

Developmental Biology: Mathematical Modelling of Development

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Advanced article

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Understanding how structures (e.g. hair, teeth, feathers, limbs and pigmentation patterns) arise from the initially unstructured fertilised egg is one of the key challenges in developmental biology. Mathematical models enable us to investigate how certain biochemical and/or bio-physical processes interact to produce pattern and form. They provide a unifying theme for spatio-temporal patterning across a vast range of biological applications by suggesting a set of underlying principles for pattern formation. Such models suggest that patterns and structures must have certain properties and these predictions motivate experiments. The results of such experiments help refine models and lead to more precise predictions. In this way, modelling, combined with experiment, can be a powerful investigative tool in helping unravel the complexity of morphogenesis (the formation of structure) in biology.

Introduction

One of the central challenges in development biology is the understanding of how structure and form arise in the growing embryo. From a spatially uniform ball of cells develop the structures we observe and which characterise the animal kingdom, ranging from spectacular pigmentation patterns to skeletal structures. Although genes obviously play a role in patterning, a study of genetics alone will not tell us how the physico-chemical properties conferred upon individual cells can lead to orchestrated patterns on length scales much larger than a single cell. Understanding the latter requires deciphering the effects of an integration of processes interacting on many scales, ranging from the intracellular level, at which gene and protein networks combine to determine cell properties, to the extracellular level, where cells set up and respond to

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signalling cues. The nonlinear and highly complex nature of these interactions leads to counter-intuitive behaviour far beyond what we can verbally reason; however, a mathematical/computational framework is ideal for understanding the outcome of such interactions. In this article, we will consider some of the key advances that mathematical modelling has made in helping us understand how tissue-level behaviours may arise from cell-level behaviour.

Modelling in Morphogenesis

Morphogenesis is the name given to the process by which structure arises. The first person to move beyond simply cataloguing form, by attempting to develop theories for the generation of them, was D'Arcy Thompson in his classic work 'On Growth and Form' first published in 1917 (see Thompson, 1992 for an abridged version). Since then, a number of modelling approaches have aimed to address the underlying physical mechanisms of morphogenesis. For example, crucial to early development is the coordinated movement and deformation of tissue. A key process in the transformation of the spherical egg into an elongated, bilaterally symmetric vertebrate body axis is convergence-extension (Keller *et al.*, 1992) by which a tissue narrows along one axis while extending along another. Early modelling work in the area includes that of Odell *et al.* (1981) who proposed the purse-string model for tissue folding, and the development of computational cell-based mechanical models for epithelial cell rearrangement (see, e.g. Weliky *et al.*, 1991). These models are primarily of cell-vertex type (see **Figure 1** for an illustration). In these models, cells are represented as polygons and Newton's Second Law is applied at the vertices to calculate their movements, and hence that of the cell, due to the forces experienced at those points. The models can exhibit tissue folding, thickening, invagination, exogastrulation and intercalation, and have been shown to capture many of the key aspects of processes such as gastrulation, neural tube formation and ventral furrow formation in *Drosophila* (see Keller *et al.*, 2003) for a review on the role of biomechanics in morphogenesis, and (Brodland and Clausi, 1994). **See also:** [Cell Migration during Development](#); [Cleavage and Gastrulation in Avian Embryos](#)

