Journal of Theoretical Biology 481 (2019) 3–5

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtb

Preface

Overview

The past 30 years have seen mathematical biology grow from being a somewhat niche area in applied mathematics into an all-encompassing discipline in its own right. The vast number of areas to which it is being applied in the biological, medical and ecological sciences has led to problems that are challenging, and advancing, cutting-edge technologies across a broad spectrum of sub-disciplines in the mathematical and computational sciences. Mathematical biology is beginning to be embedded in experimental and clincal laboratories and studies, as well as being increasingly used to inform policy-makers on disease control.

One of the reasons why the subject area has grown so much is due to the huge ongoing advances in biotechnology that are raising new questions that span a great range of spatial and temporal scales. For example, whole-cell models now typically incorporate key intercellular processes. The internal environment of cells is regulated by a number of mechanisms, of which membrane transporters are key, moving substrates across cell membranes. However, many models of transporters are not thermodynamically consistent, leading to unrealistic behaviour. In this issue, Pan et al. (pp. 10–23) show how the bond graph framework can capture thermodynamic constraints resulting in models that are therefore thermodynamically consistent. The framework is applied to two well-studied ion pumps that play important roles in transporting key substrates in cardiac cells – the ion transporter sarcoplasmic/endplasmic Ca^{+2} ATPase (SERCA) and Na^{+}/K^{+} ATPase pumps. The framework provides a systematic way to model energy transport, crucial to the function of cardiac cells – especially as their metabolism is altered during heart failure – as well as to model transporters in general.

The identification of appropriate scalings to exploit timescale separation has long been used in the analysis of dynamical systems to simplify large systems of coupled nonlinear differential equations by decomposing them into smaller sub-systems valid in different temporal regimes. The paper by Burke (pp. 24–27 The paper by) is a concise historical review of this technique as applied to the analysis of enzyme-substrate kinetics. It is shown how extracting a small parameter appropriate for the problem at hand can result in a quasi-steady state assumption (QSSA) that approximates a higher order ordinary differential equation (ODE) system by a more tractable lower order system of ODEs coupled with algebraic relationships. Eilertsen et al. (pp. 28–43) show that the standard timescale separation used in enzyme kinetics is inappropriate for identifying when concentrations and reaction rates reach their maximum values, an issue of experimental importance. They illustrate this for a number of examples and show that, in fact, the system can be further decomposed so that several dynamic regimes can be observed.

Oscillations are a common form of signalling observed across a wide range of biological systems. For example, oscillations in gene expression are important in somitogenesis, circadian rhythms *etc.*, and certain gene regulatory networks are examples of ring oscillators, containing a single negative feedback loop between biochemical species. The paper by Page (pp. 44–53) investigates a coupled system of ODEs for this phenomenon, and presents a systematic way of analysing the stability of steady states, which allows the identification of Hopf bifurcations. In this way, optimal conditions can be found for oscillations in regulatory networks. These conditions are then interpreted in a biological context to provide important insights into the functioning of regulatory networks, and a number of experimental predictions are made.

Dhawan et al. (pp. 54–60) investigates the possible role of non-coding RNA in regulating the oscillations arising at the protein and RNA levels. It develops a coupled ODE model which has two distinct time delays, and carries out detailed bifurcation and parameter sensitivity analyses, as well as simulating a stochastic version of the model for low molecule numbers. The authors find a novel mechanism for generating sustained oscillations by determining that there is a critical value of the sum of the two delays above which oscillations emerge, and they discuss the biological implications of these results.

Historically, macroscale models were derived by including microscale properties in a phenomenological way. A major area of research in mathematical biology now is the development of techniques that allow for this to be done in a systematic manner. The paper by Baker et al. (pp. 61–74) develops a mechanical cell-based model of an epithelial sheet in one spatial dimension and constructs a continuum-limit (macroscale tissue-level) partial differential equation (PDE) model that accounts for growth through cells proliferating stochastically. It is shown that this leads to a free-boundary problem for both the density of the cells within the domain and the evolution of the domain. It is further shown, using numerical simulation, that the coarse-grained PDE description very accurately captures the behaviour of the individual cell-based model.

One of the most influential mathematical models in developmental biology is the Cooke-Zeeman clock and wavefront model for somitogenesis, which shows how cell level properties, coupled with a tissue level signal, can lead to segmentation (somites). Inspired by recent experimental observations, Murray et al. (pp. 75–83) proposes a new model for somitogenesis that incorporates the hypothesis that the natural oscillation frequency of an individual cell is dependent on its position in the cell cycle. This multiscale model couples these internal cell dynamics with a mechanical model for cell-cell interaction and is numerically solved

https://doi.org/10.1016/S0022-5193(19)30358-3
0022-5193

on a growing domain. Under certain conditions, it is found that the emergent oscillator frequency is a weighted average of the constituent oscillator frequencies. A potential future application of this modelling framework is to explore the link between tissue growth and somite size.

