Mathematical modelling in the biosciences

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The spectacular biotechnological advances of the past two decades have led to an explosion of data in the biomedical sciences. We have recently completed the mapping of the human genome, we can now determine when in development certain genes are switched on, and we can accurately follow the fate of single cells. The list is endless. However, we are perilously close to falling into the practices of the nineteenth century, when biology was steeped in modes of classification and there was a tremendous amount of list-making activity. This was recognised by D'Arcy Thompson [1] in his classic work *On Growth and Form*, first published in 1917. He was the first to develop theories as to how certain forms arose, rather than simply cataloguing different forms, as was the tradition at that time.

Of course, we have come a long way since then. The identification of a gene that causes a certain disease or deformity has huge benefits for medicine. We must recognise, though, that genes only specify the properties of proteins and cells. It is the physico-chemical interactions of these cells that lead to (for example) the development of structure and form in the early embryo. Cell fate can be determined by environmental factors, and cells respond to signalling cues. Therefore, a study at the molecular level alone will not help us to understand how cells interact. Having devoted a huge amount of effort to taking Humpty Dumpty apart, we must now find out how to put him together again.

Since the interactions that govern biological processes are highly non-linear and may be non-local, they must be couched in a language that is designed to compute the results of such complex interactions. At the moment, the only language we have for doing such calculations is mathematics. Mathematics has been extremely successful in helping us to understand physics. It is now becoming clear that mathematics and computation have a similar role to play in the life sciences.

Self-organisation

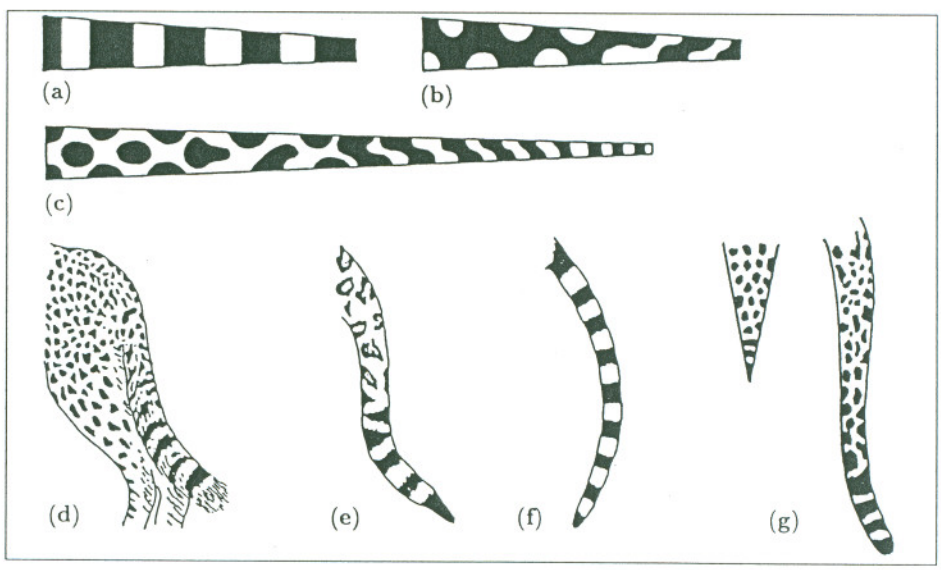
One of the key puzzles in developmental biology is the understanding of how the vast array of spatial patterns and structure we observe in the animal kingdom emerge from the almost homogeneous mass of dividing cells that constitute the early embryo. The skeleton, for example, is laid down during *chondrogenesis*, when specialised cells (chondroblasts) condense into aggregates that lead eventually to bone formation. Butterfly wings exhibit beautiful colours and patterns, and many animals develop dramatic coat markings.

