Chapter 2
Cellular Homeostasis and Membrane Potential

2.1 Membrane Structure and Composition

The human cell can be considered to consist of a bag of fluid with a wall that separates the internal, or intracellular, fluid (ICF) from the external, or extracellular, fluid (ECF): this wall is termed the plasma membrane. The membrane consists of a sheet of lipids two molecules thick: lipids being molecules that are not soluble in water but are that soluble in oil. The cell lipids are primarily phospholipids, as illustrated in Fig. 2.1, they have one end that is hydrophilic and one that is hydrophobic (are attracted to and repelled by water molecules respectively). The hydrophobic ends tend to point towards each other, and away from the aqueous environments inside and outside the cell, hence the two molecule thickness.

Substances can cross the membrane if they can dissolve in the lipids, which will not be true of most of the species that are in aqueous solution, such as ions. However, some electrically charged substances, which cannot readily pass through the lipid sheets, do cross the membrane. This is because the membrane is full of various types of protein molecules, some of which bridge the lipid layer. Sometimes these form pores or channels through which molecules can pass. Figure 2.2 shows a schematic of the membrane structure.

Outside the cell, the main positively charged ion is sodium (Na$^+$) with a small amount of potassium (K$^+$) and chloride (Cl$^-$) ions, Table 2.1. The relative quantities are reversed in the ICF. The balance of charge is provided inside the cell by a class of molecules that include protein molecules and amino acids (likewise outside the cell, but these will be ignored here). One of the key features of the cell is the balance of molecules between the inside and outside, yet at first glance it doesn’t appear that is the case for the cell in Table 2.1. It also does not seem obvious why the individual molecules do not diffuse in and out of the cell such that the ICF and ECF concentrations are equal. In general we are interested in how the cell maintains its internal conditions despite what is going on outside: the property called
Fig. 2.1 The structure of a phospholipid with both hydrophobic and hydrophilic ends (this figure is taken, without changes, from OpenStax College under license: http://creativecommons.org/licenses/by/3.0/)

Fig. 2.2 Schematic of membrane structure (this figure is taken, without changes, from OpenStax College under license: http://creativecommons.org/licenses/by/3.0/)
homeostasis. If we want to understand how the cell maintains this imbalance we first need to consider the balance of cell volume.

2.2 Osmotic Balance

Consider a litre of water with 1 mol of dissolved particles: this is termed a 1 molar, or 1 M, solution, as we saw in Chap. 1. Now consider two adjacent identical volumes with different molarities (say 100 and 200 mM) and a barrier between them. If the barrier allows both water and the solute to pass, equilibrium will be reached with equal levels of the solute (150 mM) and the barrier will not move, as might be expected. However, if the barrier allows only water to cross, enough water will have to cross the barrier for the concentrations to balance and the barrier will thus move. Equilibrium will then be reached with the same concentrations (150 mM) but different volumes, 2/3 and 4/3 L, as illustrated in Fig. 2.3. The volumes are calculated by remembering that the concentrations must balance and that the number of moles of the solute cannot change. This process can be thought analogous to pressurised chambers with initial pressures (equivalent to the concentrations) and volumes: the barrier is like a piston, moving until pressure equilibrium is reached.

Now consider a slightly different example with a cell with an intracellular concentration of a substance $P$ and an extracellular concentration of a substance $Q$: neither $P$ nor $Q$ is able to cross the membrane. There are three possibilities:

1. The concentration of $Q$ is equal to that of $P$ (isotonic): cell volume remains constant.
2. The concentration of $Q$ is greater than that of $P$ (hypertonic solution): cell volume decreases and the cell ultimately collapses if the difference in concentration is sufficiently large.
3. The concentration of $Q$ is less than that of $P$ (hypotonic solution): cell volume increases eventually rupturing the membrane if the concentration difference is sufficiently large.
A hypotonic solution is defined as one that makes the cell increase in size and a hypertonic solution is one that makes the cell decrease in size. An illustration of the three types of behaviour is shown in Fig. 2.4.
Exercise A

For the following case determine the final, equilibrium, cell volume given the starting conditions and an initial cell volume $V_0$.

