Chapter 18
Computational Modeling Under Uncertainty: Challenges and Opportunities

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Abstract Computational Biology has increasingly become an important tool for biomedical and translational research. In particular, when generating novel hypothesis despite fundamental uncertainties in data and mechanistic understanding of biological processes underpinning diseases. While in the present book, we have reviewed the necessary background and existing novel methodologies that set the basis for dealing with uncertainty, there are still many "grey", or less well-defined, areas of investigations offering both challenges and opportunities. This final chapter in the book provides some reflections on those areas, namely: (1) the need for novel robust mathematical and statistical methodologies to generate hypothesis under uncertainty; (2) the challenge of aligning those methodologies in a context that requires larger computational resources; (3) the accessibility of modeling tools for less mathematical literate researchers; and (4) the integration of models with—omics data and its application in clinical environments.

Keywords Computational modeling · Uncertainty · Challenges · HPC · Hypothesis generation

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18.1 Introduction

There are two underlying rationales that motivate the chapters in this book. The first, is the *usefulness* and *necessity* of mechanistic mathematical and computational modeling in biomedical research. The usefulness has been widely shown in several chapters (see for instance [31] by Lejon and Samaey, [26] by Hug et al.) and (for instance) from classical groundbreaking works in neuron modeling (such as [23]). The necessity of mechanistic modeling originates essentially from the limitations w.r.t mechanistic understanding when solely using classical statistical analysis in the analysis of complex systems [51].

The second rationale is that mechanistic modeling in biology needs to address uncertainty in order to generate testable hypothesis. For instance in biology when a transcript is profiled—either by PCR, array or RNA-seq—there are several sources of variability to consider: *technical*, from the experimental procedure use, and *biological*, that is for instance when the same type of cell may react in different ways to the same perturbation. At the cell level, one explanation for observed transcriptomics biological variation is that the regulation is driven at several and different layers (e.g. genetic and epigenetic regulation), but large parts of these regulatory mechanisms are still only in part possible to decipher [3, 22, 27, 32]. Furthermore, the profiles of those "other regulatory layers" are in most cases not available during modeling. A second explanation for uncertainty is the stochastic nature of some biological processes as shown in intra-cellular chemical reactions, gene expression [33] and pharmacokinetics [12] among others. In both explanations, we need to clearly face *uncertainty during the modeling, in the parameters of the model and in the biological processe*s when investigating model behaviors.

While the [16] by Geris and Gomez-Cabrero provides an overview, we find it useful to close the book with a chapter that summarizes major existing challenges and opportunities. We have identified four challenges that will be briefly discussed in the different sections of this Chapter. First, (1) there is a need for methodological development, (2) linking modeling and high-performance computing, (3) strengthen the accessibility of modeling tools targeting non-specialists and, (4) integrating omics and modeling tools for the benefit of personalized medicine. Additional challenges for the future of computational biomedicine, especially with respect to the clinical dimension, can be found in the Digital Patient Roadmap.[1]

18.2 The Need for Methodological Development

In the last decade, we have observed a shift in biological modeling analysis. In initial attempts, mechanistic ordinary differential equation (ODE) models were generated by defining a set of equations, and investigators *manually* fine-tuned the parameters. The manual fine-tuning was conducted by exploring the parameter space "in the

[1] http://www.digital-patient.net/files/DP-Roadmap_FINAL_N.pdf.

quest" of finding those parameters that agreed with experimental observed behavior (we will denote them by "good quality parameter sets"). Eventually, the manual search was made *automatic* by designing the fine-tuning problem as an optimization problem as shown in [5] by Salmuelson et al. Furthermore, with the growth of computational resources the parameter space of larger models became intractable using theoretical analysis, it became clear that investigations of either exploring the surrounding areas of good quality parameter sets (see [34] by Mannakee et al. and [47] by Van Schepdael et al.) or by exploring the set of "good quality parameter sets" ([17] by Gomez-Cabrero et al. and [7] by Cedersund) became important. We consider that those types of methodologies are necessary and they are an active research field in computational biology, however it still requires a coordinated effort to generate a solid foundation for further development. We consider two major requirements:

(1) **Rigorous definitions** In order to develop useful methodologies and tools we need to provide a robust answer to the following question: *what is a useful output from the analysis under uncertainty of a biological theoretical model*? (QUES). In [17] by Gomez-Cabrero et al. the answer proposed is (briefly) *first the grouping and secondly group characterization of good quality parameter sets*. The idea is that by exploring the "good quality parameter set" space it is possible to find competing hypothesis (from the groups of "good quality parameter sets") that could be tested at the laboratory. However, given the exploratory nature of the proposed methodology (that does not investigate all possible "good quality parameter sets" but a sample of them by an optimization methodology) the robustness of the competing hypothesis is not rigorously ensured. Reference [7] by Cedersund answers that the fundamental outputs are the set of predictions that can be then tested back in the laboratory. Furthermore [7] by Cedersund provides an initial classification of predictions: *core predictions* (well-determined predictions that allow to test the quality of the model) and *suggestions* (poorly determined predictions that may provide specific insights that can be tested in order to improve the overall quality model). Both results and proposals shown in [17, 34] by Gomez-Cabrero et al. and [7] by Cedersund represent part of the initial efforts generated to provide a formal answer to QUES; however we consider it necessary to develop further these efforts and work on generating a consensus and robust formulation for answering QUES. Relevant material on the topic can be found in [6, 9, 10, 18, 30, 46].

