Preface

This book is a followup to the scientific workshop “Managing Complexity, Reducing Perplexity” which was held in Heidelberg, May 16–20, 2011, as part of the 2010–11 Kepler Award for European Young Scientists (KEYS), established by the European Academy of Sciences (EURASC). The recipients of the award were Marcello Delitala (Italy) for mathematical sciences, Giulia Ajmone Marsan (France) for social sciences, and Andrea Picco (Germany) for biological sciences. These researchers were chosen from a group of a dozen young European scientists with a Ph.D. in Mathematics, Biology, or Medicine.

“Managing Complexity, Reducing Perplexity” was devoted to an overview of the state of the art in the study of complex systems, with particular focus on the analysis of systems pertaining to living matter. Both senior scientists and young researchers from diverse and prestigious institutions with a deliberately interdisciplinary cut were invited, in order to compare approaches and problems from different disciplines. A common aim of the talks was that of analyzing the complexity of living systems by means of new mathematical paradigms that are more adherent to reality, and which are able to generate both exploratory and predictive models that are capable of achieving a deeper insight into life science phenomena.

The book collects a selection of scientific contributions from the speakers at the meeting.

The interest in complex systems has witnessed a remarkable increase in recent years, due to an increasing awareness that many systems share a common feature, that is “complexity,” and that they cannot be successfully modeled by traditional methods used for inert matter systems. According to an opinion that is widely shared in the scientific community, a *Complex System* is any system made up of a large number of heterogeneous interacting entities, whose interactions lead to the emergence of collective behaviors that are not predictable from the individual dynamics. Complex systems are often characterized by nonlinear structures at different representation scales.

When dealing with living systems, it is necessary to face an additional source of complexity: the interacting entities express an individual strategy that modifies classical mechanics laws, and, in some cases, generates proliferative and/or destructive processes. Moreover, the expression of a strategy is heterogeneously distributed over the system. When dealing with living matter, a seminal paper by H. L. Hartwell and co-workers should be recalled:

> The living matter shows substantial differences with respect to the behavior of the inert matter. Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiates biology from other natural sciences. Organisms exist to reproduce, whereas, outside religious beliefs rocks and stars have no purpose…What really distinguishes biology from physics are survival and reproduction, and the concomitant notion of function.[1]

The interactions between individuals can occur not only through contact, but may be also distributed in space as well as on networks. Collective emerging behaviors, determined by the dynamics of interactions, cannot be described only on the basis of the knowledge of the mechanical dynamics of each element, i.e., the dynamics of a few individuals does not automatically lead to the overall collective dynamics of the whole system.

Thus, complex systems are intrinsically multiscale, and show emerging phenomena at the macroscopic level that express a self-organizing ability, which is the output of the interactions between entities at the microscopic level. Moreover, the emergence is bottom-up, from lower representation to a higher scale, with a feedback loop: the emerging patterns may affect and perturb the lower levels (the so-called immergence: a top-down phenomenon).

Due to this self-organizing ability, feedbacks, and redundancy, in a fast evolutionary framework, complex systems have in many cases a great capacity to adapt to changing landscapes, to cope with environmental changes and pressures, and maintain their structure and stability against the perturbations that occur at various scales.

An increasing number of applications in technology, economics, and social sciences resemble such systems, given their high number of composing elements and the nonlinear connections among them. "Complexity" is one of the main features of a variety of phenomena, from cell biology to fluctuations in economic markets, from the development of communication networks and the Web to traffic flows in highways, to the ecosphere evolution against climate changes, and other generic environmental issues.

Many systems of the physical world are made up of several interconnected components, which may be represented, and, at times, measured, according to different scales of observation. Interactions between different parts of the system may show emerging collective behavior and structures that require specific interpretations for each scale of observation, thus highlighting the new features that arise when passing from one scale to another. Whether you consider the individual entities or their subsets, the simultaneously occurring processes at different temporal and spatial scales characterize the system, so that the laws that govern the behavior of the "whole" are qualitatively different from the laws that govern the individual components.

The investigation on complexity has the objective of understanding what its main properties are. How does the system adapt to evolving conditions? How does

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[1] H. L. Hartwell, J. J. Hopfield, S. Leibner, and A. W. Murray, From molecular to modular cell biology, *Nature*, 402, c47–c52.

it learn efficiently and how it does optimize its behavior? Are there common rules that govern the behavior of complex systems? The development of a science of complexity cannot be reduced to a single theoretical or technological innovation, but implies a novel scientific approach.

Thus, “managing complexity” means identifying the “complexity” features of a system, modeling its dynamics, highlighting the possible rise of new structures and emerging patterns, investigating their resilience against perturbations, searching for any common features that govern the ways in which this collective behavior occurs. A mathematical approach can provide useful suggestions to help understand the global behavior of a living system by capturing its essential features.

Many mathematical models have been proposed to describe various aspects of complex living systems. There is no universal tool that is more suitable than others: each has its pros and cons, and each aims at highlighting the particular behavior of each particular system at a well-defined level of representation. A research approach should be designed to select the most significant tool to explain the collective behavior, i.e., the tool that contributes the most information for both that particular scale and for the transition from one representation scale to another one.

