Robustness of mathematical models for biological systems

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Abstract

The robustness of mathematical models for biological systems is studied by sensitivity analysis and stochastic simulations. Using a neural network model with three genes as the test problem, we study robustness properties of synthesis and degradation processes. For single parameter robustness, sensitivity analysis techniques are applied for studying parameter variations and stochastic simulations are used for investigating the impact of external noise. Results of sensitivity analysis are consistent with those obtained by stochastic simulations. Stochastic models with external noise can be used for studying the robustness not only to external noise but also to parameter variations. For external noise we also use stochastic models to study the robustness of the function of each gene and that of the system.

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1 Introduction

The notion of robustness in biological systems has received considerable interest recently by experiments and theoretical study. By saying that a system is robust we imply that a particular function or characteristic of the system is preserved despite changes in the operating environment [6] or genetic changes in its components [5]. For example, by a computer model [2] and later by experiments [1], it has been demonstrated that the adaptation mechanism found in the chemotactic signaling pathway in *Escherichia coli* is robust. For robust biological systems, we expect that mathematical models that attempt to explain these systems should also be robust. It has been proposed that the robustness of mathematical models be used as a criterion for determining plausibility of candidate models [7, 9].

One topic in the robustness analysis of mathematical models is the model's sensitivity to parameter variations. These variations may be errors in parameter estimation or changes in the components of biological systems. This

topic has been studied by the sensitivity analysis techniques [3, 6, 7]. There are two approaches for the sensitivity analysis of single parameter: repeated simulations by varying one parameter while holding all others fixed; and adjacent models for comparing the importance of each parameter variation. However, single parameter insensitivity may not be sufficient owing to interactions between several parameters. Systematic changes of many parameters at a time suffer from an exponential increase in the number of parameters that need to be changed. More sophisticated methods are needed for studying multi-parameter robustness.

Another important topic is the robustness analysis of mathematical models for the noise in biological systems. Noise existing in biological systems is classified as external noise due to environmental fluctuations or internal noise due to small numbers of some important regulatory molecules [4]. As living systems are optimized to function in the presence of stochastic fluctuations, mathematical models for biochemical networks must withstand considerable variations and random perturbations of biochemical parameters [8]. The study of the robustness to noise normally is carried out by simulations of stochastic models [8, 9].

We investigate the robustness of mathematical models to external noise and the relationship between the robustness to parameter variations and that to external noise. In Section 2 we present adjacent models and stochastic models for studying robustness properties. A neural network model with three genes is introduced in Section 3. In Section 4 we discuss single parameter robustness and the discussion for multi-parameters is presented in Section 5.

2 Methods for studying robustness

In this section we present methods used in this paper for studying the robustness of mathematical models. The first method is the adjacent model

for studying parameter variations. For a given model (the base model) with parameter p

$$\frac{dx}{dt} = f(t, x, p)\,, \tag{1}$$

we consider the solution x^* of this system with a perturbed parameter $p+\Delta p$. The difference between solutions x^* and x is

$$\frac{d(x^* - x)}{dt} = f(t, x^*, p + \Delta p) - f(t, x, p) \approx \frac{\partial f}{\partial x}(x^* - x) + \frac{\partial f}{\partial p}\Delta p\,.$$

Together with the base model (1), the adjacent model for parameter p is

$$\frac{d\mathrm{Ep}}{dt} = \frac{\partial f}{\partial x}\mathrm{Ep} + \frac{\partial f}{\partial p}\,. \tag{2}$$

Here Ep represents the drift of the solution with a unit parameter perturbation. The solutions of adjacent models for certain important parameters in the base model give insight into which parameter induces the largest error in solutions and when errors will be the largest in simulations.

In order to study external noise, Hasty et al. [4] introduced stochastic models by adding additive or multiplicative noise to mathematical models. For example, for a biological system with mathematical model (the base model)

$$\frac{dx}{dt} = f(t, x) - d_x x\,,$$

the stochastic model with additive noise is

$$dx = f(t, x)\,dt - d_x x\,dt + k\,dW(t)\,. \tag{3}$$

When considering noise in the degradation process, the stochastic model with multiplicative noise is

$$dx = f(t, x)\,dt - d_x x\,dt + k d_x x\,dW(t)\,. \tag{4}$$

Here $W(t)$ is the Wiener process whose increments are independent Gaussian random variables, and k is a scalar for adjusting the magnitude of noise.

