

Research Statement

Jennifer J. Young
jendjoy@email.unc.edu

My research in applied mathematics focuses on the computational modeling of biomechanics, specifically the development of efficient numerical tools to simulate cellular dynamics. However, I have a broad interest in computational biology, and would like to continue to conduct research in this field once I have completed my PhD.

Thus far, I have completed work on the main framework for a computational model of cellular blebbing (a protrusive activity of animal cells). This fluid-structure interaction model includes the coupled motion of a Newtonian fluid with numerous elastic structures enclosed in a viscoelastic membrane. Together with my advisor, Sorin Mitran, we are developing a continuum-microscopic computation (to be linked to the current model) that will capture the nonequilibrium microdynamics of complex cellular structures. In this research statement I will summarize my work and outline future plans.

Fluid-Structure Interaction

In animal cells, the cytoskeleton and the plasma membrane are normally attached via adhesive proteins. Blebs are fluid-filled, quasi-spherical protrusions that form when the membrane and cytoskeleton detach, and the membrane is pushed outward by the cell's internal fluid pressure [2]. To model this biological phenomena, I developed a fluid-structure interaction algorithm implemented via an operator splitting procedure (see Figure 1 for an outline).

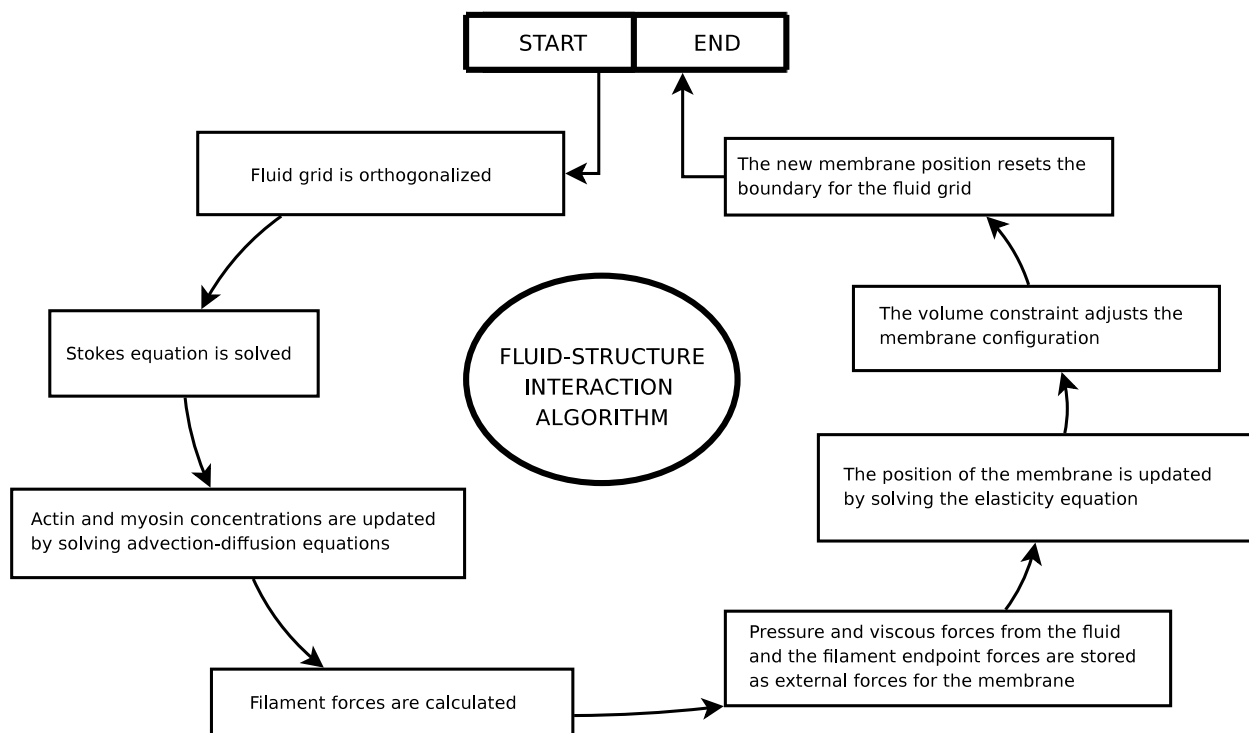


Figure 1: The sequence of steps which occurs during one time step of the simulation.

