General Details Acknowledgements

- The following notes are based on material generously passed to me by Professors Gaffney, Chapman and Fowler and Dr Hinch, which I gratefully acknowledge.

- Please pass any errors or comments to waters@maths.ox.ac.uk

Website

- http://www.maths.ox.ac.uk/courses/course/26323
- Detailed lecture notes by Hinch, Chapman & Fowler may be found at this site.
- Research opportunities: http://www.maths.ox.ac.uk/research

Background Reading

- Mathematical Biology and Ecology Part B course
- J. Keener and J. Sneyd, Mathematical Physiology (Springer-Verlag, 1998), First Edition, or Second edition Vol I: Chs. 2–7. Vol II: Chs. 11, 13, 14. (Springer-Verlag, 2009)
- Subsidiary mathematical texts are:
  - J. D. Murray, Mathematical Biology (Springer-Verlag, 2nd ed., 1993). [Third edition, Vols I and II, (Springer-Verlag, 2003).]
  - L. Glass and M. C. Mackey, From Clocks to Chaos (Princeton University Press, 1988).
  - P. Grindrod, Patterns and Waves (OUP, 1991).
- A general physiology text is:
  - R. M. Berne and M. N. Levy, Principles of Physiology (2nd ed., Mosby, St. Louis, 1996).

Overview

- We will initially focus on systems in cellular physiology and electrophysiology where the spatial variation is not present, or at least, not important. Therefore only the temporal evolution needs to be captured in equations and this typically (but not exclusively) leads to ordinary differential equations.
- We will proceed to consider systems where there is explicit spatial variation, leading to partial differential equation that additionally incorporate spatial effects; our focus will be calcium dynamics and electrophysiology.
- We will then consider the role of delayed feedback in biological dynamical systems, such as respiration and the hematopoietic system (i.e. the production of blood cells), exploring the counter-intuitive dynamics that emerges.

1 Transmembrane Ion Transport

1.1 Membrane transport

The cell membrane is a *phospholipid bilayer* separating the cell interior (the *cytoplasm*) and from the extracellular environment. The membrane contains numerous proteins, and is approximately 7.5nm thick. The most important property of the cell membrane is its selective permeability: it allows the passage of some molecules but restricts the passage of others, thereby regulating the passage of materials into and out of the cell. Many substances penetrate the cellular membrane at rates reflected by their diffusive behaviour in a pure phospholipid bilayer. However, certain molecules and ions such as glucose, amino acids and Na^+ pass through cell membranes much more rapidly, indicating that the membrane proteins selectively facilitate transport.

The membrane contains water-filled pores with diameters of about 0.8nm, and protein-lined pores, called *channels* or *gates*, which allow the passage of specific molecules. Both the intracellular and extracellular environments comprise (among other things) a dilute aqueous solution of dissolved salts, mainly NaCl and KCl, which dissociate into Na^+, K^+ and Cl^- ions. The cell membrane acts as a barrier to the free flow of these ions and to the flow of water.

The many mechanisms for facilitating transport across the cellular membrane can be divided up into active and passive processes. An active process is one which requires the expenditure of energy, while a passive process is one which results solely from the random motion of molecules, for example, diffusion.

Passive mechanisms by which molecules are transported across the cell membrane include osmosis, diffusion, and carrier-mediated mechanisms. *Osmosis*, *i.e.* the diffusion of water down its concentration gradient, is the most important mechanism by which water is transported across the cell membrane. Simple *diffusion* accounts for the passage of small molecules (*e.g.* Cl^-) through pores and or lipid-soluble molecules (such as oxygen and carbon dioxide) through the lipid bilayer. *Carrier-mediated diffusion* refers to a process by which a molecule "hitches a lift" by binding to a carrier molecule which is lipid soluble and can move readily through the membrane. *Carrier-mediated transport"* occurs when a protein which sits in the membrane has an active site which may be exposed either on the exterior or interior side of the membrane depending on the conformational state of the protein. A substrate (*e.g.* glucose and amino acids) may bind to the protein in one conformation: the protein then undergoes a conformational change, and the substrate unbinds on the other side of the membrane.

The concentration differences that exist between the intracellular and extracellular environments are set up and maintained by active processes. One of the most important of these is the Na^+-K^+ pump, which uses the energy stored in ATP molecules to pump Na^+ out of the cell and

	extra	intra
Na^+	437	50
K^+	20	397

Table 1: Typical intracellular and extracellular ionic concentrations for the squid giant axon. Units are mM=millimolar= 10^{-3}M. 1M= 1 molar = 1 mole litre^{-1}.

K^+ in. There are also a variety of exchange pumps which use the concentration gradient of one ion to pump another ion against its concentration gradient, such as the Na^+-Ca^{2+} exchanger, which removes Ca^{2+} from the cell at the expense of allowing Na^+ in. Differences in interior and exterior ionic concentrations create a potential difference across the cell which also drives an ionic current down ion-specific membrane channels. Typical intracellular and extracellular ionic concentrations are shown in Table 1.

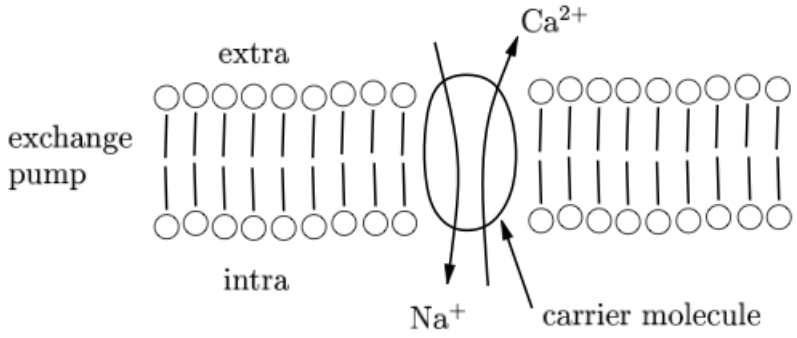


Figure 1: Representation of an exchange pump

1.1.1 Passive transport: Carrier Mediated Transport

Carrier-mediated transport occurs when a protein which sits in the membrane has an active site which may be exposed either on the exterior or interior side of the membrane depending on the conformational state of the protein. A substrate may bind to the protein in one conformation, the protein undergoes a conformational change, and the substrate unbinds on the other side of the membrane.

