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INTRODUCTION

# The mathematics of nature at the Alan Turing centenary

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Alan Turing inhabited a very individual world between the abstract and the concrete—see Mrs Turing's sketch of her son playing hockey in 1923 (figure 1). His 1936 universal Turing machine detached computation from the actuality of its physical host, and established a powerful computational paradigm, dominated by logical structure. The grip of this model on our thinking and practice continues to this day. At other times, Turing immersed himself in the embodying engineering that enabled the first real-life computers. And in Manchester in the early 1950s, in one of the more remarkable switches of focus in scientific history, he turned his attention from man-made computing machines to the hidden mathematics of emergent form in nature. The one published paper arising from this interest became one of the most cited papers in science, and potentially challenges the primacy of his own universal machine.

Turing's 1952 paper, 'The chemical basis of morphogenesis', was ground-breaking as it proposed for the first time that biological patterning arose as a self-organized emergent phenomenon in which, counterintuitively, instabilities leading to spatial pattern arise via the interaction of stablizing processes. The model, in its simplest form of a coupled system of reaction–diffusion equations, assumes that a chemical pre-pattern is set up to which cells respond by differentiating in a concentration-dependent manner. This paper has led to a rich literature in analyses (both mathematical and computational) of the model and variants thereof—together with biological/chemical experiments aiming to lend support to the model by identifying the chemicals (termed morphogens by Turing) that may be involved. The Turing centenary selection of papers here illustrate how the model has been applied in biology and how, as experimental techniques have become more sophisticated increasing biological data, the models have been updated through identification of possible morphogens, and extensions of the basic model to include other mechanisms.

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One contribution of 13 to a Theme Issue 'Computability and the Turing centenary'.

Our introductory paper is by James Murray [1], one of the formative influences in the area. It puts in context the work of Turing by providing a broad overview of the development of the field of mathematical biology since the time of Turing. It then considers two examples in depth. The first applies Turing's idea to animal coat markings. The second is in the emerging field of mathematical applications in medicine, with a reaction–diffusion model for the extensive invasion of tumour cells into regions of the brain during glioblastoma. This modelling, now being used to help neuroscientists, is based on the formation of travelling waves. In fact, Turing identified such behaviour as a possible emergent property of his system, but the model here uses a different approach, more appropriate for the particular biological application.

Turing's approach was really brought to the attention of the wider readership in the 1970s by a number of important articles. Among these, the body of work of Hans Meinhardt [2] played a crucial role. In his paper Meinhardt shows how the initially biologically unrealistic kinetics used by Turing can be expanded into biologically relevant kinetics that still preserve the fundamental principles of his theory. This approach leads to the patterning principle of 'short-range-activation, long-range-inhibition' which has been instrumental in helping experimentalists to identify possible Turing morphogen pairs. Meinhardt's paper considers a number of examples, including regulation and formation of tentacles in Hydra, establishment of polarity and shell pigmentation pattern formation.

Szalai and co-authors [3] present a semi-empirical method for determining how stationary patterns may arise owing to a Turing mechanism. They verify the model and approach by demonstrating stationary patterns in two examples of halogen-free redox reaction systems. They also show how to obtain localized structures.

The article by Painter *et al.* [4] presents a review of models based on Turing's paper, paying particular attention to morphogenesis of skin organs (hair follicles and feather germs). The model is brought up

