

Opinion article

CURRENT TRENDS AND PERSPECTIVES IN MATHEMATICAL BIOLOGY

Authors:

Frank M. Hilker¹, Pedro Cenci Dal Castel², Luiz Alberto Díaz Rodrigues³, Guilherme S. Y. Giardini⁴, Diomar Cristina Mistro³, Marcelo Rossato⁵ and Philip K. Maini⁶

1. Institute of Mathematics, Institute of Environmental Systems Research, Osnabrück University, Osnabrück, Germany
2. Intelligent Systems Engineering Department, Indiana University Bloomington, USA
3. Department of Mathematics, Federal University of Santa Maria, Santa Maria, Brazil
4. Instituto de Física, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
5. Institute of Mathematics, Statistics and Scientific Computing, State University of Campinas, Campinas, Brazil
6. Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, UK

ABSTRACT

This communication summarises a “round-table discussion” at a workshop held at the Federal University of Santa Maria, Brazil, on trends and perspectives in mathematical biology. Mathematical biology as a research field has seen many changes over the past few decades. Starting mostly from deterministic differential or difference equations, the mathematical techniques applied to biology have diversified to include stochastic processes, graph theory, topology, combinatorics and many other areas of mathematics. The complexity, heterogeneity and diversity of biological systems represent both challenges and opportunities in modelling. On the one hand, they require and nurture methodological innovations. On the other hand, they allow models to explain biological phenomena as emerging from multiple scales and to elucidate biological mechanisms, thoughts and concepts with the clarity of mathematics. All this makes mathematical biology an exciting and fruitful field. The present paper discusses (1) key biological topics to be addressed in mathematical modelling, (2) some of the mathematical techniques currently in use and the need for further methodological development, and (3) some issues in the training of the next generation of mathematical biologists.

RESUMEN

Esta comunicación resume una “mesa redonda” en un workshop celebrado en la Universidad Federal de Santa Maria, Brasil, sobre tendencias y perspectivas en biología matemática. La biología matemática como campo de investigación ha experimentado muchos cambios en las últimas décadas. Partiendo principalmente de ecuaciones diferenciales o en diferencias deterministas, las técnicas matemáticas aplicadas a la biología se han diversificado para incluir procesos estocásticos, teoría de grafos, topología, combinatoria y muchas otras áreas de las matemáticas. La complejidad, heterogeneidad y diversidad de los sistemas biológicos representan tanto desafíos como oportunidades en la modelización. Por un lado, requieren y fomentan innovaciones metodológicas. Por otro lado, permiten que los modelos expliquen fenómenos biológicos que emergen de múltiples escalas y dilucidan mecanismos, pensamientos y conceptos biológicos con la claridad de las matemáticas. Todo esto hace de la biología matemática un campo apasionante y fructífero. El presente artículo discute (1) temas biológicos clave que se abordarán en la modelización matemática, (2) algunas de las técnicas matemáticas actualmente en uso y la necesidad de un mayor desarrollo metodológico, y (3) algunas cuestiones en la capacitación de la próxima generación de biomatemáticos.

Introduction

The field of mathematical biology (here we will use the term “biology” in a very broad sense, incorporating medicine, ecology, epidemiology, etc.) has grown considerably over the past years from a research area practised by a few visionary pioneers to a well-established sub-field of mathematics that is now taught in most universities worldwide. The type of research done has also changed beyond all recognition (see, e.g., Levin et al., 1997; Cohen, 2004; May, 2004; Reed, 2004, 2015; Maini, 2023).

Mathematical modelling is very high on the radar now due to the COVID-19 pandemic. Epidemic modellers around the world have worked and continue to work on state-of-the-art models to predict the course of the pandemic, assess impact scenarios and compare exit strategies. At the beginning of the pandemic, knowledge about SARS-CoV-2 was virtually non-existent, which posed major challenges to modellers, public health officials, politicians and other decision-makers alike. With mathematical models and simulations playing a prominent role in the response to the pandemic, concepts like exponential growth, R values and herd immunity entered the discussions of the broader public, some modellers also

played an important role influencing public opinion. Thus, the field of mathematical modelling is acknowledged by society probably more than ever.

At the same time, biodiversity and ecosystems are in peril due to global change, which is occurring at unprecedented rates (e.g., Pereira et al., 2010). To make predictions in a changing world, process-based models are required. For mathematical biology these times are, therefore, as important as challenging, and this is further amplified by the availability of increasingly voluminous, varied and quickly processed data, by expanding computer power and by advents in computational algorithms.

This perspective, inspired by a “round-table” discussion at the workshop *Mathematical Biology in Springtime at 29S53W*,¹ aims to highlight three key aspects of the subject of mathematical biology going forward. First, we will put forward what we think are some key scientific topics to be addressed using mathematical modelling. Second, we will discuss some of the mathematical methods that are being used now and the extensions required. Third, we will focus on the type of training needed for young people coming into mathematical biology, as well as ways to keep expanding this field, which, although it has grown significantly, is still comparatively small when compared with other areas of science (cf. Reed, 2015).

