DYNAMICAL MODELING IN BIOTECHNOLOGY

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Lectures presented at the EU Advanced Workshop on

DYNAMICAL MODELING IN BIOTECHNOLOGY

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Foreword

This book contains the lectures given at the EU Advanced Workshop “Dynamical Modeling in Biotechnology” (Torino, May 27 – June 9 1996). The workshop has been funded by the European Commission DGXII under the program BIOTECH (1994-1998) and hosted by the Institute for Scientific Interchange (ISI).

This book appears with a considerable delay, for which we make our excuses to the authors, who have been patiently waiting for the publication of their papers. Anyway, we think that this material is still worth to publish and up to date. It covers some basic aspects of modeling, which have not been surpassed in spite of the rapid growth of this field. No effort has been made to update the articles concerning references and similar aspect, not to further delay the publication.

The investigation of chaotic dynamics, out of equilibrium statistical mechanics and disordered system has become a mature field in theoretical physics and computer science. The basic approach consists in trying to catch some essential features of a real system by building a model where the interaction of several simple elements originates a non trivial global behavior. The tools developed in this area have now a widespread application in biology.

Modelization in physics and in engineering is a growing field. However, in biotechnology, most of the theoretical studies stop at the phenomenological level. On the other side, theoretical models are often quite far from the reality of biological systems. Mathematics has long held a central position in the physical sciences, where systems, in closely controlled environments, change in a repeatable way. For biological systems, however, observations show much greater variability and thus breakthroughs and important results can only depend on a close collaborative efforts between theoretical scientists and “wet-lab” scientists. Time is now ripe for a productive interaction among biologists and theorists: the former should develop more realistic models; the latter are expected, on their side, to accept theoretical work and incorporate it into practical applications.

In this spirit we have organized this workshop, during which some applications of the theory of dynamical systems and statistical mechanics to biotechnology were presented to young researchers (master and PhD students) coming from biology, physics and mathematics.

The workshop was structured into morning lectures and afternoon computer projects followed by tutors. This allowed the immediate implementation of the models proposed during the lectures. Lecturers, tutors and students lived together two intense weeks. Lecture rooms and offices with computer facilities were made available by ISI. The first three days of the workshop were devoted to “computer alphabetization” in C and FORTRAN, covering also the use of graphics routines and of DNA databases, and to introductory lectures in theoretical biology. This period also allowed students to form several groups, which then worked at the computer projects. Ten-days projects were organized dealing with advanced topics. The home page of the workshop still exists ^a and is serving as a reference for students and lecturers to exchange materials and information. One can find there the list the lectures, projects and seminars.

A total of 30 students participated to the workshop from different European countries. Among them, 13 students were from biological or medical disciplines, the rest mostly from physics or from mathematics, engineering and computer science. The workshop has been generally appreciated. It could set a scheme for future courses on these subjects, to be held at the doctoral or post-doctoral level.

This book is divided into a first part containing the lecture notes and a second one devoted to contributed papers on specific research topics.

In the first paper, Franco Bagnoli provides a comprehensive overview of cellular automata and discusses why this approach is a flexible and powerful modelization tool for biological systems. Dietrich Stauffer presents a review of several population models. He aims at studying ageing and he shows that even simple stochastic models can be very successful in reproducing some aspects of experimental data. Giovanna Guasti explores the possibility of modeling translation process and ribosome dynamics in bacteria. This approach sheds some light on the dependence of a macroscopic quantity - bacterial population growth - on a microscopic parameter - ribosomes and tRNA abundances and composition.

Nino Boccara discusses the modeling of ecological and epidemiological systems and presents a microscopic model whose mean-field limit is represented by the “classic” Lotka-Volterra equations. Jean-Pierre Nadal presents thereafter an introduction and selected bibliography to a increasingly applied tool: neural networks and supervised learning.

The paper by Arkady Pikovsky describes the fundamentals of dynamical system theory. It offers a wide range of examples, introducing the concepts of trajectories in a phase space, stability, bifurcations, fluctuations, attractors and chaos. Numerical methods are also discussed as well as the implications

^a<http://www.docs.unifi.it/biotech96>

of “discrete” vs. “continuum” approaches to biological modeling.

Michel Peyrard analyzes the dynamical properties of “DNA openings”, which is one of the most important steps in replication and transcription. He stresses the importance of nonlinearities and how the idea of nonlinear energy localization (breathers) can be useful to interpret DNA thermal denaturation.

A general discussion of the role of modelization in biology can be found in the contribution by Franco Celada, in which he presents a comprehensive description of the immune system and suggests perspectives to its modelization.

Michele Bezzi examines some key models of the immune system and analyzes in detail the Celada-Seiden model for humoral response. Philip Seiden describes a two dimensional cellular automaton model of the dynamics of migrating, contact-inhibited cell populations. Ulrich Behn, Holger Dambeck and Gerhard Metzner present a model of the behavior of class 1 and 2 T helper lymphocytes. These cells show reciprocal inhibitory action and differ in their pattern of cytokine production. The understanding of the regulation of these two classes of T lymphocytes is thought to be of key importance in the future treatment of viral and bacterial infections and of auto-immune diseases.

In the articles section, Franco Bagnoli, Nino Boccara and Paolo Palmerini present the analysis of the behavior of a probabilistic cellular automata with two absorbing states and address questions concerning phase transitions and the analogy with percolation models. Robin Engelhardt’s paper deals with pattern formation, which is a central issue in biology due to the close relation between morphology (structure) and function. The author discusses the “chemical” mechanisms of pattern formation and the biological constraints related to the presence of morphogenetic gradients during the development and reshaping processes and the control of gene expression as a source of positional information.

Peter Goetz discusses the kinetics of microbial growth in various conditions, linking the biomass production to the bacterial metabolism and growth. His model takes into account the delay time between the change of conditions in the bioreactor and the intracellular concentration of metabolites. Markus Rarbach and Peter Goetz consider the problem of mixed bacterial cultures that is nowadays of great importance in bioreactor technology in order to set up complex biotechnological processes. The authors study the stability of a system of two microbial species with commensalistic and mutualistic interactions and compare it with mathematical models of a pure culture.

Models like the Celada-Seiden one are computationally very expensive, even using powerful workstation. Filippo Castiglione, Mauro Bernaschi and Sauro Succi describe a parallel platform optimization of this model.

In summary, this collection of lectures and papers addresses biological sys-

tems modelization from a dynamical point of view, with a particular attention to biotechnology related problems. It provides an insight into a new fascinating and fast growing area of science.

We wish to thank dr. Pietro Liò, who helped us in the organization of the workshop and participated to several activities; regrettably, he decided not to join us in editing this book. We thank also dr. Alessio Vassarotti from DGXII Commission for believing in this project from the beginning and for helping us in the organization and funding process. We finally thank Prof. Mario Rasetti, director of ISI, who agreed on hosting this workshop at his institute and pushed forward the publication of this book. We acknowledge the precious help of the staff at ISI, dr. Tiziana Bertoletti and Mrs. Enza Palazzo.

Franco Bagnoli and Stefano Ruffo, Florence, August 2000

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