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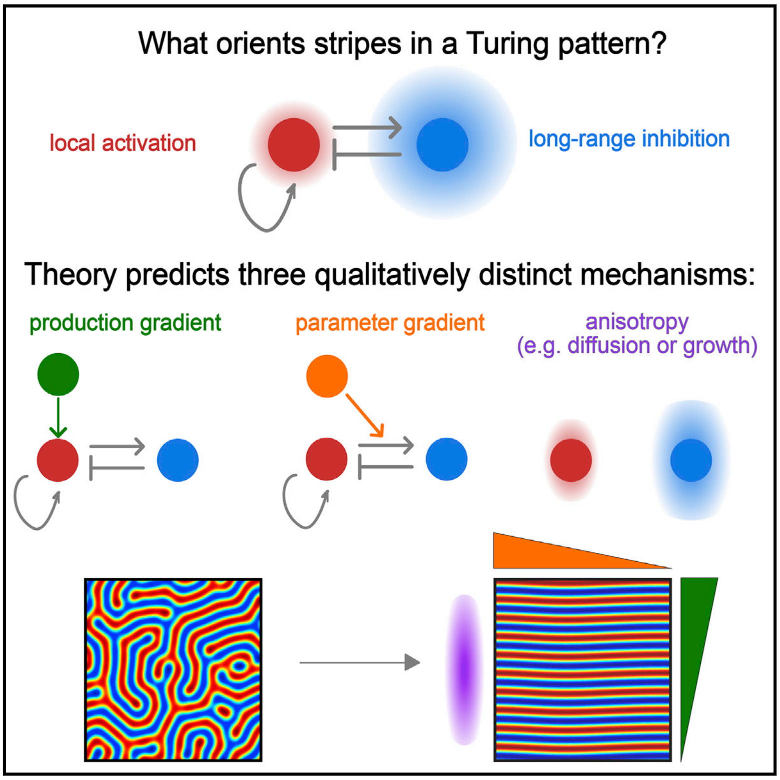
Orientation of Turing-like Patterns by Morphogen Gradients and Tissue Anisotropies

Graphical Abstract



Highlights

- A simple model predicts three ways to orient the direction of Turing stripes
- These are gradients in production rates or in model parameters and anisotropies
- The simple model predicts stripe orientation in a range of more complex models

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In Brief

How do developmental programs ensure that striped patterns always point in the same direction (e.g., what makes the fingers form parallel to the arm)? We use a simple model of Turing stripe formation to predict three distinct ways to orient stripes that apply to a wide variety of biological mechanisms.

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Orientation of Turing-like Patterns by Morphogen Gradients and Tissue Anisotropies

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SUMMARY

Patterning of periodic stripes during development requires mechanisms to control both stripe spacing and orientation. A number of models can explain how stripe spacing is controlled, including molecular mechanisms, such as Turing's reaction-diffusion model, as well as cell-based and mechanical mechanisms. However, how stripe orientation is controlled in each of these cases is poorly understood. Here, we model stripe orientation using a simple, yet generic model of periodic patterning, with the aim of finding qualitative features of stripe orientation that are mechanism independent. Our model predicts three qualitatively distinct classes of orientation mechanism: gradients in production rates, gradients in model parameters, and anisotropies (e.g., in diffusion or growth). We provide evidence that the results from our minimal model may also apply to more specific and complex models, revealing features of stripe orientation that may be common to a variety of biological systems.

INTRODUCTION

Periodic patterns are found in a wide variety of different organisms, forming across a large range of time and length scales. Well-studied examples include the regular spacing of villi in the gut (Shyer et al., 2013), hair follicle patterning on mammalian skin (Sick et al., 2006; Mou et al., 2006), the formation of regularly spaced digits in the limb (Sheth et al., 2012), branching morphogenesis in the lung (Menshykau et al. (2014), and pigmentation patterns in a variety of animals (Kondo and Asal, 1995; Nakamasu et al., 2009; Yamaguchi et al., 2007; Frohnhöfer et al., 2013).

A number of different models have been proposed to explain the formation of these periodic patterns, most notably Turing's "reaction-diffusion model," in which periodicity is generated molecularly (Kondo and Miura, 2010). The canonical reaction-diffusion model involves two diffusing molecules: a rapidly diffusing inhibitor molecule and a slowly diffusing activator molecule. Provided that the activator stimulates production of both itself and its inhibitor sufficiently strongly, and that the inhibitor diffuses sufficiently more rapidly than the activator, periodic patterns can spontaneously emerge from an initially homogeneous pattern (termed a Turing instability) (Turing, 1952).

Despite the prominence of molecular-level reaction-diffusion models, there are many other ways to generate periodic patterns—or, to put it mathematically, many other systems that exhibit Turing instabilities. These include more complex molecular circuits but importantly also a number of cell-based and mechanical models, which can recapitulate periodic patterning in silico (Maini et al., 1991; Hiscock and Megason, 2015; Murray and Oster, 1984b; Murray et al., 1988; Myerscough et al., 1998; Lubensky et al., 2011). The logic of each of these models is similar, but the underlying biology is different. For example, a reaction-diffusion model uses a short-ranged activator and a long-ranged inhibitor to generate a periodic pattern. An analogous cell-based model would be where cells signal to each other, using a short-ranged pro-mitotic signal, and a long-ranged anti-mitotic signal. Similarly, a mechanical model where a tissue buckles into a periodic shape consists of a short-ranged mechanical interaction—resistance to bending—and a long-ranged mechanical interaction—compression of the tissue.

Since the logic of each of these mechanisms is similar, it can be difficult to experimentally distinguish them (Hiscock and Megason, 2015). Furthermore, there is increasing evidence that cellular and mechanical processes are relevant in vivo. For example, a combination of cell-movement, cell proliferation, and signaling via long, cellular protrusions has been shown to be important in patterning the stripes on the zebrafish skin (Hamada et al., 2014; Yamanaka and Kondo, 2014). Equally, tissue mechanics has been strongly implicated in forming regularly spaced villi during growth of the gut (Shyer et al., 2013). Thus, a variety of models—spanning molecular, cellular, and/or mechanical processes—must be considered if we are to understand general properties of periodic patterning.

One property that has so far received little attention and forms the focus of this work is pattern orientation. Here, we focus our discussion exclusively on striped as opposed to spotted periodic patterns, since stripe orientation is more apparently functional. As an example, stripes in animal pigment patterns often have a stereotyped direction; e.g., wild-type zebrafish have stripes parallel to their long axis during normal development. However, during aberrant patterning, for example, when the pattern regenerates after damage (Yamaguchi et al., 2007), or when the pattern proceeds in the absence of some organizing signal (Frohnhöfer et al., 2013), the tight regulation of pattern orientation is impaired (Figure 1).

Several mechanisms have previously been proposed to control stripe direction. First, if the initial condition of the pattern is a single stripe, then subsequent stripes will tend to form parallel