TOPICS

As we indicated in the Introduction, the recent research activities in epidemiological modelling due to the COVID-19 pandemic are probably unparalleled in history. Yet, the pandemic proved challenging in many regards. For example, the epidemic curves looked rather different from what simple, off-the-shelf epidemic models predict. Many variables, including age structure, differences in susceptibility or heterogeneity in the exposure to the virus (often related to socio-economic factors) and individual behaviour regarding the adoption of protective measures impact the course of the pandemic. Modellers must take into account limited access to information, difficulties in model validation, uncertainties in measurements and fundamental model limitations, not only as good scientific practices, but also as important caveats when conveying model predictions and possible scenarios to the media and general public.²

The explosion in the interest in the field of epidemiological modelling also led to the integration of many researchers from adjacent fields keen to bring in their expertise. Dangerfield et al. (2023) describe how UK institutions coordinated many

research activities including Virtual Study Groups,³ Scientific Advisory Boards to government⁴ and Rapid Review Groups,⁵ which provided rapid assessments of the emerging research and assisted government advisory groups.⁶ A wide range of similar initiatives or modelling “hubs” emerged in many other countries as well (e.g. Reich et al., 2022).

More generally, consortia of research groups organised around a certain scientific problem can convey a multitude of benefits such as coordinating research activities, collecting and curating data, and leveraging research networks or software products. Such organised research networks allow rapid development of models in large numbers, which frees researchers from having to rely on a single model; a risky bet. With multiple models at hand, it is possible to compare outcomes under various scenarios from different standpoints, which helps to identify inconsistencies and convergences between models. This helps to either promote debate between research groups or build consensus and deliver collective assessments. Such model intercomparison projects have a long tradition in climatology (Cess et al., 1989) and are featured prominently in IPCC (Intergovernmental Panel on Climate Change) assessment reports (Coupled Model Intercomparison Project). Similar initiatives are underway for biodiversity research (Inter-Sectoral Impact Model Intercomparison Project) in the context of IPBES (Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services).

Epidemic modelling is very likely to remain a topical issue, given the number of emerging infectious diseases in recent years (e.g., West Nile virus in 1999, SARS-CoV in 2003, H1N1 in 2009, MERS-CoV in 2012, Ebola in 2013, Zika in 2016) and increased cross-species transmissions due to global change.

The field of ecology is at the forefront of studying the consequences of the ongoing rapid global environmental change. According to IPBES (2019), the main direct drivers of biodiversity loss are land and sea use change, direct exploitation of organisms, climate change, pollution and invasive non-native species. They pose major damage, threats and risks to ecosystem functioning and services as well as production of vital goods (Millennium Ecosystem Assessment, 2005). There is increasing recognition of the existence of ecological regime shifts, in which ecosystems abruptly and irreversibly move from one state to another under supercritical forcing (Scheffer et al., 2001). The planetary boundary framework attempts to globally aggregate the anthropogenic impact on nine processes and relate them to sustainable environmental limits (Steffen et al., 2015). These processes are climate change, biogeochemical (nitrogen and phosphorus) flows,

land-system change, freshwater use, aerosol loading, ozone depletion, ocean acidification, loss of biosphere integrity, including functional and genetic biodiversity, and introduction of novel entities, such as toxic chemicals and plastics. With the increasing societal and political recognition of global change, ecological models are increasingly aiming at ‘anticipatory’ rather than ‘explanatory’ predictions (Mouquet et al., 2015; Houlahan et al., 2017; Maris et al., 2018). On the basis of theoretical and empirical advances, ecological models progressively incorporate biological mechanisms rather than relying solely on statistical descriptions (e.g. Urban et al., 2016; Pilowsky et al., 2022). Yet, there is still no consensus emerging regarding the drivers of species richness and ecosystem functioning (Loreau, 2010). When addressing questions about environmental change, models need the ability to project into novel, future conditions (Evans, 2012). This requires not only a solid mechanistic understanding (Mouquet et al., 2015), but also underlines the importance of model transferability, i.e., how well models generalise to new contexts (Houlahan et al., 2017; Yates et al., 2018).

In developmental biology, advances in image analysis and data collection are revealing the complexities underlying cell movement and spatial patterning. These, in turn, provide challenges to experimentalists and modellers alike, who aim to develop a mechanistic understanding of how processes acting across a vast range of spatial and temporal scales combine to produce the cell and tissue level behaviour that we see. Understanding developmental biology is not only of intrinsic scientific interest, it can also help us develop therapies for developmental diseases. For example, in early development, neural crest cells delaminate from the neural tube and migrate long distances before they differentiate into key tissues in the body. If this process does not occur properly, it can lead to developmental deformities (the so-called neurocristopathies, 66 of which have been identified) (Vega-Lopez et al., 2018). A full understanding of this collective migratory behaviour would allow us to understand the mechanisms and therefore suggest ways to combat developmental diseases. Moreover, these cells have many mechanisms in common with those of cancer cells, so an understanding of how these cells are controlled in normal development suggest novel therapies (e.g., Gallik et al., 2017).

