomerular filtration. The secretion process is here modeled as a saturable process, reaching saturation at about 3 mg/dl.

In this setting, the dynamics of creatinine concentration, glomerular filtration and tubular secretion change markedly over time.

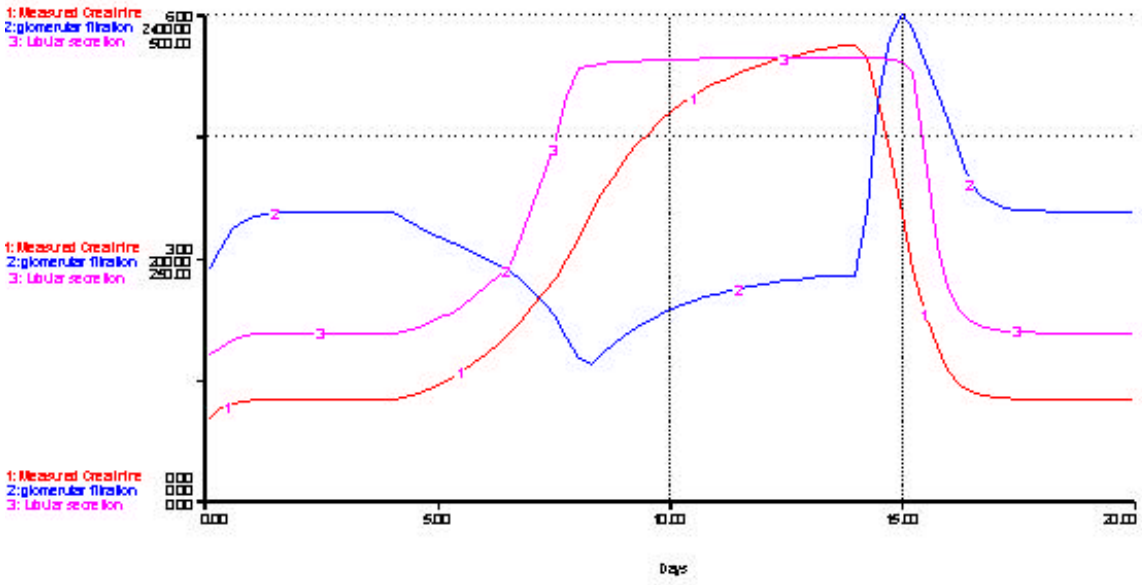

Figure 7. The temporal dynamics of renal failure and recovery. Compare the patterns of measured creatinine (red) glomerular filtration (blue) and tubular secretion (purple) at different times. Clinically, we measure line 1, creatinine. What we --and our patients!--are interested in, however, is line 2, glomerular filtration. The problem is that line 2 bears no obvious relation to line 1 except that both eventually reach a steady state. How can data from line 1 be used to infer information about line 2? **Examine Lines 1 and 2 carefully. Note that Line 2 is total glomerular filtration of creatinine, not glomerular filtration rate. Note the relationships among the slopes of the two lines at each point in time.**

Plotting measured creatinine, [Cr], against its first derivative d[Cr]/dt, a useful dynamic is seen.