Based on a large number of stochastic simulations, moments of the simulated solutions can be calculated. Then the robustness to noise can be measured by the comparison of these moments with the solution obtained by the base model and with the variance of noise in model (3) or (4).

3 Neural network models

Neural network models have been used for expressing regulatory mechanisms in genetic regulatory networks [10]. A system with N genes is

$$\frac{dx_i}{dt} = s_i g_i(t) - d_i x_i\,, \quad \text{with } i = 1, \ldots, N\,. \tag{5}$$

Here x_i, s_i and d_i are the expression level, synthesis rate and degradation rate of gene i in the system, respectively. The functions g_i are the sigmoidal transfer function

$$g_i(t) = \frac{1}{1 + \exp[-r_i(t)]}\,, \tag{6}$$

with

$$r_i(t) = \sum_{j=1}^{N} w_{ij} x_j(t) + b_i\,.$$

Here $\boldsymbol{b} = (b_i)_N$ is a vector for reaction delay, and the weight matrix $\boldsymbol{w}= (w_{ij})_{N\times N}$ defines regulatory interactions between genes. A regulation from gene j to gene i means a non-zero weight w_{ij}. A positive weight implies a stimulating effect (positive feedback) while a negative weight implies repression (negative feedback). A zero weight means no regulatory interaction.

Figure 1 gives a gene network with three genes which has been used for realizing two important expression patterns: oscillation and steady state [10]. In this network, the product of Gene A controls the expression of Gene B, which initiates the expression of Gene C. Gene B induces the expression of

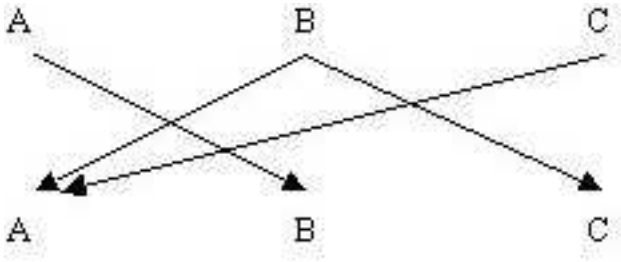

FIGURE 1: A gene network with three genes.

Gene A forming a positive feedback. Gene C in turn negatively controls the expression of Gene A, forming a negative feedback. The regulation in this network is characterized by the weight matrix [10]

$$\boldsymbol{w} = \begin{bmatrix} 0 & 10 & -10 \\ 10 & 0 & 0 \\ 0 & 10 & 0 \end{bmatrix}. \tag{7}$$

We realize a simulation with the steady state expression pattern by using (7) and

$$\boldsymbol{s} = (1,1,1)\,, \quad \boldsymbol{d} = \boldsymbol{s}\,, \quad \boldsymbol{b} = -\boldsymbol{s}\,;$$

and a simulation with the oscillatory expression pattern by using (7) and

$$\boldsymbol{s} = (4.5,1,1)\,, \quad \boldsymbol{d} = (0.6,1,1)\,, \quad \boldsymbol{b} = -(3,3,3)\,.$$

4 Single parameter robustness

In this section we will study the robustness of model (5) to parameter variations and fluctuations to each synthesis rate and degradation rate. For each synthesis rate s_i $(i = 1,2,3)$, the adjacent model (together with (5)) is

$$\frac{d\mathrm{Es}_{ij}}{dt} = s_j g_j^2(t) * e^{-r_j(t)} * [w(j,:) \cdot \mathbf{Es}_i] - d_j \mathrm{Es}_{ij} + \delta_{ij} g_j(t)\,, \tag{8}$$

with $j = 1, 2, 3$. Here $\mathbf{Es}_i = (\mathrm{Es}_{i1}, \mathrm{Es}_{i2}, \mathrm{Es}_{i3})^\top$. For each degradation rate d_i $(i = 1, 2, 3)$, the adjacent model (together with (5)) is

$$\frac{d\mathrm{Ed}_{ij}}{dt} = s_j g_j^2(t) * e^{-r_j(t)} * [w(j,:) \cdot \mathbf{Ed}_i] - d_j \mathrm{Ed}_{ij} - \delta_{ij} d_j \,, \tag{9}$$

with $j = 1, 2, 3$. Here $\mathbf{Ed}_i = (\mathrm{Ed}_{i1}, \mathrm{Ed}_{i2}, \mathrm{Ed}_{i3})^\top$.

