3.1 Cell Interactions

In contrast to unicellular organisms, in multicellular organisms cells interact with one another through cell–cell physical chemical (paracrine or hormonal) contacts. The physical cell–cell interactions occur through cell junctions with binding of proteins present within the membranes of each cell. For distant interactions, molecules secreted (ligands) are recognized by specific receptors on the target cell membrane or in the target cell, depending on the hydrophobicity of the ligand.

3.2 Types of Junctions

Three main types of cell–cell junctions define the physical strength of interactions between cells (Figure 3.1): desmosomes (zonulæ adherens), tight junctions (zonulæ occludens), and gap junctions. These junctions are cell membrane regions enriched with specific proteins interacting between two cells. In particular, the physical strength of the junction allows a resistance to shear stress (a stress applied parallel or tangential to a contact surface) imparted, for example, by vessel endothelium on blood or blood on vessel, respectively. The shear stress of a fluid or viscosity drag \( t \) is a function of its viscosity \( \eta \) and velocity \( v \) exerted on the wall of a lumen (inner radius \( r \)). Shear stress resistance characterizes the different cell junctions of a given lumen [e.g., blood vessels and the gastrointestinal (GI) tract]. The greater the viscosity [and the liquid flow \( Q \)], the higher the shear rate and the viscosity drag \( t \):

\[
t = 4\eta Q / \pi r^3.
\]

Note: In denominator \( \pi = 3.1415926... \)

3.2.1 Desmosomes

Desmosomes are found in all tissues subject to shear stress, including the skin and the GI tract. Desmosomes generate strong bonds between cells and between cells and the basal lamina. Proteins, mainly desmoglein and desmocollin, are associated in dense plaques, separated by a 30 nm intercellular space, are present in both cell membranes, and are linked to intracellular structures and tonofilaments in the two connected cells (Figure 3.1). Shear stress leads to deformation of the cell membrane and disruption of filament actin (F-actin) and of

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cytoskeleton organization. In response to disruption of F-actin, the expression of multiple proteins, including those involved in adherence and cell junctions, is up-regulated, depending on both type of cell and liquid flow. Hemidesmosomes are structures that are present on cells and use similar proteins to anchor cells to the basal lamina through interactions between integrins and proteins in the basal lamina.

3.2.2 Tight Junctions

Tight junctions are common in exchange tissues holding nephron cells in the kidneys, endothelial cells in the vessels, and enterocytes in the GI tract together. Tight junctions in cells are made through the interactions of multiple proteins, including claudins and occludins, both of which are transmembrane proteins embedded in the cytoskeleton. Tight junctions also prevent the movement of proteins with apical functions to the basolateral area of the cell membrane (and vice versa), ensuring cell polarity. Cell polarity also defines both chemical interactions and electrical gradients by the types and concentrations of receptors and channels present. As with chemical activity, cell membrane electrical potential can be different between the apical and the baso-lateral area of a cell.

3.2.3 Gap Junctions

Gap junctions are hemichannels or connexons composed of six connexin (Cx) proteins. The alignment of two connexons forms a gap junction between two cells, allowing cytoplasm sharing and the rapid transfer of both electrical and chemical signals (small molecules and ions). The type of connexins associated in the formation of the connexon (homo- and hetero-hexamers) appears to influence the function of the gap junctions (speed of electrical chemical transfers and nature of the chemical molecule transferred). The concentration of multiple (>100) gap junctions forms a complex structure or plaque. Gap junctions allow direct electrical signaling between cells, although differences (10- to 15-fold) in electrical conductance between gap junctions have been shown. Gap junctions also allow chemical molecules (<1000 Da) to move from one cell to the other and favor chemical communication through the passage of second messengers, including IP3 and Ca2+. The passage of these chemicals is selective, depending on the size and charge of the molecule and the nature of connexin subunits. Although most of the movement of ions through gap junctions does not require energy, the recycling of K+ in the cochlea, essential to the transduction by auditory hair cells through gap junctions, is facilitated by ATPase activity and connexin conformation changes.

