CHAPTER

# 2

# Mechanical Forces

The central concept of this book is force. Motor proteins and other molecular machines are able to move and do work because they generate force, for it is force that drives change and motion. But what is force? Where does it come from? And what effect does it have on proteins and cells? These questions will be answered in the following five chapters that constitute Part I of this text.

This chapter is an introduction to Newtonian mechanics. It begins with the definition of force and the calculation of the magnitudes of the various forces that act on molecules. The three fundamental mechanical elements are then introduced. These elements—the spring, the dashpot, and the mass—are the building blocks of complex mechanical devices such as protein machines. I describe how these elements move individually in response to forces, and how different combinations of elements respond to forces in different ways, some combinations moving monotonically, and other combinations undergoing oscillatory motion. The chapter ends with the definitions of work and energy.

Although much of this material is contained in standard undergraduate physics textbooks such as Resnick et al. (1992) and Feynman et al. (1963), we will discover that most of the mechanics in the textbooks is irrelevant to molecular and cellular biology. The reason is that proteins and other biomolecules are so small that the inertial forces are comparatively small and can usually be ignored, whereas the viscous forces from the surrounding fluid are usually large and dominate the mechanical responses. Consequently, gravity is negligible, and the oscillatory motions characteristic of inertial systems such as planets and pendulums, systems that occupy so much of the mechanics textbooks, simply do not occur at the single-molecule level.

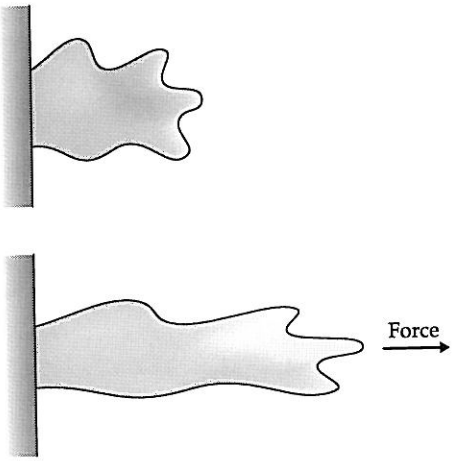



***Figure 2.1 Deformation of an elastic object***
A force, *F*, is applied at one end while the other end is held fixed.

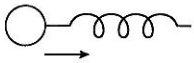
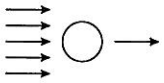
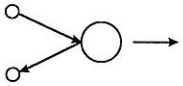
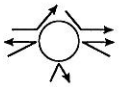
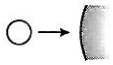
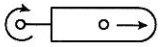
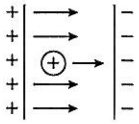
## Force

A **force** is an influence—a push or a pull in everyday experience—that causes a free particle to accelerate or that causes a constrained object, such as that shown in Figure 2.1, to become deformed. Forces arise from many different physical processes. Several of these are summarized in Table 2.1, together with their approximate magnitudes. Force is often confused with work, which is the product of the force with the distance over which the force acts. If there is no motion, then there is no work, even though a force has been exerted. This is where the confusion arises: Try to tell a weightlifter who has just tried and failed to lift the heaviest weight that no work has been done!

An object can be subject to several forces simultaneously. The **net force** is the sum of all the individual forces. This seems obvious. However, such a reckoning of forces relies on an important concept, namely that the effect of a force is independent of its physical origin. For example, an elastic force can be exactly counteracted by a viscous force. As we will see, the elastic and viscous forces discussed in this chapter can, in turn, be counteracted by the thermal and chemical forces described in Chapters 4 and 5.

The SI unit of force is the **newton**. (Other SI units can be found in the table on the rear endpapers of this book.) One newton, written 1 N, corresponds approximately to a weight of 100 grams, or about 4 ounces. Although 1 N is a modest force in our everyday experience, it is billions of times larger than the forces that operate at the molecular level. For single molecules, forces are more appropriately measured in piconewtons, where 1 pN equals $10^{-12}$ N (see the table on the back endpapers for other SI prefixes). How small is a piconewton? It is equal to the weight of one red blood cell. It is also equal to the optical pressure exerted by a laser pointer on a screen. And it is approximately equal to the maximum force generated by a muscle divided by the number of myosin molecules acting in parallel in the muscle.

*Table 2.1 Examples of forces acting on molecules*

| Type of force | Diagram | Approximate magnitude |
|---|---|---|
| Elastic |  | 1–100 pN |
| Covalent | | 10,000 pN |
| Viscous |  | 1–1000 pN |
| Collisional |  | $10^{-12}$ to $10^{-9}$ pN for 1 collision/s |
| Thermal |  | 100–1000 pN |
| Gravity |  | $10^{-9}$ pN |
| Centrifugal |  | $< 10^{-3}$ pN |
| Electrostatic and van der Waals |  | 1–1000 pN |
| Magnetic | | $<< 10^{-6}$ pN |

Newton's **first law of motion** states that if an object has no net force acting on it, then it will remain at rest or, if it is moving, it will continue to move at constant velocity. Newton's **second law** states that if an object is subject to a net force, $F$, then it will accelerate according to the equation

$$F = ma \tag{2.1}$$

where $m$ is the mass. This equation says that the larger the mass, $m$, the slower its acceleration, $a$ (if the force is constant). Many of the parameters used in this book are listed in the Table of Parameters on the endpapers. The unit of mass is the kilogram, kg, and the unit of acceleration is $m/s^2$. Thus $1\ N = 1\ kg{\cdot}m/s^2$. An important consequence of Newton's second law is that if an object is stationary or moving at constant velocity, then there is no net force acting on it (the forces are all balanced).

Several examples of mechanical forces on molecules follow. Forces can be transferred to proteins either by direct contact with the atoms of other molecules, or by the interaction of the protein with a field, such as a gravitational field or an electric or magnetic field.

***Example 2.1 Physical forces and their magnitudes at the single-molecule level***

ELASTIC FORCES. If an object is connected to a spring of stiffness $\kappa$ that is stretched a distance $x$ beyond its resting length, then the object will experience a force of $F = \kappa x$. For a motor protein, the stiffness might be about 1 mN/m = 1 pN/nm. If the spring is strained through a distance of 1 nm = $10^{-9}$ m, a distance appropriate to the size of proteins, then the force exerted on the object is 1 pN.

