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Turing patterns in development: what about the horse part?

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For many years Turing patterns — the repetitive patterns which Alan Turing proved could arise from simple diffusing and interacting factors — have remained an interesting theoretical possibility, rather than a central concern of the developmental biology community. Recently however, this has started to change, with an increasing number of studies combining both experimental and theoretical work to reveal how Turing models may underlie a variety of patterning or morphogenetic processes. We review here the recent developments in this field across a wide range of model systems.

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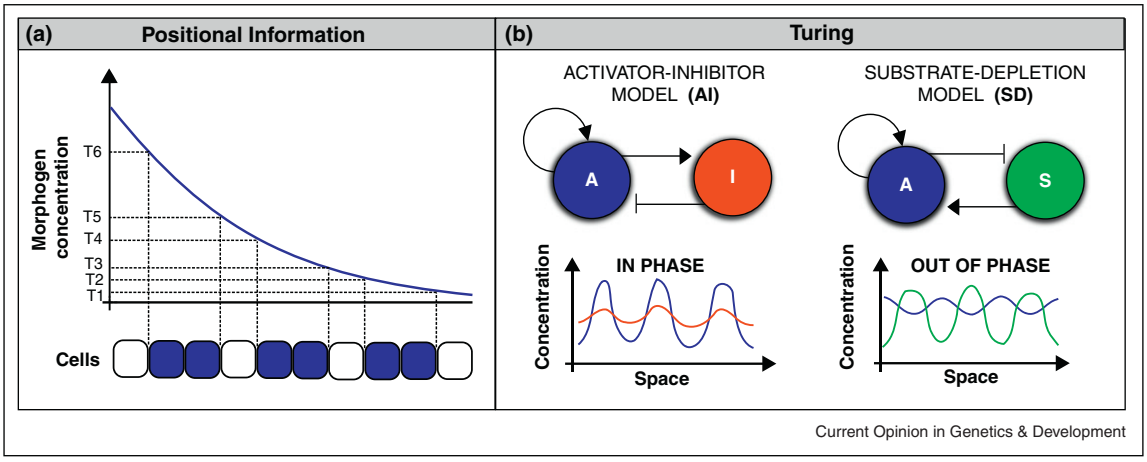
Introduction

For a long time it has been recognized that two fundamentally different mechanisms exist for creating spatially-organised patterns in multicellular systems. The more prominent theory during the last few decades has been that of positional information, as described by Lewis Wolpert over 40 years ago [1]. The most familiar form of this theory involves a diffusible molecule which is produced asymmetrically and thus creates a spatial concentration gradient. Each position along this gradient has a unique concentration, thus giving cells direct access to information about where they are in the field, and to make the appropriate cell fate choices. The alternative theory was first proposed 27 years earlier, by Alan Turing [2]. In this model two chemical species can react with each other and diffuse through the tissue (hence the common name of *reaction–diffusion* model). If the reaction and diffusion constants are set just right (e.g. A is an activator of both species, I is an inhibitor of both species and I diffuses faster than A) then an initially homogeneous concentration can spontaneously break the uniform state and form periodic patterns — peaks and valleys of concentration — which in 2D may take the form of spots or stripes, such as the coat pattern of leopards or zebras (depending on the parameter values). A critical difference of this mechanism compared to a positional information gradient is that each position in space does not have a unique concentration. Thus cells with the maximal 'peak' concentration have no way to distinguish which peak they are in — they do not have unambiguous positional information (Figure 1).

In most cases, the two theories are not considered to be alternative explanations for the same patterning task. The Wolpert model is mostly relevant to regionalization (e.g. positioning the head at one end of the embryo, and the tail at the other), while Turing mechanisms are most relevant to repetitive, periodic patterns (such as the zebra's stripes). However, the theories were for a long time seen as competing against each other — at least for their conceptual importance to the field of developmental biology — and Turing's model generally seemed to lose out [3]. Interestingly, even Turing himself apparently had doubts about the importance of his model. Regarding the zebra he allegedly exclaimed 'Well the stripes are easy, but what about the horse part?' [4]. This has been interpreted in at least two different ways. Firstly, as an acknowledgement that animal coat patterns are often considered less important to developmental biology than morphogenesis. Secondly, that Turing patterns, although elegant are rather simple — just a repetitive sequence of alternative states (on, off, on, off, etc.) — whereas building the 'horse part' of the zebra, with it's body plan, internal organs and skeletal arrangement, must require much more complicated and sophisticated patterning processes.

