

# Introduction to Ion Channel and Action Potential Modelling

## CaDiTSS Summer School

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(Heavily based on notes stolen from Martin Bishop)

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① Cell membranes and electrophysiology

② Ion Channels

③ Action potential modelling

④ Cardiac Action Potentials

# Cell membranes and electrophysiology

# The Cellular Membrane

Excitable cells are entirely surrounded by a *plasma membrane* which regulates the passage of ions into and out of the cell.

The membrane is mainly made-up of *lipids* and is  $\approx 75\text{ \AA}$  thick.

However, the membrane also contains many large, complex proteins, some of which constitute ion *channels* and *pumps* which facilitate the passage of ions into and out of the cell.

The space inside the cell is termed the *intracellular space*, whilst the space outside is termed the *extracellular space*.

As the membrane is largely impermeable to ions, differences in concentrations can build-up either side of the cell membrane, giving high concentration gradients across the thin membrane.

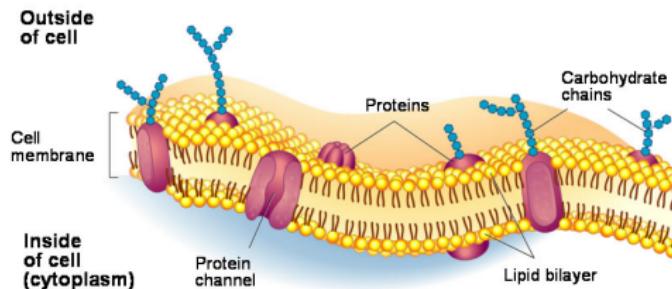


Figure: Excitable cell membrane.

**Lipid molecules** have *hydrophilic polar heads* and *hydrophobic non-polar tails*.

The hydrophilic heads are attracted to the water and face it, whilst the hydrophobic tails are repelled from it.

Lipids spread-out to a single molecule thick on air/water boundary, forming a contiguous *monolayer*.

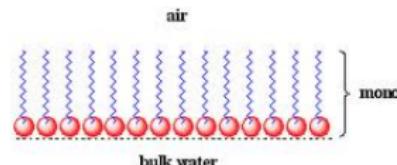


Figure: Lipid monolayer on air/water interface.

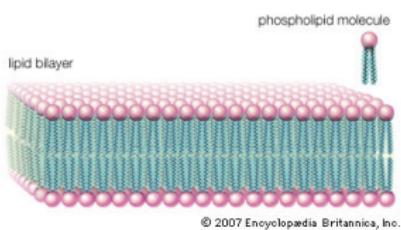


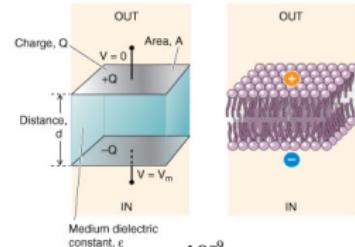
Figure: Lipid bilayer membrane.

The membrane of an excitable cell is called a **Lipid Bilayer** as it is simply made-up of two such layers of lipids.

The layers organise themselves such that the polar heads of each layer face the intracellular and extracellular aqueous medium. The non-polar tails face each other and form the internal structure of the membrane.

The membrane of an excitable cell acts like a *parallel plate capacitor*.

Ions accumulate either side of the membrane, causing a separation of charge.



**Figure:** Lipid bilayer and a parallel plate capacitor.

Using  $C = \frac{A\epsilon_r\epsilon_0}{d}$  we can calculate the approximate capacitance of a lipid bilayer (thickness of inner portion  $d = 30 \text{ \AA}$ ,  $\epsilon_r = 3$  for oil/lipid)

$$\frac{C}{A} = \frac{\epsilon_r\epsilon_0}{d} = \frac{3 \times 8.85 \times 10^{-12}}{30 \times 10^{-10}} = 0.9 \text{ } \mu\text{F/cm}^2 \quad (1)$$

This value of  $\approx 1 \text{ } \mu\text{F/cm}^2$  is very close to the measured value.

The very high value achieved by nature is difficult to replicate in non-biological capacitors. It comes about due to the combination of high membrane resistance and dielectric constant, across a membrane which is very thin.

The **Transmembrane Potential** is the difference in the potential of the intracellular space compared to the extracellular space.

## Transmembrane Potential

$$V_m = \phi_i - \phi_e \quad (2)$$

where  $\phi_i$  is the absolute potential of the intracellular space and  $\phi_e$  the extracellular potential.

There can often be a  $V_m \approx 100$  mV difference in potential levels either side of the membrane (i.e. between inside and outside of the cell).

As this difference occurs over just 75 Å, it can lead to local field strengths of  $\approx 10^9$  V/m. This is a **VERY STRONG FIELD** — for reference air conducts lightning at  $\approx 3 \times 10^6$  V/m!

During excitation and then de-excitation,  $V_m$  can change by a huge amount, i.e. over  $\Delta V_m \approx \pm 80$  mV.

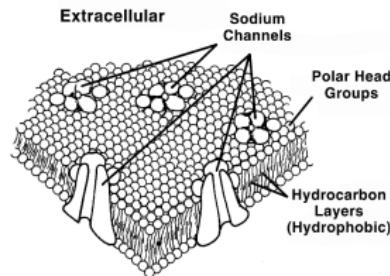
The lipid bilayer membrane has:

- a very high capacitance ( $C_m = 1 \text{ pF/cm}^2$ )
- a very high specific resistance (ignoring channels) ( $R_m = 10^9 \Omega\text{cm}^2$ )

The membrane thus acts as an insulator to the movement of ions. Ion flux does take place through channels which lowers the overall effective resistance to  $R_{m,\text{eff}} = 10^3$  to  $10^4 \Omega\text{cm}^2$ .

Channels:

- are not just passive openings for ion movement;
- are **selective** for the transit of particular, specific ions;
- control their flow of ions via **gates** that open and close.



**Figure:** Lipid bilayer membrane with ion channels.

**Diffusion** is the process by which molecules in a region of high concentration 'spread-out' into regions of lower concentration.

Diffusion is driven by the thermal energy of the molecules causing them to move at random.

Diffusive flow takes place *down a concentration gradient* i.e. from high concentration → low concentration.

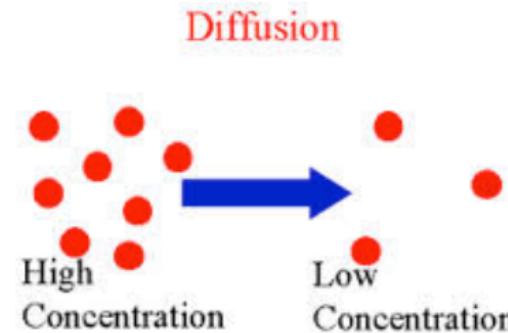


Figure: Diffusion from high to low concentration.

# Transmembrane Current

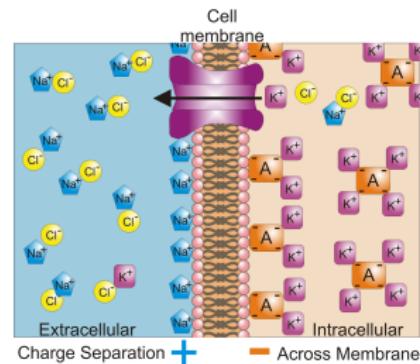
As the membrane has a resistance (i.e. it is not a perfect insulator), the existence of the transmembrane potential induces the flow of a **Transmembrane Current**  $I_m$ .

## Transmembrane Current

By convention,  $I_m$  is considered to be a *positive* current when positive ions flow from the intracellular space *out* into the extracellular space.

Currents flow across the membrane via channels, pumps and exchangers.

Ion currents arise due to a combination of diffusive and electrical forces, as well as by 'active transport'.



