Stochastic Control Analysis for Biochemical Reaction Systems

Kyung Hyuk Kim[1], Hong Qian[2,1], and Herbert M. Sauro[1]
[1] Department of Bioengineering, University of Washington, Seattle, WA 98195
[2] Department of Applied Mathematics, University of Washington, Seattle, WA 98195

Abstract
We investigate how stochastic reaction processes are affected by external perturbations. We describe an extension of the deterministic metabolic control analysis (MCA) to the stochastic regime. We introduce stochastic sensitivities for mean and covariance values of reactant concentrations and reaction fluxes and show that there exist MCA-like summation theorems among these sensitivities. The summation theorems for flux variances are shown to depend on the size of the measurement time window, within which reaction events are counted for measuring a single flux. The degree of the dependency can become significant for processes involving multi-time-scale dynamics. This dependency is shown to be closely related to the power-law scaling observed in flux fluctuations in other kinds of complex networks. We propose a systematic way to control fluctuations of reactant concentrations while minimizing changes in mean concentration levels. Such orthogonal control is obtained by introducing a control vector indicating the most-sensitive control strength and direction. We also propose a possible implication in the control of flux fluctuation: The control distribution for flux fluctuations changes with the size of the time window for single flux measurements. When a control engineer applies a specific control operation on a reaction system, the system can respond in a way that depends on the time window size that is opposite to the one expected.

Metabolic control analysis (MCA) [1] and the closely related biochemical systems theory [2] have greatly enhanced our ability to understand the dynamics of cellular networks. However, these approaches are based on a deterministic picture of cellular processes and in recent years it has become very clear that many networks, for example gene regulatory networks, operate with a significant degree of stochasticity. In these situations a deterministic formalism is inadequate and here we begin the process of developing a new theory of control based on stochastic dynamics which we call stochastic control analysis (SCA).

There have some efforts to introduce general approaches to studying stochastic models of cellular networks, however no attempt has been made to try to reformulate MCA into the stochastic regime. We introduce new stochastic measures, in particular control coefficients of *fluctuation strength* and *fluctuation correlations* with respect to concentrations and fluxes. These control coefficients quantify the global responses of the fluctuation strength and correlations due to perturbations in the system parameters. We also introduce sensitivities for the *mean* levels of concentrations and fluxes, which are closely related to the MCA control coefficients.

We will investigate the relationship among these sensitivities and show the existence of MCA-like summation theorems. As an application of the sensitivities, we will provide a systematic non-local method for controlling noise in networks.

The model system we will consider is a chemical reaction system described by the chemical master equation. We introduce sensitivity measures called control coefficients. The system variables (y) of interest can be either mean values or coefficients of variation (CV) of concentrations and reaction fluxes. We define the control coefficients for these variables as

$$C_p^y = \frac{\text{The percentage change in } y}{\text{The percentage change in } p} = \frac{d\log y}{d\log p},$$

which indicates the percentage change in y due to the percentage change in a parameter p. The change in y is from one stationary state to another corresponding to before and after the perturbation, respectively. The parameter p will be called here a control parameter, which is not affected by the system's reactions. We restrict the set of the control parameters ($\boldsymbol{p} = (p_1, \cdots, p_L)$) to be the global proportionality constants of reaction rates. E.g., for a reaction rate $v = \frac{p\,s}{K_M + s}$ with s a concentration and K_M a Michaelis-Menten constant, p is a control parameter but K_M is not.

We have found that there exist MCA-like summation theorems among the proposed stochastic sensitivities, which are valid under *any* strength of noise and *finite* perturbations of parameters $\boldsymbol{p}$. The existence of these theorems is rooted in the fact that the stochastic measures satisfy certain scaling properties under a specific kind of scale change in time and control parameters.