The abstract nature of mathematics allows for ideas from one area of science to be translated to other areas. A striking example of this is the employment of mathematical modelling ideas developed in the context of ecology in cancer cell dynamics. Animal competition models, for example, the classical Lotka–Volterra model (originally proposed for chemical

reactions) are now being used in adaptive therapy. Here, the competitors are drug-sensitive and drug-resistant cells. The idea is that, rather than using a drug at the standard of care (maximum tolerated dose) that will kill off all the drug-sensitive cells, allowing the resistant cells to grow unbounded, using the drug more sparsely by having “drug-holidays”, maintaining the tumour at a controlled size, will allow the sensitive cells to compete with the resistant cells. In this setting, mathematical modelling is being used to test out different therapeutic strategies (see, for example, Strobl et al., 2021), and this is a place where ideas from reinforce deep learning can be employed to modify treatment in an ongoing way. Indeed, more generally, mathematical modelling is now being used to inform drug design and extrapolation from the laboratory to the clinic (see, for example, the review by Kondic et al., 2022).

To build models capable of simulating therapeutic interventions in human patients, different interconnected processes have to be taken into account. Infectious diseases and cancer are good examples of how processes in different systems and on different scales (for example, intracellular reactions, intercellular communication, cell migration, and potentially the metabolism in organs far from the tissue site) depend on each other and determine the outcome of the disease. Different approaches may be used to model each temporal and spatial scale, as well as different parts of the human body. Although model interfacing is becoming less challenging (e.g., Zhou, 2014), we lack a standard framework to couple, merge and switch models. A rigorous procedure for multiscale modelling would leverage the development of powerful simulations able to accurately test and calibrate therapeutic interventions in human patients.

Advances in computing power have led to “digital twin” technologies, where in many industries now computer simulations are used to predict how equipment will perform. A key question is, can this technology be used to develop human digital twins? This is an area of research that is now being pursued in many different areas of medicine (see, for example, Laubenbacher et al., 2022).

As data collecting technologies advance, we are now on the cusp of being able to fit models to data to acquire parameter values. This is now pushing the statistical frontiers of parameter estimation and identifiability (see, for example, Browning et al., 2020). Moreover, ideas from persistent homology are now being used to characterise spatial data (see, for example, McGuirl et al., 2020; Skaf and Laubenbacher, 2022).

MATHEMATICAL METHODS

Classical approaches in mathematical biology focus on low-dimensional and deterministic systems, ignoring the complexities of stochasticity and nonlinear dynamics. Traditional mathematical tools involve ordinary and partial differential equations as well as difference equations. Mathematical biology today goes beyond linear theory and standard nonlinear systems to highly complicated nonlinear systems. There are advances in coarse graining, relating fully nonlinear systems, and in approaches involving agent-based models, network and graph theory, boolean analysis, topological data analysis, statistics, probability theory and stochastic and branching processes, to mention a few. Mathematical biology is now both an inter- and intradisciplinary field.

Artificial intelligence (AI) and machine learning (ML) approaches are being increasingly used. It is worth noting that AI is based on biology (e.g., neural networks), so it is per se an example where biology and mathematics meet. ML models require large amounts of data; they base their predictions on going through databases of inputs and outputs of a given problem. Their results can be faster and more accurate compared to classical statistical methods. More challenging, however, is to gain understanding of the causal mechanisms. ML and mechanistic modelling are therefore often seen as different paradigms, but they can complement each other in their methodological strengths and weaknesses (Baker et al., 2018). The coupling of ML and mechanistic models into hybrid approaches provide major opportunities (Reichstein et al., 2019). Examples include improved model parameterisations or the emulation of computationally challenging process-based models by ML algorithms. Also, mechanistic “sub-models” with little theoretical support can be replaced by data-driven ML models; for example, in agent-based systems the decision-making of individual agents based on input from the environment can follow ML models (e.g., Zhang et al., 2021).

A digital twin is, as already indicated, a dynamic digital representation of a real-life system (e.g., cells, tissues, organs or even the natural environment) (Madni et al., 2019). With automatic data flow between the digital and biological object, this allows a real-time monitoring and prediction of systems, with applications especially in medicine and biotechnology. This is another example where multi-scale aspects are important. Relevant spatial scales can range from the molecular to the ecosystem level. Temporal scales can range from protein processes to the billions of years of evolution of life on Earth. At each level, collective dynamics emerge from the behaviour

of individual units. Despite considerable advances in multi-scale mathematical biology, our understanding of these phenomena is still far from complete (e.g., Eftimie, 2022).

The dynamical systems traditionally studied in mathematical biology are usually autonomous and smooth. However, non-smooth dynamical systems become prevalent in the presence of management actions or policy instruments. For instance, pest control programs are triggered beyond certain economic injury levels, harvest moratoria come into place when the harvested population size drops below a critical level or the use of pesticides, fertilisers or irrigation may be forbidden if environmental indicators become flagged. Non-smooth dynamical systems can be considerably more complex in their dynamics than smooth ones. Consider, for example, the transition from regular dynamics to chaos when varying a system parameter in a certain direction. In smooth systems, this transition generally occurs in a sequence of bifurcations, often called a route to chaos (e.g. Anishchenko et al., 2014). In non-smooth systems, by contrast, this transition can take place in a single bifurcation (di Bernardo et al., 2008; Avrutin et al., 2019). Such bifurcations can give rise to dynamical structures entirely different from the ones in smooth systems.

