Mathematical Physiology MT2020

Lecture 1 Trans-membrane ion transport

Cells

The basic living unit of the body is the cell

These have different functions - e.g. red blood cells carry oxygen, nerve cells transmit electrical signals, muscle cells contract

The cell membrane is a semi-permeable layer which separates the intra-cellular cytoplasm from the extracellular fluid. The cytoplasm is fluid and contains various bits of cellular 'machinery'

Active and passive transport

The intra-cellular and extra-cellular fluids contain various salts in solution (thus as ions), notably sodium Na^+, potassium K^+, calcium Ca^{2+}, chloride Cl^- [an ion Z^- is a Z atom with an extra electron (negative charge). Similarly Z^+ has one less electron]

Extra- and intra-cellular concentrations are different:

e (extracellular) { Na^+ 437 mM, K^+ 20 mM, Cl^- 556 mM } e.g.

cell membrane

i (intracellular) { Na^+ 50 mM, K^+ 397 mM, Cl^- 40 mM }

1 mM (1 millimolar) $= 10^{-3}$ M, 1 M = 1 mole l^{-1} (litre)

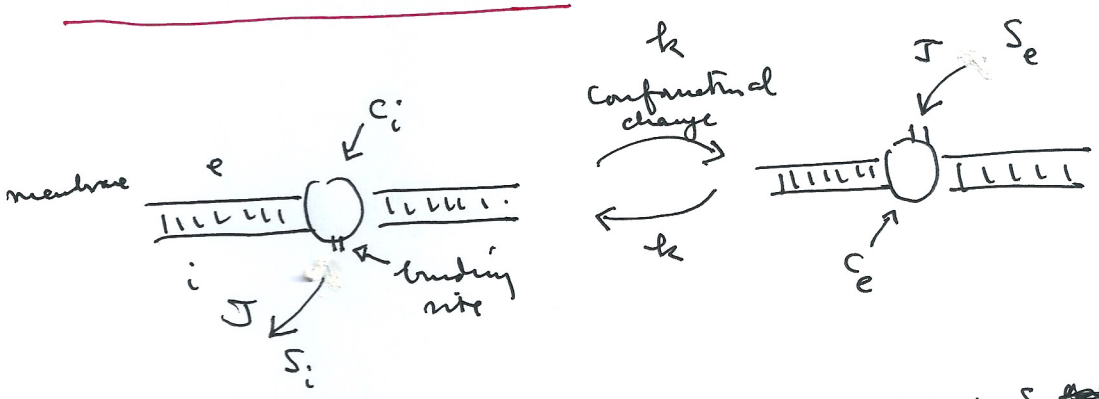
Passive transport

This arises due to the difference in ionic concentrations,

e.g. diffusive flux $\propto c_i - c_e$ (c_i, c_e internal, external concentrations)

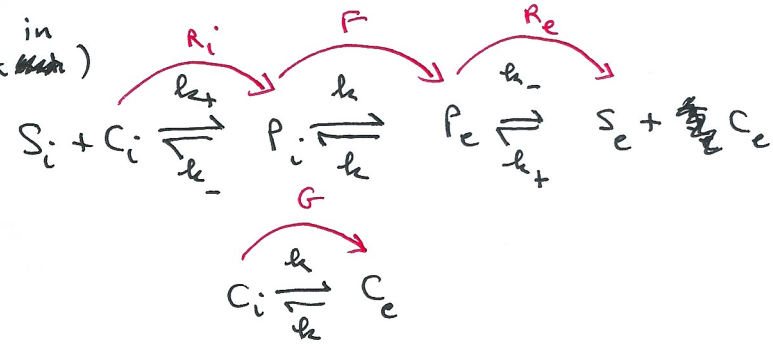
or by carrier-mediated transport – ion binds to protein in cell wall

Carrier-mediated transport



In a steady state reaction scheme where the substrate S binds to the carrier protein C to form a complex P, & the flux from C_i to C_e is J (flux in)

we have



Denote the overall rates

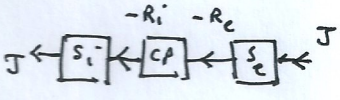
$$R_i = k_+ S_i C_i - k_- P_i$$

$$R_e = k_- P_e - k_+ S_e C_e$$

$$F = k(P_i - P_e)$$

$$G = k(C_i - C_e)$$

[S_i internal concentration, S_e external, etc.]