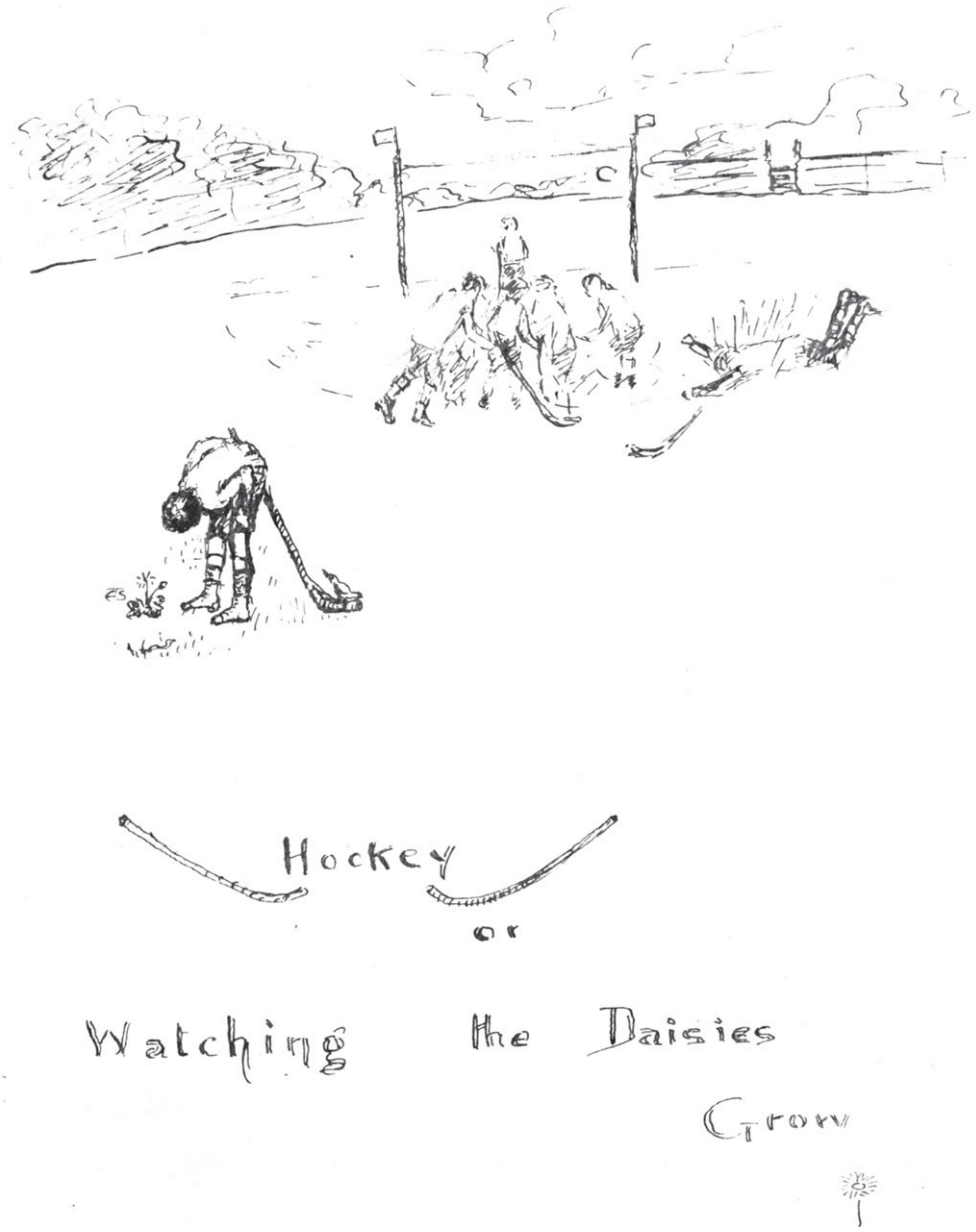


Figure 1. Drawing of Alan Turing by his mother, 1923. Courtesy of Sherborne School.

to date by considering key pathways that have been identified as having appropriate activator–inhibitor kinetics for a Turing-type patterning instability. It is shown that the model captures core experimentally observed features and the *test–predict–refine* cycle of iteration between experiment and theory reveals that there may be spatial heterogeneity already present in the domain which the model refines. As Turing himself said, recognizing the biological limitations of his de novo patterning theory, 'Most of an organism, most of the time, is developing from one pattern into another, rather than from homogeneity into a pattern'.

Yoshimoto & Kondo [5] consider patterning in insects. While it has been shown that patterning in the early *Drosophila* is most likely not from a Turing mechanism, but from a complex gradient model, the authors argue that models of the latter type are unable to explain vein patterns in certain insects. They show how a Turing-type model coupled with a gradient model can yield patterns consistent with experimental observations.