However, the last decade has seen a gradual but steady revival in the interest in Turing's model — especially in projects that have combined mathematical modeling with experimental approaches. Excitingly, new studies are increasingly countering Turing's own doubts about the relevance to morphogenesis — more examples are emerging in which the Turing mechanism may control the structural arrangement of an organ's tissues, such as branching patterns in lung development and digital pattern in limb development (described towards the end of this review). It is particularly fitting this year to review some of the key systems for which evidence is accumulating — firstly because of the recent crop of papers on this topic (12 papers over the last 2 years), and secondly because 2012 is the centenary of Alan Turing's birth.

Figure 1



(a) The classical positional information model proposed by Wolpert, in which each position in the field has a unique morphogen concentration. In this example, a periodic fate (blue cells) is specified along the space by six different thresholds T1–6 of a morphogen gradient (top graph — blue line). **(b)** Interaction networks of diffusible molecules (A,I,S) that are capable of forming a Turing pattern. On the left, an Activator (A) promotes itself and its own diffusible inhibitor (I): a periodic spatial pattern where A and I are in phase is formed. On the right, an Activator (A) consumes its own substrate (S) to auto-activate itself: a periodic spatial pattern where A and S are out of phase is formed. Positions with unique concentrations do not exist. A cell at a given peak of concentration does not have enough information to distinguish which peak it is in.

Left-right asymmetry

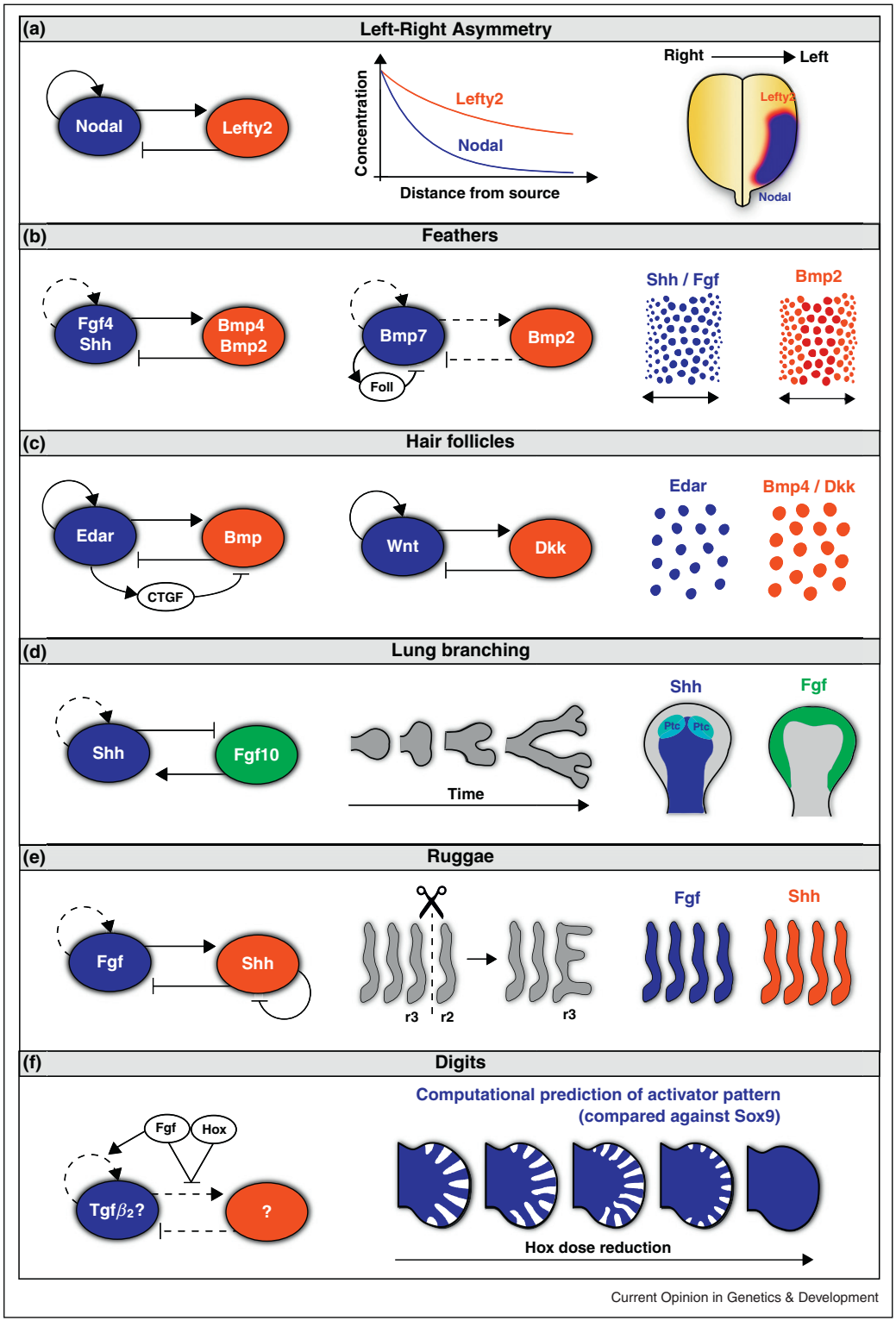
Several studies in zebrafish, frog and mouse [5,6] have revealed that left-right asymmetry in early bilaterian embryos is governed mainly by two diffusible proteins of the Tgf-family: Nodal and Lefty. The first is a ligand that signals through the receptor Alk4 and EGF-CFC co-receptors, and the second is a molecule that inhibits Nodal signaling by sequestration and competitive binding to its co-receptor. Many functional experiments had confirmed that these two proteins fulfill the requirements of an Activator and an Inhibitor (AI) in a Turing model, see [7,8,6] for an overview. In particular, genetics and luciferase assays showed that Nodal signaling stimulates the production of itself and Lefty, thus implementing both a positive feedback and a negative feedback [9–11]. More recent work [6] modeled this network with a system of PDEs similar to the AI model of Gierer and Meinhardt, and considered the asymmetrical leftwards flow of Nodal as a trigger to reliably bias the asymmetry of the subsequent expression. Very recently, an elegant experiment based on fluorescence recovery after photo-bleaching [12••] provided evidence that in zebrafish Lefty diffuses fourteenth times faster than Nodal, strengthening the hypothesis of a Turing system. It is still unknown how the diffusion of molecules with comparable sizes can differ so greatly, but recent studies have highlighted the possibility that proteo-glycans in extracellular matrix (ECM) modulate the diffusion of Nodal and Lefty [13,14]. It is important to note that this particular example displays an important difference from many other Turing systems. Since the pattern formed is just a single gradient (it is not the more typical repetitive, periodic pattern), each position along the left-right axis has a unique concentration and thus could indeed be used to provide positional information (Figure 2a).

