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Current Opinion in Chemical Engineering

Logical versus kinetic modeling of biological networks: applications in cancer research

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Mathematical modeling of biological networks is a promising approach to understand the complexity of cancer progression, which can be understood as accumulated abnormalities in the kinetics of cellular biochemistry. Two major modeling formalisms (languages) have been used for this purpose in the last couple of decades: one is based on the application of classical chemical kinetics of reaction networks and the other one is based on discrete kinetics representation (called logical formalism for simplicity here), governed by logical state update rules. In this short review, we remind the reader how these two methodologies complement each other but also present the fast and recent development of semi-quantitative approaches for modeling large biological networks, with a spectrum of complementary ideas each inheriting and combining features of both modeling formalisms. We also notice an increasing influence of the recent success of machine learning and artificial intelligence onto the methodology of mathematical network modeling in cancer research, leading to appearance of a number of pragmatic hybrid approaches.To illustrate the two approaches, logical versus kinetic modeling, we provide an example describing the same biological process with different description granularity in both discrete and continuous formalisms. The model focuses on a central question in cancer biology: understanding the mechanisms of metastasis appearance.We conclude that despite significant progress in development of modeling ideas, predicting response of large biological networks involved in cancer to various perturbations remains a major unsolved challenge in cancer systems biology.

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Current Opinion in Chemical Engineering 2018, **21**:22–31

This review comes from a themed issue on **Reaction engineering and catalysis**

Edited by **Guy Marin**, **Grigoriy Yablonsky**, **Theodore Tsotsis** and **Marc-Olivier Coppens**

https://doi.org/10.1016/j.coche.2018.02.005

Introduction

Biochemistry, as a study of chemical processes and principles in living organisms, is our ground basis for understanding life in general and complex diseases such as cancer or diabetes in particular. The most efficient scientific approach in biochemistry remains reductionism and gradual bottom-up reconstruction of complex processes through accumulation of knowledge of elementary facts (chemical transformations). These facts need to be properly organized, and mathematical modeling can be used to help reason on them.

There has been a long-standing hope that mathematical language can indeed be used to make this cognitive effort possible by providing tools for reasoning on and making predictions from the knowledge of large and complex biochemical processes driving normal life and diseases. Introduction of chemical kinetics as a mathematical modeling formalism, more than two centuries ago, is one of the most remarkable examples of collaboration between mathematicians and life scientists. It found numerous applications in understanding cancer [1••,2•,3].

The representation and description of biological systems reveals a tremendous complexity. The nature of this complexity can be seen as '*the gap between the laws and the phenomena*' [4]. The construction of large structural schemas for biochemical reaction networks such as global metabolic mechanism in human [5] or the global cancer signaling reaction network [6•] has proved to be feasible but exploiting this knowledge remains a challenge. Using these reconstructions, it is possible to imagine detailed kinetic equations for a global reaction network inside a cell but it is more difficult, if not impossible, to find reaction rate constants and work with this large system even if it is considered 'realistic' [4,7•]. Thus, the applicability of the pure bottom-up approach becomes questionable in this context.

A hope consists in defining an intermediate level of description which would match better the granularity of real life data available today. In mathematical biology, for this purpose, a number of qualitative modeling methods emerged in the past decades. These qualitative approaches focus on the possibility to reason on the complexity of biological systems but with much less quantitative details in hand compared to what is required by the classical chemical kinetics. In mathematical oncology, one of the most useful qualitative mathematical

descriptions appeared to be the discrete (logical) formalism with an impressive record of applications [8–11]. The reason for this can be the nature of the data one usually deals with in cancer research, which frequently represent a set of links between a discrete (epi)-genotype (such as deleterious mutation or protein overexpression) to a discrete phenotype (life/death decisions of a cell or an organism, induction or inhibition of metastases, disease remission or relapse).

