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Turing's Theory of Developmental Pattern Formation

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9.1 Introduction

Elucidating the mechanisms underlying the formation of structure and form is one of the great challenges in developmental biology. From an initial, seemingly spatially uniform mass of cells, emerge the spectacular patterns that characterise the animal kingdom – butterfly wing patterns, animal coat markings, skeletal structures, skin organs, horns etc. (Figure 9.1). Although genes obviously play a key role, the study of genetics alone does not tell us why certain genes are switched on or off in specific places and how the properties they impart to cells result in the highly coordinated emergence of pattern and form. Modern genomics has revealed remarkable molecular similarity among different animal species. Specifically, biological diversity typically emerges from differences in regulatory DNA rather than detailed protein coding sequences. This implicit universality highlights that many aspects of animal development can be understood from studies of exemplar species such as fruit flies and zebrafish while also motivating theoretical studies to explore and understand the underlying common mechanisms beyond a simply descriptive level.

However, when Alan Turing wrote his seminal paper, 'The chemical basis of morphogenesis' (Turing, 1952), such observations were many decades away. At that time biology was following a very traditional classification route of list-making activities. Indeed, there was very little theory regarding development other than D'Arcy Thompson's classic 1917 work (see Thompson, 1992, for the abridged version) exploring how biological forms arose, though even this was still very much at the descriptive rather than the mechanistic level.

Undeterred, Turing started exploring the question of how developmental systems might undertake symmetry-breaking and thus create and amplify structure from

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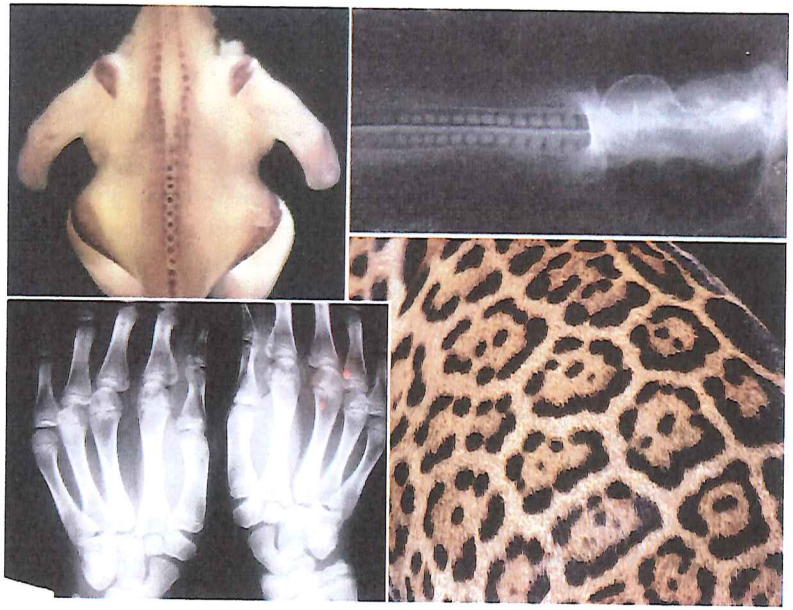

Figure 9.1 Illustrative examples of self-organization in biology. Clockwise from top left: feather bud patterning, somite formation, jaguar coat markings and digit patterning. The feather bud patterning image is courtesy of the Chuong Laboratory of Tissue Development and Regeneration, University of Southern California. The somite formation image is courtesy of the Pourquié Laboratory, Stowers Institute for Medical Research; the remaining images are taken from the public image reference at http://www.morguefile.com/.

seeming uniformity. For example, if one looks at a cross-section of a tree trunk, it has circular symmetry which is broken when a branch starts to grow outwards. Turing proposed an underlying mechanism explaining how asymmetric structure could emerge dynamically, without innate hardwiring. In particular, he described how a symmetric pattern, for instance of a growth hormone, could break up so that more hormone was concentrated on one part of the circle, thus inducing extra growth there.

