4. the cytoskeleton - network models

Write a one paragraph proposal for what you would like to do your final project. You will get some feedback on it, so you can use it as an opportunity to check whether any project ideas you may have are appropriate/acceptable. Some of last year’s projects are given below. There are three options: (i) a literature review on a topic related to cell mechanics and/or mechanotransduction, (ii) a review of a topic on cell mechanics that was not covered in class, or (iii) a computational and/or theoretical analysis of some mechanical phenomenon related to cell mechanics. Papers in the past have generally been about 4-6 pages, two column, with about 3-5 figures and 8-12 references. Here are some examples of individual projects.

- Predicting microtubules structure using molecular dynamics
- The primary cilium: A well-designed fluid flow sensor
- The tensegrity paradigm
- Mechanotransduction in hair cells Translating sound waves into neural signals
- Modeling cell membrane dynamics
- Dielectrophoresis properties and their microfluidic application: Cell concentrator
- Theoretical and experimental study of the penetration of the cell membrane
- Integrin and its role in mechanotransduction
- Finite element analysis of micropipette aspiration

homework #02 - problem 03

Final Project ME339, Fall 2008

CS Simmons

ME339 FINAL PROJECT

THE ROLE OF CELL-CELL JUNCTIONS IN CARDBIO MYOCYTE CONTRACTILITY AND MODIFICATIONS NEEDED IN MECHANICAL MODELS

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ABSTRACT

As adult cardiomyocytes (CMs) cannot recover from damage due to pathologies like myocardial infarction, researchers are looking for ways to culture functional cardiomyocytes to repopulate diseased cardiac tissue. However, as damaged tissue may interfere with cell-cell communication, the role of cell-cell junctions in cardiacmyocyte contractility must be considered. This paper examines current literature on CM contractility, evaluating first the role of the cytoskeleton in CM contractility and then the hypothesized role of cell-cell junctions. Additionally, the likelihood of adapting computational models to reflect abnormal conditions of cell-cell junctions is considered. Further examination of contractile force generation with modification of certain cytoskeletal and junctional proteins is recommended to facilitate incorporation into tissue-scale models and to understand the contribution of these various proteins to heart disease.
example: finite element simulation of pipette aspiration

assuming we know the mechanical properties of the individual filaments, what does that actually tell us about the assembly of filaments that we find in the cell?

- could we then predict the **stiffness of the overall assembly**?
- how does the filament microstructure affect **cytoskeletal properties**?
- how can we calculate the **macroscopic network properties** from the individual microscopic filament properties?

elements of the cytoskeleton
microtubules
intermediate filaments
actin filaments

Figure 4.1: The cytoskeleton provides structural stability and is responsible for forces during cell locomotion. Microtubules are thick hollow cylinders reaching out from the nucleus to the membrane, intermediate filaments can be found anywhere in the cytosol, and actin filaments are usually concentrated close to the cell membrane.
from molecular level to cellular level

three examples

- **fiber bundle model** for filopodia
- **network model** for red blood cell membranes
- **tensegrity model** for generic cell structures

### 4.1 mechanics of the cytoskeleton

assembly of crosslinked actin filaments

<table>
<thead>
<tr>
<th>cell with filopodia</th>
<th>filopodia as bundles of actin filaments</th>
<th>actin cross-linking through fascin</th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="cell with filopodia" /></td>
<td><img src="image2.png" alt="filopodia as bundles of actin filaments" /></td>
<td><img src="image3.png" alt="actin cross-linking through fascin" /></td>
</tr>
</tbody>
</table>

Figure 4.3. Bundles of actin filaments tightly crosslinked through fascin are known as filopodia. The mechanical properties of filopodia play an essential role in various different physiological processes including hearing, cell migration, and growth.

filopodia are very thin structures approximately 0.2 um in diameter, they can easily extend up to 1.5um. they typically polymerize and depolymerize at rates of approximately 10 um/min. the mechanical properties of filopodia play an essential role in various different physiological processes, including hearing, cell migration, and growth. despite their importance to cell function, the structural architecture responsible for their overall mechanical behavior remains largely unknown.

