Segmentation *in silico*

Peter Dearden and Michael Akam

A new mathematical biology is emerging. Building on experimental data from developing organisms, it uses the power of computational methods to explore the properties of real gene networks.

Life depends on the interaction of tens of thousands of genes and their protein products, orchestrated by the regulatory logic of each genome. If we are to comprehend this logic, we must hope that it can be dissected into a series of interlinked modules or networks, each of which can be studied in relative isolation. But even then the complexity of a single module can be daunting. As our knowledge increases, diagrams of gene regulatory networks look increasingly like explosions in a spaghetti factory. We need fresh methods to explore the behaviour of such networks.

On page 188 of this issue[1], von Dassow and colleagues describe how they have taken a computational approach to the problem. Their starting point is the network of genes that makes body segments in the fruitfly *Drosophila* (Fig. 1). In the past 20 years, genetic analysis has produced a wealth of experimental data on segmentation, and a textbook model of how dynamic intercellular signalling maintains a stable boundary between cells that are in distinct states[2,3] (see Box 1).

From these data, von Dassow *et al.* abstracted a set of key interactions which, they hoped, would constitute a discrete developmental module. To make it computationally tractable they had to simplify it further. Their final model has 136 coupled equations with nearly 50 free parameters for such values as half-lives, diffusion constants and binding coefficients of the gene products involved. For virtually none of these are real values known. So the authors had to use random sampling and statistical methods to explore the properties of this model over the plausible range of parameter values. The boxed item in the paper (page 189) shows the proteins and type of equations involved.

The prime result is counterintuitive: a random search of parameter space identified a surprisingly high frequency of 'solutions' that allowed the model to generate the correct pattern of segment gene expression; correct, that is, in the sense of resembling the pattern actually observed in developing *Drosophila* embryos. The values of parameters in these solutions do not converge on a single set of optimal values — the value of almost every parameter can range over orders of magnitude and still be compatible with a correct solution. It is the organization of the gene network that provides stability, not the fine-tuning of molecular interactions.

Figure 1 **Segmentation (in this case abnormal) in the *Drosophila* embryo. Normally the segment-polarity gene network generates a linear array of 14 segments, each bounded by a stripe of cells expressing the *engrailed* gene. This 'two-tailed' embryo shows how the segment-polarity network can make regular patterns, even with abnormal inputs. Signals from the mutant mother have triggered two arrays of segments to form back-to-back. Where they meet, a circular segment boundary has formed (here revealed by staining for Engrailed protein).**

It is revealing, though, that when the group first built the model it did not work at all. Despite their best efforts to distil a logically complete model from data in the literature, and from discussions with experimental workers, no parameter set provided a correct solution. Certain essential linkages in the network were missing. In a confession of humility that is all too rare among scientists, the authors point out that "Biologists' maps of gene networks are rapidly outgrowing our ability to comprehend genetic mechanisms using human intuition alone, as shown by our initial failure".

With hindsight, logical gaps in the textbook model are not difficult to spot, but no textbook or review had highlighted them. For example, it was not clear why the *engrailed* gene is not activated in front of, as well as behind, the cells expressing *wingless* (Box 1). Von Dassow and colleagues have plugged this and other gaps with plausible assumptions based on hints already buried in the experimental literature; in this case, that the gene transcription factor CiD represses *engrailed* transcription in the absence of signalling from another protein called Hedgehog. This highlights a key aspect of the work: the model is so closely tied to real data that its inadequacies immediately define a programme of experimental work to test these assumptions.

With the segmentation gene network implemented *in silico*, it becomes possible to explore how different sorts of variation affect its output. The effects of varying parameter values over small ranges are equivalent to

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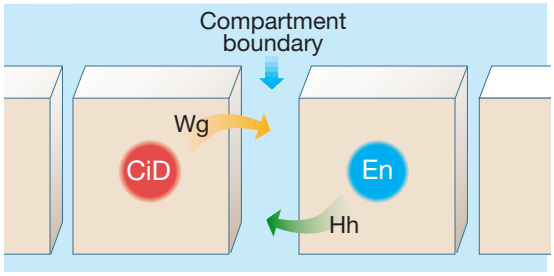
Box 1 Making segments in *Drosophila*

Cells on either side of the early segmental boundaries are maintained in distinct states by an exchange of signals between them. Anterior cells are defined by expression of the gene transcription factor Cubitus interruptus (CiD), and secrete a signalling protein called Wingless (Wg). Posterior cells are defined by expression of the Engrailed transcription factor (En), and secrete the Hedgehog signalling protein (Hh). Von Dassow *et al.*[1] have modelled the interaction between these two intercellular signalling pathways, and the transcriptional control of the relevant genes. This forms the heart of the 'segment-polarity' gene network. Once triggered, it is self-sustaining[2].



In *Drosophila*, the segment-polarity network is initially cued by a purely transcriptional patterning system that acts while the embryo is still a single multinucleate cell. This system is mediated by the 'pair-rule' segmentation genes, so called because they generate a pattern of double segment periodicity. Different combinations of pair-rule gene products activate *engrailed* and other segment-polarity genes in a periodic pattern, thereby defining the length of each segment repeat.

The segment-polarity network probably works in much the same way in all insects, and perhaps more widely. But the inputs that trigger it may be different in insects, such as grasshoppers, in which patterning of the segments occurs after cells have formed[4–6]. **P.D. & M.A.**

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those of minor mutations; small changes in the inputs used to trigger patterning mimic the natural variation in development seen from embryo to embryo. On both of these counts, the network is satisfactorily robust. Most small changes in parameter values have little effect — only at rare thresholds does the behaviour of the model switch from one stable state to another.

