Identification of Structural Weaknesses in Biochemical Models through Parameter Sensitivity Analysis

Mineo Morohashi [1,2]
moro@symbio.jst.go.jp

Mark Borisuk [1,3]
borisuk@cds.caltech.edu

Hamid Bolouri [1,4,5]
hbolouri@caltech.edu

Hiroaki Kitano [1,6]
kitano@symbio.jst.go.jp

1 Systems Biology Group, ERATO Kitano Symbiotic Systems Project, JST, M-31 Suite 6A 6-31-15 Jingumae Shibuya-ku, Tokyo 150-0001, Japan
2 Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima Bunkyo-ku, Tokyo 113-0034, Japan
3 Control and Dynamical Systems, California Institute of Technology, M/C 216-76, Pasadena, CA 91125, USA
4 Division of Biology, California Institute of Technology, M/C 216-76, Pasadena, CA 91125, USA
5 Science and Technology Research Centre, University of Hertfordshire, Hertfordshire, AL10 9AB, UK
6 Sony Computer Science Laboratories, Inc., 3-14-13 Higashi-gotanda Shinagawa-ku, Tokyo 141-0022, Japan

1 Introduction

A number of recent studies have shown that certain biochemical networks are highly robust to variations in parameters such as initial concentrations, protein synthesis/degradation rates, and kinetic reaction rates (e.g., [1, 2, 3]).

On the other hand, there have been relatively few systematic studies of parameter sensitivity in models of biochemical networks. Murray[4] analyzed the sensitivity of a Turing Reaction-Diffusion system to changes in the ratio of the two diffusion constants and found that for biologically plausible ranges of values, Turing patterns can only be obtained over a small and narrow region of the parameter space. More recently, Erb and Michaels[5] carried out an extensive numerical analysis of a 3 component hypothetical network with similarities to biological models proposed in [6, 7]. They found the model behavior was "extremely sensitive to errors in the parameters".

We use these studies as our point of departure and ask whether studies of the shape of the parameter space in biochemical networks can be used to identify weaknesses and biologically implausible structural elements in biochemical models. We selected one of the simplest models of the cell cycle proposed in [8] as a case study (for review see[6]).

This model was initially analyzed in an approximate, analytical manner by the authors and shown to have three regions of operation corresponding to three physiological states (the egg, the embryo, and the adult organism).

We have carried out a detailed bifurcation analysis of the above model using co-dimension one and co-dimension two plots to map out significant regions in parameter space. Our methodology is essentially that developed by [9] to characterize the behavior of a more recent, more complex Novak-Tyson model of the same process. We focus on the simpler model because the implications from its analysis are easier to understand, and because with the aid of hindsight, the shortcomings of this simple, early model are known.

We show that the above shortcomings result in corresponding parameter sensitivities in the model whose identification during model development could have been used to help improve the structure, and hence plausibility, of the model.

2 Methodology

The differential equations in Table 1 were proposed in [8] as a model of the concentrations of the two primary protagonists in the *Xenopus* cell cycle: active MPF (variable u) and cyclin (variable v). The model was shown to be capable of exhibiting three physiologically different behaviors: two stable steady states (cell cycle arrests) with high and low MPF activity respectively, and a limit cycle, corresponding to oscillations characteristic of the embryonic cell cycle. Which of the three behavioral regimes the system occupies is determined by the values of parameters $k1$ and $k6$ in the model.

Solutions of the equations can be represented by the system's set of steady states and the trajectory between these in phase space. The ensemble of behaviors exhibited by the system as a function of its parameters can be summarized in a bifurcation diagram. "Bifurcations" are the qualitative changes in the system dynamics as parameters are varied. The parameter values at which they occur are called "bifurcation points"[10].

We used AUTO[1], a tool for bifurcation analysis, to characterize the equations of Table 1 in terms of the parameters $k_i (i = 1, 4, 6)$. First, we constructed co-dimension one (one-parameter) bifurcation diagrams for all parameters to identify the parameter regions corresponding to the three behavioral regimes and the bifurcation points between them. Next, we tracked the Hopf bifurcation points detected in co-dimension one analysis to explore the shape of the parameter space regions defining the three characteristic regimes.

Table 1: Tyson's 2-equation model

$$\frac{du}{dt} = k_4(v-u)(\alpha + u^2) - k_6 u \quad (1)$$

$$\frac{dv}{dt} = k_1 - k_6 u \quad (2)$$

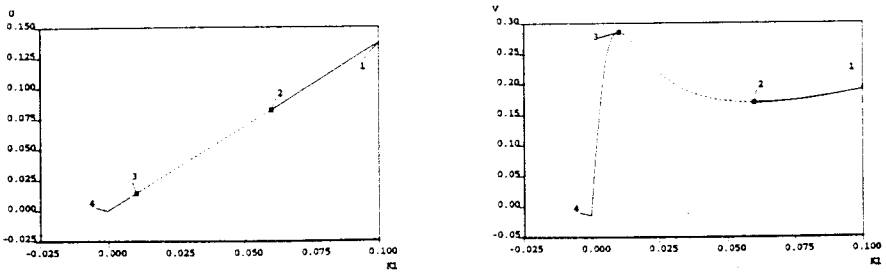
$k1, k4, k6$	:	rate constants
α	:	$k4'/k4$
u	:	(active MPF) / (total cdc2)
v	:	{(total cyclin) − (degrading cyclin)}/ (total cdc2)