Patterns in the skin — feathers

The patterning of skin appendages (such as hair follicles and feathers) are natural systems to consider a Turing model as they involve the positioning of repetitive, evenly-spaced structures (Figure 2b). The first molecular evidence for a reaction–diffusion in skin appendage patterning proposed that Sonic Hedgehog (SHH) and a member of the Fibroblast Growth Factor family (Fgf4) acted as activators of feather primordia, and that the Bone Morphogenetic Proteins (Bmp2 and Bmp4) acted as inhibitors [15•]. Moreover, bead experiments suggested that these signaling factors were cross-regulating each other, and numerical simulations were performed to support the idea.

A decade later however, an alternative model based on Bmps, this time Bmp2 and Bmp7, was presented [16], which also proposed Bmp2 as an inhibitor of feather formation but described the role of another protein in the family, Bmp7, as a chemoattractant of feather cell progenitors. The model took into account the dynamics of feather specification, which is known to start from stripes along the mid-line of the embryo which then propagates out across the whole epidermis. Bmp7 is a constitutively produced activator that in the initial phase homogeneously attracts the feathers progenitors. Bmp2 is considered as an inhibitor that stops the migration of the progenitors. Moreover, Bmp7 activates its own inhibitor

Figure 2



Abstract representations of Turing models for recently-studied examples of pattern formation. Activator (A), Inhibitor (I) and Substrate (S) are given the same color code as in Figure 1. Dashed lines indicate interactions for which strong evidence was not yet provided. **(a)** Early left-right patterning in bilaterians embryos. Several experiments confirmed that Nodal and Lefty2 interact according to an AI model (left) and are expressed in a left-specific manner in the embryo (right). Since the pattern corresponds to only half a Turing stripe (centre) these gradients could theoretically provide positional information. **(b)** Two Turing models have been proposed for feather formation: An AI model where Fgf4/Shh act as an activator and Bmp4/Bmp2 as an

Follistatin that also helps to limit its effect as an activator. According to this study, in the context of the appropriate cell movements Bmp7 and Bmp2 behave as an activator and an inhibitor respectively (although no direct evidence was given for the cross-regulation of Bmp2 and Bmp7). Interestingly, auto-regulation of Bmp7 and modulation by Follistatin has also been described in another periodic patterning system — patterning of taste papillae on the tongue — but in this case they were not proposed to form a Turing system, but rather a noise-suppression mechanism [17].