Collective cell invasion is a widespread phenomenon that occurs in, for example, embryogenesis, wound healing, disease, *etc.*. The cranial neural crest (NC) serves as an experimentally tractable paradigm model system in which to study a number of aspects of this phenomenon. Interdisciplinary studies on cranial NC in chick have shown that cell heterogeneity plays a vital role in NC cell migration and this has been represented in a simplified way by considering distinct cell types. The paper by Schumacher (pp. 84–90) derives a new model in which cell state is considered as a continuum in which cells respond to a combination of signalling cues, instead of the previously assumed specialised response to individual cues. The resultant hybrid PDE-discrete-cell-based model is solved and its predictions compared and contrasted with previous models. Experimental studies are suggested to help refine the model further.

In the above example, it is known that there is negligible cell proliferation during the invasive process. However, in many cases, cell proliferation plays a key role in cell invasion and is typically modelled by assuming that division occurs after an exponentially distributed waiting time. This is a modelling simplication that is often not realistic biologically. Therefore the paper by Gavagnin et al. (pp. 91–99) considers, instead, an age-structured model, and a multi-stage representation of the cell cycle embedded in an agent-based model, to investigate how the details of the cell cycle time distribution affect invasion speed. The authors obtain an analytic expression which allows them to determine the range of possible invasion speeds in terms of the average proliferation time in any multi-stage model.

There are many open questions concerning how stem/progenitor cell control tissue size, development and renewal. An important paradigm for this is hematopoiesis, the process by which the body manufactures blood cells. In this issue Becker et al. (pp. 100–109) proposes a model for hematopoietic stem cell (HSC) homeostasis which consists of a coupled system of ODEs in which HSCs are considered to be in one of two states (quiescent and proliferating) interacting with a specific type of niche cell in the bone marrow environment in such a way as to regulate HSC proliferation through negative feedback. A QSSA is used to reduce the order of the model and the resultant system analysed and shown to explain counter-intuitive experimental findings. This paper shows that investigating the effect of stem cells on the niche may be as important as the more commonly studied signalling from niche cells to stem cells.

In the mammalian brain, the cerebral neocortex plays an important role in many cognitive functions, and abnormal development can lead to diseases. One of the crucial aspects of neocortex development is how the numbers of neural progenitor cells and the neurons they produce are controlled to yield the correct size and composition of tissue. Picco and Woolley (pp. 110–118) show that this requires temporal changes in division strategy, leading to a coupled non-automous system of ODEs. The authors define a strategy space and explore how division strategy must evolve by fitting to experimental data using approximate Bayesian computation. One of the counter-intuitive results of this work is that the human brain may be generating more neurons than the macaque brain starting from fewer progenitor cells.

Directed cell motion arises through cell polarisation and understanding this phenomenon is very important for normal development, repair and disease. Cusseddu et al. (pp. 119–135) considers the so-called “wave pinning” model – a coupled system of reaction-diffusion equations proposed to describe the evolution of Rho GTPases, identified as being central to the phenomenon of polarisation. It generalises this model by writing it in the framework of coupled bulk-surface semilinear PDEs. The resultant model is investigated in detail via asymptotic and local perturbation analysis, as well as numerically, using the bulk-surface finite element method. The generality of this framework allows for more complex biochemistry and biomechanics to be included.

One of the challenges in modelling biological systems, as compared to many physical or chemical systems, is that in biology, organisms grow. This leads to the problem of analysing PDE models on growing domains. In addition, many biological systems have a complex geometry, and it remains an intriguing question as to how curvature, for example, could affect pattern selection and evolution. These issues are investigated in the paper by Sánchez-Garduño et al. (pp. 136–150) which analyses the Fitzhugh-Nagumo model on growing curved domains, specifically a torus and a sphere. Linear analysis of the homogeneous steady state reveals the possibility of Turing and Turing-Hopf bifurcations. The system is simulated numerically and it is shown how linear theory can fail in certain regimes. It is also shown that the patterning properties on the sphere can be quite different to those on the torus, and how patterns behave on a general evolving manifold is still an open question.

