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The clock and wavefront model revisited

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ABSTRACT

The currently accepted interpretation of the clock and wavefront model of somitogenesis is that a posteriorly moving molecular gradient sequentially slows the rate of clock oscillations, resulting in a spatial readout of temporal oscillations. However, while molecular components of the clocks and wavefronts have now been identified in the pre-somitic mesoderm (PSM), there is not yet conclusive evidence demonstrating that the observed molecular wavefronts act to slow clock oscillations. Here we present an alternative formulation of the clock and wavefront model in which oscillator coupling, already known to play a key role in oscillator synchronisation, plays a fundamentally important role in the slowing of oscillations along the anterior–posterior (AP) axis. Our model has three parameters which can be determined, in any given species, by the measurement of three quantities: the clock period in the posterior PSM, somite length and the length of the PSM. A travelling wavefront, which slows oscillations along the AP axis, is an emergent feature of the model. Using the model we predict: (a) the distance between moving stripes of gene expression; (b) the number of moving stripes of gene expression and (c) the oscillator period profile along the AP axis. Predictions regarding the stripe data are verified using existing zebrafish data. We simulate a range of experimental perturbations and demonstrate how the model can be used to unambiguously define a reference frame along the AP axis. Comparing data from zebrafish, chick, mouse and snake, we demonstrate that: (a) variation in patterning profiles is accounted for by a single nondimensional parameter; the ratio of coupling strengths; and (b) the period profile along the AP axis is conserved across species. Thus the model is consistent with the idea that, although the genes involved in pattern propagation in the PSM vary, there is a conserved patterning mechanism across species.

1. Introduction

Somitogenesis is the highly robust process by which the vertebrate trunk is divided into a series of segments called somites (Gilbert, 1997). Somite formation, which occurs rhythmically from the pre-somitic mesoderm (PSM) in a strict anterior–posterior (AP) sequence, is coincident with PSM growth (Gomez and Pourquié, 2009). As the process of somitogenesis evolves in time, mesenchymal cells in the posterior PSM differentiate into epithelial cells in a strict spatio-temporal manner (Dequéant and Pourquié, 2008). Hence, a posteriorly moving wave of differentiation is observed (see Fig. 1). One of the key challenges in somitogenesis research is to understand the mechanisms governing the spatio-temporal propagation of this wave of differentiation. Each cell in the PSM has a segmentation clock whose oscillation frequency is dependent on its relative position along the AP axis (Dequéant et al., 2006). Oscillations in the posterior PSM occur at an approximately constant rate corresponding to the frequency at which somites form (Schröter et al., 2008) but, as the wave of differentiation moves along the PSM, the oscillation frequency of a given cell decreases; somite formation occurs at the spatial position where the oscillations cease. When oscillating components of the somitogenesis clock are examined using techniques such as *in situ* hybridisation (see Fig. 1), stripes of gene expression, arising as a result of the variable oscillation frequency along the AP axis, are observed moving anteriorly (Giudicelli et al., 2007). The number of stripes varies between species (Gomez et al., 2008).

Numerous genes and proteins that oscillate at the rate at which somitogenesis proceeds have been identified across a number of species. In zebrafish, all known oscillating molecules are downstream regulators of the Notch–Delta signalling pathway (Dequéant and Pourquié, 2008) and it is thought that delayed negative feedback (*i.e.* a given protein inhibits the expression of its corresponding gene with a delay resulting from transcription and translation) plays a fundamental role in regulating the somitogenesis clock (*e.g.* Monk, 2003; Lewis, 2003; Giudicelli et al., 2007). One role of Notch–Delta signalling is to synchronise neighbouring molecular clocks (Horikawa et al., 2006). However,

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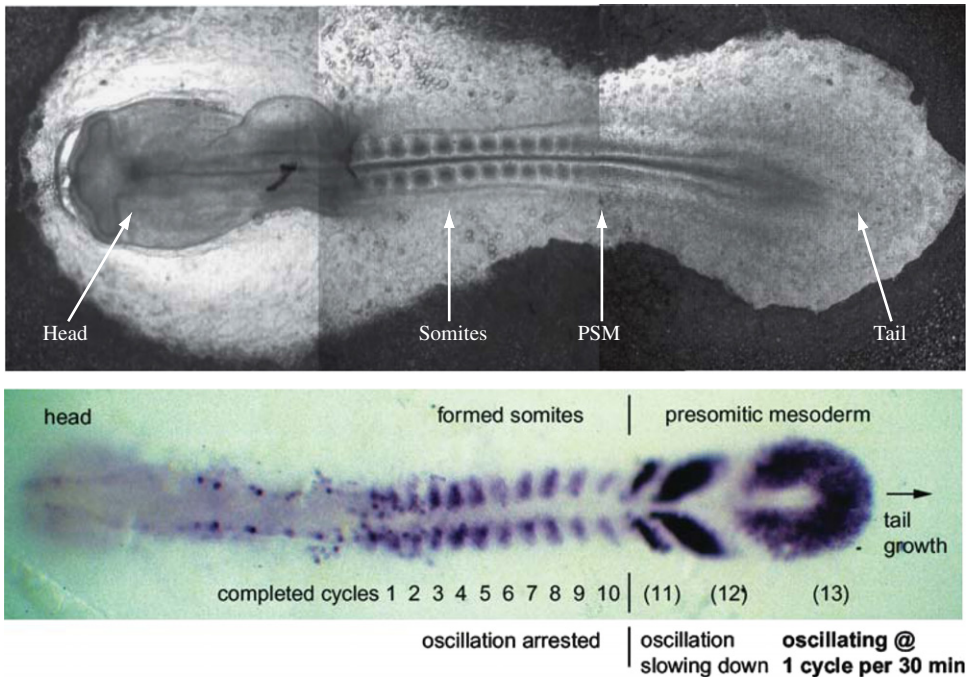