**Figure:** Ionic flow across the membrane.

In general:

$K^+$  Potassium concentration inside the cell is much *larger* than outside:  $K_i^+ \gg K_e^+$ ;

$Na^+$  Sodium concentration inside the cell is much *smaller* than outside:  $Na_i^- \ll Na_e^+$ ;

$Cl^-$  Chloride concentration inside the cell is much *smaller* than outside:  $Cl_i^- \ll Cl_e^-$ ;

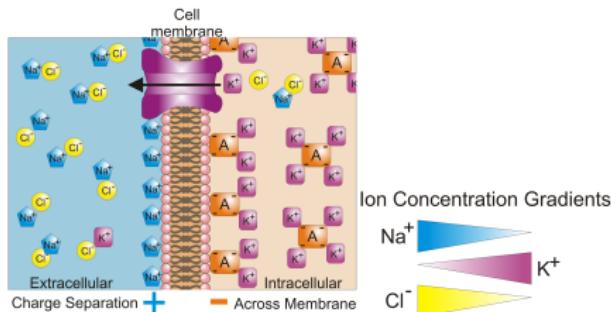


Figure: Ionic flow across the membrane with concentration gradients.

The flow of ions such as potassium, sodium, calcium and others, across the cell membrane constitutes the transmembrane current and governs the overall electrical properties of the cell.

# Ion Channels, Pumps & Exchangers

Ions move through the membrane via **Ion Channels, Exchangers or Ion Pumps**.

## Ion Channels

- Allow the *passive* flow of ions to occur *down* the electro-chemical gradient.
- They thus utilise the energy stored in the concentration gradients across the membrane.
- Ionic flow through channels is *selectively permeable* to specific ions.
- The permeability can be modulated very rapidly, changing the degree of flow.
- Permeability and its rapid change, is controlled by *channel gating* — a structural response to changes in electric field or certain ligands/ion concentrations.

## Exchangers

- Use passive flow of one ion down its gradient to push another ion up its gradient.
- Sodium-Calcium Exchanger (NCX) is the main one in the heart, for every 3  $\text{Na}^+$  going in one  $\text{Ca}^{2+}$  goes out (3:2 charge so creates a net current).

## Ion Pumps

- Pumps are *active* processes, using energy to move ions *against* their electro-chemical gradient.
- They tend to be steady processes, to maintain/restore concentrations inside the cell.

# Ion Channels, Pumps & Exchangers

Under steady-state conditions (i.e. at rest), a fixed fraction of each channel type will be open.

Macroscopically (averaging up thousands of individual proteins that are either open/active or closed/inactive), we can consider the membrane to have a particular ionic conductance to each particular ionic species.

Ion movement across the membrane is subject to both diffusion and electric forces.

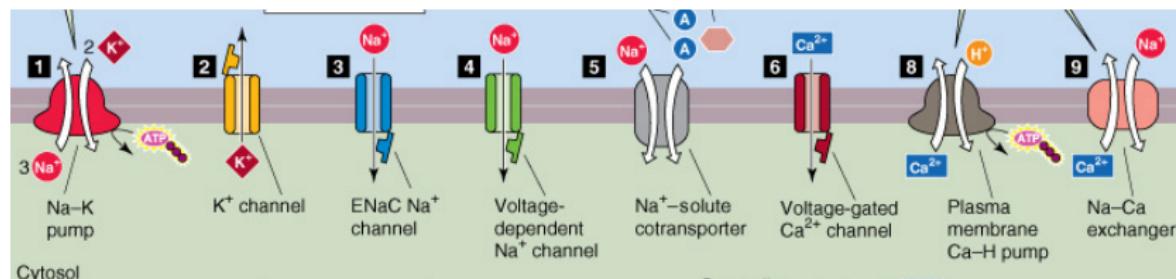


Figure: Active and passive ion transport across the membrane.

- ⇒ Ionic concentration gradients between intra- and extracellular spaces cause diffusion of ions across the membrane.
- ⇒ The rate of diffusion depends upon the difference in concentration and the membrane permeability (depending on the open channel density and the channel resistance).
- ⇒ Charged ions accumulate on the membrane because of its capacitance (separates charges).
- ⇒ These accumulated charges setup an electric field, exerting forces on ions (and charged bits of proteins) *within* the membrane.
- ⇒ To begin with, initial diffusion of permeable ions takes place. This causes a net charge transfer which alters the electric field.

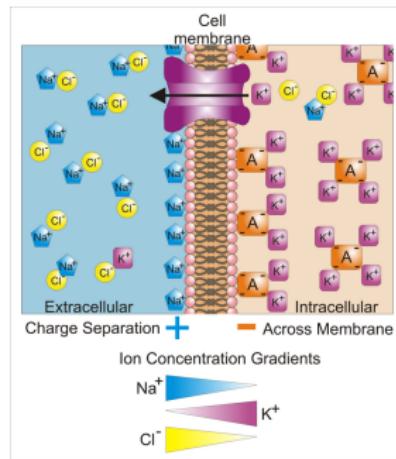


Figure: Movement of ions across a membrane.

Any description of ion flow across the membrane must therefore take into account both the forces due to *diffusion* and *electric field*.

# Single Ion Permeability

- A *concentration cell* is a two compartment system, separated by a selectively permeable membrane.
- The membrane is usually permeable to one ion species (e.g.  $P^+$ ), but not the other (e.g.  $Q^-$ ).
- Initially, the concentration of  $P^+$  and  $Q^-$  is the same in either side, thus each side is electrically neutral.

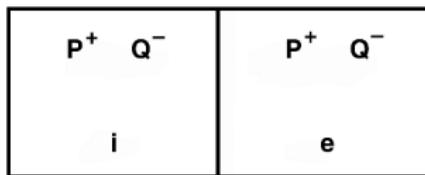


Figure: Idealised concentration cell.

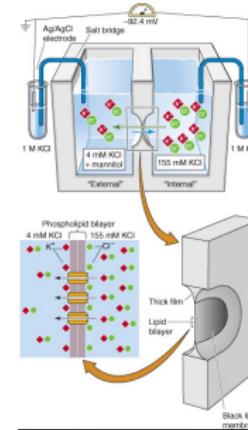


Figure: Experimental concentration cell.

If the membrane is *only* permeable to  $P^+$  and initially the concentration of  $P^+$  is higher in  $i$  than  $e$  ( $[P^+]_i > [P^+]_e$ ) meaning:

- ⇒  $P^+$  will initially diffuse from  $i \rightarrow e$  (but  $Q^-$  cannot diffuse).
- ⇒ Diffusion of  $P^+$  accumulates positive charge in  $e$ , leaving a net negative charge in  $i$ .
- ⇒ Electrostatic forces cause these charges to reside on (either side of) the membrane.
- ⇒ The resulting difference in potential across the membrane  $V_m$  is related to the charge separated  $\Delta P^+$  and the membrane capacitance  $C_m$  by  $V_m = \Delta P^+ / C_m$ .
- ⇒ The corresponding electric field  $E = V_m/d$  increases as more and more  $P^+$  ions diffuse from  $i$  to  $e$ .
- ⇒ The growing electric field increasingly hinders the diffusion until the electrical forces exactly balance the diffusion forces, terminating flow as equilibrium is reached.

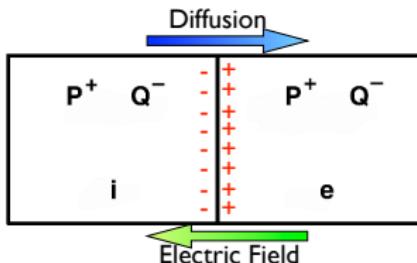


Figure: Idealised concentration cell.

## Nernst Potential

The **Nernst Potential**  $E$  for ionic species  $C$  is given by the potential difference at equilibrium across the membrane

$$E_C = -\frac{RT}{Z_p F} \ln \left( \frac{[C_p]_i}{[C_p]_e} \right) \quad (3)$$

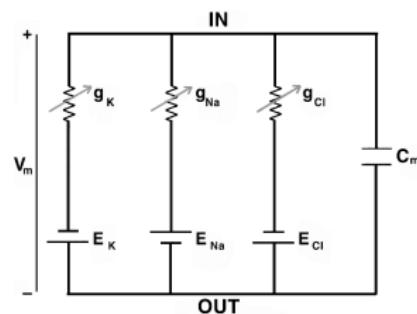
- Note the Nernst Potential for a particular ion depends only on the ratio of the concentrations for constant temperatures.
- Note that the value of  $RT/F$  is approximately 25.8 mV at 27 C.
- Ions can flow from low to high concentration if the electric field across the membrane is large enough to overcome diffusion. So our flow of ions will **reverse** (current will change direction) if the membrane voltage crosses the Nernst Potential. So another name for the Nernst Potential is the *Reversal Potential*.