### 4.2 fiber bundle model for filopodia

microstructural arrangement of actin

Figure 4.2.1. A crawling cell, drawn to scale, is shown with three areas enlarged to show the arrangement of actin filaments. The actin filaments are shown in red, with arrowheads pointing toward the plus end. Stress fibers are contractile and exert tension. The cell cortex underlies the plasma membrane. Filopodia are spike-like projections of the plasma membrane that allow a cell to explore its environments.

alberts, johnson, lewis, raff, roberts, walter [2002]

4.2 fiber bundle model for filopodia

 pushing the envelope

simplified model for cell locomotion

- protrusion ... polymerization at the leading edge of the cell
- attachment ... formation of focal adhesions to link the cell to the surface
- retraction ... contraction of stress fibers to retract the rear of the cell

Figure 4.4: Single-celled amoeba crawling around by using actin polymerization to push out pseudopods to explore new territory. Organelles move in complex patterns within the cell, alberts, johnson, lewis, raff, roberts, walter [2002]
4.2 fiber bundle model for filopodia

**pushing the envelope - critical length**

Newton’s third law: actio = reactio

\[ F_{\text{fil}} = \frac{\pi^2 EI}{[2L]^2} = \frac{\pi^2 EI}{4L} \]

\[ F_{\text{mem}} \approx 5\sqrt{n} r_{\text{act}} \text{pN/nm} \]

\[ \frac{\pi^2 EI}{4L^2_{\text{crit}}} = 5\sqrt{n} r_{\text{act}} \text{pN/nm} \]

Thus

\[ L_{\text{crit}} = \frac{\pi}{2} \sqrt{\frac{EI}{5\sqrt{n} r_{\text{act}} \text{pN/nm}}} \]

\[ E = 1.9 \cdot 10^9 \text{ N/m}^2 = 1.9 \text{ GPa} \]

\[ r_{\text{act}} = 2.5 \]

moment of inertia \( I \)

- loose assembly
- tightly crosslinked

**case I - loosely assembled actin filaments**

\[ L_{\text{crit}} = \frac{\pi}{2} \sqrt{\frac{EI}{5\sqrt{n} r_{\text{act}} \text{pN/nm}}} \]

\[ I = n l_{\text{act}} \]

\[ l_{\text{act}} = \frac{\pi r_{\text{act}}^4}{4} \]

\[ E = 1.9 \cdot 10^9 \text{ N/m}^2 = 1.9 \text{ GPa} \]

\[ r_{\text{act}} = 2.5 \]

much too low - disagrees with observations of 2um

4.2 fiber bundle model for filopodia

**case II - tightly crosslinked actin filaments**

\[ L_{\text{crit}} = \frac{\pi}{2} \sqrt{\frac{1.9 \cdot 10^9 \text{ N/m}^2 \cdot n \pi/4 \cdot [3.5 \cdot 10^{-9}]^4 \text{m}^4}{5\sqrt{n} \cdot 3.5 \cdot 10^{-12} \text{N}}} \approx 0.17769 \mu\text{m} n^{3/4} \]

\[ n = 30 \text{ filaments} \]

\[ L_{\text{crit}} = 2.278 \mu\text{m} \]

better model - agrees with observations of 2um

4.3 network model for red blood cells

**red blood cells**

Erythrocytes, red blood cells are essential to deliver oxygen to the body via the blood flow through the circulatory system. They take up oxygen in the lungs and release it while squeezing through the body’s capillaries. Adult humans have about 2-3 \( 10^{13} \), 20-30 trillion, red blood cells comprising about a quarter of the total amount of cells in the human body.
4.3 network model for red blood cells

human mature red blood cells are **flexible biconcave disks** that lack a cell nucleus and most organelles. Typical human erythrocytes have a disk diameter of 6–8µm, a thickness of 2µm, a volume of 90fL, and a surface of 136µm². They can swell to spherical shape of 150fL, without membrane distension. The membrane of the red blood cell plays a key role in regulating **surface deformability**, flexibility, and adhesion to other cells. These functions are highly dependent on its composition. The red blood cell membrane is composed of 3 layers: the glycocalyx on the exterior, which is rich in carbohydrates; the lipid bilayer consisting of lipidic main constituents and transmembrane proteins; and the membrane skeleton, a **structural network of proteins** located on the inner surface of the lipid bilayer.

4.3 network model for red blood cells

**Metabolic remodeling of the human red blood cell membrane**

**YongSoo Park**, Catherine A. Best, Thorsten Autl, Nir S. Gov, Samuel A. Safran, Gabriel Popescu, Subra Suresh, and Michael S. Feld

Fig. 1. Effects of ATP on morphology and dynamic fluctuation in RBC membrane. Topography of a healthy RBC (A) of an ATP-depleted RBC (ensemble=ATP group, B, C, and D), and of a RBC with recovered ATP level (E, ATP group, C-G), and simultaneous displacement maps of membrane fluctuation in the Fig. 1A-D, resp. The scale bars are 2 µm. The colorbar scales are in µm and mm, resp.

the human red blood cell membrane skeleton is a network of roughly 33,000 protein hexagons that looks like a microscopic geodesic dome