VISCOUS FORCES. If an object is held fixed in a moving liquid or is moving through a stationary fluid, then it will experience a viscous, or drag, force from the liquid. The force is proportional to the relative velocity, $v$, between the object and the fluid according to $F = \gamma v$. The constant of proportionality, $\gamma$, is called the drag coefficient. The drag coefficient is related to the size and the shape of the object as well as the viscosity. For example, for a sphere of radius $r$ moving through a liquid of viscosity $\eta$, the drag coefficient is $6\pi\eta r$ (Stokes' law, Chapter 3). The viscous forces on proteins are large. For a globular protein of diameter 6 nm, corresponding to a molecular mass of ~100 kDa (see Table 2.2), the drag coefficient measured by centrifugation studies at 20°C is ~ 60 pN·s/m (Creighton, 1993), in good agreement with Stokes' law. The average instantaneous thermal speed of such a protein in solution at standard temperatures is ~8 m/s (this is a consequence of thermally driven collisions from the surrounding solvent molecules, Chapter 4). The corresponding viscous force is therefore ~480 pN.

COLLISIONAL AND THERMAL FORCES. If an object is struck by another, it experiences a force equal to the rate of change in momentum ($mv$) of the striking particle, $F = d(mv)/dt$. For example, the mass of a water molecule is $\sim 30 \times 10^{-27}$ kg, the average speed associated with its kinetic energy is ~600 m/s (Chapter 4), and therefore its momentum is $\sim 18 \times 10^{-24}$ kg·m/s. If a protein were struck head-on every second by a water molecule that bounced straight back, then the average force would be equal to $36 \times 10^{-12}$ pN (twice the momentum for an elastic collision). This is a very small force. However, in solution a huge number of collisions take place per second. The collisions come from all directions, and the resulting randomly directed force, called the thermal force, drives diffusion. The average instantaneous thermal force acting on a 100 kDa protein is on the order of the viscous force, or ~500 pN (Chapter 4).

OPTICAL FORCES. Another example of a collisional force is optical pressure. Because photons have momentum, they exert a force when they are diffracted by an object. The momentum of a photon is $h\nu/c = h/n\lambda$, where $h$ is Planck's constant, $\nu$ is the frequency of the light, $c$ is the speed of light, $n$ is the refractive index, and $\lambda$ is the wavelength (in a vacuum). If an

object in water ($n = 1.33$) absorbs one green photon ($\lambda = 500$ nm) per second, the corresponding optical force on it is $1.0 \times 10^{-15}$ pN (the values for the physical constants can be found in the table on the endpapers). This is a very small force. Even if a molecule adsorbs $10^9$ photons per second, which would require very bright laser illumination, the optical force would still be only $10^{-6}$ pN.

**GRAVITY.** An object of mass $m$ experiences a gravitational force of magnitude $mg$, where $g$ is the acceleration due to gravity, equal to ~9.8 m/s$^2$ at the Earth's surface. With a mass of only $166 \times 10^{-24}$ kg, a 100 kDa protein experiences a gravitational force of only $1.6 \times 10^{-9}$ pN. At the single-molecule level, gravitational forces are very small and can be ignored.

**CENTRIFUGAL FORCES.** An object spinning in a centrifuge experiences a centrifugal force equal to $ma_c$. Ultracentrifuges are capable of generating centrifugal accelerations, $a_c$, in excess of 100,000 times that of gravity. The associated centrifugal forces on molecules are still quite modest, $\sim 160 \times 10^{-18}$ N = $\sim 160 \times 10^{-6}$ pN for our 100 kDa protein, but this is large enough to cause the protein to drift at an average speed of ~3 μm/s (using the drag coefficient from Table 2.2). The slow drift is superimposed on the rapid, randomly directed thermal motion. At this speed the protein will sediment through a distance of 100 mm, a typical length of a centrifuge tube, in about 10 hours.

**ELECTROSTATIC FORCES.** A particle with charge $q$, in an electric field of strength $E$, will experience a force $F = qE$. An ion such as sodium experiences an electrostatic force when it moves through an ion channel in the plasma membrane. The charge on the ion is $160 \times 10^{-21}$ coulombs (see the table of physical constants on the rear endpapers), and the electric field across a typical plasma membrane is $15 \times 10^6$ V/m (60 mV potential across the 4-nm-thick membrane). The corresponding force is 2.4 pN. A similar-sized force exists between two monovalent ions in water that are separated by 1 nm (Problem 2.7): The force will be smaller in a salt solution due to charge screening, but will be larger in the interior of proteins where the dielectric constant is low.

Van der Waals forces are also electrostatic: They arise from the charge separation induced by nearby atoms. Van der Waals forces can be as high as 100 pN per nm$^2$ of protein–protein interface (Appendix 3.1).

**MAGNETIC FORCES.** Magnetic forces are very small at the molecular level because molecules interact only very weakly with magnetic fields. For example, the maximum force on a proton, the nucleus with the largest magnetic moment, in the strongest nuclear magnetic resonance (NMR) machines is only on the order of $10^{-12}$ pN. Thus even for a huge protein with 3000 amino acids and 60,000 atoms, subject to a very strong magnetic field, the magnetic force is less than $10^{-6}$ pN.

*Table 2.2 Physical properties of a globular protein of molecular mass 100 kDa*

| Property | Value | Comment |
|---|---|---|
| Mass | $166 \times 10^{-24}$ kg | Mass of 1 mole/Avogadro constant |
| Density | $1.38 \times 10^{3}$ kg/m$^3$ | 1.38 times the density of water |
| Volume | 120 nm$^3$ | Mass/density |
| Radius | 3 nm | Assuming it is spherical |
| Drag coefficient[a] | 60 pN·s/m | From Stokes' law (Chapter 3) |
| Diffusion coefficient[a] | 67 μm$^2$/s | From the Einstein relation (Chapter 4) |
| Average speed[b] | 8.6 m/s | From the Equipartition principle (Chapter 4) |

*Note*: 1 nm = $10^{-9}$ m, but 1 nm$^3$ = (1 nm)$^3$ = $10^{-27}$ m$^3$.

[a]In water at 20°C

[b]Root-mean-square (the square root of the average value of the square of the velocity)

## Motion of Springs, Dashpots, and Masses Induced by Applied Forces

All mechanical devices can be built with three fundamental mechanical elements—the spring, the dashpot, and the mass. A protein or other molecule can be thought of as a mechanical device composed of atoms that have mass, connected by bonds that have elasticity, like springs. A wind-up toy can be thought of as a mechanical device composed of a spring, some bars and levers that have mass, and some hinges that contribute a little friction and damping. In this section we consider how individual mechanical elements move under the influence of an applied force. In the next section we will consider combinations of elements. The individual motions are summarized in Figure 2.2 and can be described as follows:

**MASS.** According to Newton's second law, a force causes a mass to undergo a constant acceleration equal to $F/m$ (Equation 2.1). The greater the mass—that is, the greater the inertia—the smaller the acceleration. Because acceleration is the rate of change of velocity ($a = dv/dt$), a constant acceleration means that the velocity increases linearly with time. If the initial velocity is zero, then the speed at time $t$ will be given by $v(t) = at$. Because the velocity is the rate of change in displacement, a linearly increasing velocity means that the position will increase parabolically with time. If the initial displacement is zero, then the displacement at time $t$ will be given by $x(t) = \frac{1}{2}\, at^2$. This equation describes the motion of a free-falling ball.

