

A General Model for Gene Regulatory Networks with Stochastic Dynamics

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Abstract: - We build a stochastic genetic toggle switch model using the Gillespie algorithm with time delays, as an example of a simple stochastic gene regulatory network. From this, we propose a practical modeling strategy for more complex gene regulatory networks with stochastic dynamics using the Gillespie algorithm. Here, genes interactions structure and transfer functions are made using a similar method as the one used to generate random Boolean networks, yet, its dynamics is stochastic due to being driven by the Gillespie algorithm. This model is expected to mimic realistic genes expression and regulation activities. We build random networks, in which, to each gene, an activator and repressor are randomly chosen from the set of gene expression products. Unlike previous applications of the Gillespie algorithm to simulate specific genetic networks, this modeling strategy is proposed for an ensemble approach to study the dynamical properties of these networks.

Key-Words: - Gene Regulatory Networks, Stochastic Dynamics, Random Boolean Networks, Gillespie Algorithm

1 Introduction

Since the genes of the human genome and others have now been identified, one of the next steps is to understand the behavior of all genetic regulatory networks. As an example, the human genome has between 30,000 and 45,000 genes, whose activities are regulated by a network of their own products.

The genome can be seen as a parallel processing nonlinear dynamical system. This system has been modeled by several approaches, such as random Boolean networks introduced by SK [1], to differential equations [2], piecewise linear differential equations [3] and stochastic equations [4][5].

The first approach to model GRN's was made by Stuart Kauffman, who introduced the Boolean network model. In such model, genes are represented by binary variables with two possible states: 1, when a gene is being expressed and 0, if not. Also, all genes states synchronously updated.

A gene state is regulated by other genes, directly connected to it. A random Boolean function is assigned, determining its state in the next time step from the inputs previous states.

Since real genetic networks are not synchronous Boolean nets and this model does not allow a correct simulation of stochasticity, we propose to model

genetic networks with a noisy molecular kinetic model. Here, the favoured approach is the Gillespie algorithm [7][8], recently used by a number of authors to model small genetic networks [10].

Using the Gillespie algorithm one attains temporal stochastic dynamics by calculating the probability of each possible chemical reaction event and the resulting changes in the number of each molecular species [4][7][8].

The Gillespie algorithm [5] can be used to model discrete molecular events of transcription, translation and gene control in complex reaction networks. We propose to use this algorithm to model simple bistable networks, and then increasingly complex networks.

Once the stochastic dynamics is implemented, this model will allow studying if there are stable sets of states to which the system is driven to, simulate gene regulatory networks for the purpose of inferring the structure from the functioning and characterize its dynamics, i.e., if they are ordered, critical or chaotic.

The goal is to create a general model of the gene regulatory network, with a realistic dynamics such that these problems can be studied using the ensemble approach [9].

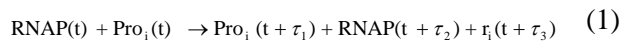
2 Problem Formulation

The main problem dwelt here is to how to model gene regulatory networks, whose dynamics is stochastic, takes in consideration the reactions times and where genes affect one another with realistic interactions.

3 Stochastic Simulation of Gene Expression

The gene expression process contains transcription and translation. These are very complex biological processes which contain a series of elementary chemical reactions. For simplicity we use the algorithm proposed in [11] which uses time delays to convert the whole gene expression process to a single delayed chemical reaction.

To represent the production of the protein resulting from gene expression we use the following equation (1), where $Pro_i(t)$ is the promoter site, RNAP is the RNA Polymerase, and r_i is the resulting protein, created from the translation of the RNA formed in transcription. The τ 's are the time that takes each of the products of the reaction to become available in the system [11].

