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Mathematical Models for Patterning and Morphological Development

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A central question in developmental biology is how size and position are determined. The genetic code carries instructions on how to control these properties to regulate the form, shape and size of structures in the developing organism. Transcription and protein translation mechanisms implement these instructions. However, this cannot happen without sampling epigenetic information on the current form, shape and size of structures in the organism. The only robust description of this nature in physics is represented by spatio-temporal partial differential equations. Reaction-transport equations starting from simple Fickian diffusion, through the incorporation of reaction, advection and phase segregation terms can represent much of the patterns seen in the animal and plant kingdoms. Morphology, requiring the development of three-dimensional structure also can be represented by these equations. The recognition that physical forces play controlling roles in shaping tissues is behind the common use of nonlinear elasticity driven by volumetric growth to model morphology. Notably, the combination of reaction-transport equations with those of elasto-growth opens up the ability to model a potentially unlimited spectrum of patterning and morphology in developmental biology.

Mechanics of Epithelial-to-Mesenchymal Transition in Confined Environments

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Despite the undisputed success of drug-eluting stents (DES), there are persistent concerns about late stent thrombosis (LST). LST is primarily attributable to greatly delayed endothelialization because the drugs used in DES inhibit endothelial cell proliferation and migration. The goal of the present work is to devise optimal strategies for drug release from DES that minimize the likelihood of LST while maintaining sufficiently high drug concentrations in the arterial wall to prevent restenosis. We have recently developed a computational model that describes the transport within the arterial wall of drugs released by DES. We now apply this model to the optimization of DES. Simulations are performed for the two common DES drugs paclitaxel and sirolimus. For the optimization, we define an objective function that maximizes drug efficacy while minimizing drug toxicity and drug concentration on the surface of the injured endothelium. Optimization is accomplished using a gradient-free algorithm based on the surrogate management framework. The two variables used in the optimization are the drug release rate from the stent and the initial drug concentration loaded onto the stent. The results demonstrate that the optimal drug delivery strategies for paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) are very different. For PES, we identified two distinct optima with vastly different drug release rates; one is for very fast release (time constant on the order of an hour) and one for very slow release (order of a year). In contrast, SES exhibit only a single optimal release rate with a time constant on the order of a year. Significantly, optimal drug release for both PES and SES requires considerably lower initial drug concentrations than those used today. To experimentally validate the computational optimization results, we have developed an in vitro artery within which a stent can be deployed. The in vitro artery consists of an annular collagen hydrogel within which vascular smooth muscle cells are embedded and whose inner surface is lined by endothelial cells. We have demonstrated the ability to deploy a stent within this artery and to quantitatively monitor endothelial wound healing as well as smooth muscle cell movement following stent deployment. Finally, we have shown that we can use particle image velocimetry to measure arterial flow disturbances induced by the stent. The present results provide a framework for optimizing DES design and propose an experimental platform for validating the optimization results.

Measuring Adhesion between Uropathogenic E. Coli and Bladder-Epithelial Cells

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Bacterial adhesion to host cells is often a first step in the infection process. For example, uropathogenic Escherichia coli, the major causative agent of urinary tract infection, bind to host bladder-epithelial cells and initiate cell invasion. This triggers a subsequent pathogenic cascade characterized by recurrent infection. There is currently growing interest in developing new antimicrobials that, instead of targeting bacterial survival and placing high selective pressure for drug-resistant mutations, target mechanisms promoting infection such as binding to host cells. This new therapeutic strategy requires a detailed understanding of the factors that contribute to bacterial adhesion. To address this issue, we adapted a novel live cell monolayer rheometer recently developed in the Fuller lab to measure adhesion between a monolayer of bladder-epithelial cells and a layer of bacteria. The bacterial strain used in this study is UTI89, a uropathogenic strain of E. coli that is capable of expressing several different extracellular components such as type 1 pili, curli, and cellulose. Using our adapted device, we can quantitatively compare the extent to which these different extracellular components affect bacterial adhesion to the cell monolayer. Additionally, we can use these measurements to assess the effectiveness of various small molecules in preventing binding to host cells.

Mechanical Properties of Bacillus Subtilis Biofilms Subjected to Large Macroscale Deformations

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Bacterial biofilms—communities of bacteria embedded in a biopolymeric extracellular matrix—are ubiquitous in nature, but their formation can also have undesired consequences. It is now appreciated that bacterial biofilms play a role in chronic infection and in industry can cause problems from contamination of food processing equipment to oil pipeline corrosion. Removal of these unwanted biofilms is clearly desirable; however, to improve removal, we must have a better understanding of the mechanical characteristics of these biofilms. To date, most studies have focused on measuring mechanical properties of biofilms subjected to small deformations and forces (i.e. in the linear viscoelastic regime), but to achieve biofilm removal, we must apply large forces and deformations that approach biofilm rupture and/or detachment. This study therefore focuses on large deformations of biofilms formed at the air-liquid interface by Bacillus subtilis, a model biofilm-forming bacterium. Additionally, in light of the recently discovered growth-induced compressive stress present in a biofilm, we also focus on the consequences of this internal stress on mechanical properties. Overall, we observe that biofilms exhibit viscoelastic properties both at small deformations (such that the compressive stress is still present), and at large deformations, as in both regimes biofilms exhibit large stress relaxation and rate-of-strain dependent mechanical properties. However, once the compressive stress is relieved, deformations become plastic as demonstrated by the inability of the biofilm to relax to its original growth-induced internal stress. Particle image velocimetry (PIV) analysis of macroscale biofilm images additionally reveal that the deformation field of the biofilm is non-uniform, suggesting that the mechanical properties of the biofilm are also non-uniform. We observe that the biofilm is more pliable near attachment surfaces and calculate local properties of the biofilm using our PIV results. Whereas previous studies have focused on the viscoelastic and average properties of biofilms, our results show that if we want to understand large deformations and biofilm removal, we must also appreciate the plastic and non-uniform nature of these naturally grown structures.