In order to achieve such behaviour Turing came up with a truly ingenious theory. He considered a system of chemicals reacting with each other and assumed that in the well-mixed case (no spatial heterogeneities) this system exhibited an equilibrium (steady) state which was stable. That is, the reaction kinetics were such that any perturbation from this equilibrium would disappear over time, returning the system to the original equilibrium state. He then posed the question of what would

happen if we now allowed spatial heterogeneity. That is, we were no longer in the well-mixed state as diffusion was now possible. He showed that diffusion could drive the equilibrium state to become unstable leading to a spatial pattern. This was remarkable in that it showed that two stabilising processes (stabilising kinetics plus diffusion, which normally smooths out spatial heterogeneities) can combine to produce instability. The system is said to have *self-organised* and the resultant pattern is an *emergent property*.

In this respect, Turing was many years ahead of his time in showing that understanding the *integration* of the parts played a role as important (if not more so) than identification of the parts themselves. The process leading to the instability is now known as *diffusion-driven instability* (DDI) and the system he studied was a special case of the following generic partial differential equation system:

$$\frac{\partial \mathbf{u}}{\partial t} = \nabla \cdot (\mathbb{D} \nabla \mathbf{u}) + \mathbf{f}(\mathbf{u}) \tag{9.1}$$

where $\mathbf{u}$ is an n-dimensional vector of chemical concentrations and $\mathbb{D}$ denotes an $n \times n$ matrix of diffusion coefficients, which is typically diagonal. The associated boundary conditions depend on the problem at hand but could be periodic, zero flux or fixed, for example, and the initial conditions are typically perturbations around the homogeneous steady state. Generally, only two chemicals are considered in theoretical modelling ($n = 2$), and the vector function $\mathbf{f}(\mathbf{u})$, which arises from the application in question and constitutes the reaction kinetics, is typically nonlinear and possesses a single steady state. In addition, when patterns emerge from system (9.1), the resulting self-organisation does not depend on fine tuning the nature of the chemical interactions described by reaction kinetics; see for example Dillon et al., (1994).

Turing termed the chemicals in his framework *morphogens* and hypothesised that cells would differentiate (adopt a certain fate) if the morphogen concentration breached a certain threshold value. In this way, the spatial pattern in morphogen concentration arising from a DDI would serve as a *pre-pattern* to which cells would respond by differentiating accordingly. In his words, "It is 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." Typical two-dimensional patterns are shown in Figure 9.2.

Turing's work was significantly extended by Gierer and Meinhardt (1972), who provided fundamental principles for patterning via the DDI mechanism. In particular, they showed that, in the case of two chemical components, DDI could occur in only two scenarios: (i) one chemical had to be self-activating and activate the production of the other chemical which, in turn, inhibited the production of the first; (ii) a substrate depletion system in which one chemical (activator) depletes the

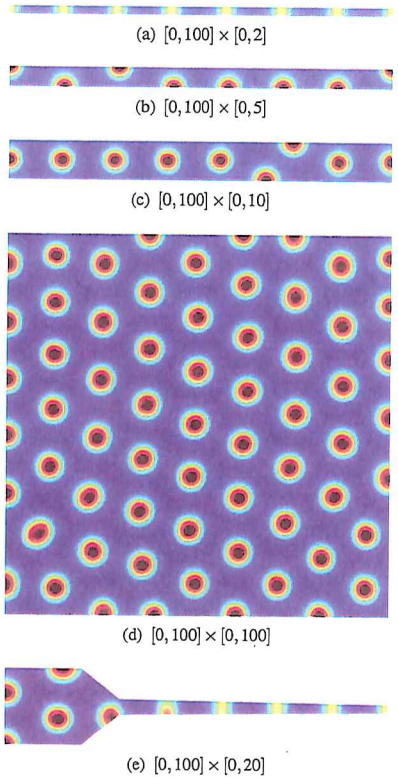

Figure 9.2 Typical patterns produced by a Turing reaction–diffusion model for two chemical reactants. Here we show the concentration of one of the chemicals, the other is out of phase with the solution. Notice that as the domain changes from (a) quasi-one-dimensional to (b)–(d) two-dimensional the patterns become more complex. In (e) the domain geometry is a simplified representation of an animal pelt, showing a transition from spots to stripes. The solution domain is given under each image except (e) where we have solved the simulated system on the tapered domain shown, which is contained within $[0,100] \times [0,20]$. The colour axis runs from 0 (blue) to 4 (red).

