

Mathematics for Understanding Disease

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“Being able to predict things or to describe them, however accurately, is not at all the same thing as understanding them.”

David Deutsch¹

The application of mathematical models to reflect the organization and activity of biological systems can be viewed as a continuum of purpose. The far left of the continuum is solely the prediction of biological parameter values, wherein an understanding of the underlying biological processes is irrelevant to the purpose. At the far right of the continuum are mathematical models, the purposes of which are a precise understanding of those biological processes. No models in present use fall at either end of the continuum. Without question, however, the emphasis in regards to purpose has been on prediction, e.g., clinical trial simulation and empirical disease progression modeling. Clearly the model that ultimately incorporates a universal understanding of biological organization will also precisely predict biological events, giving the continuum the logical form of a tautology. Currently that goal lies at an immeasurable distance. Nonetheless, the motive here is to urge movement in the direction of that goal. The distance traveled toward understanding naturally depends upon the nature of the scientific question posed with respect to comprehending and/or predicting a particular disease process. A move toward mathematical models implies a move away from static empirical modeling and toward models that focus on systems biology, wherein modeling entails the systematic study of the complex pattern of organization inherent in biological systems.

There have been significant advances in the application of mathematics to biological systems, incorporating the nature of the disease and responses to therapeutic intervention.^{2–6} There are three major approaches in applying mathematical modeling to biological systems (**Figure 1**). The information from each of these approaches arise from essentially the same system, but the modeling concepts *per se* need not be, and usually are not, interchangeable. The approaches contribute

different levels of utility and understanding. Looking at **Figure 1** from the top down: Empirical modeling represents the tracing or measurement of disease progression, wherein observed responses represent an integral of the elements that comprise them. That is, this form of modeling is a composite of the underlying system along with indiscernible organizational elements. Transforms of information such as Poincare plots, delay plots, Fourier, fractal, and wavelet approaches represent an application of techniques to aid in signal extraction related primarily to observed variability and/or periodicity in the system (see definitions in the **Supplementary Data S1** online). These transforms can reveal key interconnections among system elements. Transformation, although not explicitly reflecting the true mechanistic underpinnings, makes the system tenable because some architecture is maintained. These can also allow for both the “normal” and “abnormal” states of the biological system to be probed. The third approach, fundamental biologic whole-system modeling, reveals the connected nature of the system and observes it in sufficient detail and under such conditions as to truly capture the nature of the changes within the system that are occurring over time. This level of observation is one that can potentially recreate all of the other observed levels, although it is also the most difficult to achieve.

Illustrated in **Figure 1** from the bottom up is the translational utility of the model categories to mathematical representation of the disease. The representation of biological systems involved in the disease state, incorporating the role of feedback regulatory loops in maintaining the homeodynamic (as opposed to homeostatic)⁴ system, provides significant insights into the disease. These models are intended to simulate alterations in one or more parameters of the disease model over the duration of observation. In addition, functions of multiple parameters can provide significant insight into the maintenance of the homeodynamics of the system. This is discussed in more detail later. Basic definitions are available in the **Supplementary Data S1** online. The transform area represents a family of approaches that apply mathematical transforms to obtain an output without necessarily incorporating the explicit interconnections of the underlying

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Received 9 January 2008; accepted 15 February 2008; advance online publication 26 March 2008. doi:10.1038/clpt.2008.53

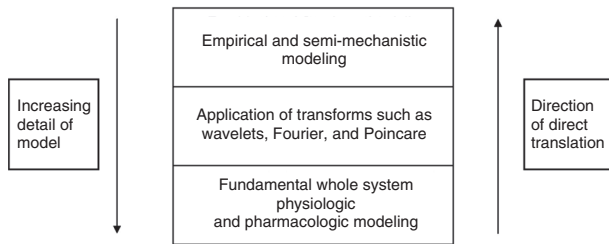


Figure 1 Three major categories of mathematical applications to understanding disease. The bottom, fundamental portion, has the greatest detail and closest operating characteristics to the disease, thus is the category that produces the most predictive models of the system. This is the level that is the ideal goal for understanding the system. As one goes up in the figure, the level of detail is reduced and the direct extraction of the mechanistic underpinnings is less directly defined. All of the higher levels can be created from lower levels, but the more detailed levels (i.e., lower levels) cannot be recreated with mathematical modeling at the higher levels. Thus, even though the same outputs or processes may be represented here, the mathematical modeling approaches at each of these levels is not fully interchangeable (i.e., mechanistic components interconnected vs. transforms revealing interconnections that may not be directly reflective of those changes).

