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Chemical Reaction Kinetics: Mathematical Underpinnings

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Synopsis

Mathematical modeling and simulation of biochemical reaction networks facilitates our understanding of metabolic and signaling processes. For closed, well-mixed reaction systems, it is straightforward to derive kinetic equations that govern the concentrations of the reactants and products. The usual way of deriving kinetic equations involves application of the principle of conservation of mass in conjunction with the law of mass action. Here, examples of kinetic models for several basic processes are discussed.

Introduction

A century has passed since Michaelis and Menten described a mechanism for enzyme- mediated conversion of a substrate into a product. The kinetics of such biochemical reaction processes can be analyzed mathematically and simulated on computers, usually by appealing to the law of mass action. Kinetic models are typically presented as systems of differential equations (DEs) or continuous time Markov chains ("► Mathematical Models in the Sciences"). There are advantages to both types of models, but in what follows, the former are developed because the equations are (i) easy to write down by applying the law of mass action and (ii) deterministic in the sense that the kinetic parameters and initial state of the reaction system completely determine the future states.

Conservation of Mass

At the most basic level, models of chemical reaction kinetics boil down to invoking the principle of conservation of mass. Suppose that the mass of a particular chemical species varies over the course of a reaction, and let $M(t)$ denote the mass of the species at time t. A short time Δt later, the mass will be

$$M(t+\Delta t) = M(t) + \text{mass influx} - \text{mass efflux},$$

where the influx and efflux are measured over the time interval from t to $t + \Delta t$. Let $\phi_{\text{in}}(t)$ and $\phi_{\text{out}}(t)$ denote the instantaneous mass influx and efflux (in mass per unit time) at time t. Then because Δt is assumed to be small, the total mass influx and efflux over the aforementioned time interval are approximately $\phi_{\text{in}}(t)\Delta t$ and $\phi_{\text{out}}(t)\Delta t$, respectively. Inserting these approximations into the above conservation equation yields

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$$\frac{M(t+\Delta t)-M(t)}{\Delta t} \approx \phi_{\text{in}}(t) - \phi_{\text{out}}(t)$$

which in the limit as $\Delta t \to 0$ gives an exact description for the rate of change of the mass:

$$\frac{dM}{dt} = \phi_{\text{in}} - \phi_{\text{out}}. \tag{1}$$

In words, this DE states that the rate of change of the mass is equal to the difference between the mass influx and the mass efflux.

Closed, Well-Mixed Systems

Experimental data from chemical reactions tends to involve concentrations (mass per unit volume) as opposed to mass alone, and therefore, it is helpful to scale the above DE by dividing by volume. Consider, for example, a simple, reversible system $A \rightleftharpoons B$ of constant volume V. Assume that the system is *closed* in that there is no flux of A nor B into or out of the system and that the system is *well mixed* in the sense that the concentrations of A and B do not vary spatially within the reaction vessel. Letting $[A]$ and $[B]$ denote concentrations, the total masses of the two species are $[A]V$ and $[B]V$, respectively. If ϕ_{AB} and ϕ_{BA} denote the mass fluxes associated with transitions from A to B and from B to A, respectively, then the conservation of mass equation implies that

$$V\frac{d[A]}{dt} = \phi_{BA} - \phi_{AB} \quad \text{and} \quad V\frac{d[B]}{dt} = \phi_{AB} - \phi_{BA}\,. \tag{2}$$

The quantities on both sides of the DEs in Eq. 2 have units of mass/time. Notice that adding the two DEs in Eq. 2 yields a single DE that describes the total mass of A and B:

$$V\frac{d}{dt}([A]+[B]) = 0,$$

which implies that the total mass $V([A] + [B])$ is constant and reaffirms that mass is conserved.

Dividing Eq. 2 by the volume V leads to DEs that govern the concentrations of the two species:

$$\frac{d[A]}{dt} = J_{\text{BA}} - J_{\text{AB}} \quad \text{and} \quad \frac{d[B]}{dt} = J_{\text{AB}} - J_{\text{BA}}, \tag{3}$$

where the chemical fluxes (or concentration fluxes) are defined by dividing the mass fluxes by the total volume; i.e., $J_{\text{AB}} = \phi_{AB}/V$ and $J_{\text{BA}} = \phi_{BA}/V$. The quantities on both sides of the DEs in Eq. 3 have units of concentration/time.