Charge associated with the connexins either repulses or attracts ions, playing a critical role in preventing or allowing for passage. In addition to these chemical and electrical exchange functions, gap junction proteins also promote cell adhesion and have tumor suppressing (C×43, C×36) and cell signaling (C×43) roles. The presence of gap junctions linking multiple cells within a tissue generates a syncytium, that is, a cluster of cells with similar response as in the heart muscle, and the smooth muscles of the GI tract.

3.3 Cell Adhesion Molecules

Within tissues, cells interact not only with other cells but also with the extracellular matrix (ECM). Cell attachment to the ECM is a key requirement of multicellular organisms. Produced by multiple cells, including fibroblasts, the ECM is composed of multiple proteins, of which the major ones are collagens, laminin, fibronectin, vitronectin, and vimentin. The ECM constitutes the basal lamina, the basal layer on which cells are anchored by integrins. These cell surface receptors are composed of one α (alpha) and one β (beta) subunit. Each heterodimer binds to a specific molecule of the ECM (e.g., α6β1 binds to laminin) with variable affinities. Integrin expression is cell specific and the strength of the binding to the ECM is variable, depending on the composition of both integrin and ECM. The binding site for the ECM is on the β chain and requires divalent cations to function whereas the α subunit may be involved in protein stabilization.

Integrins attach cells to the ECM through interactions between ECM molecules and microfilaments of the actin cytoskeleton, allowing cells to resist shear stress forces. The intensity of the force needed to deform a cell membrane or dissociate a cell linked by junctions in an epithelium is highly variable and will depend on the force as well as on the characteristics of the specific location of interest.

This cell attachment involves not only integrins but also the formation of cell adhesion complexes consisting of transmembrane integrins and many cytoplasmic proteins, including talin, vinculin, and paxillin. Integrins have a prominent role in regulating cell shape, cell migration, and cell signaling, making them pivotal in multiple cell events (including growth, differentiation, and survival).

3.4 Intracellular Connections

Cell membranes are physically connected with the cellular scaffolding or cytoskeleton. The cytoskeleton, critical in cell shape
and motion, intracellular transport (vesicles and organelles), and cell division, is composed of three kinds of filaments: microfilaments, intermediate filaments, and microtubules. Microfilaments are intertwined double-helix actin chains that are concentrated near the cell membrane. Intermediate filaments are very stable and constituted of multiple proteins, including vimentin, keratin, and laminin. Microtubules are composed of tubulin (α and β), which play a major role in intracellular transport and in the formation of mitotic spindles. Connections of the membrane with the cytoskeleton are key in maintaining 3D structures, cell shape and deformation (e.g., generation of processes), and resistance to tension.

### 3.5 Cell Membranes and Epithelia

As for individual cells, where the membrane is a selective barrier allowing the movement of water and ions through channels and of larger molecules through specific carriers, the epithelium also benefits from the selective permeability of the cells it is made of. The movement of molecules through the semipermeable membrane that is the cell membrane or of cells lining an epithelium relies on various physiological mechanisms. The intrinsic permeability of the cell membrane depends on (1) the presence of a gradient, that is, a difference in the chemical concentration or electrical charge between the cell and the extracellular compartment, and (2) the movement of molecules through diffusion, leaky channels, or facilitated or active transport. The membrane transport processes are discussed in greater detail in the next section and will be referenced in Chapter 5 for the specific working action.

### 3.6 Membrane Permeability

#### 3.6.1 Membrane Composition and Structure

Membranes are mostly made up of hydrophobic phospholipids (phosphatidylcholine, sphingomyelins, amino phospholipids, phosphatidylglycerol, and phosphatidylinositol), with one polar head and two nonpolar lipid chains. Hydrophobic means that the chemical structure is such that it repels the water dipole, in contrast to hydrophilic, which attracts water due to the inherent polar chemical composition. In an aqueous environment, the nonpolar chains are oriented away from water with the polar head in contact with the water, leading to the spontaneous formation of lipid bilayers. With the exception of the protein anchored internally to the actin or spectrin network or externally to ECM molecules, proteins can move within the lipid bilayer creating a fluid mosaic. The lipid:protein ratio can radically vary between membrane and cell types (Table 3.1).