**DASHPOT.** A dashpot is an idealized mechanical element that is fixed at one end and responds to a force applied at the other end by elongating at a constant velocity. The velocity of elongation of a dashpot is equal to $F/\gamma$, where $\gamma$

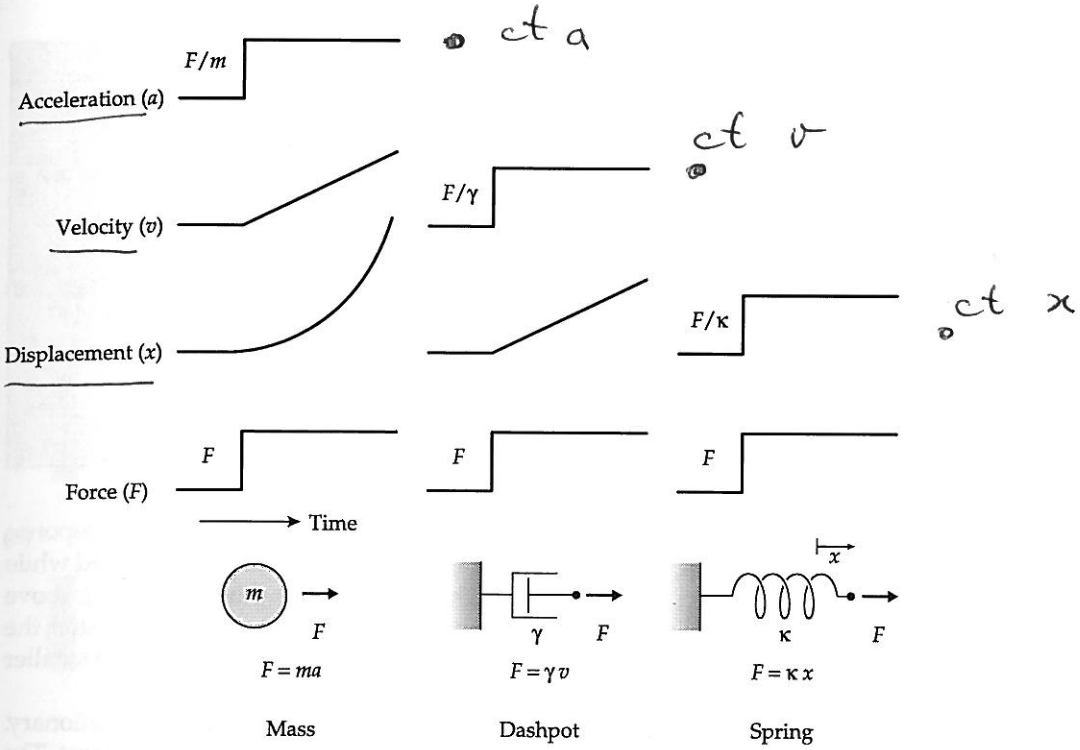



***Figure 2.2 Motion of a mass, a dashpot, and a spring under the influence of a constant external force***

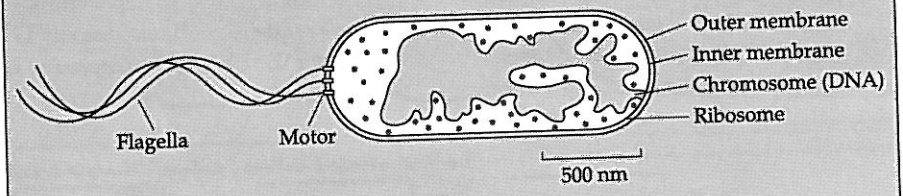
is the drag coefficient (Equation 2.2). Because the velocity is constant, the length of a dashpot increases linearly with time as shown in Figure 2.2. A dashpot is analogous to a spoon in a jar of honey. When the jar is held fixed in one hand, it is easy to pull the spoon out slowly, but to pull it out quickly requires a large force. Indeed, if one pulls fast enough it is even possible to pick up the jar. The higher the viscosity of the honey, the higher the drag coefficient, and the greater the force needed to attain a certain speed. The dashpot is used as a model to describe how an object moves in a fluid. We can think of a submerged object as being connected to an (imaginary) dashpot whose drag coefficient is proportional to the viscosity according to Stokes' law (Chapter 3).

In Figure 2.2, the right-hand end of the dashpot moves at constant speed. This is a reflection of the fact that there is no net force acting at this point: The external force $F$ is exactly balanced by the internal drag force, $F_d$. In other words, $F + F_d = 0$, in accordance with Newton's second law (if the net force were not zero, then there would be acceleration). This means that the drag force is

$$F_d = -\gamma v \tag{2.2}$$

where the minus sign represents the fact that the drag force opposes the movement. The drag coefficient, $\gamma$, has units N·s/m.

***Example 2.2 The force generated by the bacterial motor*** Consider a 2-μm-long bacterium such as *E. coli*, pictured below, swimming through water at a speed of 25 μm/s. According to Stokes' law (Equation 3.6), the drag coefficient is ~20 nN·s/m. Therefore, the motors must be able to generate a force of at least 0.5 pN.




**SPRING.** A spring is a mechanical element whose length increases in response to an applied force. Like the dashpot, one end of the spring is held fixed while the force is applied to the other end. The increase in length of the spring above its resting length equals $F/\kappa$, where $\kappa$ is the spring constant. The greater the spring constant—that is, the stiffer or less compliant the spring—the smaller the extension for a given force.

After the onset of the force, the right-hand end of the spring is stationary. There is no acceleration because there is no net force acting on this point. The external force $F$ is exactly balanced by the internal, elastic force $F_s$. In other words, $F + F_s = 0$, again in accordance with Newton's second law. This means that the force exerted by the spring is

$$F_s = -\kappa x \tag{2.3}$$

where the minus sign represents the fact that the elastic force is a restoring one that opposes the movement.

If a spring has constant stiffness, meaning that the stiffness is independent of the force or extension, then we say that it obeys **Hooke's law**. As we will see in the next chapter, Hooke's law is a good approximation for the stretching of many materials, provided that the forces and resulting extensions are not too large.

## Motion of Combinations of Mechanical Elements

When different mechanical elements are put together, their response to applied forces becomes more complex and interesting. In this section we consider how pairs of mechanical elements move. There are two qualitatively different behaviors: monotonic "creeping" motion and oscillatory "ringing" motion.