The primary challenge in the quantitative study of chemical kinetics is to mathematically model fluxes such as J_{AB} and J_{BA} in the above example. The most common approach towards doing so is to invoke the *law of mass action*, which is now developed. One must be mindful that the use of the word *law* is overpromising, but it is reassuring that the law of mass action serves as an excellent approximation for the dynamics of certain elementary reaction processes.

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Mass Action Kinetics Through Examples

Rather than stating the law of mass action in full generality, here it is explored via a collection of progressively more substantive examples.

Example 1 Recall the simple, reversible reaction $A \rightleftharpoons B$ described above. Assume that during the conversion of A to B, molecules of A do not interact with one another chemically and vice versa for the reverse reaction $B \rightarrow A$. In this case, the law of mass action states that the chemical fluxes J_{AB} and J_{BA} are proportional to the concentrations $[A]$ and $[B]$, respectively. That is, there exist constants k_+ and k_- such that

$$J_{\mathrm{AB}} = k_+[A] \quad \text{and} \quad J_{\mathrm{BA}} = k_-[B]\,.$$

These relationships are reasonably intuitive in this case: given a small time window, each molecule of A has some probability of converting to a molecule of B, suggesting that doubling the concentration of $[A]$ ought to double the flux J_{AB} (and similarly for the conversion of B to A). The constants k_+ and k_- are called *kinetic constants* or *rate constants* for this reaction, and in this example, they have units of $(\text{time})^{-1}$. The larger the value of a rate constant, the faster the associated reaction proceeds. There is a standard notational convention of writing rate constants above or below the arrows associated with each process in the reaction diagram; e.g.,

$$A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B$$

for the present example.

Armed with the mass action assumptions above, the DEs Eq. 3 take the form

$$\frac{d[A]}{dt} = k_-[B] - k_+[A] \qquad \frac{d[B]}{dt} = k_+[A] - k_-[B]\,. \tag{4}$$

If the rate constants k_+ and k_- are measured from experimental data (see also the conclusion of Example 2 below) and the initial concentrations of A and B are known, then it is possible to solve the DEs on a computer to obtain plots of [A] and [B] versus time. As an illustration, Fig. 1 shows the

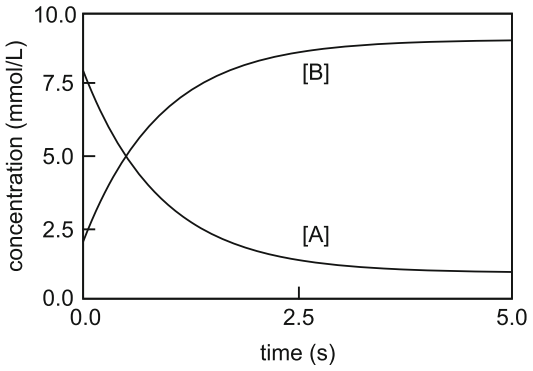

Fig. 1 Concentrations [A] and [B] as functions of time for the simple, reversible process in Example 1, using the initial conditions and rate constants mentioned in the text

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solution of Eq. 4 assuming that the initial concentrations of [A] and [B] are 8 mmol/L and 2 mmol/L, respectively, and that the forward and reverse rate constants are $k_+ = 1.0\ s^{-1}$ and $k_- = 0.1\ s^{-1}$

Because of the simplicity of this chemical process and the fact that there are no complicated interactions involved, the system of DEs in Eq. 4 can actually be solved *exactly*, meaning that it is possible to derive precise mathematical formulas for [A] and [B] as functions of time without resorting to computer approximations and/or simulations. For the particular parameter choices and initial conditions listed above, concentrations as a function of time are given by

$$[A] = \frac{2}{11}\left(39e^{-1.1t} + 5\right) \quad \text{and} \quad [B] = \frac{2}{11}\left(50 - 39e^{-1.1t}\right),$$

both of which are graphed in Fig. 1. The luxury of exact solutions is not to be expected in practice, as illustrated in the third example.