## Parallel-Conductance Model

The **Parallel-Conductance Model** represents the flow of ions through a small segment of membrane called a *membrane patch* or element, small enough such the  $V_m$  is constant across the patch, but large enough to encompass numerous channels so that their average behaviour can be represented.

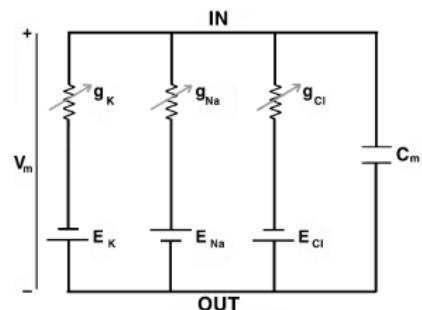
The model assumes that:

- ions pass independently through the membrane;
- conductances of each ion vary independently of each other;
- there is no single transmembrane potential that brings all ions into equilibrium.



**Figure:** Schematic of the Parallel Conductance model considering only Na, K and Cl channels.

- ⇒ Different pathways for different ions across the membrane operate in parallel and simultaneously.
- ⇒ Analyse how individual pathways operate separately, and creation of composite effects, like the transmembrane potential.
- ⇒ Each branch is thought of as a macroscopic description of the respective open ion channels.



**Figure:** Schematic of the Parallel Conductance model considering only Na, K and Cl channels.

# Ionic Currents

We can represent the individual currents from the basic ion channels Na, K, Cl and Ca by the following simple 'Ohmic' current equations following  $V = IR$ .

$$I_K = g_K(V_m - E_K) \quad (4)$$

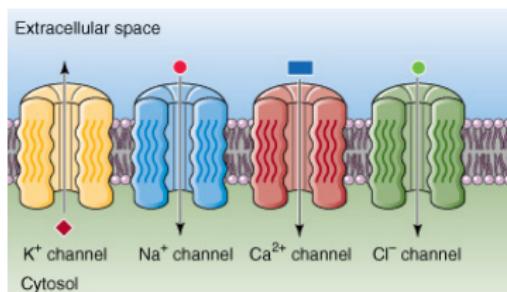
$$I_{Na} = g_{Na}(V_m - E_{Na}) \quad (5)$$

$$I_{Cl} = g_{Cl}(V_m - E_{Cl}) \quad (6)$$

$$I_{Ca} = g_{Ca}(V_m - E_{Ca}) \quad (7)$$

where  $E_p$  are the **Nernst Potentials** and  $g_p$  the conductances (in units of 1/Resistance) for each ion species.

- The term  $(V_m - E_p)$  represents the **driving force** for the particular ion  $p$ , which evaluates the *deviation from equilibrium*.
- A driving force term tries to force it back to equilibrium.
- Each current is directly proportional to its driving force.
- (For ions at orders-of-magnitude-different concentrations, a different Goldman-Hodgkin-Katz (GHK) flux equation is sometimes used instead of the Ohmic expression, e.g. frequently for L-type Calcium current in cardiac AP models).

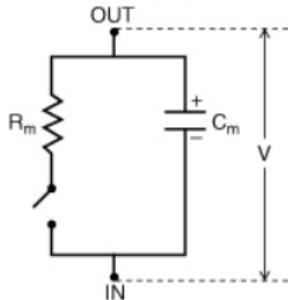


**Figure:** Schematic of the main ionic channels.

## Capacitive Current

The **Capacitive Current** is the current flowing onto the membrane causing it to charge-up the capacitor.

$$I_C = C_m \frac{dV_m}{dt} \quad (8)$$



**Figure:** Circuit diagram of capacitive current.

At steady-state,  $\frac{dV_m}{dt} = 0$  and so the capacitive current is zero,  $I_c = 0$ .

The time-course of the capacitive current decays with an exponential constant of  $\tau = R_m C_m$ .

# Ion Channels

The structure of ion channels can be determined from x-ray diffraction and electron microscopy. These methods rely on forming regular 2D lattices of purified ions and can only probe the ion structure to a few Å— not sufficient to see much detail.

## Ion channels:

- are made-up of several transmembrane segments, forming a **pore**;
- have a total length that exceeds that of the plasma membrane;
- have non-uniform walls, such that their cross-sectional area (and charge) varies along the length.

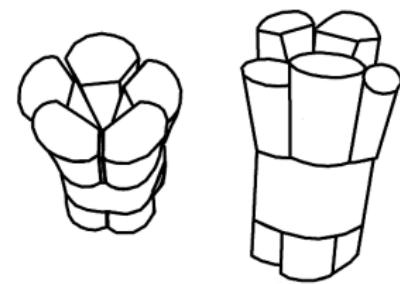
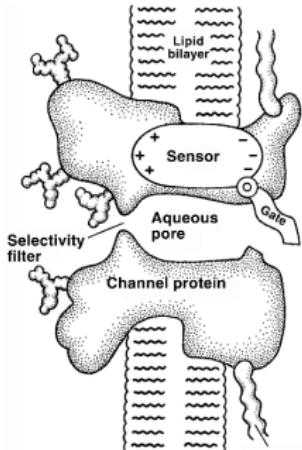


Figure: Basic structure of a membrane bound ion channel.

The barrel structure facilitates rapid gating — small rotations or changes in conformation of the contributing components give rise to substantial changes in likelihood of ions passing through a slightly altered pore.



**Figure:** Schematic diagram of the functional properties of an ion channel.

**Voltage Gating** is a property by which the conductance of the ion channel changes in response to local changes in transmembrane potential.

- ⇒ Voltage gating implies that the molecular structure of the channel protein contains effectively embedded charge or dipoles.
- ⇒ An applied electric field causes intramolecular forces that causes a conformational change in the channel, changing its conductivity.
- ⇒ This movement of charged bits of ion channel proteins results in a measurable *gating current*.
- ⇒ The displacement of charge within an electric potential changes the potential energy of the system, either adding or subtracting from the total potential energy of the protein.

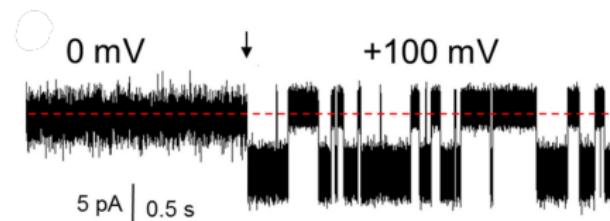
The gating current saturates when all channels are at steady state — this can be used to separate its contribution from the capacitive current which is linearly dependent upon  $dV_m/dt$ .

## Single Channel Conductance

A single open channel contributes a path for electrical current with a fixed conductance (1/resistance).

Note, before we referred to total (average) conductance of all of a particular type of ion,  $g$ .

Measurement of single channel currents is possible with pulled-glass micropipettes, but only if the channels have relatively high conductance relative to noise:



**Figure:** Current recording from a single ion channel when voltage steps from 0 to 100 mV at the time indicated by the arrow. From Maki et al. <http://dx.doi.org/10.3791/51629>

These single channel studies can give some of the best insights into gating, but whole-cell average currents are easier to measure (can be measured high-throughput). When you have hundreds of channels or more (and myocytes are relatively big with thousands of the main channels), then working with the mean proportion that are open, rather than a sum of stochastically gating channels, is not generally our main source of modelling error and uncertainty.

## Hodgkin-Huxley

Hodgkin & Huxley constructed mathematical formulae for the behaviour of individual ionic currents in the late 1940s and early 1950s.

- Their model mathematically links channel open probability with whole cell behaviour (quite remarkable given channels hadn't been discovered!)
- They showed that the total membrane current could be represented as the sum of individual types of ion currents.
- Their measurements were conducted on the squid giant nerve axon.
- They won a Nobel Prize for their efforts.

