Single neuron models 5

Biophysical models: The Hodgkin-Huxley model (2)

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Adaptive Behaviour Research Group

2006

Outline

- Part I: Theory of gate dynamics: voltage clamp formulation
- Part II: Experimental determination of gate parameters with voltage clamp
- Part III: The power of the HH formalism

Outline of Part I

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Outline of Part III

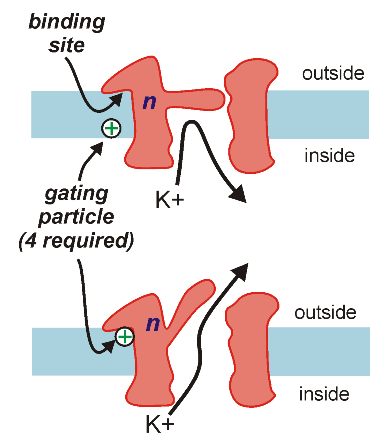
Part I

Theory of gate dynamics: voltage clamp formulation

Outline

Gates and gating particles

The K^+ current as an example



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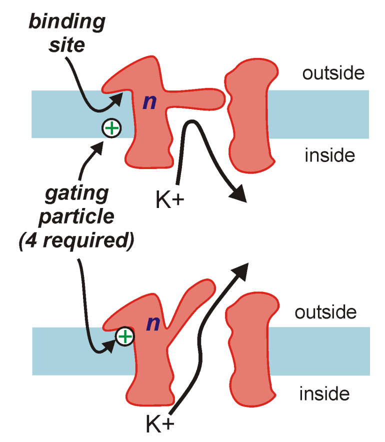

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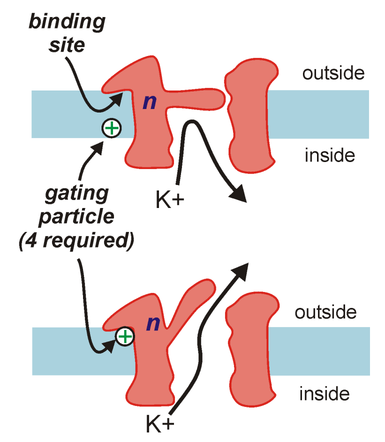

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- A simplification - but if we read ‘conformational change’ for ‘movement of gating particle’ we have a modern interpretation
- The state of the gate is controlled by these particles becoming bound to sites on the external side of the channel pore

First order kinetics

K^+-current

- Recall that the gate for the K^+-current could be described by a First order kinetics

First order kinetics: K^+-current

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

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A strategy for finding gate parameters

- We can't find the rate constants directly. But we can find quantities related to them that *are* accessible to measurement

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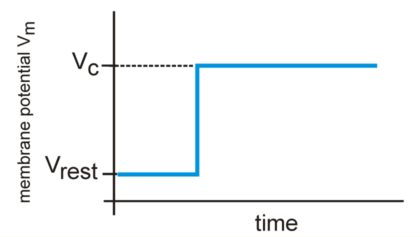
- We can't find the rate constants directly. But we can find quantities related to them that *are* accessible to measurement
- The key to this programme lies in the ability to Clamp the membrane at some voltage V_c accurately and indefinitely



Equilibrium under voltage clamp

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- solving for $n_\infty(V_c)$

$$n_\infty(V_c) = \frac{\alpha_n(V_c)}{\alpha_n(V_c) + \beta_n(V_c)} \tag{2}$$

A new gating variable: $n_\infty(V_c)$

- Equation (2) defines the variable $n_\infty(V_m)$ for any V_m

$$n_\infty(V_m) = \frac{\alpha_n(V_m)}{\alpha_n(V_m) + \beta_n(V_m)} \tag{3}$$

with the interpretation that, if V_m was held constant long enough, the gating variable $n(V_m, t)$ would approach $n_\infty(V_m)$

Another new gating variable $\tau_n(V_m)$

- Put

$$\tau_n(V_m) = \frac{1}{\alpha_n(V_m) + \beta_n(V_m)} \tag{4}$$

The choice of notation gives the game away... τ_n will turn out to play the role of a time constant

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Then (3) and (4) may be solved for α_n, β_n

$$\begin{aligned} \alpha_n &= \frac{n_\infty}{\tau_n} \\ \beta_n &= \frac{1 - n_\infty}{\tau_n} \end{aligned} \tag{5}$$

Reformulation of gate dynamics

- Substituting (5) in the rate kinetics equation (1)

Activation gate dynamics using τ_n, n_∞

$$\frac{dn}{dt} = \frac{n_\infty(V_m) - n}{\tau_n(V_m)} \tag{6}$$

Solution of *n*-gate dynamics under voltage clamp

- under clamp with $V_m = V_c$, (6) becomes

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- Equation(7) can then be solved analytically for $t \geq t_0$

$$n(t) = n_\infty(V_c) - [n_\infty(V_c) - n_\infty(V_{rest})] \exp[-(t - t_0)/\tau_n(V_c)] \tag{8}$$

Solution of *n*-gate dynamics under voltage clamp

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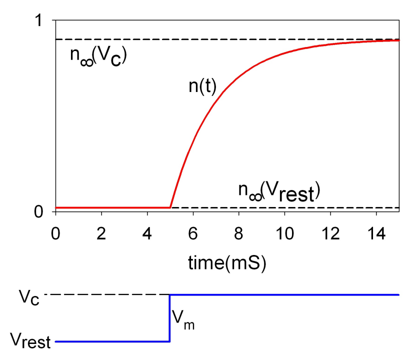

- Notice that τ_n occurs in the role of a time constant governing the speed of the exponential rise time of $n(t)$.