We describe here a simple model for carrier mediated transport. We suppose that the carrier has two conformational states, and that in the first state, labelled C_i, the substrate binding site is exposed on the cell interior, while in the second state, labelled C_e, the substrate binding site is exposed on the cell exterior (see Figure 2). We suppose that substrate molecules outside the cell (concentration S_e) can bind to C_e to produce a complex P_e, and that the substrate molecules inside the cell (concentration S_i) can bind to C_i to produce a complex P_i. Furthermore, we assume that P_i can conformally change into P_e and vice versa, and at the same rate as the conformational changes of C_i and C_e (so that the binding of the substrate does not affect the conformational changes of the protein). Thus the reaction scheme is

$$S_i + C_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_i \underset{k}{\overset{k}{\rightleftharpoons}} P_e \underset{k_+}{\overset{k_-}{\rightleftharpoons}} S_e + C_e \tag{1}$$

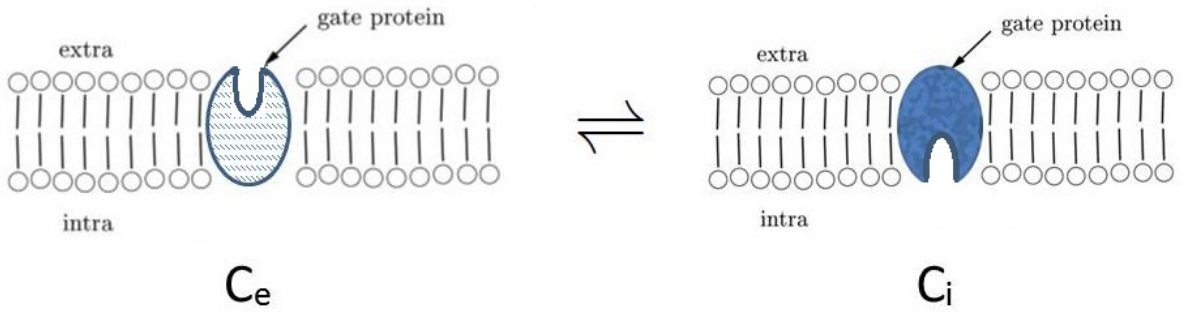


Figure 2: A schematic of the phospholipid membrane double layer, with a gating protein in one of two configurations, C_e and C_i, spanning the membrane, as part of a carrier mediated transport system.

$$C_i \underset{k}{\overset{k}{\rightleftharpoons}} C_e, \tag{2}$$

where we have assumed that the binding affinity of S_i to C_i is the same as that of S_e to C_e, and that the two conformational states C_i and C_e are equally likely. To avoid the system simply settling down to a steady state with zero flux, we assume that the substrate is supplied at a rate J to the exterior and taken away at the same rate from the interior, and we wish to determine this flux of substrate through the membrane as a function of the interior and exterior concentrations. This may be achieved using mass action kinetics (see Mathematical Biology and Ecology), and the computation is carried out on **Problem sheet 1, question 1**.

1.1.2 Active transport: the sodium-potassium pump

The carrier-mediated transport described above moves molecules down chemical gradients. Any process that works against chemical or electrical gradients requires the expenditure of energy, and is known as an active transport mechanism. We now give an example of such a process.

First we digress and introduce a little background terminology. *Metabolism* is the process of extracting useful energy from chemical bonds. The common carrier of energy in the cell is the chemical *adenosine triphosphate* (ATP). ATP is formed by the addition of an inorganic phosphate group (HPO_4^{2-}) to *adenosine diphosphate* (ADP). The process of adding a phosphate group to a molecule is called *phosphorylation*. Since the three phosphate groups on ATP carry negative charges, considerable energy is required to overcome the natural repulsion of like-charged phosphates as additional groups are added. Thus, the hydrolysis (the cleavage of a bond by water) of ATP to ADP releases large amounts of energy.

The Na^+-K^+ pump pumps sodium ions out the cell against a steep electrochemical gradient, while pumping potassium ions in. This pump alone consumes almost a third of the energy re-

quirement of a typical animal cell. The pump uses the energy stored in ATP which is released when it is dephosphorylated into ADP, through the overall reaction scheme

$$\mathrm{ATP} + 3\mathrm{Na}_i^+ + 2K_e^+ \rightarrow ADP + P_i + 3\mathrm{Na}_e^+ + 2K_i^+, \tag{3}$$

where the subscripts i and e denote the intracellular and extracellular quantities respectively. The individual components of the reaction are thought to be as follows. When the carrier protein (Na^+-K^+ ATPase) is in its dephosphorylated state, three sodium binding sites are exposed to the cell's interior. When all three binding sites are filled, the carrier protein is phosphorylated by the hydrolysis of ATP into ADP. This phosphorylation induces a conformational change, so that the sodium binding sites are exposed to the cell exterior, and their binding affinity is reduced, causing the release of sodium ions. At the same time, two potassium sites are exposed to the cells exterior. When potassium ions have bound to these two sites the carrier protein is dephosphorylated, inducing the reverse change in conformation, exposing the potassium binding sites to the cell interior and reducing the binding affinity so that the potassium is released.

If we simplify this process slightly, assuming that there is a single binding site for sodium and potassium, leading to a one-to-one exchanger rather than the three-for-two which actually happens, then the detailed reaction scheme is

$$\mathrm{Na}^+ + \mathrm{C} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{NaC} \quad \mathrm{ATP} \overset{k_p}{\rightarrow} \mathrm{ADP} \quad \mathrm{NaCP} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{Na}_e^+ + \mathrm{CP}, \tag{4}$$

$$\mathrm{CP} + K_e^+ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{KCP} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathrm{P} + \mathrm{KC}, \tag{5}$$

$$\mathrm{KC} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{K}_i^+ + \mathrm{C}, \tag{6}$$

where the carrier protein is represented by C in its unphosphorylated, unbound state, CP in its phosphorylated unbound state, NaC when bound to sodium and unphosphorylated, NaCP when bound to sodium and phosphorylated, KC when bound to potassium and unphosphorylated, and KCP when bound to potassium and phosphorylated. Using mass action kinetics, assuming that intracellular potassium and extracellular sodium are removed at a constant rate J, leads to the steady-state flow of ions through the pump

$$J = \frac{J_0[\mathrm{Na}_\mathrm{i}^+][\mathrm{K}_\mathrm{e}^+]}{[\mathrm{Na}_\mathrm{i}^+] + \alpha[\mathrm{K}_\mathrm{i}^+] + \beta[\mathrm{K}_\mathrm{e}^+]}, \tag{7}$$

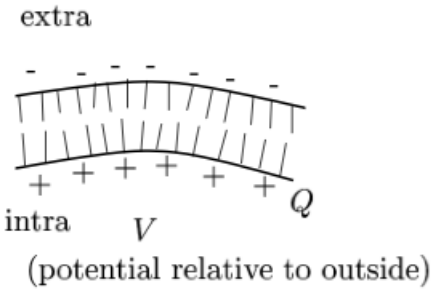


Figure 3: Schematic diagram of the build up of charge on the cell membrane

where

$$J_0 = \frac{C_0 k_3 k_4 k_5}{k_{-3}k_{-3}[P] + k_{-3}k_5 + k_4 k_5}, \tag{8}$$

$$\alpha = \frac{k_{-1}k_p + k_2 k_{-1} + k_2 k_p)k_{-3}k_{-4}k_{-5}}{k_1 k_2 k_p(k_{-3}k_{-3}[P] + k_{-3}k_5 + k_4 k_5)}, \quad \beta = \frac{k_{-1}k_p + k_2 k_{-1} + k_2 k_p)k_3 k_4 k_5}{k_1 k_2 k_p(k_{-3}k_{-3}[P] + k_{-3}k_5 + k_4 k_5)}, \tag{9}$$

where C_0 is the total concentration of carrier molecule, and $[Na_e^+]$ denotes the concentration of sodium ions in the extracellular medium, etc. Note that for both carrier-mediated transport and active transport (7) pump fluxes are linear in concentrations at small concentrations, but saturate to a maximum value at large concentrations (a feature in common with enzyme catalysed reactions).