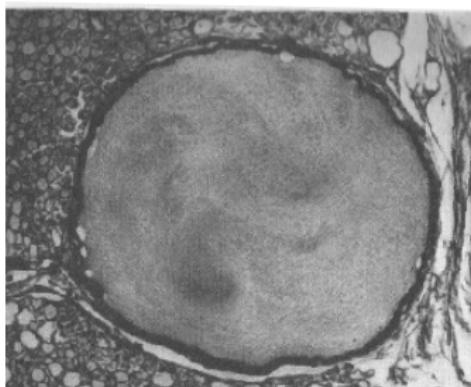


Figure: The squid giant axon (not the giant squid axon!)

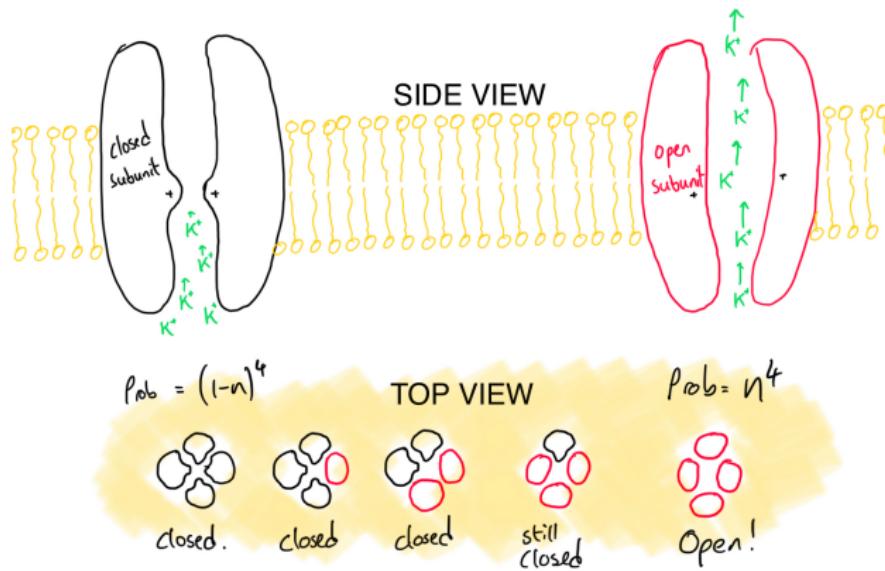
## HH Representation of Ion Channel Dynamics

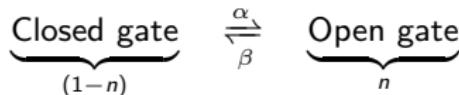
HH assumed that the potassium channel had 4 *subunits* that operated independently. All 4 need to be open for current to flow.

If  $n$  is an *activation gate* representing the probability of any one subunit being open, then

$$p_K = n^4 \quad (9)$$

represents the probability of the entire  $K$  channel being open.





The movement of a gate is represented by first-order mass-action kinetics

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n, \quad (10)$$

where  $\alpha_n$  is the rate constant of going from closed  $\rightarrow$  open and  $\beta_n$  the rate constant of going from open  $\rightarrow$  closed.

Note that  $\alpha_n$  and  $\beta_n$  will be functions of voltage for voltage-gated channels; or functions of ligand concentration for a ligand-gated channel; etc..

### Gating Variable

The probability  $n$  is called a **gating variable** and will vary over time depending on  $V_m$  and how it has influenced  $\alpha_n$  and  $\beta_n$  (which we'll come onto in a bit).

We can re-arrange the gating variable equation to read

$$\frac{dn}{dt} = \alpha_n - n(\alpha_n + \beta_n) = \frac{n_\infty - n}{\tau_n}, \quad (11)$$

where  $n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$  and  $\tau_n = \frac{1}{\alpha_n + \beta_n}$ .

**When voltage is constant**, we can solve this linear first-order ODE by hand, which yields the solution

## Gating Variable Temporal Dynamics

$$n(t) = n_\infty - (n_\infty - n_0)e^{-t/\tau_n} \quad (12)$$

where  $n_0 = n(t = 0)$ .

These equations describe the temporal behaviour of the probability of all  $n$  gates expected to be in the open position.

You'll note voltage isn't usually constant in the heart, but it can be in voltage-clamp experiments, such as the ones HH did.

## HH Channel Conductances

There is a simple relationship between the total conductance of  $N$  channels ( $g$ ) and the individual conductance of a single channel ( $\gamma$ )

$$g_K = N \cdot p \cdot \gamma \quad (13)$$

where  $p$  represents the probability of a channel being open.

In the HH model for K, we have that  $p \rightarrow n^4$  and so the total potassium channel conductance of  $N$  channels is

### Potassium Channel Conductance

$$g_K = N\gamma n^4 = \bar{g}_K n^4 \quad (14)$$

where we have written the **maximum conductance** of  $N$  potassium channels as  $\bar{g}_K = N\gamma_K$ . HH jumped straight to  $\bar{g}_K$  since individual channels hadn't been discovered.

The parallel conductance model representation of the total potassium current  $K$  still holds

$$I_K = g_K(V_m - E_K) \quad (15)$$

but where  $g_K$  is now given by the above expression incorporating  $n$ , giving

### Total HH Potassium Current

$$I_K = \bar{g}_K n^4 (V_m - E_K) \quad (16)$$

HH represented the dynamics of the sodium channel in a similar manner.

However, importantly in the case of sodium, the channel is controlled by 3 gates of type  $m$  and 1 gate of type  $h$ .

Thus, the probability that an Na channel will be open at any time is given by

$$p_{Na} = m^3 h \quad (17)$$

## Total HH Na Current

$$I_{Na} = \bar{g}_{Na} m^3 h (V_m - E_K) \quad (18)$$

It turns out that  $m$  is an activation gate (like  $n$  was for potassium), but  $h$  captures a separate *inactivation* process (not the opposite of activation, confusingly — since it is an independent process in the HH gating formalism!). With inactivation the channel closes at positive potentials, whereas with activation it opens. So  $h$  is a recovery-from-inactivation gate that opens as voltage gets negative, the opposite of what  $m$  and  $n$  do.

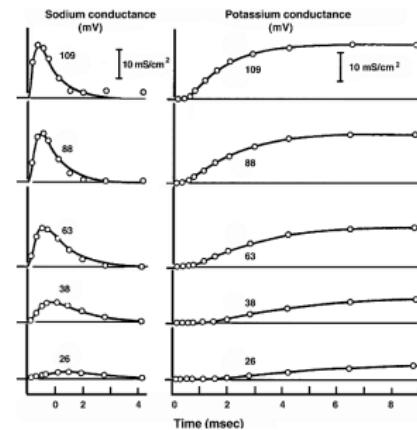
From the parallel conductance models

$$g_{Na}(t) = \frac{I_{Na}(t)}{V_m - E_{Na}} \quad g_K(t) = \frac{I_K(t)}{V_m - E_K} \quad (19)$$

Under voltage-clamp, denominator is constant in time and thus the time evolution of  $I_{Na}(t) \propto g_{Na}(t)$  and  $I_K(t) \propto g_K(t)$ .

By using different voltage clamp values, the magnitudes of the conductances thus change.

HH thus built their model to replicate these changes in conductances with respect to time and voltage.



**Figure:** Temporal evolution of  $g_{Na}$  and  $g_K$  under different magnitude voltage clamps.

# Potassium Rate Constants

For one particular voltage clamp ( $v_{m,i}$ ), an optimal fit can be obtained by adjusting  $\tau_n$  and  $n_\infty$ .

With these optimal values of  $\tau_n(v_{m,i})$  and  $n_\infty(v_{m,i})$ , corresponding rate constants  $\alpha_n$  and  $\beta_n$  can be found for the  $i$ th voltage.

Hodgkin and Huxley repeated these fittings many times for different voltages, thus building-up samples of the underlying smooth functions  $\alpha_n(v_m)$  and  $\beta_n(v_m)$ . The variations of  $\alpha_n$  and  $\beta_n$  with  $v_m$  themselves were then empirically fitted to be

## Potassium Rate Constants

$$\alpha_n = \frac{0.01(10 - v_m)}{\left[\exp\left(\frac{10-v_m}{10}\right) - 1\right]} \quad \text{and} \quad \beta_n = 0.125 \exp\left(\frac{-v_m}{80}\right), \quad (20)$$

where  $v_m$  is in mV and  $\alpha, \beta$  are in  $\text{ms}^{-1}$  and  $v_m = V_m - V_{rest}$ .

