BE/APh 161: Physical Biology of the Cell

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15 The cell as a material

The cell as a whole behaves like a **viscoelastic material**. By viscoelastic, we mean the the cell has properties that are both fluid-like and solid-like. As a reminder, the stress/strain relationship for a solid is

$$\sigma = E\varepsilon, \tag{15.1}$$

where ε is the strain, σ is the stress, and E is the Young's modulus. That is to say that the stress is directly proportional to the strain, at least for small stresses/strains. Nonlinearities start to become important for larger stresses or strains.

Conversely, the stress is proportional to the *strain rate* for a viscous fluid.

$$\sigma = \eta\dot{\varepsilon}, \tag{15.2}$$

where the overdot signifies time differentiation.

15.1 Storage and loss moduli

Imagine the following thought experiment. A material (either a cell, or something like a reconstituted actin network) is subjected to a periodic stress with frequency ω and amplitude σ_0.

$$\sigma(t) = \sigma_0 \sin \omega t, \tag{15.3}$$

After some time, the strain will also be periodic, with amplitude ε_0 and frequency ω. However, it will not necessarily be in phase with the stress, so we define a phase shift δ.

$$\varepsilon(t) = \bar{\varepsilon} + \varepsilon_0 \sin(\omega t - \delta), \tag{15.4}$$

where $\bar{\varepsilon}$ is the baseline strain from the oscillation. If $\delta = 0$, then $\sigma \propto \varepsilon$, so the material behaves like an elastic solid.[2] If $\delta = \pi/2$, then

$$\varepsilon(t) = \varepsilon_0 \sin(\omega t - \delta) = \varepsilon_0 \cos \omega t. \tag{15.5}$$

In this case, then $\sigma(t) \propto \dot{\varepsilon}(t)$, so the material behaves like a viscous solid. For phase shifts in between, the material behaves both like a solid (strain in phase with the stress) and like a viscous fluid (strain out of phase with the stress). We can define parameters to describe the solid-like and fluid-like responses of a material to stress.

[2] I am being loose with the $\propto$ symbol here. There is an additive constant, $\bar{\varepsilon}$, but that constant is zero for purely elastic responses, as we will see later in the response for a Maxwell material.

These parameters are the **storage and loss moduli**. They are defined in terms of the amplitudes of the stress and strain amplitudes and the phase shift δ. The are

$$\text{storage modulus} = E' = \frac{\sigma_0}{\varepsilon_0}\cos\delta \tag{15.6}$$

$$\text{loss modulus} = E'' = \frac{\sigma_0}{\varepsilon_0}\sin\delta. \tag{15.7}$$

These are in general both frequency dependent. They can be measured empirically. Typically the stress is imposed (so σ_0 is known), and the strain is measured. The storage modulus is measure of the solid-like response and the loss modulus is a measure of the viscous-like response.

15.2 Linear viscoelasticity

While the storage and loss moduli are experimentally determined, we do not have a generic model for how a material responds to stress. This is where the **theory of linear viscoelasticity** is useful. We will explore this idea first through example and then sharpen what linear viscoelasticity is.

15.2.1 The Maxwell model

Imagine we have a material that is both solid-like and fluid-like. I will write down a constitutive relation and then show that the material is solid like on short time scales (high frequency) and fluid like on long time scales (low frequency). The constitutive relation is

$$\sigma + \tau_M\,\dot{\sigma} = \eta\,\dot{\varepsilon}. \tag{15.8}$$

Here, $\tau_M = \eta/E$ is the **Maxwell time**. Let us now perform the experiment where we exert a periodic stress on this material. We take $\sigma(t) = \sigma_0 \sin\omega t$. Then, we have

$$\sigma_0(\sin\omega t + \tau_M\omega\cos\omega t) = \eta\,\dot{\varepsilon}. \tag{15.9}$$

As a result, we have

$$\dot{\varepsilon} = \frac{\sigma_0}{\eta}(\sin\omega t + \tau_M\omega\cos\omega t). \tag{15.10}$$