Probing the Active Process of Hair Cells: Adaptation & Spontaneous Oscillation Recovery after Overstimulation

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In the inner ear, hair cells perform the transduction of mechanical input into electrical output. An energy-consuming process enhances their sensitivity to incoming auditory and vestibular stimuli. One manifestation of this active process is spontaneous oscillation of the mechano-sensitivie organelle, the hair bundle, which is at the apical surface of each hair cell. To attain this increased sensitivity, the hair bundle is postulated to operate near a bifurcation, where an internal control parameter, vital to the active process, determines whether the bundle shows limit cycle oscillations or is quiescent. This control parameter may be linked to in vivo phenomena, such as temporary threshold shifts in response to prolonged high-intensity sounds. High amplitude, prolonged deflection of bullfrog sacculus bundles has been shown to temporarily suppress spontaneous oscillations, suggesting a readjustment of the control parameter through a bifurcation. The transition back from quiescence to limit cycle oscillations has been shown to depend on the duration of the imposed deflection and on calcium ion concentration around the mechanically gated transduction channels.
In the current study, we attach magnetic particles to the hair bundles and deflect them with an electromagnet. This technique allows us to impose strong stimuli on the bundles without risk of damage through physical contact with the stimulus probe, and without the associated hydrodynamic effects. We present experiments, performed on preparations of the bullfrog sacculus, where we identify environmental factors that affect the suppression and recovery of active oscillations. We introduce various pharmacological agents to manipulate the mechano-electrical transduction process and the myosin motor activity inside the hair bundles. We compare how these agents affect particular components of the internal control parameter by measuring the duration of the induced quiescent intervals, time scales associated with the return of the bundle's position to equilibrium, and changes in oscillation frequency before, during, and after deflection.

Chaotic Behavior of Oscillatory Hair Cells

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The inner ear is capable of detecting sounds that elicit motions below the stochastic noise levels. Hair cells are the specialized sensory cells essential for the hearing process. They convert mechanical energy from incoming sound into currents by opening and closing mechanically sensitive ion channels, in response to the induced deflections. Hair cells of certain species are also known to oscillate without external stimulation. The role of these spontaneous oscillations is not understood, but they are believed to be a signature of an underlying active mechanism. As this active process constitutes one of the most important open topics in auditory research, a deeper understanding of spontaneous motility could have important implications on understanding the extreme sensitivity of hearing. The motion of spontaneously oscillating hair cell bundles has been described with a number of theoretical models. Hair cells have been shown to flicker between the oscillatory and quiescent states; this phenomenon was modeled with dynamic feedback acting on an internal control parameter that determines the dynamic state of the cell. This simulation was also able to predict a range of values for the Lyapunov exponent, which quantifies the level of chaos in a dynamical system. A positive Lyapunov exponent was predicted, indicating chaotic motion. We will present on experimental measurements of spontaneous hair bundle oscillations, which were obtained from the sacculus of the American bullfrog. Using the delay-coordinate technique, the phase space of the oscillator was reconstructed, allowing for estimation of the Lyapunov exponent. These estimates were consistent with predictions based of the feedback model. A lower Lyapunov exponent was found during mechanical stimulation, indicating that the detection of sound reduces the level of chaos in the hair cell.

Pre-Transition Effects Mediate Forces of Assembly between Transmembrane Proteins

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We present a mechanism for a generic and powerful force of assembly and mobility for transmembrane proteins in lipid bilayers. This force is a pre-transition (or pre-melting) effect for the first-order transition between ordered and disordered phases in the host membrane. Using large scale molecular simulation, we show that a protein with hydrophobic thickness equal to that of the disordered phase embedded in an ordered bilayer stabilizes a microscopic order–disorder interface, and the stiffness of that interface is finite. When two such proteins approach each other, they assemble because assembly reduces the net interfacial free energy. In analogy with the hydrophobic effect, we refer to this phenomenon as the “orderphobic effect.” The effect is mediated by proximity to the order–disorder phase transition and the size and hydrophobic mismatch of the protein. The strength and range of forces arising from the orderphobic effect are significantly larger than those that could arise from membrane elasticity for the membranes we examine.

Assembly, Architecture, and Collective Function of Membrane Protein Lattices

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Experiments have revealed that membrane proteins can form two-dimensional lattices with regular translational and orientational protein arrangements, which may allow cells to modulate protein function. However, the physical mechanisms yielding supramolecular organization and collective function of membrane proteins remain largely unknown. Here we show that bilayer-mediated elastic interactions between membrane proteins can yield regular and distinctive lattice architectures of protein clusters, and may provide a general link between lattice architecture and lattice function. We develop general theoretical concepts of membrane protein organization and collective function based on three model systems: (1) We show how the interplay between protein-induced curvature deformations, topological defects in protein packing, and entropy can explain the observed symmetry and size of membrane protein polyhedral nanoparticles; (2) We predict that the observed tetrameric and pentameric oligomeric states of mechanosensitive ion channels yield characteristic ground-state lattice architectures of channel clusters in the form of face-on square lattices and distorted hexagonal lattices, respectively, with distinctive collective gating properties; (3) We show that bilayer-mediated interactions between chemoreceptor trimers provide a mechanism for the observed self-assembly of face-on honeycomb lattices of chemoreceptor trimers and the localization of large chemoreceptor lattices to the cell poles, and may contribute to the cooperative signaling response of the chemotaxis system.