**MASS AND DASHPOT.** Consider a mass and dashpot connected in series as shown in Figure 2.3A (left panel). This is a model for the movement of a cell or a protein through a liquid (Figure 2.3A, middle). The mass experiences an

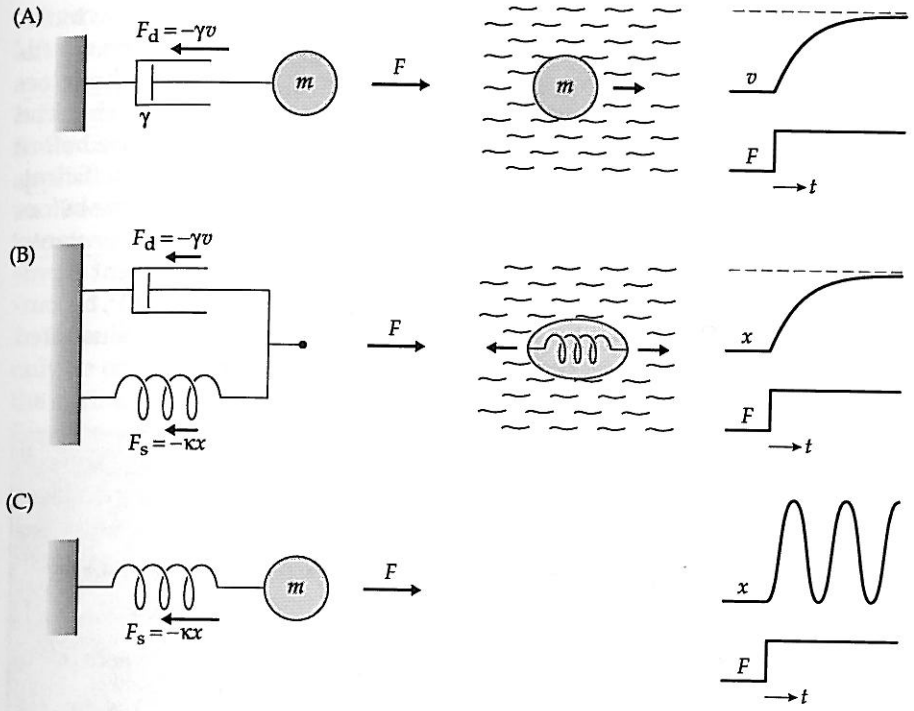



***Figure 2.3 Motion of pairs of mechanical elements***
(A) The mass and dashpot model represents an object that is damped by a viscous fluid. (B) A spring and dashpot model represents a low-mass object (like a protein) that is deformed in a viscous fluid. (C) The mass and spring model represents an undamped system.

$F_d$, whose value is $-\gamma v$. The net force on the mass is therefore $F + F_d = F - \gamma v$. The net force acting on the mass causes it to accelerate according to $ma = F - \gamma v$. Because acceleration is the rate of change of velocity, $a = dv/dt$, we can rewrite this equation as

$$m\frac{dv}{dt} + \gamma v = F \tag{2.4}$$

Now suppose that initially the mass is stationary and that at time zero a constant force $F$ is applied. At first, when the speed is low, the drag force is small, and the mass will undergo a constant acceleration ($a = F/m$), leading to a linear increase in velocity. However, as the velocity increases, the drag force becomes significant, causing a decrease in the net force acting on the mass and therefore a decrease in the acceleration. As a result, the velocity begins to level off. Finally, the drag force approaches the applied force, the acceleration drops to zero, and the velocity approaches the **terminal velocity** equal to $F/\gamma$. This motion is described by the equation

$$v(t) = \frac{F}{\gamma}\left[1 - \exp\left(-\frac{t}{\tau}\right)\right] \qquad \tau = \frac{m}{\gamma} \tag{2.5}$$

which is plotted in Figure 2.3A (right). That this equation is a solution to the previous equation can be verified by differentiating Equation 2.5 and substituting the derivative into Equation 2.4. The time constant $\tau$ at which the velocity approaches the terminal velocity depends on the mass and damping. The higher the mass, the slower the acceleration and the longer the time before the drag force becomes significant. Conversely, the higher the drag coefficient, the greater the drag force for a given speed, and so the shorter the time before the drag force becomes limiting. Smaller objects have smaller time constants: The mass is proportional to (length)$^3$, whereas the damping coefficient is proportional to (length)$^1$; therefore the time constant scales with (length)$^2$, becoming very small as the dimension gets smaller. This relationship is illustrated in the next two examples.

***Example 2.3 The inertia of a bacterium*** Consider a bacterium swimming through water at 25 μm/s. How long will the bacterium continue to coast after its motors have stopped? We model the bacterium as a mass and dashpot. The corresponding equation of motion is $m\frac{dv}{dt}+\gamma v=0$. After the motors stop and the flagella cease beating, the speed will decrease exponentially according to $v(t)=v(0)\exp(-t/\tau)$, with a time constant, $\tau$, equal to $m/\gamma$. The mass is approximately equal to $\frac{4}{3}\pi r^3\rho$, where $r$ is the radius (~1 μm) and $\rho$ is the density (~ 1000 kg/m$^3$), or ~$4\times10^{-15}$ kg. From Example 2.2, the drag coefficient is 20 nN·s/m. The time constant is therefore 0.2 μs.

The total distance that the bacterium coasts is

$$x=\int_0^\infty v(t)\cdot dt=\int_0^\infty v(0)\exp-(t/\tau)\cdot dt=v(0)\cdot\tau$$

For an initial speed, $v(0)$ = 25 μm/s, this distance is only ~5 pm = 0.05 Å, less than the diameter of a water molecule! Thus a bacterium has very little inertia to keep it moving forward (Berg, 1993).

***Example 2.4 The persistence of protein movements*** The time constant, $m/\gamma$, of a globular, 100 kDa protein is ~2.8 ps, using the mass and drag coefficients from Table 2.2. In other words, after the protein gains speed due to molecular collisions with solvent molecules, the velocity persists for only a very short time as other collisions rapidly randomize the protein's direction of travel. Given that the average instantaneous speed of such a protein is 8.6 m/s (see Table 2.2), the average distance that the protein moves before its speed is randomized by molecular collisions is only 24 pm, or 0.24 Å.