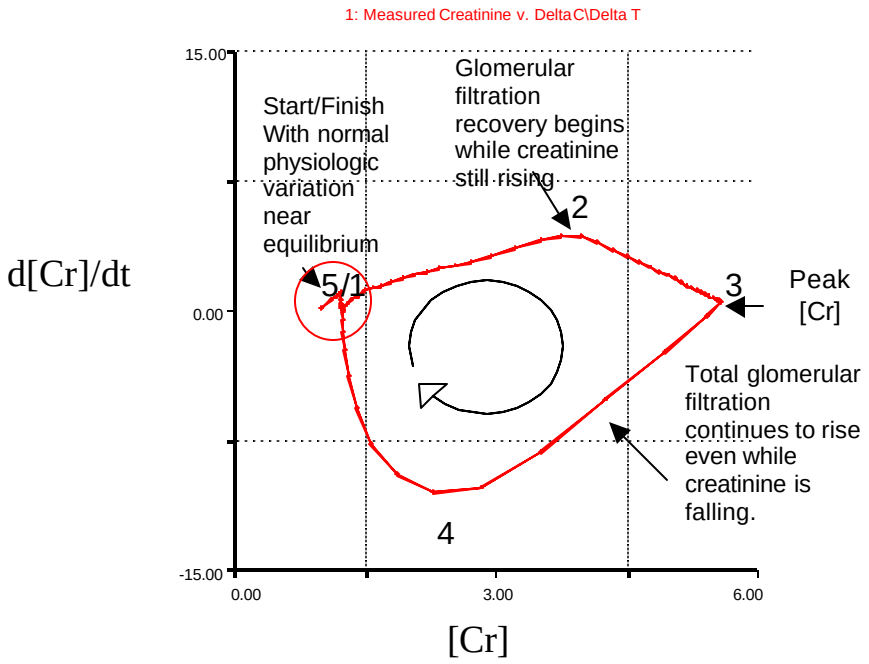

Figure 8 . The plot of d[Cr]/dt vs. [Cr] is a loop, returning to the baseline value of [Cr] with no change (a return to stable function). Inflections signal change in glomerular filtration performance. Compare with the previous figure and with figure 5.

This plot provides useful insight to the clinician. Given a "step change" (i.e. instantaneous) decrement in glomerular filtration rate followed by a spontaneous (and equally instantaneous) increment back to the GFR baseline, a dynamic plot of daily measurements of [Cr] versus time produces exponential curves. However, a dynamic plot of $\Delta[Cr]/\Delta t$ versus [Cr] provides direct insight not only into changing glomerular filtration but also into the likely peak value of [Cr] (as a zero-crossing). This result is easily tested against clinical data.

Clinically, one readily obtains $\Delta[Cr]/\Delta t$ and, of course, an average [Cr] value bracketing $\Delta[Cr]/\Delta t$. The “dynamic plot” will not be a continuous loop but

rather a collection of points. With sufficiently frequent creatinine determinations, the inflection at position 2 (in figures 5 and 8) can be discerned. It is an interesting exercise to specify various insults to the kidney (i.e. GFR manipulations) in the STELLA model (available at the textbook website) and observe the change in shape of the phase plot.

MATLAB/Simulink

MATLAB/Simulink is functionally similar to STELLA.

MATLAB (The MathWorks, Natick, MA) is an integrated technical computing environment that combines numeric computation, advanced graphics and visualization, and a high-level programming language. It is a widely-extensible system that can be used for diverse laboratory computing tasks including (but not limited to) signal acquisition, processing and analysis; experiment control; and modeling. At MATLAB's core is a robust, programmable computation engine. MATLAB's architecture promotes the use of tools that sit "on top" of MATLAB. One of these tools, Simulink, facilitates modeling, simulating, and analyzing dynamic systems.

A "conservation of mass" model analogous to that presented in Figure 2 looks like this when constructed in Simulink.