Initial conditions can also be varied more widely, to explore how this gene network might behave in different developmental contexts. For example, the model was designed with a precise periodic input to trigger activity of the segment-polarity genes throughout the whole length of the body. This mimics what happens in *Drosophila* (Box 1). In many other insects, however, segmentation spreads through a field of cells from head to tail (much as it does during early patterning in vertebrate embryos). In these cases, the segment-polarity system seems to be conserved[4], but the upstream triggers may not be[5,6]. Von Dassow *et al.* are quite happy with this: their model will generate the same segment pattern with a variety of different inputs, and the inputs can be much less precise than those known from *Drosophila*.

Our understanding of gene networks is at an early stage. We perceive their complexity only after it has been filtered by the limitations of the techniques used to study them. Genome databases and DNA-chip technology, which enables huge numbers of genes to be screened for activity, will undoubtedly provide more, and much more complicated, data than anything produced by *Drosophila* genetics. If a relatively simple gene network such as the segment-polarity system is hard to understand intuitively, we can be certain that modelling will be essential to make sense of the flood of new data.

But this will not be elegant theoretical modelling: rather, it will be rooted in the arbitrary complexity of evolved organisms. The task will require a breed of biologist–mathematician as familiar with handling differential equations as with the limitations of messy experimental data. There will be plenty of vacancies, and, on present showing, not many qualified applicants. ■

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Laser physics

The smallest random laser

Diederik Wiersma

How small can you make a light source? A common light bulb is a few centimetres in diameter. You can make light bulbs several millimetres across, but for a light-emitting device much smaller than this, we should turn to lasers. Lasers are nowadays widely used in industry, in hospitals and in many devices that we have at home. A compact disc player, for instance, makes use of a miniature laser diode only a few millimetres big. In two papers in *Applied Physics Letters*[1] and *Physical Review Letters*[2], Cao *et al.* describe a laser that is a thousand times smaller still: their laser is a small grain, 1.7 micrometres in diameter — about one-tenth of the diameter of a human hair.

The microlaser created by Cao *et al.* is not the smallest ever laser source, but it is a special type of microlaser. It uses a highly disordered structure to obtain laser action. The behaviour of light waves in disordered structures is highly complex, yet disordered materials are familiar to us all. Every substance that looks white falls into this category, including paper, white paint, fog, marble and a glass of milk. The study of the behaviour of light in such disordered materials is an active field of research[3,4].

A light wave that passes through a white object like a glass of milk will undergo a process called multiple scattering. Milk is a suspension of many small fat droplets, each with a strong tendency to scatter light: when a light wave hits a fat droplet its direction of travel will be changed in an arbitrary way. A light wave passing through a glass of milk will be scattered thousands of times by thousands of fat droplets. This is what gives milk and all other disordered substances their opaque white appearance.

It is this mechanism of multiple scattering that Cao *et al.* use to make a tiny random laser. However, multiple scattering alone is not enough to make a laser. A laser requires two ingredients: a material that amplifies light, and some feedback mechanism that (temporarily) traps the light in order for the amplification to be efficient. In normal lasers the trapping element is a cavity — two mirrors facing each other with the amplifying material in between. The light passes back and forth between the mirrors, thereby passing several times through the amplifier, until it leaves through one of the mirrors that is partially transmitting (Fig. 1a).

In the case of a random laser the cavity is replaced by multiple scattering. In 1967, Letokhov[5] predicted that the combination of multiple scattering and light amplification would lead to a form of laser action. Nonetheless, it was 25 years before random laser action was observed experimentally[6]. It became clear that the multiple scattering of light that takes place in a disordered material does not really provide a feedback mechanism, but it makes the light stay inside the material long enough for the amplification to become efficient. Instead of bouncing from one mirror to another, the light waves bounce from one particle to another thousands of times before they leave the disordered material (Fig. 1b). Because the multiple scattering is completely random, the term 'random laser' is used. The emission charac-

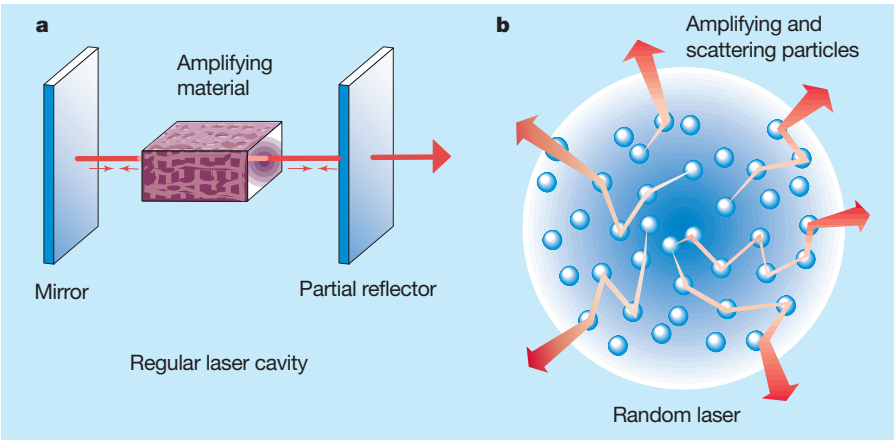

Figure 1 **Comparison between a regular laser and a 'random laser'.** a, **In a regular laser the light bounces back and forth between two mirrors that form a cavity. After several passes through the amplifying material in the cavity, the gain amplification can be large enough to produce laser light.** b, **In a random laser the cavity is absent but multiple scattering between particles in the disordered material keeps the light trapped long enough for the amplification to become efficient, and for laser light to emerge in random directions.**

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