1.1.3 The membrane potential

Different ion concentrations in the interior and exterior of a cell induce a potential difference across the membrane, which is therefore influenced by the active and passive transport of ions into and out of the cell. The membrane potential is fundamental to the study of electrophysiology in diverse settings such as nerve signal propagation and the coordinated contraction of the heart. To explore these applications in more detail we need to consider the electrical properties of the cell membrane.

Suppose we have two reservoirs containing different concentrations of a positively charged ion X^+. We suppose that both reservoirs are electrically neutral to begin with, so that there is an equal concentration of a negatively charged ion Y^-. Now suppose that the reservoirs are separated by a semi-permeable membrane which is permeable to X^+ but not to Y^-. Then the difference in concentration of X^+ on each side will lead to the flow of X^+ across the membrane. However, because Y^- cannot diffuse through the membrane this will lead to a build up of charge on one side. This charge imbalance sets up an electric field, which produces a force on the ions opposing further diffusion of X^+. it is important to realise that the actual amount of X^+ which diffuses through the membrane is small, and the excess charge all accumulates near the interface, so that to a good approximation the solutions on either side remain electrically neutral. The potential difference at

which equilibrium is established and diffusion and electric-field-generated fluxes balance is known as the *Nernst potential*. We can derive an expression for it as follows.

If c denotes the concentration of an ion S then the flux of ions due to diffusion is $\mathbf{J} = -D\nabla c$, where D is the diffusion coefficient. To this we must add the flux due to the fact that the ion carries a charge and is in the presence of an electric field, which is given by

$$\mathbf{J} = -\frac{uzc}{|z|}\nabla\phi, \tag{10}$$

where u is the mobility of the ion (defined as the velocity under a constant unit electric field), z is the valence of the ion (so that $z/|z|$ is either +1 or -1 and gives the sign of the force on the ion; positive ions move down potential gradients, negative ions move up potential gradients), and ϕ is the electric potential, so that $-\nabla\phi$ is the electric field. Thus the total flux is given by

$$\mathbf{J} = -D\nabla c - \frac{uzc}{|z|}\nabla\phi, \tag{11}$$

which is the *Nernst-Planck* equation. Now, there is a relationship (determined by Einstein) between the ionic mobility and the diffusion coefficient, which is

$$D = \frac{uRT}{|z|F}, \tag{12}$$

where R is the universal gas constant, T is the temperature and F is Faraday's constant. Furthermore, since the membrane is thin we can replace the Nernst-Plank equation (11) by the one-dimensional version

$$J = -D\left(\frac{dc}{dx} + \frac{zFc}{RT}\frac{d\phi}{dx}\right), \tag{13}$$

where x is a coordinate normal to the membrane. Now, at equilibrium the flux J is zero, giving

$$\frac{dc}{dx} + \frac{zFc}{RT}\frac{d\phi}{dx} = 0, \tag{14}$$

or equivalently

$$\frac{1}{c}\frac{dc}{dx} + \frac{zF}{RT}\frac{d\phi}{dx} = 0. \tag{15}$$

Assuming that the interior of the membrane is at $z = 0$ while the exterior is at $x = L$, we can integrate from 0 to L to give

$$[\log c]_0^L + \frac{zF}{RT}[\phi]_0^L = 0, \tag{16}$$

so that

$$\phi_i - \phi_e = \frac{zF}{RT}\log\left(\frac{c_e}{c_i}\right). \tag{17}$$

We follow the standard convention of defining the potential difference across the cell membrane as $V = \phi_i - \phi_e$, then the Nernst potential for S is

$$V_S = \frac{zF}{RT} \log \frac{c_e}{c_i} = \frac{zF}{RT} \log \frac{[S_e]}{[S_i]}. \tag{18}$$

Using the values of the intracellular and extracellular concentrations given in Table 1, typical Nernst potentials for the squid giant axon for potassium and sodium are $V_{\mathrm{K}} = -77\mathrm{mV}$ (millivolt) and $V_{\mathrm{Na}} = 56\mathrm{mV}$. Note that when more than one ion is present, and they have different Nernst potentials, the flux of each individual ion will not be zero even when there is no net current across the membrane. For example, when $-77\mathrm{mV} < V < 56\mathrm{mV}$there will be a flux of K^+ out of the cell and Na^+ into the cell through ion specific channels. This flux is balanced by the action of the Na^+-K^+ pump.

1.1.4 Ionic currents

The flow of ions across the cell membrane due to concentration differences leads to a build up of charge near the cell membrane and a potential difference across the cell membrane. Thus the cello membrane is effectively acting as a capacitor. The voltage (potential difference) across any capacitor is related to the charge stored Q by

$$V = \frac{Q}{C}, \tag{19}$$

where C is the capacitance.

Capacitance A simple example of capacitor is two conducting plates, separated by an insulator, for example, an air gap. Connecting a battery to the plates, as illustrated, using wires of low resistance leads to charge flowing onto/off the plates. It will equilibrate extremely quickly. Suppose the charge on the plates is given by $+Q_{eqm}$ and $-Q_{eqm}$ respectively. The capacitance of the plates, C, is defined to be

$$C = \frac{Q_{eqm}}{V} > 0,$$

where C is a constant, independent of V. Thus the higher the capacitance, the better the plates are at storing charge, for a given potential. The unit of C is the Farad, with 1 Farad equal to 1 Colomb per Volt.

If I is the ionic current out of the cell (the rate of flow of positive charges outwards) then the stored charge changes according to

$$I = -\frac{dQ}{dt}. \tag{20}$$

Thus, assuming the capacitance is constant,

$$C\frac{dV}{dt} + I = 0. \tag{21}$$

This equation is the basis for much theoretical electrophysiology. The difference between the various models arises in the expression used for the ionic current I.

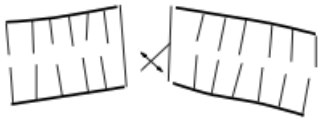


Figure 4: Schematic diagram of channel gating

The simplest model to use is to assume a linear dependence of I on V (as in Ohms law). For a single ion S, with Nernst potential V_S, this gives an ionic current

$$I_S = g_S(V - V_S), \tag{22}$$

where the constant g_S is the ion-specific membrane conductance, since the current must be zero when $V = V_S$. If more than one ion is present the currents from different ions are simply added together to produce the total ionic current I.

