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# Dynamic modeling of biochemical reactions with application to signal transduction: principles and tools using *Mathematica*☆

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**Abstract**

Modeling of biochemical phenomena is based on formal reaction kinetics. This requires the translation of the original reaction systems into sets of differential equations expressing the effects of the various reaction steps. The temporal behavior of the system is obtained by solving the differential equations. We present the main concepts on which the formal approach of these two problems is based and we show how the amount of work needed to treat them can be significantly reduced by using a mathematical program package (*Mathematica*). Symbolic and numerical calculations can be performed with the programs presented and graphic presentations of the behavior of the system be obtained. The basic ideas are illustrated with three examples taken from the area of signal transduction and ion signaling.


*Keywords:* Formal reaction kinetics; Signal transduction; Modeling; *Mathematica*

## 1. Introduction

The theoretical study of reaction kinetics has led to the development of powerful concepts and methods that can be of much help for investigating dynamical models of biochemical systems. Most problems in biochemistry can be solved by going through routine steps that are almost independent of the specific system investigated. This situation prompted us to try and fill the gap between theory and practical needs. The aims of this paper are to present in a concise way the routine steps involved and to propose practical solutions based on present day mathematical program packages. Although the routine steps may involve hard or complicated analytical calculations, both exact and approximate, and also extensive numerical investigations, these packages can help shorten the time needed to do the calculations and to improve their exactness.

☆ A *Mathematica* notebook containing all the programs presented in Tables 2–4 and their extended and deconstructed versions, with more examples and more detailed comments is available at the web site www.math.bme.hu/∼jtoth. In case *Mathematica* 3.0 or higher is not available, the program *MathReader* for reading *Mathematica* notebooks can be downloaded from the web site www.wri.com/MathSource.

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For introducing some of these possibilities we have selected three examples of increasing complexity taken from the field of receptor-mediated cell responses. Examples I and II, based partly on our own practice (e.g. Lánský et al., 2001; Rospars et al., 2000, 2003), are about the first two steps of cell transduction and involve only one or two reaction steps. The third one, about calcium oscillations, involves seven reaction steps with feedback relationships (Meyer and Stryer, 1988). Besides describing chemical reactions these examples involve translocations (Example III), and illustrate several properties of chemical dynamic systems, including the tendency to stationary (Examples I and II) as well as oscillatory (Example III) behaviors. More technical aspects are also presented, such as the description of reactions that, contrary to most steps in all examples, do not obey the mass-action law (some steps in Example III), as well as the solution of normal and stiff differential equations, the numerical handling of the latter presenting difficulties. Basic notions of reaction kinetics such as e.g. stationary point, steady state, equilibrium, stable equilibrium, detailed balanced equilibrium, or molecularity and order of a reaction step, or solution, trajectory and selectivity curves of a model, are defined. We show how the usual questions addressed when studying such systems can be solved with relatively short programs which, in the present paper, are written in *Mathematica*.

These examples and programs are intended to be applicable to as wide a range of systems as possible. They are easy to generalize. In neurochemistry, for example, the tools presented can be applied to describe the kinetics of systems as diverse as ion channels (voltage dependent or ligand gated, see Hille, 1992), transmitter release, or gating of postsynaptic receptors (see Destexhe et al., 1994).

There are three main logical *steps of investigations*. (i) The first step consists in establishing a set of chemical reactions which summarizes the knowledge of the biochemical system studied, including the speed of transition along each arrow (reaction or translocation). Three examples are presented in Section 2 which are analyzed in the following sections. (ii) The second step consists in translating the system of reactions into rate equations, i.e. as a set of differential equations, one for each time-dependent quantity in the system. This is treated in Section 3. (iii) Finally these equations must be solved to reveal the time evolution of the system or to study the solutions from other points of view (non-negativity, monotonicity, oscillations, coexistence of chemical species, etc.). This third step is described in Section 4. Details on the programming aspects with extentions for the qualitative and stochastic studies of reactions can be found in Tóth (2002).

## 2. Examples of neurochemical reactions

Three example systems taken from the field of cell signal transduction are presented.

### 2.1. Example I

The first step in cell signal transduction consists in the binding of a ligand L, e.g. photon in photoreceptor cells, odorant molecule in olfactory receptor cells or neurotransmitter in interneurons, to a receptor protein borne by the sensory or postsynaptic membrane. It can be modeled by the reaction

$$\mathrm{L} + \mathrm{R} \xrightarrow{k} \mathrm{C_{LR}}, \tag{1}$$

where $\mathrm{C_{LR}}$ stands for the ligand–receptor complex. This reaction expresses the fact that one "molecule" of the ligand L binds one molecule of the receptor R and an activated form $\mathrm{C_{LR}}$ of the receptor is formed. The positive real number $k$ is the *reaction rate coefficient* which, in this case, is a constant that characterizes the velocity of the reaction (see Section 3.2.1). Reaction (1) assumes that the reaction step is *irreversible*, i.e. there is no way (at least in the model) for the activated receptor to return to its original state. As a consequence such a model describes only the initial response of the system (Lamb and Pugh, 1992a,b). A reversible reaction might be also considered as shown below.

### 2.2. Example II

The next step of the signal transduction cascade can serve as our second example. It consists in the interaction within the cell membrane of the activated complex $\mathrm{C_{LR}}$ with G-proteins, denoted by G, and results in the activation of the G-protein as $\mathrm{G^*}$ according to the reaction scheme

$$\mathrm{G} + \mathrm{C_{LR}} \xrightarrow{k_1} \mathrm{C_{GLR}} \xrightarrow{k_2} \mathrm{G^*} + \mathrm{C_{LR}}. \tag{2a, b}$$