Preface

This volume contains expanded versions of research papers and tutorials presented at the Hybrid Systems Biology (HSB) workshops that took place in Taormina, Italy, in 2013 and Vienna, Austria, in 2014. To put these works and workshops in context, let us reflect a bit about systems biology, which is a term overloaded with meanings.

Recent years have seen a tremendous increase in the capability to conduct high-throughput experiments in the life sciences, leading to approaches nowadays summarized as "systems biology." However, the promise to mechanistically understand complex relationships as present, for example, in multi-factorial diseases has not been realized and the medical benefits seem to be meager compared with the cost of experimentation and the volume of scientific publications. In our opinion, this is at least partly due to a lack of a comparable progress in the conceptual system-level modeling domain.

The area of systems biology draws into the life sciences researchers from many other disciplines (mathematics, physics, engineering, and computer science), who are often more fluent in certain types of abstract modeling and reasoning than the average biologist. It is generally hoped that such an interdisciplinary collaboration will increase the convergence to useful and clinically relevant models, will help reduce the cost of experimentation (which is considered as the main limiting factor in biological research), and facilitate the transfer of research results toward clinical applications. However, there are bottlenecks in this ideal flow chart that hinder rapid progress. One of them is the interaction between the modeling researcher (the modeler henceforth) and the biologist, which often falls into one of two extremes, depending on who dominates the collaboration:

1. When it is the biologist, the modeler helps him or her in solving one particular problem (which is good by itself) but the outcome of the process has no significant generality in terms of methodology and computer-aided tools, and a similar work should be done almost from scratch for the next problem. Moreover, the modeler will tend to accept the set of abstractions and observational resolution of the biologist, thus inheriting the communal bias of the latter, which is often accidental, reducing the chance of real new theoretical insights.
2. The other extreme is when the modeler is more or less independent and uses biology as yet another case-study for his or her favorite formalisms and techniques. These will be applied to biological problems, not always questioning their adequacy, and sometime giving priority to the evaluation standards of the modeler's technical community over biological significance.

As a result we see numerous conferences in the style of "X and Systems Biology," whose impact on the practice of biological research is rather limited. This is not a criticism of any individual researcher – we are all influenced by the boundary conditions set by the structure of academic scientific disciplines. And, of course, not all

interactions are like this and there are successful applications of mathematics and information technology that have had an impact on the practice of biological research.

Ideally one would like to bring the contribution of abstract modeling and pragmatic mathematical analysis to the *core* of the biological scientific activity and embed it more tightly in the hypothesis–experiment loop. It is important to note that in our modern times, the mathematical support that we would like to provide biologists with is associated with software tools. Such tools implement the mathematical know-how in software similar to the computer-aided design (CAD) and simulation tools that make complex engineered systems possible, from cars and airplanes to chips and new materials.

To avoid a misunderstanding, let us first specify what is outside the scope of our intentions. We are certainly not talking about application of computer science to genomics and gene sequencing. We are not primarily interested in high-throughput experiments, big data, and machine learning, although such techniques will eventually have their (modest) place in the process of model building. There are more things that come to mind as candidates for exclusion but we need not be exhaustive.

The research directions that we want to encourage are concerned with building dynamic models of biological phenomena, from the cell level and above, and analyzing them using a variety of computational methods to debug and explore models in silico as much as possible, avoiding useless and costly experiments.

Some of these things have been done for ages in different areas and communities, for example in the theory of chemical reactions or in the study of population dynamics, and thus it is important to stress why now is a good time to re-initialize and regroup these activities, partly based on developments in hybrid systems research.

The notion of a dynamical system has evolved greatly in the second half of the twentieth century, although the specific term "dynamical system" has not been used explicitly in these developments. The computer and the brain gave rise to models based on discrete (logical, qualitative) state variables and quantity-free transition dynamics, that is, automata that often operate on a logical (not metric) time scale. Such models underlie almost everything in computers, and are used, for example, to design complex digital circuits consisting of zillions of transistors. Naturally, already in the early days, qualitative models of genetic regulatory networks based on networks of Boolean automata were proposed.

The last decades saw a kind of confluence between the classic continuous dynamical systems based on differential equations and discrete event systems in the framework of hybrid systems. Starting initially as a meeting point between computer scientists working on the verification of systems such as communication protocols or digital hardware, and control engineers interested in the design of systems such as airplanes, robots, or industrial plants, the domain gave rise to a relatively unified view of hybrid dynamics where discrete transitions and continuous activities are interleaved. Needless to say, this style of modeling where discrete transitions are considered first-class citizens is much more efficient and intuitive for mode switching dynamics such as gene activation than the various constructs employed in continuous mathematics to express discrete changes.

In terms of model analysis, discrete and hybrid systems are not amenable in general to purely analytic techniques and hence novel ones had to be developed covering the

whole spectrum from reachability-based formal verification to Monte Carlo simulation. Hybrid systems research has also led to new ways of specifying and evaluating behaviors of dynamic systems: while classic approaches focus mostly on steady-state analysis, new techniques that combine logic with quantitative measures can express more complex patterns of behaviors that occur as sequences of steps. Such methods can also explore transient behavior that are perhaps more fundamental to life than the unavoidable steady state.

It is thus believed that bringing together researchers with mathematical and computational capabilities, sharing a genuine desire to contribute to the advancement of biology, and connecting them to open-minded biologists and physicians working on problems central to the life sciences can lead to a quantum leap in the efficacy of biological research. It will hopefully lead to high-quality computer-aided methods for easily navigating in the space of hypothetical models and will drastically reduce experimentation overhead. In particular, we expect the know-how that will emerge from these activities to include:

- A better understanding of the trade-offs between different styles of modeling in terms of the complexity of analysis/simulation, faithfulness to reality, difficulty to obtain experimental data and usefulness in general.
- Improved theoretical notions concerning the formal relationships between models at different levels of abstraction and granularity: for instance, what is the relation between a continuous model and its discrete approximation, between two approximations of a spatially extended model or between stochastic and deterministic models of the same phenomenon?
- Systematic methods to abstract detailed models into simpler ones (coarse graining) or to incorporate coarse weak models inside more detailed ones. The main issue here is that coarse abstract models are less specified (under determined) and simulation and analysis methods should account for that uncertainty so as to assess the robustness of proposed models.

Wishes, visions, and ambitions are often brighter than their realizations but we hope, nevertheless, that the reader will enjoy the articles in this volume and seriously consider joining this research effort.

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