Available online at www.sciencedirect.com
SCIENCE DIRECT®
Nonlinear Analysis
Real World Applications
ELSEVIER
Nonlinear Analysis: Real World Applications 6 (2005) 563–587
www.elsevier.com/locate/na

Systems biology and deviation curvature tensor

Vasile Sorin Sabău

Hokkaido Tokai University, 5-1-1-1 Minamisawa, Minami-ku, Sapporo, 005-8601 Japan

Received 18 October 2004; accepted 10 December 2004

Abstract

In this article, we study the robustness of biological systems by means of the eigenstructure of the deviation curvature tensor. This is the differential geometric theory of the variational equations for deviation of whole trajectories to nearby ones. We apply this theory to the Van der Pohl equations and some biological models, and examine the relationship between the linear stability of steady-states and the stability of transient states. The main application is the G_1-model for the cell cycle, where Jacobi stability reveals the robustness and fragility of the cell arrest states and suggests the existence of more subtle checkpoints.

Keywords: Systems biology; Dynamical systems; Jacobi stability; Cell division cycle

1. Introduction

Recent genome sequencing projects and further functional analysis of complete gene sets provided a huge mass of molecular information for a wide range of model organisms in the last few years. The large number of structural components, interactions and control processes between them make the internal mechanism of the cell extremely difficult to deal with only by empirical considerations. It is also almost impossible to formulate any general hypothesis or framework that are consistent with all these data. To overcome this situation, the technology based on computer science with a firm mathematical background is strongly required.

The difficulty of mathematical modeling in biology comes from the differences between the notions of "*what to look for*" used in biology and mathematics. Biology

E-mail address: sorin@cc.htokai.ac.jp (V.S. Sabău).

1468-1218/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.nonrwa.2004.12.012

usually classifies the components of the biological system (e.g. genes, mRNAs, proteins) and the interactions between them by experiments and empirical observations without paying much attention to the physical-mathematical principles that lie underneath. Because of this, in general, biological models lack information which is essential for simulation analysis and do not have a mathematical background (e.g. statistics or theory of differential equations).

On the other hand, mathematical models include information which is essential for simulation analysis, but the interaction between the components of the biological systems are less visualized and less easy to understand and interpret.

We consider that both approaches are not enough by themselves to understand the complex life process. Biologists often claim that they do not need complicated mathematics to analyze their systems and that traditional empirical methods are enough. However, identifying all genes and proteins in a living cell is like listing all the components of a computer: wires, chips, transistors, condensers, display, mouse, etc. This will provide only a sort of catalog of the computer. Even knowing how these components are inter-connected, such that the computer will work, would not reveal the sophisticated underlying mathematics and engineering. Biology may provide the components of the cell (genes, proteins, mitochondrion, etc.), as well as some of the interactions between them (regulatory gene network, metabolic pathways, etc.). But, it cannot answer questions such as: how are signals encoded, how is noise fluctuation connected with adaptability, how do cells act when a malfunction occurs, or what are the design principles and circuit patterns of the cell.

In order to understand these topics a combined *biology–mathematics* approach, also called systems biology [14], is needed and the bridge between these two fields should be *computer science*.

Once we have an understanding of the system structure, we can approach the system dynamics. There are a lot of methods of doing this in mathematics and engineering and the preference for one or another depends on the availability of biological data incorporated in the model. In the present paper, we will use steady-states analysis and KCC theory to do this.

Cell simulation is a very important topic because the experiments in vitro are quite time- and money-consuming. By simulating the behavior of the cell within the computer one can save a lot of time and money in drug discovery research [14].

To conduct a system-level analysis, some mathematical tools have to be used. There have been many attempts to use mathematics in Life Science, but much of it is not of relevance to real biological modeling. There are yet interesting methods, from both the biological and mathematical points of view, for example the algebraic approach to sequence analysis and the Central Dogma of molecular biology [11], and also modeling metabolic pathways and chemical reactions by the use of differential equations [18], etc. We are also going to show in this paper that differential geometric methods, namely the KCC theory, or Jacobi stability, can be a useful tool in the study of the properties of metabolic pathways, [6].

One of the most important properties of biological systems is their *robustness* and their *fragility*. By *robustness* we mean both the relative insensitivity to alteration of their internal parameters and the ability to adapt to changes in their environment. In very robust systems,