other inhibitory chemical (known as a substrate) which, in turn, produces activator. In addition, for both these forms of interactions, patterning requires that the inhibitor diffuses more rapidly than the activator. This is now known as short-range-activation–long-range-inhibition, or local-activation–lateral-inhibition (LALI); see for example Oster (1988).

The LALI mechanism has been applied extensively in explorations of pattern-

ing and regeneration for hydra, vein formation in leaves, somite formation in early development, and butterfly wing pigmentation patterns, to name but a few examples. We direct the interested reader to some of the excellent books written on this topic for fuller details and more examples e.g. Meinhardt (1982), Murray (2003) and Meinhardt et al. (2003), and also the very readable article by Kondo and Miura (2010).

We provide an illustration for this counterintuitive notion based on one of Turing's own (slightly imperialistic) analogies involving cannibals and missionaries living on an island. Cannibals self-activate through reproduction, but the act of cannibalism is inhibited by missionaries, who can increase their numbers by converting cannibals to missionaries. Thus one can imagine a stable equilibrium of cannibals and missionaries. However, suppose there is now movement with the missionaries (on bicycles) moving faster than the cannibals. This has the potential to destabilise the equilibrium, with a core of high cannibal activity surrounded by a region of suppressed cannibalism due to missionary presence (Teuscher, 2004). While in real life, human interaction is not as simple and rarely is motion diffusive, such analogies emphasise that Turing's ideas are not restricted to developmental biology and can be found operating in spatial ecology as well as other diverse areas of nature, including chemistry and optics.

9.2 Some developmental applications

Perhaps the most colourful application of these ideas is to animal coat markings. Here, one can exploit the properties of the Laplacian operator in equation (9.1). In many cases the patterns exhibited by the model are characterised by the eigenfunctions of the Laplacian. Thus, for small domains, no pattern will form but, as the domain grows, pattern grows in complexity (see Figure 9.2). One prediction of the model is that on tapering domains, for example a tail, one should see a spot-to-stripe transition, which is indeed observed in many cases. Another prediction is that animals with striped bodies and spotted tails have coat patterns that are not an emergent property of a simple Turing model. Moreover, if an animal is such that it has a plain body colouring then its tail should also be plain according to Turing's mechanism, illustrating an example of a *developmental constraint*. In Figure 9.3 we see that the genet is an excellent example of this, but that the lemur has, unfortunately, no respect for this mathematical theory. In the latter case, a prospective explanation in terms of Turing's mechanism would require an assumption that the parameter values implicit in patterning the body are different to those in the tail, or that the pattern forms due to highly nonlinear interactions.

Another application arises from skeletal patterning in the limb. For example, in the chick limb, at the limb bud stage at which the skeletal pattern is laid down,

(a) (b)

Figure 9.3 Pigmentation patterns observed on (a) the genet, and (b) the ring-tailed lemur.

the limb has a 'paddle-shape' and therefore Turing's theory predicts that patterning complexity should be increasing along the paddle. This is precisely what happens with the humerus–radius/ulna–digits patterning transition, which occurs not only in the chick but is characteristic of many limb architectures. Experiments that reduce the size of the growing limb bud reduce digit number, while those that increase the size of the limb bud result in an increase in digit number. These experimental results are consistent with the theory.

