**Title:** Incorporating Mechanical Feedback and Mediation of Biochemical Factors in Mechanistic Models of Tissue Genesis by Stem Cells

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Mechanobiological stimuli are known to modulate tissue genesis and healing, yet underlying mechanisms of the process are not yet well understood. This provided the impetus for us to develop a mechanistic, mathematical model to predict the dynamics of tissue genesis by stem cells. This model describes experimental studies of a long bone defect surrounded by periosteum and stabilized via an intramedullary nail. This experimental platform provides controlled boundary and initial conditions and well-characterized healing outcomes. Based on experimental data, the emergent material properties and mechanical environment of the healing callus contribute to the strain stimulus sensed by progenitor cells within the periosteum. A mechanical, finite element model predicts periosteal surface strains as a function of emergent callus properties. Calculated strains are inputs to a mechanistic, multicellular-tissue model in which mechanical regulation of BMP-2 production mediates rates of cellular proliferation, differentiation and tissue production. This model consisting of nonlinear differential and algebraic equations is solved numerically to simulate cellular dynamics and tissue generation. It predicts the spatial and temporal generation of endochondral tissue measured as areas of cartilage and mineralized bone. The development of cartilage and mineralized bone vary with radial distance from the periosteum and time. Model predictions compare well with histological outcomes indicated by patterns of bone tissue regeneration. Our modeling of a mechanistic feedback system based on the mechanosensitivity of periosteal progenitor cells allows for prediction of tissue regeneration on multiple length and time scales. This model platform based on biological, computational, and engineering concepts allows quantitative, in silico hypothesis testing to elucidate conditions conducive to endogenous tissue genesis.