B18: QUANTITATIVE PHYSIOLOGY

Course details

A course of 8 lectures to provide an introduction to the physiology required for B18.

Lectures 1-4: Cellular Physiology

Lectures 5-8: Systems Physiology

There are two example sheets to accompany these lectures. The questions are clearly linked to the lecture notes and form an integral part of the course. The syllabus consists of the lecture notes and the tutorial sheet solutions.

Both courses will primarily cover the underlying physiology, but will also give an introduction to some of the Engineering techniques used in its analysis. In particular we will examine the role of models in understanding the physiological processes. The material in these lectures will assume knowledge of the core course material.

Recommended books

Cellular Physiology of Nerve and Muscle: G.G. Matthews, 4th ed., Blackwells, 2003. A very good reference although not always quite as mathematical as we want for this course.
Electronic library copy: http://oxford.eblib.com/patron/FullRecord.aspx?p=428063

Mathematical Physiology (Vols. 1 + 2): J. Keener and J. Sneyd, Springer-Verlag, 2008. A very mathematical treatment of this subject that often goes beyond what we need for this course. Read selectively and stick to the simpler examples.
Electronic library copy (1998 Ed): http://solo.bodleian.ox.ac.uk/permalink/f/n28kah/oxfaleph021933865

Molecular Cell Biology: Lodish et al. A classical biology textbook that will help you to put some of the concepts we discuss in the course in a biological context.
Various libraries in Oxford have electronic versions available, check on Solo.

The following books, in no particular order, might be useful further references:

Berne & Levy Physiology: B.M. Koeppen & B.A. Stanton, 6th ed., Mosby/Elsevier, 2010.

The Cardiovascular System at a Glance: P.I. Aaronson and J.P.T. Ward, Blackwells, 2007.

Cardiovascular Physiology: D.E. Mohrman and L.J. Heller, 6th ed., McGraw-Hill, 2006.

These books are all introductory guides to the underlying physiology and are very readable. They do contain a lot of detail and are primarily aimed at medical students, so read selectively. In particular, the sections on the diagnosis of clinical conditions are not relevant.

Two excellent introductory websites are:

http://training.seer.cancer.gov/module_anatomy/anatomy_physiology_home.html

http://cvphysiology.com/index.html

For a much more comprehensive overview of the whole subject of Biomedical Engineering refer to:

The Biomedical Engineering Handbook (Vols. 1-3): ed. J.D. Bronzino, 3rd ed., CRC press, 2006.

Lectures 1-4: Cellular Physiology

Introduction

The cell is the fundamental unit of the human body. In these lectures we will examine its structure, its function and how it operates. In particular we will examine the generation of the action potential and how this is transmitted between cells, as this is the primary means of cell-cell communication. At each stage, we will examine the mathematical relationships that are commonly used to characterize the cell's behaviour and see how this modelling work can both aid and hinder our understanding.

1 Cell structure and biochemical reactions

While the lectures provide you with some of the key concepts, it would be valuable if you consult some more traditional biology textbooks. Chapters 1-3 of Lodish Molecular Cell Biology will provide you with an excellent background. Here are examples of biological processes you should be familiar with:

- Cell cycle
- The basic forms of cell signalling

Throughout the first part of the course we will also discuss technologies for measuring cellular morphology and monitor cellular functions. This material will be captured in the lectures and exercises.

1.1 Cell structure

We start by examining the cell, since it is the fundamental unit of living matter. There are brain cells, heart cells, liver cells and so on, all the way round the body, each of which has a specific function and purpose. However, despite this all cells have some characteristics in common, as shown schematically in Figure 1.1. Cells have an outer layer, called the **membrane**, which acts as the boundary between the inside and outside of the cell. We will examine this in more detail in Lecture 2. Inside the cell, there is a **nucleus** that contains the cell's DNA, i.e. the genetic code that determines what the cell does, and many small structures that carry out the operations for the cell, termed organelles. These include ribosomes, lysosomes and mitochondria, where many of the reactions that produce energy take place. As we progress through the course, we will examine a number of these elements, primarily the membrane and the cytoplasm (the substance within the membrane that surrounds the other elements).

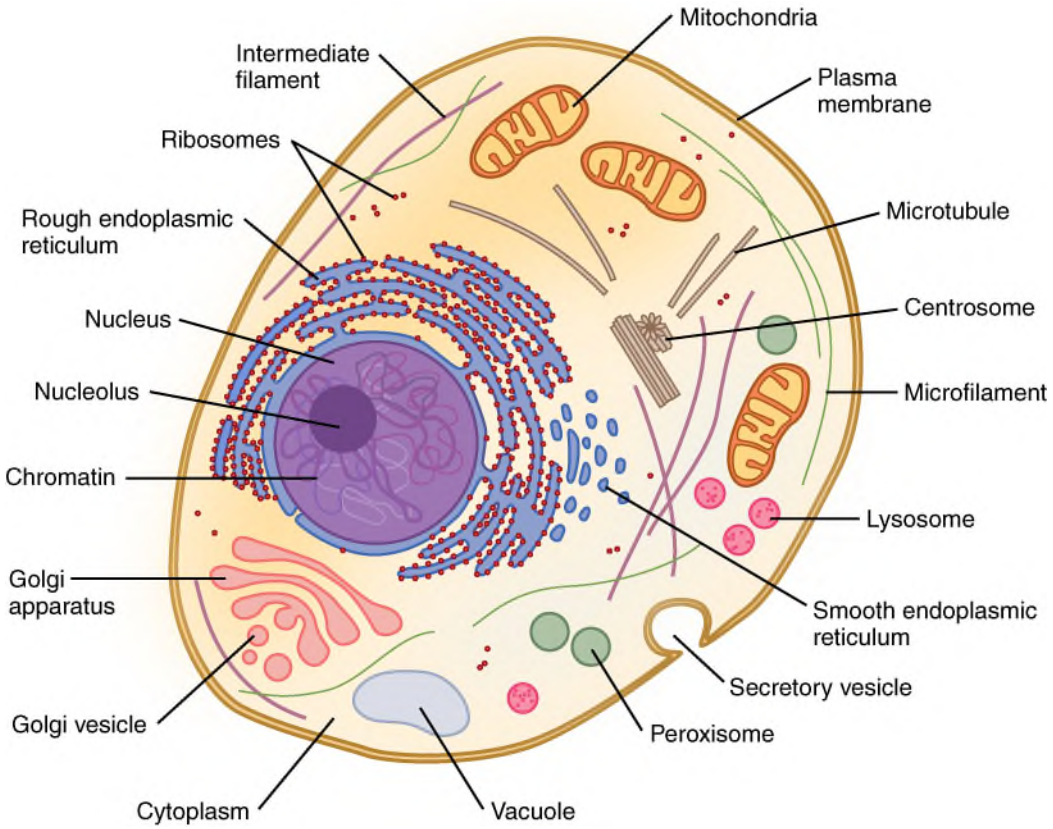

Figure 1.1 Structure of the cell

[By OpenStax College under CC-BY-3.0, via Wikimedia Commons]

1.2 Cell chemicals

Before examining the cell in detail, we need to consider the different types of chemicals found in the body and their roles, such that when we consider the functions of the cell, it will easier to understand what is occurring. The important chemicals within the body can be divided into two categories: inorganic and organic. The main inorganic substances are:

1. Water, which acts as a solvent, a biochemical reactant, a regulator of body temperature and a lubricant;
2. Electrolytes, which balance osmotic pressure and biochemical reactants;
3. Acids and bases, which act to balance pH.

The primary organic substances are:

1. Carbohydrates;
2. Lipids;
3. Proteins;
4. Nucleic acids;
5. Adenosine triphosphate (ATP).

We will only examine a couple of the most important substances and their role within the body. If you want to know more about the others, ask a chemist.

1.2.1 Proteins

There are many types of **proteins** and they perform a number of roles within the body:

1. Structural (coverings and support);
2. Regulatory (hormones, control of metabolism);
3. Contractile (muscles);
4. Immunological (antibodies, immune system);
5. Transport (movement of materials, haemoglobin for oxygen);
6. Catalytic (enzymes).

They are made up of amino acids (of which there are 20): examples of proteins are insulin, **haemoglobin** and **myosin**. Insulin plays a key role in the regulation of blood sugar levels; haemoglobin is vital to the transport of oxygen around the body and myosin is used in muscle contraction.

1.3 ATP

ATP is essentially the energy source for cells and acts akin to a battery, since it contains three phosphate groups (hence ‘triphosphate’). Figure 1.2 shows the three parts to ATP, with the third part comprising three

phosphate groups. When the third phosphate is released, energy is also liberated: ATP then becomes **ADP** (adenosine diphosphate), i.e. with only two phosphate groups. Should the second be released to yield AMP (adenosine monophosphate), more energy can be released. The ADP-ATP and ATP-ADP processes are thus essentially the storage and release of energy. The former can be expressed in the reaction equation:

$$ATP \Leftrightarrow ADP + P + energy\ , \qquad 1.1$$

and the latter similarly.