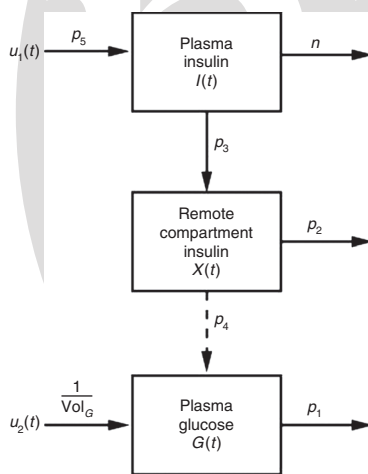


Figure 2 An illustration of the structure of the minimal model for glucose homeostasis of Bergman and Cobelli. There are two elements that simultaneously interact: insulin plasma concentrations $I(t)$ and the glucose plasma concentrations $G(t)$. The $X(t)$ term represents a function of insulin action that affects both insulin plasma concentration and glucose plasma concentration. Without the key feedback interconnections between responses, the model loses the ability to make clinical inferences on disease and risk of disease. S_G is the glucose response (p_1), S_I is the insulin sensitivity (the ratio p_3/p_2), p_2 is the insulin action parameter, p_4 is a link parameter from interstitial insulin to glucose regulation in plasma, and p_5 is a scalar for insulin input into the plasma. Volumes are typically normalized to allow comparisons across individuals. Insulin sensitivity in regulating insulin response is also modulated by the difference between the current insulin concentration and the basal insulin concentration. These components are composites of the individual parameter values in the schematic as they represent the uniquely identifiable elements. The model is shown using ordinary differential equations as follows:

$$\frac{dG(t)}{dt} = -[S_G + X(t)]G(t) + S_G G_b$$

$$\frac{dX(t)}{dt} = -p_2 \{X(t) - S_I [I(t) - I_b]\}$$

biology. This is particularly useful in oscillating, periodic, or aperiodic systems, wherein the most detailed level cannot be adequately defined. Often, the output of such a system is not readily tenable with respect to the impact of a particular intervention (i.e., introduction of a pharmacological agent) without evaluating these perturbations in the context of interconnected changes in signal frequency or location that reflect simultaneous and interdependent changes. These approaches do not, however, explicitly reflect the true underlying mechanistic interconnections. Nonetheless, they can be very helpful in understanding system stability and perturbations when the most detailed level of information is not available. By providing a unified framework, they can be useful in providing an understanding of both the “normal” and “abnormal” modes of system operation.^{2,7}

Empirical modeling^{5,6} represents a majority of the work over the past 15–20 years, relating the shape or trajectory of a disease over time to treatment interventions. These trajectories have been widely used in clinical trial simulation,^{5,6,8–11} utilizing a directly measured disease marker and comparing responses to active treatment, placebo, and no treatment. In addition, it has been posited as a rigorous method for detecting drug effect.^{5,6,8,11} At this level of observation, one has the ability to apply nonlinear mixed-effects approaches to preserve data structure and to provide a “baseline” of typical disease state progression. Superimposed on this is the change elicited by a particular intervention. This allows the analyst to discern how various effects change the trajectory of the disease. However, as emphasized earlier, the underlying mechanistic changes are frequently derived from positive and negative feedback loops, leading to nonlinearities that are “hidden” from view.

