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Multi-cell, Multi-scale Models of Vertebrate Somitogenesis

Somitogenesis is an early developmental process that establishes the first signs of segmentation in all vertebrates, patterning the precursors of the vertebrae, ribs, and skeletal muscles of the back and limbs. This process requires coordination between biological mechanisms at several scales, ranging from genetic regulatory networks to structural changes at the tissue level. Understanding how these mechanisms interact across scales and how events are coordinated in space and time is necessary for a complete comprehension of somitogenesis, including its evolutionary flexibility and how we can best apply observations at single scales and in different species to understand, prevent and one day treat somitogenesis defects in humans. So far, mechanisms of somitogenesis have been studied independently, leading to a scattered set of single-scale models. To test the consistency, integrability and combined explanatory power of current prevailing hypotheses, we built a multi-cell composite clock-and-wavefront model that includes submodels of the intracellular segmentation clock, intercellular 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 models with reasonable 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 Wnt3a levels. To our knowledge, our work presents the first embryogenesis model to successfully combine such a broad range of scales and mechanisms, representing an important step in predictive developmental modeling. The model is modular in nature, which will allow technically straightforward model extensions and comparisons between sets of hypothesized mechanisms and interactions.