(2) **Development of software tools that implement such methodologies so they may become a standard** The shift from manual search to automatic search started during last decades of 20th century and actively continued during first decade of 21st century. Several teams worked on those ideas and several tools were developed at the same time; some of those tools aimed for specific areas such as Neuroscience (Neurofitter, [45]) while some other tools were more generic such as COPASI [24]. Many of those tools are still available (and there are active research groups continuously updating them) see [5] by Cedersund et al. for further detail. On one hand, the generation of that many tools raised the awareness and use of those new methodologies; on the other hand it was clear that the wheel was reinvented many times. When considering the generation of hypothesis under uncertainty we may argue to be at the beginning of user-friendly method development. Yet no tool is able to

perform automatically the analysis presented in [17] by Gomez-Cabrero et al. or [7] by Cedersund; in those cases customized coding solutions were generated. We consider it necessary to generate user-friendly solutions able to perform automatically (or under human supervision) those analyses. However we also believe it is necessary to generate coordinated working groups to avoid the generation of similar tools simultaneously.

A final complementary development to those methodologies is the generation of novel methodologies and (user-friendly) tools allowing automatic simplification and reduction of models as shown in [14] by Eriksson et al., [44] by Tucker or through Global Sensitivity Analysis [29, 39, 43].

18.3 Integration of Computational Modeling with High-Performance Computing Techniques

Computational resources have been both the key and bottleneck for computational modeling analysis. The automatic search for "good quality parameter sets" depended on the availability of machines able to run hundreds or thousands of simulations in brief periods of time. This was possible through medium sized (20+ cores) to large sized (named supercomputers such as Mare Nostrum in the Barcelona Supercomputing Center (www.bsc.es, Spain) or SNIC solutions (www.snic.vr.se, Sweden) machines; the former was mainly affordable by computational-oriented groups able to invest funding in the resource while the latter were available through national programs that provided (and still provide) a number of hours-per-month upon request. The first computational biology analysis competed for such computational resources with theoretical physics or computational chemistry (among many others) simulations, but at that time the required resources were minor compared to the rest of research areas. Over the years, and with both the development of automatic fine-tuning tools and larger models, the computational requirements grew and computational biology is starting to compete at a similar scale of requirements than the other research domains. The present and coming future shows that the demand of computational requirements are still to grow for several reasons, among them: (i) possible increased size of the models, (ii) increased amount of data to be considered (see later the omics' section for further details) and (iii) an increased amount of users (see for instance the development of novel conferences such as HiCOMB, High Performance Computational Biology from 2002 until nowadays). For this reason the long-term resources are to be planned carefully in order to correctly asses the future needs of Biological and Medical Sciences.[2] We consider the following three aspects to be of major relevance:

(1) **High-Performance Computing (HPC) infrastructures** There is a general trend to avoid buying small-medium computational resources by every group and invest better into large-scale resources or cloud-based solutions; see for instance the

[2] http://cordis.europa.eu/fp7/ict/e-infrastructure/docs/bms-agenda.pdf.

action plan for the Digital Agenda for Europe.[3] Small-medium sized solutions tend to be expensive and, in many cases, sub-optimally used. While cloud-based solutions, if prizes are competitive, may provide a cheaper solution that will optimally reflect the needs and uses of different research groups in real-time. Furthermore, as pointed out by Peter V Coveney,[4] it is necessary to optimize the interoperability across large infrastructures and it is necessary to harmonize mechanisms such as access, advance reservation and urgent computing among others.

(2) **Parallelization** Both simulation and fine-tuning benefit from parallelization, that is the possibility to run a process as separate parallel batches therefore reducing the amount of time by using several CPUs simultaneously. Both optimization algorithms and methodologies to integrate Partial Differential Equations benefit from better and robust parallelizable algorithms. Interestingly, in the area of eScience ("the application of computer technology to the undertaking of modern scientific investigation, including the preparation, experimentation, data collection, results dissemination, and long-term storage and accessibility of all materials generated through the scientific process", Shannon Bohle[5]) there is an effort to import to computational biology those methods already developed for other areas where large-scale modeling is actively used (such as Weather Forecast modeling). Among those efforts there is the Swedish e-Science Research Center (http://www.e-science.se).

(3) **Scalability** Both for computational resources and parallelization need to consider optimal scalability of the solutions developed, given that the number of users and computational requirements is expected to grow over time [15, 21].

18.4 To Widen the Use and Applicability of Modeling as a Tool for Non-specialists

Most of the chapters of this book have been written by statisticians, mathematicians, and engineers with a strong mathematical background. This may represent the background requirements for method development in computational biology, however it does not represent the requirements for *using* computational biology. Fortunately, in the last twenty numerous biologists have been exposed to the necessary background to develop and analyze their own models. We consider that to make the use of modeling in biomedicine it is important to make the necessary knowledge and tools as accessible as possible; on this direction we consider that following points are important.