We derive the concentration summation theorems:

$$\sum_{i=1}^{L} C_{p_i}^{\langle s_j \rangle} = 0, \text{ and } \sum_{i=1}^{L} C_{p_i}^{V^s_{jk}} = 0,$$

for all species j and k. V^s_{jk} denotes concentration CV between species j and k. We obtain the summation theorems for mean fluxes: $\sum_{i=1}^{L} C_{p_i}^{\langle J_j \rangle} = 1$.

Here the reaction flux J is measured by counting the number of reaction events within a time window ϵ. The variances of J are dependent on ϵ (as will be discussed later). Therefore, we label fluxes by ϵ hereafter: J^ϵ. We also obtain the summation theorems for flux CVs, denoting flux CVs between two fluxes J_i and J_j by V^J_{ij}:

$$\sum_{i=1}^{L} C_{p_i}^{V^{J^\epsilon}_{jk}} = \frac{d \log V^{J^\epsilon}_{jk}}{d \log \epsilon}, \tag{1}$$

for all reactions j, k. The sum varies depending on the value of ϵ. More specifically, the sum value is *equal* to the slope of a log-log plot of flux CV vs. ϵ.

We investigate how the sum value of Eq.1 depends on ϵ. We have found an interesting fact that the sum value can vary significantly with the change in ϵ when the system shows wide separation of reaction time scales (see Fig.1D). For a general reaction systems, a plateau region (for intermediate ϵ) appears typically if the slow and fast fluctuations are well separated. The plateau region can be tilted if the time scales of internal and external noise is not separated far enough. In this case, the sum value of the flux CV control coefficients will deviate from zero in the region of the plateau.

As an application of the introduced stochastic sensitivities, we consider the orthogonal control of mean concentration levels and concentration CVs. Such control needs to satisfy the following

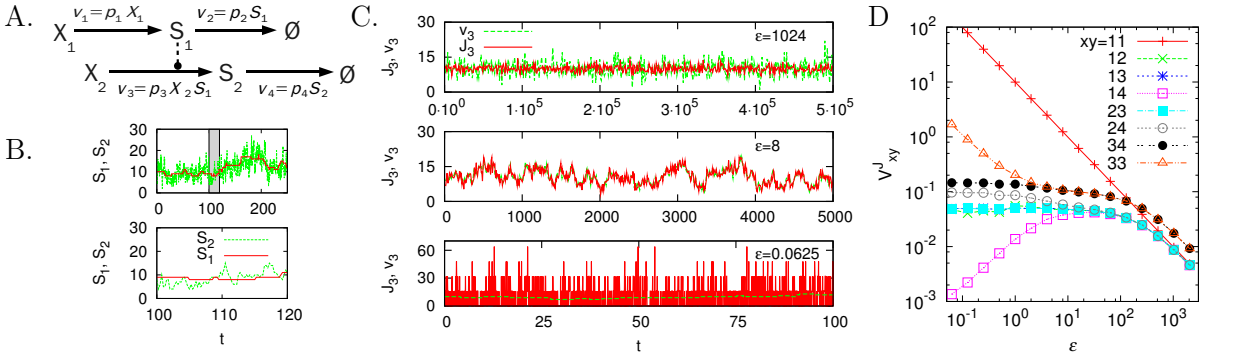
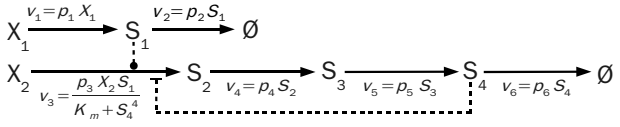


FIG. 1: Two step cascade reaction system: S_1 down-regulates the reaction of creating S_2 (A). The reaction rates involving S_1 is set 100 times slower than those involving S_2. S_1 applies an external noise onto the (internal) system of S_2. Time evolution of S_1 and S_2 is shown (B). The region of $t = [100, 120]$ is extended (B,top). J_3 is measured with three different time window sizes, $\epsilon = 0.0625, 8, 1024$ (C). J_3 matches with v_3 for $\epsilon \simeq 8$, because the internal noise is averaged out, i.e., the external noise is dominant in this time scale. Flux variance of J_3 decreases with time window size ϵ (C,D). The CV of flux J_3 shows a plateau, while the CV of flux J_1 does not (D).

