

up of viscous protoplasm surrounded by a cell membrane. This approach considers the mechanics of the whole cell, without considering the contribution of individual cellular components, such as the cytoskeleton. The second and third models focus on how the mechanical properties of a cell are determined by the structure and composition of its cytoskeleton. Each of the first three models considers the behavior of the cell in isolation. In reality, cells reside within an extracellular matrix (as discussed in Section 2.4) and the properties of the matrix and its interaction with the cell will affect the mechanical behavior of the cell in response to force applied to a tissue. The fourth model we present demonstrates this point using experimental data and finite element analyses.

2.6.1 Lumped parameter viscoelastic model of the cell

The data from the magnetic bead rheometry experiments indicate that the cell's response to a step application of force is viscoelastic, with an immediate elastic response (phase I in Fig. 2.24) followed by gradual creep (phases II and III). The viscoelastic behavior of materials (including cells and many biological tissues) can be modeled using lumped parameter models constructed from arrangements of two simple elements: the linear spring and the dashpot. In this section, we construct a viscoelastic model of the cell and compare its predictions with those obtained experimentally (Fig. 2.24). It is important to understand that the elements in these models cannot be unambiguously associated with specific cellular components; instead, we represent the action of all elastic components of the cell by a linear spring (or springs) and the action of all viscous components by a dashpot (or dashpots). This "lumping" of the response of a complex biomechanical system into a small number of elements is obviously a simplification. Nonetheless, such lumped parameter models are easy to work with and represent a good first approach to quantifying cellular biomechanics.

The two basic elements used in lumped parameter viscoelastic models (also known as equivalent circuits) are the linear spring and the dashpot. When a force, $F(t)$, is applied to a linear spring, it responds instantaneously with a deformation, x , that is proportional to the load:

$$F_{\text{spring}}(t) = k_0 x_{\text{spring}}(t), \quad (2.7)$$

where k_0 is the spring constant. The reader is reminded that x_{spring} is the spring length, *measured from the equilibrium (or resting) length of the spring*, which is the length that the spring takes when no forces are applied to it. A dashpot is a viscous element, similar to a shock absorber. When a force is applied to a dashpot,

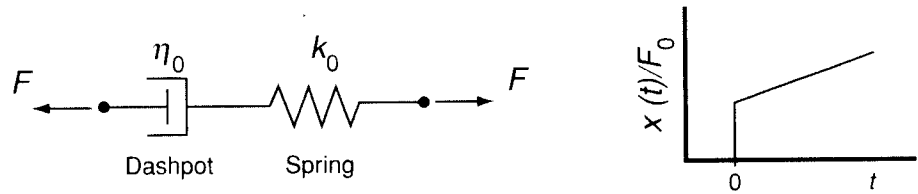


Figure 2.34

Lumped parameter model (or equivalent circuit) of a Maxwell body and the corresponding creep response to a step change in the applied force, F , from zero to F_0 at $t = 0$.

the rate of deformation is linearly related to the force:

$$F_{\text{dashpot}}(t) = \eta_0 \dot{x}_{\text{dashpot}}(t), \quad (2.8)$$

where the dot represents differentiation with respect to time and η_0 is a constant of the dashpot called the damping coefficient. Notice the sign convention implied by the above equations: the direction for positive force must coincide with the direction of positive displacement.

These elements are obviously idealized, but their force–displacement characteristics are able to describe essential features of linear viscoelastic behavior, particularly when combined in specific arrangements. One common arrangement is a series combination of a spring and dashpot, known as the Maxwell body (Fig. 2.34). The total deformation of the Maxwell body, $x(t)$, is the sum of the deformation of the spring and that of the dashpot:

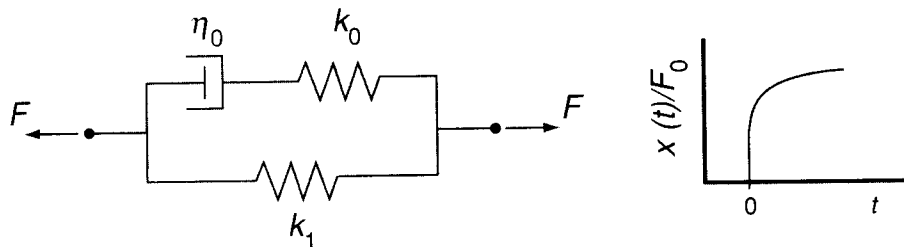
$$x(t) = x_{\text{spring}}(t) + x_{\text{dashpot}}(t). \quad (2.9)$$

By differentiating Equation (2.9) with respect to time, it is clear that the velocity of deformation is the sum of the velocities of the two elements. Furthermore, since the elements are in series, the force in the spring, $F(t)$, is transmitted to the dashpot, i.e., $F(t) = F_{\text{spring}}(t) = F_{\text{dashpot}}(t)$. By substituting the force–displacement relationships from Equations (2.7) and (2.8) into the time derivative of Equation (2.9), we can get a force–displacement relationship for the Maxwell body:

$$\dot{x}(t) = \frac{1}{\eta_0} F(t) + \frac{1}{k_0} \dot{F}(t). \quad (2.10)$$

This represents a differential equation that can be solved for the displacement, $x(t)$, if the force history, $F(t)$, is known.

Before we can integrate this equation, we need an initial condition, which is obtained by thinking about how the Maxwell body responds to the applied force.

**Figure 2.35**

Lumped parameter model of a Kelvin body and its creep response in response to a step change in force F from zero to F_0 at time $t = 0$.

A common force history is to impose a step change in force, for example an increase in force from zero to a constant value F_0 . In this case, the resulting response of the viscoelastic body is called its creep response. When a force is applied in this way, the spring element will deform instantaneously according to Equation (2.7). However, the dashpot will not deform immediately; it acquires a finite *velocity* immediately, but the displacement at time $t = 0$ is zero because a finite velocity acting over an infinitesimal duration produces no displacement. Therefore, if the force is applied at time zero, the initial condition for Equation (2.10) is $x(0^+) = F(0^+)/k_0 = F_0/k_0$.⁷ If we restrict attention to times $t > 0$ then $F(t) = F_0$ and $\dot{F} = 0$ in Equation (2.10), so that the differential equation is trivially solved to obtain the displacement of the Maxwell body per unit applied force as:

$$\frac{x(t)}{F_0} = \frac{1}{k_0} + \frac{1}{\eta_0}t. \quad (2.11)$$

The contributions of the spring and the dashpot are evident from this response (Fig. 2.34), with an immediate elastic response from the spring followed by linear deformation of the dashpot with time. Unfortunately, the Maxwell body clearly does not accurately represent the cell response shown in Fig. 2.24, indicating that this simple model is insufficient.

A slightly more complex model is the Kelvin body, which consists of a Maxwell body in parallel with a spring (Fig. 2.35). In this case, because the elements are in parallel, the deformation of the entire Kelvin body is equal to the deformation of each of the two parallel paths. Therefore, the deformation of the Kelvin body is equivalent to that of the Maxwell body and is also given by Equation (2.10), with the understanding that $F(t)$ in Equation (2.10) should now be interpreted not as the total applied force, but just the force supported by the Maxwell body,

⁷ The notation $t = 0^+$ means that we should take the limit as t tends towards zero from positive times. In other words, this is the time immediately after application of the force at time $t = 0$.

$F_{\text{Maxwell}}(t)$. $F_{\text{Maxwell}}(t)$ can be computed from

$$F(t) = F_{\text{Maxwell}}(t) + F_{\text{spring}}(t), \quad (2.12)$$

where F_{spring} is the force across the spring with stiffness k_1 and $F(t)$ is the total force applied to the Kelvin body.

