

Title: Rethinking Models of Pattern Formation

P.K. Maini, R.E. Baker and S. Schnell

PKM and REB: Wolfson Centre for Mathematical Biology, Mathematical Institute, Andrew Wiles Building, Woodstock Road, Oxford OX2 6GG. UK

SS: University of Michigan Medical School, Department of Molecular & Integrative Physiology, Brehm Center 5132, 1000 Wall Street, Ann Arbor, MI 48105-1912, USA

Email: Philip.Maini@maths.ox.ac.uk

Tagline: A new model for somite development calls prevailing models for developmental patterning into question.

The formation of spatial patterns is intrinsic to developmental biology. From an initial growing mass of cells a robust, yet intricate, spatial design emerges. These patterns pre-figure the form of the adult organism, but despite their importance, we have very few answers to the most fundamental questions about how patterning arises. In this issue, Cotterell et al. call a 40 year-old model of patterning into question.

The earliest mathematical model for self-organising patterns was proposed in 1952 by Turing, who suggested that “a system of chemical substances, called morphogens, reacting together and diffusing through a tissue is adequate to account for the main phenomena of morphogenesis.” This model showed the highly non-intuitive result that diffusion – a phenomenon previously thought to homogenise any spatial heterogeneity – could drive the emergence of patterns from a spatially uniform state. Extensive mathematical and computational investigation of this mechanism has revealed its ability to generate a bewildering diversity of patterns (Murray, 2003; Meinhardt, 2009). However, despite years of investigation, the identification of morphogen systems that behave precisely as Turing suggested remains beyond us, calling into question the utility of this model.

An alternative to this type of emergent patterning is the “positional information” model of Wolpert proposed in 1969. This class of model proposes that a specialised region of tissue (for example, the zone of polarising activity in the chick limb bud) acts as a morphogen source, while the rest of the tissue acts as a morphogen sink. Together, they set up a gradient in morphogen concentration across the embryo that ensures that cells differentiate appropriately. Like Turing models, experimental validation of this model has proven problematic. In particular, we have failed to identify signals which are robust to noise in parameter values and extend long distances.

Nevertheless, positional information is a central concept in the prevailing model used to explain a classic phenomenon in development, the formation of somites, which are aggregates of cells established within the presomitic mesoderm, in an anterior-to-posterior sequence. The phenomenon of somitogenesis has attracted huge interest because it is crucial to setting up the primary body axis; as such, it is most probably conserved across vertebrates.

Somitogenesis also exemplifies the power of interdisciplinary research. Modelling and experiment have been closely integrated for 40 years, each informing the other in an iterative predict-test-refine-predict cycle. From a modelling point of view, somitogenesis can be very reasonably abstracted to the problem of understanding the sequential formation of periodic structures along a one-dimensional domain (Fig. 1A). From an experimental point of view, the system is amenable to manipulations that rule out whole classes of underlying mechanisms. These observations can be easily translated into corresponding model perturbations, allowing modellers and experimentalists to iterate the predict-test-refine cycle further. In 1976, Cooke and Zeeman proposed that somite patterning could arise from the coupling of a propagating wave (an “arrest front” providing

positional information) with an intrinsic oscillator within cells. This is referred to as the Clock and Wavefront model, and a more recent variant, called Clock and Gradient, is the commonly accepted model explaining somite formation.

In the present issue, Cotterell et al. propose a new model for somite formation, focusing only on the arrest front. They challenge the prevailing Clock and Gradient model. In the Clock and Gradient model, it is proposed that long-range morphogen gradients of FGF and WNT signalling drive a traveling wave of differentiation that arrests the clocks, which happen to be synchronized in neighboring cells. In contrast to this, Cotterell et al. propose that the travelling arrest front arises as an emergent phenomenon from the local interactions of a reaction-diffusion mechanism, which they term a progressive oscillatory reaction-diffusion (PORD) model.

To build the PORD model, Cotterell et al. use a computational framework to explore the different ways in which gene regulatory networks can be wired to produce the (striped) segmentation patterns observed during somitogenesis (Fig. 1B). They analyse the entire space of all possible networks with three nodes (interacting components) because networks with three nodes have the potential for generating a wide range of behaviours (Tyson et al., 2003).