Membrane composition is also heterogeneous, that is, protein distribution and, to a lesser extent, lipid composition are different throughout the cell membrane. Specifically, the density of a given receptor can be much higher at a specific location, for example, acetylcholine nicotinic receptors concentrated at the motor end plate. This cell polarity, defined by an asymmetry in the protein composition of the baso-lateral and apical membrane areas as delineated by thigh junctions, is critical in the development of epithelium and tissue whose major functions include exchanges.

The heterogeneous and asymmetric lipid bilayer forming the cell membrane through a constant and dynamic redistribution of proteins constitutes a semipermeable barrier separating two compartments with different chemical and ionic compositions. These differences in charges and concentrations associated with the asymmetrical membrane proteins generate electrochemical gradients, that is, differences in the net electrical charge and concentrations of a given solute inside versus outside the cell (Figure 3.2). Although both gradients are intertwined, each can act independently of the other.

#### 3.6.2 Molecule Movements

Molecule movements between two compartments separated by a plasma membrane or an epithelium use pericellular transport (between cells), transcellular transport (through the membrane), and endocytosis and/or exocytosis mechanisms. In pericellular transport, molecules move through an epithelium using spaces between cells. During endocytosis and exocytosis, physical distortions of the cell membrane through vesicle creation or fusion allow the movement of molecules into or out of the cell without transport through the membrane (Figure 3.2).

Transcellular transport depends on multiple parameters, including the hydrophobicity of the molecule and the density of transport proteins. Small molecules use diffusion whereas larger molecules require specific transport proteins. The cell membrane is highly permeable to most hydrophobic molecules or lipid-soluble solutes such as alcohol, vitamins A and E, and steroids. In contrast, the permeability of water-soluble or hydrophilic molecules is limited to very small molecules, including water and hydrophobic molecules with specific carriers. Most membranes are impermeable to water-soluble molecules above 200 Da. Ions are relatively insoluble because of their charge in lipids; therefore, membranes are poorly permeable to ions. Ion diffusion occurs mostly through ion channels. Ion channels span the membrane and are specific to an ion or class of ions, mostly depending on size and charge. Amino acids and sugars also require specific transporters present in the cell membrane.

#### 3.6.3 Diffusion

Small molecules, gases (O₂, CO₂, and NO), and molecules soluble in polar solvents diffuse through the cell membrane. Diffusion is driven by a gradient and continues until equilibrium. The net
The diffusion rate \( J \) is proportional to the coefficient of diffusion \( D \), the surface area \( A \), the thickness of the membrane \( \Delta x \), and the gradient or difference in concentration \( \Delta C \). The net diffusion rate is defined by Fick’s law:

\[
J = -DA \frac{\Delta C}{\Delta x}.
\]  

(3.2)

The diffusion time is a function of the thickness of the membrane and the permeability coefficient (Einstein relation). The diffusion time \( t \) is a function of average diffusion distance \( \Delta x \) and the coefficient of diffusion:

\[
t = \frac{(\Delta x)^2}{2D}.
\]  

(3.3)

For small water-soluble molecules with a coefficient of diffusion equal to \( 10^{-5} \) cm²/s, the diffusion times are 0.5 m, 50 m, 5 s, 8.3 min, and 14 h for membrane thicknesses of 1, 10, 100, 1000, and 10,000 μm, respectively. The diffusion time (Table 3.2) is proportional to the diffusion coefficient \( D \), which itself is proportional to the speed of movement of the molecule in a given medium: if the molecule is large and the medium is viscous, \( D \) is small.

For small molecules, \( D \) is inversely proportional to the molecular weight (MW) in dalton: \( D = 1/MW \). For larger spherical molecules, the equation of Stokes–Einstein approximates the coefficient of diffusion (Equation 3.4), taking into account the gas constant \( R \), the absolute temperature \( T \), the number \( \pi \), the Avogadro number \( N \), the solvent viscosity \( \eta \), and the radius of the molecule \( r \):

\[
D = \frac{RT}{6N\pi r\eta} = 1.38 \times 10^{-23} \frac{T}{\pi r\eta}.
\]  

(3.4)

### 3.6.4 Protein-Mediated Membrane Transport

Movements of large molecules require intrinsic specific carriers or channels. Through conformational changes, channels form gates, allowing the passage of molecules. Transporter recognition is ligand specific but generally not absolute, and related molecules can compete for or inhibit transport. These channels can be either voltage gated or ligand gated: the former is activated by difference in the transmembrane voltage difference and the latter by binding to its specific ligand.