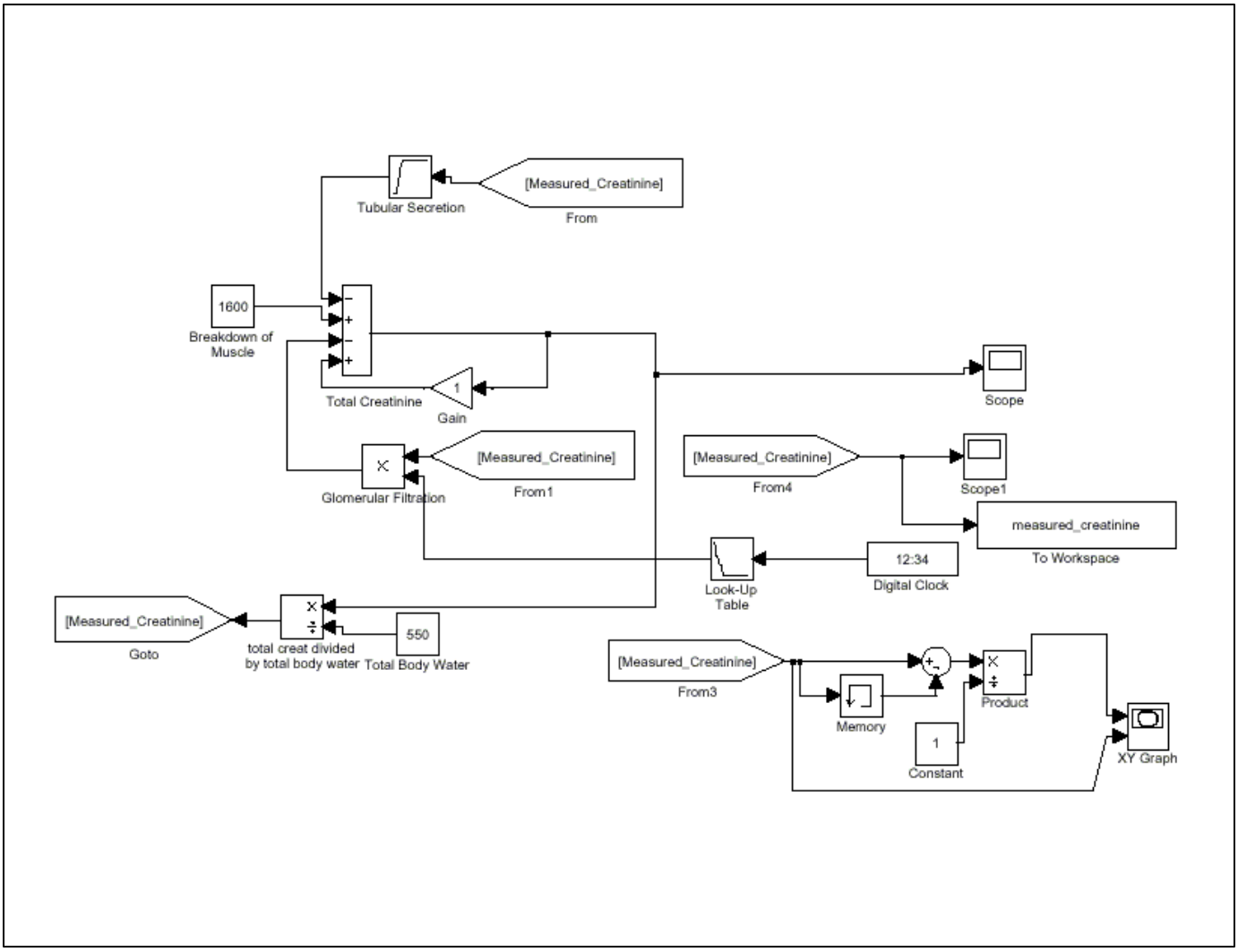

Figure 9. Simulink/MATLAB conservation-of- creatinine mass model for renal function. Compare with Figure 2.

The elements of the Simulink model do not precisely correspond to the the elements of the STELLA model although they are functionally similar. The reason for the absence of 1:1 correspondence is that Simulink is much more than a modeling environment. Options for data management and flow are more extensive and additional specifications are required.

The Simulink/MATLAB combination is highly recommended for surgeons and investigators who have some prior knowledge of the mathematics behind the modeling (e.g. ordinary differential equations, dynamic systems theory) and will take advantage of the powerful matrix approach embedded in MATLAB. The MATLAB environment is ideally suited for such problems as finite element modeling in which complex interactions among dozens of elements must be accounted for in each processing step.

Other Graphical Representations: Madonna

Although run-time and demonstration versions of STELLA and Simulink/MATLAB that run existing models are available at no cost, authoring versions of these programs that permit creation of new models may cost hundreds of dollars. An inexpensive but powerful alternative is Berkeley Madonna (Berkeley, CA). Madonna, that was originally designed as an engine to accelerate processing in STELLA, numerically solves ordinary differential equations. The latest release includes a simple graphic authoring interface that is less sophisticated but similar to STELLA. STELLA code can be executed in Madonna at quite breathtaking speeds, a feature that can be useful in complex STELLA models. A shareware download version of Madonna is available for user testing.

Computing Tools: Maple and Mathematica

Investigators who are fluent in differential equations are likely familiar with Maple (Waterloo Maple, Waterloo, Ontario, CANADA) and Mathematica (Wolfram Research, Champaign, IL), two advanced numerics packages that include powerful solvers. The absence of a graphical interface to modeling (which is a symbol-based method of writing the relevant equations) is offset by highly efficient computation. Investigators working at academic research universities may be able to obtain extremely inexpensive licenses for these packages through their libraries or information systems groups. However, effective use of these tools requires at least some background in modeling and a level of comfort with the relevant mathematics.

Purpose-Built Modeling Environments

Often the fastest way to develop a model is to adapt a model that has been previously developed by another investigator for a related application. Models are published in books, in journals and, increasingly, on the internet.

A particularly useful resource is the Society for Mathematical Biology that is an affiliation of scientists and mathematicians who model (and publish their models in the Society's journal, Bulletin of Mathematical Biology). Some models (see, for example, this general model of cardiac flow) are written in a general purpose modeling environment (STELLA).