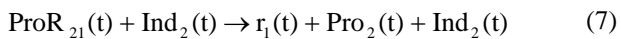
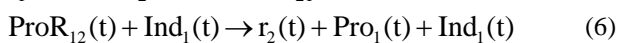
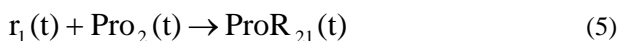
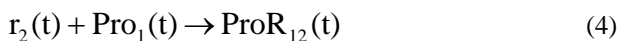
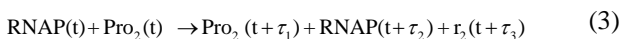
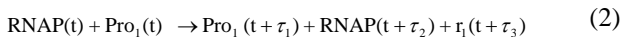


Using this equation to represent transcription and translation, we built a stochastic model of the toggle switch below.

4 The Toggle Switch Model with Stochastic Dynamics

The toggle switch [12] consists of two repressors and two promoters. Each promoter is inhibited by the repressor that is transcribed by the opposing promoter. Bistability arises from mutual inhibition.

We simulate a two identical genes toggle model using the Gillespie algorithm with the following chemical reactions:



Equations (2) and (3) represent the genes expression procession. Reactions (4) and (5) are repressing processes, and (6) and (7) reactivate the expression due to the inducers. The last two reactions, (8) and (9), are the decay processes.

In our simulations, the stochastic rate constants of all reactions are equal to 1 s^{-1} , except the decay reactions, with a stochastic rate constant of 0.001 s^{-1} . As for delays we set delay τ_1 to 1s, τ_2 to 10 s and τ_3 to 20 s. The initial numbers of the reactants are: $RNAP = 50$, $Pro_1 = 1$, $Pro_2 = 1$ and $Ind_2 = 1$. All other elements are not present initially.

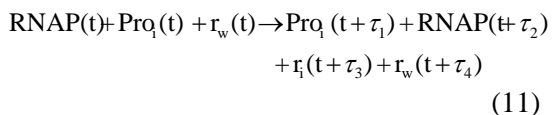
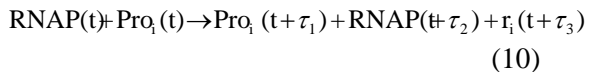
From these initial conditions we attain, after some transients, a stable state where gene 1 is off and 2 is active. By removing inducer 2 and introducing inducer 1, we toggle to the other possible stable state.

With both inducers, two stable states are possible: one where promoter 1 transcribes repressor 2 and one where promoter 2 transcribes repressor 1. Also, in this case, if the decay stochastic rate constants are non null the two stable states toggle from one to the other.

5 A General Set of Reactions

To create a model simulator able to generate stochastic gene regulatory networks, we consider, for sake of simplicity, that each gene can either be activated (11) or repressed (12) and possess, independently of these two states, a basic level of expression (10). Also, gene expression products (r_i for gene i , $i = 1, \dots, N$) should decay (13).

From this, we developed a set of equations for each gene, which vary only, from gene to gene, in what expression product is repressor (r_w) and what expression product is activator (r_j).



In this model of general stochastic networks, the ability to generate an ensemble of networks comes from the fact that j and w are different randomly chosen integer numbers (from 1 to N). Thus, when the network of interactions between the genes is being created, since j and w are random numbers, a

different wiring diagram of influences is generated at the beginning of each independent simulation.

This is similar to the ensemble approach in the Boolean networks random assignment of connections and Boolean functions [9].

This set of equations, when generalized to more than one possible activator and inhibitor, and considering also reactions between proteins, will allow complex transfer functions.

5 Conclusion

We built a stochastic genetic toggle switch model whose dynamics is driven by the Gillespie algorithm as an example of a simple stochastic gene regulatory network.

From that, in order to do an “ensemble approach” on stochastic gene regulatory networks we proposed a general modeling strategy that allows mimicking the key features of the Random Boolean networks approach, but using a dynamics driven by the Gillespie algorithm.

We believe that the method here proposed for building general stochastic gene regulatory networks allows simulating with realism a genetic network.

We believe this method will be useful for developing better inference algorithms of the gene networks structure and logic.

We are currently performing such analysis using 100 genes networks.

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