Example 2 For elementary reactions of the form $A + B \rightarrow C$ in which two reactants must interact to form a product, the law of mass action states that the rate of change of the product concentration [C] is proportional to the (mathematical) *product* of the individual reactants. Mathematically, the rate of change of [C] is equal to k[A][B] where k is some rate constant. (Schematically, one writes this as $A + B \xrightarrow{k} C$.) The basis for this more advanced application of the law of mass action relies upon rather sophisticated statistical mechanics, but here is the intuition. Suppose that molecules of A and B both move randomly in a closed, well-mixed system of constant volume. Then doubling either [A] or [B] should roughly double the probability that a molecule of A collides with a molecule of B, combining to form the product C.

With the preceding paragraph in mind, consider an autocatalytic process in which a species promotes its own production; schematically,

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B + B.$$

Further suppose that $[A]$ is held constant throughout this process; e.g., a huge abundance of A makes its depletion negligible during the reaction. Applying the law of mass action, the DE governing $[B]$ is

$$\frac{d[B]}{dt} = k_+[A]\,[B] - k_-[B]^2 \tag{5}$$

where, for emphasis, $[A]$ is regarded as constant by assumption. It is important to pause and take inventory of the physical units of the quantities in Eq. 5. The left-hand side of the equation has units of concentration/time. Thus, in order for the DE to be dimensionally consistent, both k_+ and k_- must have units of $(\text{concentration})^{-1}(\text{time})^{-1}$.

Dropping the brackets and capital letters for notational convenience, the DE $db/dt = k_+ab - k_-b^2$ happens to be exactly solvable. It is an example of a separable DE and, for readers familiar with the technique of separation of variables, one may manipulate the DE algebraically to obtain

$$\frac{1}{k_+ab - k_-b^2}\frac{db}{dt} = 1$$

and subsequently integrate both sides with respect to t, yielding

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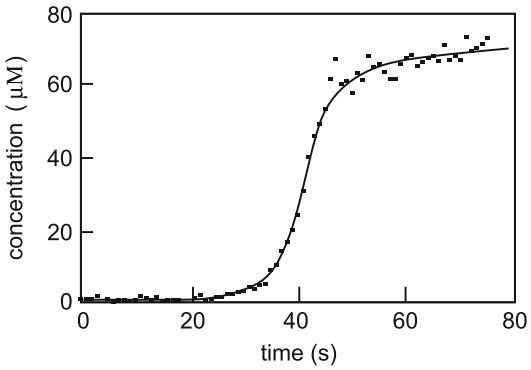

Fig. 2 Fitting a sigmoidal function of the form Eq. 6 to an actual data set from an autocatalytic process similar to the one described in Example 2

$$\int \frac{1}{k_+ ab - k_- b^2}\, db = \int 1 \;\; dt.$$

Provided that the denominator in the integral on the left-hand side is nonzero (see also the section on Equilibria below), that integral can be evaluated using a partial fraction decomposition of the integrand, ultimately allowing one to solve for b as a function of t. The solution of Eq. 5 is

$$b(t) = \frac{Cak_+ e^{ak_+ t}}{1 + Ck_- e^{ak_+ t}}, \tag{6}$$

where

$$C = \frac{b_0}{ak_+ - b_0 k_-}$$

is a constant whose value depends on the initial concentration b_0, the rate constants, and the concentration of A. If the derivation of formula Eq. 6 seems mysterious, fear not. Remember that it is rarely possible or necessary to find an exact mathematical formula for the solution of a DE, so this example is atypical in that regard. For practical purposes, computer simulations can provide approximate solutions of DEs, often with a level of precision that the user is able to specify.

Still, the rare fortune of having an exact formula Eq. 6 is worth exploiting, as it suggests what type of functions might be suited for fitting experimental data. Figure 2 shows a least squares regression fit ("► The Mathematics of Fitting Scientific Data") of a function of the form Eq. 6 to experimental data from an autocatalytic process similar to the one described in this example. Importantly, performing a regression fit produces estimates for the kinetic constants k_+ and k_-.