**SPRING AND DASHPOT.** A spring in parallel with a dashpot (see Figure 2.3B, left panel) is a model for a compliant object that is deformed in a liquid, such as a protein that undergoes a global (i.e., large-scale) conformational change. It can also be used to model a viscoelastic material, such as skin, that takes a finite time to adopt a new shape (see Figure 2.3B, middle). In this case, the applied force is opposed by the sum of the viscous and elastic forces: $F = \gamma v + \kappa x$. Because the velocity is the derivative of displacement, this equation becomes

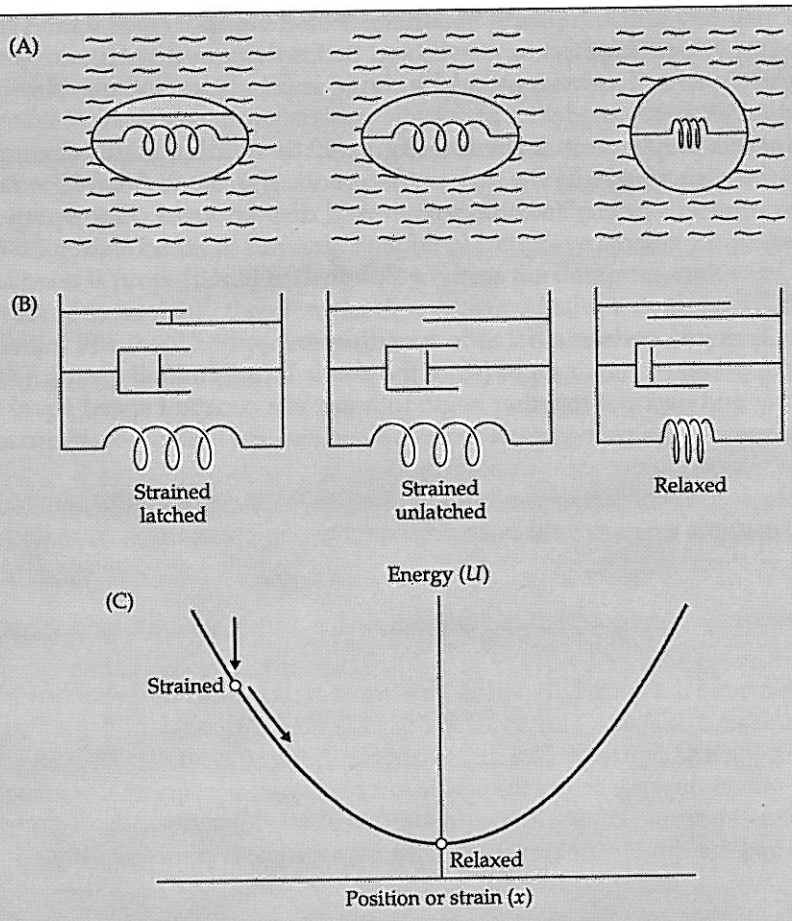
$$\gamma \frac{dx}{dt} + \kappa x = F \tag{2.6}$$

If the spring is unstrained at time zero, then an applied force will initially only be opposed by the dashpot (since the elastic force is initially zero). Thus the spring and dashpot together begin to move at a constant speed equal to $F/\gamma$. However, as the spring becomes more elongated, the elastic force increases, the speed begins to decrease, and the displacement begins to level off. Finally, the elastic force approaches the applied force, the velocity drops to zero, and the spring approaches its final extension equal to $F/\kappa$. This motion is described by the equation

$$x(t) = \frac{F}{\kappa}\left[1 - \exp\left(-\frac{t}{\tau}\right)\right] \qquad \tau = \frac{\gamma}{\kappa} \tag{2.7}$$

which is plotted in Figure 2.3B (right). This equation is analogous to that describing a mass and dashpot. However, in this case the time constant depends on the damping and stiffness: The higher the damping, the smaller the velocity and the longer the time before the elastic force becomes significant. Conversely, the higher the spring constant, the greater the elastic force for a given elongation, and so the shorter the time before the elastic force becomes limiting.

***Example 2.5 The timescale of protein conformational changes*** Consider a protein that is initially held in a strained conformation, perhaps due to an internal strut (Figure A on page 18, left panel). A mechanical model for this arrangement is a spring in parallel with a dashpot and a latch (Figure B, left panel). Now suppose that the constraint is suddenly relieved (Figure A, middle panel). This is equivalent to releasing the latch (Figure B, middle panel). We expect that the protein will change shape and relax into its unstrained conformation (Figures A and B, right panel) with a time constant on the order of $\gamma/\kappa$, the drag coefficient divided by the spring constant. Figure C shows an energy diagram in which the stiff-latched state moves into the relaxed conformation of the more compliant unlatched state. For a roughly globular protein with a molecular mass of ~100 kDa, the drag coefficient is ~60 pN·s/m (see Table 2.2 and Appendix 3.3). If the elastic element has a stiffness of ~4 pN/nm, comparable to that of the myosin crossbridge (Chapter 16), then the relaxation time constant will be 15 ns. This model provides a general picture for the timescale of protein conformational changes: Local chemical changes,




such as the breaking of the bonds between two proteins, occur very rapidly, on the timescale of ~1 ps, whereas the global conformational changes of the whole protein occur much more slowly, on the ns—or even μs—timescale. We will return to the kinetics of protein conformational changes in Chapter 5.

**MASS AND SPRING.** The mass on a spring (see Figure 2.3C, left panel) is a familiar mechanical system found in physics and chemistry textbooks, where it is used to describe the vibrations of tuning forks and atomic bonds. The net force acting on the mass is the applied force minus the elastic force, and therefore $ma = F + F_s = F - \kappa x$. Because the acceleration is the second derivative of the displacement, we can rearrange this equation to obtain

$$m\frac{d^2x}{dt^2} + \kappa x = F \tag{2.8}$$

Suppose that the mass is initially stationary and that at time zero a constant force is applied. At first, when the displacement is small and the elastic force is also small, the particle undergoes constant acceleration and the displacement increases parabolically. As the displacement increases, the elastic force increases, and, when the displacement reaches $F/\kappa$, the net force acting on the particle is zero. At this point the acceleration is also zero. However, at this time the particle has reached its maximum velocity and its inertia keeps it moving. As it overshoots what will be the new average displacement of $F/\kappa$, the restoring force in the spring increases and the particle gradually slows down and finally stops when the displacement reaches $2F/\kappa$. Now the elastic restoring force causes the particle to accelerate back to its initial position. It overshoots the average displacement as it returns to the initial position, whereupon it begins another cycle of oscillation. The resulting sinusoidal oscillation, called **harmonic motion**, is described by the equation

$$x(t) = \frac{F}{\kappa}\left[1 - \cos(\omega t)\right] \qquad \omega = \sqrt{\frac{\kappa}{m}} \tag{2.9}$$

This equation is plotted in Figure 2.3C. $\omega$ is the frequency of the oscillations expressed in units of radians per second. However, it is more familiar to express frequency in terms of cycles per second, or hertz (Hz); the relationship between the two frequencies is $f = \omega/2\pi$. If the mass is increased, the acceleration will decrease, and the longer the time until the elastic force becomes significant. A higher mass is therefore associated with a low frequency of oscillation. Conversely, when the stiffness is increased, the elastic force rises more quickly, and frequency of oscillation increases.

