LNCIS
Lecture Notes in Control and Information Sciences
357

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Biology and Control Theory: Current Challenges

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Library of Congress Control Number: 2007925171

ISSN print edition: 0170-8643
ISSN electronic edition: 1610-7411
ISBN-10 3-540-71987-3 Springer Berlin Heidelberg New York
ISBN-13 978-3-540-71987-8 Springer Berlin Heidelberg New York

Typesetting: by the authors and SPS using a Springer LaTeX macro package

Printed on acid-free paper SPIN: 11946908 89/SPS 5 4 3 2 1 0

Lecture Notes
in Control and Information Sciences 357

Editors: M. Thoma, M. Morari

Preface

Bio and Control: Introductory Ideas

Historically speaking, the connection between biology and control feedback theory goes back to the analogy suggested by NORBERT WIENER in the 40s for explaining some human behaviors by using *feedback* mechanisms: brain control of a standard arm mechanical movement. At the same period of time, ERWIN SCHRÖDINGER pointed out some similarities between physics principles and the laws governing alive organisms, and he suggested a physics-based approach for the modeling and the analysis of such organisms by using the *analogy* (electrical, mechanical, and chemical processes). Without being exhaustive on the corresponding methodologies, these simple ideas are at the origin of a large number of models that tried to reproduce the behavior of living organisms. Without any doubts, such models served and helped in defining the first inter- and trans-disciplinary programs between biology and other sciences and/or disciplines from Mathematics to Physics and Computer Sciences in the last decade.

In this context, the control feedback theory has its own place, and we hope that it is able to bring the beginning of answers in the understanding of biology dynamics. The mathematical description of signals and circuits is not only at the origin of the modern control feedback theory, but also contributed significantly at the emergence of *Systems Biology*, as mentioned by P. WELLSTEAD in his essay *Schrödinger's Legacy: Systems and Life* (ETS Walton Lecture, 2005), and this example is far to be an isolated case.

Formalism, Potential Interactions and Some Expectations...

Taking into account the current competences in the field of the classical control feedback theory, namely, analysis, observation and control of dynamical systems (linear or nonlinear, finite-dimensional or not), the *main objective* for the edition of this book is to propose a (potential) "progressive transfer" of some of the "competences" issued from control feedback theory towards the domains of the life sciences, and especially towards all the domains of life sciences in which a *dynamic behavior* can be pointed out (see also some discussions in the report of the panel on future directions in control, dynamics and systems: *Control in an information rich world*, edited by R.M. MURRAY).

In this sense, take an extremely simple example: a same molecule has different meanings and various interests of study for the specialists in the life sciences domain, depending on the type of action considered:

- Action on isolated enzymatic systems (biochemical);
- Action on a dynamical chain of reaction in the alive cell (biology);
- Action on the human organic functions (pharmacology, physiology);
- Human therapeutic actions (medicine),

and each of these actions can be translated by some particular quantitative and qualitative properties of the corresponding dynamical system modeling the considered action.

Roughly speaking, any behavior of a biological system with respect to one (or several) time scaling can be interpreted in a dynamical system framework or context by using appropriate (analysis and control) tools. Indeed, we think that some knowledge in control feedback theory could deserve to have a *better understanding* of different kinds of dynamic evolution provided that some variables of the system are measurable (or observable), even if one cannot control the object under consideration. Furthermore, several tools and methods for a *qualitative and quantitative analysis* of such evolutions hold.

Next, it is worst to note that, in biology, the notion of *structure* has a larger sense than in automatic control theory. More precisely, the structure defines the set of relations existing between the different elements that constitute the object or the set of objects under consideration. Behind each structure, there is some *complexity* (any alive organism is strongly complex) with its *own hierarchy* (any alive organism is highly organized). Thus, the notion of *closed-loop* exists (and is recognized like that since more than an half century) in the context of biological systems, and as emphasized by HENRI LABORIT *"every life evolution from and after the photosynthesis has been regulated by feedback between more ordered and less ordered structures of the environmental device"*.

