# Introduction to Focus Issue: Quantitative Approaches to Genetic Networks

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# Introduction to Focus Issue: Quantitative approaches to genetic networks

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All cells of living organisms contain similar genetic instructions encoded in the organism's DNA. In any particular cell, the control of the expression of each different gene is regulated, in part, by binding of molecular complexes to specific regions of the DNA. The molecular complexes are composed of protein molecules, called transcription factors, combined with various other molecules such as hormones and drugs. Since transcription factors are coded by genes, cellular function is partially determined by genetic networks. Recent research is making large strides to understand both the structure and the function of these networks. Further, the emerging discipline of synthetic biology is engineering novel gene circuits with specific dynamic properties to advance both basic science and potential practical applications. Although there is not yet a universally accepted mathematical framework for studying the properties of genetic networks, the strong analogies between the activation and inhibition of gene expression and electric circuits suggest frameworks based on logical switching circuits. This focus issue provides a selection of papers reflecting current research directions in the quantitative analysis of genetic networks. The work extends from molecular models for the binding of proteins, to realistic detailed models of cellular metabolism. Between these extremes are simplified models in which genetic dynamics are modeled using classical methods of systems engineering, Boolean switching networks, differential equations that are continuous analogues of Boolean switching networks, and differential equations in which control is based on power law functions. The mathematical techniques are applied to study: (i) naturally occurring gene networks in living organisms including: cyanobacteria, *Mycoplasma genitalium*, fruit flies, immune cells in mammals; (ii) synthetic gene circuits in *Escherichia coli* and yeast; and (iii) electronic circuits modeling genetic networks using field-programmable gate arrays. Mathematical analyses will be essential for understanding naturally occurring genetic networks in diverse organisms and for providing a foundation for the improved development of synthetic genetic networks. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4810923]

**"These examples should suffice to show, that by the use of the principles which they illustrate, any number of systems may be interconnected into regulatory circuits endowed with virtually any desired property." Monod and Jacob (1961)[1]**

**"The next generation of students should learn how to look for amplifiers and logic circuits, as well as to describe and look for molecules and genes." Hartwell, Hopfield, Leibler, Murray (1999)[2]**

**"Transcription factors bind in a combinatorial fashion to specify the on-and-off states of genes; the ensemble of these binding events forms a regulatory network, constituting the wiring diagram for a cell." Gerstein *et al.* (2012)[3]**

## I. INTRODUCTION

Over 50 years ago, Monod and Jacob argued that the mechanisms controlling expression of individual genes in bacteria could be interconnected to generate genetic regulatory circuits that would underlie vital functions including oscillation and differentiation.[1] The basic idea was that a diffusible protein, called a transcription factor, which is coded by one gene, could bind to the DNA molecule to modulate the rate of production of itself or other genes. Thus, the DNA combined with the transcription factors generated networks where the nodes of the network were the genes, and the transcription factors led to interactions between the genes. Although Jacob and Monod did not provide mathematical analyses, their prescient suggestions provided a basis for theoretical models of genetic control in terms of logical switching networks in which the logical states of genes updated following specific delays[4–6] or in which there was synchronous updating of all variables.[7] Alternatively, the logical structure and relationships could be embedded in differential equations[8] as either discontinuous switching functions or sigmoidal functions.

Subsequent to these early papers, there has been a continuing research in theoretical models of genetic networks.[9,10] However, sparked by advances in molecular biology and synthetic biology,[11,12] there has been an accelerating interest in these theoretical models. This Focus issue gives an overview of many of the important advances and current research directions. In Sec. II, we summarize the theoretical approaches to the analysis of models of genetic networks that are of particular interest to the nonlinear dynamics community. We discuss the applications of theoretical approaches to analysis of naturally occurring

 

biological systems in Sec. III and to synthetic biology in Sec. IV.

## II. MATHEMATICAL MODELS OF GENETIC NETWORKS

### A. Structure of genetic networks

Recent years have witnessed an explosive interest in the properties of complex networks.[13] We briefly review this material focusing on its relevance to genetic networks.