***Example 2.6 Vibration of chemical bonds*** Covalent chemical bonds can be thought of as having stiffness. The manifestation of this stiffness is that they vibrate with a frequency given by Equation 2.9. The vibration can be detected spectroscopically when the molecule absorbs light of the same frequency as the molecular vibration. For example, the fundamental vibration frequency of the H–Cl bond in HCl is $\upsilon = 89.6 \times 10^{12}$ Hz (2990 $cm^{-1}$), corresponding to a wavelength of $c/89.6 \times 10^{12} = 3.53$ μm (in the infrared) (Atkins, 1986). The appropriate mass is $\sim 1.63 \times 10^{-27}$ kg (approximately the mass of the hydrogen nucleus), and so the stiffness is $m\omega^2 = 4\pi^2\nu^2 m = 517$ N/m.

***Example 2.7 Protein vibrations*** Consider the motor protein myosin again. The motor domain has a mass of ~$160 \times 10^{-24}$ kg and the stiffness is 4 pN/nm (4 mN/m). The vibration frequency is calculated to be ~$10^9$ Hz. This corresponds to a period of oscillation of 1 ns. By contrast, the relaxation time calculated in Example 2.5 is 15 ns. Does the protein oscillate when it detaches from the actin filament, or does it creep exponentially into its relaxed state? The answer requires solution of the full model, with mass, spring, and dashpot. The solution, provided in the next section, shows that the protein creeps rather than rings.

## Motion of a Mass and Spring with Damping

In this section, we consider how a system comprising all three elements—the mass on a spring subject to damping (Figure 2.4A)—moves in response to an applied force. This is a simple mechanical model for a protein undergoing a large-scale conformational change that is damped by the surrounding fluid, and possibly by internal viscosity (Figure 2.4B). This three-element model captures the main qualitative features of more complex models in that it can display oscillatory or monotonic motions depending on the strength of the damping.

The equation of motion is

$$m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + \kappa x = F \tag{2.10}$$

The solution depends on whether the damping is small or large (Appendix 2.1). When the damping is small, $\gamma^2 < 4m\kappa$, the motion is oscillatory, like that of a mass on a spring except that the amplitude of the oscillation gradually decreases as the vibration dies out. This is shown in Figure 2.4C. We say that the motion is **underdamped**. As the damping decreases, the oscillation dies out more slowly and the motion more closely approximates harmonic motion. On the other hand, when the damping is large, $\gamma^2 > 4m\kappa$, the motion is monotonic, like that of a damped spring, as shown in Figure 2.4D. In this case, we say that the motion is **overdamped**. The overdamped motion is actually associated with two time constants, though only one time constant is apparent in Figure 2.4B. The fast time constant corresponds to the time that it takes for the mass to accelerate to a velocity of ~$F/\gamma$, whereas the slow time constant corresponds to the relaxation of the spring and dashpot. The reason why the fast component is not seen in the figure is that its amplitude is much smaller than that of the slow component: Even when the motion is moderately overdamped ($\gamma^2/4m\kappa = 3$), the amplitude of the fast component is only ~10% that of the slow component. When the system is even more strongly damped, the fast component can be ignored altogether; under these conditions, we can ignore the mass and just consider the spring and dashpot. In the highly over-

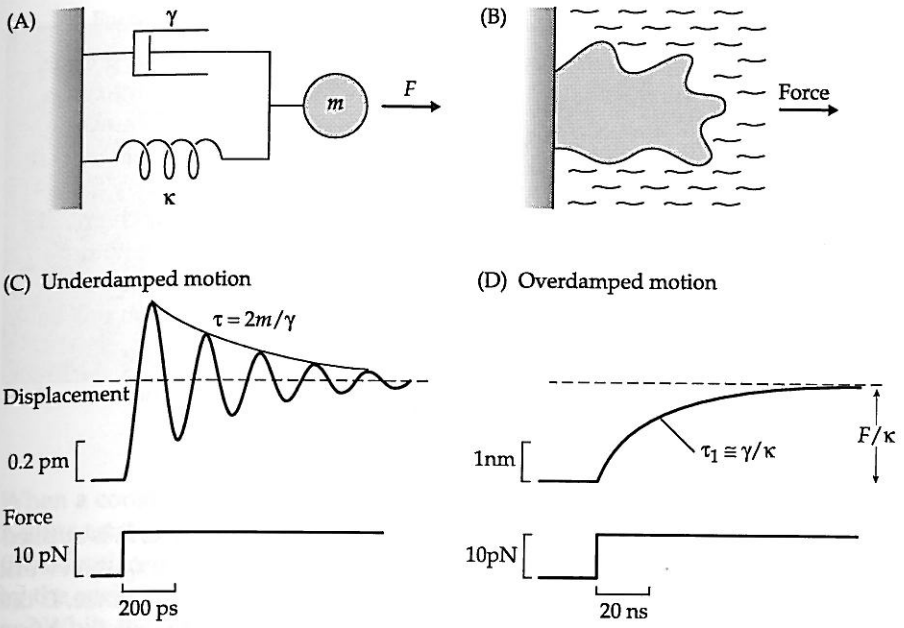



***Figure 2.4 Motion of a mass and spring with damping***
The mechanical model (A) is used to describe the motion of an elastic solid in a fluid (B). (C) Underdamped motion. In this example, $\gamma^2/4m\kappa \cong 0.007$, and the motion corresponds to that of a hypothetical globular protein that is both very large (16 MDa) and very rigid (stiffness 30 N/m) and experiences unrealistically little damping from the fluid ($\gamma$ = 150 pN·s/m). (D) Overdamped motion. In this example, $\gamma^2/4m\kappa \cong 1400$, and the motion corresponds to that of a more realistic protein of molecular mass 100 kDa and stiffness 4 pN/nm.

damped case, the inertial term can be dropped, and we can describe the motion without invoking Newton's second law!