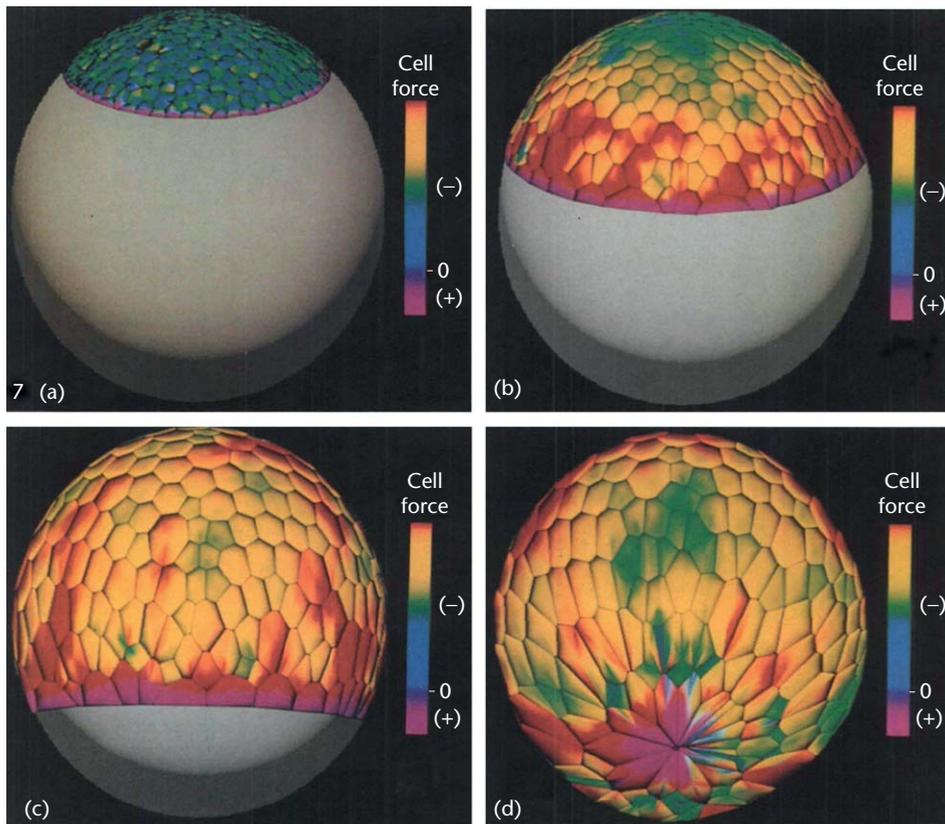


Figure 1 The model of Weliky and Oster (1990) reproduces the essential features of *Fundulus* epiboly showing that the forces they hypothesise to act on the cell vertices are sufficient to produce results of tissue movement and rearrangement consistent with experimental observations. (a) Early stage of epiboly. (b) Middle stage of epiboly. (c) Late stage of epiboly. (d) End of epiboly. Reproduced with permission from Weliky and Oster (1990). Copyright Palgrave Macmillan.

Although cell-vertex models consider the cell to be polygonal in shape and track the motion of the vertices, either through considering the balance of forces at the vertices (Weliky *et al.*, 1991) or by rearranging cells to minimise total free energy (Honda *et al.*, 2004), the simpler cell-centre models represent the cells by points where the centres of the cells are assumed to be attached by springs to nearest neighbours. The cell centres move in response to the elastic forces exerted on them, and their polygonal shape is then determined by a Voronoi tessellation, that is, the polygonal shape consisting of the perpendicular bisectors of the lines of minimum length to nearest cell neighbours (see, e.g., the application to intestinal crypt organisation in Meineke *et al.*, 2001).

Although most of the above models were proposed to describe the movement of cells in sheets, it is important to point out that cells of different types can sort out due to differing intrinsic properties, such as surface adhesivity. This led to the theory of differential adhesion and energy minimisation (Steinberg, 1963) and has been extended (Graner and Glazier, 1992) into a Potts-type model which generalises the hypothesis that cells move to minimise a certain 'energy' function. This has served as the prototype for many models for which cell shape is important. The whole area of modelling morphogenesis at the tissue-level

using computational approaches has grown enormously with the increasing speed of computation (see Further Reading). An area of current research involves determining which model framework is appropriate for a particular model application.

Pattern Formation by Local-activation-lateral-inhibition

Cell fate is determined by complex interactions in which cells incorporate extracellular cues into their decision-making. How these extracellular cues are established, maintained and interpreted has been, and still is, a source of controversy and, as such, stimulates enormous research activity both from theoretical and experimental viewpoints. Broadly speaking, there are two classes of modelling frameworks: chemical pre-pattern models and cell movement models.