First some basic terminology: Graphs are composed of vertices (or nodes) and edges. An edge connects two vertices. The degree of a vertex is the number of edges at that vertex. In some instances, edges may be directed, indicating that one node influences a second node or that there is a flow from one node to another node. In the random Erdos-Renyi graph, there are $N$ vertices and a given number of edges connecting randomly chosen vertices. Examination of real-world networks in the 1990s led to the recognition that most real graphs for naturally occurring systems are not random.[14,15] One type of deviation from randomness in naturally occurring networks is that the distribution of the degrees of vertices follows a power law (it is scale free) rather than an expected Poisson distribution.

Determination of global network topologies of naturally occurring genetic networks is an important area of research[16] in which emerging techniques have been enabled by a large number of new technologies.[17] A significant number of networks formed by gene products, including protein interaction networks,[18,19] signal transduction networks,[20] and transcriptional regulatory networks,[3,17,21,22] exhibit a high heterogeneity of node degrees. For example, for the yeast transcriptional regulatory network, the distribution of the out-degree of genes appears to be a power law, whereas the in-degree distribution appears to decay exponentially with over 90% of genes being regulated by 1–4 transcription factors.[21] However, these findings will need to be examined as technologies for determining interactions become more refined.

In addition to the global network topology, one also can identify recurring interaction motifs, which are small subgraphs that have well-defined topologies.[23] Interaction motifs such as autoregulation and feed-forward loops,[24,25] or triangles of protein interactions[18,20,26] have a higher frequency than expected based on the subgraph statistics of comparable randomly generated networks with similar degree distributions. Moreover, exhaustive analysis of the dynamic behaviors supported by three and four-node motifs revealed that dynamical stability to small perturbations in node states is highly correlated with the relative frequency of these motifs.[27] These observations support the notion that interaction motifs form functional building blocks of cellular networks.[23] In the current issue, Phenix *et al.* carry out simulations to analyze the effects of gene deletions on the expression of a trait. They consider all different two-gene network motifs with arbitrary regulation functions. These results should be useful in determining network topologies based on experiments in which the effect of having two genes deleted is similar to the effect of having a single gene deleted.[28] Also in this issue, Kadelka *et al.* analyze the way feedforward loop motifs could play a role in reducing the effects of noise and stabilizing global dynamics.[29]

Although emerging technologies are offering the prospect of determining the architecture of genetic control networks,[3] the actual structures or control parameters are not known. Consequently, researchers have focused on the analysis of simplified theoretical models. In the remainder of this section, we review simplified theoretical models of genetic networks: synchronous Boolean switching networks, Boolean delay networks, asynchronous logical networks, and differential equation models. In Sec. V, we discuss future prospects for quantitative approaches to genetic networks.

### B. Synchronous Boolean switching networks

Kauffman proposed that genetic networks could be modeled as synchronous Boolean switching devices and considered idealized models consisting of $N$ genes, each with $k$ randomly chosen inputs from other genes in the network. The inputs to a gene combine to control the output of a gene by a randomly chosen Boolean function.[7,30] All genes were updated synchronously, such that

$$X_i(t+1) = B_i(X(t)), \quad i = 1, N, \tag{1}$$

where $X_i(t) \in [0,1]$ is a Boolean variable, $X(t)$, is a Boolean state vector with $N$ components, $B_i$ is the truth table for the $i$th gene, and $t$ is a discrete time. In the original work, each $B_i$ depended on $k$ inputs. Kauffman carried out simulations to determine the number of attractors in networks as a function of $N$ and $k$. In this context, the different attractors corresponded to different cell types. Kauffman found that for networks with $k=2$, the number of attractors increased roughly proportional to $\sqrt{N}$—thus there was an incredible focusing of the $2^N$ states in the Boolean state space to a small number of attractors. There was even a quantitative matching—the hundreds of different types of cells arose as attractors from tens of thousands of genes. Although further computations have shown the number of attractors in Kauffman networks with $k=2$ grows superlinearly,[31] the basic identification of attractors in mathematical models of genetic networks with cell types is one of the basic premises of theoretical analyses.

