1. Termodinámica, primeros pasos

Material de lectura sugerido:

- Capítulo 1 de *Física Biológica. Energía, información y vida*, Philip Nelson.
- Fragmento de *Molecular Biology of the Cell*, 4th Edition, Bruce Alberts et al. (al final de la guía)

Problemas para hacer y discutir en clase:

1) *Conservación de la Energía*. Un objeto de masa m está cayendo libremente (bajo la acción de la gravedad únicamente). En un momento dado, se encuentra a una altura z bajando con una velocidad v.
    a) Escribir la energía mecánica del objeto, E. ¿Se conserva durante la caída? ¿Por qué?
    b) Calcular explícitamente la derivada temporal de la energía E, dE/dt, y mostrar que es igual a cero.
    c) Poco tiempo después de impactar en el piso, queda en reposo. ¿Qué sucedió con su energía mecánica?

2) *Formas de Energía*. Si se convencieron de que la conservación de la energía es una ley fundamental de la naturaleza y que no hay pérdida de energía en el universo sino procesos de *conversión* de energía, ¿Por qué cotidianamente tenemos que preocuparnos en no desperdiciar la energía?

3) *Primera y Segunda Ley*. Una persona se encuentra tomando una bebida muy fría al borde de una pileta de agua caliente. Sumerge una parte del vaso en el agua y piensa que a lo mejor, el vaso podría ceder 10 J de energía al agua de la pileta (que absorbería 10 Joules de energía) y de este modo su bebida se enfriaría aún más. ¿Es esto posible? ¿Contradice la primera ley de la termodinámica? ¿Y la segunda ley?

4) *Energía libre*. La energía libre es la parte *útil* de la energía total. Explique qué quiere decir esto. Hay varias formas de definir la energía libre. Una de ellas, F, se define como $F=E-TS$., donde T es la temperatura y S la entropía. ¿Cómo se relaciona la entropía con el orden de un sistema? ¿Puede un sistema reducir su energía libre F aunque su energía interna aumente?

5) *La vida y la termodinámica*. La segunda ley de la termodinámica establece que cualquier sistema aislado cambiará espontáneamente hacia estados de mayor entropía. Los sistemas biológicos son tan extremadamente complejos y ordenados que seguramente deben violar la segunda ley. Explique brevemente, en forma cualitativa cómo la vida es compatible con las leyes de la termodinámica.

6) *Procesos espontáneos*. La energía libre de Gibbs (G) es una función muy útil porque permite determinar si ciertos procesos (como reacciones químicas) se dan espontáneamente. Por definición, $G=H-TS$, donde H es la entalpía (otra función termodinámica), T la temperatura absoluta y S la entropía.
    a) ¿Cómo se relacionan los cambios de la energía libre de Gibbs con los cambios de entropía del sistema y su entorno?
    b) ¿Es correcto decir que todo proceso con un $\Delta G<0$ es espontáneo?

7) *Polimerización de la tubulina*. Los filamentos que forman el citoesqueleto de las células eucariotas son fundamentales para su organización espacial. Unos de esos filamentos, los microtúbulos, son estructuras tubulares de 25 nm de diámetro exterior y hasta 25 μm de largo

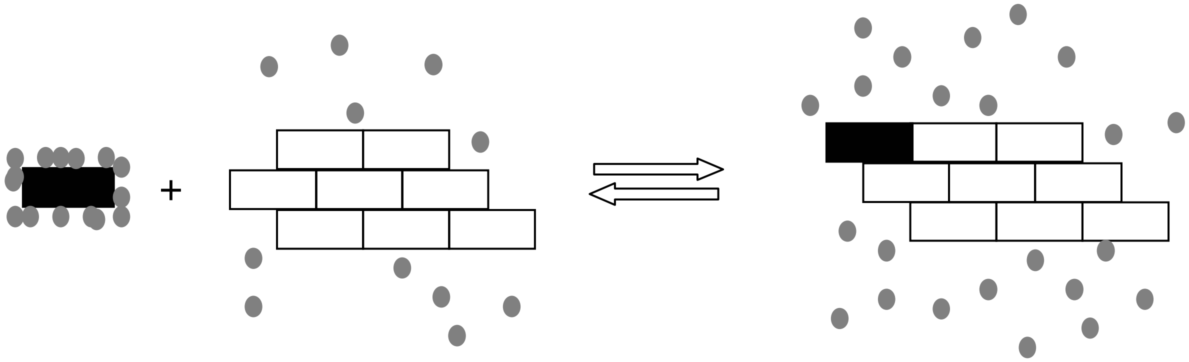
que están involucradas en procesos como la mitosis y el transporte de sustancias dentro de las células. Los microtúbulos se forman por la *polimerización* de subunidades de tubulina. La polimerización es la reacción que da lugar a la unión de estas subunidades para formar un arreglo en cadena. En este problema estudiamos la reacción de polimerización que da lugar a la formación de microtúbulos.