Chemical pre-pattern models

These models are based on the hypothesis that a spatial chemical prepattern is generated to which cells respond by

differentiating according to the state of their local environment. In a sense, the chemicals (termed morphogens) indicate to cells their position in the development field. The idea of positional information was first proposed by Wolpert (1969) who hypothesised that, in the chick limb bud, a source of chemical at one end of the bud, diffusing towards a sink at the other end, and sets up a chemical prepattern in the form of a graded concentration profile which would specify the different digits depending on a series of threshold concentrations. This model correctly predicted the outcome of various grafting experiments.

Although intuitively it is straightforward to imagine how such a model would work, in practice, the setting up of such a gradient, given the restrictions of diffusion coefficients, uptake rates and production rates, together with robustness in the face of noise and low copy numbers, is highly nontrivial. Tostevin *et al.* (2007) show that the latter problem can be ameliorated by using time averaging of the chemical concentration, whereas Houchmandzadeh *et al.* (2002) show that noise-induced variability in the bicoid gradient in *Drosophila* is filtered out downstream. Monk (1998) shows that the spatial restrictions imposed by a simple mechanism of gradient formation can be weakened considerably if the gradient were to be set up by a cell relay mechanism.

Gradient models have been extensively studied in *Drosophila* and the paper by Grimm *et al.* (2010) compares and contrasts a number of gradient models proposed for the patterning of the morphogen bicoid in light of experimental data. A comprehensive overview of morphogen gradients during development can be found in the review paper by Rogers and Schier (2011).

A more complex model for pattern formation was proposed by Turing (1952). He considered a system of reacting and diffusing chemicals and showed that a spatially uniform equilibrium state of chemical concentration, stable in the absence of diffusion, could be driven unstable in the

presence of diffusion, leading to spatial patterning. He considered these chemicals to be growth hormones and was interested in the formation of branching patterns. This model showed how symmetry breaking could arise in such systems. The concept of diffusion-driven instability is highly counter-intuitive as it shows that the interaction of two stabilising components leads to an instability. This is an example of emergent behaviour in which the integration of the parts is arguably more important than the parts themselves. He generalised his example to the case where the chemicals (termed morphogens) determined cell fate through a single threshold.

Turing's ideas were generalised and fully brought to the attention of biologists by a landmark paper published 20 years later (Gierer and Meinhardt, 1972). Gierer and Meinhardt showed that underlying diffusion-driven instability was the property of short-range activation, long-range inhibition or local-activation–lateral-inhibition. Of the two chemical cases, one chemical had to activate production of the other which, in turn, inhibited the production of the activator. Furthermore, the inhibitor had to diffuse more quickly than the activator. See **Figure 2** for an illustration of patterns in the Turing model.

Although Turing patterns have been found in chemistry (Ouyang and Swinney, 1991) conclusive evidence of a Turing model remains elusive in the context of developmental biology as the unequivocal identification of a Turing morphogen pair remains elusive. This should not detract from the paradigm-shifting effect this model has had in developmental biology, as illustrated by the enormous number of applications of the model. For example, Sick *et al.* (2006) provide circumstantial evidence that the proteins Wnt and Dkk act as a Turing pair in hair follicle patterning in mouse. Garfinkel *et al.* (2004) propose that a Turing mechanism underlies vascular mesenchymal cell self-organisation during development, and they identify the morphogens involved. Newman and Bhat (2007)