The condition for overdamping is that $\gamma^2 > 4m\kappa$. This makes intuitive sense because the system should become more damped as the drag coefficient increases: When the relaxation time-constant of the spring ($\gamma/\kappa$) becomes greater than that of the mass ($m/\gamma$), the kinetic energy of the mass is unable to sustain the oscillation. There is another way of thinking about the motion. If the system is overdamped, then the inertial force ($ma$) is always smaller than the viscous force ($\gamma v$) (Appendix 2.1). Conversely, if the inertial force is always smaller than the viscous force, then the motion is overdamped (Appendix 2.1). This is an important observation: The quality of the motion—whether it is oscillatory or monotonic—depends on the relative contribution of the inertial forces (that tend to produce oscillations) and the viscous forces (that tend to damp the oscillations out). It turns out that inertial forces are usually very small at the microscopic and molecular levels, so that the overdamped case usually applies.

***Example 2.8 Motor proteins are overdamped*** Consider the motor protein myosin again. The motor domain has a mass of ~$160 \times 10^{-24}$ kg, the drag coefficient is ~60 pN·s/m, and the stiffness is ~4 pN/nm. In this case $\gamma^2/4m\kappa$ is equal to 1400. Because this is much greater than 1, it follows that the motion is highly overdamped. Thus, when the force exerted by a motor protein abruptly changes—for example, if it enters a new chemical state as described in Example 2.5—then the protein will relax monotonically into its new equilibrium conformation without undergoing oscillations, as shown in Figure 2.4D. The time constant of the relaxation will be given by the damped spring, namely ~15 ns.

## Work, Energy, and Heat

It is important not to confuse force with work or energy. If a force, $F$, is applied to a mechanical system and the system moves through a distance $x_0$, then work has been done on it. The **work**, $w$, equals the force times the distance. If the force is a constant (independent of position), then the work done is $Fx_0$. More generally, if the force depends on the position—that is, $F(x)$—then each incremental change in position, $dx$, results in an incremental amount of work $dw = F(x) \cdot dx$; the total work is the sum of all the increments of work done as the system moves. In other words, the total work is equal to the integral

$$w = \int_0^{x_0} F(x) \cdot dx \tag{2.11}$$

The SI unit of work is the joule (J); because work is force times distance, it follows that 1 J = 1 N·m. If the force produces no movement, then the work is zero.

Energy is closely related to work and has the same units. A spring is a mechanical element that can store energy—the work done on it is converted into **potential energy**, denoted by $U$. Potential energy can also be stored in gravitational and electric fields. Another way of thinking about force is that it is the tendency for a system to move from high potential energy to low potential energy. In mathematical words, force is the negative of the gradient of the potential energy:

$$F_s = -\frac{dU}{dx} \tag{2.12}$$

The steeper the gradient, the greater the force; there is a minus sign because the force is in the direction corresponding to a decrease in the potential energy (Figure 2.5). Now, as we saw before, the force exerted by a spring, $F_s$, is $-\kappa x$. Substituting this into Equation 2.12 and multiplying by $dx$ gives $dU = -F_s \cdot dx = - -\kappa x \cdot dx = \kappa x \cdot dx$. Upon integrating we obtain

$$U = \int_0^{x_0} \kappa x \cdot dx = \tfrac{1}{2} \kappa x_0^2 \tag{2.13}$$

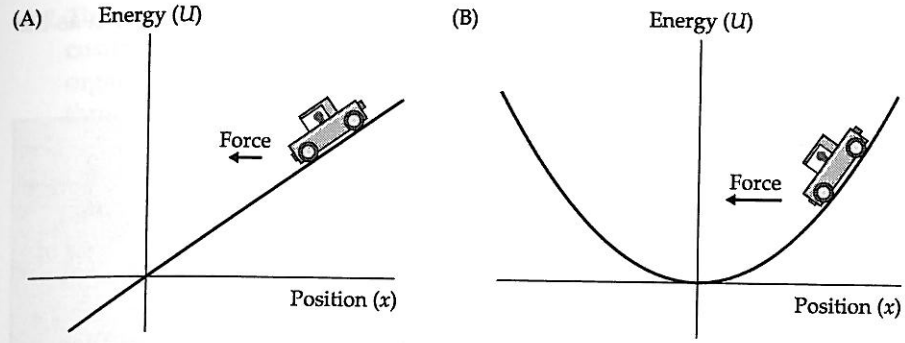



***Figure 2.5 The force is the negative of the gradient of potential energy***
(A) Constant force. (B) Force that depends on displacement.

When a constant force is applied to the mechanical system shown in Figure 2.4, the total work done on it is $Fx_0 = \kappa x_0^2$, where we have used the fact that the final displacement, $x_0$, is equal to $F/\kappa$. However, the potential energy gained by the spring, $\frac{1}{2}\kappa x_0^2$, is only half this amount. Where did the missing energy go? While the mass is actually moving, some of this energy is stored as **kinetic energy,**

$$K.E. = \tfrac{1}{2}mv^2 \tag{2.14}$$

But when the mass reaches its new steady-state position, the mean speed is zero and so the kinetic energy is also zero. The answer is that part of the work went to heating the dashpot. If we wish our system to remain at the same temperature, then this **heat,** denoted by $Q$, must be transferred to the surroundings, and we say that the heat has been dissipated. The rate at which the heat is dissipated is

$$\frac{dQ}{dt} = -F_{\text{drag}}v = -(-\gamma v)v = \gamma v^2 \tag{2.15}$$

and it can be shown that the total heat dissipated is $\frac{1}{2}\kappa x_0^2$ (Appendix 2.2). Thus we have

$$w = U + Q \tag{2.16}$$

***Example 2.9 Energy of chemical bonds*** We can think of the energy of a chemical bond, the dissociation energy, as being approximately equal to the potential energy in the bond. This energy is $\sim \frac{1}{2}\kappa r^2$ where $r$ is the extension required to break the bond, ~0.05 nm. For HCl, considered in Example 2.6, where the stiffness is ~517 N/m, the corresponding energy is $\sim 650 \times 10^{-21}$ J, in fairly good agreement with the bond energy of $\sim 720 \times 10^{-21}$ J (Moore, 1972). For a more accurate treatment, the non-Hookean stiffness of bonds must be taken into account.

This is a statement of the **Law of Conservation of Energy**, also known as the **First Law of Thermodynamics**.

***Example 2.10 Energy stored in protein conformational changes*** For a myosin molecule, the stiffness is thought to be about 4 pN/nm. For a conformational change of 5 nm, the total energy is 50 pN·nm = $50 \times 10^{-21}$ J. This is approximately half the chemical energy derived from hydrolysis of the gamma phosphate bond of ATP (Chapter 14). We can generalize this argument to global conformational changes of other protein machines. The energies are on the order of 10 to $100 \times 10^{-21}$ J, and the conformational changes are on the order of 1 to 10 nm. The corresponding stiffnesses are therefore on the order of 0.2 to 200 mN/m.