J is the flux 'through' the carrier protein So in a steady state, J is supplied to S_e (and removed from S_i)

Then (law of mass action)

$$\begin{aligned}
\dot{S}_i &= -J - R_i \\
\dot{S}_e &= R_e + J \\
\dot{P}_i &= R_i - F \\
\dot{P}_e &= F - R_e \\
\dot{C}_i &= -R_i - G \\
\dot{C}_e &= G + R_e
\end{aligned}$$

Michaelis-Menten type quasi-steady state hypothesis

$\Rightarrow -J = R_i = R_e = F = -G$ — 4 relations, so there must be 2 conservation laws:

$$P_i + P_e + C_i + C_e = C_0 \qquad \text{\# channels}$$

$$S_i + S_e + P_i + P_e = S_0 \qquad \text{total substrate}$$

As an exercise, one derives

$$J = \frac{k_- k\, C_0}{2k_+} \left[\frac{S_e - S_i}{(K_m + S_i)(K_m + S_e) - K_d^2} \right]$$

$$K_m = \frac{k_- + k}{k_+} \qquad K_d = \frac{k}{k_+}$$

Note the Michaelis-Menten-like form of this expression.

Active transport occurs through the action of 'pumps' (e.g. Na^+-K^+ pump) which use energy to transport ions up concentration gradients. The combination allows the existence of a membrane potential V, which is the electrical potential of the intracellular fluid relative to the external (i.e., $V_i - V_e$).

(note: no charge movement)

Consider a single charged ion S, or S^{z+} with z = valency (= number of +ve charges)

Suppose internal & external concentrations S_i & S_e

So the outward (diffusive) flux is $-D\frac{\partial S}{\partial x}$, x = distance outwards through the membrane

But equally any excess charge $V_i - V_e$ causes an ionic current down the electrical gradient $-u\frac{z}{|z|}S\frac{\partial \phi}{\partial x}$, ϕ = local electrical potential

u is called the mobility & $D = \frac{uRT}{|z|F}$ (Einstein)

R: gas constant
T: absolute temperature
F: Faraday's constant

In equilibrium, no net flux, $-D\frac{\partial S}{\partial x} - \frac{uz}{|z|}S\frac{\partial \phi}{\partial x} = 0$,

$$\Rightarrow \quad V \left(= V_i - V_e\right) = \frac{RT}{zF}\ln\left(\frac{S_e}{S_i}\right)$$

this is the Nernst potential

e.g. $K^+_i > K^+_e$: $V_K = -77\,mV$ (millivolt, $10^{-3}V$)

$Na^+_i < Na^+_e$ $V_{Na} = 56\,mV$

□

MP lecture 2

Ionic currents

Some basic electrical information:

ions are (neutrally-charged) atoms with extra (-ve charge) or missing (+ve charge) electrons: Na^+, Ca^{2+}, K^+, Cl^-, SO_4^{2-} (sulphate) etc.

electrical potential (V: volts) is proportional to charge (Q: coulombs)

$Q = CV$: C is capacitance

current I is rate of change of charge, unit A (amp) = Cs^{-1}

(or more generally is the flux of charge)

Units Q: C coulomb → C: capacitance: F (farad) = CV^{-1}

V: V volt

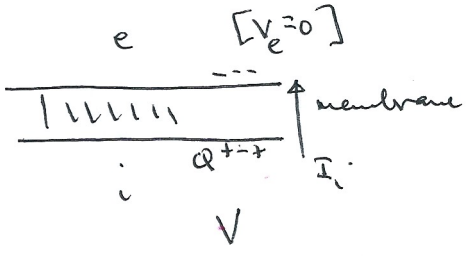
I A amp = Cs^{-1}

Other law, Ohm's law $V = IR$, R is resistance: Ω (ohm) = VA^{-1}

or $I = gV$, g is conductance S (siemens) = AV^{-1}

Power is VI : W (watt) = Js^{-1}

So we see that $1V = 1 J C^{-1}$ ∴ all electrical units are related to the coulomb



If V is intracellular potential (V)

Q is charge (/unit area)

I_i is outwards ionic current (/unit area)

C is capacitance (/unit area)

then $I_i = -\frac{dQ}{dt} = -C\dot{V}$ is an equation for V.

And we take (for a single ion S)

$$I_S = g_S(V - V_S) \qquad g_S \text{ is conductance}$$

units V: volts V
I A cm^{-2}
C F cm^{-2}
g $A V^{-1} cm^{-2} = S cm^{-2}$

Gates

We conceptualise transport through the proteins which act as gates, which can be Open or Closed.