More recently an elegant correspondence between 2D numerical simulations and patterns obtained by different perturbations of the Bmp signaling was presented [18••,19••]. This work showed that neck-specific defects observed in a specific breed of chickens could be explained by an increase in Bmp signaling and was consistent with an AI model in which Bmp acts as the inhibitor. The same model also accounted for the phenotype observed upon inhibition of Bmp-signaling in culture. The difference between the behaviours in the neck and in the body could be explained by the greater sensitivity of the Bmp signals in the neck, which was promoted by Retinoic Acid (RA). This work provides good evidence that Bmp acts as an inhibitor in a AI model, while the molecules acting as activators have yet to be found.

Patterns in the skin — hair follicles

The other main skin appendage for which a reaction–diffusion system was proposed is hair follicle specification (Figure 2c). This was first hypothesised in the early eighties [20,21], however molecular evidence only started to emerge 3 decades later. In 2006 a study in mice proposed that Wnts and their inhibitors Dkks were the Turing molecules responsible for follicular patterning [22]. A Wnt signaling lacZ reporter revealed that signaling was active on the developing hair follicle. Moreover, an inhibitor of Wnt signaling Dkk4 was also found to be expressed in the hair follicle regions and it was showed that it promotion was driven by Wnt signaling. Nevertheless, in later phases of follicular specification another Wnt inhibitor Dkk1 was found to be expressed in the regions surrounding the follicles. A two-phase model was thus proposed: in the first phase Wnts and Dkk4 specified an initial follicular pattern and in the second phase Wnts and Dkk1 specified additional follicles in the inter-follicular regions. An AI model with an extra auto-repressive loop on the Dkk node was simulated in 2D and replicated the basic behaviour of the proposed two-phase.

A parallel study proposed an alternative Turing network to explain the same process [23•,24], in which the ligand Eda is an activator of follicle formation by signaling through the Edar receptor. Exogenous Eda led to the formation of additional follicles and to the formation of stripes when a high concentration was used. It was also shown that the expression of Edar (the receptor) was initially uniform and successively became localized within the follicle progenitor. This localization was dependent on Eda signaling and led to the hypothesis that there was a fast positive feedback loop of Eda signaling. In addition, this study showed that Bmp signaling repressed the expression of the Edar receptor and therefore it was proposed that the system could work as an AI model where Eda was the activator and Bmps the inhibitor. Furthermore, it was also found that Edar signaling promoted an extracellular inhibitor of Bmp similar to Noggin named CTGF. Recently this network was explicitly modeled [25•] and it was analytically shown that although such a system could form a Turing pattern when an extra interaction was added (a self-inhibition of Edar) it was unstable over time — thus questioning the model.

Patterns in the skin — fish stripes

Ironically, one of the originally proposed Turing systems has been revealed by more recent work, not to be a strict molecular reaction–diffusion system. In 1995 a pioneering study by Kondo and Asai demonstrated Turing-type spatio-temporal dynamics of a in a natural biological system — the stripes formed by the arrangement of pigmented scales on fish [26]. The dynamic rearrangement