Because of the strikingly simple structure of Kauffman networks, they have attracted broad interest from theoreticians, especially statistical physicists. Derrida and Pomeau[32] analyzed statistical properties of trajectories as a function of $k$. Assuming a randomly constructed network, two initial states that differ by a Hamming distance of 1 will in general converge for $k < 2$ and diverge for $k > 2$. This finding has led to the characterization of an "order-disorder" transition with the value $k=2$ lying on a "critical" boundary. Although the disordered phase is sometimes called "chaotic," from the perspective of nonlinear dynamics, for systems with finite $N$, all dynamics must eventually cycle (i.e., they cannot be "chaotic" which implies aperiodicity). These early findings have been extended in a large number of ways by

considering the effects of network structure and Boolean rule structure on the dynamics.[33–36]

### C. Boolean delay networks

Despite the theoretical interest of the properties of synchronous Boolean networks, most work directed at developing models that can be used for biological systems has relaxed the requirements of synchronicity in a variety of different ways. The earliest suggestions for theoretical models proposed Boolean delay equations[4–6] in which transitions between states followed logical rules, but occurred following a fixed delay. Early studies by Ghil and Mullhaupt[37] formalized such systems mathematically and discovered that some simple networks display chaotic dynamics. These theoretical results have recently motivated the construction of analogue devices using field programmable array devices, called autonomous Boolean networks, which simulated the Boolean delay equations and experimentally demonstrated chaotic dynamics.[38] In the current issue, Sun *et al*. extend the class of Boolean delay networks by assigning different delays for both the onswitch and the offswitch and use this to determine the dynamics of a model system comprised of a positive and a negative feedback loop.[39] In addition, Rosin *et al*. carry out experimental studies demonstrating both periodic dynamics and chaotic dynamics in autonomous Boolean networks synthesized with field programmable arrays.[40] This class of experimental systems offers the promise of developing analogue models for large genetic networks.

### D. Asynchronous logical networks and nonlinear differential equations

Synchronous Boolean network models represent an extreme idealization of real networks. Although introducing fixed delays that differ for the different elements destroys the synchronous updating, it is more common to generate asynchronous networks using other means.[41,42]

A fundamental question is to be able to predict qualitative dynamics of the networks based on the logical structure of the network. Many early simulation studies demonstrated that negative feedback loops (with an odd number of inhibitory interactions) could generate oscillations and positive feedback loops (with an even number of inhibitory interactions) could generate bistability. Based on these observations, Thomas and colleagues conjectured that a necessary condition for oscillation is the presence of a negative feedback loop and a necessary condition for bistability is a positive feedback loop[43,44] and proofs are possible in some situations.[45–47] Although application of this result to networks with comparatively simple interactions and structure is straightforward, if genes have multiple inputs and complex Boolean functions, interactions between two genes may be either positive or negative depending on the states of other genes. In the current issue, Zanudo and Albert propose a refined criterion for identifying the qualitative dynamics of networks based on their logical structure. Specifically, they identify a class of complex cycles in an augmented representation of the network and show that the nodes that participate in these cycles will reach a steady state. This information can be used as part of an iterative network reduction process that yields the steady states of the system.[48]

To further analyze the connection between the logic and the dynamics of genetic networks, a new construct called the state transition diagram (or graph) is needed. Assuming that the Boolean states of a system are the nodes of a graph, the *state transition diagram (or graph)* is a directed graph showing the transitions allowed between each pair of two states.[8,41,49] The state transition diagram can be constructed for synchronous updating schemes or asynchronous updating schemes. In some situations where a given gene controls multiple downstream targets at different thresholds, it is common to extend the transition diagram to allow more than two states per gene.[42] Since this situation could be accommodated by reformulating the original network as a higher dimensional network with a single threshold for each element,[50] for convenience, we assume a single threshold per gene.

Since generically only one variable can switch at any time, the Hamming distance between each two connected vertices in the graph is one. As a consequence, the graph of the state transition diagram for asynchronous Boolean networks is a directed graph on an $N$-dimensional hypercube (for the case of $N$ genes). For the special case in which no element of the network has an input from itself, each edge of the truth table is oriented in a unique orientation, and there is a 1–1 correspondence between directed graphs on the $N$-cube, and logical switching networks with no self-input.[41] The state transition diagram enables techniques from discrete mathematics. For example, in the 4096 different networks composed of three genes with no self input,[51] 8 represent negative feedback systems (such as the repressilator[11]) expected to show stable limit cycle oscillations.[41] As the number of genes increases, there is a combinatorial explosion of different possible networks.[52] This huge number of networks, coupled with the exponential increase of the number of the states of the system, makes clear the need for theoretical methods to analyze the dynamics. In the current issue, Berenguier *et al*. describe a method to coarse-grain state transition diagrams while generating them from simulations. This method preserves the essential features of the diagram while drastically reducing its size.[53]