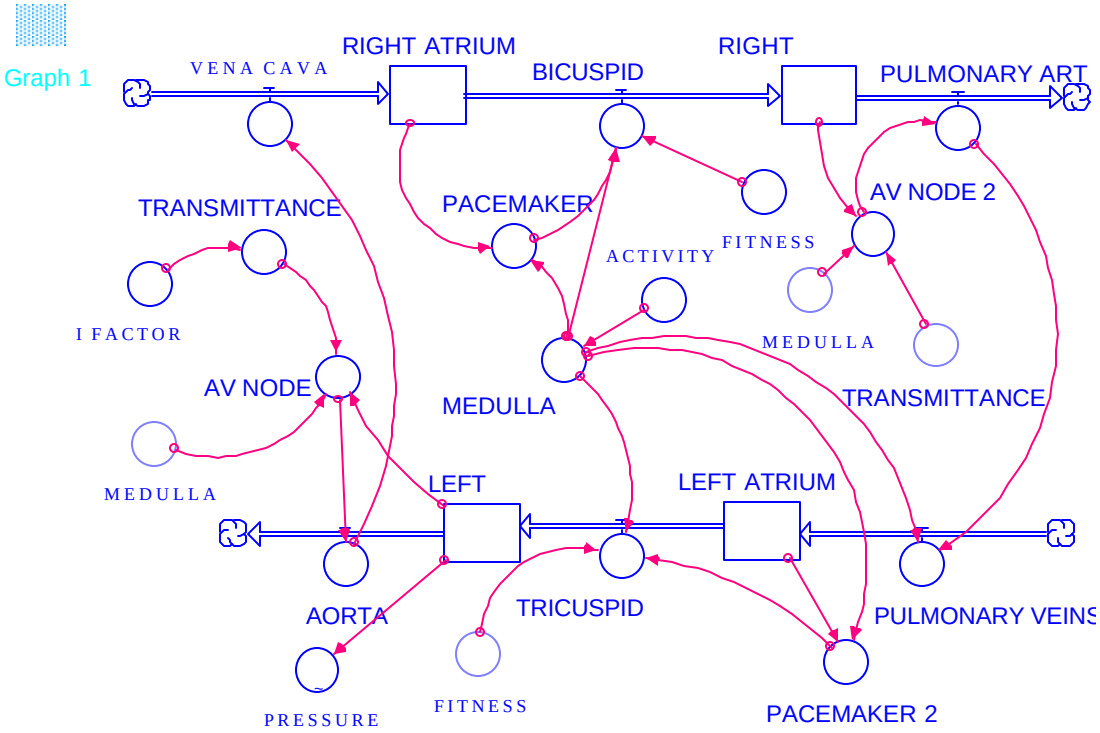

Figure 10 . STELLA model of cardiac flow. Reproduced, with permission, from Hannon B and Ruth M, Modeling dynamic biological systems. Springer-Verlag , New York, 1997, p. 119. Medula refers to brainstem regulation of the heart rate. Fitness refers to physical fitness and cardiac efficiency. Activity discriminates resting from active subjects. I Factor is an infarction factor. The model is reproduced at the website.

Some models are sufficiently complex that they are purpose-built to create a unique environment. For example, mathematical models of cell biology consist of tightly integrated functions describing molecules, subcellular organelles, and membranes defining compartments within the cells. A useful example of such a model is "The Virtual Cell" that is available free to users through a Java Applet interface to the National Resource for Cell Analysis and Modeling at the University of Connecticut.