All approaches require well-designed experiments and measurements in order to be adequately informed and therefore useful. Specific experimental approaches⁹ can help to uncover the underlying nonlinearities. These methods consider important variables such as the timing and pattern of pharmacological stress input. The time the biological system takes to return to a baseline homeodynamic state after an intervention, i.e., how long it takes the system to return to the original state, is an important element that should be determined before moving forward with further experimental designs, although this is not always practically achievable. That is, if embedded nonlinearities are not uncovered with this type of approach, then further exploration is not necessary unless additional studies are designed for evaluating changes over time with different pathophysiological states. In addition, closely examined, intact-system experiments, such as those conducted by Bergman, Cobelli, and Guyton,^{12,13,14} are critically important to the understanding of the dynamics of a system that has interconnected feedback regulatory loops. Such an examination avoids choosing an isolated (static) target when, in fact, temporally inconstant counter-regulatory changes affect the emergence of either adverse drug reactions or significantly attenuated and unexpected responses.

Specific examples from each of these categories of observation or experimentation, as applied to disease state progression, are presented here.

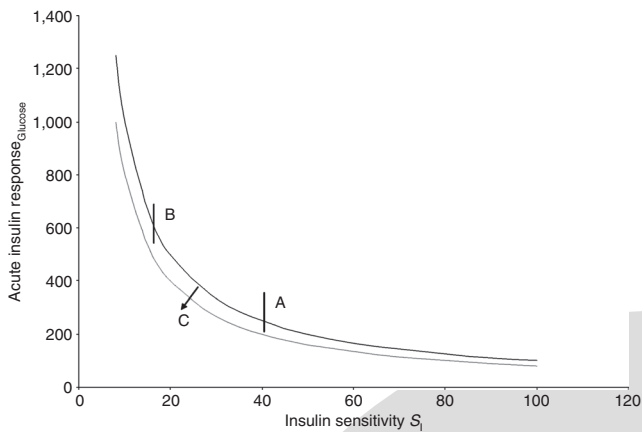


Figure 3 This graph shows the insulin sensitivity on the x-axis and the insulin response on the y-axis. The insulin sensitivity and response is estimated from the fitted parameters to the minimal model shown in [Figure 2](#). A healthy individual will have a constant product of these two parameters. Graphically, this is seen as a hyperbolic curve. Insight into disease is gleaned from the position on the hyperbolic curve. An individual may look clinically “normal” and yet have either insulin sensitivity or insulin response predominant in driving this normal appearing response. A shift along the curve may represent an increased risk for developing disease (e.g., from position A to position B). A shift off of the curve (i.e., from the upper curve to position C) represents a transition to disease. Interpretation of individual specific changes in these relationships is only possible using a mechanistically driven model.

CATEGORY 1: FUNDAMENTAL WHOLE-SYSTEM BIOLOGIC MODELING

A classic example is the minimal model for glucose and insulin regulation developed by Bergman with extensions by Cobelli.^{12,14} This is an example of capturing system-level behavior using the minimal model evaluation, although it included little pharmacological examination. The major strength of this approach is the preservation of the positive feedback loop to maintain a particular homeodynamic set point ([Figure 2](#)) between glucose and insulin. The model developed in this context provides the basis of examining true “changes” in disease. More specifically, the risk associated with change in disease status can be assessed by examining individual parameters of the disease model. The actual insight into the disease status is then arrived at using a mathematical combination of these parameters, reflecting the ability of the body to respond to a particular stimulus. Given that the goal of this system is to maintain a constant level of function through a combination of insulin release and insulin sensitivity, the product of insulin release and insulin sensitivity provides significant insights into the progression of the disease ([Figure 3](#)). These two elements are estimated parameters in the model that is informed using the appropriate system level (i.e., interconnections intact) experimental paradigm. In a healthy individual, this product should be constant, allowing the investigator to monitor changes with respect to the relative contributions of insulin release and sensitivity, based on the model system. If this product changes, it represents a shift to a diabetic state. Therefore, the model provides not only parameters but also specific interpretation that indicates risk and disease progression while preserving the inherent feedback in the system. The elements of this system are not floating

independent of one another but are coupled and constrained under the conditions that pertain to a healthy individual. This constraint represents maintaining a particular level of physiological functioning. The presence of disease or disease onset perturbs this level of physiological functioning. This approach has led to significant improvements in the understanding of the pathogenesis of diabetes (type 2) and is currently widely used.¹² In addition, it informs treatment strategy.