In this short review, the aim is not to provide a somehow comprehensive review of existing formalisms or published mathematical models in cancer applications. For good reviews on this subject, we refer the reader to several references [12–14,15••,16]. We present here a short notice about the current state of the relation between logical modeling formalism and the classical chemical kinetics modeling language, in cancer research. We aim at showing how, in recent years, these two approaches diverged and converged back, and how both of them are influenced by recent success in other fields, namely machine learning and artificial intelligence. We use an example of a relatively complex mechanism of metastasis induction in epithelial cancers to snapshot two mathematical modeling flavors currently used in cancer research.

Logical formalism as a part of asymptotology of chemical reaction networks

Kruskal defined asymptotology as "the art of describing the behavior of a specified solution (or family of solutions) of a system in a limiting case. [. . .] The art of asymptotology lies partly in choosing fruitful limiting cases to examine" [17]. Various useful asymptotic approximations of chemical reaction network equations have been exploited for a long time [18•]. Different asymptotic approximations (quasi steady-state, rate limiting step approximation, piecewise-linear, etc.) appeared to be useful according to the types of biochemical networks.

In this regard, logical equations, which were used in the late 60s to reproduce the behavior of biological networks [19••], can be matched to the asymptotic behavior of chemical kinetics equations in the limit of infinite enzyme cooperativity. Cooperative action of enzymes leads to kinetic rate functions of sigmoidal shape, which can be described by the Hill function, with the corresponding Hill coefficient parameter n. In the limit $n \to \infty$, when sigmoidal kinetic rates become step functions, the dynamics of chemical kinetics equations can be exactly mapped to discrete dynamics with asynchronous update rules [20,21,22••,23••]. In the simplest special case, it leads to the logical formalism. In this formalism, each variable can take values of 0 or 1 (false or true). The phase space of the discrete dynamics can be represented as a sparse state transition graph, which can be used to determine attractors of two kinds, fixed points or cycling attractors. In the asynchronous case, the graph is nondeterministic: many continuations are possible from a given discrete state, each being different by the value of one and only one variable.

This approximation was applied for modeling regulatory networks (such as transcription regulation networks, composed of transcriptional factors and their targets) and signaling networks. In these networks, the discrete state of a protein or a gene (active or inactive, present or absent) is usually more important than its quantity [22••]. Since cancer is characterized by profound changes in the functioning of transcriptional and signaling networks, many applications of logical modeling formalism were reported in cancer biology [8,11,24•,25,26].

Probabilistic and continuous flavors of logical modeling

In its pure form, the possibilities of logical formalism are very restrictive in cancer applications. It allows predicting appearance and disappearance of attractors and their reachability from the analysis of the state transition graph, but in practice, it requires fine tuning of predictions at a less coarse-grained level. An important suggestion was to consider the state transition graph as a Markov chain, parameterized by probabilities of transitions. The probabilities of outgoing transitions associated to each state can be set equiprobable, but they can also include information about different switching off/on time scales of various variables. In this case, each attractor is assigned a probability of being reached from a specified initial state by a random walk, which is qualitatively interpreted as a probability of observing a phenotype in an experiment. Using this approach, several models related to cancer biology were developed [27•,28], simulating probabilistic choice between different cell fates (e.g. apoptosis, necrosis, survival) and concluding on how these decisions are affected by mutations.

A natural extension of considering random walks on the state transition graphs defined by the logical models was the introduction of physical time by continuous time Markov modeling [29••]. Each variable is explicitly parameterized by the rates of switching on and off but remains discrete. The formalism has been applied for predicting appearance of metastases in epithelial cancers [8], genetic interactions [30], or mutual exclusivity or co-occurrence of mutations in bladder cancer [24•].

Alternatively, the logical framework with continuous variable values (limited in [0;1] interval) was developed [31]. This flavor of fuzzy logical modeling was successfully applied to cancer-related processes [32].

Interestingly, several studies suggested to 'roll back' from logical to ordinary differential equations, though not