Vertebrate segmentation: A test case for a cell-based multi-cell, multi-scale modeling approach

Somitogenesis, the formation of the primary segmental structure of the vertebrate body plan, requires coordination between biological mechanisms at several scales. Understanding how these mechanisms interact across scales and how events are coordinated in space and time is necessary for a complete understanding of somitogenesis, including its evolutionary flexibility and how we can best apply observations at single scales and in different species to understanding, preventing and one day treating somitogenesis defects in humans.

So far, mechanisms of somitogenesis have been studied independently. To test the consistency, integrability and combined explanatory power of current prevailing hypotheses, we built a composite clock and wavefront model including submodels of the intracellular segmentation clock, intercellular segmentation clock coupling via Delta/Notch signaling, an FGF8 determination front, delayed differentiation, clock-wavefront readout and differential cell-cell adhesion-driven cell sorting. We identify inconsistencies between existing submodels and gaps in the current understanding of somitogenesis mechanisms, and propose novel submodels and extensions of existing submodels where necessary. 2D simulations of our model with modest initial conditions robustly generate spatially and temporally regular somites, realistic dynamic morphologies and spontaneous emergence of traveling stripes of Lfng. Our model is flexible enough to generate interspecies-like variation in somite size in response to changes in PSM growth rate and segmentation clock period, and in the number and width of Lfng stripes in response to changes in PSM growth rate, segmentation clock period and PSM length.