Stochastic Multiscale Dynamics of Synaptic Membrane Protein Domains

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The efficiency and strength of signal transmission across chemical synapses rely on the stability and the characteristic size of receptor protein domains localized on the postsynaptic membrane opposite the presynaptic terminal. A class of auxiliary proteins called scaffold proteins are believed to contribute to the localization of receptor molecules by transiently trapping them in synaptic membrane domains. Recent single-molecule tracking experiments have revealed that individual receptors as well as scaffolds show rapid and highly stochastic turnover, leaving and entering synaptic domains on typical time scales as short as seconds—much shorter than the time scale of the stability of synaptic receptor domains, which can last for months or even longer periods of time. We show that the spontaneous formation, stability, and characteristic size of synaptic receptor domains can be understood within the reaction-diffusion paradigm of pattern formation. Based on a stochastic lattice model of synaptic molecular dynamics we demonstrate how long-term spatial and temporal stability of synaptic domains can be reconciled with fast and noisy turnover of the individual molecular constituents of synaptic domains. We find spatially nonuniform distributions of receptor lifetimes across synaptic membranes, and predict characteristic recycling times of the molecular components of synaptic domains which are in agreement with experimental observations. Finally, our results suggest that reaction-diffusion patterns can provide a general mechanism for the spatiotemporal modulation of membrane mechanical properties across different length and time scales.

Multiscale Dissection of Regulation in Microbial Ecosystems

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Microbial ecosystems in nature are diverse and heterogeneously distributed in space and time. We use multiscale theoretical models and biophysical experimental tools to explore how diverse communities of microbes collectively regulate global behavior. These approaches range from the scale of molecules to multicellular networks.

At the ecosystem scale, we quantify how interactions between species isolated from complex natural ecosystems dictate community level outputs such as overall metabolic rate and cell growth. We examine these interactions both in the bulk and at the single-cell level using microfluidic devices. Diverse sets of microbes are fragmented into an array of picoliter-sized microwells to measure heterogeneity in activity at the single cell level and to understand how the local neighborhood composition modulates the output of each cell. At the single-cell level, we focus on how individual species integrate information at the promoter level about external conditions and signals from neighboring species to make regulatory decisions. These results are expanded using theoretical models to analyze how the community composition, spatial distribution, local clustering, and cell-cell regulatory interactions influence global patterns of activity.

Paradoxical Signaling Regulates Structural Plasticity in Dendritic Spines

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Transient spine enlargement is an important event associated with the structural plasticity of dendritic spines. Many of the molecular mechanisms associated with transient spine enlargement have been identified experimentally. Here, we use a systems biology approach to construct a mathematical model of biochemical signaling-mediated transient spine expansion in response to calcium-influx due to NMDA receptor activation. We have identified that a key feature of this signaling network is the paradoxical signaling loop. Paradoxical components act bifunctionally in signaling networks and their role is to control both the activation and inhibition of a desired response function (protein activity or spine volume). Using ordinary differential equation-based modeling, we show that the dynamics of different regulators of transient spine expansion including CaMKII, RhoA, and Cdc42 and the spine volume can be described using paradoxical signaling loops. Our model is able to capture the experimentally observed dynamics of transient spine volume. Further, we use the model to make experimentally-testable predictions on the role of different components and parameters of the network on spine dynamics.

Chirality of Viral Capsids

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Most icosahedral viruses are classified by their T-number which identifies the capsid in terms of the number of capsomers and their relative arrangement. Certain T-numbers (T = 7 for instance) are inherently chiral (with no reection planes) while others (e.g. T = 1) areachiral. We present a Landau-Brazovskii (LB) theory for weak crystallization in which a scalar order parameter that measures density of capsid proteins successfully predicts the various observed T-numbers and their respective chiralities. We find that chiral capsids gain stability by spontaneously breaking symmetry from an unstable achiral state. The inherently achiral LB-free energy does not preferentially select a particular chiral state from its mirror reflection. Based on the physical observation that proteins are inherently chiral molecules with directional interactions, we propose a new chiral term to the LB energy as a possible selection mechanism for chirality.

Mechanics of Osmotically Shocked Bacteria

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Hypo-osmotic shocks increase transient pressure within bacterial cells, placing the cell membrane and wall in a state of tensile stress. To alleviate pressure, tension-dependent channels within the membrane open, allowing for passage of solute and water across the cell envelope. Recent experimental works have shown that cells lose the ability to withstand shocks when specific channel populations are depleted, and that survivability is strongly dependent on shock rate. However, details of the physical mechanisms behind cell failure during shocks remain unclear. We further study the effects of channel deletions, shock rate, and cell envelope mechanics on survivability using thin shell elasticity and non-equilibrium thermodynamic transport models. We find that reducing the number of channels and applying faster shocks significantly increases the time-dependent stress in the membrane and wall. This result provides insight into the mechanisms responsible for cell death, including membrane rupture and wall fracture.

Brownian Dynamics Simulation of Pressure Induced Pore-Transport Through an Incommensurate Channel

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Cells and organelles use channels embedded in their protective membranes to facilitate the transport of materials (ions, molecules, proteins, etc.) between their lumen and their surrounding environments. In a homogeneous particle environment, the flow through the pore channel can be driven by a non-equilibrium pressure differential and can be modeled with brownian dynamics simulations. We extend this simulation to include the Frenkel-Kontorova model and factor in the interaction between the flowing particles and the periodic potential of the channel. We investigate how the relation between the equilibrium spacing of the particles and the intrinsic period of the channel's potential interaction will affect the flow of particles when the pressure differential and temperature are held constant.