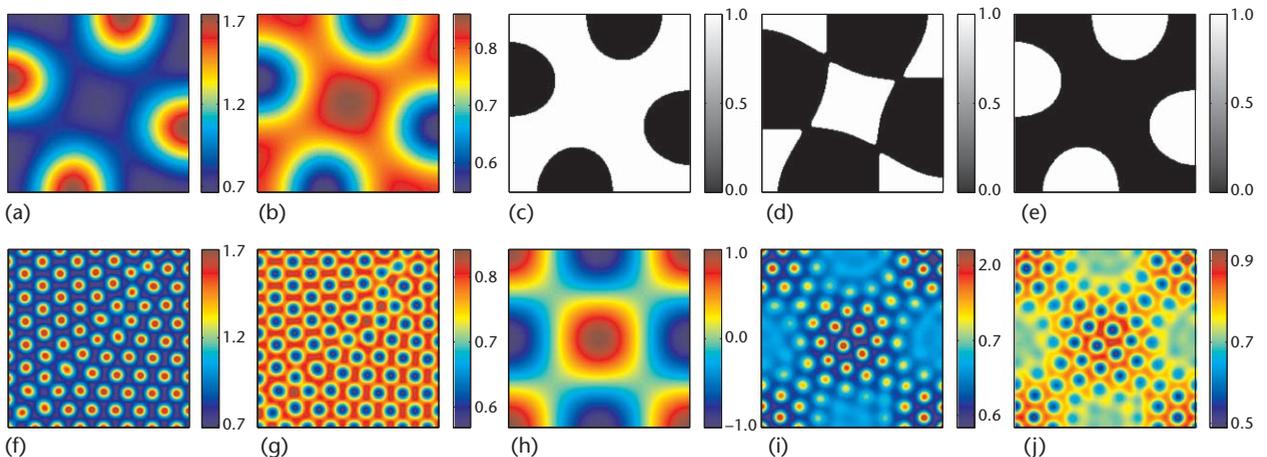


Figure 2 An illustration of the vast variety of spatial patterns arising in the Turing model (Chang *et al.*, 2009). Reproduced with permission from Chang *et al.* (2009). Copyright UBC Press. (a), (b) A typical pattern in chemical concentration. (c)–(e) The skin patterns that may arise from the chemical pattern in (a), (b). (f)–(h) More complex examples of patterns that may arise from the Turing model. (i), (j) The interaction of two Turing patterns. Colours indicate different concentration levels.

review in-depth the patterning principle underlying this modelling approach in the context of limb development, identifying transforming growth factor beta and fibroblast growth factors as possible morphogens. Turing models are also notoriously sensitive to small perturbations in initial conditions or domain geometry (Bard and Lauder, 1974; Bunow *et al.*, 1980) making them impractical for applications in which robust patterning is observed. However, it has been shown that domain growth can significantly enhance the robustness of patterning in a Turing model (Crampin *et al.*, 1999).

A spectacular application of the Turing model is to pigmentation patterning in angelfish (Kondo and Asai, 1995). In this case, insertion of stripes on the fish as it grows preserves the wavelength of the pattern, consistent with a Turing-type model. In order to try to make the link between patterning at the tissue-level and genetic information within cells, Kondo and his colleagues recognised that the parameters in the Turing-type model (e.g. production/degradation rates, interaction parameters) encode lower-scale biological information. They have therefore carried out detailed genetic manipulations to compare results with the Turing model (Nakamasu *et al.*, 2009) in order to identify links between model parameters and gene expression.

Turing-type models have also been proposed to account for the patterning of pair-rule genes in *Drosophila*. However, experimental results contradicted model predictions. In this case, it turns out that a cascade of complicated gradient-type processes interacts to produce patterning (Akam, 1989). This requires one to move away from the simple two-chemical system to a much larger system of equations. Mathematical modelling in this area has been predictive and resulted in greatly enhanced understanding of the system (see Shimmi *et al.*, 2005), incorporating Boolean models in which interactions are considered simply as promoting or inhibiting (i.e. the strength of the interaction is ignored) as well as the above differential equation approaches (von Dassow *et al.*, 2000; Albert and Othmer, 2003).