(1) **The necessary theoretical background** When biologists decide to design a model of their system under study, it is necessary for them to learn the basics

[3] https://ec.europa.eu/digital-agenda/en/pillar-v-research-and-innovation/action-53-financially-support-joint-ict-research-infrastructures.

[4] http://cordis.europa.eu/fp7/ict/e-infrastructure/docs/bms-presa-6.pdf.

[5] http://www.scilogs.com/scientific_and_medical_libraries/what-is-e-science-and-how-should-it-be-managed/.

of mathematical modeling. General and specific knowledge of modeling will be required depending on the system to investigate. The amounts of material (specially books) addressing this knowledge have been growing in both quantity and user-friendliness. Additionally, courses (such as Computational Biology in Cold Spring Harbor, directed by Professor Gregory Smith[6]) are becoming more common. We consider that it is necessary to continue this trend, but also that (i) courses where biological-strong and mathematical-strong participants are both enlisted are to be prioritized, because it allows exchanging of views and goals and creates a richer learning environment [4]; and (ii) the development of on-line courses addressing this topic needs to receive attention, so students may have introductory sessions without the need to wait for face-2-face courses.

(2) **Software environments** We consider it necessary to enhance the user-friendliness of existing (and novel tools) in order to enlist researchers in the use of modeling. Existing tools have certainly shown an increase in accessibility and friendliness, but any researcher with no experience will still need to invest large amounts of time to get confident with them. In Ph.D. programs were modeling may be a side project to investigate experimental results this situation may end in not considering modeling as a research tool. We consider that our aim must be to make "computational modeling" another accessible tool in the biologist tool-box, therefore improving user-friendliness is necessary. An example of generating a simulation environment for medical researchers is [25], which is part of the results from the European Project Synergy-COPD [19].

(3) **Syllabus implementation** When a clinician or a biologist may interact with modelers or discover a model of interest, existing syllabus usually do not provide the necessary background to understand them. We consider that initiatives such as Erasmus BioHealth Computing Program [4] and Medical Research Masters are initiatives of value where future biological and medical researchers are set to interact with modelers and computational biologists. This approaches enhances the visibility of modeling in biology and biomedicine.

18.5 Forming Stronger Ties Between Omics Data and Computational Biology

Following the Human Genome Project, array-based and Next-Generation Sequencing-based technologies have pushed transcriptomics analysis to novel boundaries [1, 35]. SNP profiling of thousands of individuals have allowed the identification of genetic risk factors for many diseases such as Multiple Sclerosis [41] or Rheumatoid Arthritis [40], however the use of such information in Computational Models is limited to say the least. A very important open question is then: *how do we integrate and omics-based knowledge into modeling*?

[6] http://meetings.cshl.edu/courses/2014/c-comp14.shtml.

While omics-data is used in the generation of predictive models (such as patient classification or risk prediction) and integrative approaches are being continuously developed to improve such models [2, 11, 28, 38, 50] what we here refer to is the use of omics data in the analysis of biological systems through mechanistic models. Eventually those integrated mechanistic models may provide in the future relevant information to be included in better prediction models making use of simulation outputs. However, at the present time we focus on the challenge of *creating models that address the individual* (*personalized modeling*). Lets consider for instance the development of a immune system model of Multiple Sclerosis Progression such as the one presented in [48]. If we gather information of DNA Methylation profiling and/or SNP genotype for a given individual, the challenge is now how we implement such information so the model is not anymore a generic model but individual specific. There exist several attempts on this direction as those shown in Synergy-COPD [19] and CombiMS, in the context of Systems Medicine and the Virtual Physiological Human. In order for omics data to be routinely used in computational biomedicine and, later on, in a clinical setting, a number of requirements need to be fulfilled, as recently identified by [49]. These include (1) the ability to work with sensitive data, (2) to work with complex and heterogeneous data (including non-textual information), (3) to work with a distributed data management under security and performance constraints, (4) to define methods allowing for the integration of bioinformatics and systems biology information with clinical observations on various length scales, and finally (5) to define tools able to define the 'physiological envelope' of a patient (ref white paper).

18.6 Conclusions

We find that Computational Biology is a crucial tool for biology and biomedicine, but to enhance its practical applicability there is an urgent need to address the uncertainty commonly observed in biological systems to ensure the uptake in the biological and clinical communities. The present chapter reviews the needs and challenges in computational biology, that are important to consider in the nearby development of the field. We summarize those needs in four major aspects:

1. Robust definitions for the generation of useful predictions,
2. Development of novel and optimization of existing HPC resources that address the state-of-the-art computational needs.
3. Development of user-friendly analysis tools and easily accessible computing resources,
4. Development of models and tools that incorporate information on the different omics widely profiled nowadays.

We hope that the reading of this book may motivate young and senior researchers to follow and work on those challenges.

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