So far we have only considered what happens if water can cross the membrane: if Q (or P) is able to cross the membrane, then the cell behaves differently. The concentration of Q must be the same inside and outside the cell: however, the total concentration inside and outside the cell must also be the same otherwise the membrane will move to adjust the concentrations.

Exercise B

If Q is now able to cross the membrane determine the final, equilibrium, cell volume given the starting conditions and an initial cell volume $V_0$. Assume that the concentration of the species, Q, that is outside the cell is fixed.

Note that in Exercise B it doesn’t matter that the total internal and external concentrations are equal unlike in exercise A where this led to equilibrium. It is also
worth questioning the assumption that the concentration of Q is fixed and not altered by Q moving into the cell. This stems from an assumption that the extracellular space is a lot larger than the cell itself and/or can easily be replenished from elsewhere, i.e. that there is an infinite reserve of Q in this case.

The requirement for the total concentration to be equal inside and outside the cell is actually a requirement that the concentration of water balances. It might seem strange to talk about water concentration since there is so much of it compared to the other species, but osmosis is essentially the process of balancing water concentration.

The total concentration is often referred to as the osmolarity: the higher the osmolarity the lower the concentration of water and vice versa. A solution containing 0.1 M glucose and 0.1 M urea would have a total concentration of non-water species of 0.2 M and thus an osmolarity of 0.2 Osm. Care needs to be taken with solutions of substances that dissociate, for example, a 0.1 M solution of NaCl is a 0.2 Osm solution since you get free Na\(^+\) and Cl\(^-\). In practice the osmolarity could be lower than this if the ions in solution interacted, but this is not common in biological systems.

**Exercise C**

For the following cases determine the final, equilibrium, cell volume given the starting conditions and an initial cell volume \(V_0\).

We have considered how the cell might maintain its volume despite imbalances in the concentrations of species inside and outside the cell. In fact we have met our first principle, the **principle of concentration balance**.
2.3 Conservation of Charge

Now consider the slightly more complex example in Fig. 2.5, which is a very basic model of a cell. Inside the cell are found organic molecules, P, which cannot pass through the barrier. The internal Na$^+$ is also trapped, whereas Cl$^-$ can pass freely through the barrier. The concentrations of P and Na$^+$ inside the cell are 100 and 50 mM respectively.

To analyse this model, there are two quantities that must be in balance: charge and concentration. The fact that the positive and negative charges must balance within any compartment is called the **principle of electrical neutrality**, which states that the bulk concentration of positively charged ions must equal the bulk concentration of negatively charged ions. Essentially this is due to the fact that under biological conditions, so few positively and negatively charged ions have to move to generate any membrane potential (which we will meet later) that we can assume that they balance at all times.

From charge balance:

\[ a = 50 \tag{2.1} \]
\[ b = c \tag{2.2} \]

From total concentration balance:

\[ 50 + a + 100 = b + c \tag{2.3} \]

Hence:

\[ b = c = 100 \tag{2.4} \]

Note that, unlike in the previous section, the concentrations of Cl$^-$ are not equal inside and outside the cell: this is due to the influence of the charge balance. In fact at this point we can more carefully define the principle of concentration balance to only refer to the concentrations of **uncharged** species. For a simple cell model the only uncharged species that can freely cross the membrane to any significant degree is water, thus the principle of concentration balance might be called the principle of osmotic balance.

![Fig. 2.5 Cell model example](image)
2.4 Equilibrium Potential

So far we have only considered concentration equilibrium: however, there is another important factor that drives ions across a cell membrane. In addition to the concentration gradient that drives ions from a region of high concentration to a region of low concentration, there is an electrical potential difference across the membrane.

For the membrane shown in Fig. 2.6, the difference in voltage between the inside and the outside of the cell is given by the Nernst equation:

\[
E_X = V_{in} - V_{out} = \frac{RT}{ZeF} \ln \left( \frac{[X]_{out}}{[X]_{in}} \right),
\]

where \( R \) is the gas constant, \( T \) is absolute temperature (in Kelvin), \( Z \) is the valence of the ion and \( F \) is Faraday’s constant (96,500 C/mol_univalent_ion). The quantity in the equation above is known as the equilibrium potential and only applies for a single ion that can cross the barrier. At standard room temperature, the equation can be re-written as:

\[
E_X = \frac{58 \text{ mV}}{Z} \log_{10} \left( \frac{[X]_{out}}{[X]_{in}} \right),
\]

where we have changed from a natural logarithm to a base-10 logarithm.