requirements. First, the concentration CV decreases with the concentration mean, and thus the control of mean and CV can be anti-correlated. In this case parameters need to be perturbed by a large amount to achieve a significant change in the level of CV. Second, the concentration CV is dependent on noise propagation, implying that a set of multiple parameters may need to be controlled simultaneously. Taking into account these requirements, we present a systematic non-local method for orthogonal control using the control coefficients.

We introduce a control vector $C^x_{\boldsymbol{p}} \equiv (C^x_{p_1}, C^x_{p_2}, \cdots, C^x_{p_L})$ defined in control parameter space. When parameters are perturbed in the direction of the control vector, the response of a system variable y (concentration mean or CV) increases. To perform orthogonal control of concentration mean and CV, the corresponding control vectors need to be estimated. The angle (θ) between the two control vectors shows how much the two controls, done along the control vectors, are correlated. If θ is close to $-180°$, the two controls are anti-correlated and the orthogonal control can difficult. If θ is close to $90°$, the two controls are orthogonal and no change needs to be made. Consider that our aim is to decrease V^s without changing $\langle S \rangle$. To accomplish this, we can perturb parameters in the direction of a vector ($\boldsymbol{\lambda}$) obtained by projecting $C^{V^s}_{\boldsymbol{p}}$ onto the parameter space perpendicular to $C^s_{\boldsymbol{p}}$. We provide an example of orthogonal control to reduce the concentration CV by investigating a linear chain reaction system with a negative feedback (Fig.2). After the parameters are perturbed along $\boldsymbol{\lambda}$ iteratively, we could reduce the noise level by 25% without changing the mean level.



Finally, we discuss a way to reduce the flux CV. Consider a scenario where a metabolic engineer aims to reduce the fluctuations in the production rate of an end product (e.g., v_6 in Fig.2). To this aim, her/his first guess is that reducing the concentration fluctuations (S_4 in Fig.2) will lead to a reduction in the rate fluctuations. The engineer introduces a negative feedback to reduce the concentration fluctuations. The question we might ask is whether this operation guarantees that the rate fluctuations are reduced. As we have shown in the previous analysis there is no definite correlation between flux and concentration fluctuations but depends on the measurement time scale, ϵ. For the negative feedback system shown above, decreasing p_6 causes a reduction in the concentration CV of S_4. We can decide to decrease p_6 to reduce the flux fluctuations. We found that the sign of the control coefficients $C^{V^J_{66}}_{p_6}$ is however negative for $\epsilon \lesssim \tau_f$ (τ_f: feedback time scale) and positive for $\epsilon \gtrsim \tau_f$. This means that controlling p_6 can have an opposite effect depending on ϵ. Therefore, in this case, we need to choose the value of ϵ sufficiently larger that the feedback time scale.

In summary, we have extended deterministic MCA to the stochastic regime for general biochemical reaction networks. We have shown that there exist MCA-like summation theorems for stochastic sensitivity measures. The summation theorems for the reaction fluxes have shown that the sum values of control coefficients for flux CVs depend on the size of the measurement time window (ϵ). In terms of the stochastic sensitivity measures, we have provided a non-local systematic way to control the noise levels of concentrations and fluxes. We hope this method to be useful for controlling noise levels in various reaction networks such as gene regulatory networks, metabolic reaction networks, and protein-protein interaction networks.

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[1] Fell, D. A. (1996) *Understanding the Control of Metabolism.* (London, Portland Press).

[2] Savageau, M. A. (1976) *Biochemical systems analysis: a study of function and design in molecular biology.* (Addison-Wesley Pub. Co.).