Agent-based model of skeletal muscle tissue predicts immobilization-induced remodeling

Kyle Martin, Shayn Peirce, and Silvia Blemker

Biomedical Engineering, University of Virginia

Introduction: Skeletal muscles adapt through biological and mechanical cues. While numerous experimental studies have captured the dramatic loss of muscle mass as a result of immobilization, no quantitative framework has been developed to explain and explore the mechanisms that govern this process. During muscle immobilization, skeletal muscle fibers and fibroblasts experience restricted mechanical signals. Diminished mechanical activation leads to alterations in the production and secretion of many important proteins, including collagen, IGF, MMP, and TNF-α, which contribute to atrophy and muscle weakness. While in vitro studies have been able to identify individual interactions, our understanding of the micro-environment in vivo during muscle atrophy is limited. The goal of this work is to develop a tissue level agent based model to study muscle adaptations to immobilization.
Methods: In agent-based modeling, agents act independently and stochastically based on rules garnered from literature. Our model includes muscle fibers, fibroblasts, five secreted factors, ECM manipulation, and incorporates rules from 34 papers. We performed simulations absent of mechanical stress and compared our model to results from published measurements of skeletal muscle fiber atrophy in the tibialis anterior due to hindlimb immobilization.
Results: Our model predicted muscle atrophy comparable to literature. We probed the sensitivity of our predictions to the rule that describes the linear relationship between protein degradation and TNF-α signaling. In this example, the baseline relationship was determined from published in vitro studies. Modulating the signaling ratio up and down by 15% resulted in dramatically different outcomes. The 15% increased ratio simulation best matched the published measurements.
Conclusions: Our atrophy simulations suggest that in vitro studies may be underestimating the contribution of TNF-α to muscle atrophy. Moreover, this model provides a “playground” for exploring the key mechanisms that govern muscle remodeling to changes in cellular and mechanical cues. Future advancements of the model will include rules associated with muscle secretions and resident macrophages to predict changes associated with multiple muscle atrophy conditions (including aging, spinal cord injury and spastic muscle), based on which we can probe potential treatments to reduce or ameliorate muscle atrophy.