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

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Abstract

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.

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 [1–3].

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 [12–16]. 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[20–23]. 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 non-deterministic: 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 network, 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 [8,11,24–26].

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 related to chemical kinetics, such as the logic ordinary differential equations [33]. In this formalism, the variables are also constrained within [0;1] interval and their rates depend on the regulator values transformed through a sigmoidal function. The formalism found successful applications in predicting sensitivity of colon cancer cell lines to various drugs [34].

Note that any logical model can be transformed into a fictitious chemical kinetics system [35], where each logic variable is associated with a reversible reaction between two chemical species, corresponding to the “active” and “inactive” variable states. As such, the total amount of each pair of chemical species is conserved and can be set to 1, or any other value. The logical regulations are represented by catalyses which might enhance (or inhibit) the reaction rate in a specified direction. Goldbeter and Koshland derived an equation for such cases [36]. Such chemical kinetics systems might in fact mimic quite closely real biochemical signaling cascades based on reversible phosphorylation [37]. Degradation and complex formation might be further introduced thus gradually reconstructing the initial complete chemical kinetics description, with a possibility to stop at any level of abstraction.

“Discretizing” chemical kinetics

An option in simplifying the analyses of complex chemical kinetics model consists in finding approximations of chemical kinetics equations such that they would require much less parameters than the complete system descriptions. In some cases, it leads to quasi-discrete approximations. Historically, the most known approximation approach in systems biology is piecewise-linear approximation of chemical reaction rates, which is qualitatively equivalent to a generalized logical description [38]. Such approximation decomposes the phase space of the dynamical system into sub-regions such that, in each region, the dynamics is driven by linear differential equations. Similarly, the dynamics of nonlinear dynamical systems can be decomposed into the action of dominant systems, each of which can be described by only few parameters [18]. The dominant systems serve a generalization of the notion of rate limiting reaction step for complex reaction networks. These dominant systems can have simple analytical solutions but do not have to be linear as in the piecewise-linear approximation method. It was also shown that for the networks of monomolecular reactions with well-separated kinetic constants, the dynamics is described by the left eigenvectors of the kinetic matrix, with coordinates close to 0 or 1, and right eigenvectors with coordinates close to 0 or ±1, i.e., the system becomes “discretized”. Analysis of dominant systems of chemical kinetics equations appeared to be insightful in modeling mechanisms of microRNA action [39,40].

Non-standard algebraic approaches were suggested to simplify the chemical kinetics equations. Discrete sign algebra approach helps derive qualitative conclusions about the Jacobian matrix of chemical ordinary differential equations [41,42]. Tropicalization (i.e., systematic application of max-plus algebra) of chemical kinetics equations can potentially provide an algorithmic basis for decomposing complex reaction network dynamics into a finite set of simple dynamical behaviors. In [43], this approach was applied to modeling cell cycle, which is a central process in cancer biology. More conceptually, introducing

qualitative and extremely simplified kinetic system descriptions (such as logical equations) might be seen as “dequantization” of continuous kinetics, by analogy with how this procedure justifies the application of tropical algebras in real-life problems [44]. One can speculate that tropical algebras should be well suited for qualitative solutions of complex models in biology because the robust cell fate decisions are made based on comparing the orders of magnitudes of biomolecule concentrations rather than on very precise values [45].

Mathematical modeling vs. machine learning and artificial intelligence

Like in other fields of model engineering, logical modeling formalism can be considered as an approach to artificial intelligence (AI). Indeed, logical equations can help infer conclusions from complex biological diagrams, or describe how different molecules inhibit or activate each other. Reasoning on such diagrams is a common approach in molecular biology. However, a human mind is able to use it only at a relatively small scale. Logical modeling formalism automates reasoning on dense diagrams containing few tens of elements [46].

This type of AI, consisting in explicitly specifying “if then” logic statements, is a characteristic of early steps in the development of expert systems in various fields, in order to help human decisions in complex situations. A current trend in AI consists in introducing machine learning approaches where the expert systems are trained on large-scale datasets, with artificial neural networks (ANN, deep learning. Interestingly, mathematical modeling of biological networks has actively borrowed the methodology of ANNs. The idea is to treat the structure of biological networks as a scaffold for a sort of ANN, and use experimental data to train the parameters of the network. Biological molecules are then treated as information processing units (neurons) and regulatory relations as synapses in ANN.