With the simple assumption

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

& n is the fraction of open gates, then $\dot{n} = \alpha(1-n) - \beta n$

or $\tau \dot{n} = n_\infty - n$, where $n_\infty = n_\infty(V)$

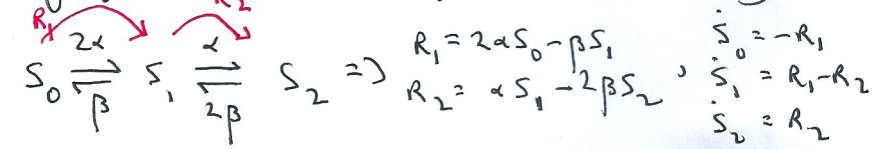
& the conductance would be gn and depend on V, as observed.

Multiple gates

We might a channel has more than one gate protein,

e.g. 2 identical gates 

If S_i is the proportion of channels having i open gates

then 

$$\Rightarrow \begin{matrix} R_1 = 2\alpha S_0 - \beta S_1 \\ R_2 = \alpha S_1 - 2\beta S_2 \end{matrix}, \quad \begin{matrix} \dot{S}_0 = -R_1 \\ \dot{S}_1 = R_1 - R_2 \\ \dot{S}_2 = R_2 \end{matrix}$$

and ...

there is a solution

$S_0 = (1-n)^2 \quad S_1 = 2n(1-n) \quad S_2 = n^2$ (note binomial coefficients)

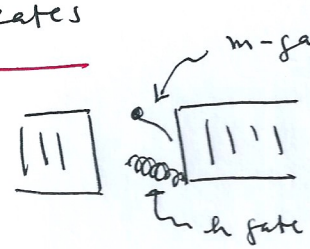
if $\dot{n} = \alpha(1-n) + \beta n$ & the conductance is $g n^2$ $(= g S_2)$

These results generalise, e.g. 3 identical gates → conductance is $g n^3$

$\dot{n} = \alpha(1-n) - \beta n$

Non-identical gates

E.g.

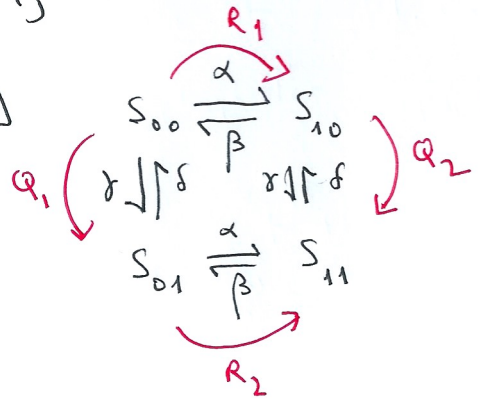


1 m-gate with $C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O_m$

$C_2 \underset{\delta}{\overset{\gamma}{\rightleftharpoons}} O_m$

Let S_{ij} be channels with i open m gates j open h gates

[ex]



$R_1 = \alpha S_{00} - \beta S_{10}$

$R_2 = \alpha S_{01} - \beta S_{11}$

$Q_1 = \gamma S_{00} - \delta S_{01}$

$Q_2 = \gamma S_{10} - \delta S_{11}$

& $\dot{S}_{00} = -R_1 - Q_1$

$\dot{S}_{01} = Q_1 - R_2$

$\dot{S}_{10} = R_1 - Q_2$

$\dot{S}_{11} = R_2 + Q_2$

& solutions $S_{00} = (1-m)(1-h)$

$S_{10} = m(1-h)$

$S_{01} = (1-m)h$

$S_{11} = mh$

$\dot{m} = \alpha(1-m) - \beta m$

$\dot{h} = \gamma(1-h) - \delta h$

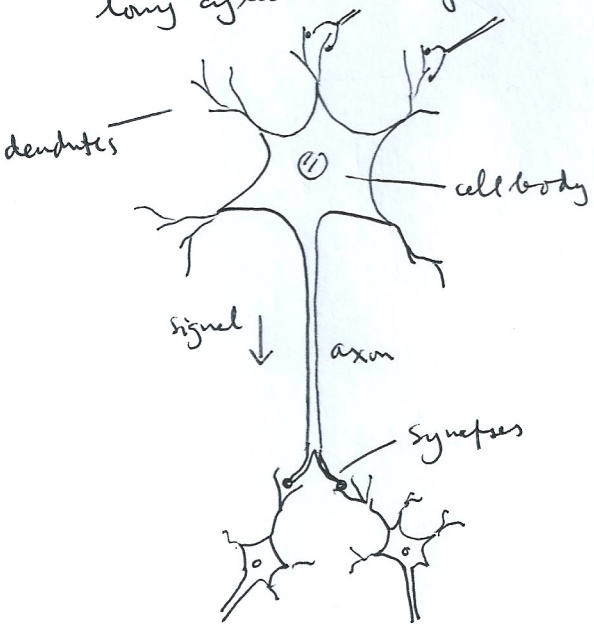
& Conductance $= g m h$

(ex.).