The description of complex living systems requires challenging mathematical structures and original theories, as well as progress in theoretical methods, in numerical algorithms, and in developing experimental strategies.

Moreover, it is necessary to bring together different kinds of scientific knowledge and different background to tackle this challenging goal: an interdisciplinary approach between scientists from different fields is necessary to define a common protocol that would be able to exchange information, and to design experiments and indicators that can provide information that would enable the validation, and therefore the refinement of already proposed models, to develop qualitative analysis, numerical simulations, and new hypothesis. This is why suitable interactions between groups of researchers from different areas (mathematics, physics, biology, sociology, and economics) are necessary to find new paradigms that can be used to model and investigate a more and more connected, interacting, and globalized world.

The above-mentioned points were common issues in the workshop and will be the key points of this book. The focus is on biological systems; the meeting was in fact devoted to the modeling and simulation in life sciences, focussing on some of the current topics in biology and medicine and the related mathematical methods: several biological systems are characterized by interconnected heterogeneous elements that, together, exhibit some properties, which are often not obvious at first. These systems are demanding for interdisciplinary approaches that are able to combine life sciences and mathematics/physics.

The main topics of the workshop were: complexity in life sciences and in biosystems, regulatory networks, cell motility, multiscale modeling and simulation of cancer, morphogenesis and the formation of biological structures, evolution and adaptation.

These topics have been developed by researchers from various disciplines and different scientific communities (biologists/mathematicians/physicists), who share a common interest in life sciences, with the aim of achieving deeper insight into these biological phenomena and, hopefully, a better understanding, simulation, and control of them.

A key issue that emerged during the discussions was the necessity of more and more direct interaction between Mathematicians/Physicist and Biologists. Indeed, interdisciplinarity was the leading issue of the workshop; the ability to interpret scientific problems from different points of view is evidently more and more important, besides the technical knowledge needed to face them.

Apart from the various talks and discussions, some round table conferences were held that led to some interesting thoughts and outcomes.

The first round table was on specific advice from senior scientists to young ones pertaining to the successful development of scientific research in biomathematics. The results can be briefly synthesized in some memorable sentences that emerged in the discussions:

- *Get wet! Mathematicians perform experiments (F. Bussolino, IRCC, Candiolo, Italy)*
- *Data Driven Modelling together with Model Driven Experiments (V. Capasso, University of Milan, Italy)*
- *Integration. Biologist be your buddy (A. Dell, Imperial College, London)*
- *Modelling, integrating data and concepts of processes (W. Jäger, University of Heidelberg, Germany)*
- *Stay close to the data (V. Quaranta, Vanderbilt University, USA)*
- *Scientific honesty … Do not put all your eggs in one basket (D. Sherrington, University of Oxford, UK)*

The second round table was on which actions are needed by young researchers to support their career development and the need of education for the next generation researchers. Here, it was pointed out that more attention should be paid to graduate education in which the borders of different sectors of sciences are crossed (e.g., Ph.D. programs combining biomedical skills with maths-physics ones), in order to establish a "common protocol" between researchers from different disciplines.

The third round table was on the perspectives of young scientists, in terms of career development and the facility of finding suitable positions. Here, the landscape is heterogeneous, because scientific communities in some countries are still stuck in rigid and classic disciplinary sectors (as, for instance, in Italy), while in other countries (e.g., the UK and the USA) things appear to be different. The suggestion was to try to be truly interdisciplinary, finding stimuli, and looking for new experiences "away from home," if necessary (*Go West, young boy!*).

However, the evident need for a real and continuous interplay between biological sciences and maths-physics emerged from all discussions.

Another issue that emerged from the discussions was the need for a strong biological approach to reduce the complexity of the system. It is in fact mandatory to develop mathematical tools for each scale that retains the key features of the system. Deeper considerations on this issue have been developed in the last contribution by M. Delitala and T. Hillen.

The book presents 13 contributions dealing with different aspects of complex biological systems.

The book starts with a contribution that frames the problem of dealing with complexity in life sciences and the choice of suitable mathematical methods.

The first contribution by T. Hillen and M. A. Lewis on the Mathematical Ecology of Cancer, highlights other important aspects of dealing with complex systems: the transversality of methods, cross-disciplinarity, and fertilization. Their contribution focuses on the important connections between ecology and cancer modeling, which bring together mathematical oncology and mathematical ecology to initiate cross-fertilization between these fields.

Focusing in more detail on some of the features of complexity, the multiscale nature of these biological systems has been shown in the following three contributions on cancer modeling; the onset and evolution of a tumor is a good example of complex multiscale problem as it is a process that normally spreads over many years and involves a large variety of phenomena that occur at different biological scales.

The chapter by P. Macansantos and V. Quaranta on heterogeneity and growth variability in cell populations focuses on recent advances, both theoretical and experimental, in quantification and modeling of the clonal variability of proliferation rates within cell populations, highlighting work carried out in cancer-related systems.