Figure 2 Legend Continues inhibitor (left), and a second model in which Bmp2 is proposed as the Inhibitor and Bmp7 as the activator (center). On the right, the typical in-phase expression pattern of Shh/Fgf4 and Bmp2 in the skin, as the feathers are specified from the mid-line of the embryo. **(c)** Turing models for hair follicle specification. On the left, a model where Eda signaling promotes Bmp that implements a negative feedback by repressing the Eda-receptor Edar. In addition, Eda promotes CTGF, an extracellular inhibitor of Bmp. All these interactions were supported experimentally, however a mathematical analysis showed that this system cannot form stable periodic patterns [25•]. In the center, an alternative Turing model proposed Wnt as an activator and Dkk as an inhibitor (the corresponding interactions were taken from the literature). On the right, typical in-phase expression patterns of Edar and Bmp4/Dkk. **(d)** A Turing model for lung branching. On the left, Shh is proposed as the activator and Fgf10 as the substrate in a Substrate-Depletion (SD) model. It is hypothesised that the auto-activation of Shh is implemented by upregulation of the Ptc receptor upon Shh-signaling. The model produces out-of-phase patterns of Fgf and Shh (right). In the center, a schematic representation of lung branching over time. **(e)** Ruggae in the mammalian palate are patterned according to a Turing model. On the left, a model where Fgf acts as the activator and Shh as the inhibitor in an AI model (auto-activation of Fgf was hypothesised). In the center, the process of ruggae regeneration that follows excision is consistent with the dynamics of a 2D Turing model, as new stripes emerged perpendicularly as extensions from the last remaining one. On the right, typical in-phase patterns for Shh expression and Fgf signaling. **(f)** Digit patterning during vertebrate limb development is consistent with a Turing mechanism. The molecules implementing the Turing mechanism are largely unknown, although Tgfβ2 has been proposed as a possible activator molecule [37]. However, it was recently shown by experiments and modeling that distal Hox genes and Fgf control (increase) the wavelength of a Turing mechanism. The modulation of the production of the inhibitor of an AI model was identified as the best strategy to control the wavelength (left). This model correctly predicts a progressive increase in number of digits as the distal Hox dose is reduced (right), which was confirmed by comparison with the Sox9 skeletal marker [36••].

of the fish stripes after some parts were laser-ablated showed a striking concordance with numerical simulations of a 2D Turing system. However, subsequent work has shown that this system is in fact driven by the interaction between different pigment cells that actively migrate through the skin to create the pattern, rather than the diffusion of molecules [27]. Nevertheless, the authors proposed that these cell interactions still follow the two main principles usually considered as the key ingredients required for a Turing system — namely local auto-activation and long range lateral inhibition [28]. Very recently it was shown that the cell rearrangements seemed to be mediated by cell–cell communication, by dendrites [29•]. Interestingly, a previous study had shown that a mutation in the gene connexin41.8, a component of the cell gap junctions, could transform the stripes of the Zebrafish into spots [30]. The role of this gap junction gene in modulating Turing patterns has very recently been confirmed through a variety of mutations capable of producing an array of different Turing patterns [31]. This has highlighted the interesting fact that the behaviour of some patterning systems can be predicted by the mathematical dynamics of a pure Turing system, even if they are not a strict reaction diffusion system.

Lung branching

Another system proposed to operate by reaction–diffusion is lung branching [32], but only recently has a Turing model been developed that describes it [33•]. This model is based on the interaction between two signaling molecules expressed in the lung bud tip: Fgf10 and Shh (Figure 2d). Fgf10 is produced at high levels only in the mesenchyme and diffuses to stimulate growth. In addition, Fgf10 signaling promotes the expression of Shh, which in turn inhibits the expression of Fgf10. An auto-catalysis on the activator (Shh) was added to fulfill the requirements of a reaction–diffusion type instability. This is justified by assuming that a positive feedback on Shh signaling through the upregulation of Ptc expression shows a non-linear response (hypothesised to be explained by multimeric Shh signaling through two Ptc receptors at the same time).

This study showed that the model can be reduced to a 2-species Substrate-Depletion (SD) model, in which Fgf10 and Shh would form out-of-phase patterns. The model has some additional constrains: it is assumed that Shh is only expressed on the epithelium, that Fgf and Ptc are only expressed in the mesenchyme, and that all the proteins can freely diffuse to the mesenchyme, epithelium and lumen. The unusual diffusion constant of the receptor Ptc is however very small and is restricted to the epithelium and mesenchyme. This study also performed simulations on a dynamic domain representing the growing lung bud, and was able to present the intriguing theoretical observation that different growth speeds change the position of the bifurcations: fast growth promote lateral bifurcation, while slow growth create bifurcations closer to the tip [33•].

Ruggae

Another recent study has revealed a Turing system in an unexpected tissue — the ridges which form on the roof of the mammalian palate, called ruggael [34•]. In mouse, the specification of new ruggae happens as the palate grows, and experimental removal of a stripe induces new stripes protruding out perpendicular from the remaining stripes (Figure 2e). Similar to the stripe ablation in zebrafish, the behaviour of the system thus fits with two-dimensional simulations of a Turing model. It was also found that the pattern of Fgf signaling activity (as revealed by Sprty2 expression) reflects the rugae pattern. Genetic and pharmacological functional experiments showed that reduction of Fgf signaling causes a disorganised rugae pattern and Shh expression was reduced. Similarly, when Shh hedgehog signalling was inhibited the ruggae pattern was disorganised. However, in this case both Fgf signalling and Shh expression were initially broadened and eventually Shh expression disappeared. The authors proposed that these experiments could be explained by a Turing AI model where Fgf is the activator and Shh the inhibitor, however the manipulative experiments were not replicated with simulations.