This state transition diagram holds for various types of asynchronous switching including: assuming updating according to some predetermined sequence,[54] stochastic updating,[54] or alternatively, by embedding the underlying logical structure in differential equations.[8] Consequently, for any of these classes of dynamical models, the following statements hold:[8,41,42,55–57]

- In-vertices of the state transition diagram are associated with a stable steady state in the associated dynamical system.
- A necessary condition for a periodic solution is a cycle in the state transition diagram.
- A necessary condition for chaotic dynamics is a vertex that is on at least two different cycles.
- An upper limit on the topological entropy of the dynamics can be determined based on the state transition diagram.

Further, since there is a 1–1 correspondence between edges in the state transition diagram and entries in the truth table, observation of dynamics enables one to reverse engineer a network and determine the logical network generating some complex dynamical behavior.[58]

One class of models are piecewise linear equations that are generated from Eq. (1):[8]

$$\frac{dx_i}{dt} = -\gamma_i x_i + \lambda_i B_i(\mathbf{X}), \tag{2}$$

where for each continuous variable $x_i$, there is an associated logical variable $X_i$, such that $X_i = H(x_i - \theta_i)$, where $H(y)$ is the Heaviside step function which equals 0 for negative arguments and is otherwise 1. Further $\lambda_i/\gamma_i > \theta_i$, where $\lambda_i$ is a production constant, $\gamma_i$ is a decay constant, and $\theta_i$ is a threshold. For the condition when all $\gamma_i$ are equal, for networks whose state transition diagram has a stable attracting cycle, the asymptotic dynamics for all initial conditions in regions of phase space associated with the cycle are either an asymptotic oscillatory approach to a threshold intersection or a stable, unique limit cycle oscillation.[59–61] This result can be proven from the properties of the return map,[57] which can be explicitly computed due to the piecewise linear nature of the equations. Similar results have been obtained in some circumstances when the $\gamma_i$ are not all equal.[62] Analytic computation of the return map sometimes permits strong insight into the origin of chaotic dynamics for particular examples of Eq. (2)[61,63,64] and explicit proof of chaos by construction.[50]

As mentioned earlier, the order-disorder transition in Boolean networks with synchronous updating has been studied intensively for a variety of different network models.[32–36] However, for the piecewise linear equations, we know of only one paper that studied this transition.[65] This was accomplished by changing the percentage of 1 s in the truth tables. In the piecewise linear equations, the definition of chaotic dynamics is consistent with the nonlinear dynamics requirements of chaos including aperiodic dynamics and sensitive dependence to initial conditions in systems with finite numbers of variables. As the percentage of 1 s in the truth table increases from 0.5 towards 1, there is a transition. The percentage of networks that display chaotic dynamics decreases and the percentage of networks that display steady states increases. As $N$ increases the transition between the regions gets increasingly sharp and there is an intervening zone in which many networks display periodic dynamics.[65]

By substituting continuous sigmoidal functions for the Heaviside step functions one obtains nonlinear equations. In numerical studies, limit cycles were preserved in equations with stable limit cycle oscillations when sigmoidal functions are substituted for step functions.[59] Theoretical results show that provided certain technical conditions hold, the qualitative dynamics will be preserved in Eq. (2) when steep continuous functions are substituted for the step functions.[66]

Due to the discontinuous right hand side of the piecewise linear models of genetic networks, there are also a variety of pathological situations that can arise in which the trajectories on the boundaries between two orthants in phase space are not well defined or in which the simultaneous switching of variables on a threshold boundary leads to ambiguity. Equations of this class have attracted interest both for the mathematical aspects and also because they arise in a large number of different practical applications.[67,68] In gene networks, autoregulation is one situation that leads to these types of singular dynamics. In the context of gene networks, Gouzé and collaborators have investigated properties of the piecewise linear equations using approaches developed by Filippov.[69] An alternative approach developed by Plahte and collaborators replaces step functions by steep sigmoids and uses singular perturbation theory to analyze dynamics as the sigmoids become infinitely steep.[66,70,71] In the current issue, Machina *et al.* examine a toy model demonstrating that rapid cycling in the neighborhood of thresholds can lead to densely interwoven basins of attraction of different attractors, and thus to sensitivity of asymptotic dynamics to the initial condition.[72] In order to develop general purpose software for qualitative analysis of gene network dynamics, these technical problems must be recognized and appropriately handled.[71,73,74]