Se sabe que si una célula en mitosis es enfriada a 0ºC, los microtúbulos del aster mitótico se desensamblan en subunidades de tubulina. Lo mismo ocurre si se ensaya el ensamblado de microtúbulos *in vitro* a altas y bajas temperaturas: **a temperaturas de 37ºC la polimerización es rápida, mientras que a 0ºC los microtúbulos formados se desensamblan**. De hecho, muchos complejos proteicos que están mantenidos por fuerzas no covalentes muestran el mismo comportamiento: se desensamblan al ser enfriados. Este comportamiento esta regido por la ecuación termodinámica básica:

$$\Delta G = \Delta H - T\Delta S$$

que vincula los cambios en la energía libre de Gibbs del sistema, ΔG, con la temperatura absoluta T y los cambios en la entalpía, ΔH (energía de uniones químicas), y en la entropía, ΔS.

a) El cambio en energía libre (ΔG) debe ser negativo para que la reacción de polimerización (tubulina----microtúbulos) ocurra a altas temperaturas (37ºC). A bajas temperaturas (0ºC), ΔG debe ser positivo para permitir el desensamblado. ¿Entiende por qué los signos de ΔG deben ser esos?
b) Decida cuál debe ser el signo de ΔH y ΔS y muestre cómo su elección da cuenta del comportamiento del sistema a altas y bajas temperaturas (asuma que los valores ΔH y ΔS no cambian con la temperatura).
c) La polimerización de microtúbulos a temperatura corporal ocurre con un claro ordenamiento de las subunidades de tubulina (ver la figura de abajo). Sin embargo, la polimerización de tubulina ocurre con un aumento de la entropía del sistema (el estado final es de mayor desorden). ¿Cómo se explica esto?



La figura representa la reacción de polimerización de una subunidad de tubulina. En esta reacción intervienen moléculas de tubulina (bloques rectangulares) y de agua (círculos grises). A la izquierda se muestra un fragmento de microtúbulo y una molécula de tubulina (en negro) rodeada de moléculas de agua ordenadas. Al polimerizarse (derecha) estas moléculas de agua son liberadas y el microtúbulo gana una subunidad más.

Biological Order Is Made Possible by the Release of Heat Energy from Cells

(extraido de Molecular Biology of the Cell, 4th Edition, Bruce Alberts et al.)

The universal tendency of things to become disordered is expressed in a fundamental law of physics—the *second law of thermodynamics*—which states that in the universe, or in any isolated system (a collection of matter that is completely isolated from the rest of the universe), the degree of disorder can only increase. This law has such profound implications for all living things that it is worth restating in several ways.

For example, we can present the second law in terms of probability and state that systems will change spontaneously toward those arrangements that have the greatest probability. If we consider, for example, a box of 100 coins all lying heads up, a series of accidents that disturbs the box will tend to move the arrangement toward a mixture of 50 heads and 50 tails. The reason is simple: there is a huge number of possible arrangements of the individual coins in the mixture that can achieve the 50-50 result, but only one possible arrangement that keeps all of the coins oriented heads up. Because the 50-50 mixture is therefore the most probable, we say that it is more “disordered.” For the same reason, it is a common experience that one's living space will become increasingly disordered without intentional effort: the movement toward disorder is a *spontaneous process*, requiring a periodic effort to reverse it (Figure 2-37).

