Texas Tech University
Department of Chemical Engineering
Seminar Series

A macro-micro modeling approach to determine in-situ heart valve interstitial cell contractile behaviors in native and synthetic environments

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Abstract
Mechanical forces are known to regulate valve interstitial cell (VIC) functional state by modulating their biosynthetic activity, translating to differences in tissue composition and structure, and potentially leading to valve dysfunction. VICs can change phenotype dynamically; in diseased valves VICs switch to a myofibroblast-like phenotype and become contractile. Activated VICs display prominent SMA stress fibers and an increase in ECM remodeling. Yet, while advances have been made toward the understanding of VIC behavior ex-situ, the VIC biomechanical state in its native extracellular matrix (ECM) remains largely unknown. We hypothesize that improved descriptions of VIC biomechanical state in-situ, obtained using a macro-micro modeling approach, will provide deeper insight into AVIC interactions with the surrounding ECM, revealing important changes resulting from pathological state, and possibly informing pharmaceutical therapies. To achieve this, a novel integrated numerical-experimental framework to estimate VIC mechanobiological state in-situ was developed. Flexural deformation of intact valve leaflets was used to quantify the effects of VIC stiffness and contraction at the tissue level. In addition to being a relevant deformation mode of the cardiac cycle, flexure is highly sensitive to layer-specific changes in VIC biomechanics. As a first step, a tissue-level bilayer model that accurately captures the bidirectional flexural response of AV intact layers was developed. Next, tissue micromorphology was incorporated in a macro-micro scale framework to simulate layer-specific VIC-ECM interactions. The macro-micro AV model enabled the estimation of changes in effective VIC stiffness and contraction in-situ that are otherwise grossly inaccessible through experimental approaches alone. While the use of native tissues provided much insight, we also utilized 3-D hydrogel encapsulation, which is an increasingly popular technique for studying VICs. Specifically, we employed poly(ethylene glycol) (PEG) gels to encapsulate VICs and study their mechanical response to the surrounding hydrogel stiffness and to varying levels of adhesion availability. Cell contraction was elicited through chemical treatments and the resulting mechanical properties of the constructs were measured through end-loading flexural deformation testing. We applied the downscale model, which was improved by 3D stress fiber visualization. The resulting cell force levels were comparable to native in-situ results. Overall, the developed numerical-experimental methodology can be used to obtain VIC properties in-situ. Most importantly, this approach can lead to further understanding of AVIC-ECM mechanical coupling under various pathophysiological conditions and the investigation of possible treatment strategies targeting the myofibroblast phenotype characteristic of early signs of valvular disease.

Bio
Professor Sacks is a world authority on cardiovascular biomechanics, particularly on the biomechanical behavior and function of heart valves and developing patient-specfiic simulation-based approaches for the treatment of valve diseases. His research is based on rigorous quantification, mathematical modeling, and simulation of the mechanical behavior of the cells and tissues of the cardiovascular system in health and disease. His approaches include multi-scale studies of cell/tissue/organ, especially how they mechanical interact as a system. For example, he has determined the how local stress environments of heart valve interstitial cells alter their biosynthetic responses in the context of altered organ-level responses. His research also includes developing novel cardiac models to simulate growth and remodeling of the myocardium in pulmonary hypertension, the first full 3D approach for left ventricular myocardium mechanical behavior, and novel that account for the compressibility of the myocardium in systole. Dr. Sacks is also active in the biomechanics of engineered tissues and scaffolds and in understanding the in-vitro and in-vivo remodeling processes from a functional biomechanical perspective.

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