A final arena concerns developmental left–right symmetry breaking. In particular, not everyone has their heart on the left-hand side. A rare genetic disorder, primary cilia dyskinesia (PCD), is associated with a left–right symmetry reversal of the vital organs, such as the heart, in about 50% of cases. This disorder is associated with immotile cilia, which are filamentous cellular protrusions and normally capable of active motion that drives surrounding fluid. Clearly, there is a link between ciliary function and developmental symmetry. The picture emerging in mammals via murine studies is that the initial left–right symmetry breaking event is driven by primary cilia driving flow within the embryonic node, a small covered indentation filled with fluid and located on the embryo surface. The resulting asymmetry of the fluid flow and transport arising from cilia rotating in a single direction then induces differential cellular signalling around the node, though there are numerous competing hypotheses concerning the details of how this signal is transmitted to the surrounding cells. Regardless, a commonly considered, and ultimately testable, hypothesis is that the interaction of the morphogens Nodal and Lefty utilises a Turing-type mechanism to amplify the tiny signal emerging from the nodal flow, instigating the differential development of the embryo's left-hand side and right-hand side (Hamada et al., 2002; Tabin 2006). As such, there is a

prospective pathway leading from the suggestion that molecular chirality dictates the direction of embryonic nodal cilia motion to the location of the heart in the mammalian bodyplan (Okada et al., 2005), with Turing's mechanism potentially driving signal amplification.

9.3 Extending Turing

Since the work of Turing there have been a number of models proposed for pattern formation. Some of these consider not only diffusible biochemicals such as morphogens but also cells. The latter can move in response to chemical gradients (a process known as chemotaxis) or deform the extracellular matrix in which they move to set up physical directional cues. In turn these mechanisms can, under certain circumstances, instigate cellular aggregation. It is hypothesised that differentiation then occurs in these aggregates. Other models hypothesise that neurosecretory mechanisms set up patterning (in, for example, molluscs). While these models are all based on different biological hypotheses and lead to systems of equations of different mathematical types, they all give pattern via the LALI mechanism. In fact, their patterns typically emerge as eigenfunctions of the Laplacian in the initial stages of self-organisation and therefore the concept of domain geometry determining pattern complexity, while developed for Turing, applies to all these newer models. This idea was exploited in an evolutionary context by Oster et al. (1988) who noticed that the variations exhibited by salamander (*Ambystoma*) 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 LALI mechanism) were very similar to the digit patterns observed in a diggerent salamander (*Proteus*). This is consistent with the observation that *Ambystoma* and *Proteus* share common developmental mechanisms.

One further property of developmental systems is growth. Kondo and Asai (2005) observed that, as the angelfish *Pomocanthus* grows to maturity, its pigmentation pattern of stripes changes. As the stripes move wider apart due to growth, new stripes are inserted so that the stripe wavelength is preserved (Figure 9.4). This is in agreement with the Turing model.

However, it would be highly misleading to suggest that the Turing model suggests that only a few equations uniformly govern the range of developmental patterning that we see. Even observations consistent with Turing's mechanism do not imply that the underlying dynamics is driven by Turing morphogens, and there is no developmental example where the molecular details can be elucidated to the extent that there is unequivocal support for a DDI.

Conversely, the fact that biological complexity surpasses the behaviours of Turing's basic two-component model does not immediately imply that a DDI is not at

(a) (b) (c)

Figure 9.4 Development of stripes on the marine angelfish *Pomocanthus*. (a) Baby. (b) Juvenile. (c) Mature.

work. For instance, the patterns driven by a Turing mechanism may arise only if certain constraints are satisfied by the model parameters such as the diffusion coefficients, and the production, degradation and interaction rates. These can, in more general settings, also be functions of processes occurring at a lower spatial scale and may even be spatially patterned. This was recognised by Turing, who said, in his original paper, that "most of an organism, most of the time, is developing from one pattern into another, rather than from homogeneity into a pattern." This idea was exploited by Maini et al. (1992) to investigate experiments by Wolpert and Hornbruch (1990) which appeared to contradict the LALI mechanism. In the experiments the anterior portion of the limb bud of a donor chick was grafted onto the anterior part of a host limb bud, so that the resultant double anterior limb bud was the same size as a normal limb bud. The LALI mechanism then predicts that, as the domain size has remained unchanged, the resultant limb should be normal. However, it is observed that two humeri develop. This can be reconciled with the LALI mechanism if one assumes that there is a spatial pattern in one of the parameters in the model upstream of the Turing patterning process, and indeed there is strong evidence to suggest this (Brümmer et al., 1991).