Non autonomous systems occur when there is periodic forcing (e.g., parameters influenced by seasons or circadian rhythms) or a change in environmental conditions such as temperature or precipitation. The latter is often modelled in the form of parameters that evolve or are ramped in a linear or accelerating trend. Just like seasonal forcing can induce complex dynamics, simple trends in parameters due to a changing world can cause rate-induced critical transitions or track system states that are unstable in a constant environment (e.g., Siteur et al., 2016; Vanselow et al., 2019; Arumugam et al., 2021).

When studying the human impact on biological systems, the human influence is often encapsulated in the form of a simple parameter (e.g., a harvest rate or the average vaccination coverage in a population). Conversely, in many socio-economic studies dealing with biological systems, the latter are often simplified to almost static objects (see also Shin et al., 2022). For a full account of the mutual feedbacks between the biological and socio-economic domains, however, one has to take into account the coupled dynamics. This requires connecting biological dynamics with human and social sciences, for which sociology, economics, behavioural psychology, law and other areas come into play. Mathematical methods that can be used in this context include, for example,

evolutionary and differential games, agent-based models and optimal control. Of course, they also deal with different time scales (e.g., slow-fast systems, singular perturbation analysis) and spatial variation (e.g., reaction-diffusion or integrodifferential equations, nonlocal effects), to mention some of the complexities involved. Such coupled social-ecological systems are fascinating in their own right (e.g., Levin et al., 2013; Galvani et al., 2016). They also play an increasing role in behavioural epidemiology. Individual decision-making, social learning and the spread of (mis-)information are key factors in the adoption of preventive measures such as vaccination, social distancing and face masks. Consequently, the spread of infection and the success of public health programmes are affected by individual behaviour (see the reviews by Funk et al., 2010; Chang et al., 2020).

EDUCATION AND TRAINING

Mathematical biology will have a bright future with new generations of scientists that have expertise in both mathematics and biology, i.e., “empiricists with stronger quantitative skills” and “theoreticians with an appreciation for the empirical structure of biological processes” (Hastings and Palmer, 2003). Universities, however, are built on disciplines. Yet, many of the most exciting areas in science are interdisciplinary. How do we overcome the barriers between disciplines and, indeed, within disciplines (intra-disciplinary)? One way to achieve this in graduate education are Centres for Doctoral Training. These are externally funded PhD programmes at universities in the UK and they have been designed to strategically increase a university’s capacity in interdisciplinary research, especially at the interfaces between traditionally organised departments. Similarly, Research Training Groups funded by the German Research Foundation promote innovative and often interdisciplinary PhD programmes at German universities. These and other externally funded initiatives have proven to stimulate lasting changes in university structures.

Such interdisciplinary programmes also promote students in learning the “language” of the other discipline, while being anchored in a home discipline. There will always be some concern about juggling interdisciplinary breadth and intradisciplinary depth. This is something for which tailored solutions can be found in individual development plans⁷, enlisting the supervisor(s)’ experience and depending on the nature of the research project and the student’s needs.

In mathematical biology education more generally, there has been an enormous spectrum of initiatives and considerable changes in the past 1-2 decades. An impressive collection of

these changes are summarised in the review by Jungck et al. (2020). Many, if not most, major research universities now have courses on mathematical biology; some universities even offer degree programmes in this area. However, the majority of universities probably still lack critical mass to offer courses or projects in mathematical biology that build upon each other and could thus reinforce learning. Furthermore, existing courses in mathematical biology are often inaccessible to students who have not yet completed the classical prerequisite courses, e.g., in linear algebra and (multivariable) calculus. A course design with such prerequisites can be an impediment to attract interested students from nearby disciplines (cf. Miller and Alben, 2012).

A major “asset” of mathematical biology is the high motivation of students to learn about applications of mathematics in biology, i.e., in living systems to which they can intuitively relate. Reed (2015, p. 1175) writes:

“Most people acknowledge the traditional important applications of mathematics to physics, from the motions of the planets to quantum mechanics, nuclear fission and the bomb, and fluid flow over airplane wings. Unfortunately, most people just aren’t very interested in physics (Voltaire had it right), so they acknowledge the importance but aren’t that moved. How about the applications of number theory to cryptography? Again, everyone sees that it is important to have secure communications, but they’re not very interested in how it gets done. Leave it to the geeks! But biology is a different story. Everyone is interested in his or her own body and how it works. Everyone wants to be free of disease and live a long time. Everyone (well almost everyone) knows that we’d better be good stewards of our ecosystems or we and our children are doomed. So, when you tell them how mathematics is contributing, they are really interested. And this has the potential, in the long run, to greatly improve the public perception of mathematics.”

To get prospective students (and also the general public) more interested in mathematics and its applications, there are a host of outreach activities. For example, universities or departments organise Open Days, where students and lecturers show how much fun mathematics is and for what it can be “used”. In some countries, including the UK, there is an established tradition of TV programmes with researchers or educators explaining science. More recently, children increasingly use social media platforms to complement their learning with short video tutorials, some of which point out modern applications of mathematics. To reach out to school

teachers, Seshaiyer and Lenhart (2020) describe a number of modelling activities, in which teachers have engaged via professional development programmes and which they have incorporated in the classroom. For undergraduate students, there are offers of summer research opportunities, internships, workshops or bursaries, which often motivate them to pursue mathematical biology in their graduate studies (e.g. de Vries and Hillen, 2008). Undergraduate research experience programmes have also been run by the Mathematical Biosciences Institute and the National Institute for Mathematical and Biological Synthesis. Both institutes have, more broadly, actively supported mathematical biology through workshops, working groups, visitor programmes, fellowships, education and outreach programmes. Synthesis centres have emerged in the past two decades and created community-oriented research infrastructure (Baron et al., 2017).