A damped wave equation is employed to model the membrane's motion and the Stokes equations for an incompressible fluid are utilized to model the cytosol. The model also includes advection-diffusion equations to monitor protein concentration levels. The cytoskeleton is represented as a set of filaments, modeled as elastic structures governed by Hooke's law. This description is in contrast to previous models which include a continuum representation of the cytoskeleton, (e.g. poroelastic [2] and two-phase fluid [1] models). My choice to model the cytoskeleton in this fashion allows for a straightforward transition to a continuum-microscopic model of the same phenomenon.

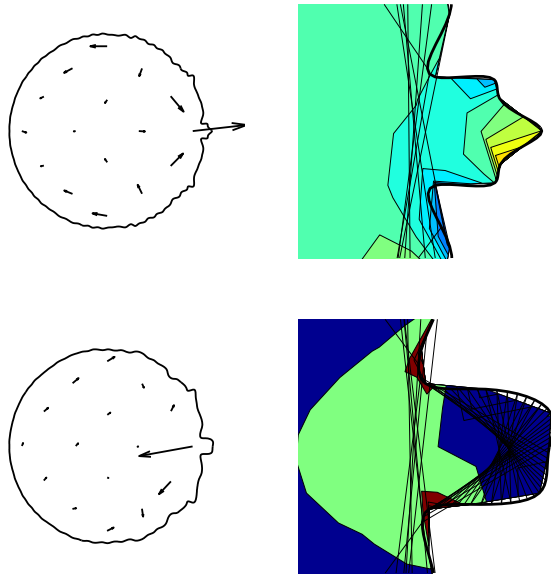


Figure 2: Some examples of snapshots of time steps in bleb formation. The whole cell pictures show velocity vectors of the cytosol. The zoom view figures show pressure contours and the cytoskeletal and retraction filaments.

A publicly available software implementation based on the Bearclaw framework [5] was developed to carry out the numerical simulation. The partial differential equations (PDEs) in this model include hyperbolic, parabolic and elliptic operators which are solved using techniques such as wave propagation methods [4], Crank-Nicolson schemes, and multigrid iterative procedures. Fractional step methods such as Strang splitting are employed to incorporate source terms into the solutions. An orthogonal, curvilinear grid is used to discretize the complex, two-dimensional domain in order to easily carry out numerical procedures.

Given a domain boundary, this type of grid is generated by solving a set of PDEs derived from the Euler-Lagrange variational principle [6]. Another interesting numerical issue that arises in this model is the problem of volume conservation. The operator splitting algorithm used in the simulation is computationally efficient but does not guarantee volume conservation over the fluid domain. Gauss' principle of least constraint is applied through a constrained, energy minimization procedure to obtain a corrected configuration that encloses the specified volume. A quasi-Newton method is utilized to solve the problem. Figure 2 depicts some examples of the realistic results that were obtained with the model.

Model Extension

Introduction: The current implementation includes a subset of the total number of filaments in a typical cytoskeleton. The underlying micromechanics of the true, complex network are represented in the model via average forces on these sample filaments. My thesis work involves the development of a micromechanical computation that can be linked to the current model, in order to more accurately

update these average forces. Direct numerical simulation of the $O(10^5)$ actin filament segments forming the cytoskeleton is computationally expensive. My thesis work investigates the possibility of speeding up such a simulation through a continuum-microscopic interaction approach, wherein the continuum-level constitutive equations, locally valid on some portion of the cytoskeleton, are updated at regular time intervals with information averaged from the full microscopic model. One problem that arises in such an approach is to be able to describe the micromechanical configuration of the cytoskeleton based upon continuum-level field variables (e.g. stress tensor). The problem is challenging because simple simulations show that the microscopic configuration cannot be described by normal, Gaussian statistics (as used in other work [3]), which is essentially a consequence of the system being far from equilibrium during cytoskeletal deformation.

My work focuses on developing approximate distribution functions that efficiently include enough information to capture this nonequilibrium behavior. The main questions are: 1. Given the current data on a random variable, can we construct what its distribution function looks like? 2. Can we use these approximate functions to predict the evolution of the distribution function at the next time step? 3. What random variables are specifically important to the reconstruction of the cytoskeleton's microstructure to accurately capture its behavior under various strains? To answer these questions, I am exploring various ways of representing distribution functions including the characteristic function and orthogonal expansions, and I am also developing various methods to instantiate the microscopic network from these resulting distribution functions.