Mediated membrane transport is more rapid than simple diffusion, can saturate, and is chemically specific and sensitive to competition. The transport rate \( J \) for a given molecule \( S \) is defined by its maximum transport rate \( J_m \), the Michaelis constant \( K_m \) and the concentration of the molecule \( [S] \), as described by the Michaelis–Menten equation:

\[
J = \frac{J_m[S]}{K_m + [S]}.
\]  

(3.5)

The transport through a carrier is limited by the speed and capacity of each carrier with a conformational change of \( 10^2 \) to \( 10^4 \) solute molecules/s. For ion channels, through an open channel, ions move at \( 10^2 \) to \( 10^6 \) ions/s. In facilitated transport, no energy is involved, whereas active transport requires energy.
(ATP mostly). Facilitated transport benefits from existing charge or concentration gradients to move molecules (e.g., GLU2 transporter and Na⁺ gradients). Active transports promote the movement against concentration or electrochemical gradients using energy, mostly ATP, to cycle between its conformational states. For example, the Ca²⁺ ATPases move two Ca²⁺ from the lumen to the sarcoplasmic reticulum per ATP and the Na⁺/K⁺ ATPase, present in the plasma membrane of the cells, moves three Na⁺ out of the cells and two K⁺ into the cell per ATP. Because of the K⁺ and Na⁺ concentrations in and out of the cells, these tend to move passively toward equilibrium, and the steady state for these ions is maintained by the constant activity of the Na⁺/K⁺ ATPases.

### 3.7 Osmotic Pressure and Cell Volume

The cell volume is directly related to the internal pressure, and hence the osmotic pressure is also affected by the cell volume.

#### 3.7.1 Osmotic Pressure

Osmosis is defined as the flow of water across a semipermeable membrane (i.e., permeable to water only) from a compartment with a low solute concentration to a compartment with a high solute concentration. Osmotic pressure is the pressure that is sufficient to prevent water from entering the cell. Osmotic pressure (\(\Pi\)) is directly associated with the number of ions formed from the dissociation of a solute (i), the molar concentration of the solute (c), and the osmotic coefficient (\(\phi\)) and can be calculated by van’t Hoff’s law:

\[
\Pi = RT(\phi c).
\]  

Osmotic pressure is a function of the concentration of solute present on either side of the membrane, and the concentration of solute also increases the boiling point and lowers the freezing point. Osmotic pressure (\(\Pi\)) is a function of the concentration of solute present on either side of the membrane. Since the concentration of solute is proportional to the solute freezing point, the osmotic pressure can also be estimated based on the freezing point depression (\(\Delta T_f\)):

\[
\Pi = RT(\Delta T_f/1.86).
\]

where \(\Delta T_f\) is the freezing point depression. Two solutions separated by a semipermeable membrane are isoosmotic (have equal osmotic pressures), hyperosmotic (A hyperosmotic compared to B), or hypoosmotic (B compared to A). Osmotic coefficients have been calculated (Table 3.3).

### 3.8 Tonicity

The plasma membrane of animal cells is relatively impermeable to many solutes but highly permeable to water. Therefore, increase in the osmotic pressure of the extracellular fluid (ECF) leads to water leaving the cells through osmosis, resulting in cell shrinking. In contrast, if the ECF is diluted, water enters the cells, resulting in cell swelling. Swelling activates channels, increasing efflux of K⁺, Cl⁻, and the water that follows by osmosis returns cells to normal size. Both cell shrinking and swelling will continue until the osmotic pressures on both sides are equal or isoosmotic.