CONCLUSIONS AND OUTLOOK

As a scientist, it is hard enough to be an expert in one area. To be an expert in two areas is very difficult. So a key aspect is being able to communicate with researchers in other disciplines. This implies having enough knowledge to understand what scientists in other disciplines are talking about. Another key aspect is being able to communicate within your own discipline. For instance, there are so many areas of mathematics coming together in biology now (e.g., from dynamical systems over networks to group theory) that it is impossible to be an expert in all of these areas. Similarly, biology itself is so diverse that its research fields are fragmented (cf. Reed, 2004). Mathematical biologists therefore need both intra- and interdisciplinary competencies.

Considering all the changes in mathematical biology that happened over the last 40 or so years, it is difficult to predict where the field will be in 10-20 years' time. What seems clear is that, on the one hand, biology continues to provide hard challenges for mathematics because of the multiple temporal and spatial scales, the heterogeneity of individuals and evolutionary dynamics. In addition, the enormous data streams in all areas of biology, as well as the pace at which computational predictions grow faster than our understanding of biological systems, will require new mathematical developments. On the other hand, there has been a tighter integration of mathematical biology with experiments over the past years. This can be seen, for example, in the growing number of examples where mathematicians are integrated into clinics and biological departments. At the same time, the progress in biology increasingly requires researchers to use quantitative skills. Biology is becoming so sophisticated

that researchers essentially cannot escape computation and advanced mathematics. Many biology journals nowadays require theory and modelling in addition to data. And they sometimes even feature mathematical approaches as cover articles—something unheard of a while back.

Progress in biology will depend on our ability to formulate theories, for which mathematics provides the quintessential clarity (Cohen, 2004; May, 2004). Therefore, “simple” theoretical models⁸ also continue to be relevant when they capture the mechanistic essence of a complex system, improve our understanding of biological phenomena, and provide novel insights or suggest new experiments (e.g., Segel and Edelman-Keshet, 2013). They can influence the way we understand biological systems and also have an impact on decision-making and management (e.g., DeAngelis et al., 2021).

ACKNOWLEDGMENTS

We are grateful to Roberto A. Kraenkel, Luciana de Oliveira, José Monbach and the workshop participants for the discussion, which was moderated by Wilson Castro Ferreira Junior. The workshop, in which the round-table discussion took place, is part of the project of internationalisation of the post-graduation of Rio Grande do Sul “Cooperação Internacional Brasil–Alemanha em Ecologia Teórica” coordinated by the Biomathematics Group from the Federal University of Santa Maria and supported by FAPERGS.

1. Held at the Federal University of Santa Maria in Santa Maria, RS, Brazil, from October 5–7, 2022.
2. Corner et al. (2015) provide an illustrated handbook with twelve practical principles for the communication about climate change uncertainties.
3. As part of the Virtual Forum for Knowledge Exchange in the Mathematical Sciences (V-KEMS), convened by the International Centre for Mathematical Sciences, Isaac Newton Institute, Newton Gateway to Mathematics and the Knowledge Transfer Network working with various representatives from the mathematical sciences community.
4. E.g., the Scientific Pandemic Influenza Group for Modelling in operational mode (SPI-M-O) became a formal subgroup of the Scientific Advisory Group for Emergencies (SAGE).
5. Established by the Royal Society's Rapid Assistance in Modelling the Pandemic initiative.

6. Recall the almost overwhelming rate of posting of new preprints during the course of the pandemic.
7. Individual development plans are mutual agreements between a graduate student and the supervisor(s). They are intended to identify needs in training, resources or research infrastructure. They clarify responsibilities of both student and supervisor(s), and are thought to improve orientation and transparency in the student's qualification process.
8. Sometimes also called generic, strategic or stylized models; see Evans et al. (2013) and references therein for terminology.