In summary, in our opinion, the fact to create some links between control theory community and that one of the life sciences could allow addressing the following problems (see also the challenges from biology briefly presented in *New issues in the Mathematics of Control* by R. BROCKET in *Mathematics Unlimited - 2001 and beyond* for some insights in neurobiology, cell biology and psychology):

- To model, observe and have a perception of the alive structures;
- To analyze the dynamic interconnections between biological systems and structures.

Finally, we also believe that this interaction between specialists in biology and control feedback theory will be useful in both directions. More precisely, biology systems need appropriate analysis tools due to their structure and hierarchy, complexity and environment interference, and we believe that these aspects may generate interesting research topics in control area. Indeed, several works, raising the potential impact of control developments to bring some beginning of answers in the context of biological systems, have been published in the recent years (special sessions or workshops at the interface between these communities, see, for instance, the proceedings of CDC 2005 and 2006). The idea of this book was conceived in the context mentioned above.

How to Read the Book?

This book is organized as follows.

- Part 1 is devoted to model selection and consists of chapters 1 through 4: modeling perspective in chronic myelogenous leukemia (first chapter), an aid for an early diagnosis of HIV/AIDS infection (Chapter 2), a multi-scale control oriented model in ovulatory processes (Chapter 3) and finally some robotics insights in modeling visually guided hand movements (Chapter 4).
- Part 2 is devoted to models for system analysis and consists of chapters 5 through 10, as follows: analysis of monotone and near-monotone biochemical network structures (Chapter 5), system and control in understanding the biological signal transduction (Chapter 6), analysis of some piecewise-linear models of genetic regulatory networks (Chapter 7), the modeling and the analysis of cell death signalling (Chapter 8), a Petri Net approach to persistence analysis in chemical reaction networks (Chapter 9), and finally some geometric ideas in stability analysis of various delay models in bioscience (Chapter 10).
- Part 3 is devoted to analysis and control aspects and consists of chapters 11 through 13: modeling and control of anesthetic pharmacodynamics (Chapter 11), a direct adaptive control of some non-negative and compartmental systems with delays (Chapter 12), and finally the analysis and control of dynamics in biological systems in presence of limitations (Chapter 13).

Note that this partition is somewhat arbitrary as most of the chapters are interconnected, and it mainly reflects the editors' biases and interests.

We hope that this volume will help in claiming many of the problems for control researchers, starting discussions and opening interactive debates between the control and biology communities, and, finally, to alert graduate students to the many interesting ideas at the frontier between control feedback theory and biology. There are, of course, many areas which are not represented through a chapter, and therefore we would like to apologize to those whose areas are not profiled.

Acknowledgements

The idea of this edited book inherits from the organization of an International Workshop on the subject in April, 24-25th, 2006, at LAAS-CNRS, Toulouse, France, co-organized with HeuDiaSyC (UMR CNRS 6599), Compiègne, France. Such a meeting was the third one of a series initiated with the 1st CNRS-NSF Workshop on *"Advances on time-delay systems"* (Paris, La Défense, France, January 2003) and continued by the International Workshop on *"Applications of time-delay systems"* (Nantes, France, September 2004).

Foremost, we would like to thank all the contributors of the book. Without their encouragement, enthusiasm, and patience, this book would have not been possible. A list of contributors is provided at the end of the book.

We also wish to thank Springer for agreeing to publish this book. We wish to express our gratitude to Dr. THOMAS DITZINGER (Senior Editor in Engineering) for his careful consideration and helpful suggestions regarding the format and organization of the book.

