Section 2.3 . FitzHugh-Nagumo model

[approximate asymptotic reduction of the Hodgkin-Huxley model]

Assumptions:
1) τ_m is small so $m \approx m_\infty(V)$ $\quad (\tau_m \ll \tau_n, \tau_h)$
(m rapidly reaches its quasistable value, using ③)

Recall eqn ③ $\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}$

2) $\tau_n = \tau_h$ (not perfect, see graph 2, but a decent approximation)

3) $n_\infty + h_\infty = \text{const}, \bar{h}$ (motivated by graph 1)
$\Rightarrow n + h = \bar{h}$ (using ② and ④)

$$\frac{d}{dt}(n+h) = \bar{h} - (n+h)$$
$$\Rightarrow (n+h) = \bar{h} + ce^{-t}$$

This system is true for all time so it eventually settles to $n + h = \bar{h}$

This reduces the Hodgkin-Huxley model (four ODEs for V, n, m, h) to the two-dimensional system for V and n: (see problem sheet 2 for this)

$$C_m \frac{dV}{dt} = I_{app} - \left(g_K (V - V_K) n^4 + g_{Na} (V - V_{Na}) m_\infty^3(V)(\bar{h} - n) + g_L (V - V_L)\right)$$
$$\tau_n(V) \frac{dn}{dt} = n_\infty(V) - n$$

We'll see if some of these parameters are small & negligible

Let's non-dimensionalise the system:

$$v = \frac{V - V_{eq}}{V_{Na} - V_{eq}} \quad \text{and} \quad t = \tau_n(V_{eq})\, t'$$

voltage

v sets to 0 rather than V_{eq}.

resting potential for Na^+

Dimensionless parameters

$$I^* = \frac{I_{app}}{g_{Na}(V_{Na} - V_{eq})} \qquad V_K^* = \frac{-(V_K - V_{eq})}{V_{Na} - V_{eq}}$$
$$\gamma_K = \frac{g_K}{g_{Na}} \qquad V_L^* = \frac{V_L - V_{eq}}{V_{Na} - V_{eq}}$$
$$\gamma_L = \frac{g_L}{g_{Na}} \qquad \varepsilon = \frac{C_m}{g_{Na}\tau_n}$$

This leads to the dimensionless system

$$\frac{dn}{dt} = n_\infty(v) - n \quad ①$$
$$\varepsilon \frac{dv}{dt} = I^* - g(v, n) \quad ②$$

where $g(v,n) = \gamma_K (v + V_K^*) n^4 + \gamma_L (v - V_L^*) - (1 - v)(\bar{h} - n) m^3(v)$ with

$\boxed{\text{Key point} : \varepsilon \ll 1}$ where $\varepsilon = \dfrac{C_m}{g_{Na}\tau_n}$

This is why we non-dimensionalize — to see the relative parameter sizes.

Key point: $\varepsilon \ll 1$, so V quickly reaches a quasisteady equilibrium in ② and $\gamma_L \ll 1$, so $g(v,n)$ simplifies:

→ you can see this through ②

$$g(v,n) = \gamma_K (v + v_K^*) n^4 - (1-v)(\bar{h} - n) m_\infty^3(v)$$

$$\frac{dv}{dt} = \frac{I^* - g(v,n)}{\varepsilon}$$

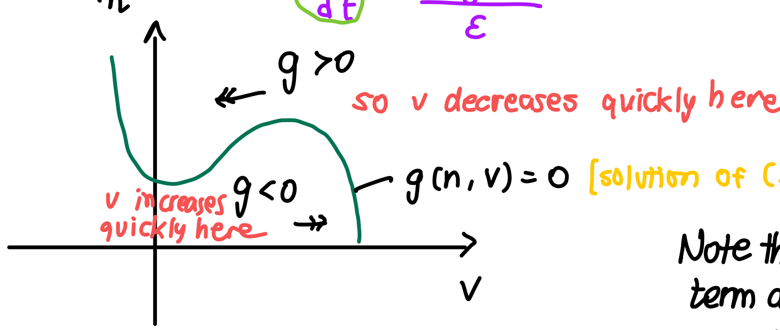
PHASE PLANE ANALYSIS

Start by considering the case $\boxed{I^* = 0}$ (i.e. no applied current, from ②, v is given by $g=0$)