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Finding forms for gating variables

- Unlike α_n and β_n, $n_\infty(V_m)$ and $\tau_n(V_m)$ are *measurable*

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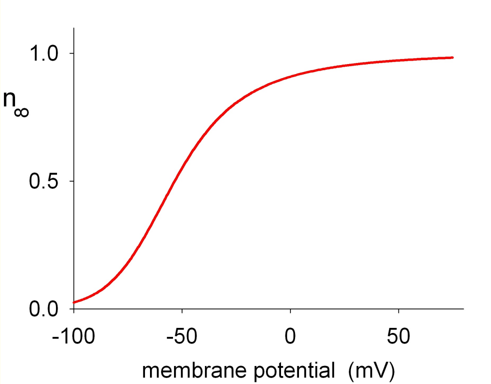
- More details are given in the next Part of the lecture
- But now, we look at the typical forms for $n_\infty(V_m)$ and $\tau_n(V_m)$ and how to interpret them

Finding forms for gating variables

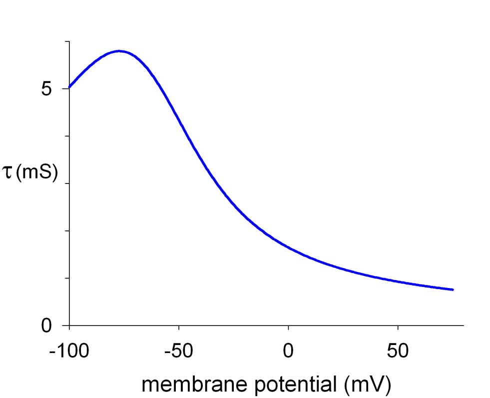
A curve fitting exercise - $n_\infty(V_c)$



- Typically $n_\infty(V_m)$ is a *monotonic increasing* function of V_m that is roughly S-shaped...

Finding forms for gating variables

A curve fitting exercise - $\tau_n(V_c)$



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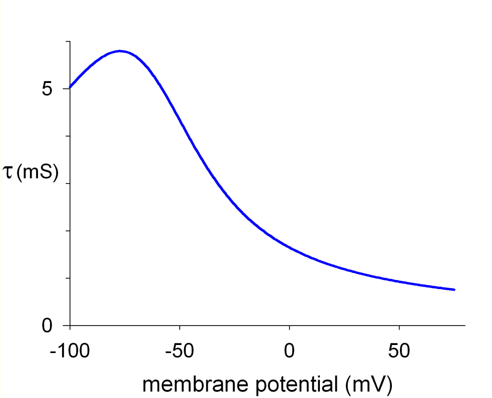

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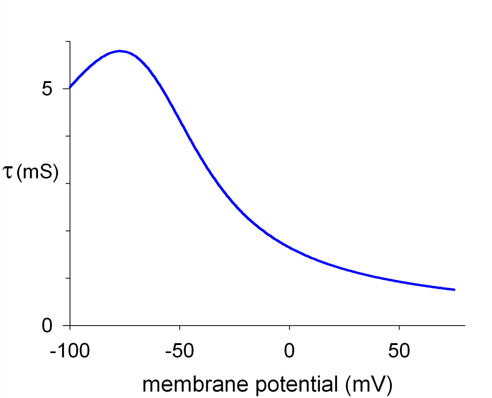

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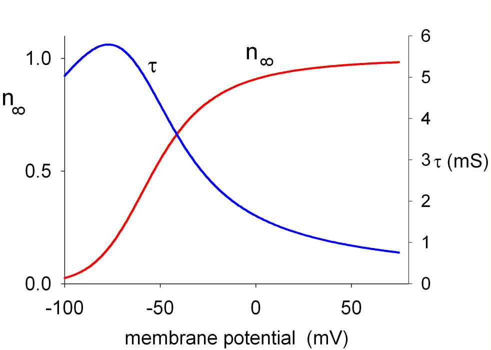
- However, the functional forms for $n_\infty(V_c), \tau_n(V_c)$ are purely *phenomenological*. The curves shown are simply best fits to data using combinations of exponentials etc.
- Also, the 'number of particles' q required to best fit the data is 4

Finding forms for gating variables

Rate constants are theoretically plausible

Sometimes τ and n_∞ are shown together



- However, by solving for α_n, β_n from n_∞, τ_n, the basic 'shape' of the functions $\alpha_n(V), \beta_n(V)$ are consistent with theoretical treatments of kinetics (Johnston & Wu page 130 and 153)

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The K^+ current: bringing the threads together

K^+ current (with kinetic rate constants)

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where n_∞, τ_n are functions of V_m; $n_\infty(V_m), \tau_n(V_m)$

The K^+ current: bringing the threads together

Relationship between two formulations

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{13}$$

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$$\alpha_n = \frac{n_\infty}{\tau_n} \tag{15}$$

$$\beta_n = \frac{1 - n_\infty}{\tau_n} \tag{16}$$

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The Na^+ current: review

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- $P(\text{gate-open}) = P(\text{m-open})P(\text{h-open}) = m^3 h$