MP Lecture 3

The Hodgkin-Huxley model

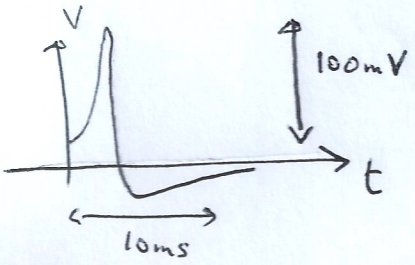
The nervous system is a communication system formed by nerve cells or neurons. Information is propagated along long cylindrical segments called axons by electrochemical signals.



Communication between cells occurs at junctions between synapses and dendrites

In the space-clamped axon (experimentally, insert an electrode to keep V independent of space),

the axon is excitable: the rest state is stable but can be perturbed to produce an action potential



[In practice, this action potential propagates along the axon.]

If I_i is the ionic current out, & I_{app} is the applied current (in)

then $I_i + C_m \dot{V} = I_{app}$

C_m capacitance / unit area ($F\,cm^{-2}$)

I current / unit area ($A\,cm^{-2}$)

The Hodgkin–Huxley model (derived experimentally) is

$$I_i = g_{Na} m^3 h (V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L)$$

Sodium current | potassium current | leakage current (mainly Cl^-)

Nernst potentials e.g. $V_{Na} = +56$ mV, $V_K = -77$ mV, $V_L = -60$ mV

(roughly) $g_{Na} \sim 120$ mS cm^{-2}, $g_K \sim 36$ mS cm^{-2}, $g_L \sim 0.3$ mS cm^{-2}, $C_m \sim 1$ μF cm^{-2}

When $I_{app} = I_i = 0$, the equilibrium $V = V_{eq}$ is the resting potential $\simeq -70$ mV

Gate variables m, n, h satisfy $\dot{m} = \alpha_m(1-m) - \beta_m m$ etc.

whence $\tau_m \dot{m} = m_\infty - m$, etc. with $\tau_m = \frac{1}{\alpha_m + \beta_m}$, $m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$

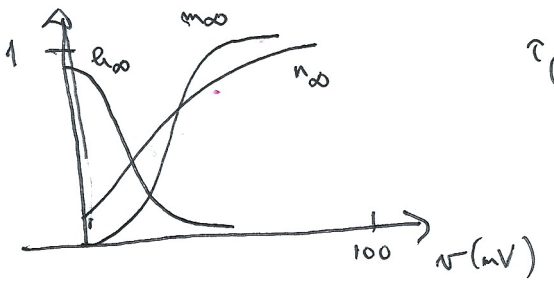
(Similarly for n & h)

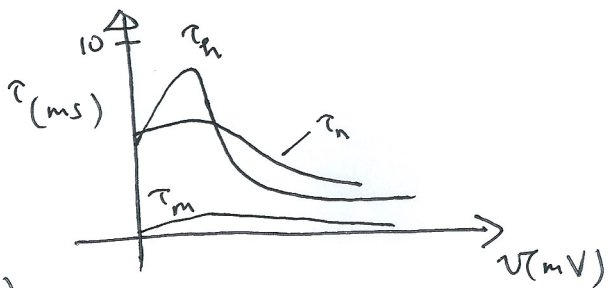
As functions of $v = V - V_{eq}$, H–H fitted to their data: (α, β in ms, v in mV)

$$\alpha_n = \frac{0.01(10-v)}{\exp\left[\frac{10-v}{10}\right] - 1} \qquad \beta_n = 0.125 \exp\left[-\frac{v}{80}\right]$$

$$\alpha_m = \frac{0.1(25-v)}{\exp\left[\frac{25-v}{10}\right] - 1} \qquad \beta_m = 4 \exp\left[\frac{-v}{18}\right]$$

$$\alpha_h = 0.07 \exp\left[-\frac{v}{20}\right] \qquad \beta_h = \frac{1}{\exp\left[\frac{30-v}{10}\right] + 1}$$





The mechanism of the action potential

Note m, h are Na^+ gates
n is K^+ gate

At rest, Na^+ & K^+ channels are more or less shut.

