Development Of Adaptive, Cell-Based Fuzzy Logic Controllers to Predict Bone-Tendon Ingrowth on Functionally Graded Scaffolds

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Disclosures: NONE

INTRODUCTION: Surgical repairs of the rotator cuff (RC) often fail (>20%); even when augmented with bioinspired patches or scaffolds to improve healing. Tissue analysis of repaired tissue demonstrates the RC's lack of regenerative capacity and tendency to replace the native gradient, or enthesis, with biomechanically weak scar tissue. Highlighting that current scaffolds are providing inadequate cues to regenerate the graded tissue across the enthesis. Consequently, our group has fabricated melt-electrowritten (MEW) scaffolds that can approach the change in elastic modulus observed in a healthy human rotator cuff, through an elegant, curved architecture. Initial computational finite element (FE) work predicted that the scaffold mechanics could drive regional cell growth in the acute phase of healing (Winston, 2025). Despite some scaffolds' early success in predicted tissue ingrowth, these models did not account for how tissue ingrowth would modulate scaffold mechanics and thus change the mechanical microenvironment that was generated in acute healing phases. Therefore, we developed a fuzzy logic controlled, adaptive finite element approach to predict tissue formation within our gradient scaffold. **We hypothesized that modulating local mechanotransducive parameters, specifically strain and hydrostatic pressure, through changes in our curved architectures would optimize collagen synthesis by tenocytes and mineralized matrix deposition by osteoblasts.** This novel fuzzy-FE approach provides a computational framework for screening mechanotransducive scaffolds based on their long-term regenerative capacity.

METHODS: Using our validated parametric FE model, MEW scaffolds were generated *in silico* (Abaqus CAE), altering select print parameters: radius of curvature (R), fiber diameter (FD), and fiber spacing (FS), which have known effects on scaffold mechanics. MEW scaffolds were modeled to be embedded in an alginate hydrogel of varying stiffness (100-10kPa). The scaffold was loaded uniaxially to 4% strain. Element principal strain and hydrostatic pressure were mapped against published strain windows for bone and tendon healing windows (Fig 1A). Elements within the windows were updated with tissue-specific material properties for tendon, scarring, or bone scenarios. Allowing scaffold models to predict N=36 scaffolds' ability to mechanically cater to both bone and tendon during the first thirty days of healing (N=1,080 total simulations).

RESULTS SECTION: Overall maximum bone healing appeared in R=50mm radius scaffolds with a maximum ingrowth of 13.1%. Maximum tendon healing occurred in R=150mm scaffolds with a maximum tendon ingrowth of 52.8%. When examining the scaffolds for their ability to cater to both bone and tendon, R=50mm were the most successful in providing mechanical stimuli for both bone and tendon (13.1% and 32.3% respectively). In contrast, bone growth in higher R=100mm and R=150mm scaffolds were more limited (2.8% and 1.53% respectively). Additionally, R=50 scaffolds began to recapture the gradient in elastic properties seen in the RC across the length of the scaffold with a 450x change in elastic modulus across the length of the scaffold (Fig 1B).

DISCUSSION: Our fuzzy-FE models adapted to tissue formation of multiple tissue types within our gradient scaffold and began to predict the temporal cascade of tissue ingrowth on our scaffold. Our models also predicted a marked difference in tissue ingrowth based on the scaffold geometry, with R=50 mm scaffolds being the best at mechanically instructing the disparate tissue types into regional growth. Our models predicted that R=50 scaffolds would be the best scaffold geometry to move forward with in *in vitro* and *in vivo* testing because of its ability to grow both bone and tendon. While these predictions are valuable, work to verify them will be invaluable in validating that these computational predictions can effectively screen scaffolds prior to benchtop or animal testing.

SIGNIFICANCE/CLINICAL RELEVANCE: To our knowledge, this is the first attempt to bridge multiscale modeling in healing tendon models and apply these methodologies to tune the microenvironment towards tendon regeneration on a scaffold substrate. These processes facilitated the in silico screening of N=36 scaffold architectures prior to implementation in our *in vitro* or *in vivo* platforms and could be a valuable screening platform in the future.

IMAGES AND TABLES:

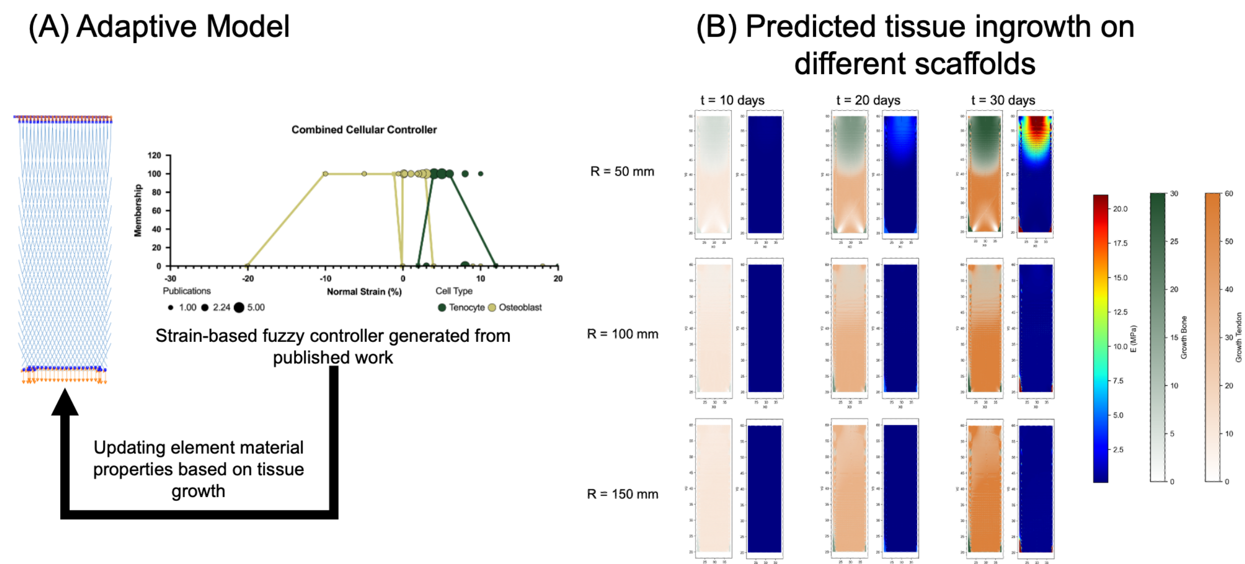

Figure 1 – (A) Flowchart of adaptive modeling with bulk scaffold model being loaded. After FEA simulation strain data is pushed through the fuzzy controllers which dictate element material properties for the next simulation. (B) Results from adaptive scaffold modeling at different radius of curvatures (R). Heatmaps show element modulus of elasticity (E) due to tissue growth in MPa in the rainbow colored scaffold heatmap. Predicted tissue ingrowth is shown in another scaffold heatmap showing green and orange color for bone and tendon ingrowth respectively.