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Contents

Part I Model Selection

Mini-Transplants for Chronic Myelogenous Leukemia: A Modeling Perspective
Peter S. Kim, Peter P. Lee, Doron Levy 3

Modeling of the HIV/AIDS Infection: An Aid for an Early Diagnosis of Patients
Djomangan Adama Ouattara, Claude H. Moog 21

A Multiscale Model for the Selection Control of Ovulatory Follicles
Nki Echenim, Frédérique Clément, Michel Sorine 45

Robotics Insights for the Modeling of Visually Guided Hand Movements in Primates
Philippe Souères, Christophe Jouffrais, Simona Celebrini, Yves Trotter 53

Part II Models for System Analysis

Monotone and Near-Monotone Systems
Eduardo D. Sontag 79

System and Control Theory Furthers the Understanding of Biological Signal Transduction
Eric Bullinger, Rolf Findeisen, Dimitrios Kalamatianos, Peter Wellstead 123

Piecewise-Linear Models of Genetic Regulatory Networks: Theory and Example
Frédéric Grognard, Hidde de Jong, Jean-Luc Gouzé 137

Modelling and Analysis of Cell Death Signalling
Thomas Eißing, Steffen Waldherr, Frank Allgöwer 161

A Petri Net Approach to Persistence Analysis in Chemical Reaction Networks
David Angeli, Patrick De Leenheer, Eduardo Sontag 181

Geometric Ideas in the Stability Analysis of Delay Models in Biosciences
Silviu-Iulian Niculescu, Constantin-Irinel Morărescu, Wim Michiels, Keqin Gu 217

Part III Analysis and Control Aspects

Modeling and Control of Anesthetic Pharmacodynamics
Carolyn Beck, Hui-Hung Lin, Marc Bloom 263

Direct Adaptive Control of Nonnegative and Compartmental Dynamical Systems with Time Delay
VijaySekhar Chellaboina, Wassim M. Haddad, Jayanthy Ramakrishnan, Qing Hui 291

Analysis and Control of Dynamical Biological Systems in Presence of Limitations
Isabelle Queinnec, Sophie Tarbouriech, Germain Garcia 317

Index 339

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Part I

Model Selection

Mini-Transplants for Chronic Myelogenous Leukemia: A Modeling Perspective

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Summary. We model the immune dynamics between T cells and cancer cells in leukemia patients after a bone-marrow (or a stem-cell) transplant. We use a system of nine delay differential equations that incorporate time delays and account for the progression of cells through different stages. This model is an extension of our earlier model [3]. We conduct a sensitivity analysis of the model parameters with respect to the minimum cancer concentration attained during the first remission and the time until the first relapse. In addition, we examine the effects of varying the initial host cell concentration and the cancer cell concentration on the likelihood of a successful transplant. We observe that higher initial concentrations of general host blood cells increase the chance of success. Such higher initial concentrations can be obtained, e.g., by reducing the amount of chemotherapy that is administered prior to the transplant, a procedure known as a mini-transplant. Our results suggest that mini-transplants may be advantageous over full transplants. We identify the regions of the parameters for which mini-transplants are advantageous using statistical tools.

Keywords: Chronic myelogenous leukemia, stem-cell transplant, bone-marrow transplant, non-myeloablative, mini-transplant, immune response, delay differential equations.

1 Introduction

Allogeneic bone-marrow or stem-cell transplantation (ABMT or ASCT) is currently the only known curative treatment for CML [11]. Prior to ABMT, the patient receives chemotherapy to lessen the disease and to lower the patient's immune cell population. This pre-treatment procedure is performed to reduce immune suppression by leukemia cells and to prevent graft rejection by the host.

Typically, the patient receives large doses of chemotherapy to eliminate almost all leukemia and immune cells. The treatment is called a full (or myeloablative) transplant, because the chemotherapy destroys, or ablates, nearly all the myeloid stem cells, which are the cells that produce new blood.

I. Queinnec et al. (Eds.): Bio. & Ctrl. Theory: Current Challenges, LNCIS 357, pp. 3–20, 2007.
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However, in some cases, patients cannot tolerate full chemotherapy, so they are given mini (or non-myeloablative) transplants. In mini-transplants, patients receive milder doses of chemotherapy that do not ablate the myeloid stem cells. As a result, the treatment depends more heavily on the donor immune cells to expand and destroy remaining leukemia cells.

In [3], we modeled the immune dynamics of a full transplant. Our results suggested that the expansion of donor T cells depends more on general host blood cells than on leukemia cells alone. This is because a successful transplant relies on a blood-restricted graft-versus-host disease, in which donor T cells react to antigen that is present on general host blood cells. This less discriminate reactivity results in greater proliferation of immune cells and often proves necessary, because leukemia cells usually do not provide sufficient stimulus.