Example 3 Here is an example that goes beyond the two previous ones: using the law of mass action to develop the well-known Michaelis-Menten model for enzyme (E)-mediated conversion of a substrate (S) into a product (P) via an intermediate substrate-enzyme complex (C). The reaction diagram for that process is given by

$$S + E \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C \xrightarrow{k_2} P + E.$$

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The free substrate S and enzyme E are converted to a substrate-enzyme complex C with rate constant k_+. Molecules of the complex C may either revert back to S and E (with rate constant k_-) or produce P and E (with rate constant k_2). There are four different concentrations to track (S, E, C, and P), each of which will be treated as a dependent variable and each of which will contribute a DE to the kinetic model. The full set of Michaelis-Menten equations reads

$$\begin{aligned} \frac{dS}{dt} &= k_- C - k_+ SE \\ \frac{dE}{dt} &= k_- C - k_+ SE + k_2 C \\ \frac{dC}{dt} &= k_+ SE - k_- C - k_2 C \\ \frac{dP}{dt} &= k_2 C, \end{aligned} \tag{7}$$

where, once again, brackets have been suppressed when writing concentrations. The system Eq. 7 may seem a bit daunting in comparison with the single DE in the autocatalysis example. The four DEs in Eq. 7 are *coupled* in the sense that changing one concentration may influence multiple equations, which is somewhat intuitive through examining the reaction diagram. After all, if the concentration of the substrate-enzyme complex C were suddenly doubled, then the reaction diagram suggests that the rates of change of all four concentrations would be affected. That same conclusion could be drawn by observing that the variable C appears on the right-hand side of all four DEs in Eq. 7.

Despite the interdependencies among these four variables, the system Eq. 7 is not nearly as bad as it may first appear. Notice that the right-hand sides of the DEs for dE/dt and dC/dt sum to 0, implying that $E + C$ must remain constant during this reaction. From a chemistry standpoint, this makes perfect sense: the total amount of free enzyme and bound enzyme remains constant for this closed system. If E_{tot}, a constant, represents the total amount of enzyme, then the variable E can be eliminated from all of the equations above since $E = E_{\text{tot}} - C$. This effectively reduces the model to three different variables: S, C, and P. In fact, one further reduction is possible: The equations for dS/dt and dC/dt are not influenced by P. Therefore, if that subsystem of just two DEs were solved yielding formulas for S and C, then a formula for P can be obtained immediately. Specifically, once C is determined as a function of time t, that function can be substituted into the right-hand side of the dP/dt equation which can then be integrated to find P.

The reduction of a system of four DEs to a somewhat less menacing set of two DEs represents a victory, albeit a partial one. The reduced system is still too complicated to solve by hand, and ultimately one must resort to computer simulations to plot approximate solutions. Figure 3 shows the solution of Eq. 7 for the specific parameter choices $k_+ = 10.0\ \text{mM}^{-1}\ \text{s}^{-1}$, $k_- = 1.0\ \text{s}^{-1}$, and $k_2 = 1.0\ \text{s}^{-1}$ and with initial conditions $S(0) = 1.0$ mM, $E(0) = 0.1$ mM, $C\ (0) = 0.0$ mM, and $P\ (0) = 0.0$ mM.

Equilibria and Qualitative Analysis

The Michaelis-Menten Eq. 7 highlighted the primary limitation of pen-and-paper mathematical analyses of chemical kinetics: when a model contains complex, nonlinear actions between