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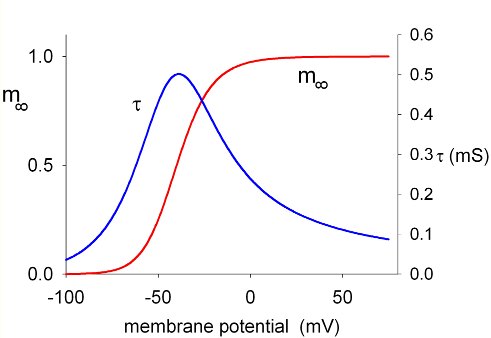
- Both m and h gates may be treated in the same way as the n gate for K^+

The Na^+ current activation gate



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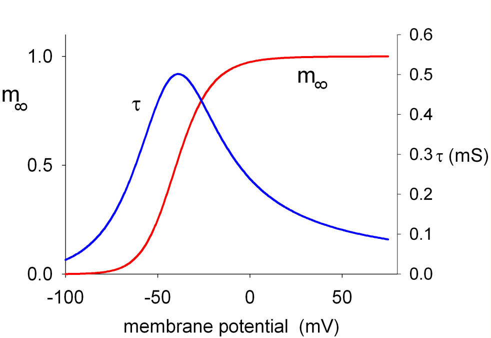
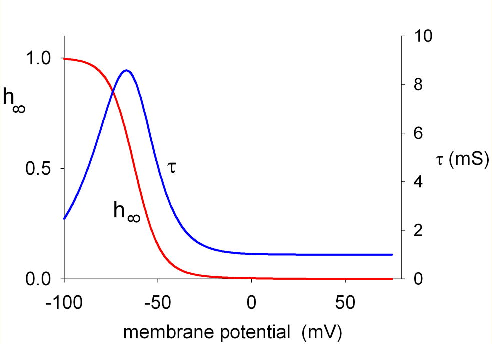


- The steady state activation $m_\infty(V_m)$ and its time constant $\tau_m(V_m)$
- Note $\tau_m \ll \tau_n$ so that Na^+ activates much more quickly than K^+ (as required)

The Na^+ current inactivation gate



- The steady state inactivation $h_\infty(V_m)$ and its time constant $\tau_h(V_m)$

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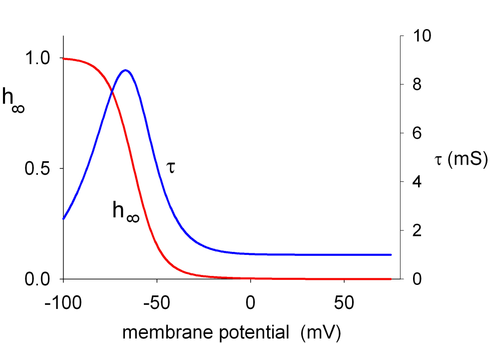
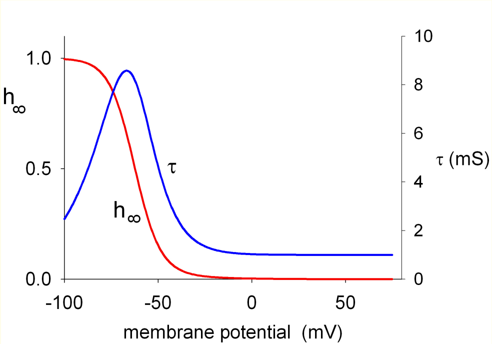


- The steady state inactivation $h_\infty(V_m)$ and its time constant $\tau_h(V_m)$
- Note that h_∞ declines with depolarisation which is how we would expect an inactivation gate to work (review qualitative description at start of lecture)

The Na^+ current inactivation gate



- The steady state inactivation $h_\infty(V_m)$ and its time constant $\tau_h(V_m)$
- Note that h_∞ declines with depolarisation which is how we would expect an inactivation gate to work (review qualitative description at start of lecture)
- $\tau_h \gg \tau_m$ so that inactivation takes place *after* activation

The Na^+ current: bringing the threads together

Na^+ current (with kinetic rate constants)

$$I_{Na} = g_{Na}(E_{Na} - V_m) \tag{17}$$

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$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \qquad \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \tag{19}$$

where $\alpha_m, \beta_m, \alpha_h, \beta_h$ are functions of V_m

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$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \qquad \frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \tag{22}$$

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Relationship between two formulations

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \qquad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} \tag{23}$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \qquad \tau_h = \frac{1}{\alpha_h + \beta_h} \tag{24}$$

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or solving for α, β

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$$\beta_m = \frac{1 - m_\infty}{\tau_m} \qquad \beta_h = \frac{1 - h_\infty}{\tau_h} \tag{26}$$

Outline

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- While computational neuroscience is clearly a theoretical area, it is intimately bound up with experimental practice because we need data for constraints

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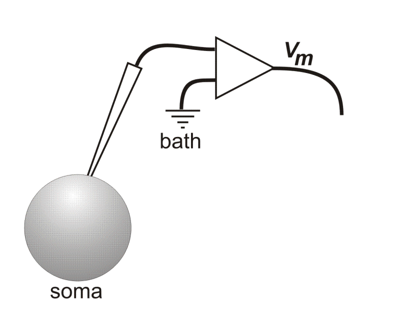
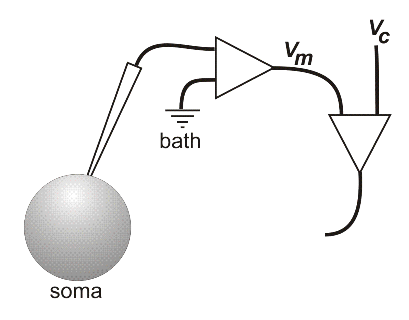
- While computational neuroscience is clearly a theoretical area, it is intimately bound up with experimental practice because we need data for constraints
- Understanding experimental methods allows us to know the origins of data and how to interpret them

Voltage Clamp
Principles



- Measure the membrane potential V_m in normal way (compare internal potential with the extracellular potential)

Voltage Clamp
Principles



- Compare V_m with the clamp voltage V_c ...