Evaluating the Variational Framework for an Electromechanical Viscoactive Constitutive Model on a Biventricular Rabbit Heart

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A rigorously validated electromechanical heart model would be useful for identifying physiological mechanisms and effective diagnostic and treatment strategies for heart disease. In this study, drawing from the work of Ortiz and Stainier [1] in viscoplasticity, we present a novel constitutive modeling framework for contractile cardiac mechanics, by formulating a single variational principle from which incremental stress-strain relations, and kinetic rate equations for active contraction and relaxation can all be derived. The variational framework straightforwardly accommodates the hyperelastic behaviors measured experimentally for relaxed and contracted tissue, along with the rate- and length- dependent generation of contractile force. Additionally, a viscous dashpot element can also be included in the framework to model the active relaxation of the myocardium following the cardiac cycle. To utilize this framework, we prescribe a three-element, Hill-like model that unifies the “active tension” and “active deformation” approaches. As in the latter approach, we multiplicatively decompose the total deformation gradient into active and elastic parts, with the active deformation parameterizing the contractile Hill element. We adopt as internal variables the fiber, cross-fiber, and sheet normal stretch ratios. The kinetics of these internal variables are modeled via definition of a kinetic potential function derived from experimental force-velocity relations. To model the myocytes activation, the kinetic equations are coupled with the calcium transient obtained from a UCLA cell electrophysiology model. Using these constitutive equations, the finite element method, and an ellipsoidal heart geometry, we model the four stages of the cardiac cycle. We evaluate different passive and active strain energy laws, viscous coefficients, force-velocity relationships, and electrophysiology conditions to identify characteristic changes in the gross contraction of the heart. We validate the model via measures such as EF, twist, apex-to-base shortening, fiber shortening, and wall stresses.

[1] Ortiz, Michael, and Laurent Stainier. "The variational formulation of viscoplastic constitutive updates." Computer methods in applied mechanics and engineering171.3(1999):419-444.

A Fluctuating Elastic Plate and a Cell Model for Lipid Membranes

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The thermal fluctuations of lipid bilayer membranes are key to their interaction with cellular components as well as the measurement of their mechanical properties. Typically, membrane fluctuations are analyzed by decomposing into normal modes or by molecular simulations. Here we propose two new approaches to calculate the partition function of a membrane. In the first approach we view the membrane as a fluctuating von Karman plate and discretize it into triangular elements to express its energy as a function of nodal displacements. We compute the partition function and covariance matrix using Gaussian integrals. We then recover well-known results for the dependence of the projected area of the membrane on the applied tension. As new applications we compute the fluctuations of the membrane of a malaria infected cell and analyze the effects of boundary conditions on fluctuations. We also compute free energies and fluctuations of membranes in which a patch could have a non-zero spontaneous curvature. Our second approach to compute the partition function of a membrane is based on the cell model of Lennard-Jones and Devonshire. This model, which was developed for liquids, assumes that each molecule fluctuates within a cell on which a potential is imposed by all the surrounding molecules. We adapt the cell model to a lipid membrane by recognizing that it is a 2D liquid with the ability to deform out of plane whose energetic penalty must be factored into the partition function of a cell. We show, once again, that some results on membrane fluctuations can be recovered using this new cell model. However, unlike some well established results, our cell model gives an entropy that scales with the number of molecules in a membrane. Our model makes predictions about the heat capacity of the membrane that can be tested in experiments.

Particle Impact on Monolayer Collapse: Experiments and Modeling

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One of the major mechanical features of lung surfactant is the ability to fold reversibly under compression. This has a number of biological benefits, including reducing the need for regeneration of the lipid monolayer at the air-water interface in lungs. For both disease prevention and drug delivery, it is interesting to consider how lipid monolayers fold and unfold in the presence of particles of various sizes, and as a function of compression rate. From a disease perspective, disruption of reversible folding by particles can have a negative impact on the functioning of the lung system. In contrast, for aerosol drug delivery, some form of disruption of the monolayer folding may be necessary for particles to cross the air-water interface. We report on experimental studies using model monolayers and outline the phase space of folding behavior. Comparison is made with simplified models of the process. Both tuning compression speeds and particle size can lead to changes from reversible to irreversible folding.

Viscoelastic Deformation of Lipid Vesicles

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Traditional continuum mechanical models of lipid bilayers treat bilayers as purely elastic materials, with elastic moduli that have no dependence on strain rate. We have directly measured a time-dependent--i.e. viscoelastic--mechanical response in giant unilamellar vesicles (GUVs). Vesicles are trapped in a microfluidic channel using a dual-beam optical trap (DBOT). By performing video microscopy as the vesicle is subjected to a step increase in optical force, we are able to directly observe both an instantaneous deformation and a transient mechanical response with a time constant on the order of 200 ms. This observation represents the first direct measurement of viscoelastic deformation in a lipid bilayer model system. Control experiments indicate that no significant heating occurs during the optical trapping process and that the time constant of the viscoelastic response is constant with varying viscosity of the surrounding medium. Viscoelasticity therefore appears to be an intrinsic property of lipid bilayers. This observation has significant physiological implications, since important physiological processes involve lipid bilayer deformation with time scales spanning many orders of magnitude.

