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The γ-crystallins of the eye lens, are among the longest-lived proteins in the human body. Synthesized in utero, they must remain folded and soluble throughout adulthood to maintain lens transparency and avoid cataracts. All vertebrate crystallin structures exhibit homologous duplicated Greek Key β-sheet domains, presumably representing gene duplication earlier in their evolution. γD- and γS-crystallin are two major monomeric crystallins of the human lens. Oxidative damage to the crystallins leads to partial unfolding followed by polymerization to high molecular weight aggregates which scatter light causing cataract disease. The kinetic stabilities of the complete γD- and γS-crystallins and their respective isolated N-terminal and C-terminal domains were determined and compared. Kinetic unfolding experiments were performed in different concentrations of GdnHCl and monitored by fluorescence spectroscopy. Kinetic rate constants and half-lives of the crystallins were calculated using linear extrapolation to define the unfolding parameters in the absence of denaturant. The extrapolated $t_{1/2}$ for the initial unfolding step of γD-crystallin was ~19 years. The extrapolated $t_{1/2}$ for γS-crystallin was not as long, ~1.6 years, though still very long. The unfolding kinetic half-lives of each of the four isolated domains were much shorter than their respective full-length duplicated parent proteins. The simplest interpretation is that the domain interface is the barrier to initiation of unfolding and source of the high kinetic stability. Given the propensity of partially folded crystallins to aggregate at the high protein concentrations present in the lens, the high kinetic stability of the crystallins would protect the lens from the initiation of aggregation reactions.

Platform: Member Organized Session: Multiscale Modeling of Biophysical Systems

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A Macro-Micro Modeling Approach to Determine In-Situ Heart Valve Interstitial Cell Contractile Behaviors in Native and Synthetic Environments

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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. 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. A novel integrated numerical-experimental framework to estimate VIC mechanobiological state in-situ was developed using flexural deformation valve leaflets to quantify the effects of VIC stiffness and contraction at the tissue level. 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 measured through end-loading flexural deformation. 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. 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.

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Multiscale Modeling of the Damage Biomechanics of Traumatic Brain Injury

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In the United States, 2.8 million people sustain a traumatic brain injury (TBI) annually. Current finite element brain constitutive material models lack nanoscale and microscale cellular damage thresholds needed to represent localized TBI injury metrics. By considering the correlation between cell death and mechanoporation-related ion homeostasis disruption, a microscale injury metric along with damage evolutions equations have been developed. Molecular Dynamics (MD) simulations of a representative neuronal membrane, an atomistic 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) hydrated phospholipid bilayer model, were performed considering various loading conditions, in the range of contact sports-related loading rates (0.2 to 4.8 m/s). Membrane pore nucleation and growth were quantified with OVITO and an in-house MATLAB analysis code and were not significantly dependent on the system size and initial configuration. The measured pore nucleation and growth informed novel damage evolution equations that captured pore nucleation and growth evolution. These evolution equations were strain rate and stress state dependent and a function of the surface tension, edge tension, and the neuron size. Nernst-Planck diffusion equations were incorporated to measure the physiological component of damage evolution by quantifying the ion homeostasis disruption. MD simulations showed stress state dependent pore nucleation and strain rate and stress state dependent pore growth, with equibiaxial deformation producing the most damage at the same von Mises strain. The intracellular ion homeostasis disruption for a representative neuron cell also agreed with experimental findings from cell culture deformations. The model predicted mechanoporation damage to be strain rate and stress state dependent. The predicted neuronal death also depended on neuron size and membrane stiffness. The present mechano-physiological damage evolution equations can be implemented in a multiscale mechano-physiological internal state variable brain constitutive material model to capture history effects and strain rate and stress state dependencies of mechanoporation damage.

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Modeling T Cell Motion in Tissues During Immune Responses

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T cells are a key effector cell type in the immune response, required to clear infection as well as to kill tumor cells. T cells are able to move through many tissues: naïve T cells migrate in lymph nodes searching for antigen on dendritic cells, while activated T cells migrate to infected peripheral tissues to clear infection. As peripheral tissues differ dramatically in structure, we hypothesize that T cells utilize environmental cues within each tissue to mediate different motility patterns. Our lab uses quantitative imaging and computational modeling to understand how patterns of T cell motion contribute to immune responses. We use two photon microscopy to visualize T cell motion in intact tissues to observe T cell behavior in native environments. We show that T cells in both lymph nodes and lung use environmental structures to set motility patterns. In lymph nodes, T cell use the fibroblastic reticular cell network to move, and T cell accumulate at ''hotspots'' that can change their motion to search the lymph node environment more thoroughly. Surprisingly, T cells in lymph nodes do not appear to position near dendritic cells, the ultimate target for T cell interaction. In inflamed lung, we find that effector T cells move with an intermittent motion, with cells going through periods of directional and confined motion. Using novel quantitative tools and modeling, we demonstrate that T cells in lung move following the vasculature and intermittent motion enables T cells to interact with target cells. Our quantitative imaging and computational modeling results show that T cell motion is influenced by specific environmental components such as vessels and stroma within tissues, suggesting that the context in which T cells move is an important determinant of T cell behavior in vivo.

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Multiscale Modeling of Ductal Carcinoma In Situ

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Breast cancer is the most common cancer in women, and one in five newly diagnosed cases are ductal carcinoma in situ (DCIS), the earliest form of