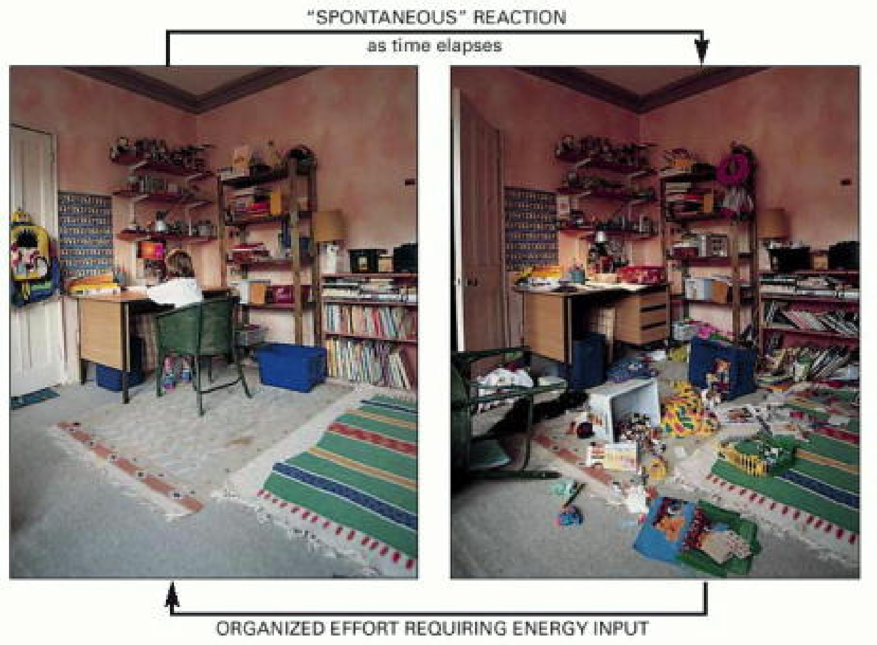


Figure 2-37. An everyday illustration of the spontaneous drive toward disorder. Reversing this tendency toward disorder requires an intentional effort and an input of energy: it is not spontaneous. In fact, from the second law of thermodynamics, we can be certain that the human intervention required will release enough heat to the environment to more than compensate for the reordering of the items in this room.

The amount of disorder in a system can be quantified. The quantity that we use to measure this disorder is called the entropy of the system: the greater the disorder, the greater the entropy. Thus, a third way to express the second law of thermodynamics is to say that systems will change spontaneously toward arrangements with greater entropy.

Living cells—by surviving, growing, and forming complex organisms—are generating order and thus might appear to defy the second law of thermodynamics. How is this possible? The answer is that a cell is not an isolated system: it takes in energy from its environment in the form of food, or as photons from the sun (or even, as in some chemosynthetic bacteria, from inorganic molecules alone), and it then uses this energy to generate order within itself. In the course of the chemical reactions that generate order, part of the energy that the cell uses is converted into heat. The heat is discharged into the cell's environment and disorders it, so that the total entropy—that of the cell plus its surroundings—increases, as demanded by the laws of physics.

To understand the principles governing these energy conversions, think of a cell as sitting in a sea of matter representing the rest of the universe. As the cell lives and grows, it creates internal order. But it releases heat energy as it synthesizes molecules and assembles them into cell structures. Heat is energy in its most disordered form—the random jostling of molecules. When the cell releases heat to the sea, it increases the intensity of molecular motions there (thermal motion)—thereby increasing the randomness, or disorder, of the sea. The second law of thermodynamics is satisfied because the increase in the amount of order inside the cell is more than compensated by a greater decrease in order (increase in entropy) in the surrounding sea of matter (Figure 2-38).