1.1.5 Gating

It is found experimentally that g_S is not constant but depends on both V and time t. One proposed explanation for this is that the channels are not always open, but may be open or closed, and that the transition rates between open and closed states depends on the potential difference V. The membrane conductance may then be written as g_S, where g_S is the constant conductance that would result if all the channels were open, and n is the proportion of open channels.

For a generic ion, let n be the proportion of *open* ion channels. Denoting the open channels by O and the closed channels by C, the reaction scheme is simply

$$\mathrm{C} \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} \mathrm{O} \tag{23}$$

where $\alpha(V), \beta(V)$ represent voltage dependent rates of switching between the closed and open states. Using a law of mass action we obtain

$$\frac{dn}{dt} = \alpha(V)(1 - n) - \beta(V)n, \tag{24}$$

or equivalently

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n, \tag{25}$$

where $n_\infty(V) = \alpha/(\alpha + \beta)$ is the equilibrium value of n and $\tau_n(V) = 1/(\alpha + \beta)$ is the timescale for approach to this equilibrium. Both n_∞ and τ_n can be determined experimentally.

1.1.6 Multiple gates

The simple model presented in §1.1.5 can be generalised to channels which contain multiple identical subunits, each of which can be in either the open or closed state.

Suppose we start by assuming that the channel consists of two "gates", which may both exist in one of two states, open or closed. The ion channel is open only if *both* "gates" are open; the ion channel is closed if any one gate within the ion channel is closed. We denote $S_i \in \{0, 1, 2\}$ as the proportion of channels with exactly i gates open. We have

$$S_0 + S_1 + S_2 = 1 \tag{26}$$

and the reaction scheme

$$S_0 \underset{\beta(V)}{\overset{2\alpha(V)}{\rightleftharpoons}} S_1 \underset{2\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} S_2. \tag{27}$$

The 2s arise because there are two possible states with one gate open and one gate closed. Since each gate is identical we have lumped these two states into one variable S_1. Using mass action kinetics gives

$$\frac{dS_0}{dt} = \beta(V)(1 - S_0 - S_2) - 2\alpha(V)S_0 \tag{28}$$

$$\frac{dS_2}{dt} = \alpha(V)(1 - S_0 - S_2) - 2\beta(V)S_2 \tag{29}$$

where, in general, V is a function of time (and possibly space too). We could also write down an equation for S_1, but this equation is superfluous since S_1 can be determined from (26).

Let n denote the *proportion of open gates;* thus

$$\frac{dn}{dt} = \alpha(V)(1 - n) - \beta(V)n. \tag{30}$$

Simple substitution shows that (26) , (28) and (29) are satisfied by

$$S_0 = (1 - n)^2, \quad S_1 = 2n(1 - n), \quad S_2 = n^2. \tag{31}$$

In fact, it is possible to derive a stronger result. Suppose

$$S_0 = (1 - n)^2 + y_0, \quad S_2 = n^2 + y_2, \tag{32}$$

so that $S_1 = 2n(1 - n) - y_0 - y_2$. It then follows that

$$\frac{dy_0}{dt} = -2\alpha y_0 - \beta(y_0 + y_2), \quad \frac{dy_2}{dt} = -\alpha(y_0 + y_2) - 2\beta y_2. \tag{33}$$

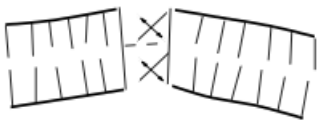


Figure 5: Schematic diagram of two identical gate units

This linear system has eigenvalues $-(\alpha+\beta)$, $-2(\alpha+\beta)$, and so y_0, y_2 decay exponentially to zero. Thus, regardless of the initial condition, the solution will still approach exponentially that given by (30) and (31) (*i.e.* (30) and (31) defines a stable invariant manifold of the full system (26), (28) and (29).

The analysis of a two-gated channel generalised easily to channels containing more gates. In the case of k identical gates the fraction of open channels is n^k, where n again satisfies (30). We will find that a model with 4 gates agree with empirical observations of K^+ channels, and will be used below.

1.1.7 Non-identical gates

Often channels are controlled by more than one protein, with each protein controlling a set of identical gates, but with the gates of each protein different and independent. Consider, for example, the case of a channel with two types of gate, m and h say, each of which may be open or closed. To illustrate we will assume that the channel has two m subunits and one h subunit. With S_{ij} the proportion of channels with $i \in \{0,1,2\}$ of the m-gates open and $j \in \{0,1\}$ of the h-gates open, the reaction scheme is

$$\begin{array}{ccccc} S_{00} & \underset{\beta}{\overset{2\alpha}{\rightleftharpoons}} & S_{10} & \underset{2\beta}{\overset{\alpha}{\rightleftharpoons}} & S_{20} \\ \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\ S_{01} & \underset{\beta}{\overset{2\alpha}{\rightleftharpoons}} & S_{11} & \underset{2\beta}{\overset{\alpha}{\rightleftharpoons}} & S_{21} \end{array} .$$

Simple substitution shows that the corresponding law of mass action equations are satisfied by

$$S_{00} = (1-m)^2(1-h), \quad S_{10} = 2m(1-m)(1-h), \quad S_{20} = m^2(1-h), \tag{34}$$

$$S_{01} = (1-m)^2 h, \quad S_{11} = 2m(1-m)h, \quad S_{21} = m^2 h, \tag{35}$$

so that the proportion of open channels is m^2h, provided

$$dm/dt = \alpha(V)(1-m) - \beta(V)m \tag{36}$$

$$dh/dt = \gamma(V)(1-h) - \delta(V)h. \tag{37}$$

As before, such solutions form a stable invariant manifold.

We now have the framework in place to enable us to start to model nerve signal propagation.

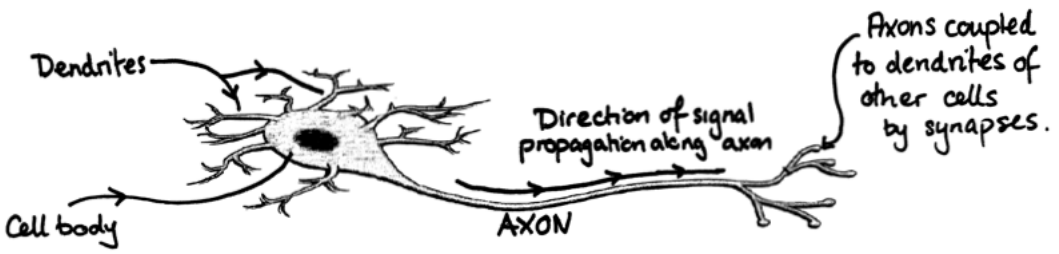


Figure 6: A schematic of an unmyelinated neuron, i.e. nerve cell.

1.2 Hodgkin-Huxley model

The nervous system is a communication system formed by nerve cells called neurons. Information is propagated along long cylindrical segments called *axons* by electrochemical signals.

