Bifurcation Diagram Analyzer for Differential Equations of Biological Models

Rikuhiro Yamada rikuhiro@kuicr.kyoto-u.ac.jp
Minoru Kanehisa kanehisa@kuicr.kyoto-u.ac.jp
Bioinformatics Center, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

Keywords: modeling, simulation, parameter tuning, bifurcation analysis

1 Introduction

Thanks to recent advances in molecular biology and bioinformatics, we can gather information about constituents of a cell at the molecular level. Next, we need to construct comprehensive models, which explain the behavior of real cells so that we can understand how the constituents make up cellular functions.

Simulations would help to build these models. However, they cannot tell if the model obtained with a given set of parameters is still valid or not when parameters representing environmental factors are varied. For example, gene expressions, protein degradations, and cell size growth could cause such variations.

With the bifurcation analysis [1, 3], we can see how the model's global behavior changes as parameters vary. Here we have developed computer-software that can carry out the bifurcation analysis and produce bifurcation diagrams so that we can observe global characteristics of the model's behavior.

This software is mostly written in JAVA language.

2 Methods and Results

In the bifurcation analysis, given an n-dimensional system with one parameter,

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}, p) \qquad \mathbf{x} \in \mathbf{R^n}, p \in \mathbf{R}^1,$$

we can see qualitative changes of the solutions as the parameter p varies.

As a trial example, we deploy the model of cell cycle control system that was built by Tyson and Novak [1, 3]. A portion of the control system is described by the following differential equations:

$$\begin{aligned} \frac{dX}{dt} &= k_1 - (k_2' + k_2'' \, Y)X, \\ \frac{dY}{dt} &= \frac{(k_3' + k_3'')(1-Y)}{J_3 + 1 - Y} - \frac{k_4 m X Y}{J_4 + Y}. \end{aligned}$$

where X and Y represent concentrations of cycline/CDK dimers and cdh1/APC complexes, respectively, and m is the parameter representing the cell mass.

Once our software accepts the JAVA function for the differential equations, it generates an XY plane indicating equilibrium points and vectors toward or away from them with a given value of the parameter. To make a bifurcation diagram the software varies the parameter such as shown in Figure 1, and generates the result such as shown in Figure 2.

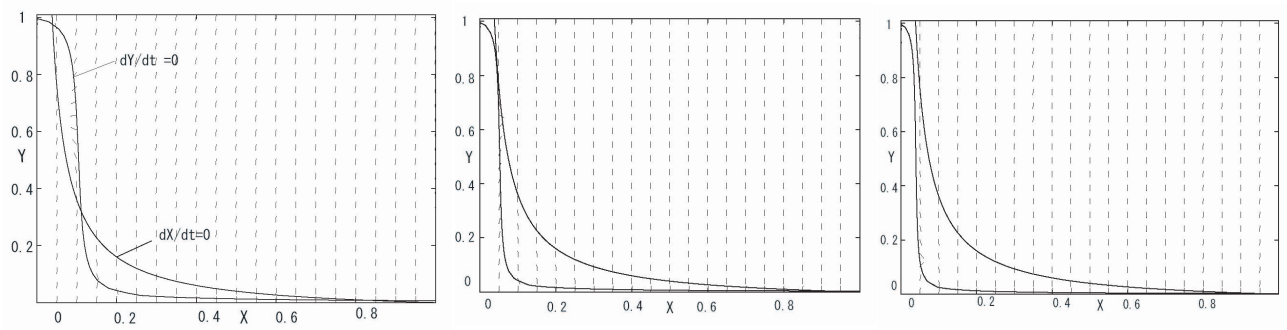

Figure 1: Example of bifurcation with the varying parameter, m = 0.3 (left), 0.6 (center), and 0.8 (right).

The bifurcation diagram represents how many and what type (stable or unstable) of equilibrium points are present with specific parameter values. With this diagram, we can see qualitative behaviors of the model system and compare with real behaviors of the cell. After the bifurcation diagram is built with a dominant parameter, we can select another less dominant parameter and perform the same analysis.

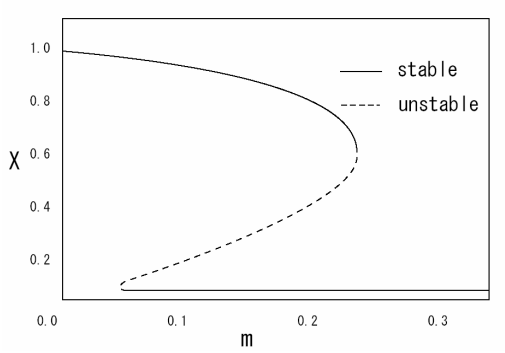

Figure 2: Example of the bifurcation diagram.

3 Discussion

This software is still at a very early stage of development. Future works include:

1. To generate the bifurcation diagram with two or more parameters.
2. To deal with larger scale models with a larger number of variables.
3. To develop a user-friendly modeling scheme because, although differential equations are flexible, they are not easy to manipulate.
4. To improve speed of calculation, which could be achieved by implementing parallel computing.

We plan to apply this tool to biological models, especially metabolic network models.

References

[1] Fall, C.P., Marland, E.S., Wagner, J.M., and Tyson, J.J., *Computational Cell Biology*, Springer, 2002.

[2] Strogatz, S.H., *Nonlinear Dynamics and Chaos*, Westview, 1994.

[3] Tyson, J.J., Chen, K., and Novak, B., Network dynamics and cell physiology, *Nature Reviews Molecular Cell Biology*, 2:908–916, 2001.