## First principles?

Energy barrier arguments (Eyring rate theory) imply reactions of the form

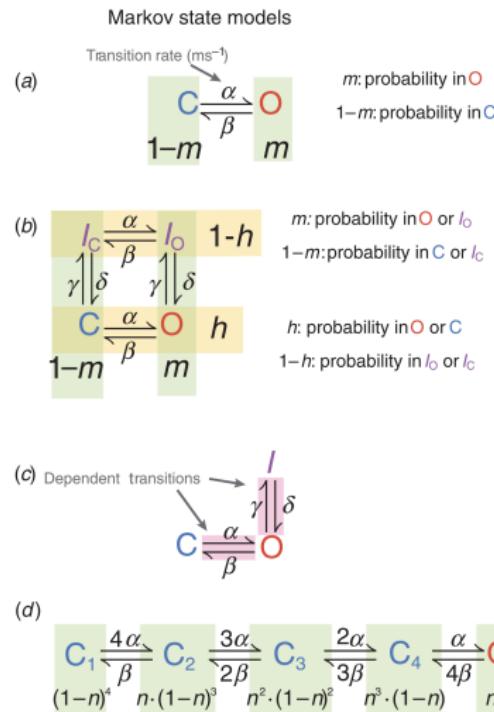
$$\alpha = \theta_1 \exp(\theta_2 v_m) \quad \text{and} \quad \beta = \theta_3 \exp(-\theta_4 v_m), \quad (21)$$

for all  $\theta > 0$ , which we've used very successfully in the past... Note the match for  $\beta_n$  but difference for  $\alpha_n$ .

# On the relationship between HH and Markov models

- HH gates can be 'multiplied out' into the possible individual states as shown in (b)
- Markov models offer a 'relaxation' of the independent gating assumptions, so that (e.g.) activation and inactivation can be dependent — 'you can only inactivate from the open not closed state', as shown in (c)
- It turns out 'powered' gates can be written as linear chains with relationships between rates shown in (d)<sup>a</sup>

Open probability  
for an equivalent  
HH-type model



$m$

$m \cdot h$

Not applicable

$n^4$

<sup>a</sup>GM wrote a blog on this

<https://mirams.wordpress.com/2019/09/30/hodgkin-huxley-and-markov/>

Markov models and HH gating equivalents, from Rudy & Silva 2006

[https://doi.org/10.1017/S0033583506004227.](https://doi.org/10.1017/S0033583506004227)

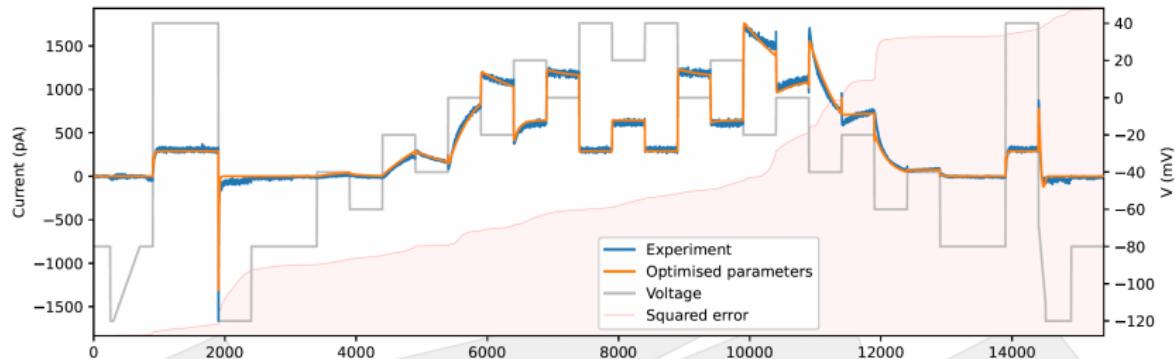
A modern approach is to simply globally optimise parameters to minimise square error between simulation and data:

<https://youtu.be/bX9kydGKwRc>

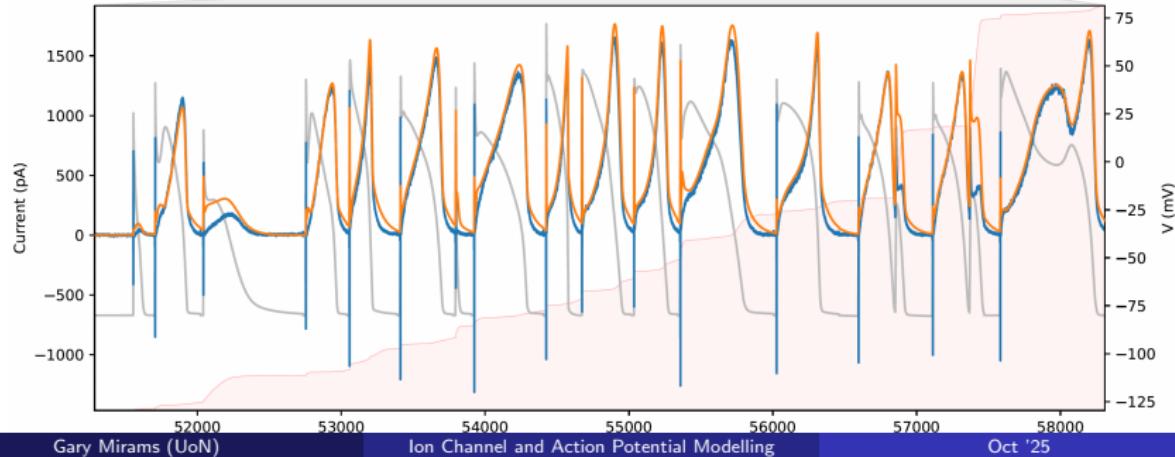
# Does this stuff really work?

Yes! Here's some unpublished stuff Michael has been doing for a mutant IKr channel

## Training:



## Validation:



Please try Hands-on Session 1 (Ion Channel modelling) now:

<https://bit.ly/caditss>

# Action potential modelling

To numerically simulate an AP we first assert that the total membrane current is composed of the sum of the ionic and capacitive currents

## Total Transmembrane Current

$$I_m = I_K + I_{Na} + I_L + I_C \quad (22)$$

where it is noted that all currents vary with time during an AP.

- In a *single cell* simulation, we assume that the situation is space-clamped (nothing is coming in/out from other cells to the sides), thus the total membrane current is zero  $I_m = 0$ . [Think about Kirchoff's Law in the Parallel Conductance Model.]
- The flow of ionic current provides the capacitive current, charging the capacitor.
- When an external stimulus is applied,  $I_m = I_{stim}$ .

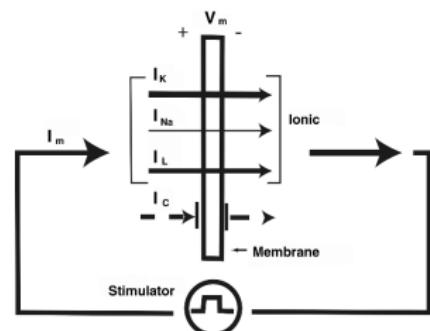


Figure: Membrane current in single cell model

## Advancing in Time

The independent variable when solving an AP model is time.

Time is discretised into a sequence of time instances, separated by a *time-step*  $\Delta t$ . In HH-like models, time-steps are usually  $1 - 25 \mu\text{s}$ .

We know that  $I_C = C_m \frac{dV_m}{dt}$  and so Eqn (22) can be rearranged to give

$$\frac{dV_m}{dt} = \frac{I_m - (I_K + I_{Na} + I_L)}{C_m} \quad (23)$$

Making the numerical approximation that

$$\frac{dV_m}{dt} \approx \frac{\Delta V_m}{\Delta t} \quad (24)$$

means that we can approximate the change in  $V_m$

$$\Delta V_m = \Delta t \frac{I_m - (I_K + I_{Na} + I_L)}{C_m} \quad (25)$$

Knowing the value of  $V_m$  at  $t = t_n$  allows us to approximate the value at  $t = t_{n+1}$

$$V_m^{t_{n+1}} = V_m^{t_n} + \Delta V_m = V_m^{t_n} + \Delta t \frac{I_m - (I_K + I_{Na} + I_L)}{C_m} \quad (26)$$

where  $I_K$  etc were calculated using the current (i.e.  $t = t_n$ ) values of the state variables.