One of the first examples of modeling cancer networks was suggested in [47], using Hopfield-like ANNs. Genetic and evolutionary algorithms have been used to fit model parameters using high-throughput omics datasets [48,49]. Very recently, backpropagation of error algorithm - main tool in ANN training - was adapted to fitting parameters of mass action-based chemical kinetics equations and applied to modeling large networks in cancer [50].

Of course, when the structure of reaction networks is used as a constraint for applying machine learning techniques, the inferred kinetic or logic parameters does not have to (and usually do not) reflect the biochemical and physical reality. In this case, such mathematical models are closer to statistical models, which can be challenged by the standard approaches in machine learning, i.e., checking performance on the training and

testing datasets, applying cross-validation, etc. The question on how well this approach will generalize for completely independent data, and how serious the issue of overfitting is, remains open.

All these methods are summarized in Figure 1.

An example of modeling metastasis induction

In this section, we propose to present a concrete example of a cancer process using both logical and chemical kinetics formalisms and show what to expect from both approaches.

The formation of metastases is the process by which a cancer cell escapes from its primary site to invade a distant site. It involves several steps among which a local invasion of the neighboring tissues, intravasation which allows the cancer cells entering the blood or the lymph system and being transported to the distant tissue to finally colonize a new organ [51]. The initial step of this process requires some important events such as the loss of adhesion of cancer cells, and a phenotypic transition called the Epithelial to Mesenchymal Transition (EMT) during which the cells change their shape. This transition is believed to be a prerequisite for invasion but has been recently raised as a subject of controversies [52].

In 2015, Chanrion and colleagues [53] have engineered transgenic mice with the possibility to activate mutations in the gut as a biological model for colorectal cancer with a particular emphasis on Notch pathway (a signaling pathway reported to be deregulated in many diseases such as cardiac and endocrine development defects, cancer, etc.). The authors have showed that when the receptor *Notch1* was constitutively activated in mice already harboring a deletion of *p53*, some metastases were found in distant organs with the dissemination of EMT-like epithelial cells, but was not the case for mice with either mutation alone. Based on some computational analyses, a hypothesis involving an interplay between the Notch and p53 pathways through the regulation of the main EMT regulators (transcription factors) was proposed and later formalized into a complex logical model [8].

A simple logical model of EMT

Logical models provide a good tool to reason on the topology of the network illustrating the biological question, especially when there are no quantitative data available but rather some qualitative information such as phenotypical observations.

The main players of the two pathways are selected and assembled into a regulatory network where nodes represent species, and edges account for a positive or negative effect of one species over the others. The construction of the influence network recapitulating the cross-talks between the two pathways shows numerous interactions between the members of Notch and the p53 pathways (Figure 2A, see legend for details).

To each node, a logical rule is defined (Supplementary material). The model was constructed using GINsim [54] and simulated with MaBoSS [55], a tool for simulating continuous time Markov processes on the Boolean model. With MaBoSS, it is possible to quantify the probability to reach a particular state of the system (Figure 2B and Supplementary Figure S1). We focus our analyses on the activity of EMT regulators, NICD, and both TP53 and TP63_TP73.

The simulations of five mutant conditions (three single mutations of Notch, TP53, and TP63_TP73 and two double mutants) show coherent results with the experimental results: only the double mutant NICD++ / TP53-- leads to the activation of the EMT regulators (Supplementary Figure S2). The probabilities of MaBoSS outputs correspond to the proportions of trajectories that lead to one or the other phenotype. For instance, for all mutants besides NICD++ / TP53--, there exist conditions for which apoptosis can be reached. For the double mutant, though, no matter the initial conditions, all solutions lead to the activation of the EMT regulators.

This approach confirms that the network is in accordance with experimental results. However, the framework does not allow the exploration of the effect of timing on the mutants (e.g. is a NICD mutation in a TP53 background different than a TP53 mutation in a constitutive NICD background?) or the strength of one inhibition or activation. For that, a more quantitative approach is needed.

An ODE model of EMT

For that purpose, we have built a reaction network model corresponding to the influence network described above. We have included information about the nature of each species. For example, TP53 is a transcription factor, thus, its activity will affect the transcription of the genes it controls. We constructed a network of the same players to account for the dynamics of the genes, the mRNA and the protein of each of the components (Figure 3A). The network was then translated into a set of nonlinear ordinary differential equations (Supplementary material).

All genes are assumed to be present (initial conditions set to 1) and ready to be transcribed if the necessary conditions are met for each of the species. For simulations

of species deletions, we set the value of the corresponding gene to 0 in the initial conditions. Since the genes are not regulated, it is equivalent to setting the value of the gene to 0.

