MOLECULAR, CELLULAR, & TISSUE BIOMECHANICS

Spring 2015

Problem Set #7 – Cell viscoelasticity

Distributed: Thursday, April 23, 2015
Due: Monday, May 4, 2015

Problem 1: Viscoelastic cell

An experimentalist wishes to monitor the *viscoelastic* properties of a cell while it is tethered to a *linear elastic* substrate and undergoing cyclic stretch. For this purpose, the following experiment is designed.

A cell is seeded onto and allowed to adhere to the surface of the elastic substrate that is initially stretched by a steady force F_i. Given the dimensions of the cell and the elastic strip, you may assume that the deformations of both are essentially one-dimensional, e.g., only in the x-direction. Also, for the purpose of this problem, you may assume that the cell adheres primarily at two points, one at either end, at a distance x_2 apart, and that the ends of the elastic strip, where the force is applied, is a distance x_1 from the cell, symmetric on both ends (see figure). Fluorescent beads are embedded in the elastic strip, and two beads, one at the site of each adhesion site, are monitored over time as the strip is periodically strained.
From this initially stretched state, a sinusoidal displacement is applied so that the distance between the two adhesion sites (the length of the cell) is:

$$x_2(t) = x_{2i} + x_{20} \exp i(\omega t)$$

and the force is measured to be:

$$F(t) = F_i + F_0 \exp i(\omega t + \phi)$$

where F_i, L_i, x_{2i}, F_0, x_{20}, ω and ϕ are all considered known from the measurement. Note that since the substrate is assumed to be linearly elastic, the extensions of the two end regions can be treated as linear springs, each of stiffness k_1; the initial (relaxed) length of each is x_{1i}. **Both k_1 and x_{1i} are also known.**

a) In performing the analysis, the cell is assumed to behave as a Maxwell body. Sketch the spring and dashpot system that is equivalent to the combination elastic substrate and cell shown in the figure. Denote spring stiffnesses by k, and dashpot viscosity by η.

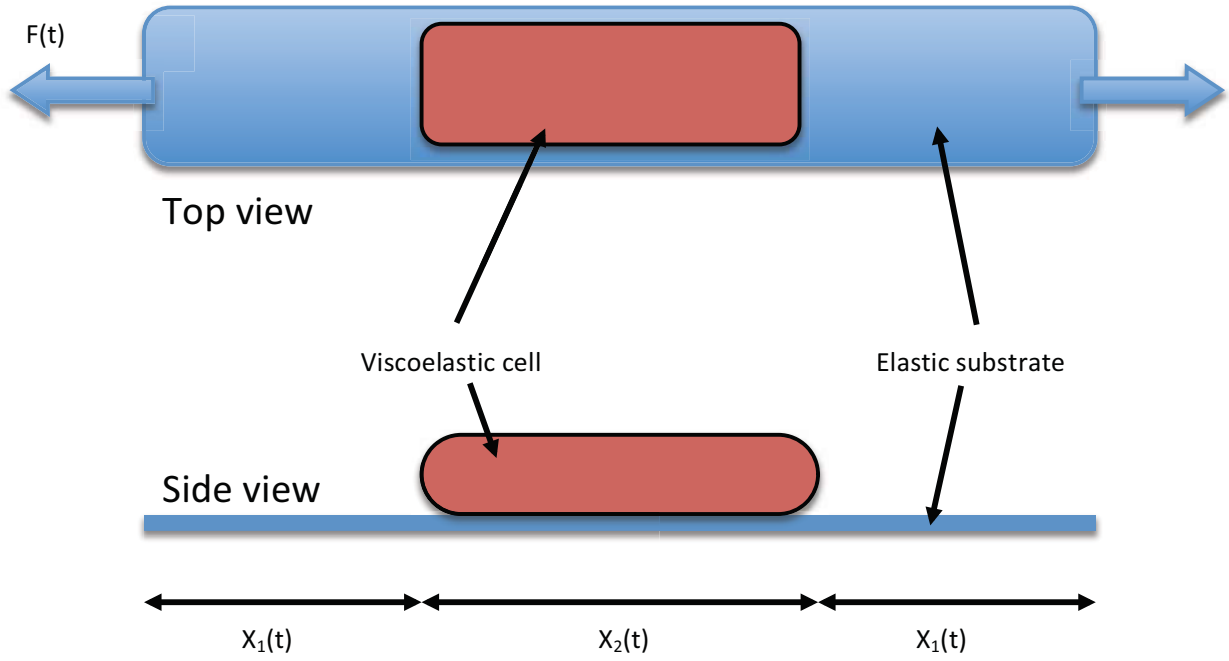
b) Analyze the deformations of this system, and obtain two algebraic equations from which the two unknowns of the Maxwell body (the viscosity of the dashpot and the stiffness of the spring) can be determined from the known parameters specified above. (For this part, you may assume that x_{2i} is known and F_i equals zero.)