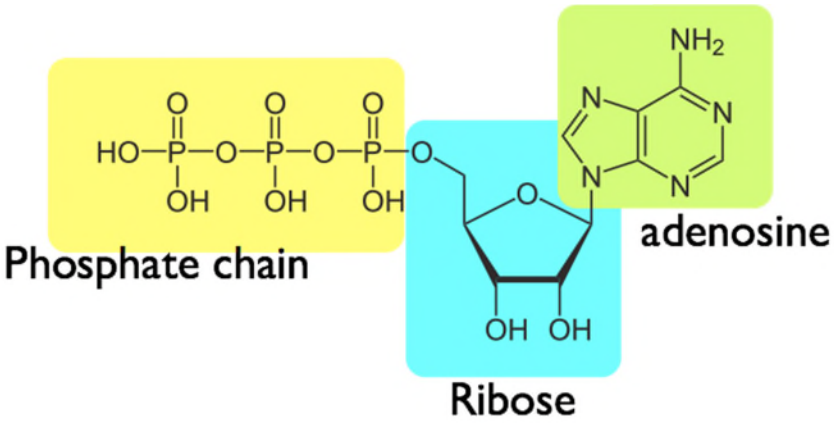

Figure 1.2 Structure of ATP

1.4 Reaction equations

To understand biological behaviour, we will need to understand the reaction equations that govern all physiological processes. You will already have encountered this elsewhere in the course, so we will assume that you are able to write down and balance the necessary equations. The one thing that we need to check is the correct use of units. Throughout this course we will use the **mole**, which is formally defined as exactly 6.02214076×10^{23} elementary entities. This number is the fixed numerical value of the Avogadro constant. Chemical equations are all based on the use of the mole, since it is a much more convenient means of describing quantities.

For a number of physiological elements, the molecules are not found in isolation, but in solution, primarily in water. We thus need a means of describing how much of the solute is present in the solution. The most common definition, although there are others, is termed **molarity**: this is the number of moles of the solute per litre of solution. It thus has units of *mol/l*, which is normally written in shorthand as *M*. We will use this all the way through the remainder of this course. Most physiological molarities are of the order of tens of milli-*M*, written *mM*, as we will see in lecture 2.

1.4.1 Mass action kinetics

We will now examine these reaction equations, starting with the very simplest.

$$A + B \xrightarrow{k} C\ .$$

k is termed the rate constant for this reaction, which simply takes two reactants, *A* and *B*, and converts them into a product *C*. The quantity of *C* increases dependent upon the quantities of both *A* and *B*, thus a simple model for rate of change with time (termed the reaction rate) is given by:

$$\frac{d[C]}{dt} = k[A][B].$$

This is called the law of mass action and systems that obey this style of equation are said to be governed by **mass action kinetics**. The rate constant will depend upon the sizes and shapes of A and B, it is also not necessarily constant and varies with temperature in particular. Note that concentrations are usually denoted by square brackets, i.e. the concentration of A is [A], for simplicity we will also lower case letters to refer to chemical concentrations where we need to write many equations like below.

Mass action kinetic is based on C being produced when A and B collide, so-called **elementary reactions**. The rate constant is thus proportional to the number of collision between A and B per unit time and the probability that the collision has enough energy to overcome the activation energy needed for the reaction to proceed. The rate constant will thus depend upon the sizes and shapes of A and B, it is also not necessarily constant and varies with temperature in particular. This equation is not always true: for very high or very low values of concentrations, the rate of change is limited by other factors. Additionally, many reactions proceed via multiple intermediate steps leading to more complex rate laws (we will meet some examples of this). Despite this, this equation is a good first approximation and will enable us to analyse relatively complicated systems in a straightforward way. Note that if there are multiple moles on the left hand side of the reaction equation, then the reaction rate is proportional to the concentrations to the relevant powers, i.e. $A + 2B \xrightarrow{k} C$ would have a reaction rate of $\frac{dc}{dt} = kab^2$.

Strictly all reactions are reversible, thus there are forward and reverse rate constants, which need not be the same:

$$A + B \underset{k_-}{\overset{k_+}{\rightleftarrows}} C$$

We can now write down three equations, one for each of the chemical substances:

$$\frac{da}{dt} = k_- c - k_+ ab.$$

$$\frac{db}{dt} = k_- c - k_+ ab.$$

$$\frac{dc}{dt} = k_+ ab - k_- c.$$

Note that if we add the first and third equations together, the rate of change of $a + c$ is equal to zero. The sum of these concentrations is thus a constant, which we define here as: $a + c = a_o$, i.e. a_0 can be regarded

as the initial amount of A before any was converted to C. The equilibrium values can be found by setting the rates of change to zero in the three equations, giving:

$$K = \frac{k_-}{k_+} = \frac{\bar{a}\bar{b}}{\bar{c}}$$

where the over-bar refers to equilibrium or steady-state values and *K* is termed the equilibrium constant, which measures the relative preference for the species to be in the combined, C, or separate, A+B, state. This equation can be used to determine the equilibrium constant using the equilibrium values of the concentrations. The rule for determining the constant is to multiply all the product concentrations to the power of their coefficients and divide by the product of the reactant concentrations, again each to the power of their coefficients.

1.4.2 Enzyme kinetics

We will also consider a different type of reaction here: one where the reaction is catalysed by an enzyme. Enzymes are essentially substances that help other molecules called substrates change into products but which are unaffected by the reaction. Enzymes basically work by lowering the free energy of activation of the reaction, i.e. they make it easier to move from one state to another. They are particularly efficient at speeding up biological reactions and are highly specific, thus allowing very precise control of the reaction speed. A simple example might be a protein the 'fits' a particular molecule in such a way that it causes a bond to be stressed making that bond more easily broken thus reducing the activation energy. Alternatively a protein might have 'sites' to which the species in involved in the reaction bind, so that the enzyme increases the rate at which the species are brought together.

The first model to consider enzyme reactions was proposed by Michaelis and Menten in 1913. The enzyme *E* converts the substrate *S* into the product *P* in two stages. *S* and *E* combine to give a complex *C* (or ES), which then breaks down into *P* and *E*:

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftarrows}} C \xrightarrow{k_{+2}} E + P$$

In theory this reaction can also work backwards, but normally *P* is continually removed, which prevents the reverse reaction from occurring.

We can write down the four differential equations in the same style as previously for the four different substances, *S*, *E*, *C* and *P*:

$$\frac{ds}{dt} = k_{-1}c - k_{+1}se$$

$$\frac{de}{dt} = k_{-1}c - k_{+1}se + k_{+2}c$$

$$\frac{dc}{dt} = k_{+1}se - (k_{+2} + k_{-1})c$$

$$\frac{dp}{dt} = k_{+2}c$$

Note that this set of equations is redundant: the second and third equations add to give $\frac{de}{dt} + \frac{dc}{dt} = 0$, which means that the sum of *E* and *C* is constant over time and normally represented by the variable $e + c = e_o$. There are two common approaches to analysing this system of equations: the equilibrium approximation and the quasi-steady-state approximation. We will examine them both briefly here.

Equilibrium approximation

The first method was the original one proposed by Michaelis and Menten and is assumes that the substrate is always in equilibrium with the complex, i.e. the first stage of the reaction is in equilibrium. The rate of formation of the product, termed the **velocity** of the reaction is then given by:

$$V = \frac{dp}{dt} = k_2 c = \frac{k_2 e_o s}{K_S + s},$$

where $K_s = \frac{k_{-1}}{k_1}$, similarly to before. At small substrate concentrations, the reaction rate is proportional to the amount of available enzyme and the amount of substrate: however, at large substrate concentrations, the rate is limited by the amount of enzyme present. The dissociation reaction is thus termed rate limiting. The equation above is often written in the form:

$$V = \frac{V_{\max} s}{K_S + s},$$

with V_{max} being the maximum velocity with which the reaction can proceed. This equation is known as the **Michaelis-Menten equation** and is used widely in physiological modelling.

Quasi-steady-state approximation

The second approximation assumes that the rates of formation and the breakdown of the complex are equal, thus $\frac{dc}{dt} = 0$. Solution of the remaining equations gives a similar result to the previous reaction velocity:

$$V = \frac{V_{\max} s}{K_m + s},$$

where $K_m = \frac{k_{-1} + k_2}{k_1}$. Clearly the two approximations give very similar results, but they are based on very different assumptions. The example sheet will ask you to derive these results.

A more detailed model was proposed by Briggs and Haldane, where the complex has two phases (*ES* and *EP*). This also has the same form as equation 1.16, but with a different constant. Keener and Sneyd also

provide details of an array of increasingly complex reaction systems. We will look at a couple of further simple examples (but the more complex ones shown in the lecture are outside the scope of this course).

1.4.3 Enzyme co-operativity

Some enzymes can bind more than one substrate molecule, where the binding of one substrate molecule affects the binding of subsequent molecules. This is known as co-operativity and is involved in one of the most important bindings: that of oxygen to haemoglobin in the blood. Although the analysis is quite complicated, the final result is relatively simple: if *n* substrate molecules can bind to the enzyme, the rate of reaction is given by:

$$V = \frac{V_{\max} s^n}{K_m^n + s^n}.$$

This is known as the **Hill equation**. It is frequently used as an approximation for reactions where the intermediate steps are not well known.

This is particularly true in the case of oxygen binding to haemoglobin, where the reaction equation:

$$Hb + 4O_2 \underset{k_-}{\overset{k_+}{\rightleftarrows}} Hb(O_2)_4$$

implies a fraction filling of available haemoglobin sites of:

$$S = \frac{[O_2]^n}{K^n + [O_2]^n},$$

with $n = 4$. In fact, a much better fit to experimental data is found with $n = 2.5$, implying that the later sites prefer to fill up if the early sites are already full. The mechanism for this positive co-operativity is not yet completely understood.