9.4 Critiquing Turing

Such difficulties highlight why Turing's mechanism remains as a tantalising hypothesis rather than an established or refuted mechanism within developmental biology. In particular, while morphogens have since been discovered it is still a matter for strenuous debate as to whether morphogen pairs exist and if they or, more generally, diffusively driven instabilities form pre-patterns as Turing envisioned. There is tentative evidence that the transforming growth factor beta and fibroblast growth factors may play Turing-type roles in limb development (Newman and Bhat, 2007) and that Nodal and Lefty gene products may be a Turing pair (Solnica-Krezel, 2003). In addition, Sick et al. (2006) highlighted that Wnt

and Dkk may be a Turing morphogen pair in hair follicle formation in mice, while Garfinkel et al. (2004) provided evidence for a Turing mechanism underlying vascular mesenchymal cell self-organisation during development and identified the morphogens involved. However, the jury is still out. On the other hand, in chemistry, as opposed to developmental biology, it has been unequivocally shown that Turing patterns can arise, in the now famous CIMA (Chloride–Iodide–Malonic-Acid) reaction (Figure 9.5), demonstrating proof of principle. The collection of articles edited by Borckmans et al. (2007) reviews advances in Turing patterns in chemistry as well as other pattern formation phenomena that occur in chemistry.

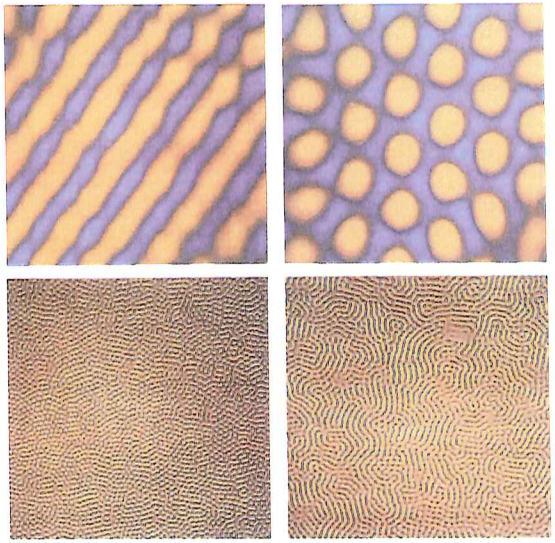

Figure 9.5 Illustrative examples of chemical Turing patterns for the CIMA (Chloride–Iodide–Malonic-Acid) reaction within a continuously fed open gel reactor. Reprinted with permission from Ouyang and Swinney (1991) Transition to chemical turbulence. *Chaos* 1:411–420. © 1991, American Institute of Physics. The gel is loaded with starch, which changes from yellow to blue if sufficient iodide concentrations establish during the CIMA chemical reaction. The illustrated patterns are essentially stationary states, though some slow movement of interfaces was observed after the pattern had effectively stabilised; the differences between the frames reflect variations in the control parameters of the system, particularly the initial concentrations of the CIMA reactants.

From a theoretical point of view, detailed studies of the Turing model reveal a sensitivity to noise in, for example, the initial fluctuations that drive the instability (Bard and Lauder, 1974) or in the domain geometry on which the reaction is taking place (Bunow et al., 1980). This is obviously a problem in cases where precise

patterning is necessary or observed (for example, the number of digits) but not in, for example, the case of some animal coat markings. However, additional aspects of developmental biology, in particular when growth is incorporated into the models, can alleviate initial condition sensitivities (Crampin et al., 1999), though such questions remain unexplored for the prospect of sensitivity to changes in the shape of the domain boundary, or the conditions imposed at these boundaries.

More generally, while genetics alone is insufficient to understand developmental pattern formation, Turing's ideas for morphogen dynamics nonetheless take place within the framework of the cellular molecular biology driving the differential gene expression inherent in the emergence of structure during development. For instance, modern studies reveal that even very simple developmental systems involve complex interactions of numerous receptors and morphogens, while morphogen production requires signal transduction, gene expression and protein production. This complexity is still being unravelled though it is subsumed within simple representations of a very small number of morphogens and their interactions within Turing's framework.