**In vivo**, protein concentration is the most important parameter generating onctic pressure, which contributes to the net flow of a given solute. Both the shrinking and swelling drastically impair cell function and potentially, in extreme cases, its survival. In living organisms, cells are suspended in a mixture of permeant and nonpermeant solutes. In those conditions (1) the steady volume of a cell is determined by the concentration of nonpermeant solutes in the ECF, (2) permeant solutes generate only transient alterations of the cell volume, and (3) the greater the cell permeability to a permeant solute, the faster the time course to transient change.

#### 3.9 Electrical Properties of Cell Membranes

The electrical properties of the cell membrane are derived from their insulator potential associated with the composition, especially the amount of lipid present. For example, myelin produced by Schwann cells leads to the insulation of axons, with multiple layers of the cell membrane preventing loss of electrical charges. The electrical properties of the cells are also a function of the constantly maintained disequilibrium of the ions generated by the tight control of ion movements and charges present on either side of the membrane. Additionally, cell transport through channels for ions or carriers for proteins also affects the electrical charges present on each side of the cell membrane, leading to alterations in the local membrane potential.

**3.9.1 Forces Acting on Ion Movements**

Several forces act on the components surrounding the membrane. The two main categories are electrical forces and chemical gradient forces.

In living animal cells, a comparison of the composition of the cytosol and the ECF underlines the presence of proteins
(generally negatively charged) and K⁺ at high concentrations inside the cell, whereas Ca²⁺, Na⁺, and Cl⁻ concentrations are higher in the ECF. Permeant molecules, including some ions, move continuously in or out of the cell through leaky channels of the cell membrane following electrical and chemical gradients. The difference in charge between the inside and outside of a cell creates a membrane potential or the amount of energy (electrical) associated with the electrochemical gradient present. The net gradient for a given ion and cell remains stable because ATP-dependent ion pumps, especially the Na⁺/K⁺ ATPase, continuously and actively maintain these equilibriums.

### 3.9.2 Distribution of Permeable Ions

Taking into account the ions that cannot diffuse, the distribution of permeable ions is predicted by the Donnan–Gibbs equilibrium: in the presence of a nondiffusible ion (e.g., protein), a diffusible pair of ions of the same valence distributes to generate equal concentration ratios, for example,

\[
[K⁺]_{in} \times [Cl⁻]_{in} = [K⁺]_{out} \times [Cl⁻]_{out}. \tag{3.8}
\]

The overall membrane potential at any time is a function of the distribution (inside versus outside) and membrane permeability to Na⁺, K⁺, and Cl⁻ (Figure 3.3).

The Donnan–Gibbs equilibrium explains the critical role of the Na⁺/K⁺ ATPase pump in constantly removing Na⁺ ions out of the cells to maintain osmotic pressure and cell volume. It also clarifies the electrical difference generated by the asymmetric distribution of permeable ions between the intracellular and extracellular compartments at equilibrium. Along the membrane on the extracellular side, the charges created by Cl⁻ are balanced by the K⁺ ions that are present inside the cell. This effect is also critical in the movement of ions across the capillary wall mostly generated by the higher protein concentration in the plasma compared to the ECF.

#### 3.9.3 Membrane Potential

The relationship between the chemical and electrical forces acting on ions across the plasma membrane and the generation of the resting membrane potential is defined by taking into account the ion valence \(Z_{ion}\) and ECF \([ion]_{out}\) and (intracellular fluid) ICF \([ion]_{in}\) concentrations as described in the Nernst equation:

\[
E_{ion} = \frac{RT}{FZ_{ion}} \log_{10} \left( \frac{[ion]_{out}}{[ion]_{in}} \right) \tag{3.9}
\]

where \(R\) is the gas constant, \(F\) is the Faraday constant, and \(T\) is the absolute temperature. At 37°C, the equation can be simplified to \(E_{Cl⁻} = 61.5 \log_{10}([ion]_{out}/[ion]_{in})\). For Cl⁻, with intra- and extracellular Cl⁻ concentrations of 9.0 and 125.0 mM, \(E_{Cl⁻} = −70\) mV, a value identical to the one measured experimentally. In neurons, calculated \(E_{K⁺}(−90\) mV) differs from measured \(E_{K⁺}(−70\) mV). Similarly, the difference between calculated \(E_{Na}\)