1.4.4 Enzyme inhibition

To afford great control over the reaction rate sometimes an enzyme inhibitor is present. These are likely either to be **competitive** or **allosteric** inhibitors.

Competitive inhibitors

The inhibitor species combines with the enzyme to form a compound, which essentially removes some of the enzyme from the system, preventing it forming the product. The reactions are thus:

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftarrows}} C_1 \xrightarrow{k_{+2}} E + P$$

$$E + I \underset{k_{-3}}{\overset{k_{+3}}{\rightleftarrows}} C_2$$

There are now six differential equations:

$$\frac{ds}{dt} = k_{-1}c_1 - k_{+1}se$$

$$\frac{de}{dt} = k_{-1}c_1 + k_{+2}c_1 - k_{+1}se + k_{-3}c_2 + k_{-3}c_2 - k_{+3}ie$$

$$\frac{dc_1}{dt} = k_{+1}se - (k_{+2} + k_{-1})c_1$$

$$\frac{dp}{dt} = k_{+2}c_1$$

$$\frac{di}{dt} = k_{-3}c_2 - k_{+3}ie$$

$$\frac{dc_2}{dt} = k_{+3}ie - k_{-3}c_2$$

Thankfully, this isn't as complicated as it looks. The normal assumption made in the analysis is that the compounds are both in quasi-steady-state. We can also see that if we add the differentials for the enzyme and the two compounds that they are zero (so these variables always add up to a constant, again called e_o). The rate of formation of the product is then found to be:

$$V = \frac{dp}{dt} = k_2 c_1 = \frac{V_{\max} s}{s + K_m\left(1 + i/K_i\right)}.$$

Where $K_i = k_{-3}/k_{+3}$. This is left for you to derive in the example sheet, which also asks you to consider what the effect of the inhibitor is. Note that if *i* is set to zero, we get back to the Michaelis-Menten equation, as expected. Sometimes, the reaction equations are re-written in schematic form:

$$\begin{array}{ccccccccc} E & + & S & \rightleftarrows & ES & \rightarrow & E & + & P \\ + & & & & & & & & \\ I & & & & & & & & \\ \Uparrow\Downarrow & & & & & & & & \\ EI & & & & & & & & \end{array}$$

Allosteric inhibitors

In this case the inhibitor binds to the enzyme in such a way as to prevent the product being formed. For example, the inhibitor might bind to a different site on the enzyme preventing the complex converting into the product. This can be modelled as the inhibitor binding to the complex, written in schematic form:

$$\begin{array}{ccccccccc} E & + & S & \rightleftarrows & ES & \rightarrow & E & + & P \\ & & & & + & & & & \\ & & & & I & & & & \\ & & & & \Uparrow\Downarrow & & & & \\ & & & & ESI & & & & \end{array}$$

The rate of formation of product is now:

$$v = \frac{V_{max} s}{K_m + \left(1 + \frac{i}{K_i}\right) s}$$

This is quite similar to the previous equation, but you should be able to spot the difference. In practice this is only true for an allosteric inhibitor that is **uncompetitive**, i. e. it doesn't bind to E to form EI. It is possible to have inhibitors that are both allosteric and competitive in which case the analysis becomes more complex.

2 Cellular homeostasis and membrane potential

2.1 Membrane structure and composition

Essentially 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 soluble in oil. The cell lipids are primarily phospholipids, i.e. they have one end that is hydrophilic and one that is hydrophobic (are attracted to and repelled by water molecules respectively). The hydrophobic ends thus tend to point towards each other, hence the two molecule thickness. Substances can cross the membrane if they can dissolve in the lipids. However, some electrically charged substances which cannot 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 pass through the lipid layer. Sometimes these form pores or channels through which molecules can pass. Figure 2-1 shows a schematic of the membrane structure.

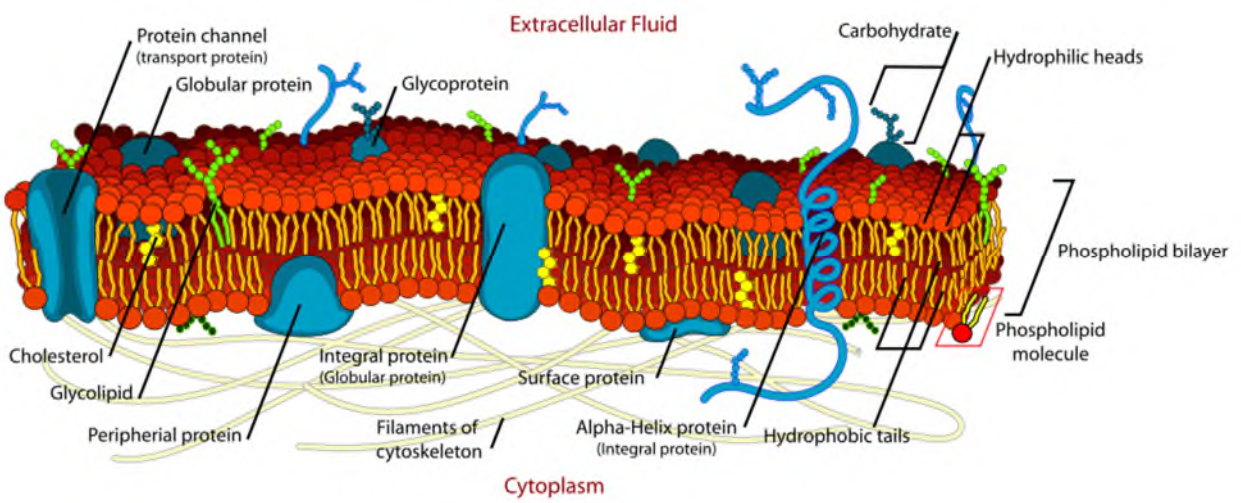

Figure 2-1 Schematic of membrane structure

[By LadyofHats Mariana Ruiz (Public domain), via Wikimedia Commons]

Outside the cell, the main positively charged ion is sodium (Na+) with a small amount of potassium (K+) and chloride (Cl-) ions. 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 acidic 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: note from Table 2.1 that the total charge inside does not quite balance. Also, it 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. To consider these issues we need first to consider the balance of cell volume.

Table 2.1 Compositions of intracellular and extracellular fluids for a typical cell

	Internal concentration (mM)	External concentration (mM)	Can it cross membrane?
K+	125	5	Y
Na+	12	120	Y/N
Cl-	5	125	Y
P-	108	0	N
H_2O	55,000	55,000	Y

2.2 Osmotic balance

Consider a litre of water with 1 mole of dissolved particles: this is termed a 1 molar, or 1M, solution, as we saw in lecture 1. Now consider two adjacent identical volumes with different molarities (say 100 mM 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 litre and 4/3 litre, Figure 2-2. 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.

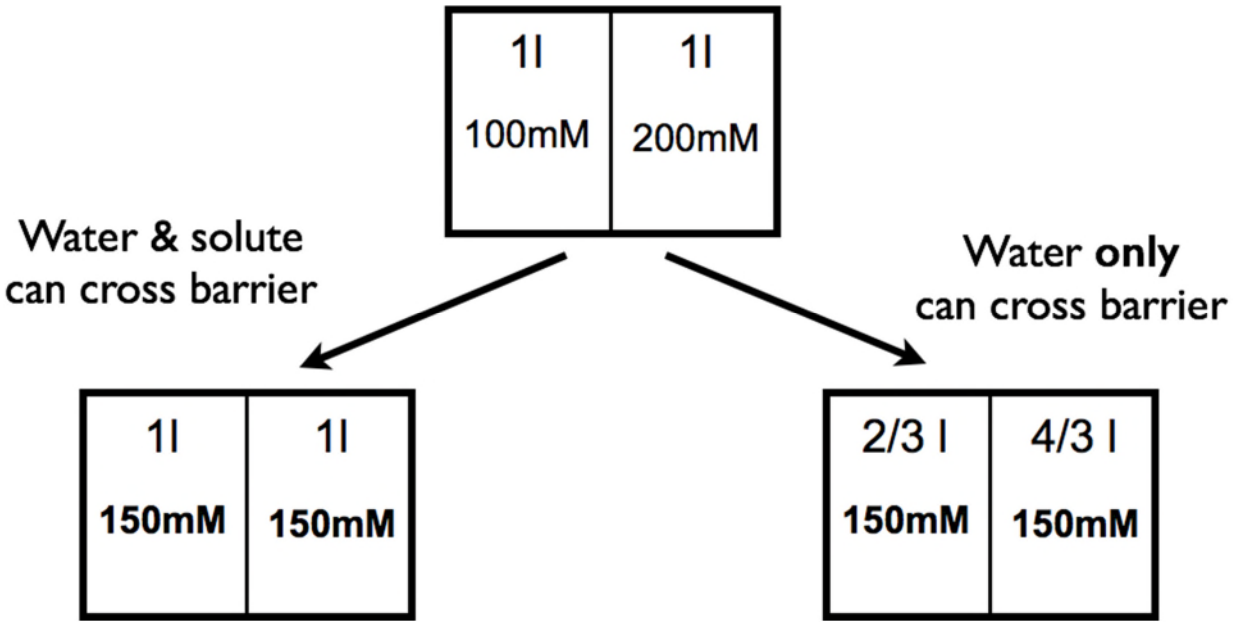

Figure 2-2 Example of balance of concentration with solute able to cross (left) and with solute unable to cross (right)

Now consider a slightly different example with acell 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 less than that of *P* (hypotonic solution): cell volume increases.
3. The concentration of *Q* is greater than that of *P* (hypertonic solution): cell volume decreases.