This raises the question of whether Turing's idea is of limited applicability in light of the biological interaction networks emerging in the "omics" era. In particular, extensive changes in predicted system behaviour occur when removing a morphogen or the receptor from a three-component model of hair follicle patterning involving the receptor Edar, connective tissue growth factor and bone morphogenetic protein (Klika et al., 2012). Hence, simply neglecting diffusing elements or receptors to reduce a model of developmental self-organisation to the canonical two-component Turing system is, in general, insufficient and more sophisticated approaches are required.

However, as we have already discussed, numerous developmental systems nonetheless behave in a manner that, at the very least, is suggestive of a Turing system. Hence, even when a literal interpretation of a DDI via pairs of Turing morphogens may ultimately be difficult to justify, there is nonetheless the question of whether Turing morphogens are representations for more complex functional units. These could be a collection of cellular receptors, genes and their products or even whole cells.

Evidence for such a reinterpretation of Turing morphogens is emerging from zebrafish skin patterning studies, which indicate that pigment cells could be functional Turing 'morphogens' (Nakamasu et al., 2009). Such reinterpretations are very much an open area of research and may also alleviate further difficulties with the standard Turing model, for instance the need to have vastly different diffusion rates between the activator and the inhibitor for pattern formation *without* parameter fine-tuning. This approach may also eliminate the need to consider the time delays associated with gene expression, which are troublesome in that incorporating such delays into the classical two-component Turing morphogen model leads to abberrant behaviours (e.g. Seirin-Lee et al., 2010). Even when patterning does occur in the delayed Turing model, there is an extensive patterning lag and a temporal sensitivity that is difficult to reconcile with the highly regulated temporal order observed in many (but not all) developmental phenomena. An alternative reconciliation of such difficulties with empirical observation is that biological interaction networks involving putative Turing morphogen pairs also provide additional stabilising feedback dynamics for reducing temporal sensitivity. Again, this hypothesis remains to be explored.

There are other cases where the application of a Turing-type model, even with a reinterpretation of the interacting elements, cannot be reconciled with experimental data. For example, the model was proposed to account for the stripe-like patterns of the pair-rule genes in the *Drosophila* embryo, but experimental results showed that it is possible to knock out one stripe while keeping the others. This contradicts the Turing model and, in fact, patterning in this case seems to arise from a cascade of interacting gradients in various chemicals (Akam, 1989). Another example is the case of shell pigmentation patterns on molluscs. It has been shown that an astonishingly large variety of these patterns can be produced by Turing-like models on a growing domain (Meinhardt et al., 2003). However, the evidence is increasingly pointing to a neurosecretory mechanism (Boettiger et al., 2009), another of the LALI models.

9.5 The impact of Turing

As can be seen in this brief article, the Turing model has been applied to a wide range of patterning phenomena in developmental biology. The richness in behaviour of this seemingly simple set of equations is remarkable and much wider than we have covered here. This modelling framework has also motivated an enormous amount of mathematical analysis and computational study. Moreover, it has caused a paradigm shift in the thinking of developmental biologists, especially after the short-range-activation–long-range-inhibition idea championed by Meinhardt.

Turing's work has therefore inspired modelling efforts for describing self-organisation built on different biological hypotheses and has provided a framework of patterning principles and developmental constraints consistent with the diffusively driven instability and LALI mechanisms. Indeed, it is ironic to note that this framework, developed during an era of biological list-making, risks being lost in the present era of data generation and collection. In addition, these concepts have also raised more than their fair share of controversy. However, while it is in the nature of modelling that all models are simplifications, the worth of a model in biology must be measured in the number of experiments it motivates that may not have been

done otherwise and in the amount it changes the way experimentalists think. By this measure, Turing's 1952 paper is one of the most influential theoretical papers ever written in developmental biology.

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