REFERENCES

- [1] Anishchenko, V. S., Vadivasova, T. E., and Strelkova, G. I. (2014). *Deterministic Nonlinear Systems: A Short Course*. Springer, Cham.
- [2] Arumugam, R., Lutscher, F., and Guichard, F. (2021). "Tracking unstable states: ecosystem dynamics in a changing world". *Oikos*, 130:525–540.
- [3] Avrutin, V., Gardini, L., Sushko, I., and Tramontana, F. (2019). *Continuous and Discontinuous Piecewise-Smooth One-Dimensional Maps*. World Scientific, Singapore.
- [4] Baker, R. E., J.-M. P., Jayamohan, J. and Jérusalem, A. (2018). "Mechanistic models versus machinelearning, a fight worth fighting for the biological community?" *Biology Letters*, 14:20170660.
- [5] Baron, J. S., Specht, A., Garnier, E., Bishop, P., Campbell, C. A., Davis, F. W., Fady, B., Field, D., Gross, L. J., Guru, S. M., Halpern, B. S., Hampton, S. E., Leavitt, P. R., Meagher, T. R., Ometto, J., Parker, J. N., Price, R., Rawson, C. H., Rodrigo, A., Sheble, L. A., and Winter, M. (2017). "Synthesis centers as critical research infrastructure". *BioScience*, 67:750–759.
- [6] Browning, A. P., Warne, D. J., Burrage, K., Baker, R. E., and Simpson, M. J. (2020). "Identifiability analysis for stochastic differential equation models in systems biology". *Journal of The Royal Society Interface*, 17:20200652.
- [7] Cess, R. D., Potter, G. L., Blanchet, J. P., Boer, G. J., Ghan, S. J., Kiehl, J. T., Le Treut, H., Li, Z.-X., Liang, X.-Z., Mitchell, J. F. B., Morcrette, J.-J., Randall, D. A., Riches, M. R., Roeckner, E., Schlese, U., Slingo, A., Taylor, K. E., Washington, W. M., Wetherald, R. T., and Yagai, I. (1989). "Interpretation of cloud-climate feedback as produced by 14 atmospheric general circulation models". *Science*, 245:513–516.
- [8] Chang, S. L., Piraveenan, M., Pattison, P., and Prokopenko, M. (2020). "Game theoretic modelling of infectious disease dynamics and intervention methods: a review". *Journal of Biological Dynamics*, 14:57–89.
- [9] Cohen, J. E. (2004). "Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better". *PLoS Biology*, 2:e439.
- [10] Corner, A., Lewandowsky, S., Phillips, M., and Roberts, O. (2015). *The Uncertainty Handbook*. University of Bristol, Bristol.
- [11] Dangerfield, C. E., David Abrahams, I., Budd, C., Butchers, M., Cates, M. E., Champneys, A. R., Currie, C. S., Enright, J., Gog, J. R., Goriely, A., Déirdre Hollings-worth, T., Hoyle, R. B., INI Professional Services, Isham, V., Jordan, J., Kaouri, M. H., Kavoussanakis, K., Leeks, J., Maini, P. K., Marr, C., Merritt, C., Mollison, D., Ray, S., Thompson, R. N., Wakefield, A., and Wasley, D. (2023). "Getting the most out of maths: How to coordinate mathematical modelling research to support a pandemic, lessons learnt from three initiatives that were part of the COVID-19 response in the UK". *Journal of Theoretical Biology*, 557:111332.
- [12] de Vries, G. and Hillen, T. (2008). "Teaching mathematical biology in a summer school for undergraduates". In: Deutsch, A., Bravo de la Parra, R., de Boer, R. J., Diekmann, O., Jagers, P., Kisdi, E., Kretzschmar, M., Lansky, P., and Metz, H., editors, *Mathematical Modeling of Biological Systems, Volume II. Modeling and Simulation in Science, Engineering and Technology*, pages 369–377. Birkhäuser, Boston, MA.
- [13] DeAngelis, D. L., Franco, D., Hastings, A., Hilker, F. M., Lenhart, S., Lutscher, F., Petrovskaya, N. and Tyson, R. (2021). "Towards building a sustainable future: Positioning ecological modelling for impact in ecosystems management". *Bulletin of Mathematical Biology*, 83:107.
- [14] di Bernardo, M., Budd, C. J., Champneys, A. R., and Kowalczyk, P. (2008). *Piecewise-Smooth Dynamical Systems*. Springer, London.
- [15] Eftimie, R. (2022). "Grand challenges in mathematical biology: Integrating multi-scale modeling and data". *Frontiers in Applied Mathematics and Statistics*, 8:1010622.