Predicting DNA Unlooping with Phase-Space Sampling

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DNA-binding proteins can regulate genetic expression by holding two sites in close proximity, forming a closed loop. Such complexes may require strong bending of DNA segments on the order of one persistence length or less. Both this elastic bending and the thermal fluctuations of the DNA molecule are necessary to describe the resulting behavior. To explore this problem, we consider a discrete model of a wormlike chain, kept in the fixed extension ensemble. By using a novel method to sample conformations in both position and momentum space, we can obtain a distribution of constraint forces as a function of chain length, extension, and flexibility. Our coarse-grained model allows us to explore the space of these parameters more efficiently than a detailed molecular dynamics approach. We find that increasing contour length decreases average force by relieving bending stress, but that the additional freedom allows fluctuations in the constraint force to increase. This implies that the probability of large forces may go up even as the mean goes down, impacting the lifetime of such bound states in a way unforeseen by purely equilibrium methods.

Nonaffine Deformation in Three-Dimensional Filamentous Networks

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Randomly cross-linked filamentous networks are building blocks of different biological and non-biological systems such as cytoskeleton and extracellular matrix. 2D models have been so far primarily used to study the mechanical properties of these systems [1]. Here, different representations of 3D fiber networks are generated by placing fibers with random orientation in a cubic domain. Then a 3D non-affinity measure is created for probing the mechanical behavior at different length scales and investigating the effects of various characteristic lengths. The 3D nonaffinity measure is and extension of the 2D strain-based nonaffinity measure [2] and is defined as the fluctuation of the actual deformation gradients relative to their affine estimates. It is shown that while all non-affinity measure components have a power-law variation with the probing length scale, the degree of non-affinity decreases with increasing the scale of observation. Furthermore, similar to 2D networks, both the fiber bending stiffness and the density of the network control the amount of non-affinity in 3D networks. Nevertheless, the two power-law scaling regimes previously reported for two-dimensional systems do not appear in three-dimensional networks.

A Study of Formation and Motion of Topological Defects in Viral Capsids

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We investigate the structural behavior of icosahedral viral capsids under external stimuli like indentation. Some viruses are found to be enclosed in capsids made up of lipid bilayer embedded with viral proteins. We model such shells using thin-shell elasticity for lipid layer superimposed with discrete particle-particle interactions between the proteins. Thus our model is a hybrid of continuum and discrete mechanics. Lennard-Jones and Morse potential have been used as preliminary models for the potential interactions between the proteins. They replace the stretching component of energy from the Helfrich model for lipid bilayers. In general, plastic flow in a material can be attributed to motion of dislocations in the material structure. Also, plastic deformations are not fully reversible when deforming forces are removed. For energy minimization under an indenting force, our model shows that viral capsids undergo formation and movement of crystallographic defects. Also when the indenting force is removed the capsid does not fully recover its original shape. Both of these observations suggest that viral capsids can have plastic response under large deformations. Foppl von Karman number is a dimensionless parameter obtained as a ratio of two dimensional Young's modulus and the bending modulus of a shell-like structure. We investigate the response of our hybrid model with variation in the dimensionless Foppl-Von-Karman (FVK) number of the capsid by measuring the asphericity or the deviation from a spherical structure. A smaller value of FVK number indicates that the structure is more resistant to bending than for in-plane stretching. Thus, at smaller FVK number a spherical shape is energetically favorable. Similarly, larger FVK number indicates dominant in-plane stretching response which gives rise to faceted structures. As FVK number is increased from very small values to very large values, a distinct change from spherical to faceted shape is observed in the capsid. This is called as a buckling transition. In our simulations with the hybrid model for smaller achiral structures with T numbers 3, 4 and 9 the asphericity response under decreasing FVK number is similar to that of a fully continuum model but the buckling transition occurs at relatively lower FVK numbers. Also, certain chiral shells like the one with T-number 7 show breaking of icosahedral symmetry during the buckling transition.

A Study of Transient Streaming Potential with Piezo-Effect in Bone

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Bone repeats continuously to change itself through the process of bone remodeling by external stimuli. Bone remodeling is a continuing process through the coupling of bone formation following bone resorption. The most recent, mechanoelectric characteristics of bone have been studied in two categories such as piezoelectricity and streaming potential. However, from the electrokinetic point of view, two theories are closely related to each other. The mechanism of streaming potential generation with respect to transient surface potential is important to research the effect of piezoelectricity in bone. In this study, an equation of the transient streaming potential was proposed and analyzed to couple the streaming potential with piezoelectricity in bone. The proposed equation of transient streaming potential is verified the numerical method and experimental method. The streaming potential of numerical method rapidly increases in case of impulse and gradually decreases by unloaded. Peak potential is higher than steady state streaming potential. The streaming potential equation in the steady state has been used for bone. Unlike the result of study based on the previous equation, the result of proposed equation in this study explain the electroviscous effect on the longer relaxation time.