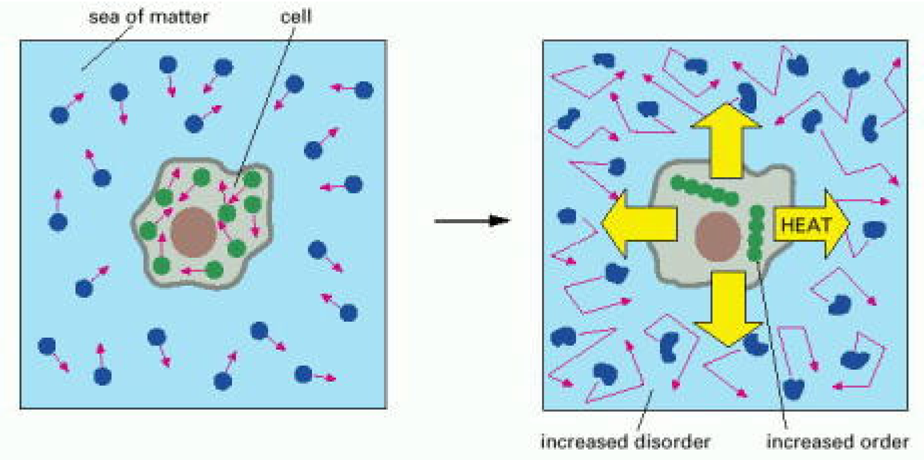


Figure 2-38. A simple thermodynamic analysis of a living cell. In the diagram on the left the molecules of both the cell and the rest of the universe (the sea of matter) are depicted in a relatively disordered state. In the diagram on the right the cell has taken in energy from food molecules and released heat by a reaction that orders the molecules the cell contains. Because the heat increases the disorder in the environment around the cell (depicted by the *jagged arrows* and distorted molecules, indicating the increased molecular motions caused by heat), the second law of thermodynamics—which states that the amount of disorder in the universe must always increase—is satisfied as the cell grows and divides. For a detailed discussion, see Panel 2-7 (pp. 122–123).

Where does the heat that the cell releases come from? Here we encounter another important law of thermodynamics. The first law of thermodynamics states that energy can be converted from one form to another, but that it cannot be created or destroyed. Some forms of energy are illustrated in Figure 2-39. The amount of energy in different forms will change as a result of the chemical reactions inside the cell, but the first law tells us that the total amount of energy must always be the same. For example, an animal cell takes in foodstuffs and converts some of the energy present in the chemical bonds between the atoms of these food molecules (chemical bond energy) into the random thermal motion of molecules (heat energy). This conversion of chemical energy into heat energy is essential if the reactions inside the cell are to cause the universe as a whole to become more disordered—as required by the second law.

The cell cannot derive any benefit from the heat energy it releases unless the heat-generating reactions inside the cell are directly linked to the processes that generate molecular order. It is the tight *coupling* of heat production to an increase in order that distinguishes the metabolism of a cell from the wasteful burning of fuel in a fire. Later in this chapter, we shall illustrate how this coupling occurs. For the moment, it is sufficient to recognize that a direct linkage of the “burning” of food molecules to the generation of biological order is required if cells are to be able to create and maintain an island of order in a universe tending toward chaos.

