

Genetic Networks with Stochastic Fluctuations

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Keywords: gene regulatory network, stochastic fluctuation, quasi-equilibrium, master equation

1 Introduction

Stochastic fluctuations may not only affect the dynamics of biological systems but also be exploited by living organisms to actively facilitate certain functions. Explicitly considering all variables and chemical reactions in a cell is unrealistic for a gene regulatory network from modeling, analysing and computing viewpoint. However, in a cell, many different time scales characterize the gene regulatory processes, which can be exploited to reduce the complexity of the mathematical models. For instance, the transcription and translation processes generally evolve on a time scale that is much slower than that of phosphorylation, dimerization or binding reactions of transcription factors. In addition, there are also many conservation conditions, such as total DNA number in a cell, which are important in modeling the gene networks. In this paper, we focus to model the gene regulatory networks with stochastic noise by using the property of fast-slow dynamics, and further investigate the biological implications of noise.

2 Master Equation

Consider a system containing m chemical reactions with n molecular species, where m and n are positive integer numbers. Let $u(t) = (u_1, \dots, u_n)$ be state of the species, i.e. u_i is the number of the i -th species at t , which is a non-negative integer. Then the dynamics of the system is described by the master equation with initial state $u(0)$ at $t = 0$

$$\frac{\partial p(u, t)}{\partial t} = \sum_{k=1}^m [w_k(u - v_k)p(u - v_k, t) - w_k(u)p(u, t)] \quad (1)$$

where $p(u, t)$ is the probability for the state u at t . $v_k = (v_{k,1}, \dots, v_{k,n})$ is an integer vector for the change of state, i.e. $v_{k,j}$ is the change in the number of the j -th molecule by the k -th reaction. $w_k(u)$ is a transition rate (≥ 0) from state u to state $u + v_k$ by the k -th reaction. Notice that $u \pm v_k$ should be non-negative although $v_{k,j}$ can be negative.

Next we exploit the fast-slow reactions to simplify the master equation. Without loss of generality, assume that the first m_f reactions are fast reactions. Rearrange the state variables by $u = (x, y)$, where $x = (x_1, \dots, x_{n_x})$, $y = (y_1, \dots, y_{n_y})$. x_i is the number of a molecule synthesized in a fast chemical reaction, such as a dimer due to dimerization reaction or a DNA and protein complex due to binding reaction with the conservation of DNA number. y_i is the number of the mRNA produced by transcription reaction, or the total number of a protein produced by the translation reaction of the mRNA. Notice that y_i for a protein is the total number including dimers and other complexes.

Next, we suppress the explicit time dependence of $p(u, t)$ for readability. Define a marginal function $p(y) = \int p(x, y) dx$, where the integration is simply a summation over all discrete x . Then, the joint probability function is written by the marginal probability and conditional probability as

$$p(x, y) = p(x|y)p(y). \quad (2)$$

3 Quasi-Equilibrium

Substituting $p(x, y) = p(x|y)p(y)$ into eqn.(1) and summing over x , we have the master equation for the evolution of $p(y)$ in terms of y but with unknown moments of x . Rearrange terms of eqn.(1) for fast reactions based on each reaction and its reverse reaction. For instance, when the reaction- j is the reverse reaction of the reaction- i , there are terms $[w_i(u - v_i)p(x - vx_i|y) - w_j(u)p(x|y)]p(y)$ and $[w_j(u - v_j)p(x - vx_j|y) - w_i(u)p(x|y)]p(y)$ in eqn.(1), where vx_i is a partial vector of v_i corresponding to the change of x . Since both number of mRNA and the total number of protein are not affected by fast reactions but by transcription and translation reactions, the partial vectors corresponding to y are zero vectors. Assume that fast reactions reach quasi-equilibrium much fast compared with transcription and translation processes. Then the probability flux related to each fast reaction approaches zero

$$w_i(u - v_i)p(x - vx_i|y) - w_j(u)p(x|y) = 0. \quad (3)$$

In such way, we can obtain all steady-state equations for all fast reactions. By multiplying appropriate x_j^k and summing those equations over x with the consideration of conservation conditions, we can derive the unknown moments of each x_i conditional on y in the master equation, in terms of y . Therefore, the master equation has form

$$\frac{\partial p(y)}{\partial t} = \sum_{k=m_f+1}^m [w_k(y - vy_k)p(y - vy_k) - w_k(y)p(y)] \quad (4)$$

where $w_k(y)$ is the transformed transition rate of $w(u)$, and are generally not polynomials of y due to the moments of x . Clearly the complexity of the original master equation is significantly reduced by eliminating all fast variables.

4 Gene Regulatory Network

Assuming that the change vy_i is much lower than y , we further simplify eqn.(4) by the Fokker-Planck equation. By Taylor expansion of $w_k(y - vy_k)p(y - vy_k)$ to order two, we then have the Fokker-Planck equation

$$\frac{\partial p(y)}{\partial t} = \sum_{k=m_f+1}^m \left[- \sum_{i=1}^{n_y} vy_{k,i} \frac{\partial}{\partial y_i} + \sum_{i,j=1}^{n_y} \frac{vy_{k,i}vy_{k,j}}{2} \frac{\partial^2}{\partial y_i \partial y_j} \right] w_k(y)p(y) \quad (5)$$

which can be solved in a much easy way numerically, and also be equivalently changed into the forms of the Langevin equations.

Let $K_i(y) = \sum_{k=m_f+1}^m vy_{k,i}w_k(y)$ and $K_{ij}(y) = \sum_{k=m_f+1}^m vy_{k,i}vy_{k,j}w_k(y)$ for all i and j . Then the Langevin equations for $i = 1, \dots, n_y$ are

$$\frac{dy_i}{dt} = K_i(y) + \eta_i \quad (6)$$

where the η_i are Gaussian noises that have zero mean $\langle \eta_i(t) \rangle = 0$ and covariances $\langle \eta_i(t)\eta_j(t') \rangle = K_{ij}\delta(t - t')$.

We can further simplify the master equation with deterministic dynamics by the cumulant evolution equations. Comparing with eqn.(1), it is much easy to derive the cumulant evolution equations from eqn.(5) or (6).