Osteocyte Mechanobiology in Healing Live Allograft Biological Systems

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With increasing life expectancy, pathologies related to massive bone loss following cancer or catastrophic trauma carry $10 billion financial burden on the U.S. healthcare system. Successful techniques to repair large tissue defects can be however difficult and will require the addition of materials such as allograft bone. Product of continuous remodeling, human Haversian cortical bone is a hierarchical composite where microdamage stimulate tissue resorption by osteoclasts cells before tubular lamellar structures called osteons are formed by osteoblast cells that lay an extracellular matrix composed of Type I collagen fibrils mineralized by hydroxyapatite nano platelet crystals glued together with non-collagen proteins and proteoglycans. Trapped osteoblasts further differentiate into mechano-sensitive osteocytes that are able to sense stimulation produced by microdamage. Osteocytes have the particularity to bear a large number of cytoplasmic processes extending into canaliculi to create a syncytial network with the neighboring cells with which they communicate in a fashion similar to the nervous system to regulate healthy bone turnover. It is essential to quantify the relationship between in situ mechanical stimulation and the cell biological response during healing. Dual experimental and numerical top-down 3D investigations create Live Allograft Biological Systems (LABS) composed of progenitor and mature osteocytes reseeded on donor human femoral fresh cadaver bone.
The live systems were subjected to micro bending tests to produce, image and model the growth of controlled nascent sub-microscopic damage near live osteocytes. The balance of the energies at the global scale identified the multiscale local constitutive fracture mechanisms scale by scale to quantify in situ stress field near live osteocytes. The hierarchical finite element model represents the explicit bone tissue and cell 3D morphology under boundary conditions calculated by digital volume correlation. Mineralization is identified locally by grey scale in micro CT imaging and nano-indentation measurements while UV and fluorescent confocal microscopy quantifies the released chemicals upon loading.
The live systems mechanically closely behave as fresh human cadaveric bone. The numerical model computes nascent diffuse damage within the 3D osteon lamellae near the live progenitor and mature osteocytes. The systems reveal in vitro cell reorganization as in vivo. The fluorescent observations revealed the calcium membrane transport adaptation of the cells to the in situ mechanical cyclic loading at successive stages of differentiation. The systems created are functional and allow osteoconduction, osteoinduction and osteogenicity monitoring.

Cell Motility and Traction Force Generation in Three-Dimensional Fibrin Hydrogels

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Cell migration is an essential aspect of wound healing, immune function, and cancer metastasis. However, at present very little is known about how cells move through biologically realistic, three-dimensional (3D) environments. In this talk I describe our work to elucidate the physical processes by which living cells adhere to and move through 3D fibrin matrices, which mimic the environment that cells encounter during wound healing. We used multicolor, time-lapse confocal imaging to quantify both cytoskeletal motion and cell-generated matrix deformations for human fibroblasts embedded in soft, porous fibrin matrices. We found that under these conditions cells assemble contractile cytoskeletal cables that act in a locally autonomous fashion to exert forces on the surrounding matrix. Surprisingly, the detailed molecular mechanism of force propagation from the cell cytoskeleton to the surrounding fibrin matrix is consistent with previously proposed models for how cells move across hard, two-dimensional surfaces (e.g. a microscope coverslip). These observations, together with those from our studies of mechanotransduction at cellular integrin complexes (Morimatsu et al., Nano Lett., 2015) and cadherin-based adhesions (Buckley et al., Science, 2014) point to underlying commonalities in how cells detect and respond to mechanical force in a wide variety of physiological circumstances.

Traction Force Microscopy: To 3D and Beyond

Juan del Alamo
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In our organism, cells are embedded in three-dimensional (3D) extracellular matrices (ECM) with highly inhomogeneous material properties. Cells collectively deform the ECM in all spatial directions by applying 3D traction forces. Additionally, many cell types can dynamically reinforce the ECM by secreting matrix proteins, or degrade it by secreting proteolytic enzymes. Despite the complexity of these cell-ECM interactions, most in vitro studies performed in the last two decades have measured single-cell two-dimensional (2D) traction forces on substrata of constant mechanical properties. Thus, there is a demand for novel assays and analyses that can probe cell-ECM mechanical stress interactions in more realistic cellular environments.

This talk will summarize our recent advances in the development of traction force microscopy (TFM) techniques for 3D ECMs with either constant or spatially varying mechanical properties. We will also present novel high-throughput microscopy techniques to determine collective contractile forces exerted by multiple-cell cultures. We will illustrate the practical application of these methods to determine cell-ECM mechanical stresses in relevant biological processes such as cancer cell invasion into 3D ECMs, cell-cell mechanical forces during the transendothelial migration of leukocytes, and high-throughput screening of cardiomyocyte contraction.

Investigating Cell Dynamics using Spatial Light Interference Microscopy (SLIM)

Gabriel Popescu
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Most living cells do not absorb or scatter light significantly, i.e., they are essentially transparent, or phase objects. Phase contrast microscopy proposed by Zernike in the 1930's represents a major advance in intrinsic contrast imaging, as it reveals inner details of transparent structures without staining or tagging. While phase contrast is sensitive to minute optical path-length changes in the cell, down to the nanoscale, the information retrieved is only qualitative. Quantifying cell-induced shifts in the optical path-lengths permits nanometer scale measurements of structures and motions in a non-contact, non-invasive manner. Thus, quantitative phase imaging (QPI) has recently become an active field of study and various experimental approaches have been proposed.
Recently, we have developed Spatial Light Interference microscopy (SLIM) as a highly sensitive QPI method. Due to its sub-nanometer pathlength sensitivity, SLIM enables interesting structure and dynamics studies over broad spatial (nanometers-centimeters) and temporal (milliseconds-weeks) scales. I will review our recent results on applying SLIM to basic cell studies, such as intracellular transport and cell growth. I will end with a discussion on new method, inspired from interferometry, for measuring cell-generated forces.

Field Theoretic Simulations of a Compressible Lipid Membrane: Implications for Surface Tension

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Field-theoretic simulations offer access to biologically relevant length scales which would be expensive with traditional particle based models. This talk will discuss a method which explicitly incorporates the local compressibility of the membrane. This field theory is validated by comparison with "one-dimensional membrane" models which permit unambiguous mapping of the physical behavior. The model is then extended to the two-dimensional case where the particle comparison is not available. Finally, we apply our model to discuss the connection between the physical frame tension and the observed fluctuation tension in membrane simulations.