Voltage Clamp
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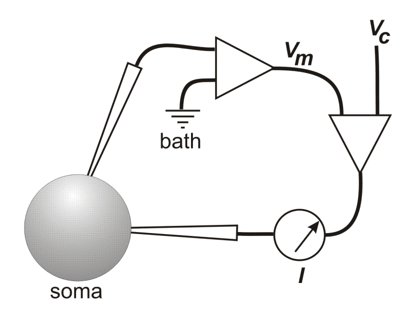

- … and use the difference to drive a current source *I*

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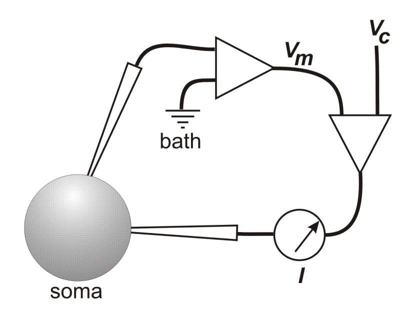
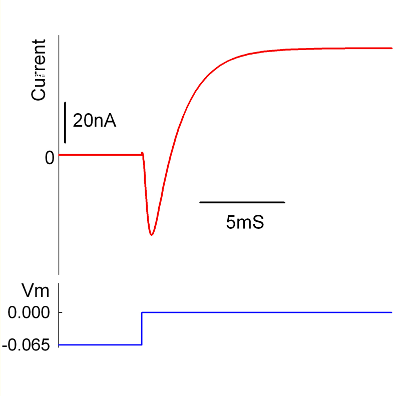


- ... and use the difference to drive a current source I
- In this way the current supplied, I_{clamp}, is exactly equal and opposite to that due to the ion flux across the membrane, I_{ion}

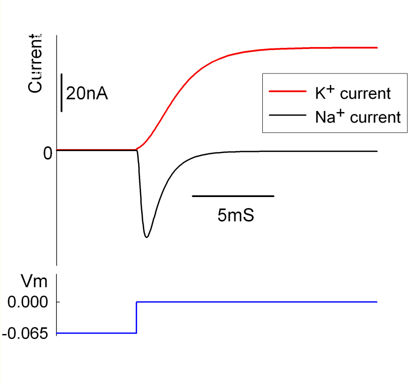
$$I_{clamp} = -I_{ion}$$

Voltage Clamp
An example in simulation



- Model with AP generating K^+ and Na^+ currents currents used as ‘virtual data’
- $V_c = 0$, and total clamp current I_{clamp} is shown
- It is conventional in physiology papers to show this rather than I_{ion}

Voltage Clamp
Dissecting currents

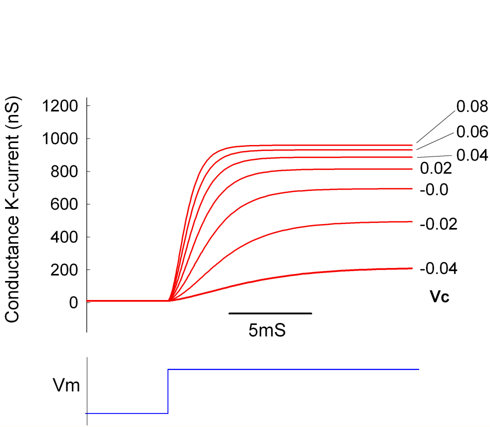


- By poisoning current-specific channels, we can dissect out individual currents
- Note clamp currents are again shown (e.g. I_K is negative, but the I_{clamp} required is positive)

Outline

Outline

Finding g_{max}

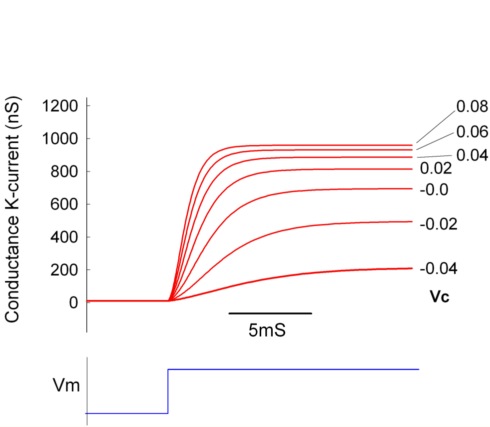


- Can measure conductance g_K using

$$g_K = I_K/(V_m - E_K)$$

since $V_m = V_c$, and we know I_K and E_K

Finding g_{max}



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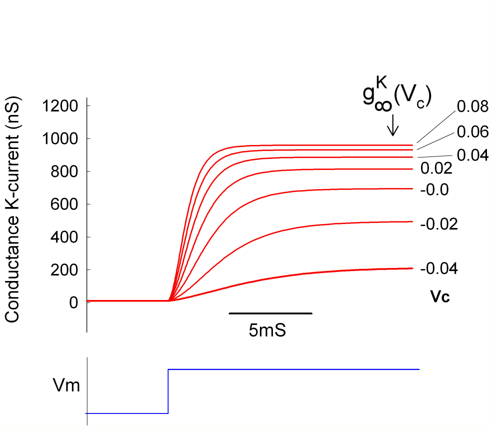
$$g_K = I_K/(V_m - E_K)$$