There can only be a single potential across the membrane, the membrane potential, thus if there are two ions that can cross the membrane (in the real cell these are \( K^+ \) and \( Cl^- \)), then the equilibrium potential must be the same for both. Hence:

\[
E_m = 58 \text{ mV} \log_{10} \left( \frac{[K^+]_{out}}{[K^+]_{in}} \right) = -58 \text{ mV} \log_{10} \left( \frac{[Cl^-]_{out}}{[Cl^-]_{in}} \right),
\]

which on re-arranging becomes:

\[
\frac{[K^+]_{out}}{[K^+]_{in}} = \frac{[Cl^-]_{in}}{[Cl^-]_{out}}.
\]

This is known as the Donnan or Gibbs-Donnan equilibrium equation.
Exercise D

Suppose that two compartments, each of one litre in volume, are connected by a membrane that is permeable to both K⁺ and Cl⁻, but not permeable to water or the protein X. Suppose further that the compartment on the left initially contains 300 mM K⁺ and 300 mM Cl⁻, while the compartment on the right initially contains 200 mM protein, with valence −2, and 400 mM K⁺.

(a) Is the starting configuration electrically and osmotically balanced?
(b) Find the concentrations at equilibrium.
(c) Why is [K⁺] in the right compartment at equilibrium greater than its starting value, even though [K⁺] in the right compartment was greater than [K⁺] in the left compartment initially? Why does K⁺ not diffuse from right to left to equalize the concentrations?
(d) What is the equilibrium potential difference?

Exercise D is an interesting example of the counter intuitive differences in ion concentration that can arise due to the balance of electrical configuration. However, it is not like our cell model because we had only a fixed total amount of each ion available and the whole system was thus closed.

2.5 A Simple Cell Model

We started out by trying to understand cell homeostasis and how an imbalance in concentrations of ions inside and outside of the cell could be maintained. We now have three principles to apply when we analyse cell concentrations:

1. Concentration (osmotic) balance.
2. Electrical neutrality.

We are now ready to try and build a simple model of a cell at equilibrium, Fig. 2.7. Inside the cell is found Na⁺, K⁺ and Cl⁻ as well as some negatively charged particles, termed P, that represent an array of different molecules, including

![Fig. 2.7 A simple cell model](image-url)
proteins. Outside the cell is found Na\(^+\), K\(^+\) and Cl\(^-\) where K\(^+\) and Cl\(^-\) are free to cross the membrane.

**Exercise E**

Figure 2.7 is incomplete since some of the concentrations have not been given.

(a) Write down and solve the appropriate equations to calculate the unknown concentrations in the figure. Note that the charge of P is \(-11/9\) (about \(-1.22\)),\(^1\) which means that the charge equilibrium equation must be written down carefully.

(b) What is the value of the membrane potential in this example?

(c) If the cell membrane was permeable to sodium, calculate the equilibrium potential for sodium. What would happen to the cell?

This exercise takes us close to a realistic model of the cell: you should find that the values of concentration that you get are the same as Table 2.1. Note that it will remain in this state indefinitely without the expending of any metabolic energy: a very efficient structure. However, you will have found that if the cell is permeable to Na\(^+\), its equilibrium potential is very different from the membrane potential you calculated when the membrane is impermeable to Na\(^+\). Thus if the membrane were permeable to sodium then it would be impossible to achieve equilibrium due to the proteins etc also present in the cell: the cell would grow until rupture.

### 2.6 Ion Pumps

Unfortunately, the real cell actually does expend metabolic energy in order to remain at equilibrium. The reason for this is that the cell wall is actually permeable to Na\(^+\), which implies that our model cell will not remain in an equilibrium state. The answer to this problem is that there is something called a sodium pump, which we will now examine briefly.

An ion pump is a mechanism that absorbs energy to move ions against a concentration or electrical gradient, rather like a heat pump. The ion pump gets its energy from ATP as we met in Chap. 1. For Na\(^+\), as fast as it leaks in due to the concentration and electrical gradients, it is pumped out. Na\(^+\) thus effectively acts as if it cannot cross the membrane, but the cell is now a **steady state**, requiring energy, rather than an equilibrium state, which requires no energy.