- [16] Evans, M. R. (2012). “Modelling ecological systems in a changing world”. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367:181–190.
- [17] Evans, M. R., Grimm, V., Johst, K., Knuuttila, T., Langhe, R., Lessells, C. M., Merz, M., O’Malley, M. A., Orzack, S. H., Weisberg, M., Wilkinson, D. J., Wolkenhauer, O., and G. Benton, T. (2013). “Do simple models lead to generality in ecology?” *Trends in Ecology & Evolution*, 28:578–583.
- [18] Funk, S., Salathé, M., and Jansen, V. A. A. (2010). “Modelling the influence of human behaviour on the spread of infectious diseases: a review”. *Journal of the Royal Society Interface*, 7:1247–1256.
- [19] Gallik, K. L., Treffy, R. W., Nacke, L. M., Ahsan, K., Rocha, M., Grren-Saxena, A., and Saxena, A. (2017). “Neural crest and cancer: Divergent travelers on similar paths”. *Mechanisms of Development*, 148:89–99.
- [20] Galvani, A. P., Bauch, C. T., Anand, M., Singer, B. H., and Levin, S. A. (2016). “Human–environment interactions in population and ecosystem health”. *Proceedings of the National Academy of Sciences*, 113:14502–14506.
- [21] Hastings, A. and Palmer, M. A. (2003). “A bright future for biologists and mathematicians?” *Science*, 299:2003–2004.
- [22] Houlahan, J. E., McKinney, S. T., Anderson, T. M., and McGill, B. J. (2017). “The priority of prediction in ecological understanding”. *Oikos*, 126:1–7.
- [23] IPBES (2019). Global assessment report on biodiversity and ecosystem services of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. IPBES secretariat, Bonn, Germany.
- [24] Jungck, J. R., Robeva, R., and Gross, L. J. (2020). “Mathematical biology education: Changes, communities, connections, and challenges”. *Bulletin of Mathematical Biology*, 82:117.
- [25] Kondic, A., Bottino, D., Harrold, J., Kearns, J. D., Musante, C., Odinecs, A., Ramanujan, S., Selimkhanov, J., and Schoeberl, B. (2022). “Navigating between right, wrong, and relevant: The use of mathematical modeling in preclinical decision making”. *Frontiers in Pharmacology*, 13:860881.
- [26] Laubenbacher, R., Niarakis, A., Helikar, T., An, G., Shapiro, B., Malik-Sheriff, R. S., Sego, T. J., Knapp, A., Macklin, P., and Glazier, J. A. (2022). “Building digital twins of the human immune system: toward a roadmap”. *npj Digital Medicine*, 5:64.
- [27] Levin, S., Xepapadeas, T., Crépin, A.-S., Norberg, J., de Zeeuw, A., Folke, C., Hughes, T., Arrow, K., Barrett, S., Daily, G., Ehrlich, P., Kautsky, N., Mäler, K.-G., Polasky, S., Troell, M., Vincent, J., and Walker, B. (2013). “Social-ecological systems as complex adaptive systems: modeling and policy implications”. *Environment and Development Economics*, 19:111–132.
- [28] Levin, S. A., Grenfell, B., Hastings, A., and Perelson, A. S. (1997). “Mathematical and computational challenges in population biology and ecosystems science”. *Science*, 275:334–343.
- [29] Loreau, M. (2010). “Linking biodiversity and ecosystems: towards a unifying ecological theory”. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 365:49–60.
- [30] Madni, A. M., Madni, C. C., and Lucero, S. D. (2019). “Leveraging digital twin technology in modelbased systems engineering”. *Systems*, 7:7.
- [31] Maini, P. K. (2023). “Mathematical biology: Looking back and going forward”. In: Morel, J.-M. and Teissier, B., editors, *Mathematics Going Forward*, pages 413–416. Springer, Cham.
- [32] Maris, V., Huneman, P., Coreau, A., Kéfi, S., Pradel, R., and Devictor, V. (2018). “Prediction in ecology: promises, obstacles and clarifications”. *Oikos*, 127:171–183.
- [33] May, R. M. (2004). “Uses and abuses of mathematics in biology”. *Science*, 303:790–793.
- [34] McGuirl, M. R., Volkening, A., and Sandstede, B. (2020). “Topological data analysis of zebrafish patterns”. *Proceedings of the National Academy of Sciences*, 117:5113–5124.
- [35] Millennium Ecosystem Assessment (2005). *Ecosystems and Human Well-being: Synthesis*. Island Press, Washington, DC.
- [36] Miller, L. A. and Alben, S. (2012). “Interfacing mathematics and biology: a discussion on training, research, collaboration, and funding”. *Integrative and Comparative Biology*, 52:616–621.