An important property of neurons is *excitability*. If a small current is applied to the cell for a short time, then the membrane potential changes slightly, but returns directly to its equilibrium potential (the *resting* potential) once the applied current is removed. However, is a sufficiently large current is applied for a short time the membrane potential undergoes a large excursion (called an *action potential*) before returning to its resting value. It is by the propagation of such action potentials along the axons of neurons that signals are transmitted.

The most important landmark in the study of the generation and propagation of signals is the work by Hodgkin and Huxley, who developed the first quantitative model of the propagation of an electrical signal along a squid giant axon (where "giant" here refers to the size of the axon, not the squid!). This work is remarkable, not only due to its influence on electophysiology, but also for its stimulation of a new field in applied mathematics, the study of excitable systems, that has resulted in a vast amount of research.

In the next Chapter we will consider the propagation of action potentials along the axon. In building up to that model we first consider the Hodgkin-Huxley model of the excitability of an axon without the extra complication of spatial variation in the membrane potential. Such a system can be realised experimentally by inserting a thin electrode along the centre of the axon. The interior of the axon will quickly equilibrate, and there will be no spatial variation in the membrane potential, or any current, along the inside of the axon. This is known as the **space clamp technique**.

If we suppose we are applying an external inward current I_{ext} to the cell (for example due to the experimental injection of electrolytes into the axon), then the total outward current is $I_i - I_{\text{ext}}$, where I_i is the outward ionic current as before. Then equation (21) gives

$$C\frac{dV}{dt} + I_i - I_{\text{ext}} = 0, \tag{38}$$

where C is the membrane capacitance. In the squid giant axon, as in many neurons, the most important ionic currents are due to the movement of sodium and potassium ions.

Experimentally it is found that the potassium conductance may be modelled by a gated channel

of the form described in §1.1.5 with an exponent of 4, so that the conductance is $g_K n^4$ where

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n. \tag{39}$$

While this seems to imply that the potassium channel is controlled by a protein with four identical gates, the exponent is actually determined as a reasonable fit to measured ionic currents, and not from any detailed physiological knowledge of the potassium channel itself. The equilibrium value n_∞ is found to be an increasing function of V. Thus at elevated potentials, n is increased, thereby turning on, or *activating*, the potassium current. The Nernst potential for potassium is below the resting potential, so that the potassium current is an outward current at potentials greater than the resting potential. The function $n(t)$ is called the potassium activation.

For the sodium conductance, experimental data suggests that there are two processes at work, one which turns on the sodium current and one which turns it off. The model of Hodgkin-Huxley assumes a channel controlled by proteins, with a conductance of the form $g_{\mathrm{Na}} m^3 h$ where

$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m, \quad \tau_h(V)\frac{dh}{dt} = h_\infty(V) - h. \tag{40}$$

Again, while this seems to imply a channel with three m gates and one h gate, the exponents are determined as a reasonable fit to measured ionic currents, and not from a detailed knowledge of the sodium channel itself. At the resting potential, m_∞ is small and h_∞ is close to one. For elevated potentials h_∞ decreases and m_∞ increases. Thus m is called the *sodium activation*, and h is called the *sodium inactivation*. The Nernst potential for sodium is above the resting potential, so that the sodium current is an inward current at potentials greater than rest.

In (38), I_i is the ionic current into the exterior, which is made up from sodium, potassium and leakage contributions. The leakage current across the membrane is the current which is not due to ion channels, and thus is not ideally named. It is linear but is not zero at $V = 0$ (due to ion pumps for example). Thus

$$I_L = g_L(V - V_L), \tag{41}$$

where g_L and V_L are constants. The Hodgkin-Huxley model is

$$I_i = I_{Na} + I_K + I_L = g_{\mathrm{Na}} m^3 h(V - V_{\mathrm{Na}}) + g_K n^4 (V - V_K) + g_L(V - V_L), \tag{42}$$

Aside V_{Na}, V_K, V_L will vary with temperature as this will alter the value of the transmembrane potential where the ion currents are zero (look up the *Nernst equation* and the *Nernst potential*); below we only consider a constant temperature. Understanding the effect of varying temperature is beyond the scope of these lectures.

Summary In this section, we have the framework for modelling the temporal variations of a space clamped axon plasma membrane potential, which thus allows us to model nerve signal propagation.

1.2.1 The Huxley Hodgkin model for a space clamped axon

The Hodgkin Huxley equations for an axon are given by

$$0 = C\frac{dV}{dt} + g_{Na}m^3h(V - V_{Na}) + g_K n^4(V - V_K) + g_L(V - V_L) - I_{ext} \quad (43)$$

$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m, \quad (44)$$

$$\tau_h(V)\frac{dh}{dt} = h_\infty(V) - h, \quad (45)$$

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n. \quad (46)$$

Note that equation (43) can be rewritten as

$$C\frac{dV}{dt} = I_{\text{ext}} - (g_{\text{Na}}m^3h + g_{\text{K}}n^4 + g_L)(V - V_{\text{eqm}}) \quad (47)$$

where

$$V_{\text{eqm}} = \frac{g_{\text{Na}}m^3hV_{\text{Na}} + g_{\text{K}}n^4V_{\text{N}} + g_LV_{\text{L}}}{g_{\text{Na}}m^3h + g_{\text{K}}n^4 + g_L} \quad (48)$$

is the *resting potential* or equilibrium potential. It is convenient to rewrite the Hodgkin Huxley equations in terms of the deviation of the cell plasma membrane potential from the resting potential $\nu = V - V_{\text{eqm}}$, where the resting potential $V_{\text{eqm}} = -70\text{mV}$, in the following form

$$0 = C\frac{d\nu}{dt} + g_{Na}m^3h(\nu - \nu_{Na}) + g_K n^4(\nu - \nu_K) + g_L(\nu - \nu_L) - I_{ext} \quad (49)$$

$$\tau_m(\nu)\frac{dm}{dt} = m_\infty(\nu) - m \quad (50)$$

$$\tau_h(\nu)\frac{dh}{dt} = h_\infty(\nu) - h \quad (51)$$

$$\tau_n(\nu)\frac{dn}{dt} = n_\infty(\nu) - n \quad (52)$$

where

$$\nu_K = V_K - V_{eq} = -12\text{mV}, \quad \nu_{Na} = V_{Na} - V_{eq} = 115\text{mV}, \quad \nu_L = V_L - V_{eq} = 10.6\text{mV},$$

$$g_{Na} = 0.12\Omega^{-1}\text{cm}^{-3}, \quad g_K = 0.036\Omega^{-1}\text{cm}^{-3}, \quad g_L = 3 \times 10^{-4}\Omega^{-1}\text{cm}^{-3}, \quad C = 1\mu\text{Farad cm}^{-2}$$

with Ω denoting the Ohm, that is the unit of resistance. Note that the system is at equilibrium when $\nu = 0$.