---

**FIGURE 3.3** Ion exchanges and the creation of an electrochemical gradient across the cell membrane. The influence of protein (A⁻), Cl⁻, K⁺, and Na⁺ extracellular and intracellular concentrations and the role of Na⁺/K⁺ ATPase active transport roles in the generation of the electrochemical gradient are represented.
(+60 mV) and measured $E_{Na}^{\text{r}}$ suggests that other ions may play a role in the equilibrium potential in those cells. These differences from the optimal membrane potentials of each of these ions are actively maintained through the action of the Na\(^+/\)K\(^+\) ATPases pumping three Na\(^+\) out and two K\(^+\) per ATP molecule.

The K\(^+\) efflux is counterbalanced by the electrical gradient of more negative charges (the bulk of which are proteins) inside the cell. The constant activities of the Na\(^+/\)K\(^+\) ATPases pumping K\(^+\) inside and removing Na\(^+\) prevent these ions from reaching the equilibrium associated with their respective electrochemical gradients.

### 3.10 ATPases

ATPases are evolutionary conserved proteins with three major types: P, V, and F. The P type involves a phosphorylated intermediate and includes Na\(^+/\)K\(^+\) ATPases and Ca\(^{2+}\) ATPases. Mostly present on cell organelles (storage granules and lysosomes), the V type accumulates H\(^+\) in vesicle lumen. Most cell membranes also contain Na\(^+\)/H\(^+\) exchangers to prevent the acidification of the cytosol becoming active when the pH of the cytosol decreases, with Na\(^+\) moving following its electrochemical gradient in exchange with the movement of H\(^+\) out of the cell.

In contrast to P and V ATPases, which consume ATP, the F type represented by ATP synthase of the inner mitochondrial membrane is a major source of ATP. ATP production depends on the oxygen conditions. In anaerobic conditions, one glucose molecule produces two pyruvate molecules transformed in lactate, yielding a net energy of two ATPs. In aerobic conditions, pyruvate molecules enter the citric acid cycle in the mitochondria and through oxidative phosphorylation yield up to 30–32 ATP molecules.

#### 3.10.1 Role of ATPases

In excitable cells, following an action potential in which Na\(^+\) and K\(^+\) ions move in and out of the cell respectively, the cell repolarizes with an efflux of K\(^+\) ions. K\(^+\) channels are slow to close and the K\(^+\) efflux generates a hyperpolarization of the cell membrane. The equilibrium is re-established by the activity of the sodium/potassium ATPase pump moving three Na\(^+\) ions out and allowing two K\(^+\) ions in through active transport through a conformational change.

The efflux of Na\(^+\) provides the driving force for multiple facilitated transport mechanisms, including glucose, amino acid membrane transport, and creates an osmotic gradient that promotes the absorption of water. In the enterocytes of the GI tract, on the baso-lateral surface of the cell, Na\(^+\) is pumped out of the cell through the activity of Na\(^+\)–K\(^+\) ATPase pumps creating a gradient that favors the influx of Na\(^+\) from the apical side of the cell.

#### 3.10.2 Regulation of Na\(^+/\)K\(^+\) ATPase Activity

The activity of the ATPase pump is endogenously down-regulated through increases in cyclic adenosine monophosphate (cAMP) associated with G protein coupled receptor activations and up-regulated through decreases in cAMP by ligands leading to G protein coupled receptor inhibition. Thyroid hormones, insulin, and aldosterone increase the expression of Na\(^+/\)K\(^+\) ATPase pumps and therefore the activity. In contrast, in the kidney, dopamine induces the phosphorylation of the Na\(^+/\)K\(^+\) ATPase pump, inhibiting its activity.

### 3.11 Cell Membrane and pH Regulation

Mechanisms in cells allow the regulation of H\(^+\) intracytoplasmic concentrations including through the activity of the Na\(^+/\)H\(^+\) ATPase, which prevents H\(^+\) increases into the cytosol by pumping H\(^+\) in specific cell compartments. Intracellular H\(^+\) concentration is influenced by ECF and plasma H\(^+\) concentration.