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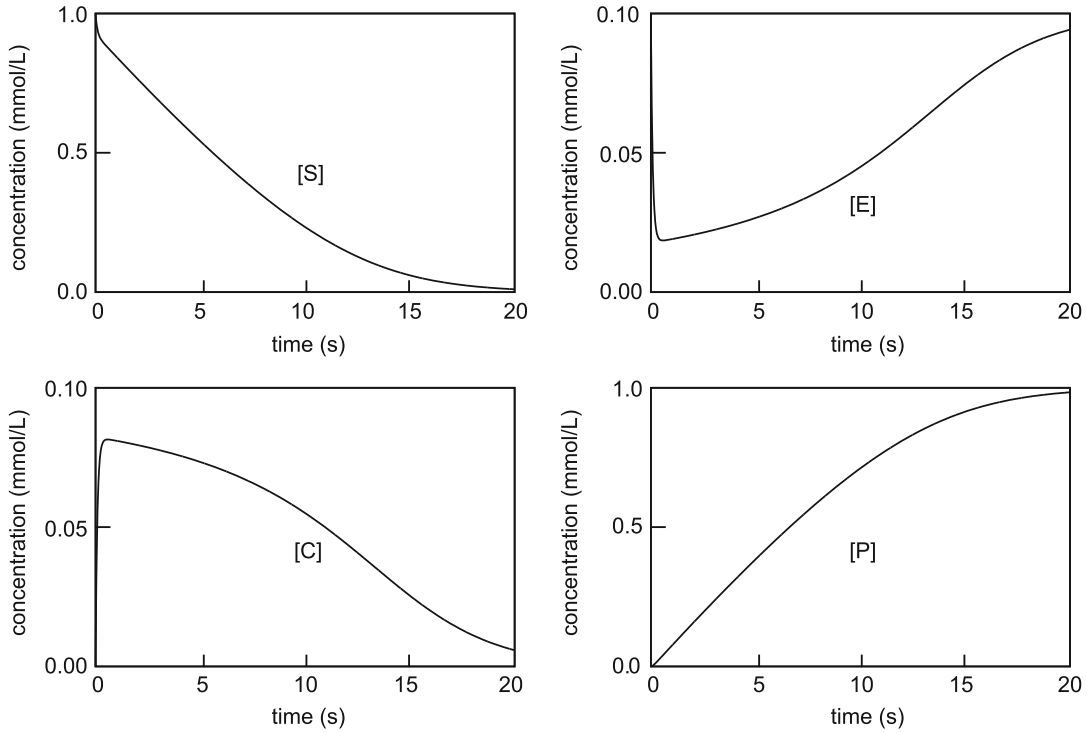

Fig. 3 Solutions of the Michaelis-Menten Eq. 7 for the particular parameter set given in the text

dependent variables which are interdependent on one another, finding exact formulas for all of those variables is an intractable problem. In order for those models to provide useful quantitative predictions, one would need to use a computer to approximate the behaviors of all of the variables. On the other hand, it may still be possible to extract powerful qualitative information from model equations without actually attempting to solve the equations. For example, it is often possible to determine how/whether a particular reaction will achieve chemical equilibrium, a steady state in which each concentration approaches some constant in the long run (see "► Equilibria and Bifurcations in the Molecular Biosciences" for details).

Recall the DE model Eq. 5 for an autocatalytic process: $db/dt = k_+ab - k_- b^2$, where k_+ and k_- are (positive) kinetic constants and a represents a (positive constant) concentration of an abundant reactant. Identifying the equilibrium states of this process amounts to finding specific values of the dependent variable b for which $db/dt = 0$; i.e., so that the concentration b will not change. The trivial possibility $b = 0$ represents an equilibrium that is not terribly interesting from a chemistry standpoint. By algebra, there is another possibility:

$$b = b_{\text{eq}} = \left(\frac{k_+}{k_-}\right)a \tag{8}$$

is a nontrivial equilibrium value for this process. The appearance of the ratio of forward and reverse rate constants is certainly plausible here – if the forward reaction is much faster than the reverse reaction, then it makes sense that b_{eq} should be larger.

In some sense, Eq. 8 gives the more "natural" or "chemically relevant" equilibrium of Eq. 5. To clarify this remark, it helps to factor the right-hand side of the autocatalysis DE, yielding

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$$\frac{db}{dt} = b(k_+ a - k_- b).$$

Bearing in mind that a, k_+, and k_- are positive constants, suppose that the initial concentration of b is *near* but not equal to the trivial equilibrium $b = 0$. More exactly, suppose that b is positive but smaller than b_{eq}, and examine the two factors of the right-hand side of the DE. Both of the factors are positive based upon our assumption that $0 < b < b_{eq}$, which means that $db/dt > 0$. Because the rate of change of b is positive, b would have to *increase* away from the trivial equilibrium 0 and towards the nontrivial one b_{eq}. Likewise, if the concentration b was ever larger than b_{eq}, then the two factors on the right-hand side of the DE have an opposite sign, implying that $db/dt < 0$. Hence, b would then decrease and gradually relax back to b_{eq}. In this example, $b = 0$ is an example of a (mathematically) *unstable* equilibrium. If the initial condition $b(0)$ is near, but not at, zero concentration of b, then one expects the system to evolve to a state far from the $b = 0$ equilibrium. By contrast, the equilibrium $b = b_{eq}$ is an example of a *stable, attracting* equilibrium: starting from any initial concentration that is sufficiently close to b_{eq}, one expects b to approach b_{eq} in the long run (steady state).