Cell movement models

These models postulate that cells move in response to chemical/mechanical cues and, in certain regions of parameter space, form aggregates. The cells in these aggregates then differentiate accordingly. For example, the Keller–Segel model (Keller and Segel, 1970) considers how cells may respond to chemicals (termed chemoattractants) by moving up chemical gradients (the process of chemotaxis). Keller and Segel showed that this system gave rise to a rich variety of patterning behaviour and applied it to aggregation patterns in bacterial populations. This type of model has been used to account for reptilian patterning, either as spatial patterns in snakes (Murray and Myerscough, 1991) or propagating patterns in crocodiles (Murray *et al.*, 1990).

Chemotaxis models have been very successful in their application to pattern formation in the cellular slime mould

Dictyostelium discoideum (Dd), which serves as an important paradigm for developmental processes in higher organisms. In this case the chemoattractant cyclic AMP (cAMP) forms complex spiral patterns to which the Dd amoebae respond by a streaming motion, leading to aggregations and eventual formation of a fruiting body (Höfer *et al.*, 1995). Many mathematical models have been proposed to describe this behaviour. They differ in the details of the signal transduction pathway and in modelling cells. Some opt for a continuum approach whereas others choose a cell-based approach. All are shown to capture in detail experimental observations and show that the change in wavelength of cAMP with wave number may be an emergent phenomenon instead of requiring changes in biochemistry. Central to all these models is the idea of an excitable system coupled to an adaptive chemotactic response, suggesting that these may be the primary mechanisms of the observed biological behaviour. **See also:** [Bacterial Chemotaxis](#); [Dictyostelium: Cell Sorting and Patterning](#)

The Oster–Murray–Harris model (Oster *et al.*, 1983) investigates the mechanical interaction of cells with the extracellular matrix (ECM) and shows that the forces cells exert on the ECM can destabilise the spatially uniform steady state and lead to patterns of cell aggregation. This model considers movement up adhesive gradients (haptotaxis) and has been applied to skeletal patterning in the limb bud and feather germ formation in chick (see [Figure 3](#)).

Mathematical structure

From a mathematical point of view all the above models are represented by partial differential equations: in the case of gradient models this is typically a single nonlinear parabolic equation, in the case of Turing-type models a coupled system of nonlinear parabolic equations; for chemotactic models a mixture of parabolic–hyperbolic equations; the mechanochemical models are of parabolic–hyperbolic–elliptic type. There is another class of models that are of integro–partial–differential equation type. For example, the neuronal models for pattern formation, first proposed to describe visual hallucinations (Ermentrout and Cowan, 1979), and then adapted and applied to patterning in sea shells (Ermentrout *et al.*, 1986), represent neuronal coupling through an integral equation. Meanwhile the model of Armstrong *et al.* (2006) uses an integral formulation for cell–cell adhesion with applications to the differential adhesion hypothesis and somitogenesis.

Model properties

Apart from the gradient models, these models are all self-organising, in that the patterns arise due to the intrinsic dynamics, rather than due to externally imposed heterogeneity (as in the gradient models). The patterns are therefore examples of emergent phenomena. Despite being based on very different biology, these models behave in a surprisingly similar manner. They are based on the general