\(^1\)Some other texts round down to a charge of \(-1.2\), which appears to be very close to that here, but will result in quite different concentrations for some of the ions if you try to use it.
The common symbol for the pump is shown in Fig. 2.8, which also shows that the pump needs K\(^+\) ions outside the cell to pump inside in return for Na\(^+\) ions inside. The protein on the cell outer surface needs K\(^+\) to bind to it before the protein can return to a state in which it can bind another ATP and sodium ions at the inner surface. Since the K\(^+\) ions bound on the outside are then released on the inside, the pump essentially swaps Na\(^+\) and K\(^+\) ions across the membrane and is thus more correctly known as the Na\(^+\)/K\(^+\) pump and the membrane-associated enzyme as a Na\(^+\)/K\(^+\) ATPase. We will revisit the ion pump in Chap. 4.

### 2.7 Membrane Potential

Now that we have reconsidered the cell as a steady state device (rather than an equilibrium device), we need to reconsider the membrane potential. Previously in Exercise E we had \(E_m = E_K = E_{Cl} = -81\) mV. However, now we also have a contribution from Na\(^+\) with \(E_{Na} = +58\) mV, the membrane potential will have to settle somewhere between these extremes. This actually depends upon both the ionic concentrations and the membrane permeability to the different ions. Clearly if the permeability to a particular ion is zero, it contributes nothing to the potential, whereas with a high permeability it contributes significantly more. The permeability of the membrane to different ions is absolutely vital in our understanding of the operation of the cell.

The permeability of a membrane to a particular ion is simply a measure of how easily those ions can cross the membrane. In electrical terms, it is equivalent to the inverse of resistance (i.e. conductance). We will consider why the permeabilities are different for different ions in Chap. 3, but for now, we will note that the permeability is related to the number of channels that allow the ions to pass through and the ease of passage through the channels.

The relationship between membrane potential and the concentrations and permeabilities of the different ions in the cell is known as the **Goldman equation**:

\[
E_m = 58\text{ mV } \log_{10} \left( \frac{p_K [K^+]_o + p_{Na} [Na^+]_o + p_{Cl} [Cl^-]_o}{p_K [K^+]_i + p_{Na} [Na^+]_i + p_{Cl} [Cl^-]_i} \right), \tag{2.9}
\]

where \(p\) denotes permeability. Note that because Cl\(^-\) has a negative valence the inner and outer concentrations are the opposite way round to those for Na\(^+\) and K\(^+\). For a membrane that is permeable to only one ion, the Goldman equation reduces immediately to the Nernst equation.
In practice, the contribution of Cl\(^-\) is negligible and hence the equation is usually encountered in the form:

\[
E_m = 58 \text{ mV} \log_{10} \left( \frac{[K^+]_o + b[Na^+]_o}{[K^+]_i + b[Na^+]_i} \right),
\]

where in the resting state \(b = p_{Na}/p_K\) is approximately 0.02. For the typical resting state with the concentrations given previously, the membrane potential is approximately \(-71 \text{ mV}\). The membrane potential is closer to the value for K\(^+\), since the permeability to K\(^+\) is much greater than that for Na\(^+\). However, changes in the relative permeability can produce large changes in the membrane potential between these two values.

Since the membrane potential is equal to neither the values for Na\(^+\) nor for K\(^+\), there is a leakage of both K\(^+\) out of and Na\(^+\) into the cell: hence the role of the Na\(^+\)/K\(^+\) pump to maintain the membrane potential at a steady state value. A more complete model for cell is shown in Fig. 2.9 that also includes the forces acting on the ions. Note that the net charge on the inside of the cell is negative therefore the electrostatic forces acting on both Na\(^+\) and K\(^+\) in inward, whereas on Cl\(^-\) it is outward. It is easy to see why at the very least a pump for Na\(^+\) is required.

Although we have ignored Cl\(^-\) in the calculation of the membrane potential, it is affected by it: the equilibrium membrane potential for Cl\(^-\) is \(-80 \text{ mV}\), so either the concentration will change (as in some cells) or a Cl\(^-\) pump is used to maintain a steady state level of Cl\(^-\). Less is known about this pump than the Na\(^+\)/K\(^+\) pump.