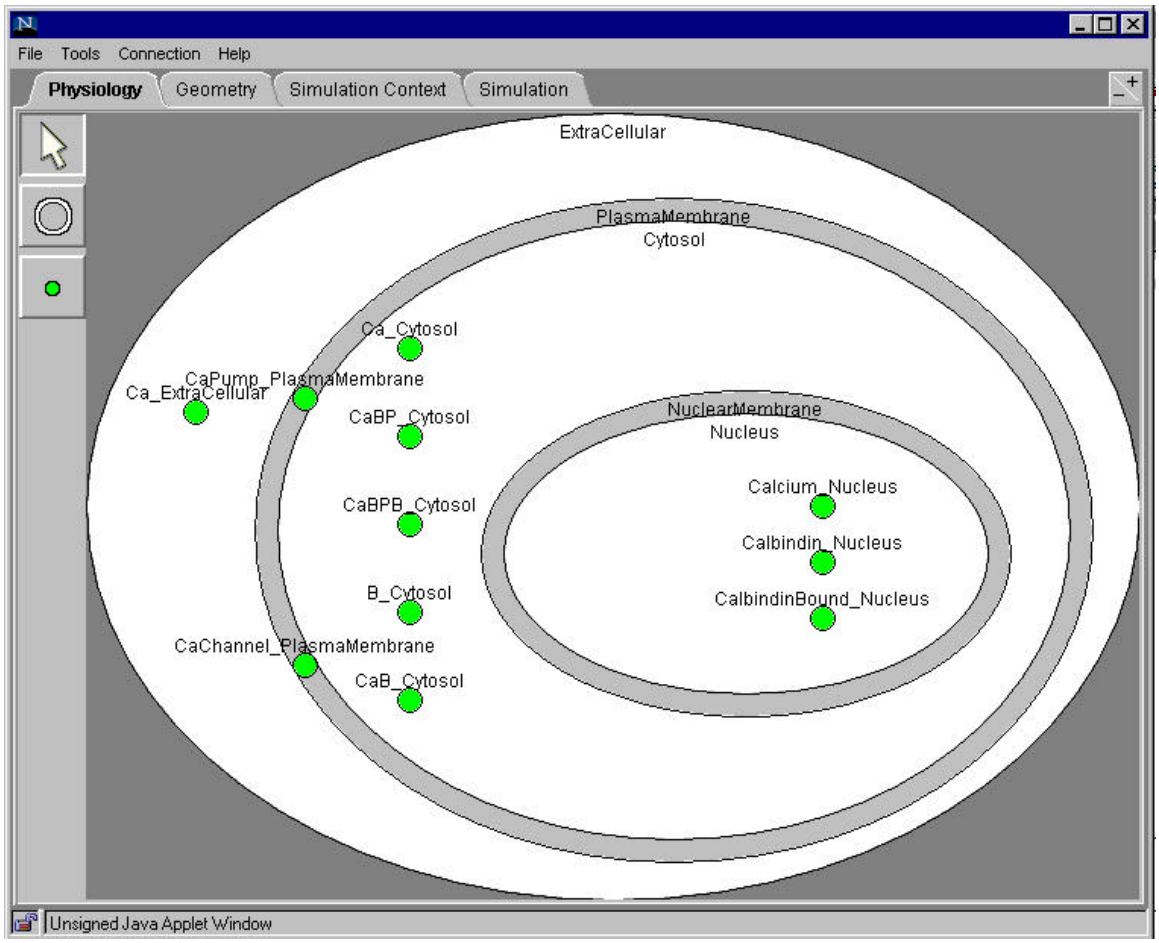

Figure 11. The biological interface to the current version of the Virtual Cell. This purpose-built modeling environment includes tools necessary to describe and test molecular flows within and across membrane-defined compartments. It is specially adapted to microscopic studies using molecular probes.

An alternative approach to the challenge of modeling a eukaryotic cell is embedded in the E-CELL project. The E-CELL project was launched in 1996 at Keio University (Japan) in order to model and simulate various cellular processes with the ultimate goal of simulating the cell as a whole. The first version of the E-CELL simulation system, that is a generic software package for cell modeling, was completed in 1997. The E-CELL system enables modeling not only of metabolic pathways but also of other higher-order cellular processes such as protein synthesis, signal transduction, and

membrane transport within the same framework. These various processes are then integrated into a single simulation model.

Using the E-CELL system, Tomita and colleagues have successfully constructed a virtual cell with 127 genes sufficient for ``self-support''. The gene set was selected from the genome of *Mycoplasma genitalium*, the organism having the smallest known genome. The set includes genes for transcription, translation, the glycolysis pathway for energy production, membrane transport, and the phospholipid biosynthesis pathway for membrane structure.

Tomita and colleagues are presently constructing the following E-CELL models: (1) human erythrocyte, (2) *E. coli* signal transduction for chemotaxis, (3) gene expression network in *E. coli* lactose operon, and (4) human mitochondria. The basic model of a human erythrocyte has been recently completed. All of the parameters, such as the kinetic constants, are based on experimental data available in published literature. With ample nutrition, this “virtual” erythrocyte reaches a steady state, and its metabolite concentrations in the steady state are comparable with those in real mammalian erythrocytes reported by laboratory experiments. *In silico* experiments on the erythrocyte model that artificially hinders specific enzymatic activities (e.g. hexokinase, G6PDH, phosphofructokinase, and pyruvate kinase) explain the associated anemias.