The contribution by P. Gerlee and S. Nelander is focused on the impact of phenotypic switching in a model of glioblastoma invasion. Simulations of the stochastic model and simulations, obtained by deriving a continuum description of the system, show interesting results on the wave speed of the solutions and suggest a possible way of treating glioblastomas by altering the balance between proliferative and migratory behavior.

The contribution by D. Trucu and M. A. J. Chaplain on Multiscale Analysis and Modelling for Cancer Growth and Development, presents a novel framework that enables a rigorous analysis of processes that occur at three (or more) independent scales (e.g., intracellular, cellular, tissue). Then, a new model is proposed that focuses on the macroscopic dynamics of the distributions of cancer cells and of the surrounding extracellular matrix and its connection with the microscale dynamics of the matrix degrading enzymes, produced at individual cancer cell level.

The need for new mathematical frameworks and tools to deal with some features of the biological phenomena is also evident in the contribution by J. Calvo, J. Soler and M. Verbeni who propose a nonlinear flux-limited model for the transport of morphogens. They introduce flux-limited diffusion as a new tool to obtain mathematical descriptions of biological systems whose fate is controlled by morphogenic proteins.

The biological aspects of multiscale phenomena and the influence of lower scales at macroscopic level is evident in the contribution by A. Dell and F. Sastre on glycosylation: a phenomenon shared by all domains of life. Biological complexity is not linearly related to the number of genes among species: it is well known that the total number of genes in humans is not very different from organisms such as fruit flies and simple plants. The authors point out their attention on a specific phenomenon, the Glycosylation, that occurs after genes have been translated into proteins, and that results in the greatest diversity of the products of gene expression.

The emergence of collective behavior from interactions at a lower lever (including learning, adaptation, and evolutionary dynamics) has been dealt with in detail in the following two contributions.

The chapter by E. Agliari, A. Barra, S. Franz and T. Pentado-Sabetta proposes some thoughts on ontogenesis in B-cell immune networks. It focuses on the antigen-independent maturation of B-cells and, via statistical mechanics tools, studies the emergence of self/non-self-discrimination by mature B lymphocytes and highlights the role of B–B interactions and the learning process at ontogenesis, that develop a stable memory in the network.

In the chapter by M. Delitala and T. Lorenzi, on the mathematical modeling of cancer under target therapeutic actions, the authors focus on emerging behavior in cancer dynamics. Due to the interaction between cells and therapeutical agents, it is shown how competition for resources and therapeutical pressure can lead to the selection of fitting phenotypes and evolutionary behavior, such as drug resistance.

The emergence of patterns and the formation of biological structures is also well represented in the following three contributions.

The contribution by H. Freistühler, J. Fuhrmann and A. Stevens focuses on travelling waves emerging in a diffusive moving filament system. They have derived a model that describes populations of right and left moving filaments with intrinsic velocity, diffusion, and mutual alignment. Analytical investigations and numerical simulations show how interesting patterns are composed of several wave profiles that emerge and the role of different parameters.

The chapter by M. Neuss-Radu on a mathematical model for the migration of hematopoietic stem cells proposes a model, together with a qualitative and computational analysis. The results are compared with experimental results, and possible factors and mechanisms are suggested that can play an important role in emerging behavior to obtain a quantitative description.

The contribution by Jude D. Kong, Sreedhar S. Kumar and Pasquale Palumbo deals with Delay Differential Equation (DDE) models exploited in the specific framework of the glucose-insulin regulatory system, highlighting how those types of models are particularly suited to simulate the pancreatic insulin delivery rate.

The final contributions are related to the different perspectives of management complexity problems in different research fields, and to the different tools that may be employed in the task.

"Physics and Complexity" by D. Sherrington attempts to illustrate how statistical physics has driven the recognition of complex macroscopic behavior as a consequence of the combination of competition and inhomogeneity, and offers new insights and methodologies of wide application that can influence many fields of science.

The last short contribution by M. Delitala and T. Hillen develops some reasonings on the language of Systems Biology and on the need for a multiscale approach to retain some complexity features of the system.

In conclusion, this book has the aim on one hand of offering mathematical tools to deal with the modeling of complex biological systems, and on the other of dealing with a variety of research perspectives. The mathematical methods reported in this book can in fact be developed to study various problems related to the dynamical behavior of complex systems in different fields, from biology to other life sciences. Therefore, applied mathematicians, physicists, and biologists may find interesting hints in this book: to help them in modeling, in developing several analytic problems, in designing new biological experiment, and in exploring new and sometimes unusual perspectives.

This book has been possible thanks to the success of the workshop. Thus, we wish to thank all those who contributed directly or indirectly to the successful organization of the Workshop: the President of the European Academy of Sciences for the initiative of the Award, Vincenzo Capasso, and Willi Jäger for his continuous support, the Direction of BIOMS for the generous financial support, and the local committee of the University of Heidelberg (Willi Jäger, Maria Neuss-Radu, Anna Marciniak-Czochra, and Ina Scheid) for their essential support together with the local Academy of Sciences and Humanities who offered this great opportunity to young researchers and all the speakers and participants. Financial support was also provided by the FIRB project—RBID08PP3J, coordinated by M. Delitala.

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All information regarding the workshop can be found at the conference website: http://www.eurasc.org/kepler2010.

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