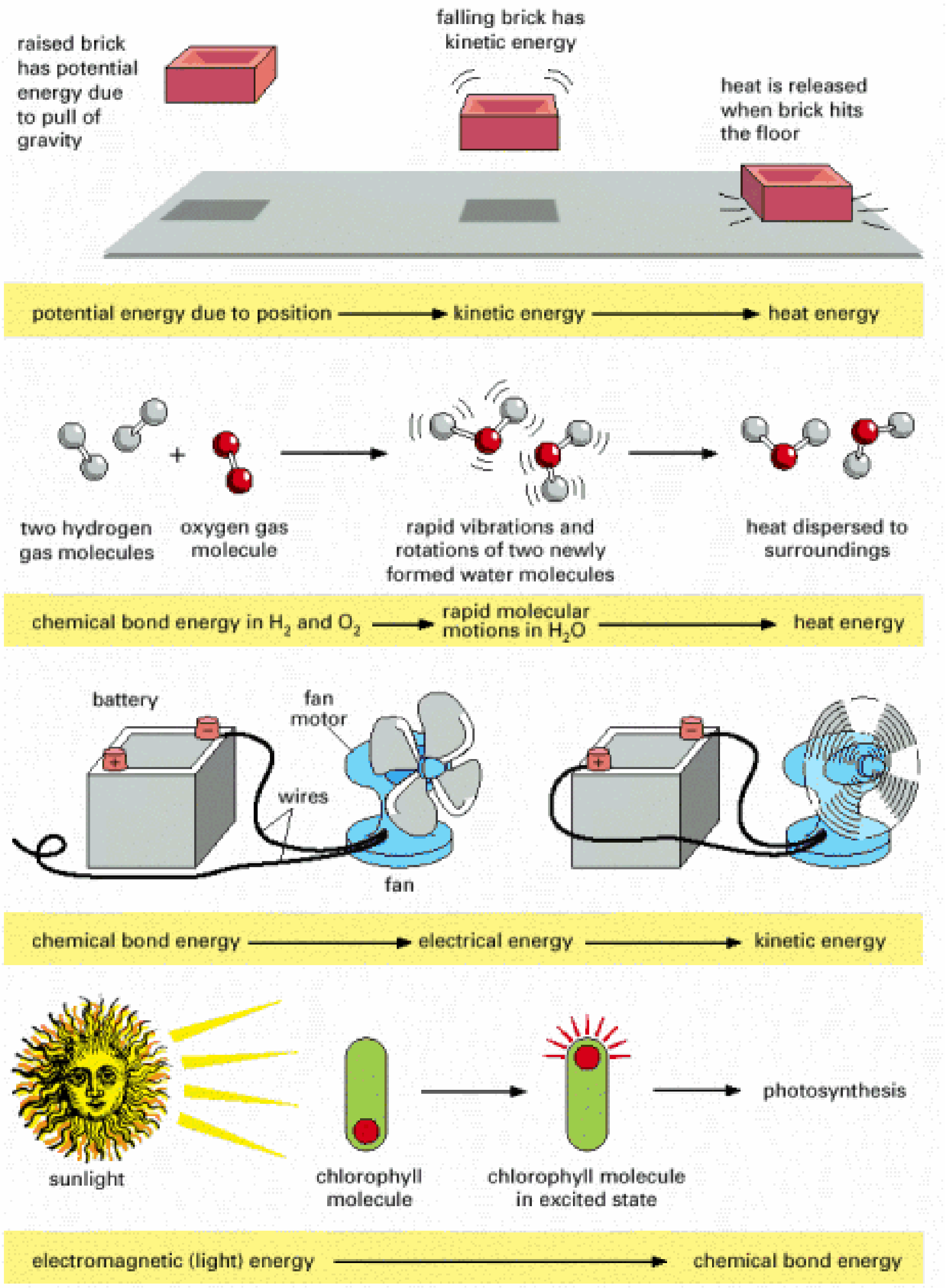


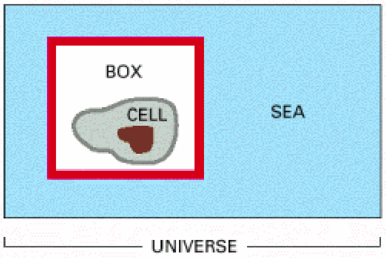
Figure 2-39. Some interconversions between different forms of energy. All energy forms are, in principle, interconvertible. In all these processes the total amount of energy is conserved; thus, for example, from the height and weight of the brick in the first example, we can predict exactly how much heat will be released when it hits the floor. In the second example, note that the large amount of chemical bond energy released when water is formed is initially converted to very rapid thermal motions in the two new water molecules; but collisions with other molecules almost instantaneously spread this kinetic energy evenly throughout the surroundings (heat transfer), making the new molecules indistinguishable from all the rest.

Panel 2-7. Free Energy and Biological Reactions

THE IMPORTANCE OF FREE ENERGY FOR CELLS

Life is possible because of the complex network of interacting chemical reactions occurring in every cell. In viewing the metabolic pathways that comprise this network, one might suspect that the cell has had the ability to evolve an enzyme to carry out any reaction that it needs. But this is not so. Although enzymes are powerful catalysts, they can speed up only those reactions that are thermodynamically possible; other reactions proceed in cells only because they are *coupled* to very favorable reactions that drive them. The question of whether a reaction can occur spontaneously, or instead needs to be coupled to another reaction, is central to cell biology. The answer is obtained by reference to a quantity called the *free energy:* the total change in free energy during a set of reactions determines whether or not the entire reaction sequence can occur. In this panel we shall explain some of the fundamental ideas—derived from a special branch of chemistry and physics called *thermodynamics*—that are required for understanding what free energy is and why it is so important to cells.