Since a difference in membrane potential from the equilibrium value for an individual ion causes a movement of ions across the membrane we can introduce a new concept, that of membrane conductance, as defined by:

\[
i_K = g_K(E_m - E_K),
\]

\[
i_{Na} = g_{Na}(E_m - E_{Na}),
\]

\[
i_{Cl} = g_{Cl}(E_m - E_{Cl}).
\]
Since $E_m = -71\, \text{mV}$, $E_K = -80\, \text{mV}$ and $E_{Na} = 58\, \text{mV}$ from above, the potassium current is positive and the sodium current is negative. By convention, an outward current is positive and an inward current is negative. In the steady state the net current is zero, which is the basis of the Goldman equation. The conductance is related to both the permeability and the number of available ions in the solution. Note that conductance is the inverse of resistance and so in electrical terms, the membrane can be considered as a resistor as in Fig. 2.10.

The meaning of permeability can be explored in more detail by remembering that the membrane is full of protein channels that permit different ions to pass through. These channels can be considered to be controlled by a gate that is either open or closed (this mechanism is known as channel gating). Although the channels are slightly more complicated than this, it is a valid first approximation: we will examine this in more detail in Chap. 3. Rather like an electrical switch, each channel is thus either ‘on’ or ‘off’ as far as current is concerned. Since there are a very large number of channels, the permeability of the membrane can be controlled to a high degree of accuracy by the opening of different numbers of channels. This ability to change the membrane permeabilities is a major factor in the behaviour of cells and this will be examined in Chap. 3 when we consider the action potential.

### Exercise F

A simple model for a cardiac myocyte (heart muscle cell) can be built using the concentrations of the ions to which the membrane is permeable given in the table.

<table>
<thead>
<tr>
<th>Ion</th>
<th>Internal concentration (mM)</th>
<th>External concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Na^+$</td>
<td>10</td>
<td>145</td>
</tr>
<tr>
<td>$K^+$</td>
<td>140</td>
<td>4</td>
</tr>
<tr>
<td>$Cl^-$</td>
<td>30</td>
<td>114</td>
</tr>
<tr>
<td>$Ca^{2+}$</td>
<td>$10^{-4}$</td>
<td>1.2</td>
</tr>
</tbody>
</table>

(a) Calculate the equilibrium potentials for all the ions in the cardiac myocyte and hence determine if the cell is in equilibrium.
(b) Using the principles of electrical neutrality and osmotic balance determine the internal concentration and overall charge of other charged species (e.g. proteins) within the cell that are unable to cross the cell membrane, assuming zero external concentration of any other species.

(c) Show that this cardiac myocyte cell is not in a steady state.

This final exercise explores a cell with a specific function that we will meet in Chap. 7. Whilst a lot of the values for ionic concentrations, charges and potentials are not wildly different from the model cell we have considered in this chapter, this cell is neither in equilibrium nor even in steady state. We might have been wrong to ignore any other charged species outside the cell. Otherwise, like the simple cell model, we might worry that this cell would expand until rupture. Note that ions pumps wouldn’t help here as the concentrations we have do not satisfy all the principles and thus the cell cannot be in steady state; the ion pumps only helped to maintain the steady state in the simple cell model. It turns out that cardiac myocytes never reach a steady state and the concentrations fluctuate over a cycle, these values (probably) just representing the ‘resting’ state. We will return to this in Chap. 7.

2.8 Conclusions

In this chapter we have considered how the cell can maintain homeostasis despite differences in concentration of ions and other charged species both inside and outside of the cell membrane. You should now understand the principles of concentration balance, electrical neutrality and Gibbs-Donnan equilibrium and be able to apply them to a cell model. You should also be able to calculate equilibrium potentials for individual ions as well as the membrane potential and understand why these are not always the same value. Finally you should now appreciate why cells use energy to maintain homeostasis.
Physiology for Engineers
Applying Engineering Methods to Physiological Systems
Chappell, M.; Payne, S.
2016, XIV, 167 p. 71 illus., 27 illus. in color., Hardcover
ISBN: 978-3-319-26195-9