Others have attempted to extend this work by incorporating dynamic modeling of the glucose and insulin elements simultaneously.¹⁵ However, it is unclear whether maintaining a physiological set point is present as a constraint or, at least in the context of categorizing severity of disease, as potential interconnections affecting glucose and insulin disposition.

Another version of this approach used physiological feedback loops involved in regulating temperature, in relation to the pharmacological perturbation of the 5-HT_{1A} receptor.^{16,17} In this case, a small perturbation (i.e., low dose) of the system resulted in a prominent temperature oscillation, whereas a large perturbation (high dose) resulted in no apparent temperature oscillation, possibly because of an overdamping effect on the system. This is a hallmark of many feedback systems, because it is a hallmark of dynamical systems.² Full-system approaches have been applied to the cellular biology of cancer, human immunodeficiency virus, and calcium homeostasis as well, thereby throwing light on the complex interconnection of signals that may increase, decrease, or remain unchanged over the course of the observation after a perturbation to the system.^{18–20}

CATEGORY 2: THE APPLICATION OF TRANSFORMS WAVELETS, FOURIER, POINCARÉ, AND FRACTALS

The examination of heart rate variability (HRV) and its relationship with cardiac events is a critically important area of study. It was discovered that, if an individual has a significantly reduced HRV, as measured by the electrocardiogram R–R interval, the risk for a serious cardiac event increases dramatically.²¹ One can therefore presume that the Cardiac Arrhythmia Suppression Trial study’s goal of reducing ventricular ectopic depolarizations, and thereby reducing irregularities in cardiac function, may actually have increased patients’ risk for adverse cardiovascular events. This suggests that the nature of the oscillatory signals is important for maintaining regulatory feedback loops, although the HRV in and of itself does not explicitly indicate the mechanistic underpinnings that are creating this effect. That is, some of what is perceived as “noise” in the system is critically important to the response of the system. The capture of this variability with transforms allows its nature to be understood, conveyed more readily, and studied in the context of its effect on cardiac function that otherwise may have remained hidden.

An example of the utility of wavelets in understanding HRV^{22–24} is seen in a study examining the linkage between HRV and the administration of atropine. Traditional analysis of these raw data was unable to identify a specific relationship between HRV and atropine. Wavelet analysis, however,

demonstrated a time series interbeat-interval event which was a function of the cumulative power of the system and the atropine concentration.

CATEGORY 3: EMPIRICAL DISEASE PROGRESSION MODELING

There are multiple examples of empirical disease progression modeling, one of the first being the description of changes in Alzheimer's disease over time and, subsequently, the effect of the drug tacrine on changes in the disease.^{25–27} This approach identified that tacrine exerts a symptomatic effect on the disease. That is, as soon as the drug is discontinued, the patient returns to a level of functioning as though he/she had never taken the medication. It follows, therefore, that tacrine only extends the duration of a particular stage of the disease and does not impact the rate of change in the disease. Other diseases that have been modeled using this approach include diabetes,^{11,28} schizophrenia,¹⁰ and Parkinson's disease. The model of Parkinson's disease is an excellent example of the ability of this approach to distinguish a symptomatic effect from a protective or disease-modifying effect.^{29,30} Specifically, the effect of levodopa on Parkinson's disease progression was evaluated against the background of concerns that this treatment may be actually accelerating the progression of the disease. Clinical trial simulations using DATATOP (model development dataset) and ELLDOPA (model external validation dataset), however, demonstrated a beneficial, disease-slowing effect of levodopa.

Several investigators have also added more mechanistic underpinnings at this level, producing semimechanistic pharmacokinetic/pharmacodynamic descriptions in areas of study such as the electroencephalogram effects of opioids³¹ and HMG-coenzyme A response over time.³² A major concern is that models selected in a statistically driven manner (models selected using statistical criteria) and their level of utility must be appropriate to the question posed.