We can integrate this ODE to get

$$\varepsilon = \sigma_0\left(-\frac{\cos\omega t}{\eta\omega} + \frac{\sin\omega t}{E}\right) + C, \tag{15.11}$$

where C is an integration constant. If we take $\varepsilon(0) = 0$, then $C = \sigma_0/\eta\omega$, giving

$$\varepsilon = \sigma_0 \left(-\frac{\cos \omega t}{\eta\omega} + \frac{\sin \omega t}{E} \right) + \frac{\sigma_0}{\eta\omega} \tag{15.12}$$

We can rearrange our expression for the strain by multiplying both sides by E to get

$$E\varepsilon = -\frac{\sigma_0}{\tau_M \omega} \cos \omega t + \sigma_0 \sin \omega t + \frac{\sigma_0}{\tau_M \omega}. \tag{15.13}$$

Now, if $\omega\tau_M \gg 1$, i.e., for high frequencies, the first and last terms are negligible and we have

$$E\varepsilon = \sigma_0 \sin \omega t = \sigma, \tag{15.14}$$

which is the constitutive relation for an elastic solid. For low frequencies, the second term is negligible and we have

$$E\varepsilon = -\frac{\sigma_0}{\tau_M \omega} \cos \omega t + \frac{\sigma_0}{\tau_M \omega} \tag{15.15}$$

so

$$\dot{\varepsilon} = \frac{\sigma_0}{\eta} \sin \omega t = \sigma/\eta, \tag{15.16}$$

which is the constitutive relation for a viscous fluid. So, the material with this constitutive relation is elastic on short time scales and viscous on long time scales.

15.2.2 The creep function

Instead of investigating how the material response to an oscillatory stress, imaging we instead suddenly impose a stress σ_0 upon the material. So, we have

$$\sigma(t) = \sigma_0 \theta(t), \tag{15.17}$$

where $\theta(t)$ is the Heaviside step function.

We will now compute the creep function for a Maxwell material. Inserting this into the constitutive relation (15.8), and noting that the time derivative of a Heaviside function is a Dirac delta function, we have

$$\sigma_0 \theta(t) + \sigma_0 \tau_M \delta(t) = \eta \dot{\varepsilon}. \tag{15.18}$$

We can solve this differential equation by integrating.

$$\varepsilon = \int_{-\infty}^{t} \mathrm{d}t' \left(\frac{\sigma_0}{\eta} \theta(t') + \frac{\sigma_0}{E} \delta(t') \right) = \frac{\sigma_0}{\eta} t\theta(t) + \frac{\sigma_0}{E} \theta(t) \tag{15.19}$$

$$= \frac{\sigma_0}{E} \left(1 + \frac{t}{\tau_M}\right) \theta(t).$$

In general, we can write the response to a step in stress as

$$\varepsilon(t) = \sigma_0 J(t) \theta(t), \tag{15.20}$$

where $J(t)$ is called the **creep function**. For a Maxwell material,

$$J(t) = E^{-1}(1 + t/\tau_M). \tag{15.21}$$

We note that for $t \gg \tau_M$, $J(t)$, and therefore also $\varepsilon(t)$ diverge. So, for long times, a Maxwell material behaves like a fluid with $J(t) \approx \eta^{-1} t$ and $\varepsilon(t) \approx \sigma_0 \eta^{-1} t$, so that $\dot{\varepsilon} \approx \sigma_0/\eta$, the constitutive relation for a viscous fluid.

Similarly, for $t \ll \tau_M$, $J(t) = E^{-1}$, so that $\varepsilon = \sigma_0/E$. the constitutive relation for an elastic solid.

15.2.3 The creep function and linear superposition

The **principle of linear superposition** states that for any linear operator $\mathcal{L}$, if $\mathcal{L} f_i = g_i$, then

$$\mathcal{L}\left(\sum_i f_i\right) = \sum_i g_i. \tag{15.22}$$

In linear viscoelasticity theory, the constitutive relations are all of the form

$$\mathcal{L}\varepsilon = g(\sigma, \dot{\sigma}, \ddot{\sigma}, \ldots). \tag{15.23}$$

For example, for a Maxwell material, we can define the linear operator

$$\mathcal{L} = \eta \frac{\mathrm{d}}{\mathrm{d}t}, \quad \text{and } g(\sigma, \dot{\sigma}) = \sigma + \tau_M \dot{\sigma}. \tag{15.24}$$