ENERGY RELEASED BY CHANGES IN CHEMICAL BONDING IS CONVERTED INTO HEAT



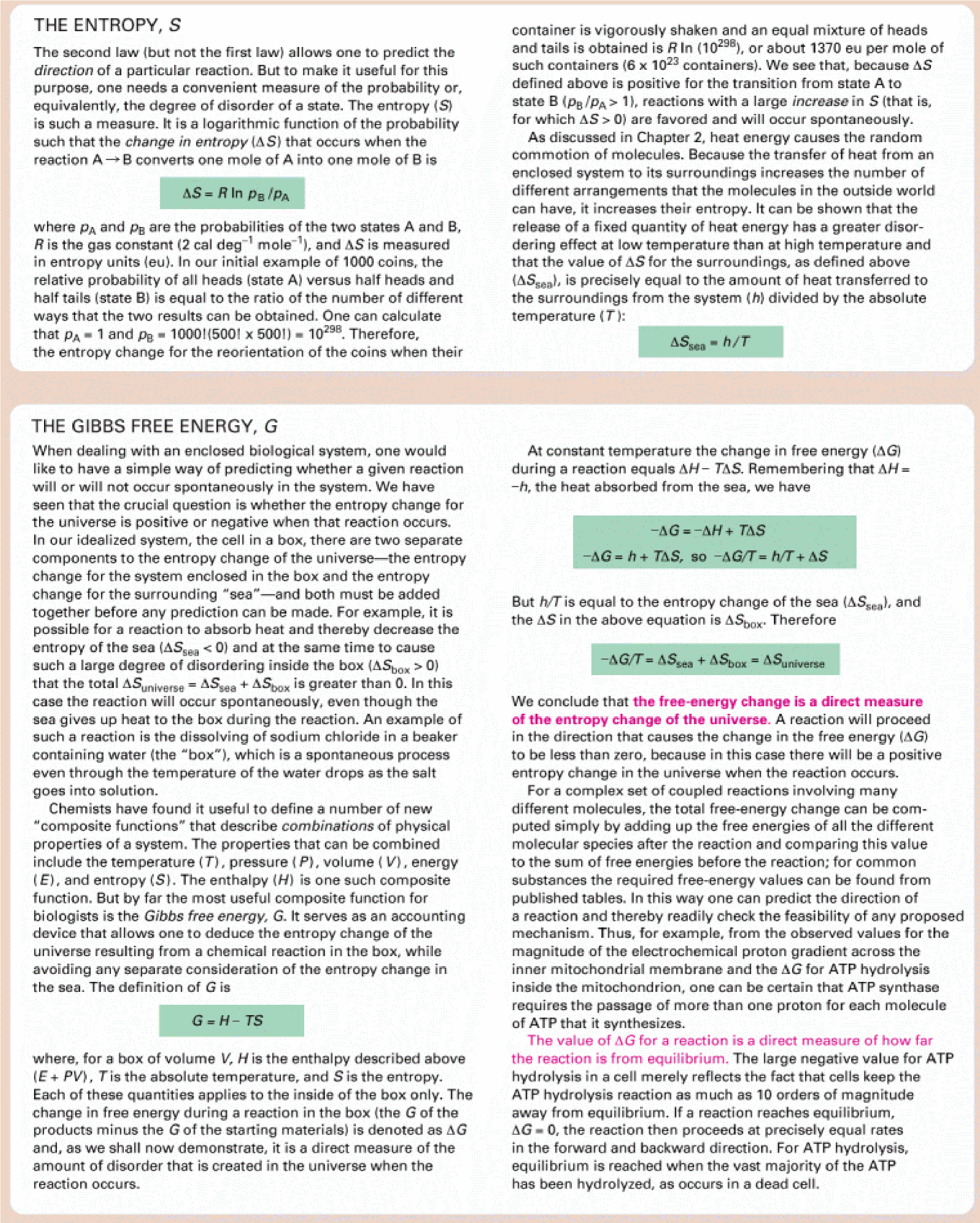
An *enclosed system* is defined as a collection of molecules that does not exchange matter with the rest of the universe (for example, the "cell in a box" shown above). Any such system will contain molecules with a total energy E. This energy will be distributed in a variety of ways: some as the translational energy of the molecules, some as their vibrational and rotational energies, but most as the bonding energies between the individual atoms that make up the molecules. Suppose that a reaction occurs in the system. The first law of thermodynamics places a constraint on what types of reactions are possible: it states that "in any process, the total energy of the universe remains constant." For example, suppose that reaction A→ B occurs somewhere in the box and releases a great deal of chemical bond energy. This energy will initially increase the intensity of molecular motions (translational, vibrational, and rotational) in the system, which is equivalent to raising its temperature. However, these increased motions will soon be transferred out of the system by a series of molecular collisions that heat up first the walls of the box and then the outside world (represented by the sea in our example). In the end, the system returns to its initial temperature, by which time all the chemical bond energy released in the box has been converted into heat energy and transferred out of the box to the surroundings. According to the first law, the change in the energy in the box (ΔE_{box}, which we shall denote as ΔE) must be equal and opposite to the amount of heat energy transferred, which we shall designate as h: that is, $\Delta E = -h$. Thus, the energy in the box (E) decreases when heat leaves the system.

