Modeling of the Interaction of Oscillatory Networks and Biomechanics in Somitogenesis

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***Short Abstract* — Somitogenesis is regulated by a subcellular regulatory network clock and a tissue-scale wavefront. We present here an extension of the Goldbeter and Pourquié clock with reinforced connectivity between the three oscillatory network pathways and a Delta/Notch cell-cell synchronization mechanism. We couple each clock to the local external environment through FGF/Wnt signaling and integrate with a multi-cell GGH simulation using CompuCell3D. Our model is able to reproduce many developmental events, including cell-cell synchronization, somite segmentation and epithelialization. We are presently working to expand it to three dimensions and to predict the effects of perturbation experiments.**

***Keywords* — Development, Somitogenesis, Gene pathways, Synchronization, Modeling, Biophysics, GGH model.**

SOMITOGENESIS is the first segmentation process to happen in the development of vertebrate embryos. It takes place right after gastrulation, when an internal tissue layer (the mesoderm between the hypoblast and the epiblast) undergoes a series of cleavage cycles that give rise to structures called somites. It is from these that the vertebrae, the dorsal skin and many muscles will be generated.

Past research on this subject can be divided into three main categories, which also correspond to different length scales: i) the *embryo/tissue scale* which describes the temporal sequence of morphological events [1] and chemical gradients inside the tissue [2]; ii) the *cellular scale*, which deals with mechanical cell-cell/matrix interactions [3,4] as well as signaling events [5]; and iii) the *subcellular scale* where genetic regulation [6] and protein expression [7] are taken into account. Although all these aspects are relevant, our current understanding of somitogenesis is still largely segregated between these domains, with less interconnection than is needed for a full understanding of the phenomenon.

Our aim is to develop a three-dimensional mathematical model that will take into account all these facets without overemphasizing one scale to the detriment of another. To do this we use the CompuCell3D environment [8], which allows us not only to describe multiple cells with distinct properties, but also to assign to each of them an internal set of ODEs that represents the putative pathways that regulate secretion and subsequent diffusion of chemicals within the tissue and ultimately determine the behavior and fate of the cells. This approach will allow us to check the internal consistency of the many single-scale theories as well as to identify and fill missing links between scales.

In our simulations the pre-somitic mesoderm cells are generated from a growing layer of source cells that represents the tailbud. Each daughter cell inherits an internal clock that is an extended version of the one proposed by Goldbeter and Pourquié [6] altered to include a Delta/Notch synchronization mechanism [5] and reinforced connections between the three oscillatory pathways (Fgf, Wnt and Notch). Cells also produce an fgf8 signal from a decaying intial mRNA level that gives rise to the wavefront gradient. When this signal decays below a threshold, cells initiate segmentation by changing their adhesive properties according to their clock phase.

Our preliminary results in two dimensions [9] reproduce many developmental events *in silico* including cell-cell synchronization, the cascade of events leading to epithelialization of cells and correction of errors due to noise and/or cell misplacement. We are presently working to model simulated perturbation experiments. This comprehensive model will help us to understand how birth defects associated with segmentation happen (like alagille syndrome) and also provide the foundation for further multiscale modeling of later developmental events.

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