since $V_m = V_c$, and we know I_K and E_K

- Also, $g_K = g_{max}^K n^q$, with $0 \leq n \leq 1$

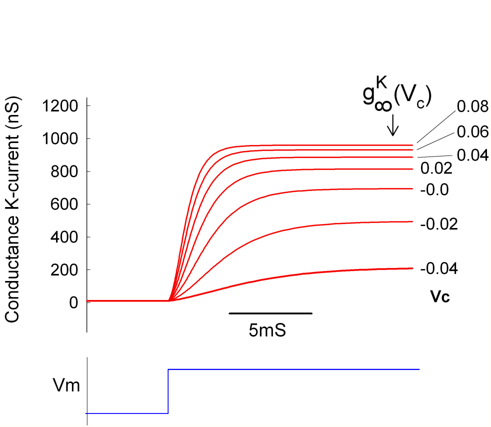
Finding g_{max}



- Conductance at equilibrium $g^K_\infty(V_c)$ is

$$g^K_\infty(V_c) = g^K_{max} n^p_\infty(V_c)$$

Finding g_{max}



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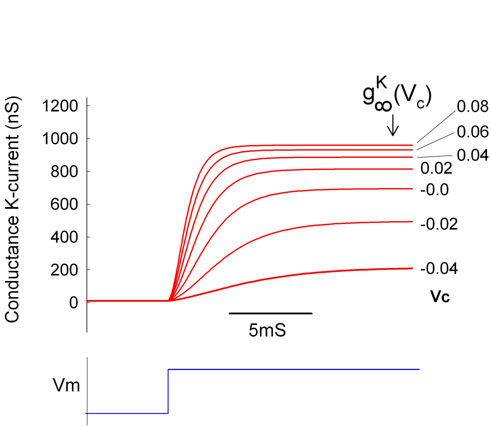

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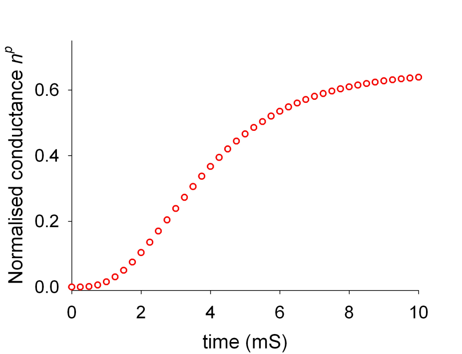
- As V_c increases, it appears that $g^K_\infty(V_c)$ increases and is reaching its limiting value g^K_{max} with $n^p_\infty(V_c) = 1$
- So, with sufficiently large V_c

$$g^K_\infty(V_c) \approx g^K_{max}$$

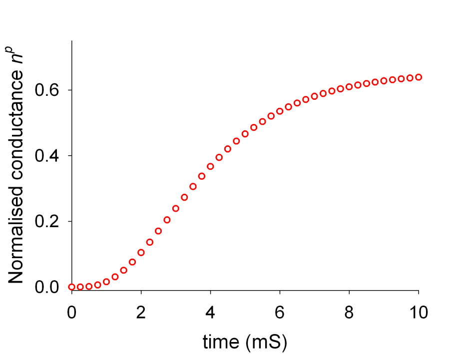
Outline

Finding p
The data



- The following phase of analysis occurs for fixed V_c

Finding p
The data

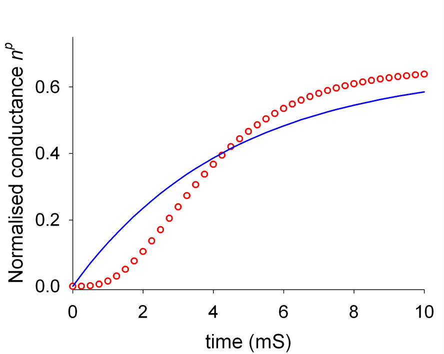


- The following phase of analysis occurs for fixed V_c
- The (virtual cell) data points are for the *normalised conductance* $n^p(t)$

$$n^p(t) = \frac{g^K(t)}{g^K_{max}}$$

which lies between 0 and 1 (typically, $g^K_{max} \ll 1$)

Finding p
Fitting the data

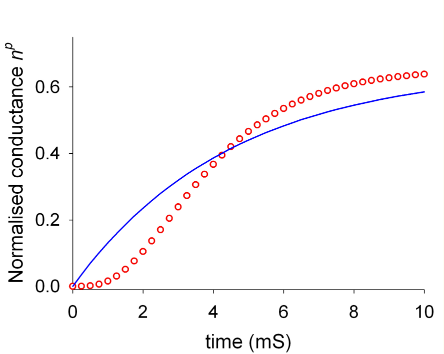


- Let p^* be an estimate of p; calculate the corresponding estimate n^*_∞ of n_∞

$$n^*_\infty = \left(n^p_\infty\right)^{\frac{1}{p^*}}$$

$p^* = 1$ and $n^*_\infty = n^p_\infty = 0.656$

Finding p
Fitting the data



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- Using n^*_∞ in the solution in (8) for $n(t)$, vary τ_n for the best fit to the data (automatically or by hand)

