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Editorial

Biochemical Problems, Mathematical Solutions

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MSI Special Issue: Biochemical Problems, Mathematical Solutions

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Biochemistry is a young discipline. Recognizable biochemical studies—characterized by an attempt to isolate specific chemical actors from cells and to study their interactions *in vitro* as a bridge to understanding their *in vivo* functions—date back only to the mid-nineteenth century, with most of the key contributions to the development of the discipline coming late in the century and into the early twentieth century [9, 18]. It should therefore not be a surprise that mathematical biochemistry, the systematic application of mathematics to the problems of biochemistry, is itself a young endeavor. There were certainly some early contributions in mathematical biochemistry, such as Hill's treatment of the sigmoidal O_2 binding curve of hemoglobin [30], Briggs and Haldane's attempt to understand the steady-state approximation in biochemical kinetics using a scaling argument [7], Laidler's detailed studies of the transient phase in enzyme kinetics [37, 49], Bartholomay's work on the relationship between stochastic and deterministic treatments of enzyme kinetics [4, 5], or Goodwin's ambitious effort to develop a statistical mechanics of the cell [23], but much of this work was of a sporadic nature, and not part of the organized program of research of a community of scholars. Work in the area started to pick up in the late 1960s and 1970s. At that time, relatively little quantitative data was available so that studies of specific systems were difficult. Most of the work published in this period therefore consisted either of the development of general theory [33, 57, 64], or of studies of abstract (but hopefully informative) systems [13, 24, 36, 52], with some notable exceptions [6, 21, 29].

From these seeds, a significant area of research has grown within the larger mathematical biology community. The growth of the field has been fed by the generation of more and more detailed measurements by our experimental colleagues, ranging from the traditional *in vitro* experiments using purified components to *in vivo* observations of biochemical processes at single-molecule resolution, with a wide range of techniques covering the ground between these extremes. Anyone who has tried to create a model of a biochemical system knows that these data sets are still incomplete in a host

of different ways: some parameters have never been measured, others only in highly artificial lab conditions, and yet others only in specific species or types of cells. And yet, it is increasingly the case what we can write down and study biochemical models in which we have some degree of confidence in many, sometimes most, of the parameters.

Modeling work requires a solid foundation of theory and of methods of analysis, both analytical and numerical. While much of the machinery for treating biochemical systems is common to some of our sister fields in mathematical biology, there are some peculiarities which, if not unique, are particularly prominent in biochemical systems. One of these peculiarities is that biochemistry is an inherently multiscale discipline [25]. Every real biochemical system involves interactions on multiple time [42, 55], spatial [34] and concentration scales [35], the latter being important from the point of view of the magnitude of random fluctuations that can be expected [3]. The extent to which multiscale effects can be averaged out depends greatly on the subsystem studied but also on the goals of a study. For example, cell-to-cell variability might not be so important if we are trying to understand a phenomenon observed as an average output of a fermentor containing a large number of cells.

Additionally, biochemical systems involve very large numbers of coupled components. The very language used to describe how proteins and metabolites relate to each other at different scales within biochemical systems suggests this: complexes, cycles, cascades, etc. In some apparently very simple systems, combinatorial complexity arises from the multiplicity of binding sites on a protein, sometimes requiring special modeling languages [27, 31]. This complexity means that, as a rule, a model of a biochemical system will only consider a subset of the potentially relevant species and reactions. Understanding when we can neglect a given component [32, 51, 63, 65] or interaction with the rest of the cell consequently results in an interesting set of questions ripe for mathematical exploration [54].

Another complication is that *in vivo* biochemistry typically operates in a highly compartmentalized environment. If we consider an animal or plant, for instance, the cell contains a number of organelles, the cells themselves are compartments that communicate with other cells, sometimes directly through gap junctions [43, 48] and sometimes indirectly through the extracellular space [62], itself a distinct compartment. The arrangement of cells within the extracellular matrix can be complex, with nontrivial consequences for modeling, as is the case for instance for the "plywood" structure of heart tissue [53]. At a higher level of organization, tissues and organs can be thought of as compartments as well, communicating with their neighbors and with more distant organs through the circulatory system. Even in bacteria, the nucleoid can act as a kind of compartment whose distinctive physico-chemical characteristics affect the processes occurring therein [2].

A single special issue on mathematical approaches to biochemical problems can hardly do justice to the full range of research in mathematical biochemistry. Nevertheless, we have tried to put together a special issue showing some of the diversity in the field, both in terms of areas of research and in terms of methods. Two of the papers in this collection are in the tradition of classical applied mathematics, tackling problems amenable to formal theorems. Edwards and Woods contribute to answering an important and frequently recurring question in the study of cellular metabolism: How does a cell select the more appropriate of (say) two alternative metabolic pathways under given conditions [14]? There is not a unique answer to this question as the regulation of metabolism is a complex topic. Edwards and Woods specifically focus on a pair of network motifs [41, 66], the precursor shutoff valve and threshold separation, studying these motifs under conditions of sharp (switch-like) activation. The tools they use derive from dynamical systems theory, using a partitioning of the phase space for which state-transition

diagrams can be derived and studied.