c) In reality, during the time that the cell is adhering to the substrate, it generates an internal tension or prestress, causing x_1 to increase and x_2 to decrease from their original values before cell attachment. How would you accommodate this affect in your analysis? (Hint: would the Maxwell body still be an appropriate model?)

d) What intracellular proteins would be responsible for the prestress, and how would the magnitude of the prestress be determined? That is, in what measured parameters would it be reflected and how would you determine the prestress from changes in these parameters?

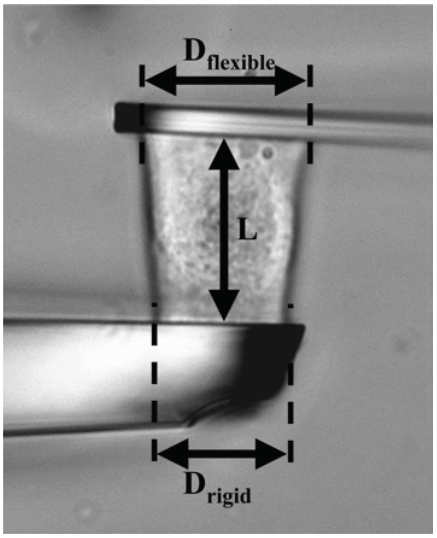
e) During the course of the experiment, the cell is expected to remodel by alignment of the actin filaments and the formation of stress fibers. How would you expect this to affect the parameters of the model?

f) Finally, consider the frequency dependence of G' and explain how you would obtain the spring constant for the substrate with the cell attached, without making any measurements in addition to those mentioned above.



Problem 2: Cell Stretching

In a series of experiments conducted by Desprat, et al., a cell is tethered to two surfaces, and deformed under a constant stress of σ_0 (see figure). Note that the authors fit the experimental data to two different models, one comprised of springs and dashpots, and the other described simply in terms of the creep compliance, defined as:



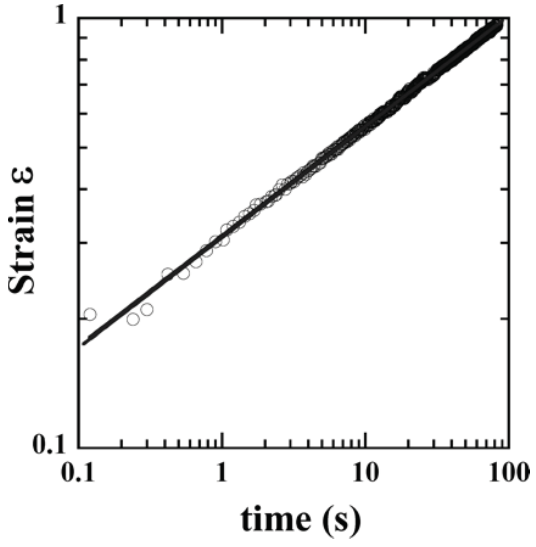
$$J(t) \equiv \frac{\varepsilon(t)}{\sigma_0} = kt^{\alpha}$$

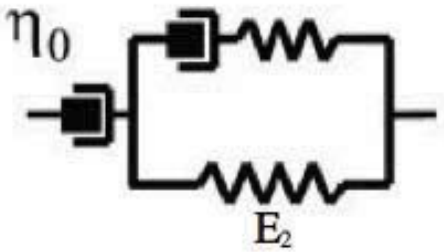
where k and α are parameters determined from the fit to the experimental data.

a) Using the data shown in the plot below (open circles), determine the values of k and α. The level of stress, σ_0, is 100 Pa.

b) As a practical matter, it is difficult to apply the stress as a true step function. If the stress is applied as a linear ramp from 0-100 Pa over a period of 100 ms, then held constant, compute the corresponding strain. Plot this strain as a function of time on a linear scale for the period $0 < t < 500$ ms.