Encoding Mechano-Memories in Actin Networks

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The ability of cells to sense and adapt to external mechanical stimuli is vital to many of its biological functions. A critical question is therefore to understand how mechanosensory mechanisms arise in living matter, with implications in both cell biology and smart materials design. Experimental work has demonstrated that the mechanical properties of semiflexible actin networks in Eukaryotic cells can be modulated (either transiently or irreversibly) via the application of external forces. Previous work has also shown with a combination of numerical simulations and analytic calculations shows that the broken rotational symmetry of the filament orientational distribution in semiflexible networks leads to dramatic changes in the mechanical response. Here we demonstrate with a combination of numerical and analytic calculations that the observed long-lived mechano-memory in the actin networks arise from changes in the nematic order of the constituent filaments. These stress-induced changes in network topology relax slowly under zero stress and can be observed through changes in the nonlinear mechanics. Our results provide a strategy for designing a novel class of materials and demonstrate a new putative mechanism of mechanical sensing in eukaryotic cells.

Asymmetries Arising from the Space-Filling Nature of Vascular Networks

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Cardiovascular networks span the body by branching across many generations of vessels. The structural features of the network that accomplish this density and ubiquity of capillaries are often called space-filling. Some strategies do not lead to biologically adaptive structures, requiring too much construction material or space, delivering resources too slowly, or using too much power to move blood through the system. We empirically measure the structure of real networks to compare with predictions of model networks that are space-filling and constrained by a few guiding biological principles. We devise a numerical method that enables the investigation of space-filling strategies and determination of which biological principles influence network structure. Optimization for only a single principle creates unrealistic networks that represent an extreme limit of the possible structures that could be observed in nature. We first study these extreme limits for two competing principles, minimal total material and minimal path lengths. We combine these two principles and enforce various thresholds for balance in the network hierarchy, which provides a novel approach that highlights the trade-offs faced by biological networks and yields predictions that better match empirical data.

A Multi-Scale Integrated Model of the Mitral Valve: From Cellular Biophysics to Surgical Repair

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The mitral valve (MV) is one of the four heart valves located in between the left atrium and left ventricle and regulates the unidirectional blood flow and normal functioning of the heart. High-fidelity computer simulations provide a means to connect the cellular function with the organ-level MV tissue mechanical responses, to ultimately design optimal MV repair strategies. As in many physiological systems, one can approach heart valve biomechanics from using multiscale modeling (MSM) methodologies, since mechanical stimuli occur and have biological impact at the organ, tissue, and cellular levels. Yet, MSM approaches of heart valves are scarce, largely due to the major difficulties in adapting conventional methods to the areas where we simply do not have requisite data. There have been few attempts have been made to connect the underlying valve interstitial cell (VIC) function with changes in tissue and organ level stresses. To better understand the interrelationships between tissue-level loading and cellular responses, we developed an integrated experimental-computational approach. We explored the interrelationship between the MVIC stiffness and deformation to layer-specific tissue mechanical and structural properties using a macro-micro finite element computational model. The simulated MVIC moduli for the four layers were found to be all within a narrow range of 4.71–5.35 kPa, suggesting that MVIC deformation is primarily controlled by each tissue layer's respective structure and mechanical behavior rather than the intrinsic MVIC stiffness. This novel result further suggests that while the MVICs may be phenotypically and biomechanically similar throughout the leaflet, they experience layer-specific mechanical stimulatory inputs due to distinct extracellular matrix architecture and mechanical behaviors of the four MV leaflet tissue layers. This also suggests that MVICs may behave in a layer-specific manner in response to mechanical stimuli in both normal and surgically modified MVs. We also present a novel solid-mixture model for VIC biomechanical behavior that incorporated 1) the underlying cytoskeletal network, 2) the oriented α-SMA stress fibers with passive elastic and active contractile responses, 3) a finite deformable elastic nucleus. We implemented the model in a full 3D finite element simulation of a VIC based on known geometry. Current results suggest substantial functional differences between VIC from different valves at the subcellular level. Moreover, this first VIC computational biomechanical model is but a first step in developing a comprehensive, integrated view of the VIC pathophysiology and interactions with the valve ECM micro-environment based on simulation technologies.

Identification of Unique Material Properties and In-Vivo Formulation of Energy Laws for Passive Myocardium

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Remodeling of the material properties of passive myocardium underlies several heart diseases. For instance, changes (i.e., stiffening) in the response of passive myocardium are linked to heart failure with preserved ejection fraction (HFpEF), a debilitating heart condition affecting more than 50% of HF patients in the US. However, despite its severity and widespread clinical presentation, there is no consensus on how to diagnose HFpEF, track its progression, and understand its underlying mechanisms.
In order to use material properties as diagnostic markers to identify the onset and progression of HFpEF, it is crucial that the material properties are identified uniquely so that there is no dependence on the initial guess and fine-tuning of the solution algorithm. Moreover, in order to characterize the material response of the myocardium, its energy law should be formulated based on in-vivo data. In doing so, the physiological operating conditions and the tissue intrinsic pre-stress are automatically taken into account.
We developed a new approach termed DEMO (Direct Equilibrium Matching Optimization) to uniquely identify material properties in the finite kinematics regime. Our method is based on in vivo data that are acquired through clinical exams, i.e., displacements acquired through MRI, ventricular geometry and microstructure acquired through diffusion tensor MRI, and intraventricular pressure acquired through catheterization. In contrast with common approaches, we define an objective function to minimize the difference between applied (e.g., pressure) and internal forces, rather than between experimental and computed displacements. Through the internal forces, the resulting objective function depends directly on the myocardial stiffness coefficients. This explicit dependency allows to analyze uniqueness of the identified material properties. A second, fundamental component of DEMO consists in identifying the non-linearities and the deformation gradient invariants in the material law. Moreover, these material laws are polyconvex and contain a limited number of coefficients, usually one related to the isotropic response and one to the anisotropic response. Changes in these coefficients are linked to changes in the tissue microstructure: a stiffening of the isotropic response may be related to fibrosis while a change in the anisotropic response may be related to changes in the myocytes.
We conclude by presenting the verification and validation of our method and by comparing it with other material energy laws presented in the literature. We carry out these examples both at the material point level and in an anatomical ventricular geometry.