The parameter values were chosen so as to fit the known behavior of single mutants. It is important to note that the parameter set provided here might not be the only one. Some tools exist to optimize the search for parameter values, either using data [56,57] or applying constraint-based methods such as temporal logic [58]. With this parameter set, in the presence of DNA damage and ECM, TP53 can be activated but the activity of NICD is not strong enough to activate the EMT regulators (Figure 3B).

The simulations of the single mutants are in accordance with the logical model and the experimental observations (Supplementary Figure S3): the double mutant *NICD overexpressed - TP63 deletion* does not lead to EMT whereas the double mutant *NICD overexpressed - TP53 deletion* shows some activation of the EMT regulators (>65%). Note that another choice of parameter set might be able to show a more drastic activation of EMT in the double mutant, but for our purpose here, we consider that EMT is triggered.

The chemical kinetics formalism allows the exploration of more quantitative aspects such as the impact of the order of mutations (supplementary material). We tested the sequential activation of Notch and p53 mutations. For both *in silico* experiments, the results show that the same levels of activations of all species are reached but with different dynamics.

Advantages and drawbacks of both approaches

The simulation of the same biological question in the two formalisms presented here show advantages and drawbacks of both. The logical formalism reasons on the topology of the network and confirms that the network is coherent with the experimental results. There are only few parameters that need to be set in this context but it does not constitute a major difficulty. The use of MaBoSS adds a mean to quantify these Boolean solutions but the results and their interpretation remain coarse-grained. The same model translated in nonlinear ordinary differential equations allows the introduction of more biochemical details about the process. The details of transcription and translation processes of the species included in the network are added to account for the dynamics of the miRNA and the transcription factors. This more refined model necessitates to carefully fine tune parameters though. This is when the difficulty appears. Choosing the right parameter set that is able to reproduce experimental observations can become a very difficult task. For a model of such dimension, it is handable, but for higher dimension, it becomes impossible without the help of optimization methods.

Conclusion

Significant progress in cancer research was made by comprehensive cataloguing of elementary steps of related molecular mechanisms. This created a demand for developing predictive formal models of cellular behavior. Modeling large biochemical networks, using pure bottom-up approach and the classical chemical kinetics methodology, faces difficulties related to poor availability of quantitative system parameters. This challenge led to appearance of multiple semi-qualitative modeling languages representing biochemical reaction networks at various levels of abstraction. Until recently, the main formalism for qualitative modeling in cancer research was logical (discrete) modeling. However, both classical chemical kinetics and logical modeling formalisms have been significantly revised recently and adapted to the characteristics of real-life large-scale data existing in cancer research. Interestingly, developing new methods in mathematical modeling of cancer biology are influenced today by the tools developed in the field of artificial intelligence, and especially, machine learning methods based on training large and complex networks.

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Figure Legend

Figure 1: Summary of approaches from continuous and logical modeling and their transformation to hybrid semi-qualitative modeling formalisms. Summary of the approaches to mathematical modeling applied to the biochemistry of cancer. These approaches are related to the classical chemical kinetics or discrete modeling formalisms. Two ways of "discretizing" chemical kinetics via developing useful approximations are accompanied by making the classical discrete approach more flexible via introducing continuous time or variables. Appearance of large-scale datasets and the recent success of machine learning approaches in cancer research has stimulated development of hybrid mathematical modeling approaches which borrowed ideas and tools from these fields.

Figure 2: Logical model of the early steps of metastasis. (A) TP53 and its homologs, TP63 and TP73, are activated by DNA damage. They share similar and distinct functions (PMID:10769197). For simplicity, in this model, TP63 and TP73 are lumped together into a single node. They have been reported to show different interactions with Notch pathway and some miRNAs (in particular mir200 and mir34a) than those of TP53, but may still be able to trigger apoptosis in the absence of TP53. Notch is activated by external signals (ECM for extracellular matrix). NICD corresponds to the intracellular domain of Notch which can interact with TP53, TP63, TP73, and the EMT regulators. Finally, the activation of the EMT transcription factors depends on both NICD and the absence of miRNA, themselves regulated by TP53 and its homologs. (B) Pie chart recapitulating the probabilities of the solutions of the logical model using MaBoSS

Figure 3: Kinetic model of the early steps of metastasis. (A) Reaction network of the metastasis model. Regulations of genes, mRNA and proteins dynamics are represented. Positive influences (or catalyses) are drawn as arrows ending with circles and negative influences (or inhibitions) as arrows ending with a T-shape. (B) Simulations of wild type conditions over time, with DNA damage and ECM active.