In all of these examples, although genes play a key role, genetics say nothing about the actual *mechanisms* that produce spatial pattern. The first major advance in this field was made by Alan Turing [2]. He was interested in *morphogenesis* – the process by which form and structure arise. He considered a system of chemicals reacting and diffusing, modelled by equations of the form

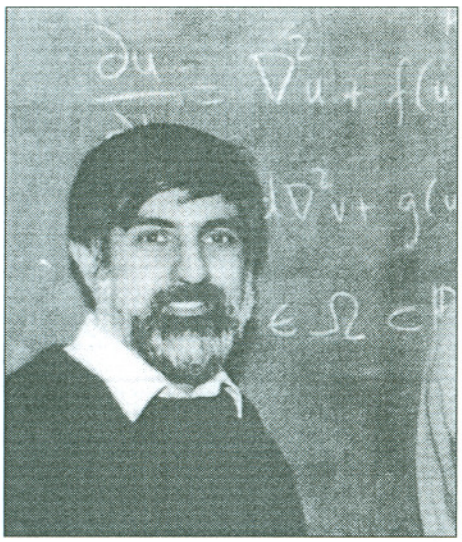
$$\partial \mathbf{u}/\partial t = \mathbf{D}\nabla^2\mathbf{u} + \mathbf{f}(\mathbf{u}, \mathbf{p}),$$

where $\mathbf{u}(\mathbf{x}, t)$ is the vector of chemical concentrations at spatial point $\mathbf{x}$ and time t, $\mathbf{D}$ is a diagonal matrix of diffusion coefficients, and $\mathbf{f}$ models the reaction kinetics, which are functions of the chemical concentrations and various kinetic parameters $\mathbf{p}$. The problem was completed by imposing certain boundary conditions – for example, periodic if one wants to model a cylindrical structure, or zero-flux if one wants to model an impermeable boundary. Turing showed that one could choose equations of this form which exhibited a uniform steady state that was stable in the absence of diffusion, but became destabilised when diffusion was introduced and evolved to a spatially varying state – a spatial pattern. This phenomenon is known as *diffusion-driven instability* and is an example of *self-organisation* or an *emergent property*. Assuming that one of these chemicals was a growth hormone, Turing then postulated that points where the concentration of hormone was highest would grow fastest, resulting in spatial structure. For this reason, the chemicals were termed *morphogens*. More generally, one assumes that these chemicals activate a gene switch if they breach a threshold value, causing cells to differentiate. This theory thus hypothesises that the structures one sees overlie a pre-pattern in chemical concentrations.

Although the identification of mor-



(a)-(c) Some computed solutions of a Turing reaction-diffusion model. (d)-(g) Typical animal coat markings. (h) Photograph of a common genet exhibiting a spotted body and striped tail (from Murray, 1993, with permission).



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phogens has thus far proved elusive, Turing structures have now been shown to exist in chemical systems. When Turing first proposed his theory, he met with some hostility from chemists who were convinced that such patterns could not arise in chemical systems. This is a nice example of mathematics driving research in other scientific areas.

A number of theories based on different biological hypotheses have since been proposed for self-organisation, but many of these models rely on the common patterning mechanism of *short-range activation, long-range inhibition*. It is thus possible to make predictions that do not rely on specific biological details. One such prediction is that a spotted animal with a striped tail is more likely to occur than a striped animal with a spotted tail. This is an example of a developmental constraint. The book by James Murray [3] has an excellent in-depth discussion of this and related issues.