State variables can be advanced in time using a similar method, as like  $V_m$  they are also associated with an ODE in time.

For example, for  $n$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (27)$$

which can be rearranged to give

$$\Delta n = \Delta t [\alpha_n(1 - n) - \beta_n n] \quad (28)$$

and then the next value of  $n$  is found by

$$n^{t+1} = n^t + \Delta t [\alpha_n(1 - n^t) - \beta_n n^t] \quad (29)$$

Similar procedures also hold for  $\Delta m$  and  $\Delta h$ .

## Adaptive ODE Solvers

N.B. here we are describing the 'Forward Euler' method for solving the ODEs, it is a simple explicit method, but can get unstable and inaccurate. Myokit and most other simulation packages use smart error-controlling adaptive-timestep implicit solvers like CVODE (or `ode15s` in MatLab).

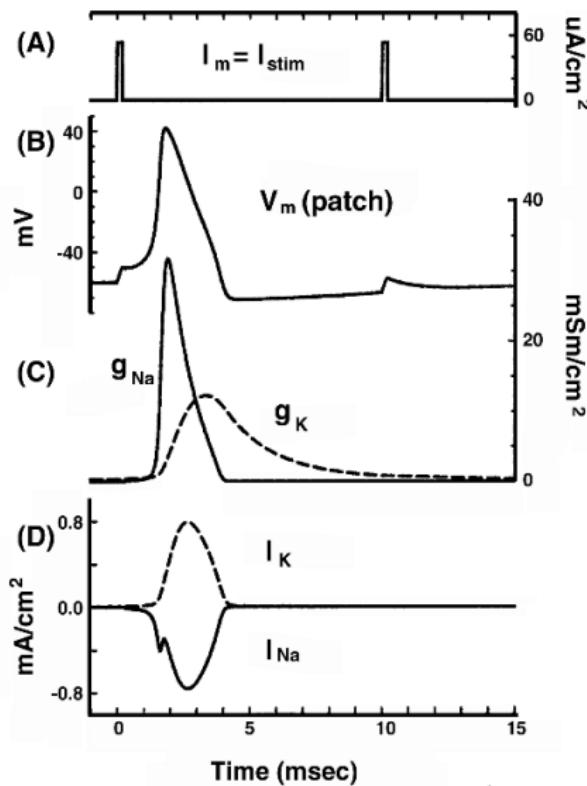
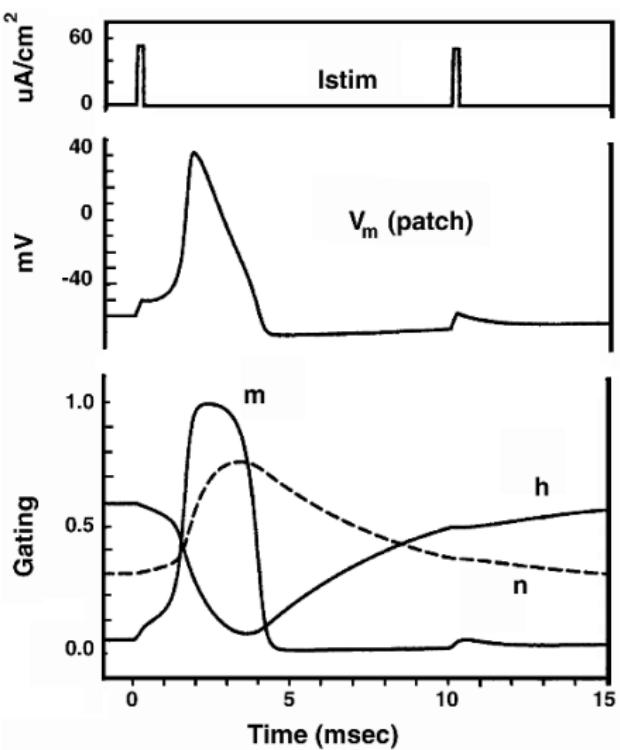
- ① Choose a value of  $V_{rest}$  i.e.  $V_m$  at  $t = 0$ , usually  $-60\text{mV}$  or so.
- ② Use this value of  $V_m$  to derive values of  $\alpha_{n,h,m}$ ,  $\beta_{n,h,m}$  previously.
- ③ Use these values to derive values of

$$n_0 = n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad m_0 = m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \quad h_0 = h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} \quad (30)$$

- ④ With these initial values of  $V_m$ ,  $n$ ,  $m$  and  $h$ , we can compute the corresponding initial values of the ionic currents  $I_K$ ,  $I_{Na}$  etc.

- ① With these current (initial) values of  $V_m$ ,  $n$ ,  $m$  and  $h$ , we can now compute their corresponding rates of change (Eqns (23) & (27) etc).
- ② As shown above, these rates of change are used to approximate the next values of  $V_m^{t+1}$ ,  $n^{t+1}$ ,  $h^{t+1}$ ,  $m^{t+1}$ .
- ③ With the new values of the state variables, all other dependent variables may be updated to their values at  $t + 1$  (i.e.  $\alpha_{m,n,h}$ ,  $\beta_{m,n,h}$  etc).
- ④ Recompute the corresponding rates of change at  $t + 1$ , and use them to update the state variables to  $t + 2$ .
- ⑤ ...
- ⑥ Remember, however, that at certain times the stimulus current may be active (usually the first ms or so), and thus  $I_m$  in the calculation of  $\Delta V_m$  will not be zero at this time.

# Computed Action Potential



**Figure:** Example of a computed AP following a stimulus along with the temporal variation of the gating variables and currents.

See NumericalNotes in the 'slides' folder of the Github repo:

<https://bit.ly/caditss>

# Cardiac Action Potentials

Many cells in the body have the ability to undergo a transient depolarization and repolarization.

Such types of cells include:

- ① nerve cells
- ② cardiac pace-maker cells
- ③ cardiac non pace-maker cells
- ④ skeletal muscle cells
- ⑤ gut cells

Excitation of these cells is either triggered by external mechanisms (e.g., motor nerve stimulation of skeletal muscle or cell-to-cell depolarization in the heart) or by intracellular, spontaneous mechanisms (e.g., cardiac pacemaker cells).

# Cardiac vs Nerve Action Potentials

Cardiac action potentials differ considerably from action potentials found in neural and skeletal muscle cells.

The main difference is duration:

- in a typical **nerve cell**, the action potential duration is about 1 ms;
- in **skeletal muscle cells**, the action potential duration is approximately 2-5 ms;
- in a **cardiac muscle cell** the action potential is usually between 200 – 400 ms.

Another difference between cardiac and nerve and muscle action potentials is the role of calcium ions in depolarization:

- in nerve and muscle cells, and also in non-pacemaker cardiac cells, the depolarization phase of the action potential is caused by an opening of *sodium* channels;
- in cardiac pacemaker cells, calcium ions are involved in the initial depolarization phase of the action potential.

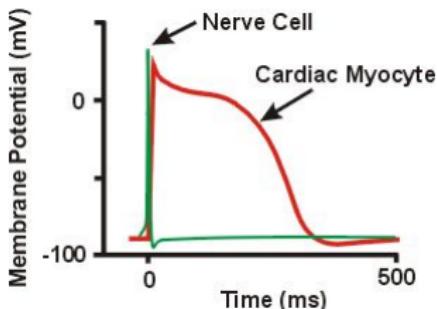


Figure: Comparison between ventricular cardiac AP and a neuronal AP

# Types of Cardiac Action Potentials

There are two general types of cardiac action potentials:

## Non-Pacemaker APs

Also called *fast response* action potentials because of their rapid depolarization.

They are found throughout the heart except for the pacemaker cells, and are generally also involved in contraction of the cardiac muscle.

Examples include ventricular and atrial myocytes.

## Pacemaker APs

Pacemaker cells generate spontaneous action potentials that are also termed *slow response* action potentials because of their slower rate of depolarization.

These are normally found in the sinoatrial and atrioventricular nodes of the heart.