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 Figure 2-3.

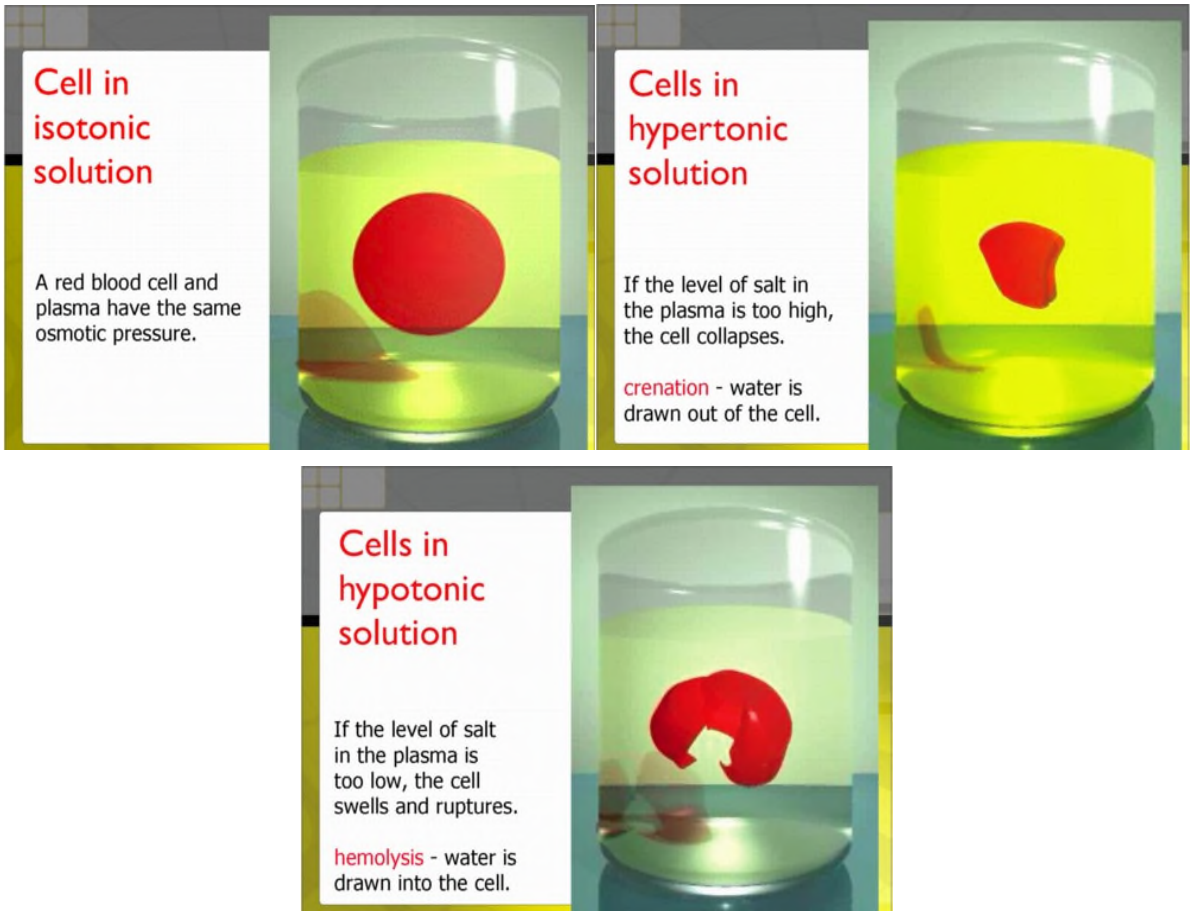

Figure 2-3 Red blood cell behaviour in solutions of different concentration

[Prof. Z.F. Cui lecture notes, 2003-4]

If *Q* 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. Since the only way that these two requirements can be met is for the concentration of *P* to be zero, the cell expands to infinite size.

The requirement for the total concentration to be equal inside and outside the cell is essentially a requirement that the concentration of water balances. 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 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. See Matthews, Chapter 3, for a more thorough guide to this and for some more examples.

2.3 Conservation of charge

Now consider the slightly more complex example in Figure 2-4, 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 mM and 50 mM respectively.

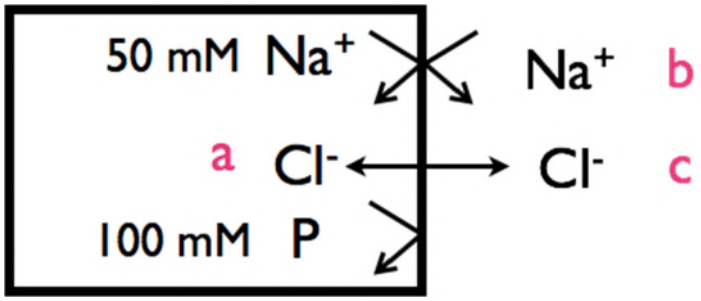

Figure 2-4 Cell model example

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 that we can assume that they balance at all times.

From charge balance: $a = 50$

$b = c$

From concentration balance:

$$50 + a + 100 = b + c$$

Hence: $b = c = 100$

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, which was ignored in the previous section.

2.4 Equilibrium potential

Thus 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 Figure 2.5, the difference in voltage between the inside and the outside of the cell is given by the Nernst equation:

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

where *R* is the gas constant, *T* is absolute temperature (K), *Z* is the valence of the ion and *F* is Faraday's constant (96,500 coulombs / 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:

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

where we have changed from a natural logarithm to a base-10 logarithm. The proofs of these equations are found in Matthews, Appendix A.

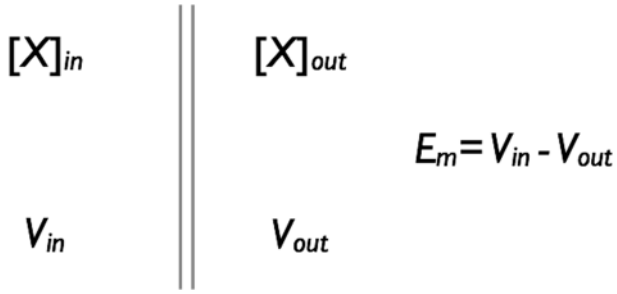

Figure 2-5 Membrane and membrane potential

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:

$$E_m = 58\ mV \log_{10}\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right) = -58\ mV \log_{10}\left(\frac{[Cl^{-1}]_{out}}{[Cl^-]_{in}}\right),$$

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.**

2.5 A simple cell model

We will now consider an example of a model cell at equilibrium, Figure 2-6. 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 proteins. Outside the cell is found Na+, K+ and Cl- where K+ and Cl- are free to cross the membrane. We have three principles to apply when we analyse cell concentrations:

1. Concentration/osmotic balance.
2. Electrical neutrality.
3. Gibbs-Donnan equilibrium.

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.

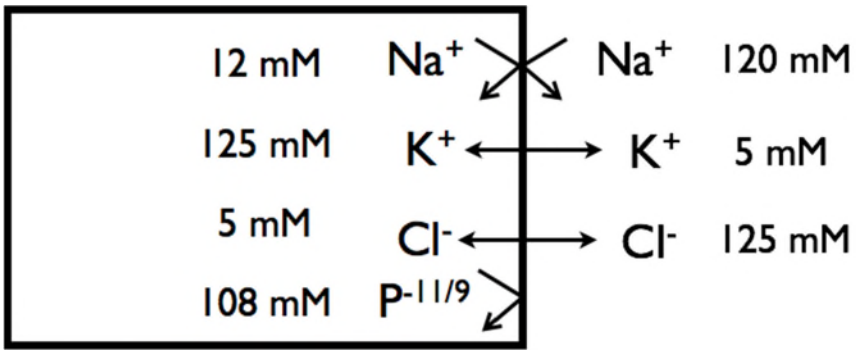

Figure 2-6 Example of model cell

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

2.6 Ion pumps

An ion pump is a mechanism that absorbs energy to move ions against a concentration or electrical gradient, rather like a heat pump. 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 this is now a steady state, requiring energy, rather than an equilibrium state, which requires no energy.

The symbol for the pump is shown in Figure 2-7, 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

[1] If you read Matthews you will find he uses 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 use it.

membrane-associated enzyme as a Na+/K+ ATPase. The use of ATP as an energy store was discussed in lecture 1.

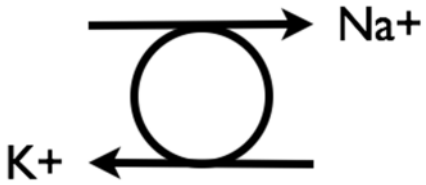

Figure 2-7 The sodium/potassium pump

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 we had $E_m = E_K = E_{Cl}$ = -80mV. However, now we also have a contribution from Na+ with E_{Na} = +58mV, 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 essentially 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 later in the course, 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**:

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

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:

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

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 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 Figure 2-8 that also includes the forces acting on the ions. Note that the net charge on the inside of the cell is negative therefor 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.

