

Preface

The past decade has seen explosive growth in the use of mathematical and computational tools to address problems in the biosciences and medicine. The challenges are novel and unique: how do we cope with the vast amount of experimental data being generated, the huge number of components involved and their complex interactions?

Increasingly, theoreticians are beginning to make real advances in this field and much of their success has stemmed from changes in the nature of their research. It is now very clear that for interdisciplinary research to have a true impact, an intimate engagement with the science is required—the mathematics cannot be done in a vacuum. The articles in this special issue bear testament to that approach as, to varying degrees, they assess model behaviour critically in the light of experimental data.

The paper by Othmer *et al.* presents a detailed review of pattern formation in three classical experimental systems, the fruitfly *Drosophila*, the bacterium *E. coli* and pigmentation patterning in fish. It presents a range of models that have been proposed in each case, compares and contrasts them in terms of their properties, and critiques them in the context of experimental data. The paper also addresses the effects of domain growth on patterning, a subject area that has received surprisingly little attention given its importance.

It has been known for decades that reaction-diffusion models can produce arrays of repeating patterns similar to those observed in nature. Headon and Painter review this mainly in the context of feather germ patterning in the chick and discuss in detail how such models must now be validated and extended in light of the new biological findings that allow concrete definitions of the hypothetical chemical players proposed by these models. They define a number of challenges that must be met by both the experimental and theoretical communities if we are to gain greater insights into the underlying mechanisms that give rise to repeated patterns during morphogenesis.

Cai *et al.* study homeostasis and control of cell population levels in the epidermis. Specifically, they investigate multi-scale regulation between extracellular secreted factors and intracellular models and delimit regions in parameter space where the model predicts homeostasis. The focus in their paper is on the proto-oncogene, c-Myc, an intracellular transcription factor which affects both proliferation and differentiation.

Miura and Tanaka study how capillary networks form in human umbilical vein endothelial cells. This problem has attracted much attention and a number of modelling approaches based on different biological hypotheses have been proposed. To validate/invalidate such models it is important to determine biologically realistic parameter values within the models. This paper shows how, with the rapid recent advances in imaging techniques, it is now becoming possible to obtain

the sort of quantitative data necessary to enable such evaluations.

Zhu *et al.* consider the problem of cartilage patterning in the limb bud. They formulate a caricature reaction-diffusion model on a growing domain and solve the resultant equations using a discontinuous Galerkin finite element method. They show that the model can capture the increase in patterning elements as the domain grows due to dramatic changes in various parameters linked to the distribution of Hox gene products in the apical ectodermal ridge.

Merks and Koolwijk review a number of cell-based models in the context of *in vitro* experiments and show that several models, based on different biological assumptions, are qualitatively consistent with experimental observations. They focus particularly on chondrogenesis and vasculogenesis, and suggest that in order to make further progress in model validation we now require a concerted effort aimed at careful quantification of parameters so that the validation process can be sufficiently refined to allow distinction between models. As an example, they illustrate how this might be done for the increasingly used Cellular Potts model.

This selection of papers illustrates the real need for an iterative process between model prediction, experimental validation and model refinement in light of experimental results. It is only through many cycles of this process that mathematical modelling will realise its full potential as a potent tool in helping us answer some of the most exciting scientific questions of this century. The start-of-the-art is nicely summed up by Othmer *et al.*: “...we are at the beginning of a transition in the modeling of development in biology. Models are changing from qualitative descriptions to explain some peculiar or non-intuitive data, to quantitative models that make predictions that can be tested experimentally to drive the biology forward. As mathematical models of biological mechanisms continue to provide significant new insights into the underlying biology that can be directly assayed *in vivo*, we will observe a revolution in biology that transforms it from a qualitative, observation-driven discipline, to a quantitative, analysis-driven discipline.”

P. K. Maini and R. E. Baker
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