Since both the E-Cell and Virtual Cell models are accessible without cost over the internet, interested readers can explore and contrast them at their convenience. Both models assume that the user has some familiarity with kinetic theory. The models appear to be complementary.

Summary

Mathematical models can be profitably applied to diverse problems and projects in surgical research. The time invested in constructing and evaluating models pays handsome dividends through explicit hypothesis formulation and testing *in silico*. The results of mathematical models are routinely applied at the bedside. Similar application to routine problems encountered at the bench provides the investigator with insight into the magnitude of the problem and the experimental directions most likely to yield useful data.

Suggested Readings, References and URLs.

E-cell. www.e-cell.org

The E-cell website provides not only executable code but also detailed information about the E-cell project, user manuals and related tools. At the time of this writing, the downloadable binaries will run under the LINUX OS on Intel and Alpha processors using the RedHat 5.2 and 6.1 kernels. (The system will be able to run on Linux 6.2 after March 1, and a Windows release will occur in Fall, 2000.) The authors have indicated their intention to make the source code available. See the Tomita reference, below.

Edelstein-Keshet L. Mathematical models in biology. McGraw Hill, NY, 1988

An especially useful reference text for modeling novices. The clarity of the presentation is excellent and the review of relevant mathematics is done with elegant simplicity.

Hannon B and Ruth M. Modeling dynamic biological systems. Springer-Verlag, NY, 1997.

This text is based on a variety of STELLA models. The models presented range from the simple to the sophisticated, and several are relevant to physiologic processes. The prose is clear and easily understood even by rank amateur modelers.

Jelliffe RW and Jelliffe SM. A computer program for estimation of creatinine clearance from unstable serum creatinine levels, age sex and weight. Mathematical Biosciences 14:17-24, 1972

This classic paper is among the first to report a computational solution to a dynamic model of creatinine kinetics.

Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. Ann. Rev. Med. 39:465-490, 1988.

This is an easily digestible review of the relationship between serum creatinine and renal function. Readers who wish to further develop

the model presented in this chapter will wish to incorporate features discussed in this paper.

Madonna. http://www.berkeleymadonna.com/index.html

The Berkeley Madonna website includes the shareware download of the current version of this software. Links are included to hundreds of models. An authoring version can be purchased online.

Maple. http://www.maplesoft.com/

The Maple website contains useful information about the capabilities of this suite of symbolic and numerical solvers. Licenses for Maple are often available through university IS departments at nominal cost.

Mathematica. http://www.mathematica.com/

The Mathematica website is a rich source of information concerning this powerful suite. There is a substantial discount (over 90%) offered to students who are working in accredited programs towards a degree.

MATLAB/Simulink. http://www.mathworks.com/

The MATLAB website provides enormous help to the end-user through information, help files and forums. Although there is no direct download, the sales force is very responsive and will typically provide a time-limited trial to potential customers. The power of MATLAB/Simulink needs to be explored first-hand to appreciate its potential.

National Resource for Cell Analysis and Modeling.
http://www.nrcam.uchc.edu/

This website provides Java code and an interface to the purpose-built model of cell dynamics, the Virtual Cell. The general computational framework is unique and especially adaptable to microscopy in which molecular probes have been used to interrogate specific molecules and gradients.

Society for Mathematical Biology. http://www.smb.org

The Society for Mathematical Biology website contains numerous links to modeling resources as well as to an online (electronic) version of the Society's journal, the Bulletin of Mathematical Biology.

STELLA. http://www.hps-inc.com/

The STELLA website contains not only run-time versions of the STELLA software but also links to a variety of models that illustrate modeling concepts. The authoring version includes well-written documentation that is readily absorbed even by those with no prior modeling experience. The tutorials are fast and effectively illustrate the capability of the package.

Tomita M, Hashimoto K, Takahashi K, Shimizu TS, Matsuzaki Y, Miyoshi F, Saito K, Tanida S, Yugi K, Venter JC, Hutchison CA 3rd E-CELL: software environment for whole-cell simulation. Bioinformatics 15:72-84, 1999

This seminal paper describes the development and application of E-cell. It is a monument to modeling complexity and a testament to the power and potential of computational biology to address complex systems relevant to clinical care.