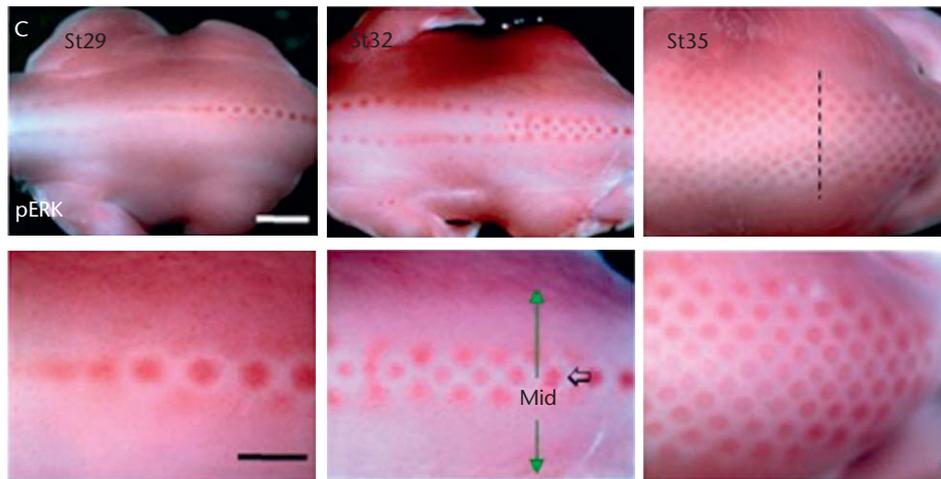


Figure 3 Patterns for feather buds forming on the skin of a chick embryo (Lin *et al.*, 2009). This sequence of experimental snapshots illustrates the sequential formation of feather buds (top row) and more detailed views (bottom row). Reproduced from Lin *et al.* (2009). Copyright (2009) with permission from Elsevier.

patterning principle of short-range-activation, long-range-inhibition, (or local-activation–lateral-inhibition) and patterns are typically, in one spatial dimension, undulating peaks and troughs, whereas in two spatial dimensions they are stripes, spots and labyrinthine patterns (Maini *et al.*, 1997). They can also exhibit wave behaviour. Although mathematical analysis can be carried out in certain special cases, in general these models are mathematically intractable and have to be solved using computational techniques. An enormous amount of research has gone into categorising the properties of these models.

As a consequence of these models, although being based on very different biological hypotheses, having the same underlying general patterning principle of local-activation–lateral-inhibition they make common predictions. For example, they predict that pattern complexity will increase with domain size, thus, for example, it is more likely for a spotted animal to have a striped tail than a striped animal have a spotted tail.

These mechanism–diffusion predictions do mean that it can be difficult to distinguish between models. However, the double-anterior limb experiments of Wolpert and Hornbruch (1990) do allow one to distinguish between pre-pattern and cell movement models. In these experiments, a donor anterior limb is combined with a host anterior limb to create a limb of size similar to that of a normal limb. All the above models predict that, as the domain size does not change in these experiments, the complexity of pattern should not change. That is, a single humerus should form. However, the experiments show that two humeri appear. This contradicts a straightforward application of all the above models. However, the parameters in these models (growth/decay/reaction/diffusion rates) arise from processes occurring at lower scales and the properties of these models have been analysed mainly for the case where these are constant. In reality, this is highly unlikely, as they are liable to vary in space and time. For example, if one makes

the very reasonable hypothesis that the diffusion-coefficients vary across the limb (due e.g. to a variation in gap junction permeability) then the resultant modified Turing-type model is entirely consistent with the results of the double anterior limb experiments (Maini *et al.*, 1992). These results are harder to reconcile with a pure cell movement model.

Both the reaction–diffusion-type models and integro–partial differential equation models have been applied to the pigmentation patterns on sea dwelling mollusks. Again, both models produce the same patterns. However, recent research suggests that the patterns most likely arise as the result of neurosecretory processes, favouring the integro–partial differential equation model (Boettiger *et al.*, 2009).

Different Modelling Mechanisms

A different model approach assumes that cells can exist in two different states, with noise or external cues able to cause a switch between them. This is known as a bistable model and one of the most famous examples is the clock-and-wavefront model (Cooke and Zeeman, 1976). It was proposed to account for the spatio-temporal pattern of somites, aggregates of cells that form in a propagating sequence from head to tail and give rise to the segmented nature of our body axis. The model postulates that a wave of competence to form somites sweeps along the antero-posterior axis of the embryo and interacts with a cell-intrinsic oscillator to ‘parcel’ cells up into somites. There is now a good deal of experimental evidence in favour to support this model, with both the clock and gradient identified at the molecular level (Dubrulle *et al.*, 2001; Palmeirim *et al.*, 1997). Several models for aspects of somite formation have been proposed – see Baker *et al.* (2008) for a review.

