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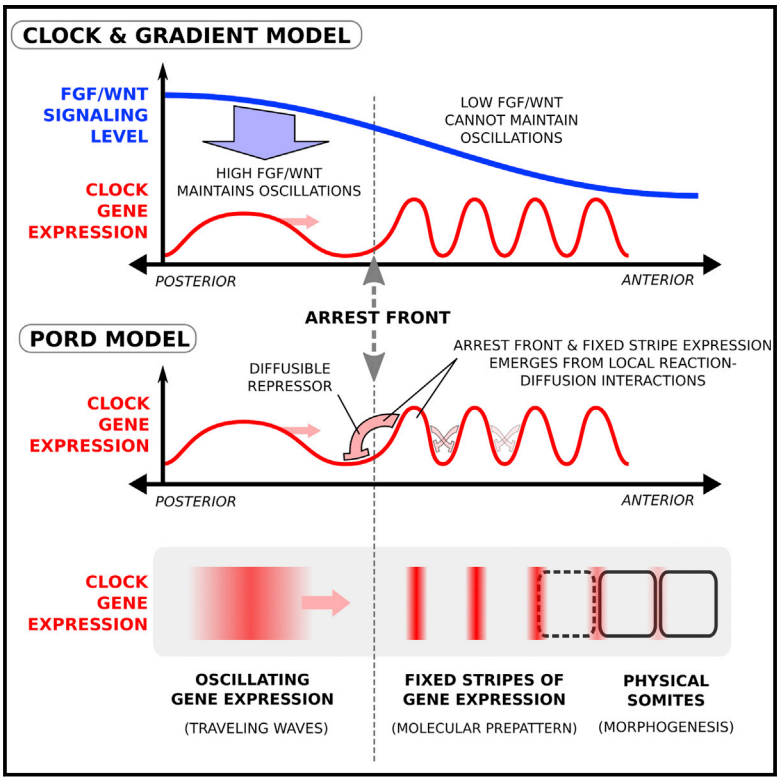
Cell Systems

A Local, Self-Organizing Reaction-Diffusion Model Can Explain Somite Patterning in Embryos

Graphical Abstract



Highlights

- A systematic computational screen identifies networks based on behavior
- Computation shows that somitogenesis can be explained by short-range interactions
- Short-range and long-range models are tested head-to-head in silico and in vivo
- Short-range models explain aspects of somitogenesis that previous models cannot

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In Brief

Using a systematic computational approach and in vivo experiments, Cotterell et al. challenge a 40-year-old model that explains large-scale embryonic patterns in terms of long-range gradients. Instead, they show that these patterns can arise from short-range interactions and that a modified reaction-diffusion mechanism can drive the self-organization observed during somitogenesis.

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A Local, Self-Organizing Reaction-Diffusion Model Can Explain Somite Patterning in Embryos

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SUMMARY

During somitogenesis in embryos, a posteriorly moving differentiation front arrests the oscillations of "segmentation clock" genes, leaving behind a frozen, periodic pattern of expression stripes. Both mathematical theories and experimental observations have invoked a "clock and wavefront" model to explain this phenomenon, in which long-range molecular gradients control the movement of the front and therefore the placement of the stripes in the embryo. Here, we develop a fundamentally different model—a progressive oscillatory reaction-diffusion (PORD) system driven by short-range interactions. In this model, posterior movement of the front is a local, emergent phenomenon that, in contrast to the clock and wavefront model, is not controlled by global positional information. The PORD model explains important features of somitogenesis, such as size regulation, that previous reaction-diffusion models could not explain. Moreover, the PORD and clock and wavefront models make different predictions about the results of FGF-inhibition and tissue-cutting experiments, and we demonstrate that the results of these experiments favor the PORD model.

INTRODUCTION

During the development of all vertebrate embryos, the presomitic mesoderm (PSM), which lies on either side of the neural tube, is progressively segmented from anterior to posterior (from approximately day 1 to day 3 in the chick embryo) into a series of transient epithelial balls called somites, which later give rise to vertebrae, muscle blocks, and skin. This physical "budding" process is prefigured by a molecular patterning process that sequentially produces stripes of gene expression along the PSM, again in an anterior-to-posterior sequence (for example *Lfng*); each stripe of expression will, in future, correspond to a subsequent somite boundary. The control of this molecular segmentation process has been a paradigmatic example of pattern formation for the last 50 years and as such has a long conceptual history of proposed underlying mechanisms (Kulesa et al., 2007). These expression stripes are very regular in size and are widely believed to result from the interaction of two dynamical systems. First, cells of the PSM exhibit oscillations of gene expression—mostly components of the Notch signaling pathway (Palmeirim et al., 1997; Forsberg et al., 1998; McGrew et al., 1998; Aulehla and Johnson 1999; Holley et al., 2000; Jouve et al., 2000; Jiang et al., 2000; Sawada et al., 2000; Bessho et al., 2001a, 2001b; Oates and Ho, 2002). Along the PSM, these oscillations are spatially organized into traveling waves, but this feature is not important for the questions or models discussed here. The important feature is that the oscillations are locally well synchronized: neighboring cells are in very similar phases of the cycle. Second, these oscillations are arrested in an anterior-to-posterior progression. The position where oscillations are frozen travels posteriorly through the PSM (thus prefiguring the progression of morphological segmentation itself). This traveling position is called the arrest front (Herrgen et al., 2010). It is widely believed that the moment when cells stop oscillating is when their fate has become committed to a given part of a presumptive somite. The progressive freezing of the oscillations effectively transforms a temporal oscillation into a spatial periodicity. (The distinction between the definitions of the *arrest front* and the *determination front* is addressed in the discussion below).

Our study focuses on how the posterior movement of the arrest front is controlled (rather than the oscillations). Currently prevailing models to explain the arrest front focus on large-scale morphogen gradients. Both FGF and WNT signaling display long spatial gradients with highest levels observed in the embryo's posterior (Dubrulle et al., 2001; Dubrulle and Pourquié, 2004; Sawada et al., 2001; Aulehla et al., 2003). As the tailbud elongates due to growth, the gradients travel posteriorly through the PSM (probably involving progressive decay of mRNA rather than diffusion; Dubrulle and Pourquié, 2004) and a given signaling intensity therefore moves at the same velocity as overall growth of the tissue (Figure 1A). Because molecular oscillations are only seen posteriorly to the arrest front, it is proposed that morphogen signaling has the role of maintaining the oscillations and that arrest occurs once signaling drops below a certain level. Support for this idea has come from experimentally inhibiting and enhancing FGF signaling, both globally and locally, resulting in somite size changes that are consistent with this hypothesis (Dubrulle et al., 2001; Sawada et al., 2001; Naiche et al., 2011). For example, a sudden but transient global reduction in FGF signaling (using the inhibitor SU5402)