CONCLUSIONS

Predictive power can be achieved by the reductionist and inductive processes of empirical modeling. However, as stated in the introductory quotation by Deutsch, no amount of predictive power alone can imply understanding. Certainly, the application of mathematical modeling can provide significant insights into the nature of disease and the response of the disease to pharmacological intervention. But such insights require the implementation of systems biology models. The level of detail required is dictated by the nature of the question posed regarding the disease and, by extension, the level of knowledge required in order to sufficiently address the question. The level of utility of the model will naturally depend upon the extent to which this requirement is met.

Mathematical modeling efforts aimed at an integrated, mechanistic, and/or quantitative description of the current understanding of dynamic biological systems may hold advantages over more empirical models by allowing for: (i) the simultaneous modeling of multiple therapeutic interventions and multiple disease indications;^{12,13,19,20,33} (ii) greater insight into

the underlying system, as evidenced by other simultaneous system-based modeling applications;^{31,32} and (iii) a more reliable means of extrapolating beyond the observed data, a common requirement for supporting decision making during drug development.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/cpt>

CONFLICT OF INTEREST

The author declared no conflict of interest.

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1. Deutch, D. *The Fabric of Reality* (Penguin, New York, 1997).
2. Macheras, P. & Iliadis, A. *Modeling in Biopharmaceutics, Pharmacokinetics, and Pharmacodynamics: Homogeneous and Heterogeneous Approaches* (Springer, New York, 2006).
3. Riggs, D. *The Mathematical Approach to Physiological Problems* (Williams & Wilkins, Baltimore, 1963).
4. Bassingthwaite, J., Liebovitch, L. & West, B. *Fractal Physiology* (Oxford Univ. Press, New York, 1994).
5. Chan, P.L. & Holford, N.H. Drug treatment effects on disease progression. *Annu. Rev. Pharmacol. Toxicol.* **41**, 625–659 (2001).
6. Mould, D.R., Denman, N.G. & Duffull, S. Using disease progression models as a tool to detect drug effect. *Clin. Pharmacol. Ther.* **82**, 81–86 (2007).
7. Doukoumetzidis, A., Iliadis, A. & Macheras, P. Nonlinear dynamics in clinical pharmacology: the paradigm of cortisol secretion and suppression. *Br. J. Clin. Pharmacol.* **54**, 21–29 (2002).
8. Post, T., Freijer, J., DeJongh, J. & Danhof, M. Disease system analysis: basic disease progression models in degenerative disease. *Pharm. Res.* **22**, 1038–1049 (2005).
9. Kimko, H.C. & Duffull, S.B. *Simulation for Designing Clinical Trials: A Pharmacokinetic-pharmacodynamic Modeling Perspective (Drugs & the Pharmaceutical Sciences)* (Marcel Dekker, New York, 2002).
10. Kimko, H.C., Reece, S.S., Holford, N.H. & Peck, C.C. Prediction of the outcome of a phase 3 clinical trial of an antischizophrenic agent (quetiapine fumarate) by simulation with a population pharmacokinetic and pharmacodynamic model. *Clin. Pharmacol. Ther.* **68**, 568–577 (2000).
11. deWinter, W. *et al.* A mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin and gliclazide on disease processes underlying type 2 diabetes mellitus. *J. Pharmacokin. Pharmacodyn.* **33**, 313–343 (2006).
12. Bergman, R. Orchestration of glucose homeostasis: from a small acorn to the California oak. *Diabetes* **56**, 1–15 (2007).
13. Guyton, A.C. Blood pressure control—special role of the kidneys and body fluids. *Science* **252**, 1813–1816 (1991).
14. DallaMan, C., Rizza, R. & Cobelli, C. Meal simulation model of the glucose-insulin system. *IEEE Trans. Biomed. Eng.* **54**, 1740–1749 (2007).
15. Silber, H., Jauslin, P., Frey, N., Gieschke, R., Simonsson, U. & Karlsson, M.O. An integrated model for glucose and insulin regulation in healthy volunteers and Type 2 diabetic patients following intravenous glucose provocations. *J. Clin. Pharmacol.* **47**, 1159–1171 (2007).
16. Zuideveld, K.P. *et al.* A set-point model with oscillatory behavior predicts the time course of 8-OH-DPAT-induced hypothermia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **281**, R2059–R2071 (2001).
17. Zuideveld, K.P., van Gestel, A., Peletier, L.A., Van der Graaf, P.H. & Danhof, M. Pharmacokinetic-pharmacodynamic modelling of the hypothermic and corticosterone effects of the 5-HT_{1A} receptor agonist flesinoxan. *Eur. J. Pharmacol.* **445**, 43–54 (2002).
18. Kitano, H. Cancer as a robust system: implications for anticancer therapy. *Nat. Rev. Cancer* **4**, 227–235 (2004).
19. Peterson, M. & Riggs, M. Calcium Homeostasis and Bone Remodeling: Development of an Integrated Model for Evaluation and Simulation of Therapeutic Responses to Bone-Related Therapies (Annual meeting of the Population Approach Group Europe, Copenhagen, Denmark, 2007).
20. Perelson, A.S. *et al.* Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature* **387**, 188–191 (1997).
21. Goldberger, A. Fractal mechanisms in the electrophysiology of the heart. *IEEE Eng. Med. Biol.* **11**, 47–52 (1992).
22. Mager, D.E. & Abernethy, D.R. Use of wavelet and fast Fourier transforms in pharmacodynamics. *J. Pharmacol. Exp. Ther.* **321**, 423–430 (2007).
23. Mager, D.E. *et al.* Kullback-Leibler clustering of continuous wavelet transform measures of heart rate variability. *Biomed. Sci. Instrum.* **40**, 337–342 (2004).