We looked at the creep function for a single step in stress. Now, let's say we take two steps in stress. For concreteness, the stress prior to the first step is stress is σ_{init} the magnitude of the steps, which happen at time t_0 and t_1, are $\Delta\sigma_0$ and $\Delta\sigma_1$.

$$\sigma(t) = \sigma_{\text{init}} + \Delta\sigma_0 \theta(t - t_0) + \Delta\sigma_1 \theta(t - t_1). \tag{15.25}$$

We can directly apply the superposition principle to get the response in terms of the creep function for the single step.

$$\varepsilon(t) = \sigma_{\text{init}} J(t) + \Delta\sigma_0 J(t - t_0)\theta(t - t_0) + \Delta\sigma_1 J(t - t_1)\theta(t - t_1). \tag{15.26}$$

If we extend this to many steps, we have, again by superposition,

$$\varepsilon(t) = \sigma_{\text{init}} J(t) + \sum_i \Delta\sigma_i \, J(t - t_i)\theta(t - t_i). \tag{15.27}$$

This result is useful for interpreting experiments where more than one step in stress are taken.

We can consider the case of infinitessimal steps, which is what we would get with smoothly varying stress. Defining $\Delta t_i = t_i - t_{i-1}$, we have,

$$\sum_i \Delta\sigma_i \, \theta(t - t_i) = \sum_i \Delta t_i \, \frac{\Delta\sigma_i}{\Delta t_i} \, \theta(t - t_i) \approx \int_0^t \mathrm{d}t' \, \frac{\mathrm{d}\sigma(t')}{\mathrm{d}t'}. \tag{15.28}$$

Thus, we have

$$\varepsilon(t) = \sigma_{\text{init}} J(t) + \int_0^t \mathrm{d}t' \, J(t - t') \, \dot{\sigma}(t), \tag{15.29}$$

where we have arbitrarily taken $t_0 = 0$. Thus, we see that for any applied stress, we may use the known creep function to compute the strain by evaluating an integral. We can perform integration by parts to get

$$\begin{aligned}\varepsilon(t) &= \sigma_{\text{init}} J(t) + \left(J(t - t')\sigma(t')\right)\big|_0^t - \int_0^t \mathrm{d}t' \, \frac{\mathrm{d}J(t - t')}{\mathrm{d}t'} \, \sigma(t') \\ &= J(0)\sigma(t) + \int_0^t \mathrm{d}t' \, \sigma(t') \, \frac{\mathrm{d}J(t - t')}{\mathrm{d}(t - t')},\end{aligned} \tag{15.30}$$

an alternative and sometimes more convenient expression.

We can use this expression to derive the response of a Maxwell material to oscillatory forcing. We take $\sigma(t) = \sigma_0 \sin \omega t$. For a Maxwell material, $J(0) = E^{-1}$ and $\mathrm{d}J/\mathrm{d}t = \eta^{-1}$. We consider the case where we start the oscillation from rest at $t = 0$. Then,

$$\varepsilon(t) = \frac{\sigma_0}{E} \sin \omega t + \frac{\sigma_0}{\eta} \int_0^t \mathrm{d}t' \, \sin \omega t' = \frac{\sigma_0}{E} \sin \omega t - \frac{\sigma_0}{\eta\omega} \cos \omega t + \frac{\sigma_0}{\eta\omega}. \tag{15.31}$$

This expression is valid for positive times. For negative times, $\varepsilon = 0$. This is the same expression we got in section 15.2.1.