Finding p
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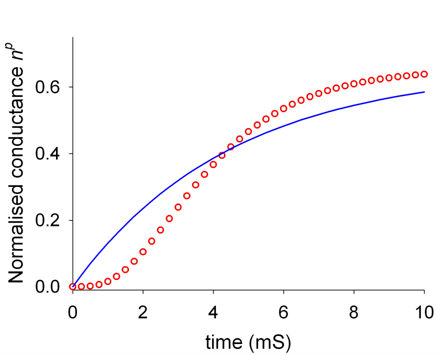


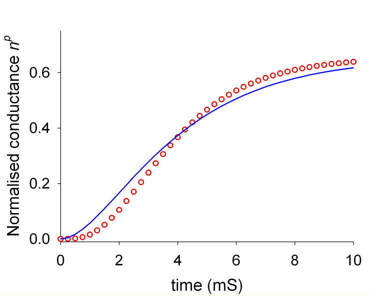
$p^* = 1$ and $n_\infty^* = n_\infty^p = 0.656$

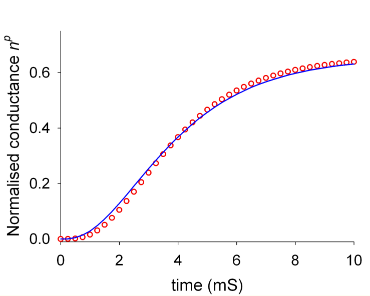
- Let p^* be an estimate of p; calculate the corresponding estimate n_∞^* of n_∞

$$n_\infty^* = \left(n_\infty^p\right)^{\frac{1}{p^*}}$$

- Using n_∞^* in the solution in (8) for $n(t)$, vary τ_n for the best fit to the data (automatically or by hand)
- The blue line is the best fit for $p^* = 1$

Finding p
Fitting the data

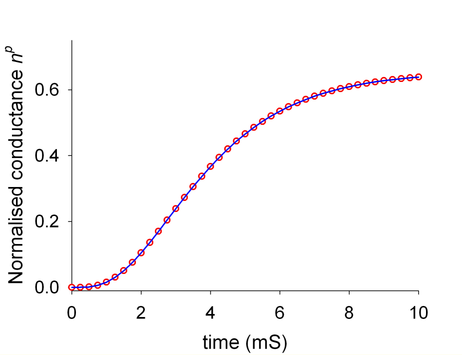




$p^* = 2$ and $n^*_\infty = (n^p_\infty)^{\frac{1}{2}} = 0.81$

$p^* = 3$ and $n^*_\infty = (n^p_\infty)^{\frac{1}{3}} = 0.869$

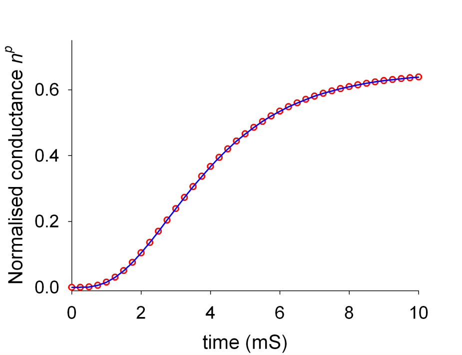
Finding p
Fitting the data



- $p = 4$ gives a good fit ...

$p^* = 4$ and $n_\infty^* = n_\infty^p = 0.9$

Finding p
Fitting the data

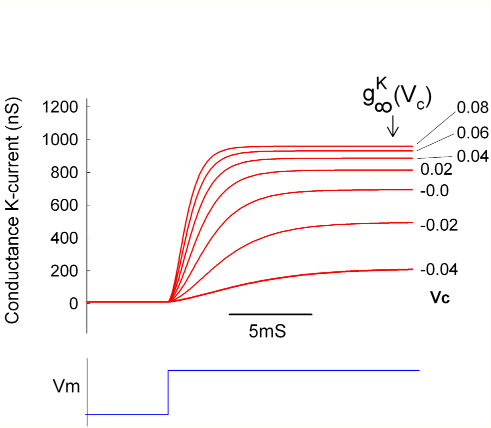


- $p = 4$ gives a good fit ...
- In fact it's an exact fit - because it was used to derive the 'data' !