## Summary: Generalizations to More Complex Mechanical Systems

By considering three mechanical elements—a mass, a spring, and a dashpot—we have introduced many of the mechanical concepts required to understand how forces influence proteins and cells. The mass and spring with damping illustrate that systems can respond to mechanical forces in two ways: They can oscillate or they can move monotonically.

The mechanical models considered in this chapter can be generalized in two ways. The first way is to increase the number of mechanical elements to include several masses, springs, dashpots, and even other elements such as latches and stops; the equations of motion are solved by balancing the forces across each element (Jaeger and Starfield, 1974). Molecular dynamics (McCammon and Harvey, 1987) is an example of such a generalization: Each atom in a protein and the surrounding fluid is represented by a point mass, each bond is represented by a spring (which need not have constant stiffness), and the damping is dropped from the equations (it is an "emergent" property of the system). The ensuing motion is complex and best solved numerically by computer.

The second way to generalize the model is to consider the mechanical behavior of "continuum" solids that have material properties such as elasticity, density, and viscosity. This "coarse" approach is taken in the next chapter.

## Problems

**2.1** Suppose that a force of 1 pN is applied to a globular 100 kDa protein. In the absence of damping, how fast will the protein be moving after 1 ns? During this time, how far will the protein have moved? Given the damping coefficient quoted in Table 2.2, what is the actual terminal velocity of

**2.2** The motor protein kinesin can generate a force of 6 pN. Given that the viscosity of cytoplasm is ~1000 times that of water (for large objects like organelles), how fast could a single kinesin molecule move a bacterium through a cell (see Example 2.2)?

**2.3** During mitosis, the chromosomes move several micrometers over the course of about 30 minutes. Calculate the average speed. If the viscosity of the cytoplasm is 1000 times that of water, what force is required (assuming a chromosome has the same drag coefficient as a bacterium)?

**2.4** The probes used in atomic force microscopes (AFMs) typically have stiffnesses of ~1 N/m. Given that the mass is ~100 ng, what is the resonance frequency in vacuum (without damping)? The damping coefficient of a probe in water is ~1 μN·s/m. Is the motion in water overdamped or underdamped?

**2.5** The chemical energy available from the hydrolysis of ATP is ~$100 \times 10^{-21}$ J. How far can a motor protein exert a force of 6 pN before $100 \times 10^{-21}$ J of work is done?

**2.6** In Example 2.2, it was stated that the bacterial motors must generate a force of 0.5 pN in order to propel the bacterium at a speed of 25 μm/s. What is the power output of the bacterium? How many equivalent ATPs must be hydrolyzed per second in order to power this movement?

**2.7** Coulomb's law states that the force between two charges $q_1$ and $q_2$ separated by a distance $r$ is

$$F = \frac{1}{4\pi\varepsilon_0\varepsilon}\frac{q_1 q_2}{r^2}$$

where $\varepsilon_0$ is the electric constant, also called the permattivity constant, equal to $8.854 \times 10^{-12}$ C$^2$/N·m$^2$ and $\varepsilon$ is the dielectric constant (equal to 1 for a vacuum, ~3 for oils, and 80 for water). Calculate the force between two electronic charges separated by 1 nm in pure water. [Answer: 2.9 pN.] Note that the force would be smaller in a salt solution due to screening of the charge by the salt ions, but it will be larger in the interior of proteins where the dielectric constant is similar to that of oil.

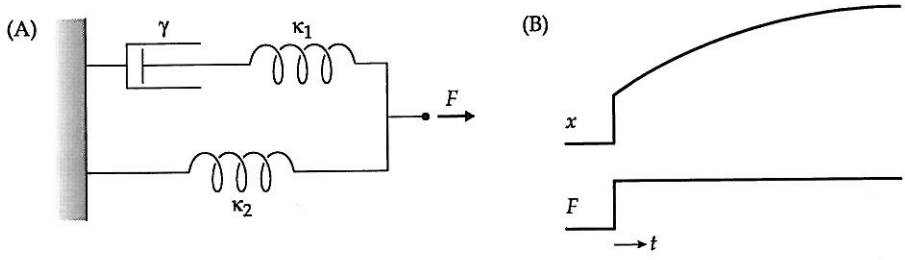
**2.8** If two springs are placed in parallel, show that their stiffnesses add. If they are placed in series, show that their compliances add (the **compliance** is the reciprocal of the stiffness). If two dashpots are placed in parallel, show that the total drag coefficient is the sum of the individual coefficients. If the dashpots are placed in series, show that reciprocals of the drag coefficients add.

**2.9** A Voigt element consists of a spring and a dashpot in series. When one end is held fixed and a constant force is abruptly applied to the other at time zero, how does the system move?

**2.10** Show that the motion of the Maxwell element (Figure A, below), in response to a force $F$, is

$$x(t) = x_0 - (x_0 - y_0)\exp\left(-\frac{t}{\tau}\right) \qquad x_0 = \frac{F}{\kappa_2} \qquad y_0 = \frac{F}{\kappa_1 + \kappa_2} \qquad \tau = \gamma\left(\frac{1}{\kappa_1} + \frac{1}{\kappa_2}\right)$$

as plotted in Figure B.



CHAPTER

# 3

# Mass, Stiffness, and Damping of Proteins

The purpose of this chapter is to get a feeling for what proteins are like as mechanical devices. How rigid are they? How quickly do they move and change shape? And what is the quality of their motion: When a protein is struck by a force, does it ring like a tuning fork (underdamped motion), or does it creep monotonically into a new shape (overdamped motion)? To answer these questions, I begin this chapter with a discussion of the material properties of proteins—their density, their elasticity, and the frictional forces that damp their motion. Proteins have similar densities and rigidities to hard plastics and Plexiglas. However, owing to their small size, the viscous forces from the surrounding fluid are large compared to the inertial forces. Consequently, the global motions of proteins are overdamped, meaning that proteins relax monotonically into new conformations. Thus a protein, as a mechanical device, is like a little plastic toy. But if we were to scale it up by a factor of $10^7$ so that a 5-nm-diameter protein becomes a 50-mm-diameter device that would fit into the palm of one's hand, then we would have to increase the viscosity by the same amount (i.e., bathe it in treacle) in order to damp out any tendency for oscillation.

## Mass

Mass equals density, $\rho$, times volume, $V$:

$$m = \rho V \tag{3.1}$$

The densities of various amino acids, proteins, organelles, and cells are given in Table 3.1. Proteins are composed of relatively light elements—carbon, oxygen, nitrogen, and hydrogen—and are about 40% denser than water, with different proteins having slightly different densities. We take the average density of proteins to be $1.38 \times 10^3$ kg/m$^3$.