15.2.4 Storage and loss moduli for a Maxwell material

To compute the storage and loss moduli, we subject a material to oscillatory stress and write the response in terms of the amplitude and phase shift using the constitutive relation. We already worked out the result two different ways.

$$\varepsilon(t) = -\frac{\sigma_0}{\eta\omega} \cos \omega t + \frac{\sigma_0}{E} \sin \omega t + \frac{\sigma_0}{\eta\omega} \tag{15.32}$$

To compute the storage and loss moduli, we need to write the strain in the form

$$\varepsilon(t) = \bar{\varepsilon} + \varepsilon_0 \sin(\omega t - \delta). \tag{15.33}$$

We use the trigonometric identity that

$$a \sin x + b \cos x = \sqrt{a^2 + b^2} \sin(x + \delta), \tag{15.34}$$

$$\text{with } \tan \delta = \frac{b}{a}. \tag{15.35}$$

This gives

$$\varepsilon(t) = \frac{\sigma_0}{\eta\omega} + \sigma_0 \sqrt{(\eta\omega)^{-2} + E^{-2}} \sin(\omega t - \delta), \tag{15.36}$$

$$\text{with } \tan \delta = \frac{E}{\eta\omega} = \frac{1}{\tau_M \omega}. \tag{15.37}$$

Note that

$$(\eta\omega)^{-2} + E^{-2} = \frac{1}{E^2}\left(1 + \left(\frac{E}{\eta\omega}\right)^2\right) = \frac{1 + \tan^2 \delta}{E^2}. \tag{15.38}$$

Then, we have

$$\varepsilon(t) = \frac{\sigma_0}{\eta\omega} + \frac{\sigma_0}{E}\left(1 + \tan^2 \delta\right) \sin(\omega t - \delta). \tag{15.39}$$

We introduce another trigonometric identity, $\tan^2 x = \sec^2 x - 1$, to get

$$\varepsilon(t) = \frac{\sigma_0}{\eta\omega} + \frac{\sigma_0}{E \cos \delta} \sin(\omega t - \delta). \tag{15.40}$$

From this expression, we see that

$$\cos \delta = \frac{\sigma_0}{\varepsilon_0 E}. \tag{15.41}$$

So, the storage modulus is

$$E' = \frac{\sigma_0}{\varepsilon_0} \cos \delta = \frac{\sigma_0^2}{E \varepsilon_0^2}. \tag{15.42}$$

From equation (15.36), we have

$$\varepsilon_0 = \sigma_0 \sqrt{(\eta\omega)^{-2} + E^{-2}}, \tag{15.43}$$

so

$$E' = \frac{1}{E\left((\eta\omega)^{-2} + E^{-2}\right)} = \frac{E(\eta\omega)^2}{E^2 + (\eta\omega)^2} = E \frac{(\tau_M \omega)^2}{1 + (\tau_M \omega)^2}. \tag{15.44}$$

To find the loss modulus, we not that

$$\sin\delta = \tan\delta\cos\delta = \frac{E}{\eta\omega}\frac{\sigma_0}{\varepsilon_0 E} = \frac{\sigma_0}{\varepsilon_0\eta\omega}. \tag{15.45}$$

Then, the loss modulus is

$$E'' = \frac{\sigma_0^2}{\varepsilon_0^2\eta\omega} = \frac{1}{\eta\omega\left((\eta\omega)^{-2} + E^{-2}\right)} = \frac{E^2\eta\omega}{E^2 + (\eta\omega)^2} = E\frac{\tau_M\omega}{1 + (\tau_M\omega)^2}. \tag{15.46}$$

A plot of the storage and loss moduli as a function of the oscillation frequency ω is shown in Fig. 9. The storage modulus asymptotes to the Young's modulus at high frequency. At low frequency, the loss modulus is given by $\eta\omega$.

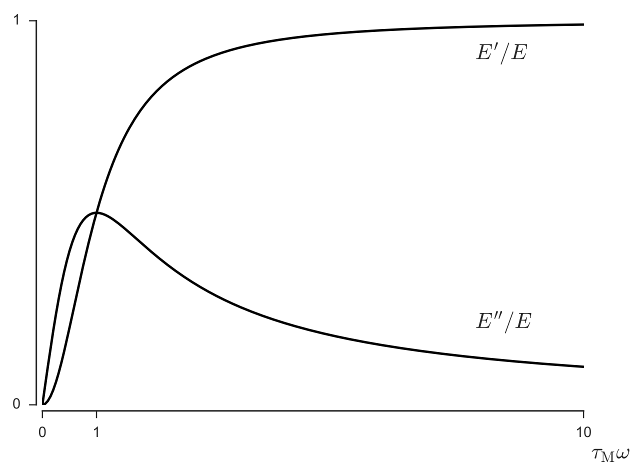

Figure 9: The storage and loss moduli (scaled by the Young's modulus of the elastic element) for a Maxwell material as a function of frequency.