In the plasma, the H\(^+\) concentration is very low compared to other ions (~0.0004 mEq/L) and is expressed as the negative log of the H\(^+\) concentration (or pH). The plasma pH ranges from 7.38 to 7.42, with extreme acidosis at 7.0 and extreme alkalosis at 7.7. Throughout the body, pH values are very variable with, for example, gastric HCl (0.8), urine (as low as 4.5), and pancreatic juice (8.0). Because pH homeostasis is essential to organism survival through enzymatic and membrane and capillary exchanges, the pH is tightly monitored through central and peripheral sensors and regulated by buffers, the lung, and kidney activities. Like other chemicals, the organism has sensing mechanisms with properties comparable to those observed in smell and taste senses, including pH sensors, and a constant feedback regulation and monitoring of the ECF and plasma pH.

#### 3.11.1 pH Sensors

Chemoreceptors sensing H\(^+\) concentrations in the plasma and cerebrospinal fluid, respectively, are located peripherally in the aortic arch (aortic bodies) and at the bifurcation of the internal and external carotid in the neck (carotid bodies) and centrally in the brain medulla. The blood–brain barrier is poorly permeable to H\(^+\) but allows CO\(_2\) diffusion. The addition of CO\(_2\) displaces the equilibrium bicarbonate hydrogen toward the formation of more H\(^+\), increasing the pH of the cerebrospinal fluid (CSF):

$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow H^+ + \text{HCO}_3^-.$$  \hspace{1cm} (3.10)

This decrease in pH is sensed by chemoreceptors that stimulate lung ventilation to bring H\(^+\) and CO\(_2\) concentrations within range.

#### 3.11.2 pH Regulation

In mammals, pH regulation is achieved through (1) buffers and the activities of (2) the lung and to a lesser extent (3) the kidneys. Buffers are molecules that combine with H\(^+\), neutralizing its effects. The presence of buffers moderates greatly the addition of H\(^+\) to a solution. Buffers such as H\(_2\)PO\(_4^-\) and HCO\(_3^-\) are present in cells and ECF, respectively. Also, an increase in
plasma CO$_2$ is associated with an increase in H$^+$ in the CSF sensed in the medulla, leading to a rapid increase in lung ventilation to remove CO$_2$ and maintain ECF pH. If despite buffer effects and ventilation modulations, pH acidification or alkalination persist, the kidney can secrete or absorb H$^+$ ion and HCO$_3^-$ ion. Following conversion of CO$_2$ into HCO$_3^-$ by carbonic anhydrase in proximal tubule cells, HCO$_3^-$ is reabsorbed and H$^+$ is secreted. Alternatively, H$^+$ is secreted as ammonium ion NH$_4^+$. In the distal nephron, intercalated cells or either type A or B functioning during acidosis or alkalosis excrete H$^+$ or HCO$_3^-$ and K$^+$, respectively (see Equation 3.10).

### 3.11.3 Gas Exchanges and pH Regulation

Cells of the organism receive signaling molecules, nutrients, and O$_2$ through the cardiovascular system and the ECF. As described above, removal of CO$_2$ produced by cellular metabolism is critical to the maintenance of a pH compatible with normal cell function. CO$_2$ is carried in the blood as (about 70%) bicarbonate ions HCO$_3^-$ (see Equation 3.10) by a carbonic anhydrase in the red blood cells (RBCs), 7% is dissolved in the plasma, and 23% is bound to hemoglobin at a site other than O$_2$. The binding to CO$_2$, however, decreases hemoglobin O$_2$ binding, in effect allowing more O$_2$ release in a region with high CO$_2$ concentrations. This effect (Bohr effect) is observed when increases in the partial pressure of CO$_2$ or lower pH values result in the off-loading of oxygen from hemoglobin.

### 3.12 Summary

In multicellular organisms, cell interactions depending on cell junctions and adhesions to the ECM modulate individual cell function and epithelium membrane permeability. In addition to diffusion, molecules are transported through protein carriers with or without energy requirements. The chemical and electrical imbalance between compartments separated by the lipid bilayer cell membrane is actively maintained by ATPases. These electrical and chemical disequilibria generate electrochemical gradients and the membrane potential critical in cell functions.

### Additional Reading