E also can change during a reaction due to work being done on the outside world. For example, suppose that there is a small increase in the volume (ΔV) of the box during a reaction. Since the walls of the box must push against the constant pressure (P) in the surroundings in order to expand, this does work on the outside world and requires energy. The energy used is $P(\Delta V)$, which according to the first law must decrease the energy in the box (E) by the same amount. In most reactions chemical bond energy is converted into both work and heat. *Enthalpy* (H) is a composite function that includes both of these ($H = E + PV$). To be rigorous, it is the change in enthalpy (ΔH) in an enclosed system and not the change in energy that is equal to the heat transferred to the outside world during a reaction. Reactions in which H decreases release heat to the surroundings and are said to be "exothermic," while reactions in which H increases absorb heat from the surroundings and are said to be "endothermic." Thus, $-h = \Delta H$. However, the volume change is negligible in most biological reactions, so to a good approximation

$$-h = \Delta H \cong \Delta E$$

THE SECOND LAW OF THERMODYNAMICS

Consider a container in which 1000 coins are all lying heads up. If the container is shaken vigorously, subjecting the coins to the types of random motions that all molecules experience due to their frequent collisions with other molecules, one will end up with about half the coins oriented heads down. The reason for this reorientation is that there is only a single way in which the original orderly state of the coins can be reinstated (every coin must lie heads up), whereas there are many different ways (about 10^{298}) to achieve a disorderly state in which there is an equal mixture of heads and tails; in fact, there are more ways to achieve a 50-50 state than to achieve any other state. Each state has a probability of occurrence that is proportional to the number of ways it can be realized. The second law of thermodynamics states that "systems will change spontaneously from states of lower probability to states of higher probability." Since states of lower probability are more "ordered" than states of high probability, the second law can be restated: "the universe constantly changes so as to become more disordered."



THE ENTROPY, S

The second law (but not the first law) allows one to predict the *direction* of a particular reaction. But to make it useful for this purpose, one needs a convenient measure of the probability or, equivalently, the degree of disorder of a state. The entropy (S) is such a measure. It is a logarithmic function of the probability such that the *change in entropy* (ΔS) that occurs when the reaction $A \rightarrow B$ converts one mole of A into one mole of B is

$$\Delta S = R \ln p_B / p_A$$

where p_A and p_B are the probabilities of the two states A and B, R is the gas constant (2 cal deg^{-1} mole^{-1}), and ΔS is measured in entropy units (eu). In our initial example of 1000 coins, the relative probability of all heads (state A) versus half heads and half tails (state B) is equal to the ratio of the number of different ways that the two results can be obtained. One can calculate that $p_A = 1$ and $p_B = 1000!(500! \times 500!) = 10^{298}$. Therefore, the entropy change for the reorientation of the coins when their container is vigorously shaken and an equal mixture of heads and tails is obtained is $R \ln (10^{298})$, or about 1370 eu per mole of such containers (6×10^{23} containers). We see that, because ΔS defined above is positive for the transition from state A to state B ($p_B / p_A > 1$), reactions with a large *increase* in S (that is, for which $\Delta S > 0$) are favored and will occur spontaneously.