15.2.5 Elastic and viscous elements

We can think of the Maxwell model diagrammatically as an elastic element in series with a viscous element, as show in Fig. 10. When a constant stress is applied to the ends of the diagram, the elastic spring responds instantly, while the viscous damper gradually releases this stress.

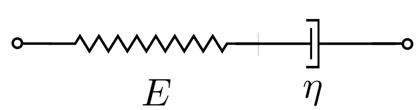

Figure 10: Diagram of a Maxwell material.

We could derive the constitutive relation from the diagram. The stress is the same throughout the diagram, but the strains add. We can consider the stress and strain on each element.

$$\sigma = \sigma_e = \sigma_v \tag{15.47}$$

$$\varepsilon = \varepsilon_e + \varepsilon_v. \tag{15.48}$$

We also have the familiar constitutive relation for individual elements.

$$\sigma_e = E\varepsilon \tag{15.49}$$

$$\sigma_v = \eta\,\dot{\varepsilon}. \tag{15.50}$$

To derive the constitutive relation, we differentiate the above strain equation with respect to time.

$$\dot{\varepsilon} = \dot{\varepsilon}_e + \dot{\varepsilon}_v. \tag{15.51}$$

Using the constitutive relations for the individual elements, we then have

$$\dot{\varepsilon} = \frac{\dot{\sigma}_e}{E} + \frac{\sigma_v}{\eta}. \tag{15.52}$$

But $\sigma = \sigma_e = \sigma_v$, so we have

$$\dot{\varepsilon} = \frac{\dot{\sigma}}{E} + \frac{\sigma}{\eta}. \tag{15.53}$$

Multiplying both sides by η gives the constitutive relation for a Maxwell material.

$$\sigma + \tau_{\mathrm{M}}\,\dot{\sigma} = \eta\,\dot{\varepsilon}. \tag{15.54}$$

We can construct other models from diagrams. The main idea is:

1) For elements in series, strains add and stresses are equal.
2) For elements in parallel, stresses add and strains are equal.

Linear viscoelasticity involves connecting these elements together taking the familiar linear constitutive relations for each element.

15.2.6 The Kelvin-Voigt solid

Now, instead of considering the elastic and viscous elements in series, consider them in parallel, as in Fig. 11. This is called the **Kelvin-Voigt model**. We can derive the constitutive relation using the same method as before. Because the elements are in parallel, their stresses add and the strains are equal.

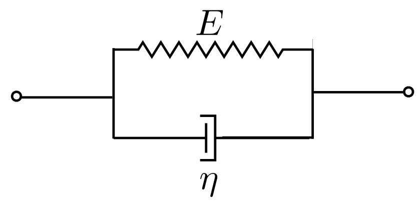

Figure 11: Diagram of a Kelvin-Voigt solid.

$$\sigma = \sigma_e + \sigma_v = E\varepsilon + \eta\dot{\varepsilon}. \tag{15.55}$$

We can compute the creep function of a Kelvin-Voigt solid.

$$\eta\dot{\varepsilon} + E\varepsilon = \sigma_0\theta(t). \tag{15.56}$$

We solve this by integrating factor.

$$\varepsilon(t) = \frac{\sigma_0}{E}\left(1 - \mathrm{e}^{-t/\tau_\mathrm{M}}\right)\theta(t), \tag{15.57}$$

giving a creep function of

$$J(t) = E^{-1}\left(1 - \mathrm{e}^{-t/\tau_\mathrm{M}}\right). \tag{15.58}$$

So, for $t \gg \tau_\mathrm{M}$, $J(t) \to E^{-1}$, giving $\varepsilon = \sigma_0/E$, the constitutive relation for an elastic solid. For $t \ll \tau_\mathrm{M}$,

$$J(t) \approx \frac{1}{E}(1 - (1 - t/\tau_\mathrm{M})) = t/\eta, \tag{15.59}$$

which we saw before is the creep function for a viscous fluid. So, for a Kelvin-Voigt solid, deformation is initially resisted by viscous (frictional) dissipation until the material is eventually stretched as a solid.