Eilertsen and coworkers turn their attention to a classical problem, but with a new dimension [15]: Under what conditions can the steady-state approximation be applied to chemical networks open to mass flow? The specific focus of this paper is the Michaelis-Menten mechanism. Surprisingly, this question has received relatively little prior attention in the context of open systems [22, 60, 61] despite the significant effort devoted to the corresponding closed system over many decades [7, 20, 26, 28, 58]. The small number of papers on the open system is perhaps surprising given that cells are open systems. The tools used in this study mainly derive from Fenichel's geometric singular perturbation theory [16, 17].

Many models in mathematical biochemistry are far too complex for pen-and-paper analysis. As a result, simulation is an important tool in the field. But simulations require parameters, and these are often missing from the literature. When direct measurements of relevant parameters are unavailable, some cleverness must be applied to obtain parameter estimates. Sometimes, the best one can do is to vary some of the unknown parameters to determine the region of parameter space where biologically sensible behavior emerges. This special issue includes two papers presenting numerical studies of complex models. Both, as it turns out, consider questions relating to cell differentiation, which is a major area of research in mathematical biochemistry. Both also study models consisting of coupled delay-differential equations, which are frequently used in biochemical modeling where delays may represent gene expression times [6, 46], transport times either within a cell [1, 8, 47] or between tissues [38], signal transmission times through a biochemical network [19, 56], or the duration of the cell cycle [45].

The formation of somites, paired blocks of mesoderm that appear to either side of the neural tube, is a key event in vertebrate development. It has long been hypothesized that a clock was involved in coordinating the appearance of somites [10]. Local synchronization is required for proper somite development. In their contribution, Pantoja-Hernández and Santillán study how various parameters describing the coupling of cells affect the ability of the pre-somitic mesoderm, the tissue which is the precursor of somites, to synchronize [50]. Their model takes the form of coupled delay-differential equations. The number of cells communicating within a local network and the connection strength are varied, and heterogeneity of the cells is also considered.

The fields of pharmacokinetics and pharmacodynamics, which are firmly rooted in medical science, have long provided insights into the dispersal of drugs through the body, their accumulation in certain tissues, and their eventual clearance [44]. The significant computational power now available in a typical desktop computer has allowed these studies to become more ambitious, considering more detailed cellular biology and biochemistry. This has led to the emergence of a subfield called quantitative systems pharmacology (QSP), whose goal is to understand "how drugs modulate cellular networks in space and time and how they impact human pathophysiology" [59]. In this Special Issue, Le Sauteur-Robitaille and coworkers develop and study a QSP model for the effect of estrogen on mammary stem cell differentiation [39]. The highlight of the paper is their careful, detailed estimates of the parameters, which include traditional pharmacokinetic parameters relating to the transport and distribution of estrogen in various tissues but also physiological parameters such as the effects of age and body weight on estrogen kinetics, as well as parameters relating to the proliferation and differentiation of mammary stem cells. The resulting model consists of a set of delay-differential equations. By simulating a randomly generated population with a distribution of body weights, the

authors demonstrate that the dynamics of the stem cell compartment are surprisingly insensitive to individual variability. Body weight is therefore perhaps a less interesting physiological variable in this context than other differences between individuals, which is at once a prediction and an observation that opens the door to further experimental and theoretical studies into sources of inter-individual variability.

A major trend in mathematical biochemistry is direct collaboration between experimental and theoretical groups. This Special Issue presents an example of such a collaboration in a paper by Lee and coworkers, which includes experimental work from the McKenna lab and a theoretical analysis of the data by the Portet group [40]. The question driving this research is mechanistic in nature: 2'-5'-oligoadenylate synthetases (OAS) are activated by viral double-stranded RNA (dsRNA) in an early step of the innate immune response. But what is the mechanism of activation? The authors study a particular human OAS known as OAS2. They consider three possible models and, using Akaike information methods, determine that the likeliest mechanism is one that involves cooperative binding of multiple OAS2 enzymes to a single dsRNA. Again, this is a study that can drive further experiments, not only to confirm the prediction, but to examine the structural basis of the cooperative activation, among other questions of interest.

Mathematical research sometimes leads to algorithms that can be turned into software for use by experimentalists. So it is with the work of Ecoffet and coworkers, who have created software to generate realistic trajectories based on cryo-electron microscopy (cryo-EM) structures [11]. Cryo-EM generates images of biological macromolecules frozen at a moment in time. Since molecules are caught at different points in their working cycles, it is sometimes possible to order the images to get a sense of the larger-scale motions. The software of Ecoffet and coworkers goes a step further by generating a movie linking the static frames generated by cryo-EM. In their contribution to this Special Issue, these authors present a study of the computational properties of their software [12], which will be of direct interest to practitioners in the field.

This Special Issue shows only some of the diversity of the effervescent field of mathematical biochemistry. The bench biochemists are generating masses of data whose complexity requires mathematical methods, often embodied in software, for their proper understanding. Theoreticians are increasingly working directly with experimentalists, not only to analyze data *post hoc*, but often to design experiments that will be maximally informative. The next few decades promise to be exciting.

Conflict of interest

All authors declare that there is no interest in this paper.

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