Stochastic models for studying external noise in each reaction rate can be constructed by adding a stochastic process to the corresponding reaction rate. Similar to model (4), the stochastic model for studying fluctuations in each s_i $(i = 1, 2, 3)$ takes the form

$$dx_j = s_j g_j(t)\, dt + \delta_{ij} k s_j g_j(t)\, dW(t) - d_j x_j\, dt \,, \tag{10}$$

with $j = 1, 2, 3$. Here k is a scalar for adjusting the magnitude of noise in the synthesis process. The stochastic model for each d_i $(i = 1, 2, 3)$ is

$$dx_j = s_j g_j(t)\, dt - d_j x_j\, dt - \delta_{ij} k d_j x_j\, dW(t) \,, \tag{11}$$

with $j = 1, 2, 3$.

Figure 2 gives simulations of Es_{i3} $(i = 1, 2, 3)$ from adjacent models (8) for the steady state expression pattern (left) and the oscillatory expression pattern (right). Variations in parameter s_3 have more influence on simulation results. Compared with the steady state pattern, parameter variations in the oscillatory pattern have much larger influence on network behaviour. Similar simulations can be obtained from adjacent models for degradation rates (9) but they are not presented here due to the limit of space. Similarly variations in parameter d_3 have more influence on simulation results and the oscillatory pattern is more sensitive to variations in degradation rates.

For stochastic model (10) with same $k = 0.15$ for each i $(i = 1, 2, 3)$, Figure 3 gives simulations of x_3 for the steady state expression pattern (left) and the oscillatory pattern (right). Similar to Figure 2, noise related to

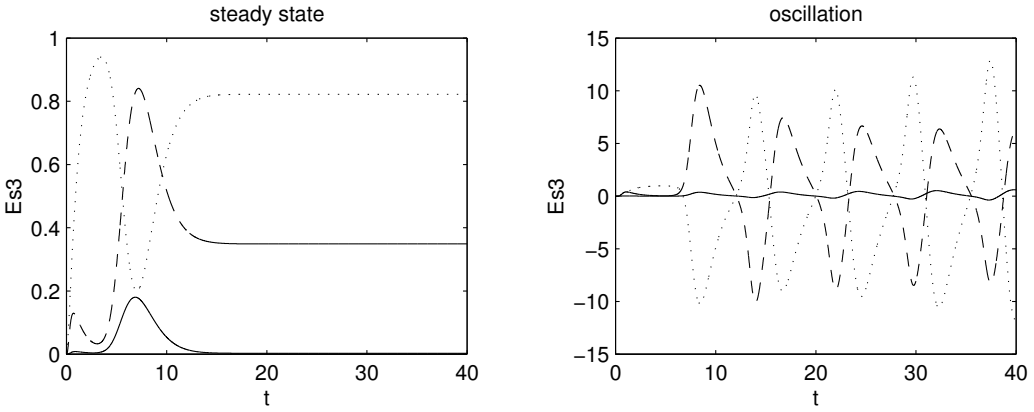

FIGURE 2: Simulations of Es_{i3} for the steady state pattern (left) and the oscillatory pattern (right). (Es_{13}: line, Es_{23}: dash, Es_{33}: dot)

