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Editorial

Computational Methods for Identification and Modelling of Complex Biological Systems

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Mathematical and computational models are key tools for understanding biological phenomena. In the last decades, scientific and technological advances have facilitated their evergrowing adoption in biologically oriented research. The strongly interdisciplinary character of these areas, in which biologists work along with researchers from physical sciences, engineering, and medicine, fosters the cross-fertilization between scientific fields. However, the large degree of structural and parametric uncertainty typically associated with biological processes makes it nontrivial to analyze them using techniques imported from fields in which these issues are less prevalent. Thus, there is a need for new methodological developments that fill this gap. The present special issue addresses this need by providing an overview of current open problems and presenting recent results regarding mathematical inference and modelling of biological systems.

A total of 18 submissions were received for this special issue. Six of them, contributed by research groups from Africa, America, Asia, and Europe, were finally accepted for publication. Among the published papers there is a clear distinction between methodological and application papers: there are three methodological papers that address model analysis from a structural viewpoint and three papers that present recent applications. Admittedly, there is a certain overlap between both categories, since some application

papers incorporate new methodological developments, while the methodological papers include biological applications as case studies.

The application papers deal with three different types of diseases: cancer, diabetes, and viral infections. One paper addresses the modeling of one of the hallmarks of cancer: angiogenesis, the formation of new blood vessels that is both driven by and needed for the development of tumors. In “Dynamic Modeling of the Angiogenic Switch and Its Inhibition by Bevacizumab”, D. Csercsik and L. Kovács present a model that describes the effect of a therapeutic drug, Bevacizumab, in the inhibition of vascularization. The model is built on previous work by the authors, incorporating a description of vasculature dynamics while keeping the number of states and parameters as low as possible. The paper reports results of its fit to tumor volume data resulting from two therapies and discusses identifiability issues and other aspects. The model is part of ongoing work currently being carried out in the ERC project Tamed Cancer. In this framework, the model is expected to be refined and validated in the near future and eventually to be used for therapy optimization in open-loop and closed-loop.

H.-C. Wei et al. give a novel method to evaluate the neurological damage associated with diabetes (in “Assessment of Diabetic Autonomic Nervous Dysfunction with

a Novel Percussion Entropy Approach”). The approach is based on computing the so-called percussion entropy index (PEI) to obtain information on the similarity in the pattern of changes of two noninvasively measured digital volume pulse signals. Using data taken from 114 individuals, the authors show that two-dimensional PEI is safely applicable to differentiate between healthy subjects, those with well-controlled diabetes, and subjects with poor blood sugar control. The advantageous properties of the proposed method are also shown by comparing it to other possible approaches such as multiscale entropy index and low- to high-frequency power ratio computing.

A. A. M. Arafa et al. (“A Non-Integer Variable Order Mathematical Model of Human Immunodeficiency Virus and Malaria Coinfection with Time Delay”) propose a novel mathematical model to investigate the spreading of HIV and malaria infection and the mutual interactions between the dynamics of the two infections. This is an important application of mathematical modeling, since the coinfection of HIV and malaria has become endemic in several developing countries. Thus, there is an urgent need for a better understanding of the dynamics of this coinfection, in order to design effective vaccination strategies. A feature of the modeling approach exploited by the authors is the use of variable (instead of constant) fractional order derivatives with time delay. This feature is utilized to effectively describe the variable memory of the infection progression in distinct patients, taking also into account the important effect of time delay after contagion, required for the individuals and mosquitoes to become infectious.

The three methodological papers address topics such as reachability, observability, identifiability, and model discrimination of nonlinear models, using structural approaches.

The review by A. F. Villaverde (“Observability and Structural Identifiability of Nonlinear Biological Systems”) focuses on two properties that characterize the ability to infer model unknowns by measuring the model output. The first one, observability, describes the possibility of reconstructing the state vector, while the second one, structural identifiability, refers to the parameter vector. The latter can be considered as a special case of the former, and both properties can be studied locally for nonlinear models using the differential geometry approach. The paper by A. F. Villaverde provides a brief tutorial of this approach, surveys the recent literature, and discusses the relationship between these properties and other concepts. Finally, it suggests some possible directions for future research.

H. A. Harrington et al. (“A Parameter-Free Model Comparison Test Using Differential Algebra”) propose a model discrimination procedure that is applicable for noisy measurements without performing parameter estimation. The candidate models are given in the form of parameterized polynomial ordinary differential equations. Using differential algebra, invariants can be written from the system models which are polynomial in the inputs, outputs, and their derivatives, and the coefficients of monomials are rational in the parameters. By substituting the measured and computed values of the inputs, outputs, and their derivatives into the invariants at different time-instants, a set of linear equations

can be obtained which is uniquely solvable for the true model in the noise-free case, but not solvable for others. For the realistic noisy case, probability bounds can be computed for the rejection of models, and the derivatives can be estimated using Gaussian Process Regression.

G. Szlobodnyik and G. Szederkényi study the reachability properties of a special class of discrete reaction networks having at most one input and one output species beyond the possible catalyzers from a computational point of view (“Reachability Analysis of Low-Order Discrete State Reaction Networks Obeying Conservation Laws”). The subconservativity of a discrete reaction network ensures the boundedness of its state-space. The authors show that the reachability problem can be rewritten as an Integer Linear Programming feasibility problem. This computational framework allows deciding the reachability problem and counting the number of feasible discrete trajectories in polynomial time in the number of species and in the distance of initial and target states, if the number of reactions is fixed.

Overall, the aforementioned contributions show that (1) biological problems pose challenges that are different to those of physical and engineered systems; (2) for this reason, they are an important driver of innovation in mathematical and computational techniques for dynamic modelling; (3) as a result of recent developments, these methodologies are already capable of providing key information in biomedical applications; (4) however, the identification of open challenges also highlights the need for further advances.

As a final remark, we would like to note that another special issue dealing with biological modeling has been recently published in *Complexity*: “Mathematical Modeling and Dynamic Analysis of Complex Biological Systems” (MMDACBS, <https://www.hindawi.com/journals/complexity/si/860912/>). There are similarities and differences between the MMDACBS special issue and the present one, which can thus be seen as complementary collections. While the present special issue has an emphasis on biomedicine, the MMDACBS is more oriented towards biotechnological applications. The methodologies considered in the MMDACBS special issue include different types of flux analysis and statistical techniques for black-box modelling, while the present special issue focuses on the reverse engineering, modelling, and identification of kinetic models. Furthermore, as of writing this editorial, submissions are being accepted for another related special issue: “Dynamical Analysis of Biological Systems”, edited by Popescu, Voit, and Udriste (<https://www.hindawi.com/journals/complexity/si/394076/cfp/>). The proliferation of special issues on this topic, which can also be noticed in other multidisciplinary journals, is an indication of the strong interest among the scientific community in the development and application of dynamical modelling tools for unravelling the complexity of biological systems.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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