Setting $\varepsilon = \gamma_L = 0$ in ② gives $\dfrac{n^4}{\bar{h} - n} = \dfrac{(1-v)\, m_\infty^3(v)}{\gamma_K (v + v_K^*)}$ (*) an algebraic relationship between n and v

(identified as small)

large & -ve $\dfrac{dv}{dt} = \dfrac{\cancel{I^*}^{\,0} - g(v,n)^{\,>0}}{\varepsilon}$

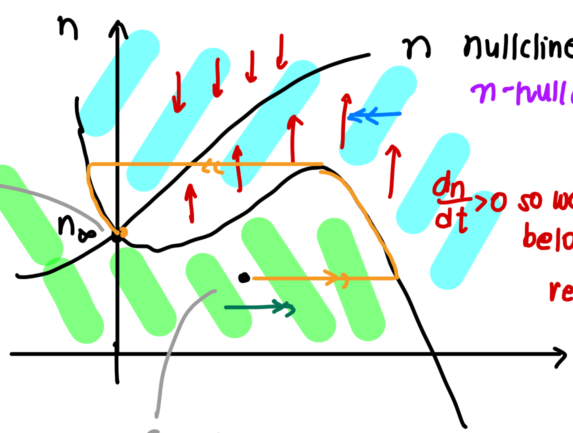


Since $\varepsilon \ll 1$ we know that the system quickly jumps onto this nullcline

Note that including this γ_L term doesn't change these qualitative features.

Now we just need to add the $n=0$ nullcline ($n = n_\infty(v)$)

(nullclines in general are when you set the $\frac{d}{dt}$ to zero)



n-nullcline when $\frac{dn}{dt} = 0 \Rightarrow n = n_\infty(v)$ by eqn ①

$\frac{dn}{dt} > 0$ so we move up below the n-nullcline, recall by ① $\frac{dn}{dt} = n_\infty - n$

PHASE PLANE ANALYSIS

until we go back to equilibrium (recall that eqm is when $v=0$) $v=0 \Rightarrow V = V_{eq}$ (when both $\dot{v} = \dot{n} = 0$)

v-nullcline when $\frac{dv}{dt} \Rightarrow g(v,n) = I^* = 0$ by eqn ②

Perturbing around the fixed point we see that trajectories spiral around so the fixed point is a spiral.

STABILITY

Linearize near the fixed point, $n = n_\infty$, $v = 0$

Set $v = v$

$n = n_\infty + N$, $v, N \ll 1$

and ODEs become
$$\frac{d}{dt}\begin{pmatrix} N \\ v \end{pmatrix} = \overbrace{\begin{pmatrix} -1 & \frac{dn_\infty}{dv} \\ -\frac{1}{\varepsilon}\frac{\partial g}{\partial n} & -\frac{1}{\varepsilon}\frac{\partial g}{\partial v} \end{pmatrix}}^{\underline{\underline{M}}}\begin{pmatrix} N \\ v \end{pmatrix}$$

Stability is given by $\det(\underline{\underline{M}})$ and $\mathrm{tr}(\underline{\underline{M}})$ $\Rightarrow$ $\det(\underline{\underline{M}}) < 0 \Rightarrow$ saddle

trace

$\det(\underline{\underline{M}}) > 0$ and $\mathrm{tr}(\underline{\underline{M}}) < 0$

$\Rightarrow$ node or spiral

Trace and determinant method

Eigenvalues can be written as

$$\lambda = \frac{\mathrm{Tr}(\underline{\underline{M}}) \pm \sqrt{(\mathrm{Tr}\underline{\underline{M}})^2 - 4\det(\underline{\underline{M}})}}{2}$$

We have $\det(\underline{\underline{M}}) = \frac{1}{\varepsilon}\left(\left.\frac{\partial g}{\partial v}\right|_{n=n_\infty} + \left.\frac{\partial g}{\partial n}\right|_{n=n_\infty}\frac{\partial n_\infty}{\partial v}\right)$

Now $\det(\underline{\underline{M}}) > 0$

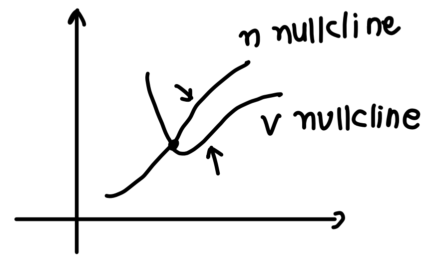
Proof Now slope of n nullcline $= \frac{dn_\infty}{dv}$