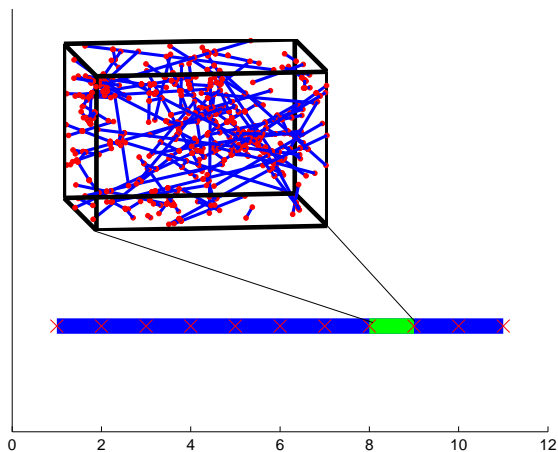


Figure 3: A one-dimensional macroscopic string where each segment is really a three-dimensional microscopic network of crosslinked fibers.

Distribution Function Development: To understand how to construct such functions, test cases, such as the one-dimensional string described below, are utilized to look for patterns and correlations between variables such as strain, elastic moduli, filament network density, crosslink density, and filament lengths, positions and orientations. We begin with a one-dimensional string that is periodically stretched and compressed longitudinally. This string is actually composed of many microscopic, crosslinked fibers, which are not visible at the length scale of the whole string. When this string is placed under an extensional strain, its behavior will depend on the response of the microscopic fiber network, thus its motion can be modeled by a variable speed wave equation: $u(x,t)_{tt} = (c(x,t)^2 u(x,t)_x)_x$ where $u(x,t)$ is the longitudinal displacement and $c(x,t)$ is the wave speed.

A time step of the code implementation contains the following steps. Each one-dimensional segment of string will be represented by a three-dimensional block of crosslinked fibers (see Figure 3). The positions, orientations, and lengths of these filaments (all random variables) and their crosslinks to one another are instantiated using the approximate distribution functions computed from the statistical information of the microscopic network in that block at the previous time step. The block is

then displaced according to the macroscopic motion. The internal filaments and crosslinks are rearranged to find a new configuration of minimal energy. This is done via a gradient search procedure, where the goal is to minimize the system's stored extensional and bending energies:

$$Energy = \sum_{j=1}^m \left[\frac{k}{2} (L^j - L_0^j)^2 + \int_0^{L_0^j} \frac{EI w''(x)^2}{2} dx \right]$$

where k is the filament spring constant, L^j and L_0^j are the current and equilibrium lengths respectively of the j^{th} filament or crosslink segment, E is the elasticity modulus, I is the second moment of inertia, and $w''(x)$ is the second derivative of the deflection function. Once the minimum has been found, the forces on each block face are computed by summing the forces of the individual filaments that are attached to that face. Hooke's law: $F = -K\Delta x$ is used to find K , where F is the total normal force, Δx is the overall extension of the block and K is the block spring constant (all values computed for the longitudinal direction in this one-dimensional case). This K is then used to update the wave speed for that segment of string when solving for the macroscopic motion.

Preliminary Results: From this simple string example, some basic notions are already clear. For example, data was collected on the angles each filament makes with the longitudinal axis (direction of strain). As the strain grows, the average of this angle decreases. This result can be explained by the fact that in order to minimize energy the filaments tend to align themselves in the direction of strain (see Figure 4).

More importantly, the preliminary data suggests that thermal equilibrium cannot be assumed. In a Gaussian distribution, only the first two cumulants are non-zero (the mean and variance). Our preliminary data shows that the higher order cumulants of random variables such as filament position and length are non-zero (see Figure 4), thus justifying our search for distribution functions that incorporate more statistical data.