As discussed in Chapter 2, heat energy causes the random commotion of molecules. Because the transfer of heat from an enclosed system to its surroundings increases the number of different arrangements that the molecules in the outside world can have, it increases their entropy. It can be shown that the release of a fixed quantity of heat energy has a greater disordering effect at low temperature than at high temperature and that the value of ΔS for the surroundings, as defined above (ΔS_{sea}), is precisely equal to the amount of heat transferred to the surroundings from the system (h) divided by the absolute temperature (T):

$$\Delta S_{sea} = h / T$$

THE GIBBS FREE ENERGY, G

When dealing with an enclosed biological system, one would like to have a simple way of predicting whether a given reaction will or will not occur spontaneously in the system. We have seen that the crucial question is whether the entropy change for the universe is positive or negative when that reaction occurs. In our idealized system, the cell in a box, there are two separate components to the entropy change of the universe—the entropy change for the system enclosed in the box and the entropy change for the surrounding "sea"—and both must be added together before any prediction can be made. For example, it is possible for a reaction to absorb heat and thereby decrease the entropy of the sea ($\Delta S_{sea} < 0$) and at the same time to cause such a large degree of disordering inside the box ($\Delta S_{box} > 0$) that the total $\Delta S_{universe} = \Delta S_{sea} + \Delta S_{box}$ is greater than 0. In this case the reaction will occur spontaneously, even though the sea gives up heat to the box during the reaction. An example of such a reaction is the dissolving of sodium chloride in a beaker containing water (the "box"), which is a spontaneous process even through the temperature of the water drops as the salt goes into solution.

Chemists have found it useful to define a number of new "composite functions" that describe *combinations* of physical properties of a system. The properties that can be combined include the temperature (T), pressure (P), volume (V), energy (E), and entropy (S). The enthalpy (H) is one such composite function. But by far the most useful composite function for biologists is the *Gibbs free energy, G*. It serves as an accounting device that allows one to deduce the entropy change of the universe resulting from a chemical reaction in the box, while avoiding any separate consideration of the entropy change in the sea. The definition of G is

$$G = H - TS$$

where, for a box of volume V, H is the enthalpy described above ($E + PV$), T is the absolute temperature, and S is the entropy. Each of these quantities applies to the inside of the box only. The change in free energy during a reaction in the box (the G of the products minus the G of the starting materials) is denoted as ΔG and, as we shall now demonstrate, it is a direct measure of the amount of disorder that is created in the universe when the reaction occurs.

At constant temperature the change in free energy (ΔG) during a reaction equals $\Delta H - T\Delta S$. Remembering that $\Delta H = -h$, the heat absorbed from the sea, we have

$$-\Delta G = -\Delta H + T\Delta S$$
$$-\Delta G = h + T\Delta S, \text{ so } -\Delta G/T = h/T + \Delta S$$

But h/T is equal to the entropy change of the sea (ΔS_{sea}), and the ΔS in the above equation is ΔS_{box}. Therefore

$$-\Delta G/T = \Delta S_{sea} + \Delta S_{box} = \Delta S_{universe}$$

We conclude that **the free-energy change is a direct measure of the entropy change of the universe**. A reaction will proceed in the direction that causes the change in the free energy (ΔG) to be less than zero, because in this case there will be a positive entropy change in the universe when the reaction occurs.

For a complex set of coupled reactions involving many different molecules, the total free-energy change can be computed simply by adding up the free energies of all the different molecular species after the reaction and comparing this value to the sum of free energies before the reaction; for common substances the required free-energy values can be found from published tables. In this way one can predict the direction of a reaction and thereby readily check the feasibility of any proposed mechanism. Thus, for example, from the observed values for the magnitude of the electrochemical proton gradient across the inner mitochondrial membrane and the ΔG for ATP hydrolysis inside the mitochondrion, one can be certain that ATP synthase requires the passage of more than one proton for each molecule of ATP that it synthesizes.

The value of ΔG for a reaction is a direct measure of how far the reaction is from equilibrium. The large negative value for ATP hydrolysis in a cell merely reflects the fact that cells keep the ATP hydrolysis reaction as much as 10 orders of magnitude away from equilibrium. If a reaction reaches equilibrium, $\Delta G = 0$, the reaction then proceeds at precisely equal rates in the forward and backward direction. For ATP hydrolysis, equilibrium is reached when the vast majority of the ATP has been hydrolyzed, as occurs in a dead cell.