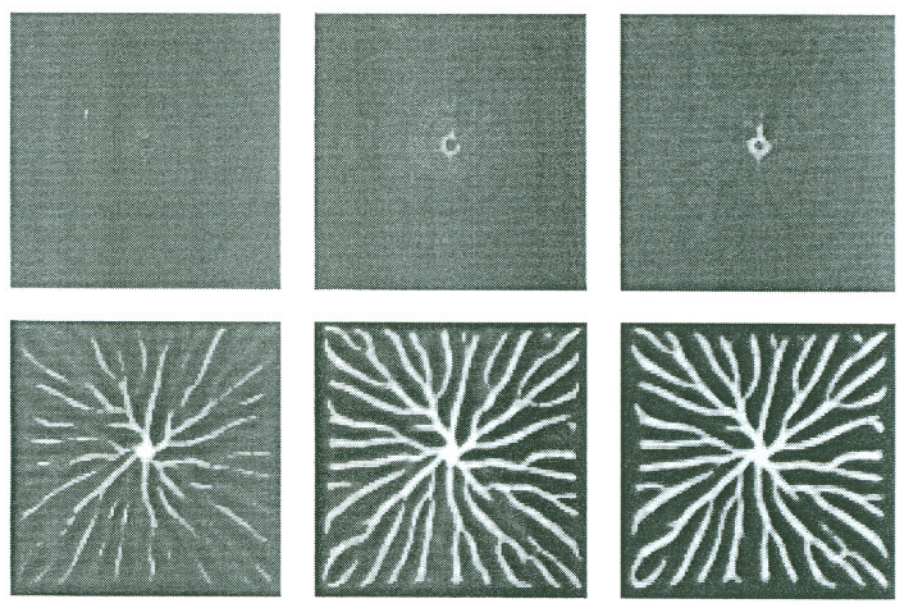
It transpires that models of the same general form as that above can exhibit a wide variety of patterns, such as propagating fronts, spiral waves, target patterns and toroidal scrolls. Indeed, the *Hodgkin-Huxley model* for electrical signalling in nerve axons (for which they won the Nobel prize) is of the above form. The most famous example in chemistry of pattern formation is the *Belousov-Zhabotinsky (BZ) reaction*, in which bromate ions oxidise malonic acid in a reaction catalysed by cerium, resulting in sustained periodic oscillations in the cerium ions. If, instead, the catalysts Fe^{2+} and Fe^{3+} and phenanthroline are used, the periodic oscillations are visualised as colour changes between reddish-orange and blue. This system has been thoroughly modelled mathematically and it emerges that the key to patterning here is a phenomenon termed *excitability*. An excitable system is one in which the steady state is stable to small perturbations, but to large (supra-threshold) perturbations, the system undergoes a large deviation before coming back to its original steady state. During this transient period, the system does not respond to perturbations. Coupling diffusion to this type of kinetic behaviour allows for waves of activity to propagate through the medium.

Excitable media also play a role in the aggregation of certain amoeboid species, such as the cellular slime mould *Dictyostelium discoideum* (Dd), which has served as an important model paradigm because it is simple enough to allow experimentation, yet sufficiently sophisticated to exhibit many physico-chemical processes that are similar to those observed in higher organisms. Under starvation conditions, these amoebae signal each other via the chemical messenger cyclic AMP, resulting in the propagation of spiral waves of the chemical. The amoebae move up gradients of cyclic AMP, resulting in the formation of aggregations. The formation of aggregates seems to be a vital component of the Dd life cycle, as it appears to be necessary to enable the cells to differentiate into a spore type that can survive harsh conditions. This species has been extensively studied theoretically and the modelling has resulted in crucial biological insights that could not have been gained easily in any other way.

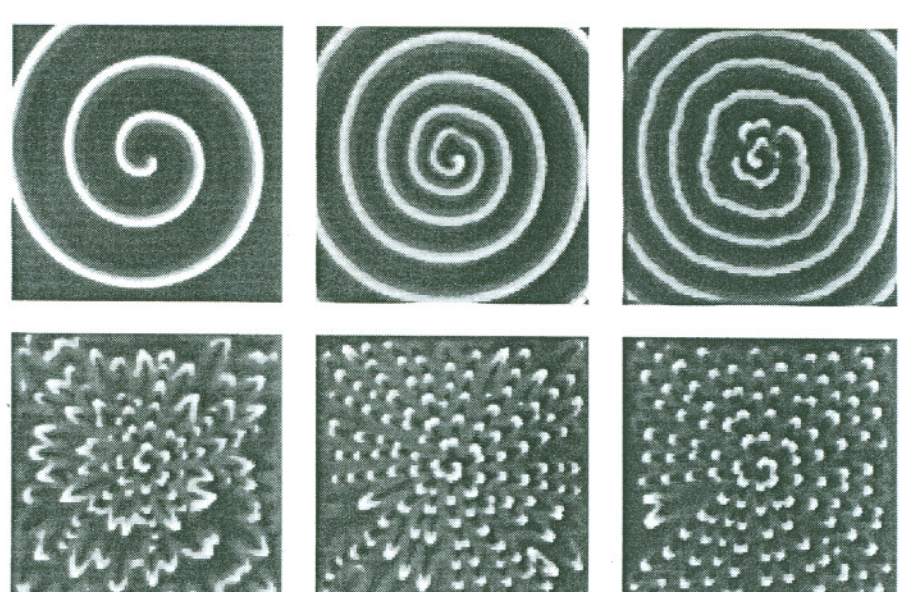
This example illustrates the power of mathematics as the universal scientific language because, although the details of the biology underlying Dd aggregation are very different from the chemistry underlying the BZ reactions, the resulting mathematical equations are very similar, so that insights gained in one field can be transferable to another, seemingly very different field.