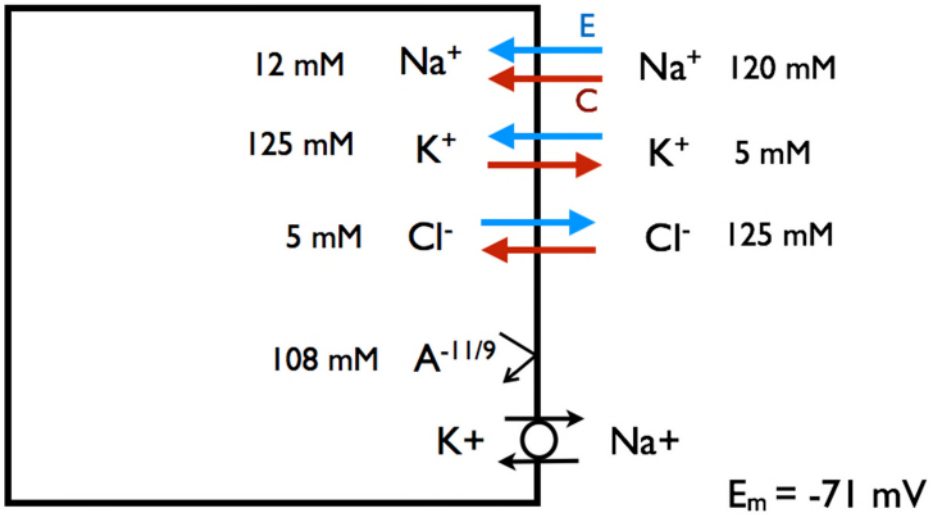

Figure 2-8: Steady state cell model, showing the electrical (E) and chemical (C) forces acting on the ions.

Although we have ignored Cl- in the calculation of the membrane potential, it is affected by it: its resting membrane potential is -80 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 $E_m = -71mV$, $E_K = -80mV$ and $E_{Na} = 58mV$ 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 of 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 Figure 2-9.

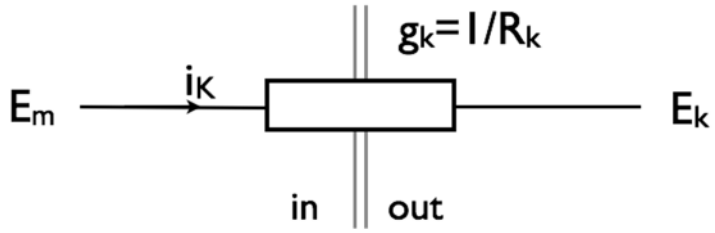

Figure 2-9: Modelling the cell membrane as a resistance/conductance for each ion.

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 the next lecture. 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 the next section when we consider the action potential.

3 The action potential

Thus far we have considered properties of cells that are universally found throughout the body. We now begin to consider more specific properties found in certain types of cell that are vital for the correct functioning of the human body. In particular, we will focus here on 'excitable' cells, which can generate active electrical responses that act as signals for other events. The basic signal of the nervous system is the action potential, with which we will begin.

3.1 Na+/K+ action potential

As mentioned earlier, it is the relative permeability of the membrane to Na+ and K+ that determines the membrane potential. In the resting state, the ratio is 0.02, as given in lecture 2, but if the membrane permeability to Na+ were suddenly increased by a significant factor, this ratio would increase and the membrane potential swing from close to E_K (-80 mV) to close to E_{Na} (+58 mV). This is essentially all that is required to generate the **action potential**, which is a transient change in the membrane potential of the cell. The action potential depends arises because the gates which determine the permeability of the membrane are controlled by the membrane potential.

The process of the action potential follows these steps, as summarised in Figure 3-1:

A. Resting state: The number of Na+ channels that are open are small and $b = p_{Na}/p_K \sim 0.02$.
B. Depolarization: If the membrane potential becomes more positive then more Na+ channels open, thus b will increase and E_m will become even more positive. This positive feedback loop means that there is a large and rapid swing in E_m, meaning that the action potential continues irrespective of any further external influence. Thus the action potential is known as an 'all or nothing' event.
C. Repolarization: The Na+ channel actually has two gates: m that is normally closed and h that is normally open. Upon depolarization m opens rapidly, but h closes much more slowly and it is this timing difference that leaves time for depolarization before repolarization kicks in. Additionally, there are voltage sensitive K+ channels with n gates that are normally closed that also respond slowly to the depolarization. Thus p_K also increases on depolarization and like the h gate this drives E_m back toward the resting value.
D. Undershoot: Due to the n gate p_K is greater than usual so that b ends up being smaller than the resting value, which causes E_m to undershoot until the n gates eventually return to normal.
E. Refractory period: Whilst the membrane potential may have returned to the resting state the h gates will initially still be shut blocking the Na+ channels even if the m gates were to reopen. Thus there is a period in which a new action potential cannot be generated.

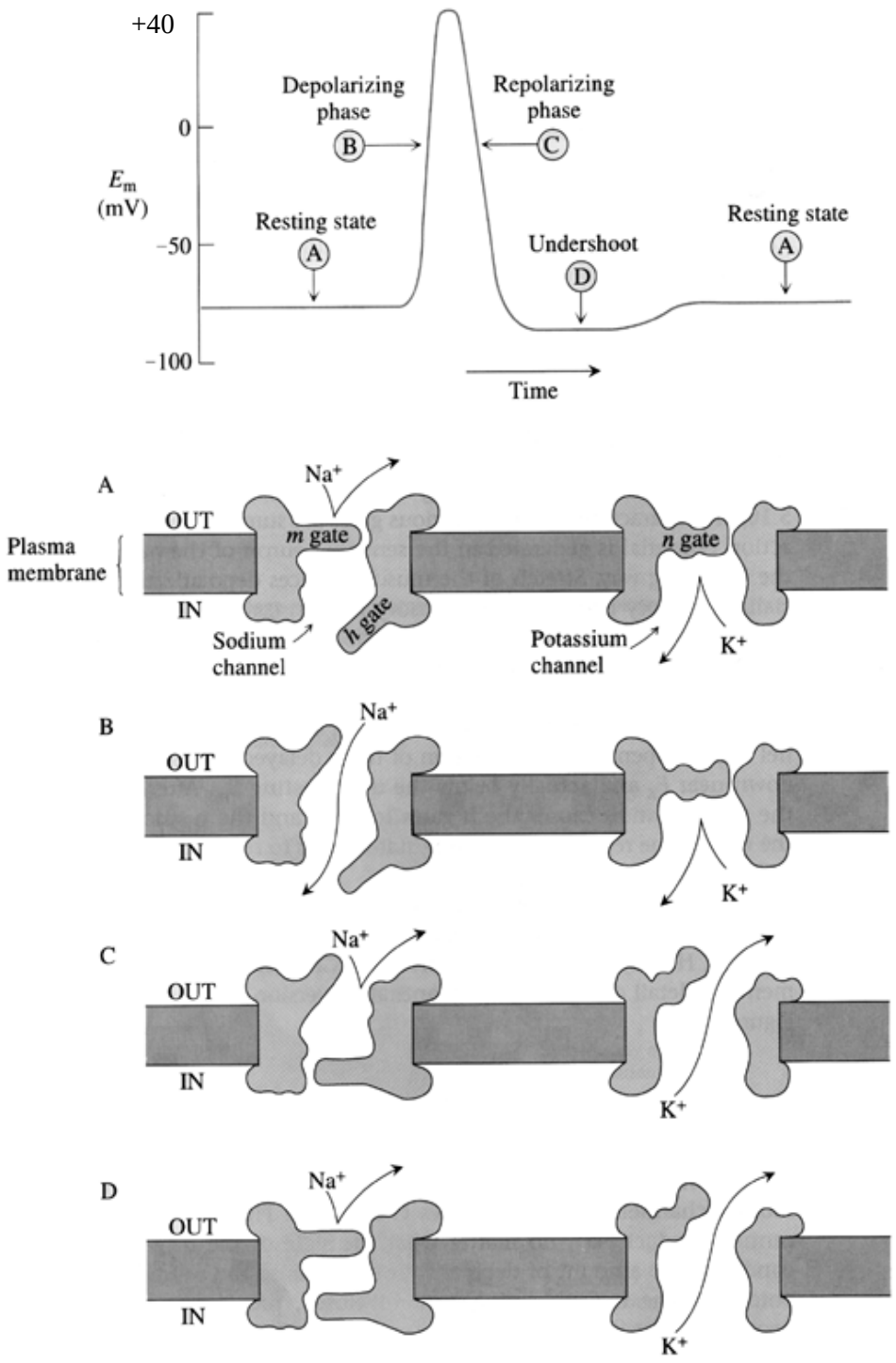

Figure 3-1 States of voltage-sensitive channels during action potential [Matthews]

In practice the action potential only occurs once a certain threshold of membrane potential is reached, usually around 10-20 mV above resting. For smaller depolarization the efflux of K+ induced by the change in E_m exceeds the efflux of Na+, leading to a negative feedback process that suppresses further depolarization. The actual value of this threshold depends upon a variety of factors, particularly the packing

density of the Na+ channels and the relationship between the membrane potential and the opening pattern. Some neurons are highly sensitive, whilst others require a very large depolarization to stimulate a potential.

The action potential is propagated from cell to adjacent cell since when the depolarization occurs in one cell it will naturally bring the adjacent cell above the threshold stimulating that cell and so on along the nerve fibre. This is also the mechanism by which electrical signals as transmitted down nerve fibres. This may seem slightly surprising, since we might wonder why a nerve fibre doesn't act like a wire and simply carry the electrical signal along it. However, cells, as we have seen, as generally very leaky and a lot of the current flows out of the cell making them poor conductors. Instead the action potential mechanism is employed to achieve a net flow of the signal down the nerve, where an action potential in one region causes another to fire in the neighbouring region of the same cell.