The formation of vegetation stripes on the landscape scale has been investigated mathematically via coupled systems of PDEs where, for mathematical simplicity, it is often assumed that seed disperal can be modelled by a diffusion term. Bennett and Sherratt (pp. 151–161) considers, instead, a model which explores the effects of long-range seed dispersal via a non-local convolution term. The stripe-forming capabilities of this model are analysed and shown to produce stationary or slowly moving patterns, which are consistent with data. The robustness of patterns to changes in key ecological parameters and processes is examined.

An important feature of biological, and ecological, behaviour, is that the same processes are used over and over again. A classic example of this is the phenomenon of chemotaxis, which serves as a guidance mechanism occurring in many different organisms and at many different length scales. The paper by Painter (pp. 162–182) presents a review of the classic model for this phenomenon – the Patlak-Keller-Segal (PKS) model. While the original model assumes that the attractant is a chemical, at the abstract level of a mathematical model, the attractant could be anything (an example of how the same mathematics can be used across many different fields to address seemingly different problems). A variety of models that build on the PKS model are reviewed, in the areas of microbiology, development, immunology, cancer and ecology, as well as in the social sciences (crime), and the diverse spatio-temporal patterning behaviour of these model systems presented. The paper finishes with a semi-light-hearted application that introduces the notion of “research drift” in academic clique formation. This is also the first academic paper I have read that cites Mae West.

Mathematical modelling is playing an increasingly important role in suggesting strategies to prevent spread of disease at the population level and, as mentioned above, inform policy-makers. In the battle to combat the spread of an infectious disease, knowing when to stop treatment is still an open question. In this issue, Dessavre et al. (pp. 182–193) shows how combining two potential indicators of disease elimination predicted by critical slowing down theory, coupled with detrending the data, can be used to address this problem. It is shown that the latter is crucial to obtaining accurate predictions and it is demonstrated that for a simulated metapopulation model, using multiple subpopulations results in much better detrending and, subsequently, better statistical indicators of a critical transition in disease dynamics.

The paper by Pitcher et al. (pp. 194–201) presents a review of the modelling literature in hepatitis C virus (HCV) spread. The ma-

jority of new HIV infections arise from people who inject drugs (PWID) and elimination strategies target this subpopulation. Analysis of mathematical models, which are mainly coupled systems of deterministic ODEs, has shown that harm reduction alone is unlikely to acheive elimination targets among PWID but suggests that combination strategies in which this treatment can be combined with HCV treatment can improve elimination.

Malaria continues to be one of the deadliest diseases known to humankind. Ngwa et al. (pp. 202–222) proposes a deterministic ODE model that takes into account transmission within the mosquito population, as well as the human population. It is shown how inclusion of the gonotrophic cycle essentially introduces an age-structure into the model. A number of theorems on the stability of steady states are proved and these are then interpreted in an epidemiological context. The study shows that targeting a combination of transmission processes is the most desirable control strategy, as well as highlighting how important various processes are in their contribution to disease spread.

Panovska-Griffiths et al. (pp. 223–232) report on a study in which the authors carry out a literature review and analysis of the four major influenza pandemics over the past century to project forward to the effectiveness of different treatment strategies. In particular, it is determined under which conditions certain immunisation treatments would be effective. This study has important implications for policy-makers.

Clearly, the behaviour of mathematical models depends on the parameter values in the model. Therefore, it is important to parameterise the models we use, but to do so requires data that are not readily available. Recent advances in technology now mean that we are beginning to acquire such data but they can be noisy and non-quantitative. One of the major challenges facing the field is how to use such data for parameter estimation. The paper by Barac et al. (pp. 233–248) presents a pipeline that estimates parameters using Gaussian process learning. The use of the method is illustrated by fitting to artifical data generated from a reaction-advection-diffusion equation model for Fgf10 expression in the developing murine limb solved on a growing domain, and the complexities inherent in doing so, and future directions in which this field must go are discussed in detail.

It is impossible to provide a comprehensive coverage of the field of mathematical biology in a single journal issue, but this special issue of 20 papers goes a long way towards illustrating the diversity and richness of the field, and how it is advancing biology, medicine, ecology, epidemiology and mathematics. Furthermore, it highlights many of the exciting challenges ahead.

Acknowledgements

I would like to thank Mark Chaplain for all his hard work in bringing this issue together, and to thank all the authors who have contributed to it. Many of these authors were former graduate students of mine and I consider it a great honour to have worked with them. Finally, I am truly indebted to Jim Murray who introduced me to the field of mathematical biology 37 years ago, endured me as a graduate student, and has been a mentor and a great friend ever since.

Philip K. Maini
Wolfson Centre for Mathematical Biology, Mathematical Institute, Andrew Wiles Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, UK

E-mail address: maini@maths.ox.ac.uk