By rearranging Equation (2.12) and substituting a suitably modified form of Equation (2.7) for $F_{\text{spring}}(t)$, the analogue to Equation (2.10) for a Kelvin body is:

$$\dot{x}(t) = \frac{1}{\eta_0}(F(t) - k_1 x(t)) + \frac{1}{k_0}(\dot{F}(t) - k_1 \dot{x}(t)) \quad (2.13)$$

or, after some rearranging,

$$F(t) + \frac{\eta_0}{k_0} \dot{F}(t) = k_1 \left(x(t) + \frac{\eta_0}{k_1} \left(1 + \frac{k_1}{k_0} \right) \dot{x}(t) \right), \quad (2.14)$$

where $x(t)$ is the total displacement of the body.

As for the Maxwell body, we solve for the creep response by imposing a step force and considering times $t > 0$, in which case $F(t) = F_0$ and $\dot{F} = 0$. For this case, Equation (2.14) simplifies to:

$$F_0 = k_1(x(t) + \tau \dot{x}(t)), \quad (2.15)$$

where we have defined τ , the relaxation time, as:

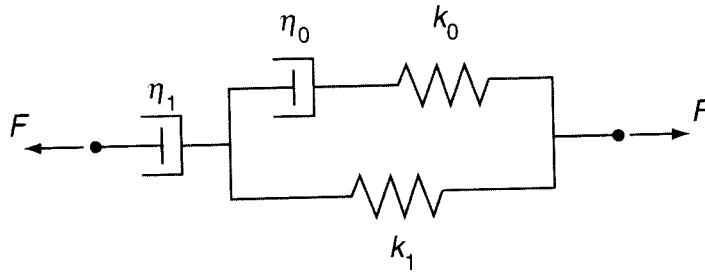
$$\tau = \eta_0 \frac{k_0 + k_1}{k_0 k_1}. \quad (2.16)$$

To solve the differential Equation (2.15) for $x(t)$, we need an initial condition. Once again we recognize that the displacement of the dashpot is zero at time $t = 0^+$, so that the force must be carried by the springs only, i.e., $F_0 = k_0 x(0^+) + k_1 x(0^+)$. In this case the solution of Equation (2.15) is:

$$\frac{x(t)}{F_0} = \frac{1}{k_1} \left(1 - \frac{k_0}{k_0 + k_1} e^{-t/\tau} \right). \quad (2.17)$$

The Kelvin body does a much better job of representing the creep behavior of the cell subjected to magnetic bead traction than does the Maxwell body (compare Figs. 2.24 and 2.35). However, there is still a discrepancy between the model predictions and the experimental data for cellular deformation during phase III (Fig. 2.24).

The model predictions can be further improved by adding a dashpot in series with the Kelvin body (Fig. 2.36), giving a total of four components: two dashpots and two springs. The creep response for this model is simply the superposition of the response of the Kelvin body and the series dashpot, and therefore is given

**Figure 2.36**

Lumped parameter model proposed by Bausch *et al.* [42] for the viscoelastic creep response of a cell subjected to a sudden force by magnetic bead rheometry. This model is used to interpret the data shown in Fig. 2.24.

by:

$$\frac{x(t)}{F_0} = \frac{1}{k_1} \left(1 - \frac{k_0}{k_0 + k_1} e^{-t/\tau} \right) + \frac{t}{\eta_1}. \quad (2.18)$$

As can be seen in Fig. 2.37, the model provides an excellent fit to the experimental data obtained by Bausch *et al.* [42]. The quality of the fit suggests that there must be (at least) two components of the cell that are responsible for generating viscous responses and (at least) two components that generate an elastic response. Of course, this model tells us nothing about what those components might be. It is even possible that all of the viscous behavior could come from a single component that relaxes with two different time scales.