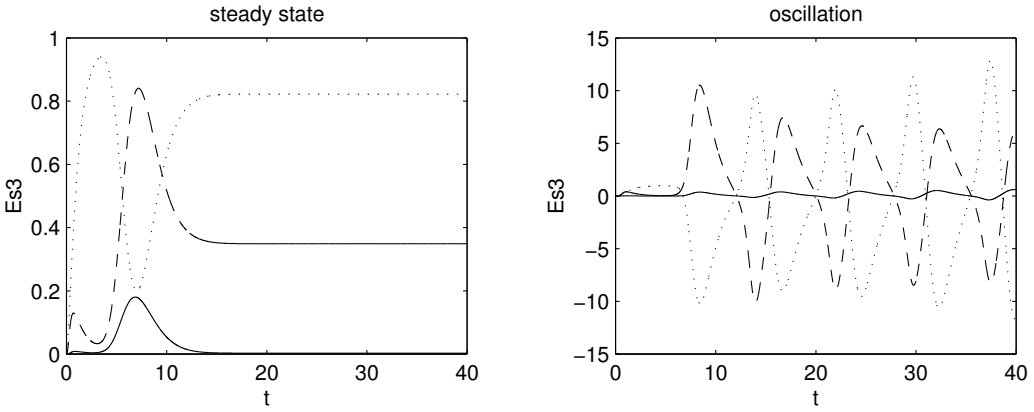

FIGURE 3: Simulations of x_3 from model (10) for the steady state pattern (left) and oscillatory pattern (right). (model with noise in s_1: line, s_2: dash, s_3: dot).

s_3 or d_3 has more influence on the system. In addition, fluctuations in the oscillatory pattern are much larger than those in the steady state pattern.

In addition to the qualitative results in Figures 2 and 3, we give quantitative results of the robustness properties of model (5). For the steady state expression pattern, we are interested in the drift of expression levels for the deterministic model

$$D_j(p) = x_j(p) - x_j\,,$$

where x_j is the expression level of gene j in system (5), $x_j(p)$ is the expression level obtained from (5) in which parameter p is perturbed. Based on N stochastic simulations, we use the mean of drifts and standard deviation of x_j,

$$\begin{aligned} MD_j(p) &= \frac{1}{N}\sum_{k=1}^{N}\left[x_j^{(k)}(p) - x_j\right] \equiv \bar{x}_j(p) - x_j\,, \\ SD_j(p) &= \sqrt{\frac{1}{N-1}\sum_{k=1}^{N}(x_j{}^{(k)}(p) - \bar{x}_j(p))^2}\,, \end{aligned}$$

to measure the robustness properties to external noise. Here $x_j{}^{(k)}(p)$ is the expression level of x_j in the kth simulation. It is obtained from a stochastic model with a stochastic component in parameter p.

Table 1 gives quantitative results from the deterministic and stochastic simulations for the steady state expression pattern. For the deterministic model (5), we vary each s_i $(i = 1, 2, 3)$ by $s_i^* = s_i(1 + 0.15)$ and fix all other parameters. Similar considerations are applied to each d_i. The first row of Table 1 gives drifts of x_3 with each perturbed parameter. Results in the last two rows are based 1000 simulations from models (10) and (11). We use the same $k = 0.15$ in noise terms of these stochastic models. These data give quantitative evidence to support the results in Figures 2 and 3.

The drifts of x_3 $(D_3(p))$ obtained by deterministic simulations are consistent with the means of drifts $(MD_3(p))$ obtained by stochastic simulations.

TABLE 1: Simulation results of x_3 for single parameter robustness

	$p = s_1$	$p = s_2$	$p = s_3$	$p = d_1$	$p = d_2$	$p = d_3$
$D_3(p)$	2.9E-4	3.1E-2	8.3E-2	−2.6E-4	−3.4E-2	−7.4E-2
$MD_3(p)$	−9.1E-6	−2.1E-3	4.7E-3	8.6E-6	−2.1E-3	7.4E-3
$SD_3(p)$	1.8E-4	2.6E-2	8.9E-2	1.9E-4	2.5E-2	9.1E-2

This observation suggests that stochastic simulations can study robustness properties not only for external noise but also for parameter variations. In the following section we use stochastic simulations to measure the robustness properties of model (5) to multiple parameters.

5 Robustness to multi-parameters

For multi-parameter problems we do not address all of the possible combinations of the parameters. Instead we just study the robustness to noise in synthesis and degradation processes of each gene. The following models will be used in stochastic simulations:

$$dx_j = [s_j g_j(t) - d_j x_j]\, dt + \delta_{ij}[k_1 s_j g_j(t)\, dW_1 - k_2 d_j x_j\, dW_2]\,, \qquad (12)$$

with $j = 1, 2, 3$ for each gene i $(i = 1, 2, 3)$. Here we use $k_1 = k_2 = 0.15$.

