Biocomplexity researchers announce multi-scale model of early embryonic development in vertebrates

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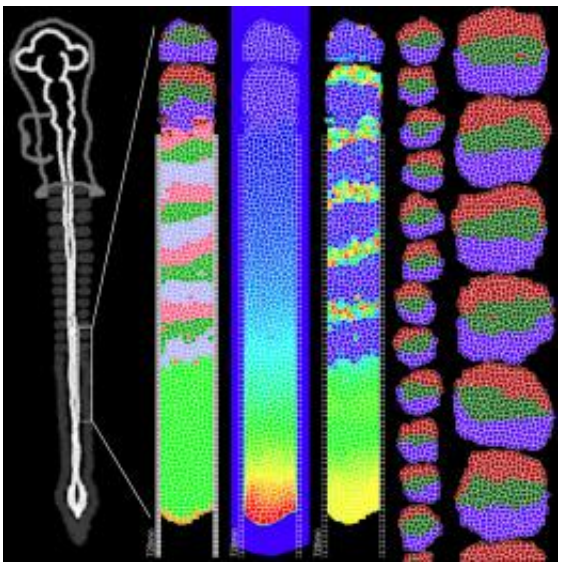

Simulations reproduced features of somitogenesis involving mechanisms at different scales. Depicted, from left, sketch of a dorsal view of a chicken embryo, simulations of dynamic morphology and cell rearrangements during somite formation, evolving patterns of diffusible extracellular Fgf8 protein signaling (blue to red, from top), intracellular Lfng gene expression (blue to yellow, from top), and interspecies-like variation in somite size and frequency of formation. White borders represent cell boundaries, cells prior to somite formation are light green, somites and forming somites anterior, posterior and core compartments are represented by red, blue and green, respectively. Orange cells account for addition of new cells prior to somite formation.

(PhysOrg.com) -- Scientists at Indiana University's Biocomplexity Institute have developed a computational model for the intricate cellular dance that occurs during the earliest stages of animal development when embryonic segments called somites form. Somites eventually give rise to the internal scaffolding of life: For common earthworms that scaffolding is 100 or so body segments; in humans it's a segmented mass of cell layers in the early embryo that leads to the formation of muscles, vertebrae, limbs, ribs and the tailbone.

By developing a unified, multi-scale model of somitogenesis -- a process that establishes the earliest evident segmentation in vertebrate embryos -- both a case study for other scientists creating similar predictive, informative multi-scale models of development and important insights into the vertebrate body plan and its evolution have been achieved, according to Biocomplexity Institute Director James Glazier. Glazier is also a professor in the IU Bloomington College of Arts and Sciences' Department of Physics.

"The striking timing and dynamic structures involved in somitogenesis depend on mechanisms operating across a range of scales, as well as interactions between scales," Glazier said referring to a host of mechanisms that occur from the subcellular to the tissue scale. "The adaptability of segment number and size has been key to the evolution of varied body plans throughout history, and it's the nature of this robust plasticity that we are trying to learn more about. Evolvability requires a mechanism that is robust to changes in somite number and size.

"Previous work has been suggestive, but has never examined whether the interaction of molecular regulation and tissue-level structure was robust enough to provide such plasticity. Our current work shows that this interaction is that robust," he said.

Taking insights from the Cook and Zeeman Clock-and-Wavefront model

from the 1970s that showed organisms make segments one at a time and add them on to the tail end of the embryo, the researchers generated two-dimensional simulations of somite generation at regular intervals in time and space for a chicken embryo. Chick embryos have 52 pairs of somites, with a new pair formed every 90 minutes; humans have 33 somite pairs, with a pair formed every 90 minutes; mice have 65 pairs, with a pair formed every 120 minutes.

"Surprisingly, the molecular mechanism that generates somites makes quite a few mistakes," Glazier said. "Biophysical processes like differential adhesion then help clean up these mistakes, but they aren't perfect."

When those biophysical processes fail, the results can be devastating: While nearly 8 percent of humans can easily accommodate 13 pairs of ribs, rather than the normal 12 pairs, 1 percent have an extra cervical vertebrae and may face distressing, sometimes incurable, health issues.

"From a medical point of view, while many defects in segmentation result in the death of the embryo by miscarriage, others can lead to congenital scoliosis," Glazier said. "A number of other, less common, congenital diseases can also result from segmentation defects."

Since segmentation occurs very early in development, when a mother often doesn't yet know she's pregnant and should avoid medications and alcohol, segmentation failure resulting from genetic conditions or from exposure to toxins or medicines during early pregnancy can have devastating results.

"By understanding how perturbations at a single scale propagate to other scales will be essential to evaluating whether the perturbations are likely to have therapeutic or dangerous effects," Glazier pointed out. "While such powerful predictive tools are still some way in the future, they will

only be possible with the aid of flexible, well-crafted, well understood multi-scale models."

By combining specialized hypotheses for specific subcomponent mechanisms of somitogenesis, the researchers were able to create a model robust and flexible enough to describe the process in animals as different in size, shape and gestation time as chickens, garden snakes, mice and zebrafish. The model was simulated in the Glazier-Graner-Hogeweg (GGH)-model-based CompuCell3D (CC3D) simulation environment, which reproduced spatially and temporally regular formation of an unlimited number of somites.

More information: Lead author on the paper, "A Multi-cell, Multi-scale Model of Vertebrate Segmentation and Somite Formation," which appeared online earlier this month in *PLoS Computational Biology*, was former IU Ph.D. student Susan D. Hester (now a postdoctoral researcher at the University of Arizona). Co-authors were Ph.D. student Julio M. Belmonte, research associate J. Scott Gens, research scientist Sherry G. Clendenon and Glazier.

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