$p^* = 4$ and $n_\infty^* = n_\infty^p = 0.9$

Outline

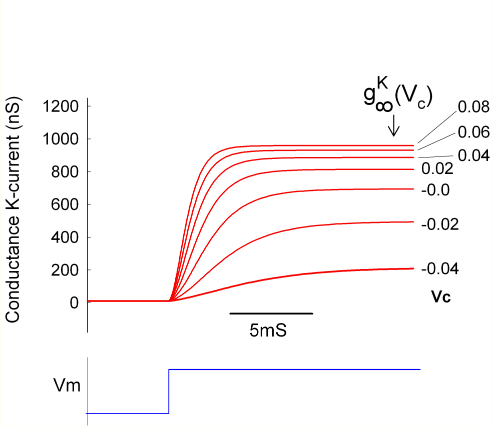
Finding $n_\infty(V_c)$



- Armed with g^K_{max} and p we can now find $n_\infty(V_c)$

$$n_\infty(V_c) = \left[\frac{g^K_\infty(V_c)}{g^K_{max}}\right]^{\frac{1}{p}}$$

Finding $n_\infty(V_c)$



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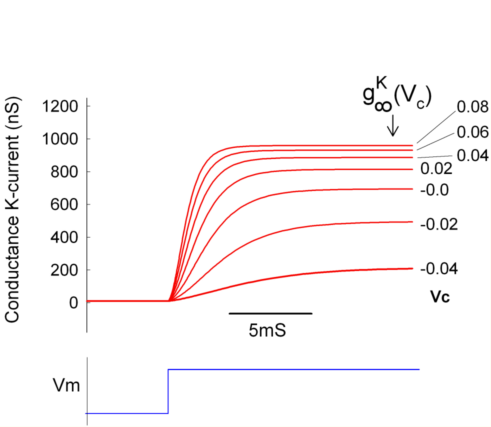
- Then find $\tau_n(V_c)$ by fitting $n(t)$ at each V_c (described by (8)) to the corresponding data

Finding $n_\infty(V_c)$



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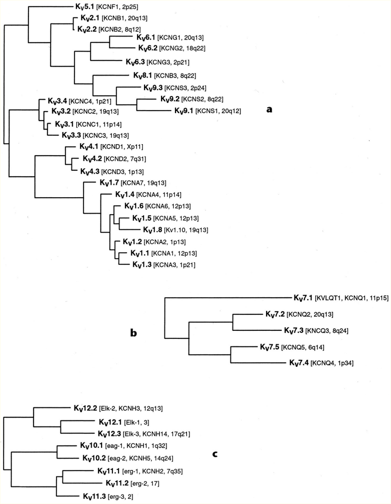
- Then find $\tau_n(V_c)$ by fitting $n(t)$ at each V_c (described by (8)) to the corresponding data
- Finding parameters for the Na$^+$ current requires more complex voltage clamp protocols...

Outline

Modelling the ‘zoo’ of ion-channels is potentially tractable



- Most K^+, Na^+ voltage gated currents can be described using the formalism developed here

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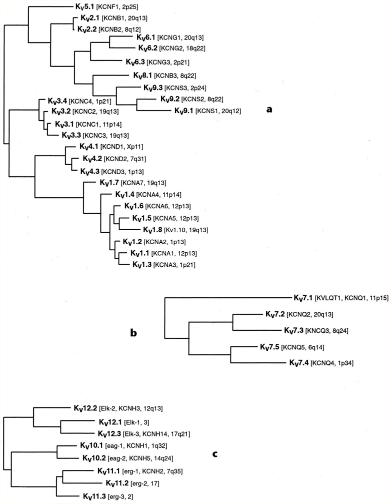


- Most K^+, Na^+ voltage gated currents can be described using the formalism developed here
- The diversity of K^+ channels is illustrated in the figure (determined using genetic and proteomic techniques). These are, all in principle, amenable to the HH formalism. (Same applies to Na^+ channels)

Outline

8 The ‘zoo’ of active ionic-current

9 Neural excitability and neural computation

10 Augmenting the formalism

Active currents allow a wide diversity of behaviour
Mechanism for neural computation

- The diversity of active currents supports a corresponding diversity of neural behaviours

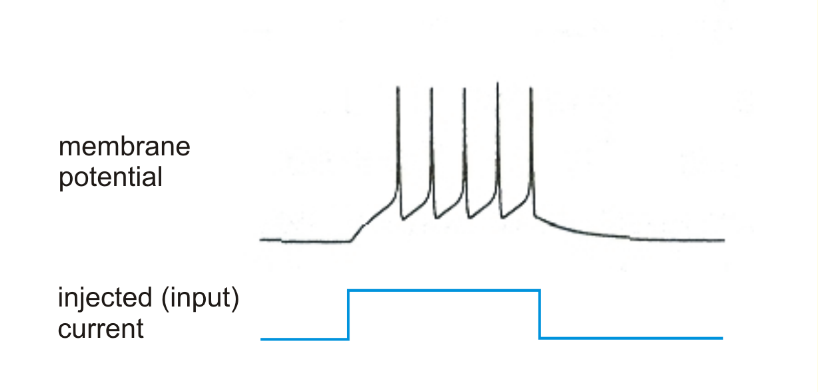
Active currents allow a wide diversity of behaviour

Mechanism for neural computation

- The diversity of active currents supports a corresponding diversity of neural behaviours
- These behaviours supply the building blocks or mechanisms on which neural computation is founded