The paper by Chen *et al.* [6] on 'Patterns of periodic holes created by increased cell motility' extends the Turing framework to pattern formation in cultured vascular mesenchymal cells (VMCs). Their reaction–diffusion model (the Gierer–Meinhardt model) is applied to the morphogens BMP-2 and MGP and many of the model parameters are determined experimentally. They validate key nonlinearities in this model by experiment and then consider a model in which the VMC density is coupled to the reaction–diffusion model via chemotaxis. An experimental assay is set up to determine the diffusion coefficient for the cell density and analysis of the coupled model then shows how altering cell motility

can profoundly affect the form of the patterns exhibited. This research could have important implications for tissue engineering.

One of the major controversial issues regarding Turing's original model is its inability to produce patterns that are robust to natural biological variations present during development. Two papers look at different aspects of this problem. Kank, Zheng and Othmer [7] investigate the robustness of the location of threshold boundaries to perturbations in parameters and boundary inputs for a number of chemical prepattern models in both deterministic and stochastic settings. In particular, it investigates the ability of different types of response functionals to dampen the effects of noise. The paper by Maini and his co-authors [8] on 'Turing's model for biological pattern formation and the robustness problem' investigates robustness of patterns produced on growing domains in the face of stochastic noise and expression delay. While domain growth can greatly enhance the robustness of Turing patterns in the deterministic system (without delay), it is shown that the situation becomes less straightforward when stochasticity is introduced.

The subsequent articles in this tribute to Alan Turing's influence, and the continued fruitful interaction between theory and nature, trace a less direct, but still fundamental impact on the science.

Ehud Shapiro's [9] 'A Mechanical Turing Machine: Blueprint for a Biomolecular Computer' is already something of an unpublished classic. It describes a mechanical device based on the ideas of Turing's 1936 paper, an embodied biomolecular Turing machine. As one of the referees commented: 'This paper is a coherent articulation of a theoretical vision for molecular computing machines that operate within cells, written years prior to the author's seminal experimental work (with Kobi Benenson *et al.*) that helped launch a wave of research into disease-diagnosing-and-curing biochemical circuits. ... It would be good to publish it, at long last—and it would be especially nice for the paper to appear in a Turing Centenary issue'. Among a number of improvements in presentation, the author has updated the original manuscript with a Postscript telling how the field has progressed since it was originally written. We follow the referee in hoping that the appearance of this paper will reinforce the perception of the author 'as a visionary and luminary in this burgeoning field'.

Natasha Jonoska and Nadrian Seeman [10] also take the Turing research programme to the molecular level, reporting on recent work in relation to two computing models by DNA self-assembly, while providing a nice introduction to current directions in the area. According to the authors: 'In the last few decades, research done in biology, chemistry and physics has resulted in an explosion of new findings about molecular interactions. These findings often reveal transfer of information at a molecular level resulting in proliferation of the science of computing within established, on a first glance unrelated, scientific fields. The notion of 'computing', up till recently a theoretical concept, acquires a new meaning within these intrinsically experimental disciplines'. Turing would surely have found this incarnation of self-assembly interesting, and would have appreciated the role of experiment in the authors' approach to the challenges arising.

The paper of Anne Condon and her co-authors [11] 'Less haste, less waste: On recycling and its limits in strand displacement systems', is more concerned with the operative efficiency of recent incarnations of DNA computation. The technical content, focused on DNA strand displacement, is inevitably beyond anything, Turing could have envisaged, with the work of Watson, Crick, Wilkins and Franklin having only appeared a year before Turing died. In fact, the paper hardly mentions Turing. But his spirit can still be detected in this visceral take on the resource-related capabilities of DNA computing.

Dorner, Goold and Vedral's [12] 'Toward quantum simulations of biological information flow' inhabits Turing's multi-disciplinary terrain in a very contemporary and fittingly adventurous manner. It investigates transport in biological molecules based on the hypothesis that it may be possible that biological transport processes operate between purely classical diffusion and ballistic motion, exploiting quantum coherence. The authors propose an analogue quantum simulator to study electron transport in biology. The paper can be seen as a significant step towards the realization of analogue quantum simulators using existing technology, while providing new insights into the nature of quantum effects in biology.

Alan Turing had lifelong interest in quantum mechanics and the computational content of biology: which makes this cutting-edge research an appropriate conclusion to an interesting centenary tribute.

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