24. Mager, D., Gronich, N., Gowan, K. & Abernethy, D. Pharmacodynamic model of atropine effects on heart rate variability using a wavelet based biomarker of vagal tone. *Clin. Pharmacol. Ther.* **570**(suppl.1), PII-68 (2007).
25. Holford, N.H. & Peace, K. The effect of tacrine and lecithin in Alzheimer's disease. A population pharmacodynamic analysis of five clinical trials. *Eur. J. Clin. Pharmacol.* **47**, 17–23 (1994).
26. Holford, N.H. & Peace, K.E. Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. *Proc. Natl. Acad. Sci. USA* **89**, 11471–11475 (1992).
27. Holford, N.H. & Peace, K.E. Methodologic aspects of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. *Proc. Natl. Acad. Sci. USA* **89**, 11466–11470 (1992).
28. Frey, N., Laveille, C., Paraire, M., Francillard, M., Holford, N.H. & Jochemsen, R. Population PKPD modelling of the long-term hypoglycaemic effect of gliclazide given as a once-a-day modified release (MR) formulation. *Br. J. Clin. Pharmacol.* **55**, 147–157 (2003).
29. Chan, P.L., Nutt, J.G. & Holford, N.H. Levodopa slows progression of Parkinson's disease: external validation by clinical trial simulation. *Pharm. Res.* **24**, 791–802 (2007).
30. Holford, N.H., Chan, P.L., Nutt, J.G., Kiebertz, K. & Shoulson, I. Disease progression and pharmacodynamics in Parkinson disease—evidence for functional protection with levodopa and other treatments. *J. Pharmacokin. Pharmacodyn.* **33**, 281–311 (2006).
31. Cox, E., Kerbusch, T., Van der Graaf, P. & Danhof, M. Pharmacokinetic-pharmacodynamic modeling of the electroencephalogram effect of synthetic opioids in the rat: correlation with the interaction at the mu-opioid receptor. *J. Pharmacol. Exp. Ther.* **284**, 1095–1103 (1998).
32. Mandema, J.W. et al. Model-based development of gemcabene, a new lipid-altering agent. *AAPS J.* **7**, E513–E522 (2005).
33. Perelson, A.S., Neumann, A.U., Markowitz, M., Leonard, J.M. & Ho, D.D. HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* **271**, 1582–1586 (1996).



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