Reaction-diffusion scheme for the "clock and wavefront model" of vertebrae formation

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At an early stage of development, the anterior-posterior body axis of a vertebrate embryo is divided into segments called somites, which give rise to the periodic pattern of vertebrae. They are formed one after another starting from the anterior end of the embryo, with each new one directly caudal to the previous one. In spite of intensive efforts, mechanism of this spontaneous periodic segmentation remains a matter of debate.

Cell differentiation is controlled by concentration of signaling molecules, called morphogens. In vertebrate embryos, a wave front of antagonistic morphogens is propagating from the anterior towards the posterior end. Moreover, time oscillations of gene expression are observed in the undifferentiated tissue ahead of the front, called presomitic mesoderm (PSM). These two phenomena are the key ingredients of the "clock and wavefront" model of somitogenesis. It postulates that oscillations in PSM cells are synchronised and arrest upon arrival of the wave front. Therefore stationary local concentrations behind the front are determined by the phase of oscillation at the moment of its arrival. This gives rise to a periodic spatial pattern which then induces cell differentiation according to local morphogen concentration. So far, theoretical investigations into this model were based on postulated deterministic equations. Internal noise is suspected to play a significant role in prevertebrae formation due to small morphogen populations, but lack of microscopic foundation of the model has prevented studies of intrinsic fluctuations.

We designed a minimal reaction-diffusion model capable of reproducing the "clock and wavefront" behavior. It consists of two interconnected blocks. One is a two-variable bistable system that models propagation of the antagonistic wave front. The other is a different two-variable system which can be either oscillatory or multistable, depending on position of the wave front. Results of numerical integration of the reaction-diffusion equations are in agreement with the "clock and wavefront" model, i.e. temporal oscillations of species concentrations are observed ahead of the wave front while behind it a stable, spatially periodic structure emerges.

In order to study internal fluctuations, we wrote a chemical master equation and ran kinetic Monte Carlo simulations based on it. They have shown that synchronization of oscillations in nearby cells is necessary for formation of regular somites. To introduce this synchronization, we extend the "clock and wavefront" model by adding a bistable internal state of a cell. Simulations show that this extended model is capable of producing a spatially periodic pattern of concentrations even when fluctuations are taken into account.

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