We also have introduced

$$m_\infty(\nu) = \frac{\alpha_m(\nu)}{\alpha_m(\nu) + \beta_m(\nu)} \qquad \tau_m(\nu) = \frac{1}{\alpha_m(\nu) + \beta_m(\nu)} \quad (53)$$

where

$$\alpha_m(\nu) = \alpha_m(V), \qquad \beta_m(\nu) = \beta_m(V), \tag{54}$$

and similarly for $h_\infty(\nu), n_\infty(\nu), \tau_h(\nu), \tau_n(\nu)$.

Given the properties of the gating functions

$$m_\infty(\nu),\ h_\infty(\nu), n_\infty(\nu), \tau_m(\nu), \tau_h(\nu), \tau_n(\nu),$$

we can see understand the qualitative form of a nerve pulse in the Huxley Hodgkin model for a space clamped axon.

The membrane is *excitable*. The resting potential, which now corresponds to $\nu = 0$ is stable for a sufficiently small perturbation to the system. A finite perturbation causes an excursion in the membrane potential away from the resting potential called an *action potential*. Suppose we consider a large increase of ν away from the equilibrium (resting) potential of, say, 10mV. From figure 7 we see that τ_m is small. Hence, from equation (50) we see that m can be approximated by its pseudo-steady state on the timescale of a nerve pulse and we can take

$$m \sim m_\infty(\nu). \tag{55}$$

Thus m increases as ν increases, and the conductivity of the membrane with respect to Na^+ increases. Now since $\nu - \nu_{\text{Na}} < 0$, and positive ions flow move down potential gradients, then sodium ions flow into the cell and the membrane potential ν increases. Hence m continues to increase, and we initially have a positive feedback loop. However, as ν increases, h_∞ drops and h approaches $h_\infty(\nu)$ turning off the Na^+ current, though on a slower timescale as τ_h is larger. As ν increases, n_∞ increases and the membrane conductivity with respect to K^+ increases, though again on a slower timescale. Now, since $\nu - \nu_{\text{K}} > 0$ potassium ions flow out of the cell and we have that ν decreases. Now as ν drops, n_∞ becomes smaller. The Na^+ current remains essentially off as $m \approx m_\infty(\nu)$, small, for small ν. The K^+ current is also turned off as $n_\infty(\nu)$ reduces, but on a slow timescale. Hence the potential, ν drops below zero before resetting to the equilibrium value $\nu = 0$.

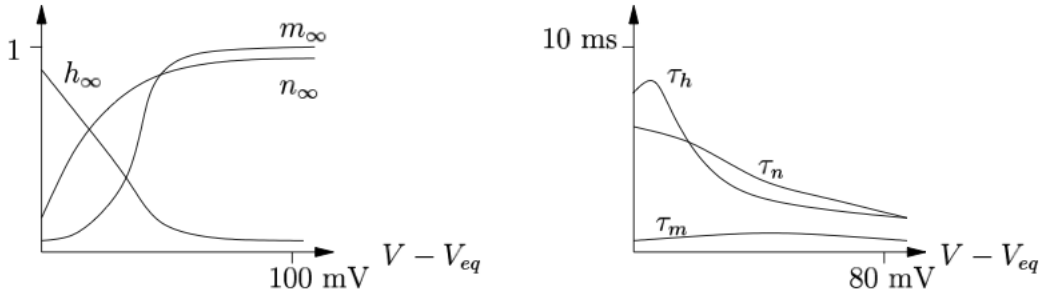


Figure 7: Graphs of the gating functions $m_\infty(\nu),\ h_\infty(\nu), n_\infty(\nu), \tau_m(\nu), \tau_h(\nu), \tau_n(\nu)$.

1.2.2 Quantitative behaviour and model simplification

The observation that $\tau_m(\nu)$ is smaller than all other timescales entails that m can be approximated by its pseudo-steady state on the timescale of a nerve pulse and we can take

$$m \sim m_\infty(\nu), \tag{56}$$

and this can be confirmed numerically.
We can also plot the variables $n(t), h(t)$ during the action potential; a core approximation one can deduce from this figure is that

$$n + h \sim 0.85 \tag{57}$$

is a reasonable approximation for the duration of the action potential.

Why this occurs can also be seen as follows. Add the equations for $n,\ h$ to obtain

$$\tau_n(\nu)\left[\frac{d}{dt}(n+h)\right] + [\tau_h(\nu) - \tau_n(\nu)]\frac{dh}{dt} = (n_\infty(\nu) + h_\infty(\nu)) - (n+h),$$

Note also that

$$n_\infty(\nu) + h_\infty(\nu) \sim \text{const} = 0.85$$

for all ν. We thus have the (a posteriori) observation that $\tau_n,\ (\tau_h - \tau_n)$ are sufficiently small that the term

$$(\tau_h(\nu) - \tau_n(\nu))\frac{dh}{dt}$$

does not sufficiently influence the dynamics to prevent $n + h$ being reasonably approximated by its asymptotic V dependence, $n_\infty + h_\infty$.

Given these approximations the Huxley Hodgkin equations reduce to the two dimensional system

$$C\frac{d\nu}{dt} = -g_{Na}m_\infty^3(\nu)(0.85 - n)(\nu - \nu_{Na}) - g_K n^4(\nu - \nu_K) - g_L(\nu - \nu_L) + I_{ext} \tag{58}$$

$$\frac{dn}{dt} = \alpha_n(\nu)(1-n) - \beta_n(\nu)n, \tag{59}$$

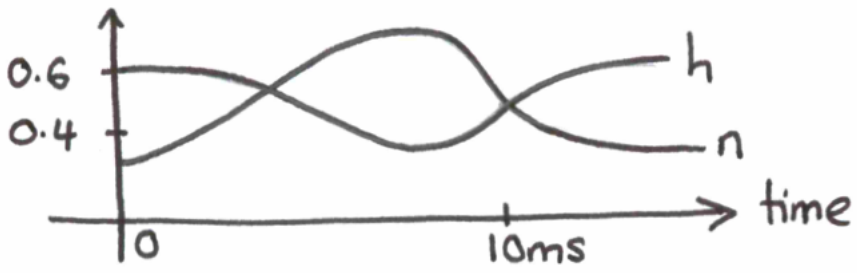


Figure 8: The gating variables during a Huxley Hodgkin equations' predicted action potential, via numerical solution.

with the experimentally determined parameter values

$$g_{Na} = 0.120\Omega^{-1}\text{cm}^{-3}, \quad g_K = 0.036\Omega^{-1}\text{cm}^{-3}, \quad g_L = 3\times 10^{-4}\Omega^{-1}\text{cm}^{-3},$$

$$\nu_{Na} = 115\text{mV}, \quad \nu_K = -12\text{mV}, \quad \nu_{Na} = 10.6\text{mV}, \quad C = 1\mu\text{Farad/cm}^2,$$

where "Ω" is one Ohm, the unit of resistance.