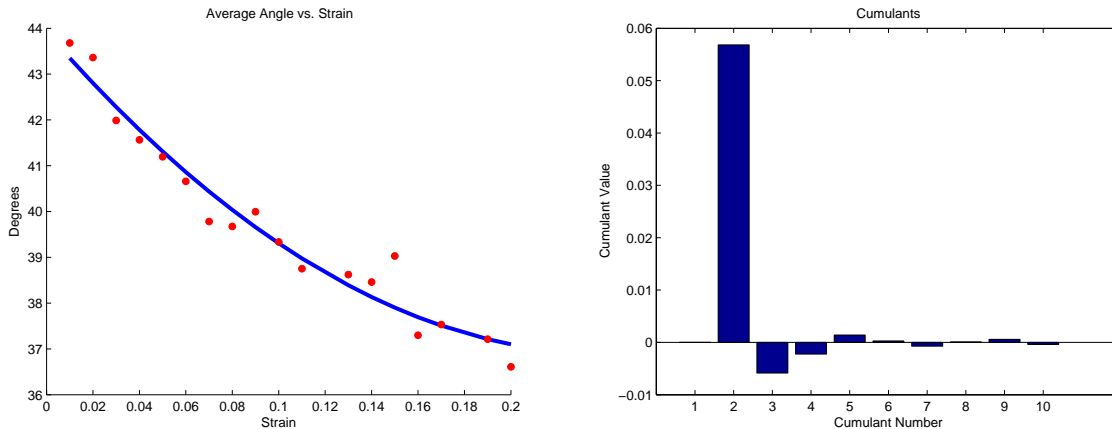


Figure 4: (a) Average angle of filaments to the longitudinal axis vs. strain. (b) The first ten statistical cumulants of the x position of the filament centers for a 3D block of filaments after a strain has been applied.

Future Work

Once I have completed work on comparing various procedures to deduce locally valid distribution functions in the context of cytoskeletal mechanics, I am interesting in applying these algorithms to

the blebbing phenomenon. Besides this application, these algorithms will be useful in many areas of biomechanics. Possible applications that I am interested in working on in the future include red blood cell (RBC) deformation as it squeezes through a capillary and modeling the eye during a retinal detachment. Both situations would require accurate simulations of the microdynamics of a complex network, (spectrin network for the RBC and the retina in the eye), and utilizing distribution functions that capture nonequilibrium behavior to model these structures would be a novel approach.

Elaborating further on the second research topic, there has not been a great deal of research on the computational modeling of the dynamics of the retina as it peels away from the back of the eye during a detachment. The retina is a layered tissue composed of millions of interconnected nerve cells. The main body of the eye contains vitreous fluid, which if it seeps through a hole or tear in the retina can force the retina to pull away from the blood vessels that transmit visual information, causing the person to lose sight in that region of their visual field. People with severe myopia or those with a condition known as retinoschisis are more prone to detachments because their retinas are thinner and weaker in localized areas. Modeling a retinal detachment is clearly a fluid-structure interaction problem with multiple scales of interest. Questions I want to explore include: 1. Can distribution functions be utilized to instantiate an accurate, heterogeneous, microscopic description of the retina in people with highly localized thin spots and holes? 2. Can an efficient continuum-microscopic solver be developed to model this problem three-dimensionally and on relevant time scales? 3. Head trauma is known to be a cause of retinal detachments. Knowing patients' retinal microstructure in advance, can I predict who is more likely to experience a retinal detachment after a head trauma, based on variables such as locations of thin spots, direction and magnitude of the trauma force, etc.

My research ideas fit into the broad topics of multi-scale modeling, fluid-structure interaction, and computational biomechanics. I look forward to the opportunity to collaborate with new colleagues on common research goals

References

- [1] W. Alt and M. Dembo. Cytoplasm dynamics and cell motion: two-phase fluid models. *Mathematical Biosciences*, 156(1-2):207–228, March 1999.
- [2] G. T. Charras, M. Coughlin, T. J. Mitchison, and L. Mahadevan. Life and times of a cellular bleb. *Biophysical Journal*, 94(5):1836–1853, March 2008.
- [3] Weinan E and B. Engquist. Multiscale modeling and computation. *Notices of the AMS*, 50(9):1062–1070, Oct 2003.
- [4] R. LeVeque. Wave propagation algorithms for multidimensional hyperbolic systems. *Journal of Computational Physics*, 131:327–353, 1997.
- [5] S. Mitran. Bearclaw, 2001. <http://coanda.amath.unc.edu/bearclaw>.
- [6] Y. Zhang, Y. Jia, and S. Wang. 2d nearly orthogonal mesh generation with controls on distortion function. *Journal of Computational Physics*, 218(2):549–571, November 2006.