Medical applications

Intriguingly, the heart is another example of an excitable system, allowing electrical activity to propagate across its surface as the signal for the heart to beat. Many heart abnormalities arise as the result of disturbances to this wave propagation, and these have been studied using simple models of the above general form. More sophisticated models have been developed that allow one to predict what effect a single gene mutation will have on the global dynamics of the heart. We are now enter-



Development of spiral waves leading to cell streaming in a mould for slime mould aggregation.



ing the realm of the 'virtual human', in which even surgical procedures may be first tested in virtual reality – after all, we do not allow commercial airline pilots to fly a plane until they have completed several hours of training on a flight-simulator, yet we are happy to let surgeons loose on our brains without equivalent training! *In silico* drug-testing is already approaching reality and is attracting a lot of interest from pharmaceutical companies. The reduction in the costs (presently some 450m euros) of bringing a drug to market by the use of good models is beginning to motivate such companies to invest in modelling research.

Recently, the multi-national pharmaceuticals giant Hoffman-LaRoche approached Denis Noble and his colleagues in the Department of Physiology, Oxford, to help with a problem that arose during the approval process for one of their drugs by the US Food and Drug Administration. The FDA had noticed a glitch in the electro-cardiograms of people taking the drug, and clinicians had concluded that the drug was dangerous. Noble applied the drug to his virtual heart model and found that it developed the same glitch. He found that the glitch was not a sign of major malfunction and the drug was approved [4].

These types of models are highly computational, as they involve intricate molecular details linked to cellular activity. As computing power increases daily, more complicated models can be analysed. Such models also throw up interesting mathematical questions, such as how can one properly model the interactions of processes occurring over many different length and time scales.

The second biggest killer in the developed world, after heart disease, is cancer. Despite the huge proliferation of experimental data and clinical treatments, there has been no decrease in the death rates due to the most common cancers. This is largely because there is still no basic consensus models of tumour growth and survival, metastasis (the process whereby potentially fatal secondary tumours are formed from a primary tumour), tumour angiogensis (whereby nutrients are diverted to the tumour), and extra-cellular matrix breakdown by tumour cells. One of the challenges of the next decade is to develop mathematical models that clarify these fundamental processes and that can predict new strategies of clinical therapy. At present this area is attracting a lot of research, and modelling is being used to address such problems as effective drug-delivery strategies and ways of decreasing angiogenesis.

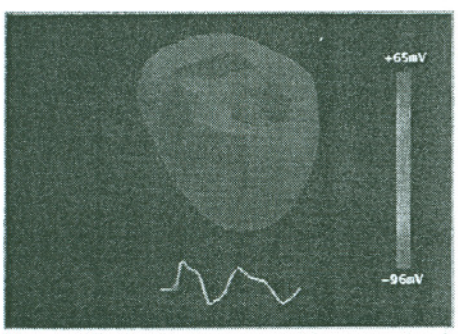
Bioinformatics

As technology continues to advance, we must develop ways to exploit and interpret the flood of data, not drown in it. Probability theory, statistics, stochasticity and high-powered computing will play an important role in the rapidly emerging field of bioinformatics. Some of the important questions here are pattern finding, data mining and pattern recognition, to name but a few. Presently a major aim is to understand how protein structures form, and how specific protein structure determines function. Here, there may be a role for topology, geometry, electrostatics and mechanics.