An interesting question is the extent to which different classes of models might offer differing perspectives and insights on a given network. In this issue, Chaves and Preto consider how Boolean models, piecewise linear ordinary differential equations, and fully nonlinear differential equations can all be used to help understand and model dynamics in a circadian rhythm oscillation.[75] The simpler models can help to fix the gross structure and help in developing the refined model, where the unifying theme is the state transition diagram which is invariant for all three classes of model. In contrast, Sun *et al.* describe a model system with positive and negative feedback and show that two oscillations that reflect different mechanisms of oscillation when considered from the perspective of a Boolean delay network may correspond to the same symbolic sequences in the state transition diagram.[39]

## III. ANALYSIS OF NATURALLY OCCURRING GENETIC NETWORKS

Several different classes of models have been used for the analysis of naturally occurring genetic networks. Determination of the appropriate model for any given network necessarily involves combining theoretical analysis with experimental studies to determine the relevant transcription factors, the ways in which their production is controlled, and the targets of the transcription factors. Even though the main objective of the current issue is to survey the analysis of network structures, the theoretical analysis of each aspect of the network faces strong challenges. For example, as discussed in this issue, at subcellular level the binding of transcription factors to the DNA molecules presents significant challenges for both experimental and theoretical analyses.[76]

Logical models provide a simplified way to capture the main genes, the transcription factors, and their interactions without specifying the detailed kinetics. An early example is the analysis of bacteriophage lambda that showed how the

interaction of both positive and negative feedback loops were necessary to understand the interaction of the virus with a bacterium and whether the virus would cause lysis of the bacterium or would incorporate into the bacterium's genome leading to the state of lysogeny.[77] In the current issue, Chaves and Preto provide a case study of how to go from logical models, to piecewise linear models, to more realistic nonlinear kinetic models in the analysis of the circadian rhythm in cyanobacteria.[75]

In higher organisms in which gene control may involve interactions between multiple factors, it seems likely that understanding of behavior will only be possible with the development of models that combine qualitative and quantitative features. Developmental biology provides compelling scientific problems involving both time and space. Early examples include models that demonstrated how the interaction of 11 genes could lead to multiple cell types involved in flower morphogenesis[78] and studies that analyzed the factors regulating control of a single gene in sea urchin development.[79,80] Discoveries of remarkable organization in the geometric arrangements of expression of transcriptions factors in early development of insects has led to the development of mathematical models based on logical interactions[81–85] as well as partial differential equations in which transcriptional control is based on neural network or logical interactions.[86–88] In the current issue, Kim *et al*. combine biological studies with mathematical modeling to partially dissect mechanisms controlling the expression of one gene (*tailless*) involved in early development in *Drosophila*.[89]

## IV. SYNTHETIC BIOLOGY

Synthetic biology is an exciting new field bringing together engineers, physicists, mathematicians, and biologists to design, model, and construct synthetic gene networks, and to use these networks to rewire and reprogram organisms, endowing them with novel functions for a range of applications.[90–92] Initial studies led to the synthesis of gene circuits with predictable behavior including the toggle switch,[12] the repressilator—an oscillating network,[11] and a stable negative feedback system.[93] In all these cases, nonlinear dynamical models provide a theoretical foundation for understanding the observed dynamics. For the toggle switch and the repressilator, logical models[5,8] provide a conceptually simple way to predict the emergent dynamics based on the network architecture. Further, for the development of the genetic toggle switch,[12] modeling work preceded and guided the design and construction phases. Specifically, the toggle design made use of a mathematical model to deduce the parameter regimes and criteria required for bistability and robust switching. These criteria included balanced and strong constitutive promoters, effective transcriptional repression, and the formation of repressor protein multimers with similar degradation rates.