Notice that in the previous paragraph, there was no attempt to solve the autocatalysis DE, and yet valuable qualitative information was extracted: a characterization of the long-term steady-state dynamics of the system for every possible initial condition. Such qualitative analysis can be extended to "higher-dimensional" systems (i.e., more dependent variables) like the Michaelis-Menten Eq. 7; for details, see Chapter 6 of Strogatz (1994). Mathematically, what should it mean to have an equilibrium of Eq. 7? In order for that system to be in chemical equilibrium, none of the four concentrations S, E, C, and P can change over time, meaning that all four of the derivatives in Eq. 7 must *simultaneously* be zero. To seek equilibria, begin by focusing on the last of the four DEs in Eq. 7: $dP/dt = k_2 C$. Since k_2 is a positive constant, it must be the case that $C = 0$ in order to achieve $dP/dt = 0$. Substituting $C = 0$ into the right-hand sides of the other three DEs, the only remaining terms all contain the (mathematical) product SE. Apparently, the system would be in equilibrium if *one* of the concentrations S or E was zero, the other being completely arbitrary. This would seem to suggest that there are infinitely many equilibria, but there is a lesson here: when working with mathematical models in chemistry or any other field, do not lose sight of reality. Would it make sense for this system to have infinitely many equilibrium states to choose from? Recall that E_{tot}, the total amount of the enzyme in the free or bound state, is conserved, and $E + C = E_{tot}$. Since C must be 0 when equilibrium is achieved, it follows that $E = E_{tot}$ at steady state, which in turn forces $S = 0$. Finally, what will be the steady-state (a stable equilibrium in this case) value of the product concentration P ? As a step towards answering this, observe that there is another conserved quantity lurking in the original system of four DEs: the expressions for dS/dt, dC/dt, and dP/dt sum to zero. This implies that the quantity $S + C + P$ remains constant (call it τ) during this enzymatic process. Because both S and C approach zero at steady state, it follows that P must approach τ.

The above was a purely heuristic argument that the closed, well-mixed Michaelis-Menten system should approach the stable, attracting equilibria $S = 0$, $E = E_{tot}$, $C = 0$, and $P = \tau$ in the long run. There are standard mathematical techniques (Strogatz 1994) for rigorously analyzing the stability of equilibria of systems of DEs such as this one.

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Discussion and Further Reading

The law of mass action offers a very systematic process for writing down DE-based chemical kinetic models, but the last example is a step towards understanding the challenges and roadblocks of the modeling process. Solving a system of DEs on a computer usually requires the user to provide (i) initial conditions for each dependent variable (concentration) and (ii) values for each parameter (kinetic constant). Biochemical reaction networks can easily have hundreds of parameters, most of which would be difficult, costly, or impossible to measure experimentally. It helps that, in many cases, values of individual rate constants may be less important than ratios of rate constants in terms of influencing dynamical behavior. Also, when rate constants have different orders of magnitude, it may happen that some processes are *much* faster than others. The plots of $[E]$ and $[C]$ in Fig. 3 illustrate this concept – after the rapid adjustment near $t = 0$, both concentrations evolve over a much slower time scale. This phenomenon is a consequence of the order-of-magnitude difference between k_+ and the other two rate constants, and the complexity of the model can be reduced by approximating the rapid initial transient as being instantaneous.

Readers interested in more advanced mathematical modeling techniques may wish to read about asymptotic methods, principal components analysis, sensitivity analysis, and scaling and non-dimensionalization, as a means for reducing the number of parameters in a model. For a mathematical reference on chemical kinetics see, for example, Beard and Qian (2008), and for general references on mathematical models in biology, biochemistry, and biomedicine, see Keener and Sneyd (2009), Murray (2002/2003), or Plonsey and Barr (2000).

Cross-References

- ► Equilibria and Bifurcations in the Molecular Biosciences
- ► Mathematical Models in the Sciences
- ► The Mathematics of Fitting Scientific Data

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