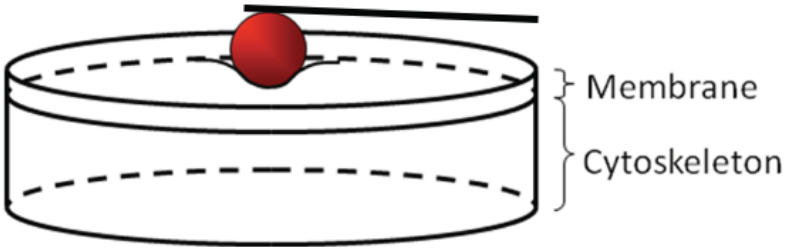
c) Consider now the spring and dashpot model representation shown in the figure. Recognizing that this model is simply a three element standard linear solid (SLS) model and a dashpot in series, and given the relationship between the stress and strain for the SLS model from earlier class notes, obtain the governing differential equation for this system. (Note: by using the SLS model result, in combination with the constitutive law for a single dashpot, you can reduce the algebra considerably!)





Problem 3: Cell and membrane indentation

Consider a cell that is probed with an atomic force microscope (AFM) tip consisting of a polystyrene bead attached to the cantilever (see Figure below). For simplicity, assume that cell can be approximated by a model consisting of an elastic membrane and an elastic cytoskeleton, and you can assume that the size of the cell is much larger than that of the bead.



Let's take a look at the contribution of the membrane and the cytoskeleton separately. For parts *(d)* – *(f)*, assume the following material properties.

$G, E \sim 500$ Pa
$\nu = 0.5$
$K_b = 10^{-17}$ Nm
$N = 10^{-6}$ N/m
$R = 0.5$ μm

a) Using a scaling approach, derive an expression for the force, $F_{membrane}$, required to indent the membrane by a distance, δ. You can assume that membrane deformations occur over a distance, *a,* that is similar to the bead diameter.
The general membrane equation is given by:

$$P = -N\frac{\partial^2 u_3}{\partial x_1^2} + K_b\frac{\partial^4 u_3}{\partial x_1^4}$$

where *P* is the pressure acting on the membrane, *N* is the membrane tension, and K_b is the membrane bending stiffness. The first term on the right hand side describes the contribution of the membrane tension, while the second term describes the contribution of membrane bending.

b) Using a scaling approach, derive an expression for the force, F_{cyto}, required to indent the cytoskeleton by a distance, δ. You can assume that cytoskeletal deformations occur over a distance, *a,* that is comparable to the bead diameter.

c) The exact solution for the indentation of an elastic medium with a spherical tip is given by the Hertz equation

$$F = \frac{4}{3}\frac{E}{1-\nu^2}R^{0.5}\delta^{1.5}$$

d) Where F is the force, E is the Young's modulus, n is the Poisson's ratio, R the radius of the sphere, and d the indentation depth. Compare the results from your expression obtained in part (b) with the results from the Hertz equation for an indentation of 100 nm. Why do they differ? Is the difference important?

e) Let's take a quick look at very small indentations first. In the following, we'll assume that we can calculate the forces for the membrane and the cytoskeleton independently from each other for any given indentation. For an indentation, δ, of 10 nm, what forces do the membrane ($F_{membrane}$) and the cytoskeleton (F_{cyto}) contribute? For the cytoskeleton, you can use the exact (Hertz) equation. Regarding the membrane forces, does tension or bending dominate?

f) Now let's look at an indentation, δ, of 1,000 nm. What are the contributions of the cytoskeleton and the membrane now? Regarding the membrane forces, does tension or bending dominate?

g) Can this elastic model describe the frequency dependence of the cellular mechanical properties that is observed in real experiments? Explain your answer.

20.310J / 3.053J / 6.024J / 2.797J Molecular, Cellular, and Tissue Biomechanics
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