3.2 Ca^{2+} contribution

Action potentials do not only occur in neurons: they can be found in muscle cells, as will be considered later. In most neurons, however, voltage-dependent Ca channels are also found, which can contribute significantly to the action potential. This is because they often inactivate more slowly than the corresponding Na+ channels, causing a much slower repolarization with a plateau phase caused by the Ca channels and the increase in intracellular Ca. This increase can be important in its own right: in lecture 4 we will see that this is the trigger for release of neurotransmitters, which are important in cell-cell communication. Intracellular Ca can also activate other kinds of ion channels (often K+ channels that are activated by Ca), which can lead to a hyperpolarizing undershoot after repolarization, Figure 3.2, due to the increase in p_K. Since the increase in Ca concentration lasts much longer than the normal timing of the action potential, the resulting hyperpolarization is some hundreds of times longer than it. Clearly this is dependent on having enough Ca influx during the action potential and enough Ca activated K+ channels. In some case the levels of Ca may build up gradually over many action potentials before it is sufficient to activate the K+ channels and cause the hyperpolarization (normally called the after-hyperpolarization to distinguish it from the undershoot). This can be a way of obtaining rhythmic bursts of activity punctuated by periods of silent behaviour, particularly in neurons that control rhythmic events.

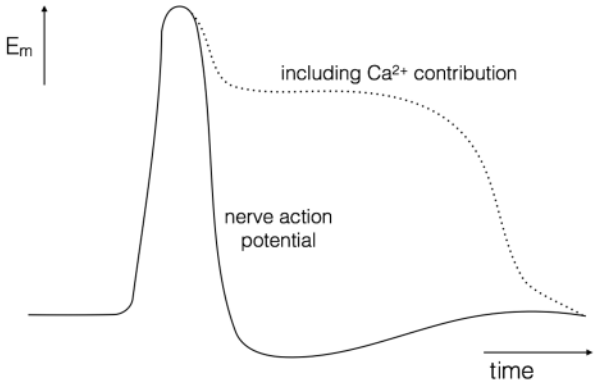

Figure 3-2 Time course of action potential with and without calcium-activated K+ channels [Matthews]

3.3 Hodgkin-Huxley model

The generation and propagation of signals have been studied for at least 100 years: however, the most important piece of work during this time was performed by Hodgkin and Huxley between 1949 and 1952. Hodgkin and Huxley studied the squid giant axon and developed the first quantitative model of the propagation of the electrical signal. This model was such an important step in the understanding of electrical activity that it has been called "the most important model in all of the physiological literature", Keener and Sneyd.

Using a simple model of the cell, as shown in Figure 3-3, a current balance can be written. The cell is assumed to have compliance C_m and to have current inputs through potassium, sodium and other channels (these last being lumped together and termed leakage). There is also an applied current, which we will examine in more detail later. The Hodgkin-Huxley model basically comprises a series of four equations:

$$C_m \frac{dv}{dt} = -\bar{g}_K n^4 (v - v_K) - \bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_L (v - v_L) + I_{app},$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

where the parameters in the last three equations are non-linear functions of the voltage:

$$\alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25 - v}{10}\right) - 1},$$

$$\beta_m = 4 \exp\left(\frac{-v}{18}\right),$$

$$\alpha_n = 0.01 \frac{10 - v}{\exp\left(\frac{10 - v}{10}\right) - 1},$$

$$\beta_n = 0.125 \exp\left(\frac{-v}{80}\right),$$

$$\alpha_h = 0.07 \exp\left(\frac{-v}{20}\right),$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right)+1}.$$

The potential is defined as the deviation from the steady state value, measured in units of mV. The remaining parameters all have fixed values as shown in Table 3.1.

Table 3.1 Fixed parameter values for the Hodgkin-Huxley model

g_K	**36 mS/cm^2**
g_{Na}	**120 mS/cm^2**
g_L	**0.3 mS/cm^2**
v_K	**-12 mV**
v_{Na}	**115 mV**
v_L	**10.6 mV**
C_m	**1 μF/ cm^2**

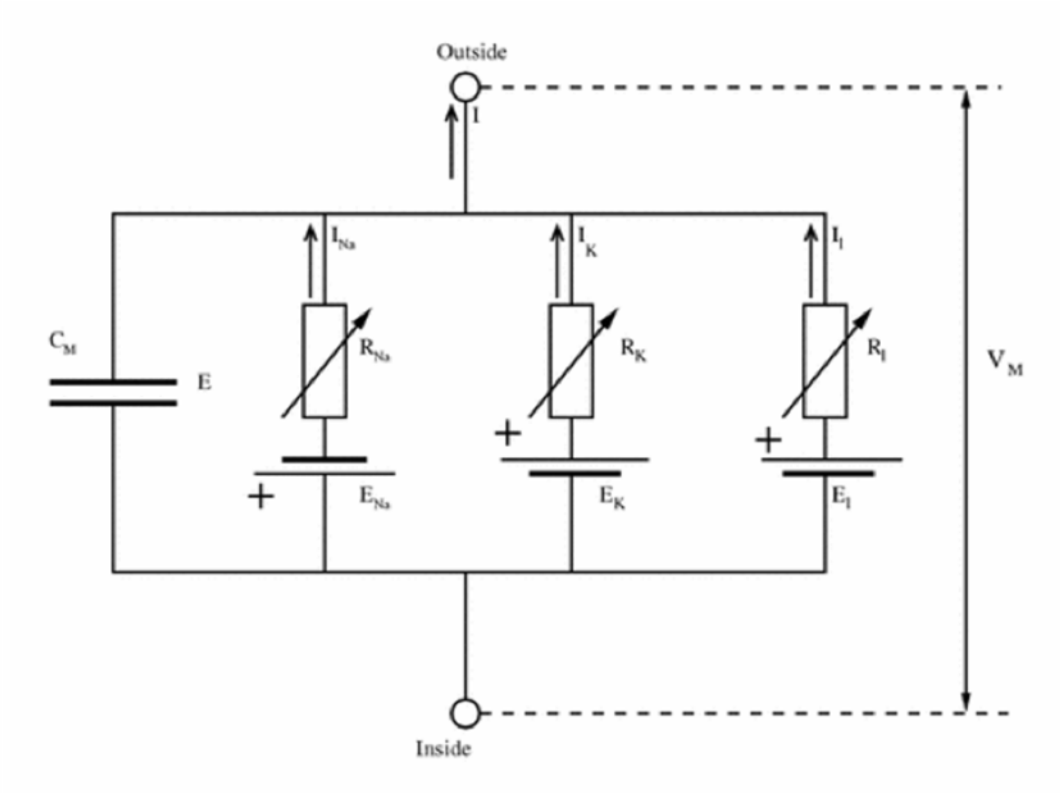

Figure 3-3 Schematic of Hodgkin-Huxley model

Notice that the letters *m*, *n* and *h* refer to the *m*, *n* and *h* gates respectively (actually the gates are named after the variables named by Hodgkin-Huxley in their model): when the values are equal to 0, the gates are closed (The first equation shows that both *m* and *h* gates are needed for Na+ to flow, but only the *n* gate is required for K+). The powers in *m* and *n* in the equation were chosen based on experimental data and are

often interpreted as the number of binding sites on the two gates. Equations 2 through 4 are simply first order kinetic models with forward and backward rate constants like those we met in the first lecture. These give a sigmoidal response to a change in potential that matches that seen in experimental data, the powers on the *m* and *n* gates result in a steeper slope in their sigmoidal response.

We will perform some simple analysis of the Hodgkin-Huxley model here to illustrate how a simple model can be used to simulate and to understand the behaviour of a physiological system. The first thing we examine is the steady state behaviour of the variables *m*, *n* and *h* and the time constants: note that since the relevant three equations are all first order, the steady state values and time constants are easily derived. Note that in the steady-state with the potential at zero (remember that this is relative to the reference value), the *h* gates are largely open and the *m* and *n* gates largely closed. When the voltage increases, the gates go from open to closed and vice versa. The time constants for the *n* and *h* gates are much larger than for the *m* gate, so the *m* gate responds much more rapidly, as expected.