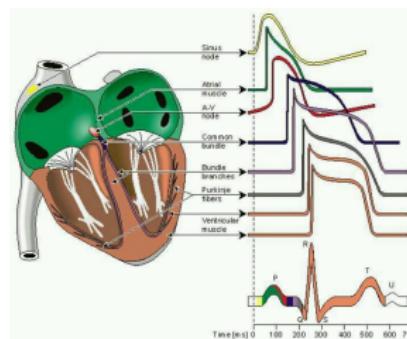


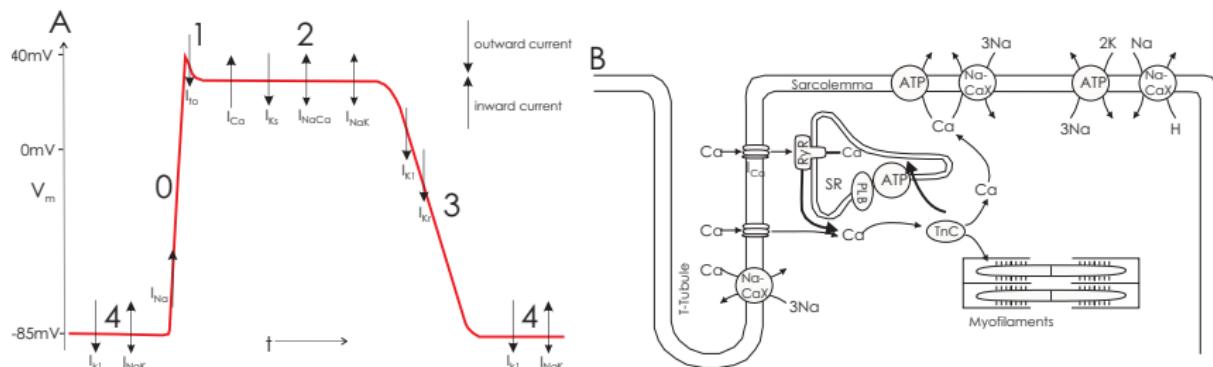
Figure: Different types of cardiac APs within the heart

# Cardiac Action Potential

The major ions whose movement governs the course of the AP include sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ) and calcium ( $\text{Ca}^{2+}$ ), and to a lesser extent, chloride ( $\text{Cl}^-$ ), ions.

The major difference between the cardiac and neuron AP is the role of calcium.

This is because calcium plays a key role in contraction (the main role of the cardiac myocyte).

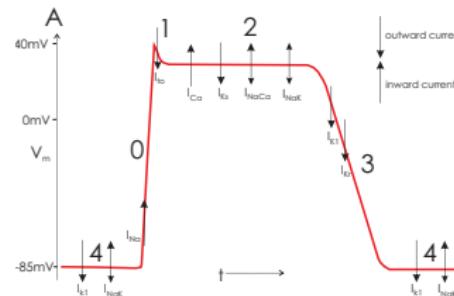


**Figure:** Schematic representation of a cardiac AP from a typical cardiac ventricular mammalian cell, depicting the change in  $V_m$  over time following electrical stimulation.

# Phases of the Cardiac Action Potential

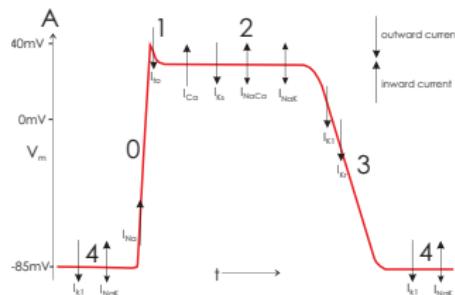
The cardiac AP can be thought of as occurring in a series of five phases:

- **Phase 4:** corresponds to the resting state of the cell ( $V_m = -85 \text{ mV}$ ).
  - this negative value is related to the electrochemical gradient for potassium across the plasma membrane which is relatively permeable to  $\text{K}^+$
  - the intracellular concentration of  $\text{K}^+$  is higher than the extracellular  $\text{K}^+$  concentration
  - the tendency for potassium to move down its concentration gradient out of the cell is balanced by a negative intracellular resting potential that favours potassium influx
  - this concentration gradient is maintained by the sodium-potassium ion exchange pump ( $\text{Na}^+/\text{K}^+$  pump)
  - with the negative resting potential being maintained largely by the inward rectifying potassium current ( $I_{\text{K}1}$ ).



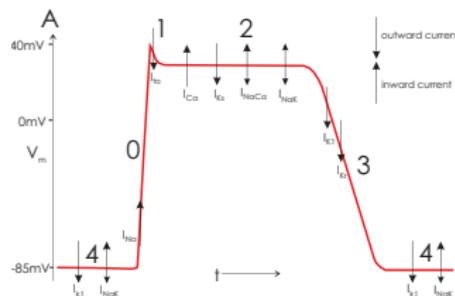
# Phases of the Cardiac Action Potential

- **Phase 0:** describes the rapid depolarisation occurring following an electrical stimulus, called the AP upstroke.
  - causes the cell to depolarise from its resting potential to reach its maximum level of depolarisation (approximately 40mV)
  - this rapid depolarisation of the cell results from the opening of the fast  $\text{Na}^+$  channels following the initial stimulus
  - allows sodium ions to flow quickly into the cell forming the fast sodium current ( $I_{\text{Na}}$ )



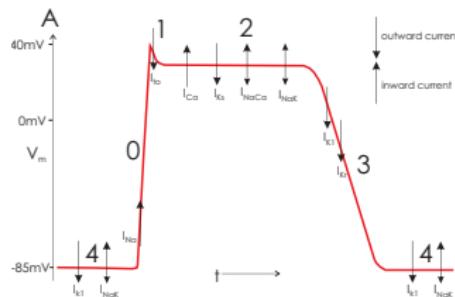
# Phases of the Cardiac Action Potential

- **Phase 1:** is the initial repolarisation occurring immediately following the upstroke, due to:
  - ① the inactivation of the fast sodium current;
  - ② the activation of the short-lived transient outward current ( $I_{to}$ ) from the movement of  $K^+$  and  $Cl^-$  ions



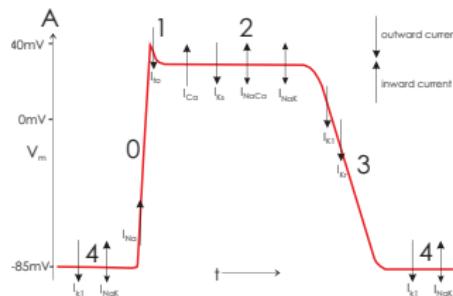
# Phases of the Cardiac Action Potential

- **Phase 2:** is the subsequent plateau phase of the AP, sustained by a balance between:
  - ① the inward movement of  $\text{Ca}^{2+}$  through the prolonged L-type calcium current ( $I_{\text{Ca}}$ )
  - ② the outward movement of  $\text{K}^+$  through the slow-delayed rectifier current ( $I_{\text{Ks}}$ )
- Calcium influx prolongs the duration of the action potential and produces a characteristic plateau phase.
- During the plateau phase of the AP, the sodium-calcium exchanger current ( $I_{\text{NaCa}}$ ) plays an important role in removing calcium from the cell.