We now non-dimensionalise with $v = \nu/\nu_{Na}$ and $\tau = t/[5\text{ms}]$, as $\tau_n(\nu) \sim O(5\text{ms})$, and we have

$$\epsilon\frac{dv}{d\tau} = I^*_{ext} - g(v,n) \stackrel{def}{=} I^*_{ext} - \left[m^3_\infty(v)(0.85-n)(v-1) + \gamma_K n^4(v+v_K) + \gamma_L(v-v_L)\right] \quad (60)$$

$$\frac{dn}{d\tau} = k(v,n) \stackrel{def}{=} \frac{1}{\tau^*_n(v)}\left[n_\infty(v) - n\right], \quad (61)$$

with

$$\epsilon = \frac{C}{g_{Na}[5\text{ms}]} = 2\times 10^{-3}, \quad \gamma_K = \frac{g_K}{g_{Na}} \sim 0.3, \quad \gamma_L = \frac{g_L}{g_{Na}} \sim 3\times 10^{-3},$$

$$I^*_{ext} = \frac{I_{ext}}{g_{Na}\nu_{Na}}, \quad v_K = -\frac{\nu_K}{\nu_{Na}} \sim 0.1, \quad v_L = \frac{\nu_L}{\nu_{Na}} \sim 0.1, \quad \tau^*_n(v) = \tau_n(\nu)/[5\text{ms}] \sim O(1).$$

We can now sketch the nullclines, and noting the different timescales of the membrane potential response to the gating variable response (as $\epsilon \ll 1$) we can consider the phase plane trajectories in terms of fast and slow dynamics.

Plotting nullclines We set I^*_{ext} here.

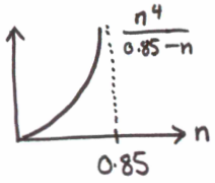
The nullclines are curves on which $dn/dt = 0$ and $dv/dt = 0$.

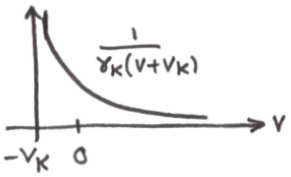
$$-\varepsilon\frac{dv}{d\tau} = g = m_\infty^3(v)(0.85-n)(v-1) + \gamma_K n^4(v+V_K) + \gamma_L(v-V_L)$$

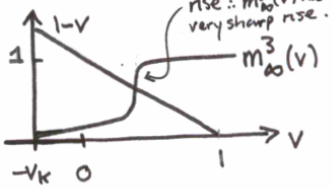
γ_L small $\therefore$ neglect this term below.

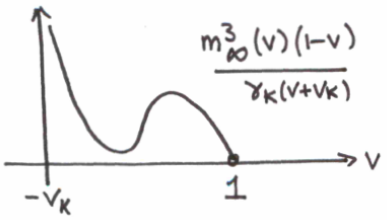
$$\frac{dn}{d\tau} = k = \frac{1}{\tau_n^*(v)}\left[\alpha_n(v)(1-n) - \beta_n(v)n\right]$$

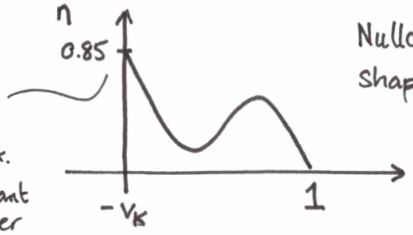
v nullcline $\qquad \dfrac{n^4}{0.85-n} = \dfrac{m_\infty^3(v)(1-v)}{\gamma_K(v+V_K)}$











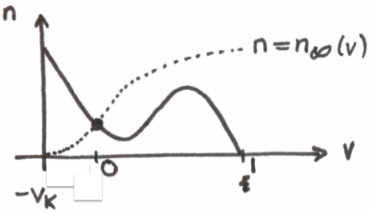
LHS and RHS blow up for $n=0.85$ and $v=-V_K$.
(γ_L corrections important here, but do not alter overall dynamics).

Nullcline has same qualitative shape as $\dfrac{m_\infty^3(v)(1-v)}{\gamma_K(v+V_K)}$ since $\dfrac{n^4}{0.85-n}$ is monotonic increasing.

n nullcline $\qquad \dfrac{dn}{d\tau} = 0$ when $n = n_\infty(v)$, by construction.

Also nullclines cross when $v=0$, again by construction.

Nullclines



The nullclines intersect when the v-nullcline is decreasing. Note that

$$\left(\frac{dn}{dv}\right)\Big|_{g=0} = -\frac{g_v}{g_n}.$$

Also, $g = m_\infty^3(v)(v-1)(0.85-n) + \gamma_K n^4(v+V_K) + \gamma_L(v-V_L)$

Increasing wrt v $\therefore g_v > 0$

and $g_n|_{v=0} = m_\infty^3(0) + 4\gamma_K n^3 V_K > 0 \therefore \left(\dfrac{dn}{dv}\right)\Big|_{g=0} < 0$ at $v=0$.

Classification of the equilibrium point One can deduce that the stationary point is stable from qualitative features of the phase plane without resorting to the excessive calculation. Perturbing around the stationary point as follows

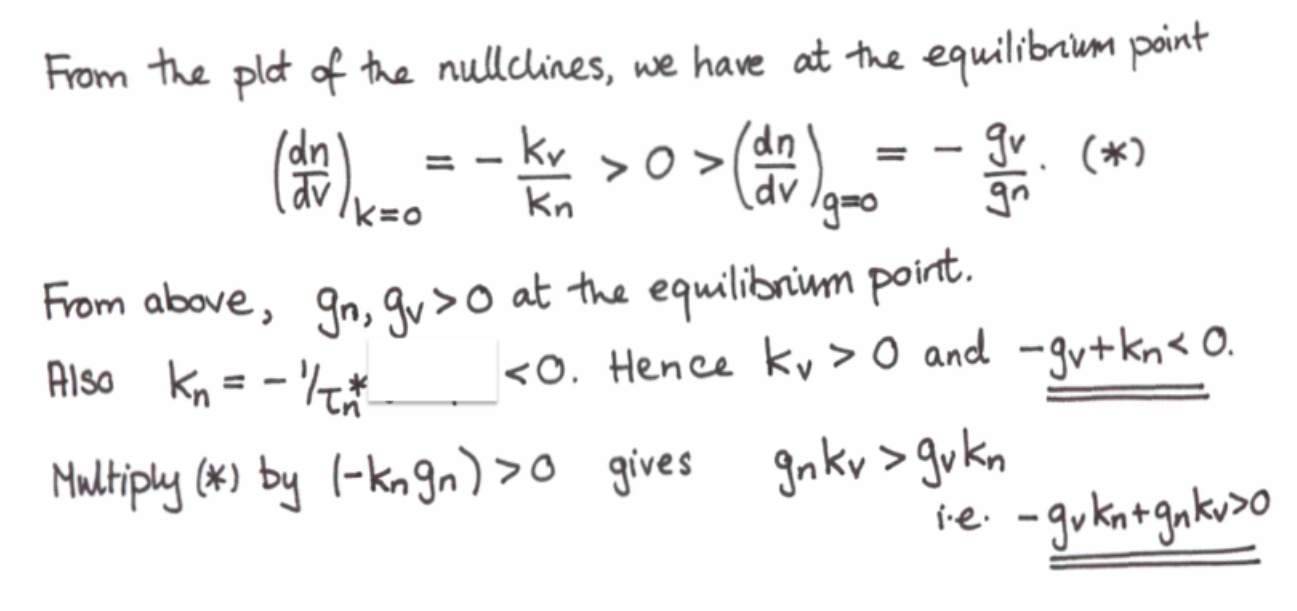
$$n = n_\infty(0) + \hat{n}, \quad v = \hat{v} \tag{62}$$