From such fits, viscoelastic constants that describe the creep response of a cell can be estimated and used to compare the response of one cell with that of another cell, or to determine the response of a cell to a variety of inputs. Bausch *et al.* [42] did these comparisons and found that while the viscoelastic constants measured at different sites on an individual fibroblast cell are approximately equal (for forces up to 2000 pN), the constants can vary by up to an order of magnitude from cell to cell. Why such a variation from cell to cell? The viscoelastic constants estimated by the lumped parameter model are indicative of the properties of the whole cell, but those properties are determined in part by the properties of the cell membrane, in part by the properties of the cell cytoplasm, and in part by the structure of the cytoskeleton. As we discussed in Section 2.3, the cytoskeleton is a dynamic structure that is constantly changing its composition and organization, meaning the cytoskeletal architecture in one cell can differ substantially from that in another. We will show in the next two sections that these structural differences can have profound effects on the mechanical properties of the whole cell, explaining some of the variations seen in the viscoelastic properties from one cell to another.

Up to this point we have considered only step increases in force. An alternate way of forcing magnetic beads attached to a cell is to subject them to an oscillating

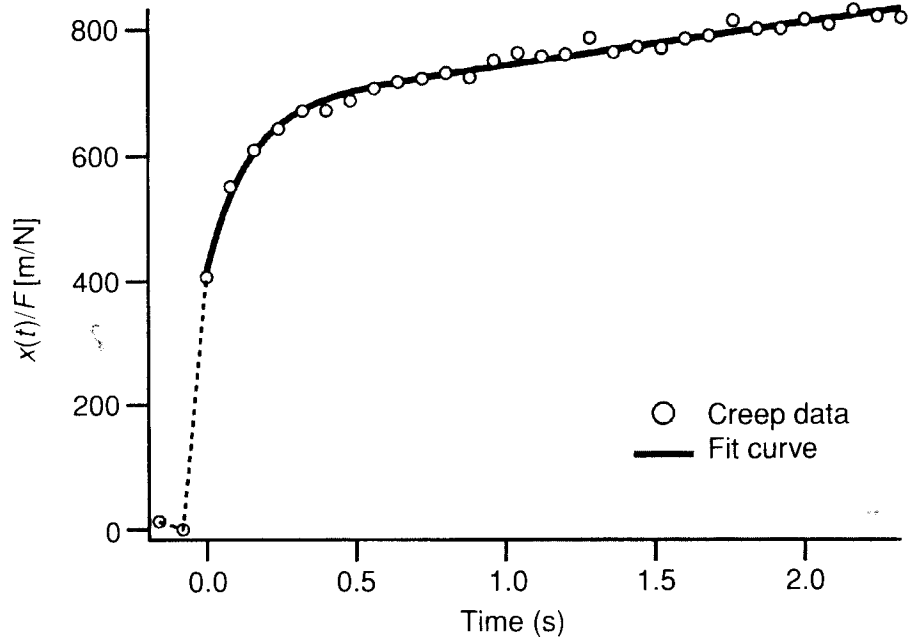


Figure 2.37

Comparison of experimentally obtained creep data (similar to that of Fig. 2.24) with model predictions from the lumped parameter model in Fig. 2.36. The applied force (F) was 1100 pN. The dashed line represents the instantaneous elongation of the body ($1/(k_0 + k_1)$) and the solid line is fit to the data using Equation (2.18). From Bausch *et al.* [42] with kind permission of the authors and the Biophysical Society.

force of the form

$$F(t) = F_0(1 + \sin \omega t). \tag{2.19}$$

For a Kelvin body, the initial condition is still $x(0^+) = F_0/(k_0 + k_1)$, but the response of the bead is slightly more complex. It can be shown that the displacement has both exponential and harmonic components, being given by

$$x(t) = \frac{F_0}{k_1} \left(1 - \frac{k_0}{k_0 + k_1} e^{-t/\tau} + \frac{\tau \omega \left(1 - \frac{\eta_0}{k_0 \tau} \right) (e^{-t/\tau} - \cos \omega t) + \left(1 + \frac{\eta_0 \tau \omega^2}{k_0} \right) \sin \omega t}{1 + (\tau \omega)^2} \right) \tag{2.20}$$

where the constant τ is given by Equation (2.16).