Multiparameter Sensitivity as a Robustness Measure for Dynamic Biochemical Models

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1 Introduction

Robustness is the ability to resume reliable operation in the face of different types of perturbations. Robustness can be used as a criterion to characterize the performance of biochemical systems. It is particularly true that all kinetic parameters simultaneously differ from their nominal values *in vivo*. Monte Carlo simulation has been used to quantify system's robustness to such fluctuations in parameters. On the other hand, the sum of the squared magnitudes of single-parameter sensitivities was presented as multiparameter sensitivity (MPS) in a liner model. Recently, we showed that MPS equals to a normalized variance of system's output simulated by Monte Carlo simulation. We also demonstrated that MPS is applicable to nonlinear biochemical models, and named its numerical version quasi-multiparameter sensitivity (QMPS). Use of QMPS with an efficient parameter search revealed the mechanisms by which circadian clock robustly ticks. QMPS can replace the widely used Monte Carlo method in terms of the calculation speed and theoretical bases.

2 Methods

2.1 Dynamic Model

Generally a dynamic model of biochemical networks is formulated by differential equations:

$$\dot{\mathbf{x}} = \mathbf{F}\left(t, \mathbf{x}, \mathbf{p}\right), \tag{1}$$

where, t is time, $\mathbf{x}$ is the variable vector that indicates molecular concentrations, $\mathbf{p} = (p_1, \ldots, p_n)$ is the kinetic parameter vector, and n is the number of kinetic parameters.

2.2 Quasi-multiparameter Sensitivity (QMPS)

Let $q(\mathbf{p})$ be a given target function or system's output simulated by solving Eq.1. Multiparameter sensitivity (MPS) of the target function is defined as:

$$|MPS|^2 = \sum_{i=1}^{n} \left(\frac{p_i}{q(\mathbf{p})} \frac{\partial q(\mathbf{p})}{\partial p_i} \right)^2 = \sum_{i=1}^{n} \left(\frac{\partial \ln q(\mathbf{p})}{\partial \ln p_i} \right)^2. \tag{2}$$

The numerically calculated MPS is named QMPS. It can be calculated by $n+1$ simulation runs, where n is the number of kinetic parameters. Monte Carlo simulation requires more simulation runs because the parameter space expands exponentially as n increases. Note that although MPS can be calculated by summing the squared single-parameter sensitivities, it quantifies robustness to simultaneous fluctuations in all kinetic parameters. The mathematical proof is shown in [1].

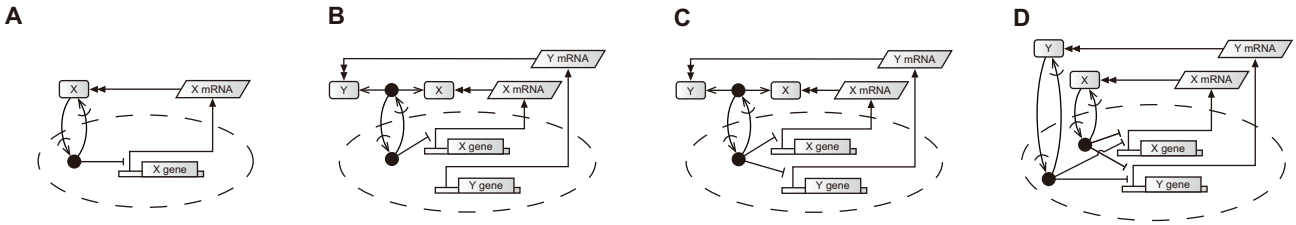

Figure 1: Biochemical network maps of the circadian clock models with different types of loop coupling logics. A: The single feedback model, B: the semi-dual feedback model, C: the dual feedback model, D: the redundant feedback model.

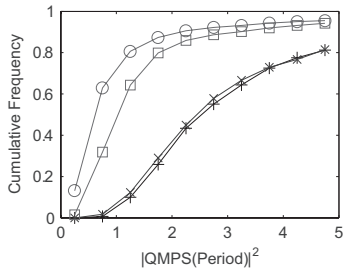

Figure 2: Cumulative frequency distributions of QMPS. The single feedback model (plus), the semi-dual feedback model (cross), the dual feedback model (circle), the redundant feedback model (square).

3 Results and Discussion

A simple or single transcriptional-translational feedback loop is sufficient for sustained oscillations. However, circadian clocks implement multiple, complicated feedback loops. To reveal the mechanism by which such a complex feedback system evolves, we quantified the robustness of four competing models (Figure 1).

To make the analysis independent from a particular choice of kinetic parameter values, the two-phase search (TPS) method [2] was employed to search all possible parameter sets that generate circadian oscillations. The QMPS values were calculated for the resultant parameter solutions, and the distributions of QMPS were compared among the four competing models (Figure 2). The dual feedback model provided QMPS values lower than any other models [3].

By performing global numerical analysis by QMPS and TPS, we demonstrated that the dual feedback model, employed by a real biological system, is the most reasonable choice for creating a robust oscillator. The low computational cost for QMPS is essential in this type of global analysis. QMPS can replace Monte Carlo method in terms of the calculation speed and theoretical bases.

References

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