where $0 < |\hat{n}|, |\hat{v}| \ll 1$ and linearising gives

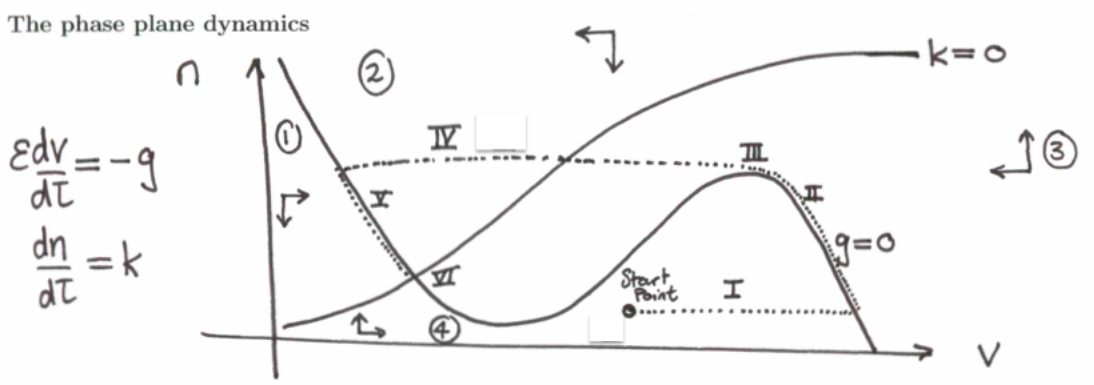
$$\frac{d}{dt}\begin{pmatrix} \hat{v} \\ \hat{n} \end{pmatrix} = \begin{pmatrix} -g_v/\epsilon & -g_n/\epsilon \\ k_\nu & k_n \end{pmatrix}\begin{pmatrix} \hat{v} \\ \hat{n} \end{pmatrix} \stackrel{def}{=} \mathbf{M}\begin{pmatrix} \hat{v} \\ \hat{n} \end{pmatrix} \tag{63}$$

Recall that the stationary point is linearly stable if and only if

$$\mathrm{Tr}(\mathbf{M}) = -g_v/\epsilon + k_n < 0, \qquad \epsilon\det(\mathbf{M}) = -g_v k_n + g_n k_v > 0. \tag{64}$$



Hence we have that the stationary point is *linearly* stable.



For $n = \frac{1}{2}$, v large, $dv/d\tau < 0$. For $n = 0$, $dn/d\tau > 0$. Thus in region ③ trajectories have v decreasing and n increasing. Directions in other regions can be readily determined.

I. $\varepsilon \ll 1$. Trajectory is nearly horizontal away from g=0 nullcline.

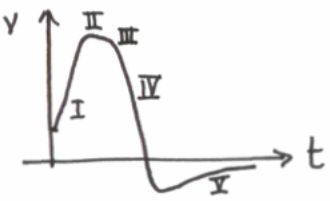
II. After reaching g=0 nullcline, trajectory rises (on a relatively slow timescale), as n is increasing in this region of the phase plane. It remains pinned to the g=0 nullcline.

III. Trajectory leaves g=0 nullcline.

IV. Trajectory is nearly horizontal until it reaches the g=0 nullcline once more.

V. Trajectory pinned to the g=0 nullcline, though n is decreasing in this region of the phase plane.

VI. Trajectory gets close to the stable equilibrium point and tends to equilibrium.

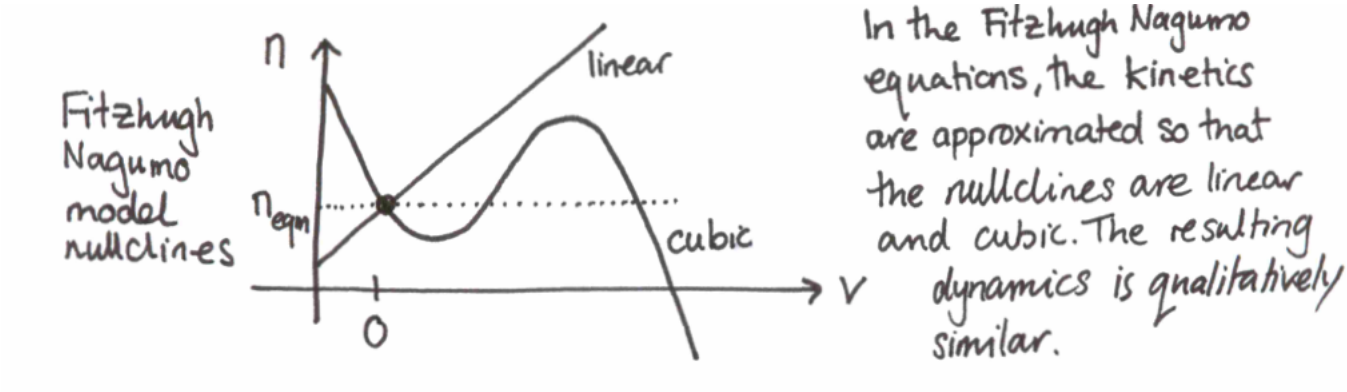


A sketch of the membrane potential dynamics with time, and the corresponding part of the phase plane trajectory.

1.3 Fitzhugh-Nagumo equation

1.3.1 The Fitzhugh Nagumo equations

Here the nullclines associated with the functions $g(n, v)$ and $k(n, v)$ are approximated by, respectively, a cubic polynomial and a straight line.



In particular, if we let $w = n - n_{\text{eqm}}$, the Fitzhugh Nagumo equations are

$$\epsilon \frac{dv}{d\tau} = Av(v-a)(1-v) - w + I^*_{ext}, \quad \frac{dw}{d\tau} = -w + bv,$$

where $0 < A \sim O(10)$, $a \in (0,1)$ and, for excitable systems, b is sufficiently large to guarantee there is only one equilibrium point. These have a directly analogous phase behaviour to the Huxley-Hodgkin equations, though the quantitative details are different.

In the example sheets, you will also consider the possibility of **oscillations** rather than excitable behaviour in the Fitzhugh-Nagumo equations once $I^*_{ext} \neq 0$.