

Stochastic Biochemical Control Theory

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Abstract

We provide a general control theory capable of describing stochastic dynamics of biochemical networks at a cellular level. We investigate how changes in a genotype or environment are propagated into a phenotype for different network topologies and regulatory patterns. The random events of biochemical reactions make reaction rates and concentrations to fluctuate. When such fluctuations are considerable, the mean values of the rates can be different from the deterministic case without fluctuations. As a correction, we introduce elasticities of the reaction rates on concentration variances. We find that summation theorems and connectivity theorems hold for concentrations and their variances, respectively.

Introduction

We analyze the sensitivities of biochemical networks near stationary states to small external perturbations. The perturbations propagate into the networks by causing reaction rates to change. This leads to concentration changes and vice versa. Thus, it is necessary to quantify how sensitive the rates are to the changes in concentrations to perform sensitivity analysis. We can measure such *local* sensitivity using a notion of an *elasticity*. The local changes eventually cause system-wide effects, i.e., the steady states are changed. Such *global* response can be measured by *control coefficients*.

We introduce new measures of the local and global sensitivities for stochastic systems and discover relationships between these sensitivities: summation theorems and connectivity theorems. We describe the global sensitivities of stochastic systems in terms of the local sensitivities. These results will be helpful to understand the stochastic properties of various network motifs.

Local Sensitivity: Elasticity

If the biochemical networks show considerable fluctuations in concentrations, the reaction rates will also fluctuate. Such fluctuations can affect mean reaction rates due to the non-linearity in the rate equations; the fluctuations in the concentrations can disproportionately displace the reaction rates. As a first approximation, we can interpret the mean reaction rates as functions of concentration variances $\langle\sigma\rangle$ as well as mean concentrations $\langle s\rangle$ and enzyme activities e with $\langle.\rangle$ denoting an ensemble average. Thus, we denote mean rate functions using \tilde{v} ,

$$\tilde{v}(\langle s\rangle, \langle\sigma\rangle, e) \equiv \langle v(s, e)\rangle. \quad (1)$$

In the stochastic framework we see that we need to introduce the notion of the elasticity of

the rate with respect to the variance and mean of concentration:

$$\varepsilon_{\sigma_{ij}}^{\tilde{v}} \equiv \frac{\langle \sigma_{ij} \rangle}{\tilde{v}} \frac{\partial \tilde{v}}{\partial \langle \sigma_{ij} \rangle} \quad \text{and} \quad \varepsilon_s^{\tilde{v}} \equiv \frac{\langle s \rangle}{\tilde{v}} \frac{\partial \tilde{v}}{\partial \langle s \rangle}. \quad (2)$$

The variance elasticity is shown to give a correction to the mean reaction rate:

$$\tilde{v} = v(1 + \varepsilon_T^{\tilde{v}}), \quad (3)$$

where $\varepsilon_T^{\tilde{v}} \equiv \sum_{ij} \varepsilon_{\sigma_{ij}}^{\tilde{v}}$. Monte-Carlo simulations support this approximation as in Fig. 1. The variance elasticity also gives a correction to the traditional deterministic elasticity to concentration:

$$\varepsilon_s^{\tilde{v}} = \varepsilon_s^v + \frac{\partial \varepsilon_T^{\tilde{v}}}{\partial \langle s \rangle} \langle s \rangle.$$

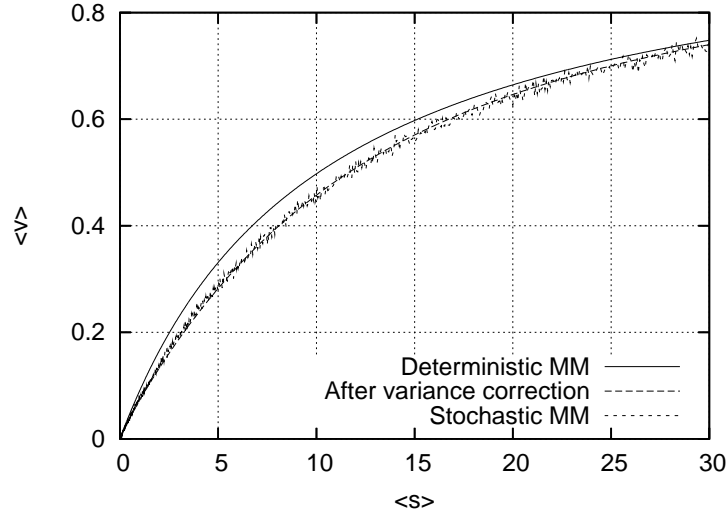


Figure 1: A Michaelis-Menten reaction $S \rightarrow P$ with a rate $V = V_0 S / (K_M + S)$ with $V_0 = 1$, $K_M = 10.1$ and S (P) the number of substrate (product) molecules. As an initial condition, $S = 100$ and $P = 0$. S and P are measured at given series of time. Each independent runs are repeated and ensemble averages are taken. The mean reaction rate $\langle V \rangle$ is measured from the mean number change of the product molecules.

Global Sensitivity: Control Coefficient

Now, we investigate the global responses to the external perturbations. We introduce four sets of new control coefficients for mean concentrations $\langle s \rangle$, mean fluxes \tilde{J} , concentration variances $\langle \sigma_s \rangle$, and flux variances $\langle \sigma_j \rangle$. We have found that there exist summation theorems and connectivity theorems for each four sets of coefficients, respectively.

These control coefficients are defined for mean concentrations and variances as follows:

$$C_e^s = \frac{d\langle s \rangle}{de} \frac{e}{\langle s \rangle}, \quad \text{and} \quad C_e^\sigma = \frac{d\langle \sigma \rangle}{de} \frac{e}{\langle \sigma \rangle}.$$

As a simple example, consider a general biochemical network where all reaction rates v_i are proportional to enzyme activities e_i . In this case, we have shown the following summation theorems:

$$\sum_i C_{e_i}^s = 0, \quad \sum_i C_{e_i}^\sigma = 0, \quad \sum_i C_{e_i}^{\tilde{J}} = 1, \quad \text{and} \quad \sum_i C_{e_i}^{\sigma\tilde{J}} = 2,$$

and connectivity theorems:

$$\sum_i C_{e_i}^s \left(\varepsilon_s^{\tilde{v}_i} + \sum_{jk} \varepsilon_{\sigma_{jk}}^{\tilde{v}_i} \frac{\partial \ln \sigma_{jk}(s, e)}{\partial \ln s} \right) = -1, \quad \sum_i C_{e_i}^{\tilde{J}} \left(\varepsilon_s^{\tilde{v}_i} + \sum_{jk} \varepsilon_{\sigma_{jk}}^{\tilde{v}_i} \frac{\partial \ln \sigma_{jk}(s, e)}{\partial \ln s} \right) = 0, \quad \text{etc.}$$

All these new summation relationships have been confirmed by simulations (unpublished). Furthermore, we also have extended the above simple case to that rates are nonlinear function of the external parameters.

We currently apply these results to a range of network motifs such as negative (positive) feedback (feedforward) pathways, branched networks, gene expression cascades, etc.

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