In this paper we present an extension of the model of [3], in which we made two major changes: First, we assume that all target cells have two possible states: alive and dying. Dying target cells are cells that are in the process of dying due to cyotoxic interactions with T cells. These cells linger for about five minutes, during which they may still stimulate other circulating T cells. In addition, we also introduce discounting factors for cell death rates to prevents from double-counting cell deaths due to the natural decay and the cytotoxic T cell responses.

In this paper, we use the extended model to study the dynamics of minitransplants and to determine conditions that increase the chance of a successful cure. For full and mini-transplants, chemotherapy indiscriminately kills a large number of non-leukemic host blood cells. Since these cells stimulate donor immune cells, high levels of chemotherapy might reduce the potency of the anti-leukemia immune response. In this study, we seek to understand the trade off between eliminating leukemia and host immune cells and maintaing the stimulus to donor immune cells. Under certain circumstances, we find that minitransplants may prove more advantageous not only due to its reduced toxicity to the patient but also because it preserves a larger population of host blood cells that provide a high enough stimulation to drive the expansion of donor immune cells.

The paper is organized as follows. In Section 2, we present the state diagrams and the corresponding delay differential equations that govern the dynamics of the various cell populations. In Section 3, we present a summary of the parameter estimates that we used in the model. In Section 4, we summarize a previous result from the original paper, [3]. Then, we discuss a typical solution of the revised model and analyze the sensitivity of the revised model with respect to the parameters, using Latin Hypercube sampling. In particular, we focus on the sensitivity of the model to the initial leukemia and general host cell concentrations. We also demonstrate that minitransplants, in which chemotherapy is administered in weaker doses, may increase the chances of a successful transplant. In Section 5, we discuss our interpretations of our results and outline future directions of study.

2 The Model

We follow our previous work [3], and track the time evolution of six cell populations. From the donor, we consider anti-cancer T cells, anti-host T cells, and all other donor cells (exclusive of the two populations explicitly mentioned). From the host, we consider cancer cells, anti-donor T cells, and general host blood cells, The anti-cancer T cells represent the cells that respond to a cancer-specific antigen and exclusively mediate the GVL effect, while the anti-host T cells represent those that respond to a general blood antigen and mediate blood-restricted GVHD. The cancer population, general donor, and general host populations can each exist in two states: alive or dying (due to previous interaction with cytotoxic T cells). This two-state formulation is a modification that is not present in [3]. As a result, our new model consists of nine delay differential equations (rather than six as in [3]).

In the following subsections we present the state diagrams and the corresponding equations for the cell populations. The various state diagrams follow the notation shown in Figure 1. The rectangles stand for the possible states for each population. The arrows represent transitions between states. The terms next to the arrows denote the rates at which cells move from one state to another. Most transitions have an associated time delay indicated by the values in the circles. The values in the circles represent the time it takes to complete the associated transition. Each circle can be thought of as a gate that holds cells in a given state until the appropriate time elapses.

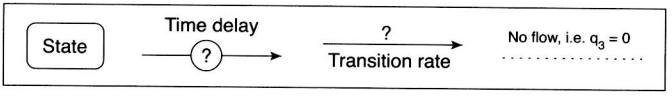

Fig. 1. The symbols used in the state diagrams

The model only explicitly measures population levels in each of the six base states, one for each cell population. Each term in the equations represents the beginning or the termination of a path connected to the base state (located at or near the center of each state diagram, denoted by the population label). The interaction initiation terms contain no delays, and the rates are proportional to the product of the two interacting populations and a mixing coefficient, k, in accordance with the law of mass action [10]. Termination terms contain each rate and delay encountered along their associated paths. Thus, the value of a given population variable, for example T_C, will at times be less than the total number of such cells, because it will not include cells that are within the pipeline of interactions with other populations.

In [3], our model formulation allowed population levels to cross zero. This artifact required us to impose a stopping criterion that forced all populations to