A Computational Model for Biomechanical Analysis of Bone Formation in the Cranial Vault

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ABSTRACT

Craniosynostosis is a common and complex craniofacial condition (~4 per 10,000 live births) that imposes a substantial financial and emotional burden on patients and their families. Craniosynostosis is a condition defined by premature closure of cranial vault sutures, which is associated with abnormalities of the brain and skull. Many causal relationships between discovered mutations and premature suture closure have been proposed but an understanding of the precise mechanisms remains elusive.

This research develops a computational framework of biological processes underlying cranial growth that will enable a hypothesis driven investigation of craniosynostosis phenotypes. Bones of the cranial vault are formed by the differentiation of mesenchymal cells into osteoblast cells on a surface that surrounds the brain, eventually forming mineralized bone. Signaling pathways causative for the cell differentiation start from some actions of extracellular proteins driven by information from genes. We assume that the interaction of cells and extracellular molecules which are associated with cell differentiation can be modeled using Turing's reaction-diffusion model, which is a mathematical model for pattern formation controlled by two interacting molecules (activator and inhibitor). In this study we hypothesize that regions of high concentration of an activator develop into primary centers of ossification, the earliest bone. In addition to the Turing model, we use another diffusion model dealing with a morphogen associated with bone growth from the primary ossification centers. Effects of mechanical stimuli due to brain growth underlying cranial vault are considered to elucidate the mechanism of growth of cranial vault.

These mathematical models were solved using the finite volume method. The computational domain and model parameters are determined using a large collection of experimental animal models. The results show that the five ossification centers that form in our model occur at the same position as those identified in experimental data. As bones grow from these ossification centers, sutures form between the bones. This study may help uncover fundamental mechanisms associated with birth defects such as craniosynostosis as well as answer basic questions in developmental biology.

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