Their search of possible network topologies identified 210 topologies with four motifs capable of producing striped patterns. Two of the motifs that produced stripes are essentially the Clock and Gradient model. However, those motifs are not robust to extrinsic noise and represent only 14% of the possible segmentation-producing gene regulatory networks. The majority of the other topologies can be reduced to a two-node network motif comprising an activator molecule and a diffusible repressor. This simple reaction-diffusion motif is robust to extrinsic noise and produces the stable periodic patterns of gene expression observed during somite formation. The authors then carried out a series of experiments in chick embryos designed to distinguish between the Clock and Gradient and PORD models and demonstrated that their PORD model is consistent with the resultant observations.

The PORD model also provides a new explanation for another striking feature of somitogenesis: the regulation of somite size. The size of somites is tightly associated with body size in vertebrates; this observation is consistent with a global positional information model which scales with body length. However, Cotterell et al. show that this observation is also consistent with their new model. Although the basic PORD model does not require long-range gradients to make regular somites, in principle the travelling wave of FGF signal can couple growth to the dynamics of the reaction-diffusion model, allowing feedback between body size and pattern wavelength, which allows somite size to scale with body size.

In total, the work by Cotterell et al. is a truly intra- and inter-disciplinary study that throws open to debate the long-held clock and wavefront model paradigm. The latter model has been hugely influential in developmental biology, guiding decades of experimentalists to look for—and find—molecules that participate in the oscillations and propagating signals on which the model is predicated. The PORD model casts these molecules in a new light. It proposes that somitogenesis is the result of a local reaction-diffusion system rather than a dynamic global positional gradient.

There are, of course, limits to the theoretical work by Cotterell et al. For example, the computational search across the swathes of potential gene regulatory networks is still restricted to a limited region of parameter space. Nevertheless, the approach pursued by Cotterell et al. is highly innovative and provides the foundation for future investigations into pattern formation in developmental biology. Just as the clock-and-gradient model has profited from many years of experimental work, so too may the PORD model, as researchers look for its activator molecule and diffusible repressor. In addition, it is plausible that reaction-diffusion and positional information mechanisms could work together to robustly pattern the embryo, as shown for limb digit patterning (Maini et al. 1992). The proposal of a new model should generate much excitement, discussion and, hopefully, a healthy

controversy amongst both theoreticians and experimentalists that will enhance, even further, our understanding of one of the most important patterning events in embryology.

Figure 1: Unbiased exploration of three-node networks reveals motifs that potentially underlie a new model for progressive somite patterning.

(A) Cotterrell et al. implemented an approach to explore the minimal network motifs that can reproduce the somite patterning of at least two stripes of gene expression.

(B) They discovered four minimal motifs in their Network Design Space. Two of the network motifs are versions of the clock-and-gradient model, but these networks are not robust to extrinsic noise. The minimal and more robust somite-patterning network is composed of two nodes: activator molecule (green) and diffusible repressor (red).

References:

Cooke, J. and Zeeman, E. C. (1976). A clock and wavefront model for control of the number of repeated structures during animal morphogenesis. *J. Theor. Biol.* **58**: 455-476.

Maini, P. K., Benson, D. L. and J. A. Sherratt (1992). Pattern formation in models with spatially inhomogenous diffusion coefficients. *IMA J. Math. Appl. Med.* **9**: 197-213.

Meinhardt, H. The algorithmic beauty of seashells. 4th Ed. (Springer, 2009).

Murray, J. D. Mathematical biology II: Spatial models and biomedical applications. 3rd ed (Springer, 2003).

Turing, A. The chemical basis of morphogenesis. Phil. Trans. R. Soc. (London) B **237**: 37-72.

Tyson, J.J., Chen, K.C., Novak, B. (2003). Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. *Curr. Opin. Cell Biol.* **15**:221-231.

Wolpert, L. (1969). Positional information and the spatial pattern of cellular differentiation. *J. Theor. Biol.* **25**: 1-47.