- [37] Mouquet, N., Lagadeuc, Y., Devictor, V., Doyen, L., Duputié, A., Eveillard, D., Faure, D., Garnier, E., Gimenez, O., Huneman, P., Jabot, F., Jarne, P., Joly, D., Julliard, R., Kéfi, S., Kergoat, G. J., Lavorel, S., Le Gall, L., Meslin, L., Morand, S., Morin, X., Morlon, H., Pinay, G., Pradel, R., Schurr, F. M., Thuiller, W., and Loreau, M. (2015). “Predictive ecology in a changing world”. *Journal of Applied Ecology*, 52:1293–1310.
- [38] Pereira, H. M., Leadley, P. W., Proença, V., Alkemade, R., Scharlemann, J. P. W., Fernandez-Manjarrés, J. F., Araújo, M. B., Balvanera, P., Biggs, R., Cheung, W. W. L., Chini, L., Cooper, H. D., Gilman, E. L., Guénette, S., Hurtt, G. C., Huntington, H. P., Mace, G. M., Oberdorff, T., Revenga, C., Rodrigues, P., Scholes, R. J., Sumaila, U. R., and Walpole, M. (2010). “Scenarios for global biodiversity in the 21st century”. *Science*, 330:1496–1501.
- [39] Pilowsky, J. A., Colwell, R. K., Rahbek, C., and Fordham, D. A. (2022). “Process-explicit models reveal the structure and dynamics of biodiversity patterns”. *Science Advances*, 8:eabj2271.
- [40] Reed, M. C. (2004). “Why mathematical biology is so hard?” *Notices of the AMS*, 51:338–342.
- [41] Reed, M. C. (2015). “Mathematical biology is good for mathematics”. *Notices of the AMS*, 62:1172–1176.
- [42] Reich, N. G., Lessler, J., Funk, S., Viboud, C., Vespignani, A., Tibshirani, R. J., Shea, K., Schienle, M., Runge, M. C., Rosenfeld, R., Ray, E. L., Niehus, R., Johnson, H. C., Johansson, M. A., Hochheiser, H., Gardner, L., Bracher, J., Borchering, R. K., and Biggerstaff, M. (2022). “Collaborative hubs: Making the most of predictive epidemic modeling”. *American Journal of Public Health*, 112:839–842.
- [43] Reichstein, M., Camps-Valls, G., Stevens, B., Jung, M., Denzler, J., Carvalhais, N., and Prabhat (2019). “Deep learning and process understanding for data-driven Earth system science”. *Nature*, 566:195–204.
- [44] Scheffer, M., Carpenter, S., Foley, J. A., Folke, C., and Walker, B. (2001). “Catastrophic shifts in ecosystems”. *Nature*, 413:591–596.
- [45] Segel, L. A. and Edelstein-Keshet, L. (2013). *A Primer on Mathematical Models in Biology*. Society for Industrial and Applied Mathematics, Philadelphia, PA.
- [46] Seshaiyer, P. and Lenhart, S. (2020). “Connecting with teachers through modeling in mathematical biology”. *Bulletin of Mathematical Biology*, 82:98.
- [47] Shin, Y. A., Lacasse, K., Gross, L. J., and Beckage, B. (2022). “How coupled is coupled human-natural systems research?” *Ecology & Society*, 27:4.
- [48] Siteur, K., Eppinga, M. B., Doelman, A., Siero, E., and Rietkerk, M. (2016). “Ecosystems off track: rate induced critical transitions in ecological models”. *Oikos*, 125:1689–1699.
- [49] Skaf, Y. and Laubenbacher, R. (2022). “Topological data analysis in biomedicine: A review”. *Journal of Biomedical Informatics*, 130:104082.
- [50] Steffen, W., Richardson, K., Rockström, J., Cornell, S. E., Fetzer, I., Bennett, E. M., Biggs, R., Carpenter, S. R., de Vries, W., de Wit, C. A., Folke, C., Gerten, D., Heinke, J., Mace, G. M., Persson, L. M., Ramanathan, V., Reyers, B., and Sörlin, S. (2015). “Planetary boundaries: Guiding human development on a changing planet”. *Science*, 347:736.
- [51] Strobl, M. A., West, J., Viosat, Y., Damaghi, M., Robertson-Tessi, M., Brown, J. S., Gatenby, R. A., Maini, P. K., and Anderson, A. R. (2021). “Turnover modulates the need for a cost of resistance in adaptive therapy”. *Cancer Research*, 81(1135-1147).
- [52] Urban, M. C., Bocedi, G., Hendry, A. P., Mihoub, J.-B., Pe’er, G., Singer, A., Bridle, J. R., Crozier, L. G., De Meester, L., Godsoe, W., Gonzalez, A., Hellmann, J. J., Holt, R. D., Huth, A., Johst, K., Krug, C. B., Leadley, P. W., Palmer, S. C. F., Pantel, J. H., Schmitz, A., Zollner, P. A., and Travis, J. M. J. (2016). “Improving the forecast for biodiversity under climate change”. *Science*, 353:aad8466.
- [53] Vanselow, A., Wieczorek, S., and Feudel, U. (2019). “When very slow is too fast - collapse of a predator-prey system”. *Journal of Theoretical Biology*, 479:64–72.
- [54] Vega-Lopez, G. A., Cerrizuela, S., Tribulo, C., and Aybar, M. J. (2018). “Neurocristopathies: New insights 150 years after the neural crest discovery”. *Developmental Biology*, 444:S110–S143.
- [55] Yates, K. L., Bouchet, P. J., Caley, M. J., Mengersen, K., Randin, C. F., Parnell, S., Fielding, A. H., Bamford, A. J., Ban, S., Barbosa, A. M., Dormann, C. F., Elith, J., Embling,

C. B., Ervin, G. N., Fisher, R., Gould, S., Graf, R. F., Gregr, E. J., Halpin, P. N., Heikkinen, R. K., Heinänen, S., Jones, A. R., Krishnakumar, P. K., Lauria, V., Lozano-Montes, H., Mannocci, L., Mellin, C., Mesgaran, M. B., Moreno-Amat, E., Mormede, S., Novaczek, E., Opper, S., Ortuño Crespo, G., Peterson, A. T., Rapacciuolo, G., Roberts, J. J., Ross, R. E., Scales, K. L., Schoeman, D., Snelgrove, P., Sundblad, G., Thuiller, W., Torres, L. G., Verbruggen, H., Wang, L., Wenger, S., Whittingham, M. J., Zharikov, Y., Zurell, D., and Sequeira, A. M. (2018). “Outstanding challenges in the transferability of ecological models”. *Trends in Ecology & Evolution*, 33:790–802.

[56] Zhang, K., Yang, Z., and Başar, T. (2021). “Multiagent reinforcement learning: A selective overview of theories and algorithms”. In: Vamvoudakis, K. G., Wan, Y., Lewis, F. L., and Cansever, D., editors, *Handbook of Reinforcement Learning and Control*, pages 321–384. Springer, Cham.

[57] Zhou, H.-X. (2014). “Theoretical frameworks for multiscale modeling and simulation”. *Current Opinion in Structural Biology*, 25:67–76.