Subsequent to these initial founding papers in synthetic biology, there has been an accelerating interest in the area with significant achievements including development of: tunable oscillators;[94,95] tunable mammalian switches utilizing RNA interference to enable selective regulation of any gene;[96] bacterial systems capable of detecting light edges projected into the bacterial culture;[97] networks capable of counting cellular metabolic events;[98] circuits that lead to differential gene expression based on past events and therefore act as memory devices;[99] genetic circuits for oscillation and toggle switches that can function *in vitro* and do not need to be inserted in living cells;[100,101] synthesis of combinatorial controllers capable of realizing various logical functions.[102,103] With few exceptions (e.g., Ref. 99), these papers report nonlinear dynamic models that reproduce the observed dynamics. However, despite these impressive advances, the basic task of constructing a predictable gene network from biomolecular components is still far from straightforward, usually requiring significant molecular biology expertise and many months before a new network with acceptable behavior is realized.[104,105] In this issue, Purcell *et al*. raise the important question of understanding the interaction between the dynamics of a synthetic gene network oscillator and the intrinsic dynamics engineered in *Mycoplasm genitalium*.[106] They believe that in some cases, it will be necessary to develop detailed theoretical models of the whole cell dynamics in order to understand the dynamics of both the synthetic oscillator and of the host cell.

Another aspect of synthetic biology is to understand the interaction of the engineered organism with the environment. Although biological systems would appear to be intrinsically nonlinear, classical methods of system identification can be effective in understanding the effects of environmental changes on organisms.[107] In the current issue, Fiore *et al*. show that systems identification methods can be used to analyze the response of yeast to periodic changes in the sugar concentrations in the growth medium.[108] However, under periodic stimulation, synthetic genetic oscillators are expected to have a number of properties, such as entrainment and chaotic dynamics, which would not be predicted using traditional systems identification techniques.[109] Using a micro-fluidic device, Fiore *et al*. study the dynamics of a synthetic genetic oscillator and compare observed dynamics with theoretical predictions.[110]

## V. THE FUTURE OF GENETIC NETWORKS

Emerging technologies have generated vast amount of data concerning the structure and function of the genetic networks that underlie the existence of all life on earth. Amidst the sea of data, scientists are now searching for unifying principles and methodologies that can be used to understand the organization of the networks and to provide techniques that could be used to modify or synthesize genetic networks for a variety of practical purposes.

As suggested by the quotations at the start of this article, analogies between logical circuits and genetic networks now provide a main direction for theoretical analysis of genetic networks and several articles in this issue consider different aspects of this approach.[39,40,48,53,72,75] However, as these articles make clear, current approaches are not adequate to deal with many of the practical problems confronted by real networks. In particular, better methods are needed to understand the relationships between structure and dynamics

in very large networks;[48,53] time delays due to physical processes of synthesis or diffusion can play a major role in determining the dynamics,[39,40] transcription factors do not have on-off control and may have different thresholds for different processes so that strictly Boolean logic may not be suitable.[75] In view of these difficulties, it is possible that the current formalism that stresses the analogy with logical networks will be succeeded by alternative formulations. One such formulation uses a neural network in which the concentrations of excitatory and inhibitory transcription factors are added together in a weighted sum in order to determine their influence on transcriptional control.[87,89] In another approach, kinetic equations for genetic networks are described by functions based on polynomial expressions.[111] Of course, it is also possible that simplified models will not offer adequate insights and that emerging theory will require realistic models for subcellular[76] or cellular[106] processes.

Independent of the class of theoretical model that proves most useful to understand the structure of genetic networks, a profound problem involves the comparative structure of genetic networks in different organisms and the evolution of these networks. DNA binding sites for transcription factors appear to be conserved in different species[89] and this can be an important clue in helping to decode mechanisms of transcriptional control in different species. Yet, it seems that the principles underlying the evolution of genetic networks are still scarcely understood.[112]

Finally, the emergence of synthetic biology provides a critical interface for theoretical and experimental approaches to analysis of genetic networks. Synthetic biology would benefit tremendously from the development of more effective modeling approaches that increase the predictability of gene network engineering and thereby decrease the need for extensive *post-hoc* tweaking to get a functional network up and running. Typically current approaches in synthetic biology rely on using a small set of biomolecular components plundered from different natural systems, which are then constructed and analyzed *in vivo*. This design-build-test cycle is often carried out without guidance from a priori mathematical modeling. In the small number of instances which do utilize computational assistance, mathematical predictions are seldom a practical, quantitative tool to guide the engineering of gene networks that rely on a delicate variety of component properties. Modeling efforts are mainly used for data interpretation, rather than for guiding design and construction. Enhanced modeling platforms, which are coupled to characterized libraries of biomolecular components, could serve to fast-track design efforts in synthetic biology, accelerating the rational development of functional gene circuits.[102]

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