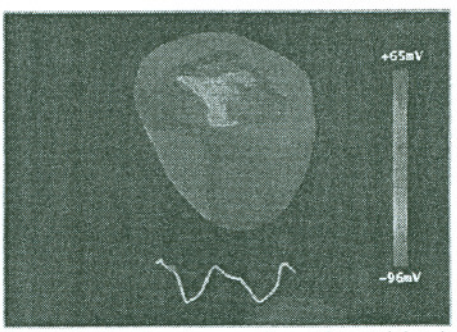
Summary

We are entering the post-genomic period, and it is clear that mathematics has an ever-increasing role to play in biomedicine. In 1997 the International Union of Physiological Sciences set up the Physiome Commission to 'promote anatomically and biophysically based computational modelling for analysing integrative function in terms of underlying structure and molecular mechanisms'. More recently, the research councils have set up programmes funding research at the interface between computation, mathematics and the life sciences.

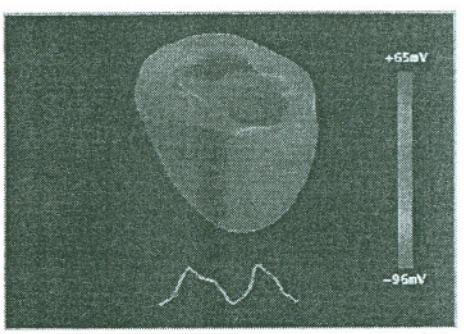
Mathematical biology is a rapidly growing subject and the number of full-time university faculty engaged in this type of research is increasing. The subject area itself has expanded enormously and the above represents a very brief review. Other areas of active research include neural networks, neurophysiology, immunology, epidemiology and ecology. It is clear that the life sciences will continue to pose exciting, novel and challenging problems for mathematicians.



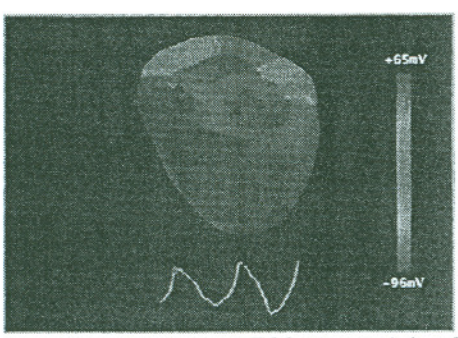
Frame 1. Excitation has occurred in septum but is not yet visible on surface.



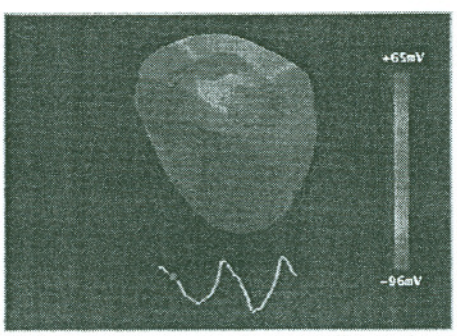
Frame 2. Break-out on surface of ventricles is abnormal ...



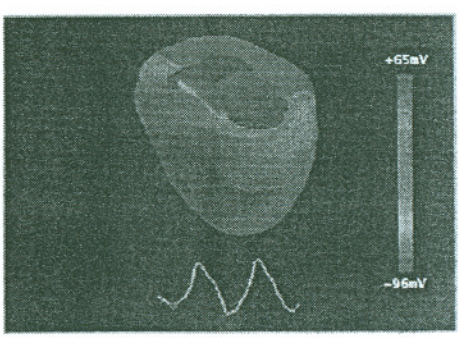
Frame 3. ... and initiates multiple wavelets of re-entry ...



Frame 4. ... to produce ECG characteristic of Torsade de Pointes.



Frame 5. The re-entrant tachycardia continues indefinitely ...



Frame 6. ... (continued).

Time evolution of multiple re-entrant waves in a 3D model of the dog heart (courtesy of Denis Noble).

References

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3. J. D. Murray, *Mathematical Biology*, Springer-Verlag, 1993.
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