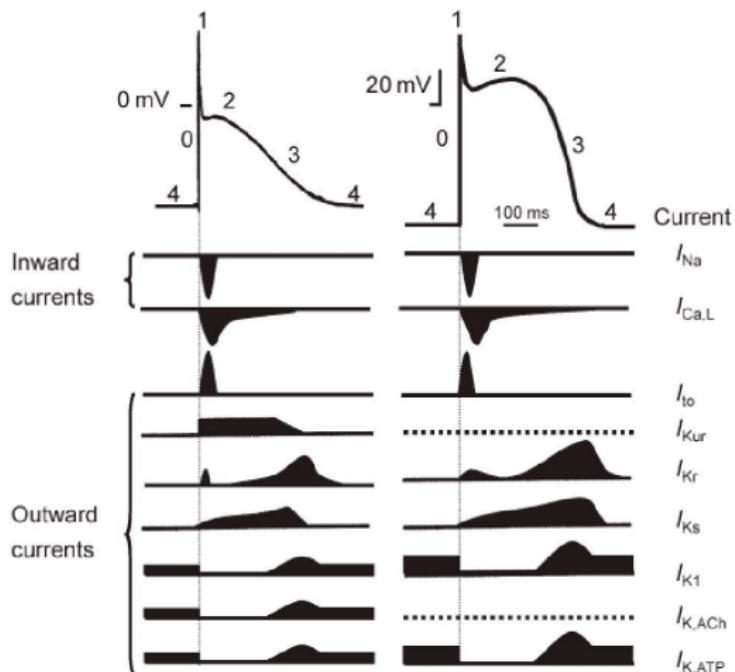


# Phases of the Cardiac Action Potential

- **Phase 3:** is the repolarisation phase, which follows the plateau phase.
  - L-type calcium channels close, leaving a net outward current from the slow delayed rectifier channels which remain open
  - additional potassium currents, such as the rapid delayed rectifier current ( $IKr$ ) and the  $IK1$ , making-up the total potassium current  $IK$ , are also recruited
  - This large exit of positive charge from the cell eventually causes it to repolarise back to its original resting potential (and phase 4), where the  $IK1$  and  $INaK$  play an important role in maintenance of the cell's resting potential



# Ionic Currents During Atrial & Ventricular APs



# A modern action potential model

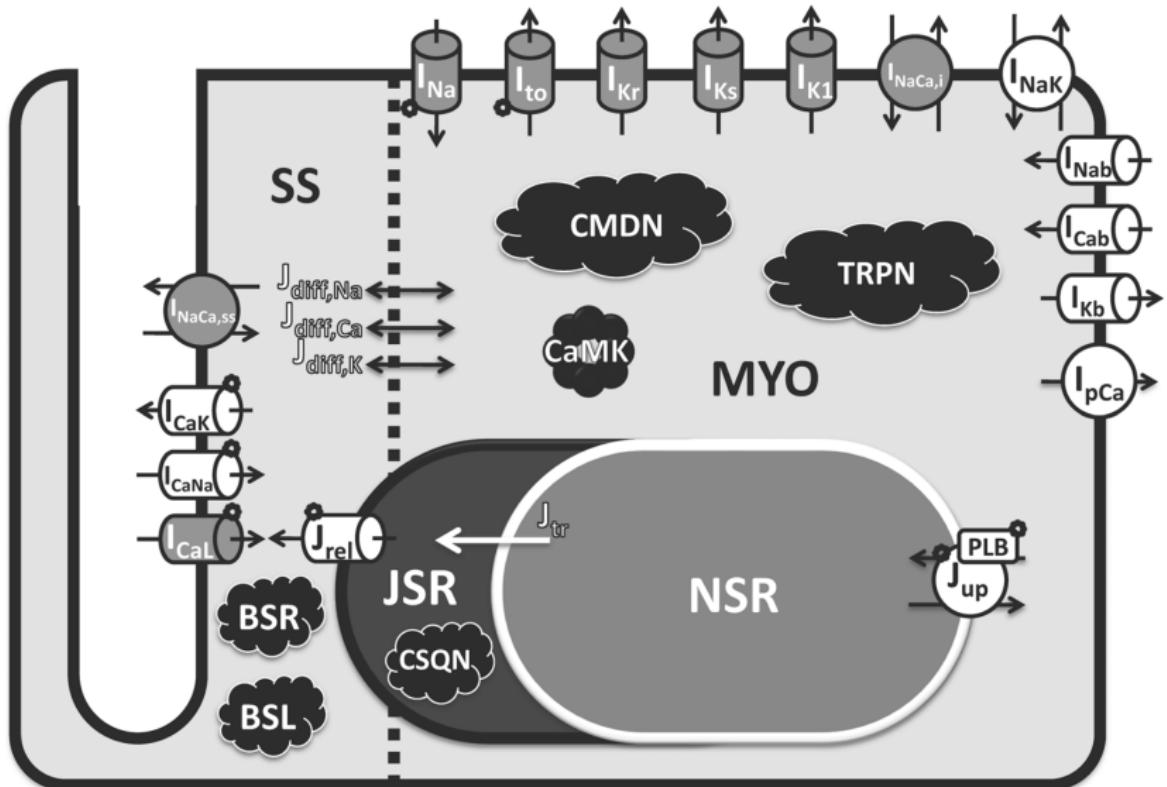


Figure: The O'Hara et al. 2011 human ventricular myocyte model  
<https://doi.org/10.1371/journal.pcbi.1002061>.

# Action potentials and arrhythmogenesis

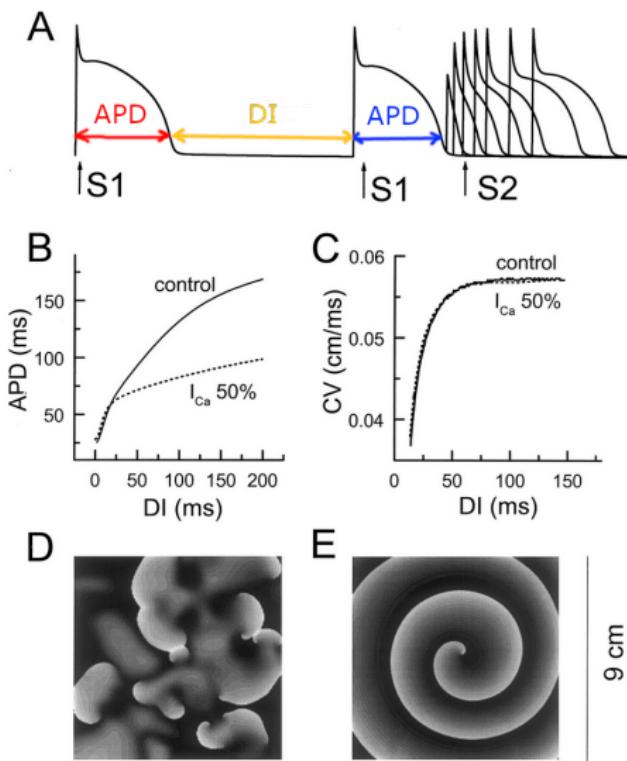


Figure: S1-S2 restitution and emergent tissue behaviour, more on that tomorrow!

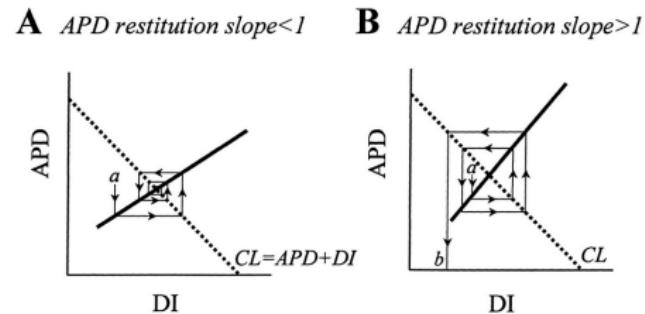


Figure: Stability of APD on a Poincaré map-style plot. Left: stable APD, Right: unstable APD

Figures from Weiss et al. 1999 (<https://doi.org/10.1161/01.CIR.99.21.2819>)

- Varying the maximal conductances of each channel can be used to represent different cell types, species, disease states, variation in individual people, and heterogeneity in myocytes the heart between and within different regions.
  - Unpicking what variation comes from what is difficult and under-studied!
  - A perfect model for a cardiac muscle cell might not be a great model for cardiac tissue (which includes other cell types like fibroblasts).
- Mutations can be modelled quite accurately at the individual ion channel level and this is a sensible basis for a 'twin'
  - Compensatory mechanisms (and basic homeostasis mechanisms for controlling channel expression  $\approx$  maximal conductances) are poorly understood at present, and could muck things up!
- Different drug regimens can be applied to different ion channels (some drugs block multiple channels and this is important in determining pro-arrhythmic risk).
  - when it is appropriate to simply scale down the proportion of available channels, or model with Markov diagrams like we did earlier, is not clear at the moment
- Open questions:
  - how best to pick and parameterise the ion channel models?
  - how best to fit conductances?
  - what training and validation to use?
  - how important is cell-cell variability in electrophysiology within the whole heart?
  - what detail of calcium subsystem is appropriate/necessary for different emergent behaviour?
  - how can we put bounds on predictions to account for all our uncertainties?

Please try Hands-On Session 2 (Action Potential modelling) now:

<https://bit.ly/caditss>