A Biophasic Transversely Isotropic Poroviscoelastic Constitutive Model for the Cornea

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The cornea refracts incoming light rays while being considered as a protective shield for the eye. We have recently shown that material properties of corneal tissue can be obtained from analyzing the unconfined compression experimental measurements using a linear transversely isotropic biphasic material model [1]. In particular, we observed that although the linear transversely isotropic biphasic model gives reasonable estimates for the in-plane and out-of-plane material properties, it is unable to fully curve-fit the experimental stress-relaxation history [2]. Here, we create a linear transversely isotropic poroviscoelastic model by combining a viscoelastic material law with the transversely isotropic biphasic model. This new material model incorporates viscoelastic contributions from both the fluid flow and the intrinsic viscoelasticity. We report the results of our parametric study as well as the efficacy of the proposed theory in representing the unconfined compression experiments on corneal tissue. We conclude that that this new model is able to accurately capture the unconfined viscoelastic behavior of soft tissue with a transversely isotropic skeleton.

A Mathematical Model for Oxygen Transport in the Human Placenta

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The human placenta is the sole of organ of exchange between the mother and the growing fetus. Efficient oxygen and nutrients transfer in the organ is vital for the normal development of the baby. The fetal part of the organ consists of a tree of villi, inside which capillaries carry blood from the umbilical artery to the umbilical veins. The maternal part is a blood basin, into which the fetal tree is immersed. As the blood of the mother and that of the fetus do not mix, the surface of the villous tree constitutes the exchange surface of the system.
Taking advantage of the precise 2D placental structure provided by the placental histology, we construct a 3D model of oxygen transport in the placenta by extending 2D histological cross-sections along the third dimension. The model simultaneously accounts for both diffusion and convention of oxygen in the intervillous space and allows one to predict oxygen uptake of a placentone.
The diffusion-convection equation governing oxygen exchange is first numerically solved for different densities of circular fetal villi in a placentone. These calculations provide estimations of the oxygen uptake of a placentone with an arbitrary villi density and demonstrate the existence of an optimal villi density maximizing the uptake. This optimality is explained as a trade-off between the incoming oxygen flow and the absorbing villous surface.
As a next step, the assumption of circular villi is relaxed and an approximate analytical solution is proposed. It is shown that only two geometrical characteristics – the villi density and the effective villi radius – are required to predict the fetal oxygen uptake. Two combinations of physiological parameters that determine oxygen uptake in a given placenta are also identified: (i) the maximal oxygen inflow of a placentone, and (ii) the Damköhler number. Analytical formulas for fast and simple calculation of oxygen uptake are derived, and two diagrams of oxygen transport efficiency in an arbitrary placental cross-section are provided.
Finally, an automatic image analysis method is developed allowing one to analyze large histological human placenta cross-sections and to determine areas, perimeters and shapes of villous, intervillous space and fetal capillary compartments. This method is applied to 24 cross-sections from 22 healthy and 2 pathological pregnancies. It is demonstrated that the villi density of a healthy human placenta lies within 10% of the optimal value, while its overall geometry efficiency is rather low (around 30–40%).

Implementation of Abdominal Aortic Aneurysm Growth and Remodeling Model into Finite Element Code

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Abdominal aortic aneurysm (AAA) is local dilatation of infrarenal abdominal aorta, characterized by loss of functional elastin and smooth muscle. AAA is typically asymptotic disease; however, complications such as dissection, rupture, and embolization can lead to death. In the last decade significant progress was made in numerical modeling of AAAs. Nevertheless, our ability to predict whether a specific lesion will arrest, continue to enlarge either slowly or rapidly, or ultimately rupture remains wanting.

The goal of this research is to improve and extend recent 1D growth and remodeling (G&R) models limited to cylindrical geometry (e.g., [1]) to axisymmetric, and ultimately to a general 3D geometry. This requires an implementation of AAA G&R models into a nonlinear finite element analysis program (FEAP).

Aortic wall is composite structure organized into layers. These layers entail different structural components. Healthy aorta is composed of three layers: intima, media, and adventitia. Each of these layers contains different amount of constituents (elastin, collagen fibers, and smooth muscle cells). The model is based on constrained mixture model and theory of evolving configurations, as proposed in [2]. Nonlinear material behavior, described by strain energy functions, is implemented in FEAP by modifying user material (umat) subroutine that calculates Cauchy stress and tangent modulus. Special attention is given to enforcement of incompressibility by augmented Lagrange method. Contrary to some implementations in the finite element code, employment of a deviatoric split of the stresses proved to be unstable and the obtained results that are in conflict with theoretical framework. We, therefore, used mixed formulation, as had been verified in several studies (e.g., [3]).

Finite element growth and remodeling model of aorta was tested on cases of changed hemodynamics, and aging of healthy aorta. The results strongly agreed with semi-analytical results from Matlab.

The simulated development of an AAA was initiated by prescribing a loss of elastin in an initially healthy, but aged aorta, thus avoiding assumptions on pre-stretches and orientations of constituents in already existing aneurysm. Future models should consider degradation of elastin to be dependent on concentration of elastase, and not only on time.