Slope of v nullcline $= -\dfrac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$ since $g(v,n) = 0$

Differentiate $g(v, n(v)) = 0$ wrt v:

$\frac{\partial g}{\partial n}\frac{\partial n}{\partial v} + \frac{\partial g}{\partial v} = 0$, $\frac{\partial n}{\partial v} = \dfrac{-\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$.

and from graph: slope of n nullcline > slope of V nullcline



$$\Rightarrow \quad \frac{dn_\infty}{dv} > -\frac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$$

. This implies that

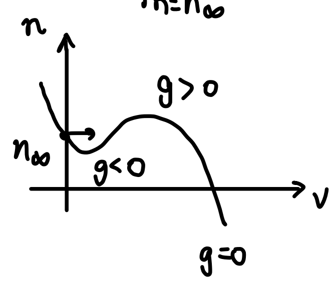
$\det(\underline{M}) > 0$ and $tr(\underline{M}) = -(-\frac{1}{\varepsilon}\frac{\partial g}{\partial v}\Big|_{n=n_\infty}$

Fixed point is stable if $tr(M) < 0 \Rightarrow \frac{\partial g}{\partial v}\Big|_{n=n_\infty} > -\varepsilon$

$\frac{\partial g}{\partial v}\Big|_{n=n_\infty} > 0$ because of picture

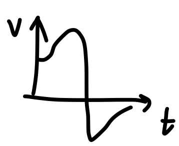
& definitely $\frac{\partial g}{\partial v}\Big|_{n=n_\infty} > -\varepsilon$

Fixed point is stable.



$\frac{\partial g}{\partial v}\Big|_{n=n_\infty}$ means: rate of change of g in the v direction while keeping n fixed (start on $g=0$, or v nullcline)

Although the fixed point is stable, a small increase in v will lead to a large excursion - this is the action potential again. If we plotted v versus t we would obtain the graph we drew earlier.



Limit cycles

If we apply a current then this will push us off the equilibrium point and send us round the trajectory before starting the process all over again - we only need a bit of energy to achieve this.

Slightly different to a conventional limit cycle because in this case you need to give a bit of energy to kick it round the cycle (i.e. it doesn't continue on the loop w/o energy input)

The FitzHugh-Nagumo model is the reduction of the four-dimensional Hodgkin-Huxley model to a two-dimensional system.

The FitzHugh-Nagumo equations are an analytically similar pair of equations that have the same behaviour.

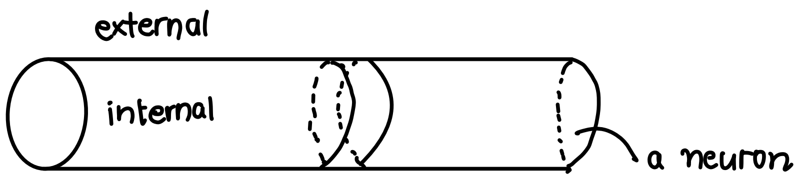
easier to handle this mathematically

FitzHugh-Nagumo model	FitzHugh-Nagumo equations
$\varepsilon \dot{v} = I^* - \underbrace{g(v,n)}_{\text{implicit function}}$	$\varepsilon \dot{v} = I^* + f(v) - w$
$\dot{n} = n_\infty(v) - n$	$\dot{w} = \gamma v - w$ ← linear fcn
	cubic fcn ↙ $f(v) = v(v-a)(1-v) \quad 0 \le a \le 1$

Fun fact of the day: Nerve signals can travel at speeds of 270 mph. This allows you to react quickly to various stimuli, such as pulling your hand away from a hot surface or reacting to a sudden loud noise

Wave propagation in neurons

We now explore spatial dependence of the Hodgkin-Huxley model.



