

Biological experimentation *in silico*

Nina H. Fefferman

DIMACS Center, CoRE Building, 4th Floor, Rutgers University, 96 Frelinghuysen Road, Piscataway, NJ, 08854, USA (e-mail: fefferman@math.princeton.edu)

This special issue was born during a workshop on mathematical modeling in biological systems (specifically, the epidemiology and evolution of influenza, organized by Catherine Macken and Alan Perelson) at the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS), in 2006. As the researchers sat around our conference dinner, discussing our recent work, publications, the talks we'd heard and our interests in future pursuits, it became clear that we were talking, as biologists, about mathematical models in two very separate ways: analytical models — mathematics about which things could be proven, and computational models — simulations in which things could be observed. We used language about them interchangeably and, all being mathematical biologists, this was natural and we were content. As the conversation continued, however, we started exchanging stories about the reactions to our work from the less mathematically inclined in the biological community and we realized that maybe we hadn't yet done a good job of communicating with our colleagues about what these types of models are or how they worked, and the idea for this special issue was born.

This issue is therefore addressed to a general biological audience and mathematical biologists alike, and it is the hope that the most staunchly non-mathematical among us may still enjoy the results found within.

The papers gathered here focus on the empirical investigations made possible by computational experimentation, beginning now to be called "experimentation *in silico*". This term

captures perfectly both the power and the weakness of these methods.

Just as lab or field biologists cannot always understand or control all of the contributing elements of a full biological system, but perform gradual, controlled, simplified experiments to learn more about biological processes, so do these computational methods allow exploration of (sometimes otherwise impossible) questions by empirical investigation. The occasional criticism that the simulated environment may not capture the reality of the system of interest is directly analogous to concerns about laboratory experimentation to yield understanding about biological processes in nature. The real responsibility lies in the careful and conservative interpretation of the results, but the experiments themselves can provide insight into the processes of the system whether or not they provide any level of realism.

From the other side, criticism against these types of models is sometimes leveled by more mathematically rigorous theoreticians. That theories may rarely be proven rigorously, and support for them is merely observed, is clearly another valid concern, but perhaps an invalid complaint. These methods are not meant to issue proof any more than are the field experiments that provide parameter values for the application of the analytic models. But this represents less of a shortcoming and more of a difference in goal. A common first step in the proof of any rigorous mathematical theorem is the personal search for a counterexample. This search itself may easily be thought of as an experiment. Failure to find an instance that disproves the conclusion does not

mean the conclusion is correct, but the process of the search can lend greater insight into the nature of the theorem to be proven. Given the full complexity of biology, it is frequently useful to provide others with the insights gained experimentally, even in the absence of proof of their formal conclusions.

This special issue brings together a diversity of fields, questions, methods, and interpretations of the conclusions for computational models from the fields of neuroscience, group behavior, immunology, epidemiology, public health, sociobiology, bioinformatics, and ecology. They were solicited to span a breadth of interests and functions. They demonstrate the ability of experiments *in silico* to extend the exploration of discovery beyond the physical, temporal, or physiological capabilities of real-world investigations, and with greater specificity and appli-

cability than analytically provable mathematical systems could usually provide.

It is our hope that this issue will reach the non-specialist, explaining what these types of experiments can do, and how they can fit into the complex world of biological and biomedical research. These experiments *in silico* are slowly coming into their own recognition as valuable tools in the empirical biologist's bag of tricks. They occupy their own niche, complementing both the analytic mathematical models, and the real-world lab and field based empirical experiments.

It has taken a long time to assemble this volume and it could not have been done without the support of the journal, especially its former Editor-in-Chief Philip T. B. Starks, each of the contributors, and DIMACS, where the project was born.