Fig. 1. Top: sequential somite formation in the chick PSM. Image supplied by kind permission of Paul Kulesa, Stowers Institute for Medical Research. Bottom: patterns of gene expression in the zebrafish PSM illustrated via *in situ* hybridisation (Giudicelli et al., 2007).

perturbations in the Notch–Delta signalling pathway also influence somite length and oscillation period (Herrgen et al., 2010).

Molecular gradients that travel along the AP axis have been hypothesised to be manifestations of the wavefront of differentiation (Dubrulle et al., 2001). In zebrafish, Fgf mRNA is produced only in the posterior PSM. As these molecules have relatively short protein half-lives, gradients are, therefore, established along the AP axis that are fixed with respect to the regressing tail of the embryo. However, a causal relationship between the observed travelling gradients and regulation of the cellular oscillations has yet to be established. Detailed quantitative measurements of somitogenesis at the cellular scale and above have recently been undertaken. Giudicelli et al. (2007) have measured the distance between the anteriorly moving stripes of gene expression in zebrafish, Gomez et al. (2008) have made similar measurements in snake, as well as measuring the length of the PSM as somitogenesis progresses; Schröter et al. (2008) have quantified the variation in somite length and oscillator period as somitogenesis proceeds: the former is temperature compensated while the latter decreases with temperature. Herrgen et al. (2010) and Schröter and Oates (2010) have measured relative variation in somite length and oscillator period in somitogenesis mutants. These relatively recent data provide a means of quantitatively testing mathematical models of somitogenesis, of which there is a relatively long history.

Cooke and Zeeman (1976) proposed a 'clock and wavefront' model in which cellular clocks and a moving gradient determined 'when' and 'where' somites form, respectively. The discovery of the molecular components of the somitogenesis clock and moving molecular gradients added significant experimental backing to this model. Baker et al. (2008) considered partial differential equation (PDE) models which phenomenologically incorporated both the travelling wavefront and cellular oscillations. These models were derived at the cell population scale and aimed to relate a coarse-grained description of cell–cell communication mechanisms to the formation of pattern. In recent years, given the discovery of molecular clocks and gradients, mathematical models of somitogenesis have focused on capturing the underpinning molecular mechanisms. For example, Lewis and coworkers (Lewis, 2003; Giudicelli et al., 2007) have developed and parameterised models of the molecular clock in zebrafish. These models were applied in a multicellular context by Horikawa et al. (2006), who considered a 1D chain of somitogenesis oscillators coupled together via Notch–Delta signalling. By treating oscillator phase as the dependent variable, Morelli et al. (2009) and Herrgen et al. (2010) have developed a model of intermediary scale between the phenomenological models considered by Cooke and Zeeman (1976) and Baker et al. (2008), and the molecular model considered by Horikawa et al. (2006).

A common feature of models attempting to capture the patterning of stripes and somite formation along the AP axis is that a travelling wavefront of differentiation is assumed to exist *a priori* (Tiedemann et al., 2007; Giudicelli et al., 2007; Baker et al., 2008; Morelli et al., 2009; Herrgen et al., 2010). The characteristics of the wavefront, such as the wave speed and profile, are, therefore, inputs which are crucial to the properties of the emergent patterning behaviour of the respective models. While this modelling assumption is validated, to a certain extent, by observations of travelling molecular gradients of morphogens, such as Fgf and Wnt (Dubrulle et al., 2001), there is not yet definitive evidence that demonstrates a causal relationship between the propagation of the wavefronts and the slowing of cellular oscillations.

1.1. Outline

In this paper we consider a continuum model of a population of somitogenesis oscillators. We focus solely on building a model which accounts for the evolution of a prepattern that determines the positions at which somites form. Our model demonstrates that oscillator coupling is sufficient to establish the emergent patterns observed in somitogenesis. Moreover, a travelling wave that slows cellular oscillations is an emergent property of the model. As the model is mathematically tractable, we derive expressions for the velocity of the travelling wavefront and its profile. We parameterise the model using experimentally known quantities and subsequently make a number of predictions that are in agreement with available experimental data. The layout of the paper is as follows: in Section 2