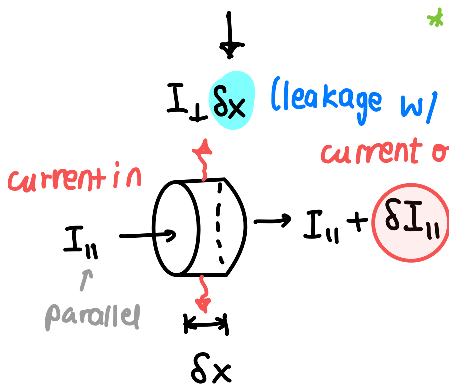
* the axon behaves like an electric cable

$I_\perp$ = transmembrane current per unit length

$I_\parallel$ = axial current

R = axial resistance (unwillingness of axon to transmit current down it)

C = capacitance per unit length (ability to store charge)



(leakage w/ these axons because they are not perfectly insulated)

In a segment δx the total change is $CV\delta x$.

if I apply to something w/ capacitance C, a voltage V, then the total charge held by this small segment is $CV\delta x$

Charge conservation: $\frac{\partial}{\partial t}(CV\delta x) = \underbrace{-I_\perp \delta x}_{\text{current lost through walls}} + \underbrace{I_\parallel}_{\text{current in left}} - \overbrace{(I_\parallel + \delta I_\parallel)}^{\text{current out right}}$

(only this increases the total charge $CV\delta x$)

Assuming C = const.

$$C\frac{\partial V}{\partial t}\delta x = -I_\perp \delta x + \cancel{I_\parallel} - \cancel{I_\parallel} - \delta I_\parallel$$

$$\Rightarrow C\frac{\partial V}{\partial t} = -I_\perp - \frac{\delta I_\parallel}{\delta x}$$

Taking the limit as $\delta x \to 0$

$$\boxed{C\frac{\partial V}{\partial t} = -I_\perp - \frac{\partial I_\parallel}{\partial x} \quad (*)}$$

* the axon's internal electrical potential V is now a function of distance x along the cable and time t.

$-\delta V = I_\parallel R \delta x$ Definition of resistance (i.e. $\Delta V = I_\parallel R_{total}$)

$\Rightarrow \frac{\partial V}{\partial x} = -I_\parallel R \Rightarrow I_\parallel = -\frac{1}{R}\frac{\partial V}{\partial x}$

So in $(*)$,

$$\boxed{C\frac{\partial V}{\partial t} = -I_\perp + \frac{1}{R}\frac{\partial^2 V}{\partial x^2}} \quad (\dagger)$$

This is called the Telegraph equation (or the cable equation) assuming the axon has a circular cross section

If the neuron perimeter is $p = \pi d$, then $I_\perp = p(I_i - I_{app})$

$\uparrow$ diameter

need it per unit length

$\underbrace{I_i - I_{app}}$ current per unit area between inside and outside as defined earlier

capacitance per unit length

and $C = pC_m$

Capacitance per unit area

If R_c = resistivity of medium, then $R = \frac{R_c}{A}$ where $A = \frac{1}{4}\pi d^2$ is the neuron cross-sectional area. In (+) this gives $\cancel{\pi d}\, C_m \frac{\partial V}{\partial t} = -\cancel{\pi d}(I_i - I_{app}) + \frac{\cancel{\pi d^2}}{4R_c}\frac{\partial^2 V}{\partial x^2}$

$$\Rightarrow \quad C_m \frac{\partial V}{\partial t} = I_{app} - I_i + \frac{d}{4R_c}\frac{\partial^2 V}{\partial x^2}$$

Non-dimensionalization

$$V = \frac{V - V_{eq}}{V_{Na} - V_{eq}}, \quad I_i = g_{Na}(V_{Na} - V_{eq})\, g(n, v), \quad x = l\hat{x}, \quad t = T_n \hat{t}$$

to be chosen later

(same as earlier non-dimensionalization)

where l is to be chosen later

This gives

$$\begin{cases} \varepsilon \frac{\partial v}{\partial t} = I^* - g(n, v) + \varepsilon^2 \frac{\partial^2 v}{\partial x^2} \\ \frac{\partial n}{\partial t} = n_\infty(v) - n \end{cases}$$

See problem sheet ② for derivation of this

This is the $\boxed{\text{space dependent version of the FitzHugh-Nagumo model}}$ - it's the same but just with a $\frac{\partial^2 v}{\partial x^2}$ term. [spatial variation of V adds diffusion term]

Let's analyze action potentials in this case. We could analyse the equations above but it is easier to analyse the space-dependent FitzHugh-Nagumo equations (the equations that display the same qualitative behaviour but are easier to analyse)

$$\varepsilon \frac{\partial v}{\partial t} = f(v) - \omega + \varepsilon^2 \frac{\partial^2 v}{\partial x^2} \qquad f(v) = v(v-a)(1-v)$$

$$\frac{\partial w}{\partial t} = \gamma v - \omega$$

and γ large enough that $(0,0)$ is the unique steady state.