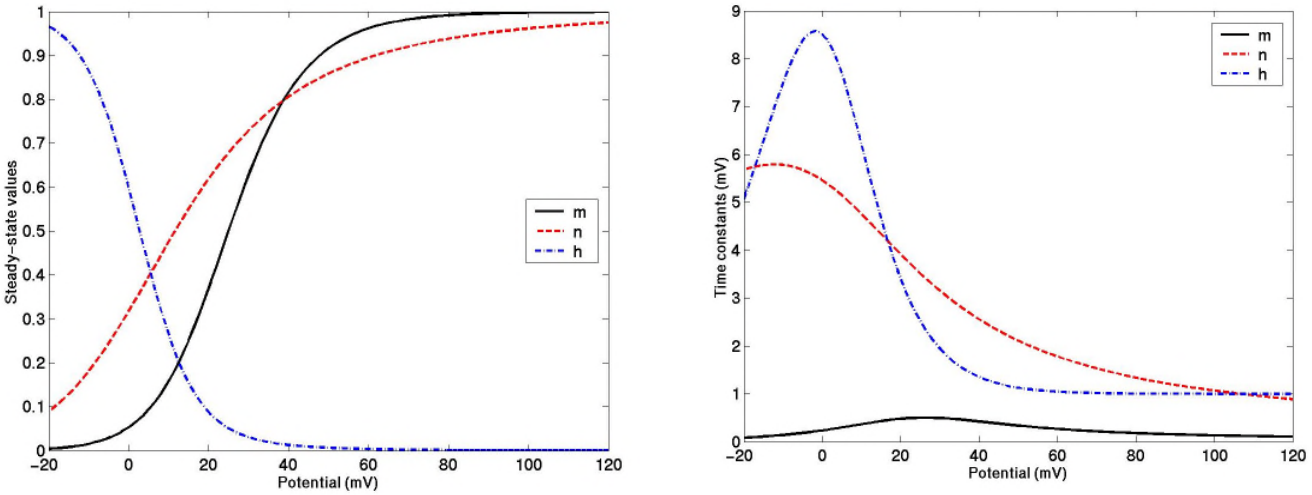

Figure 3-4 (a) Steady state values and (b) time constants for *m*, *n* and *h*

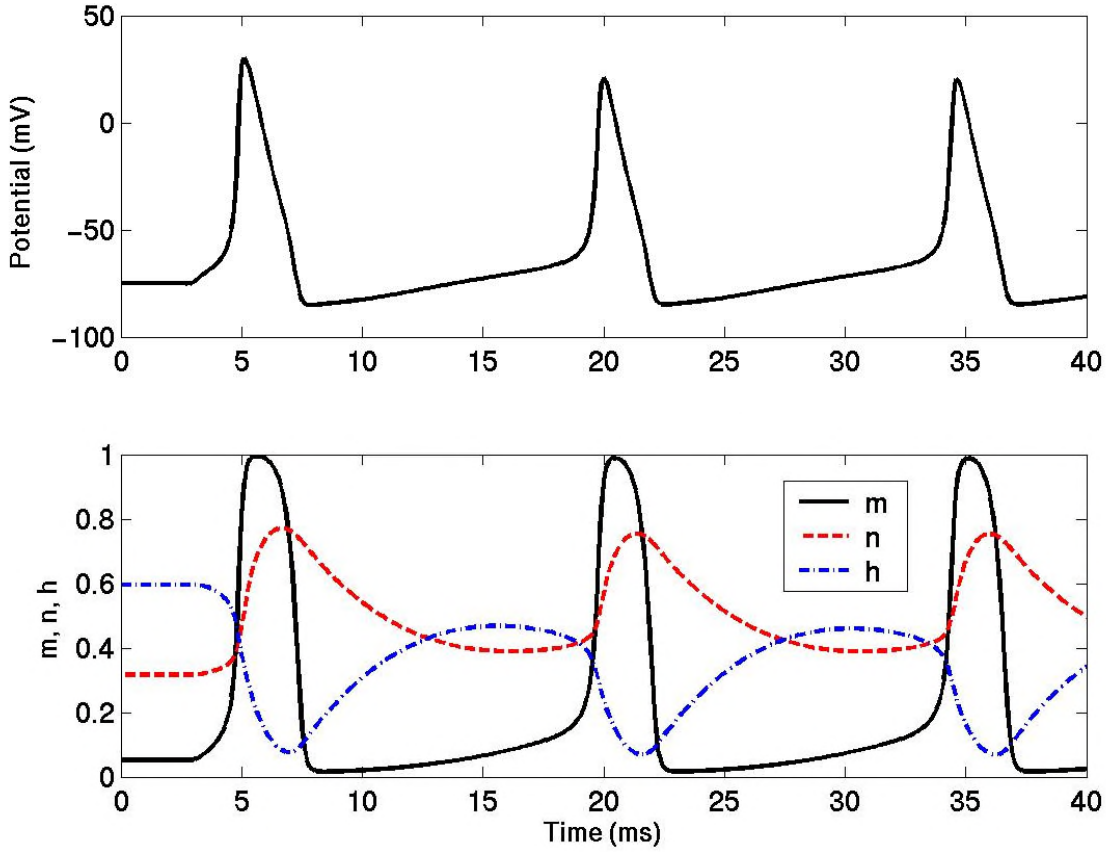

Figure 3-5 Time series of action potential with applied stimulus

We now apply a stimulus to the system in the form of the applied current: this is equivalent to a neighbouring cell providing a change in potential. If a small stimulus is applied, nothing happens, but if it reaches a threshold value, the action potential suddenly occurs. In Figure 3-5, a stimulus is applied at 2 seconds and left on: the system 'fires' and there is then a refractory period before it fires again. Note that the *m* gate opens very rapidly, with the *n* and *h* gates responding more slowly, as in the model schematic shown earlier.

It may seem slightly confusing that in Lecture 2 we considered Na+/K+ and Cl- ions, whereas here we have considered Na+/K+ and Ca2+. Na+ and K+ are the dominant ions in the cell's behaviour, whereas the other ions play roles in different aspects of the cell's behaviour, so have to be considered as and when they are relevant. More detailed models of the cell's behaviour include all the different ions.

4 Transport and cell-cell transmission

4.1 Transport

One of the important processes that occurs everywhere in the body is transport, i.e. how substances move from one place to another. The different types of mass transport can be thought of in terms that are analogous to heat transfer (where we have conduction and both forced and natural convection). For example, 'forced' convective transport is achieved by pumping the fluid from one place to another: this is essentially how oxygen is transported around the body, i.e. by blood being pumped through blood vessels (we will examine this in later lectures). We will consider a number of different processes here very briefly, as, although there are only a handful of mechanisms that can be used and the law of conservation of mass always holds, there are many different conditions under which transport occurs.

4.1.1 Diffusion

We have already considered how concentration differences drive species such as ions in and out of the cell. For a given entity present in solution within a region we can write down, via conservation of mass:

$$\frac{\partial u}{\partial t} = f - \nabla . \boldsymbol{J}$$

Which essentially says that the rate of change of the concentration the concentration *u* with time equals the rate of production of it within the region, *f*, and the rate at which it leaves across the surface of the region, which is determined by the flux ***J***. Intuitively we expect the flux should be related to the concentration gradient, which is the basis of Fick's law:

$$\boldsymbol{J} = -D\nabla u$$

If we substitute that into the conservation law then we arrive at the diffusion equation:

$$\frac{\partial u}{\partial t} = \mathrm{D}\nabla^2 u + f$$

Where in this case we have assumed that *D*, the diffusion co-efficient, is a constant. Since no energy is involved diffusion is a passive means of transport. The value of *D* is related to the size and geometry of the chemical species as well as things like temperature and viscosity. If the size of the solute is much greater than that of the solvent then an estimate of *D* can be found from the Stokes-Einstein equation:

$$D = \frac{kT}{6\pi\mu a}$$

where *k* is the Boltzmann constant, μ is viscosity and *a* is the radius assuming an approximately spherical molecule. We can re-write this it terms of the molecular weight:

$$D = \frac{kT}{3\mu}\left(\frac{\rho}{6\pi^2 M}\right)^{\frac{1}{3}}$$

Since ρ is approximately constant for large protein molecules we arrive at the result that $D \propto M^{-1/3}$, whereas for smaller molecules, for example respiratory molecules, $D \propto M^{-1/2}$ is more accurate.

4.1.2 Carrier-mediated transport

Some substances are insoluble in the cell membrane, yet pass through by a process called carrier-mediated transport. Essentially a substance combines with a carrier protein at the outer membrane boundary and by means of a conformational change is released on the inside of the cell. This is still essentially a passive transport process since no energy cost is involved. One of the most important examples of this is the transport of glucose into the cell to provide a source of energy.

Although the precise mechanics of this process are not completely understood, a simple model for this transport is that the glucose substrate binds with an enzyme carrier protein to form a complex, which can change (the conformational change) from an 'internal' protein to an 'external' protein and vice versa. The external protein can reduce to the glucose substrate outside the cell with the enzyme carrier protein in its 'external' state, which then reduces to an 'internal' state. This is shown in the reaction equations below:

$$\begin{array}{ccc} C_e + S_e & \underset{k_-}{\overset{k_+}{\rightleftarrows}} & P_e \\ k \uparrow\downarrow k & & k \uparrow\downarrow k \\ C_i + S_i & \underset{k_-}{\overset{k_+}{\rightleftarrows}} & P_i \end{array}$$

The differential equations for this process are:

$$\frac{dp_i}{dt} = kp_e - kp_i + k_+ s_i c_i - k_- p_i$$
$$\frac{dp_e}{dt} = kp_i - kp_e + k_+ s_e c_e - k_- p_e$$
$$\frac{dc_i}{dt} = kc_e - kc_i + k_- p_i + k_+ s_i c_i$$
$$\frac{dc_e}{dt} = kc_i - kc_e + k_- p_e - k_+ s_e c_e$$

Analysis of this is pretty complicated, but it turns out that in the steady state we can calculate the rate of supply and demand:

$$J = k_- p_i - k_+ s_i c_i = k_+ s_e c_e - k_- p_e$$
$$J = \frac{1}{2} K k C_0 \frac{S_e - S_i}{(S_i + K + K_d)(S_e + K + K_d) - K_d^2}$$

where $K = k_-/k_+$, $K_d = k/k_+$ and $C_o = p_i + p_e + c_i + c_e$. The most important features of this are that at low levels flux transport is proportional to concentration difference, so it looks like a diffusion process, and that there is saturation at high levels of external glucose.