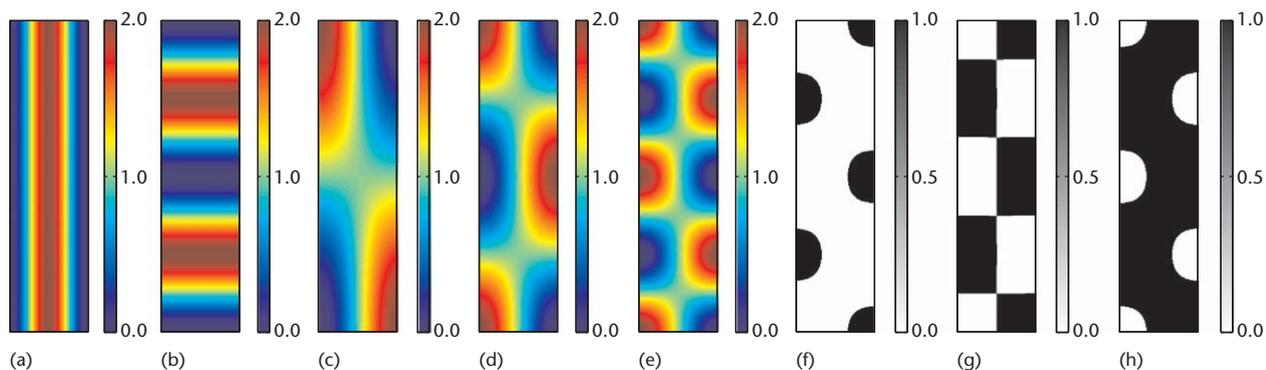


Figure 4 An example of the patterns possible on a long thin domain (Chang *et al.*, 2009). (a)–(e) Illustrate the range of patterns possible and the idea of a developmental constraint can be seen by understanding that the pattern in (b) is much more likely to occur in a Turing system than the pattern in (a). Furthermore, if the domain was tapering then the pattern would change from essentially a two-dimensional pattern (i.e. pattern that varies in both horizontal and vertical directions, such as that in (c)) to one that is essentially one-dimensional, such as that shown in (b) (which only varies in the vertical direction). (f)–(h) Illustrate the skin patterns possible as a result of (e). Reproduced from Chang *et al.* (2009). Copyright (2009) with permission from Elsevier.

The above models generally consider pattern formation on a length scale greater than that of a cell and therefore cannot account for pattern-forming processes that act intrinsically on a cell scale. The most well known of such patterning mechanisms is the membrane-bound notch–delta signalling system (Collier *et al.*, 1996). This gives rise to fine-grained patterns that are on the level of a single cell. The resultant models tend to be of differential-discrete type and have been analysed in great detail (Webb and Owen, 2004).

Finally, we have detailed the above models largely in the context of patterning at a single scale but have alluded to the fact that pattern formation in many biological contexts is a multiscale process, occurring as a result of the integration of processes taking place on many spatio-temporal scales. The aforementioned models combine the discrete cell-based approaches with the continuum-level chemical description. For example, morphogen dynamics, operating at a spatial level, are represented by a system of continuum reaction–diffusion type equations but cells are represented by discrete units, responding to and altering the morphogen patterns (Dallon and Othmer, 1997).

Evolution

The similarities in pattern-forming properties of many of the above models mean that it can be difficult to distinguish experimentally between them. On the other hand, they suggest that certain properties should appear from this general class of models that are actually independent of the fine (or even not so fine) details of the biology. One of these is the idea of developmental constraints (see Figure 4). For example, Turing's diffusion-driven instability applied to animal coat markings suggests that we should be more likely to observe an animal with a spotted body and striped tail than the converse. This has implications for evolution. For example, Oster *et al.* (1988) noticed that the variations exhibited by salamander *Ambystoma mexicanum* limbs

when treated with mitotic inhibitors (which decreased the domain size of the budding limb leading to a loss of digits, precisely as predicted by the local-activation–lateral-inhibition mechanism) were very similar to the digit patterns observed in the salamander *Proteus anquinus*. This suggests that *Ambystoma* and *Proteus* share common developmental mechanisms with implications for their evolutionary tree.

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