Digital patterning

Polydactyly — the development of extra digits — is a relatively common abnormality during limb development, both for humans and in mouse mutants. Already many years ago, this observation lead to the hypothesis that a Turing mechanism may be the underlying patterning mechanism [35]. However, one key prediction of a Turing model had not been clearly documented until recently. Although many previous polydactylies contain multiple normal-sized digits, which may result from the development of an abnormally wide limb bud, a Turing model would predict that mutating certain genes (controlling the correct parameters) should produce digital patterns in which the widths of all the digits is altered (i.e. the wavelength and thus digit number changes) without altering the domain size. The most recent study to employ a Turing model revealed that certain Hox mutants show this exact phenotype [36••]. As more copies are removed of four 'distal Hox genes' (*Hoxd11-Hoxd13*, and *Hoxa13*) the wavelength of the digital pattern becomes narrower and narrower (i.e. both the digital and interdigital width shrinks), while having minimal impact on the handplate size. This effect was seen most clearly in a $Gli3^{-/-}$ background, which has a larger than normal handplate width, but the same relationship between Hox dose and wavelength was found to be true in the $Gli3^{+/+}$ background as well. The study then used an accurate limb bud shape as a 2D domain within which to simulate a reaction–diffusion model. A comparison of

simulation results with the real phenotypes, indicated that both Hox genes and FGF signaling modulate the wavelength of an underlying Turing mechanism — the distal Hox genes in a spatially uniform manner, and FGF signaling in a proximo-distal graded manner which accounts for the 'radial' arrangement of digits during this early patterning phase. Although this study was able to infer regulatory roles of genes which appear to modulate a Turing mechanism, and thus strengthen the Turing hypothesis for digit patterning, the core reaction–diffusion molecules remain to be identified.

Conclusions

One of the most important questions in the field is the identity of the Turing molecules. Evidence exists in most of the examples described above for some of the key molecules. However, multiple questions remain, even for those that have been relatively well-studied: Given that many developmental systems exhibit widespread redundancy in their regulatory networks, can simple 2-species systems accurately represent the underlying mechanism? Moreover, are there principles underlying the pairs of diffusible molecules used in specific Turing systems? Out of all the examples listed above, only two use the same pair of molecules: both lung branching and ruggae patterning are proposed to use Shh and Fgf as the main molecules. But interestingly, even in this case they implement a different type of Turing system: in ruggae Fgf and Shh act as the activator and inhibitor respectively (A and I), while in lung branching the same pairs acts as the substrate and activator (S and A) of a SD model (Figure 1). If correct, this means that Shh is autoactivating in lung development, but auto-repressing in ruggae.

It is quite likely that some of our current 2-species models are too abstract, and miss relevant molecular components. Interestingly, the recent theoretical analysis of an 'Eda-Bmp' hair follicle patterning model [25•] went a step further in making a more realistic model, but in doing so showed that this system exhibits an unexpected temporal instability. However, the difficulty in building successful detailed models will in fact be one of the greatest aides in revealing the relevant design constraints, and thus helping us to identify the relevant and necessary Turing molecules. This theoretical gap between abstract models and the molecular reality might explain why in some examples (such digit patterning) it has not yet been possible to find the Turing pair. A second reason may be related to fish stripe patterning — that a more complex patterning process (involving cell movement rather than molecular reaction–diffusion) may sometimes exhibit spatiotemporal dynamics almost identical to a much simpler Turing model. We thus expect that future work may have to consider more complex Turing models involving more than 2 genes, with more detailed information about the spatiotemporal dynamics of the patterning process.

In summary, after many years as a neglected hypothesis, Turing-type reaction–diffusion models are now being taken more seriously by mainstream developmental biology. This is partly a reflection of the increased integration of theoretical and experimental approaches in biology, as Turing models were traditionally the domain of mathematicians, while experimentalists tended to prefer the more intuitive concept of positional information. This increased interest in Turing models is resulting in a wider range of model systems being studied, and the field is now growing to include more structural examples (lungs, ruggae and digits) in addition to the more traditional models of coat colour patterns. It is gradually becoming clearer that the relevance of Turing patterns is not restricted to the zebra's stripes, but will increasingly explain 'the horse part' as well.

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