4.1.3 Active transport

The processes considered thus far are all passive processes, where ions move down pressure or concentration gradients. There are many processes, however, that require energy to take place, and are thus

termed active transport. A case of this is where the concentration of the species inside the cell is actively reduced thus pushing along the passive process. For example, glucose is rapidly bound within the cell keeping its concentration low, this phosphorylation of glucose requires hydrolysis of ATP.

Another case is the ion pumps we saw in Lecture 2, there a Na+/K+ pump was used to keep the levels of Na+ high outside the cell and K+ high inside the cell. This requires energy to overcome the gradients and this energy was supplied in the form of ATP. Since the Na+/K+ pump is essentially a reaction, we can write down a reaction equation for it:

$$ATP + 3Na_i^+ + 2K_e^+ \rightarrow ADP + P_i + 3Na_e^+ + 2K_i^+$$

However, this is a rather simplified version of the actual processes. A more precise schematic is shown in Figure 4-1. In its dephosphorylated state, Na+ binding sites are exposed to the intracellular space; when these ions are bound, the carrier protein is phosphorylated by the release of energy involved in ATP converting to ADP. This exposes the Na+ binding sites to the extracellular space, reducing the binding affinity of these sites and releasing the bound Na+. A similar process happens, but from extracellular to intracellular, for K+.

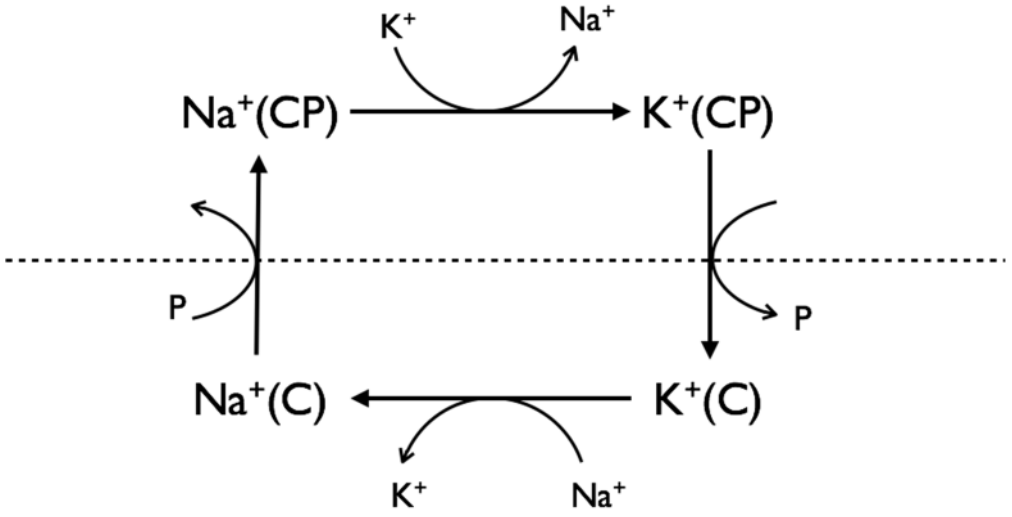

Figure 4-1 Schematic of Na+/K+ pump

This can be converted into a mathematical model by writing down three reaction equations (which we won't do here). Note that this is still a simplified version, where the rate of exchange is one Na+ for one K+ ion, rather than the actual three for two. The corresponding differential equations can be written down (again we won't do this here as it is highly complicated), where the intracellular Na+ and extracellular K+ are supplied at a constant flux *J* (and extracellular K+ and intracellular Na+ are removed). In the steady state, this rate can be expressed as:

$$J = C_o K_1 K_2 \frac{\left[Na_i^+\right]\left[K_e^+\right]}{\left(\left[K_e^+\right]K_2 + \left[K_i^+\right]K_{-2}\right)K_n + \left[Na_i^+\right]K_1 K_k},$$

where the rate constants are functions of the individual rate constants in the detailed model. The important features of this are that is very similar to an enzyme reaction, i.e. it has dynamics similar to a Michaelis-

Menten reaction, being nearly linear at small concentrations of intracellular Na+ and saturating at large concentrations.

4.2 Cell-cell transmission

So far, we have considered the cell largely in isolation: we now need to think about how information is passed between cells. There are two ways in which this information can be passed: electrical and chemical. The point where the transfer takes place is termed a synapse: there are thus both electrical and chemical synapses. In both cases there are special structures at the point where the input cell (the presynaptic cell) communicates with the output cell (the postsynaptic cell).

4.2.1 Electrical synapse

At an electrical synapse, the action potential spreads directly to the postsynaptic cell, since the cell membranes touch and the intracellular spaces are connected through special ion channels called gap junctions.

4.2.2 Chemical synapse

At a chemical synapse, an action potential results in the release of a chemical substance (called a neurotransmitter). This moves through the extracellular space separating the two cells, and alters the membrane potential of the postsynaptic cell. The best understood chemical synapse is the one between a motor neuron and a muscle cell, termed a neuromuscular junction, Figure 4.3. The process proceeds as follows:

- The action potential arrives at the presynaptic cell and causes depolarization.
- Depolarization causes Ca2+ channels to open.
- Ca2+ enters the presynaptic cell.
- Synaptic vesicles fuse with the membrane.
- Neurotransmitter is released into synaptic cleft.
- Neurotransmitter binds to special channels found on the post-synaptic cell surface.
- Channels open allowing Na+ and K+ to cross, permeability of both thus increases.
- Depolarization of post synaptic cell.

Whilst the absolute permeabilities of both Na+ and K+ increase by roughly the same amount, the relative permeability to Na+ increases since it started at a lower absolute level. This causes the membrane potential to rise by some 50-60 mV and hence an action potential is generated, the channels closing after a short time (approximately 1 ms).

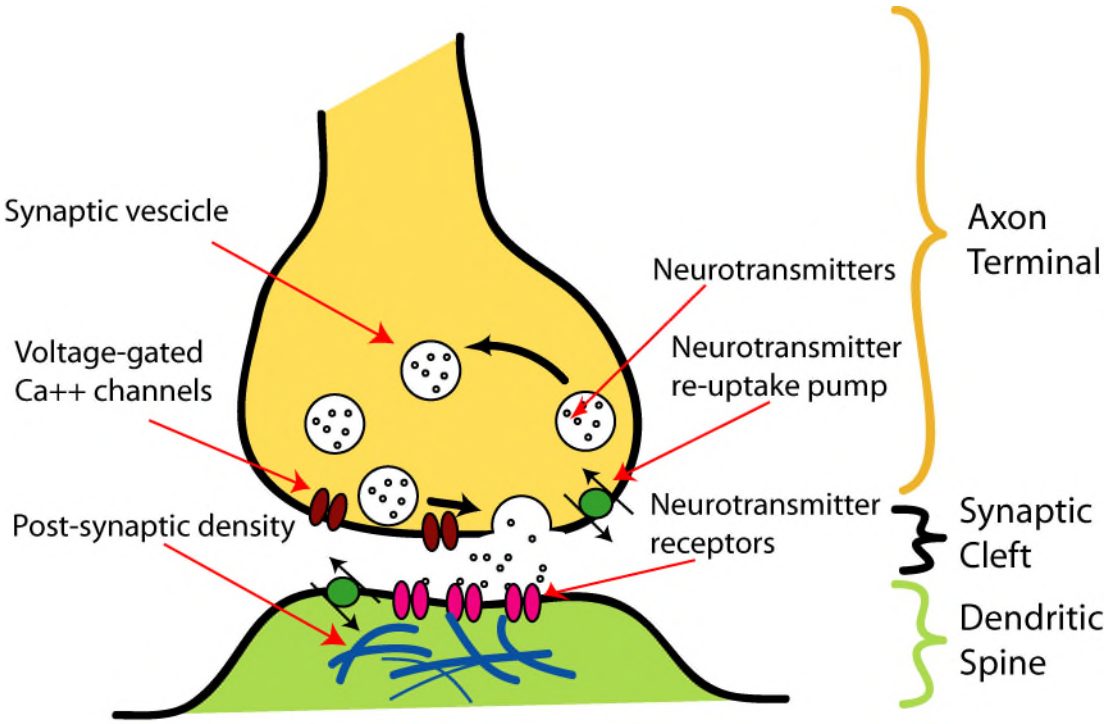

Figure 4-2 Schematic of neurotransmitter release

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The neurotransmitter in this case is called acetylcholine (ACh). This is stored in units of about 10,000 molecules and so is released in packets, or quanta: a single action potential normally results in the release of more than 100 packets. These packets are stored in large numbers of tiny membrane-bound structures known as synaptic vesicles. ACh is released when the vesicles fuse with the muscle cell membrane at special sites called release sites or active zones, which are only found on the membrane surface opposite the postsynaptic cell. The vesicle membranes are continuously recycled, being filled, emptied and re-filled. Many other neurotransmitters exist along with a range of different channels that respond to them.

We have considered the neuromuscular junction in some detail: chemical synapses between two neurons are essentially the same, although there are some important differences. Probably the most important is that a neuron may receive synaptic connections from thousands of different neurons, unlike a muscle cell which receives an input from only one neuron. See Matthews Chapter 9 for a more detailed treatment. We have also not had enough time to examine the processes in muscle cells: see Matthews Chapters 10+11.