Based on 1000 simulations, we calculate moments of the expression levels obtained from (12). The definitions for the mean of drifts and standard deviation of x_j are defined by

$$MD_j(i) = \frac{1}{N}\sum_{k=1}^{N}\left[x_j^{(k)}(i) - x_j\right] \equiv \bar{x}_j(i) - x_j\,,$$

$$SD_j(i) = \sqrt{\frac{1}{N-1}\sum_{k=1}^{N}(x_j{}^{(k)}(i) - \bar{x}_j(i))^2}\,,$$

TABLE 2: Simulation results of x_3 by (12) with noise in s_i and d_i

	$i=1$	$i=2$	$i=3$
$MD_3(i)$	4.64E-6	5.9E-3	7.1E-3
$SD_3(i)$	2.78E-4	3.74E-2	0.1324

where ${x_j}^{(k)}(i)$ is the expression level of x_j in the kth simulation. It is obtained from model (12) with stochastic components in s_i and d_i. For the steady state expression pattern, Table 2 lists the means of drifts and standard deviations of x_3. Noise in s_1 and d_1 $(i = 1)$ has less impact on the system due to simple functions of Gene 1 (only stimulating Gene 2). For Gene 2 $(i = 2)$, fluctuations of the system are larger than those of Gene 1 because of more functions of Gene 2 (stimulating both Gene 1 and Gene 3). The system with noise in s_3 and d_3 $(i = 3)$ is still robust but numerical simulations have the largest fluctuations. This is due to the critical negative feedback function of Gene 3 in the system. These results indicate that the influence of a gene on robustness properties depends on its functions in the system.

Finally, the robustness of model (5) to external noise which is related to the synthesis and degradation processes of all genes. This stochastic model has been studied in [9], with $j = 1, 2, 3$

$$dx_j = [s_j g_j(t) - d_j x_j]dt + k_{1j} s_j g_j(t)\, dW_{1j} - k_{2j} d_j x_j\, dW_{2j}\,. \tag{13}$$

Figure 4 gives simulations of model (13) for the steady state pattern (left) and the oscillatory pattern (right) with $k_{1j} = k_{2j} = 0.15$ $(j = 1, 2, 3)$. The steady state pattern is robust but the oscillatory pattern is strongly influenced by external noise. The period and amplitude of oscillations fluctuate widely in time. This result serves as an evidence for questioning the suitability of neural network models for describing oscillatory phenomena in genetic regulatory networks.

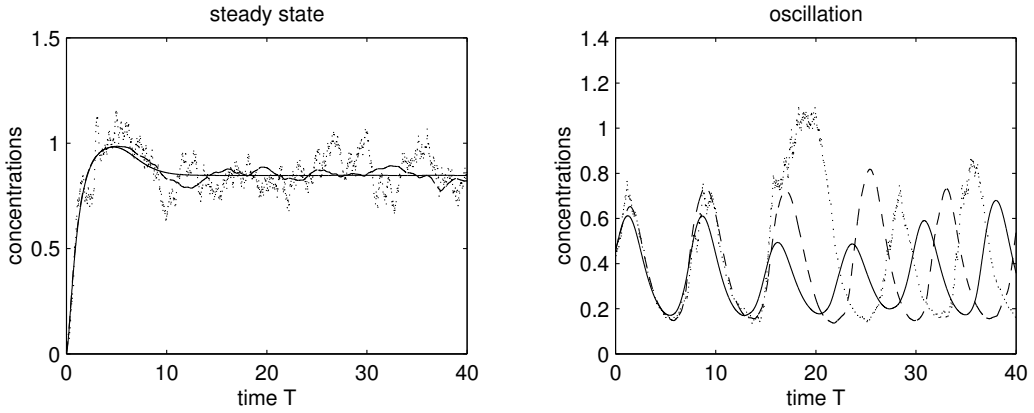

FIGURE 4: Simulations of model (13) for the steady state pattern (left) and the oscillatory pattern (right). (x_1: line, x_2: dash, x_3: dot).

6 Conclusions

For studying the robustness of mathematical models for biological systems, we should address three sources of uncertainty: errors in estimated parameters; external noise for environmental fluctuations; and internal noise due to small numbers of regulatory molecules. The analysis for each source of uncertainty is the first step in finding robustness properties of mathematical models. It would be very important to search relationships between the robustness properties of each source and the impact of combined sources on mathematical models. The work in this paper is an attempt in this direction. It is suggested that stochastic simulations be used to study the robustness not only to external noise but also to parameter variations. In this paper a neural network model with three genes has been used as the test problem. Future work will be based on the applications of stochastic simulations to more complicated biological systems.

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