15.2.7 Jeffreys fluid

A **Jeffreys fluid** is a good linear viscoelastic description of cells and their cortices. It consists of a Kelvin-Voigt element in series with a viscous element. As a result, at long time scales, the viscous element dominates the dynamics and the material behaves like a viscous fluid. This is commonly seen in cells at very long time scales, since the actin network have time to turn over and be reconstructed, thereby giving liquid-like behavior. At very short times, frictional losses resist deformation as the actin filaments slide against one another. At intermediate times, the cell responds elastically as the intact filaments are compressed and stretched.

Now, cell cortices also consume energy and exert stress on themselves via activity of myosin motors. This is called **active stress**. We therefore add an active stress element in parallel with the Jeffreys fluid to model the active stresses exerted by the fluid. The resulting diagram is shown in Fig. 12.

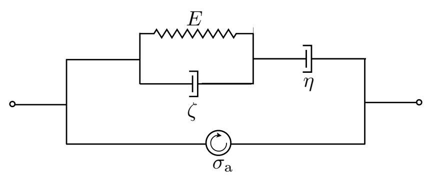

Figure 12: Diagram of an active Jeffreys fluid.

To work out the constitutive relation, we recall our rules: elements in series have additive strains and equal stresses and elements in series have additive stresses and equal strains. Thus, we have

$$\sigma = \sigma_a + \sigma_J \tag{15.60}$$

$$\sigma_J = \sigma_{KV} = \sigma_v \tag{15.61}$$

$$\varepsilon = \varepsilon_{KV} + \varepsilon_v. \tag{15.62}$$

Using the constitutive relation for Kelvin-Voigt and a viscous element, we have

$$\sigma_J = E\varepsilon_{KV} + \zeta\,\dot{\varepsilon}_{KV} = \eta\,\dot{\varepsilon}_v = \sigma_v \tag{15.63}$$

Now, differentiating equation (15.62), we have

$$\dot{\varepsilon} = \dot{\varepsilon}_{KV} + \dot{\varepsilon}_v = \dot{\varepsilon}_{KV} + \frac{\sigma_J}{\eta}, \tag{15.64}$$

where we have used the constitutive relation for a viscous element in the last equality. We can differentiate again and rearrange to get

$$\ddot{\varepsilon}_{KV} = \ddot{\varepsilon} - \frac{\dot{\sigma}_J}{\eta}. \tag{15.65}$$

Differentiating the constitutive relation for the a Kelvin-Voigt element, we have

$$\dot{\sigma}_J = E\dot{\varepsilon}_{KV} + \zeta\,\ddot{\varepsilon}_{KV}. \tag{15.66}$$

We have from $\dot{\varepsilon}_{\mathrm{KV}}$ from equation (15.64) and for $\ddot{\varepsilon}_{\mathrm{KV}}$ from (15.65), which gives

$$\dot{\sigma}_{\mathrm{J}} = E\left(\dot{\varepsilon} - \frac{\sigma_{\mathrm{J}}}{\eta}\right) + \zeta\left(\ddot{\varepsilon} - \frac{\dot{\sigma}_{\mathrm{J}}}{\eta}\right). \tag{15.67}$$

This can be rearranged to give

$$\sigma_{\mathrm{J}} + \tau_1\dot{\sigma}_{\mathrm{J}} = \eta(\dot{\varepsilon} + \tau_2\ddot{\varepsilon}), \tag{15.68}$$

with $\tau_1 = (\eta + \zeta)/E$ and $\tau 2 = \zeta/E$. We have $\sigma_{\mathrm{J}} = \sigma - \sigma_{\mathrm{a}}$, which gives

$$\sigma - \sigma_{\mathrm{a}} + \tau_1(\dot{\sigma} - \dot{\sigma}_{\mathrm{a}}) = \eta(\dot{\varepsilon} + \tau_2\ddot{\varepsilon}), \tag{15.69}$$

the constitutive relation for an active Jeffreys fluid. In the homework, we will compute the creep function and the storage and loss moduli for this material, a good model for cells.