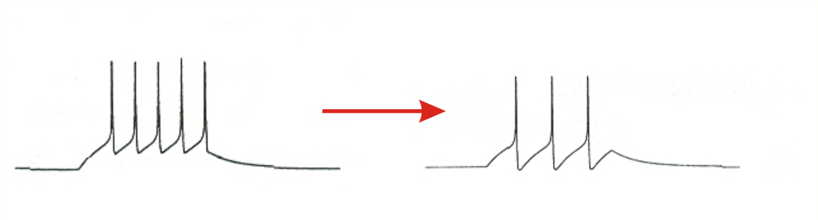
Neural excitability

Basic action potential generation with Na^+, K^+



Neural excitability

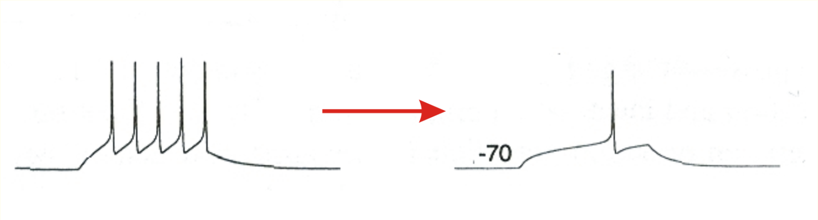
Enhanced repolarisation - reduction of firing rate



Ca^{2+}-activated K^{+} current, and high threshold Ca^{2+} current I_L

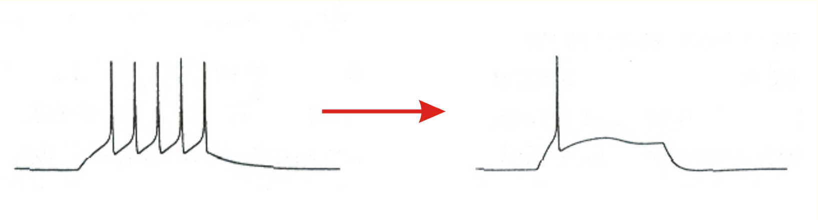
Neural excitability

Delay to onset of firing - temporal filter



Transient K^+ current I_A

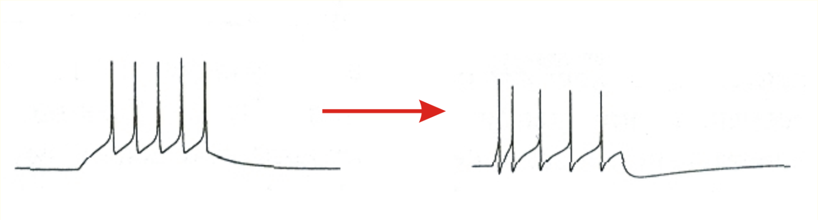
Neural excitability
Decreased response



persistent K^+ current I_M

Neural excitability

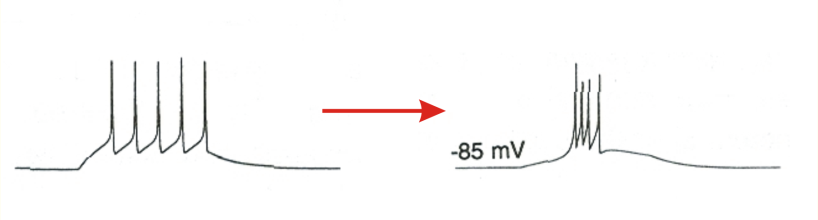
Firing rate accommodation or adaptation



Slow Ca^{2+}-activated K^{+} current, I_{AHP}

Neural excitability

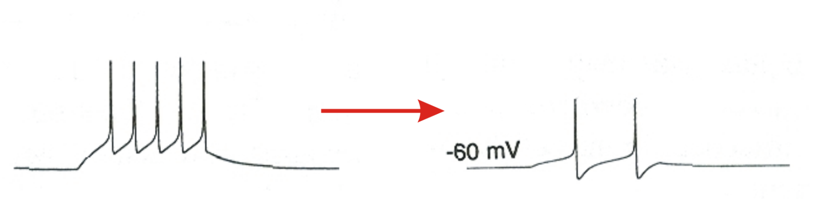
Rebound bursting 1



Bursting when excited from hyperpolarisation but...

Transient Ca^{2+} current I_T

Neural excitability
Rebound bursting 2



No bursting when excited from resting potential

Transient Ca^{2+} current I_T

Outline

8 The 'zoo' of active ionic-current

9 Neural excitability and neural computation

10 Augmenting the formalism

HH formalism augmented
Ca^{2+}-currents

- Basic form of HH-current

$$I(V_m, t) = g_{max} m(V_m, t)^P n(V_m, t)^Q (E_{rev} - V_m)$$

showing dependence of variables on V_m and t

HH formalism augmented

Ca^{2+}-currents

- Basic form of HH-current

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  showing dependence of variables on V_m and t

- Ca^{2+}-currents require an extension of the formalism where the driving force $(E_{rev} - V_m)$ is replaced by a more complex voltage dependent term, and there may be additional gating variables dependent on $[Ca^{2+}]_{in}$, as well as those dependent on V_m and t

HH formalism augmented

Synaptic input and morphology

- Synaptic input can be framed (phenomenologically) in a conductance based framework allowing incorporation in the HH formalism

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- Dividing the membrane into smaller iso-potential *compartments* overcomes this problem
- Both issues dealt with next time...

Summary

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Summary

- There is an alternative formulation of the Hodgkin Huxley equations in terms of variables (n_∞, τ_n) more amenable to experimental determination (than their rate-kinetic counterparts α, β)
- This alternative is based on the voltage clamp technique
- Carefully constructed experiments are required to determine n_∞, τ_n
- The HH formalism is extremely powerful, and can be extended to accommodate most channels, synaptic input and morphology

References and further reading

Reread references given in the last lecture (which will have incorporated the voltage clamp formalism into their descriptions)