3 Results and Discussion

As an example of co-dimension one bifurcation plots, Figure 1 shows the relationship between $k1$ and variables u (normalized MPF concentration) and v (normalized cyclin concentration). The numbers plotted in the diagram are labels which correspond to either a start/end point of tracking, or a bifurcation point. In the figure, the parameter ranges corresponding to the two steady-state regimes are plotted as a solid line, and unstable solution points are represented by a dashed line. The unstable points represent the spontaneous limit cycle (embryonic cell cycle). The Hopf bifurcation points are at labels 2 and 3.

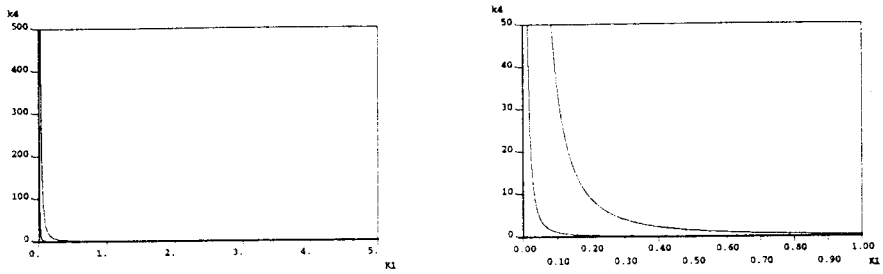
The co-dimension two bifurcation plot for $k1$ vs. $k4$ is shown in Figure 2: (b) is an expanded view of (a). Nominal values of $k1$ (the rate of synthesis of cyclin) and $k4$ (the autocatalytic rate of synthesis of active MPF), for oscillatory behavior (taken from biological experiments [11]) are $k1 = 0.01$, and $k4 = 100$. The plausible range of values of $k4$ is reported in [8, 9], as 10–1000. For $k1$ we assume a broader range equal to nominal +/− two orders of magnitude, i.e. approximately 0–1. As can be seen from the figure, the range of $k1$ and $k4$ values for which the system can have oscillations (the region between the two bifurcation lines) is very narrow. Thus, oscillations in the system will always be highly sensitive to either $k1$ or $k4$.

[1] `http://indy.cs.concordia.ca/auto/main.html`



(a)$k1$ vs. u (b)$k1$ vs. v

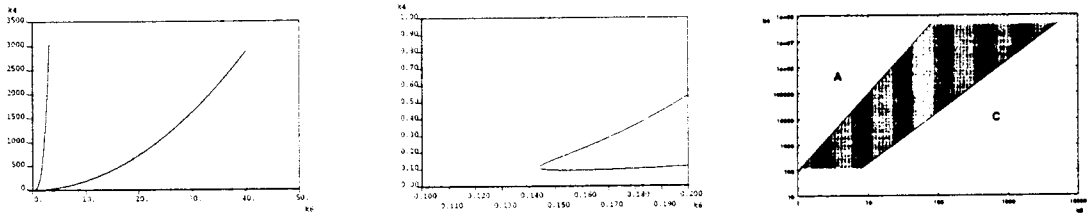
Figure 1: Co-dimension one bifurcation plots for $k1$



(a)$k1$ vs. $k4$ (b)$k1$ vs. $k4$ (zoomed view of (a))

Figure 2: Co-dimension two bifurcation plots for $k1$ and $k4$

Figure 3 shows the co-dimension 2 bifurcation plot for $k6$ and $k4$: (b) is an expanded view of (a) near the origin. By contrast, (c) is a logarithmic plot of the bifurcation loci at high values of $k4$ and $k6$. The plausible ranges of $k4$ and $k6$ as reported in [8] are 10–1000 and 0.1–10, respectively. Note that the region of oscillatory behavior (the space between the two lines) becomes larger, i.e., the system becomes more robust the more $k4$ and $k6$ exceed their plausible ranges. This characteristic further indicates the model is not optimally robust in the manner observed in other biochemical networks [1, 2, 3].



(a)$k6$ vs. $k4$ (b)$k6$ vs. $k4$(zoomed view of (a)) (c)logarithmic plot

Figure 3: Co-dimension two bifurcation plots for $k6$ and $k4$

4 Concluding Remarks

Our bifurcation analysis for Tyson's 1991 model of the cell cycle identified two examples of parameter sensitivity in the model which correspond to corrections to the model published by Tyson *et al.* in

subsequent years[8, 6, 12]. Although our methodology is still in very early stages of development, we hope it can be used routinely to reveal structural weakness in models and suggest improvements. We intend to go on to test our methodology on more complex models.

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