Perturbation increasing v

$\Rightarrow$ Na^+ gates open

$\Rightarrow$ Na^+ floods in

$\Rightarrow$ v increases

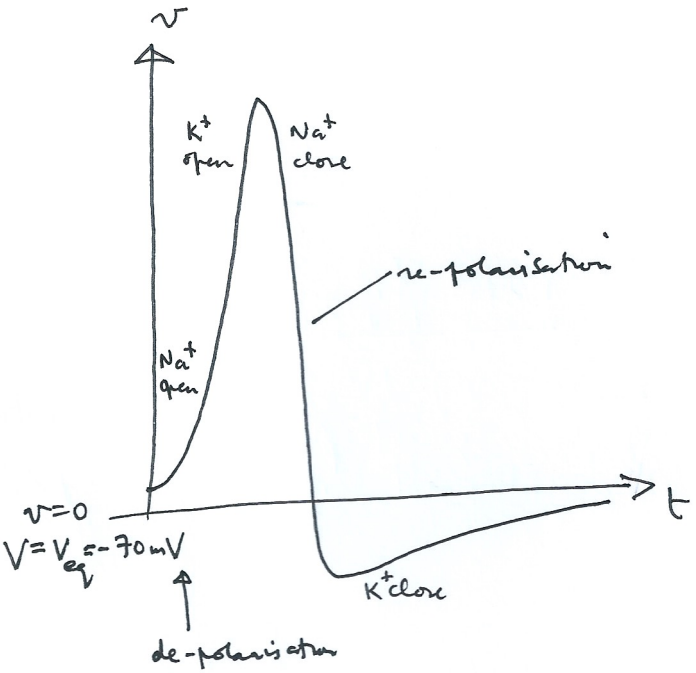
$\Rightarrow$ $\begin{cases} h \text{ gates close}, Na^+ \text{ gates close} \\ n \text{ gates open}, K^+ \text{ gates open} \end{cases}$

$\Rightarrow$ K^+ floods out

$\Rightarrow$ v decreases (<0)

$\Rightarrow$ K^+ gates close

$\Rightarrow$ return to resting potential



The FitzHugh-Nagumo reduction

τ_n is small $\Rightarrow$ $n \simeq n_\infty(v)$

Take $\tau_n = \tau_h$ & $n_\infty + h_\infty = \bar{h}$ constant

$\Rightarrow$ $\tau_n(\dot{n}+\dot{h}) = \bar{h} - (n+h)$ $\Rightarrow$ $n+h = \bar{h} \approx 0.8$ after transient

$\Rightarrow$

$$C_m \dot{v} = I_{app} - \{ g_K (v - v_K) n^4 + g_{Na} (v - v_{Na}) m^3(v) (\bar{h} - n) + g_L (v - v_L) \}$$

$$\tau_n \dot{n} = n_\infty(v) - n$$

$v_K = V_K - V_{eq}$ etc.

Non-dimensionalisation (ex.).

$v = V - V_{eq}$, $v_{Na} = V - V_{Na}$, etc.

Scale $v \sim v_{Na}$, $t \sim \tau_n$ (constants assumed)

$I_i = g_{Na} v_{Na}\, g$ $\qquad I_{app} = g_{Na} v_{Na}\, I^*$

$\Rightarrow$

$$\dot{n} = n_\infty(v) - n$$

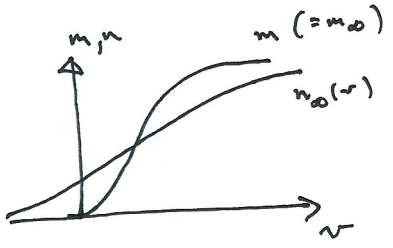
$$\varepsilon \dot{v} = I^* - g(v,n)$$

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

$\gamma_K = \frac{g_K}{g_{Na}} \sim 0.3$ $\qquad \gamma_L = \frac{g_L}{g_{Na}} \sim 0.003$, $v_K^* = -\frac{v_K}{v_{Na}} \sim 0.1$

$v_L^* = \frac{v_L}{v_{Na}} \sim 0.1$

$\varepsilon = \frac{C_m}{g_{Na} \tau} \sim 0.2 \times 10^{-2}$



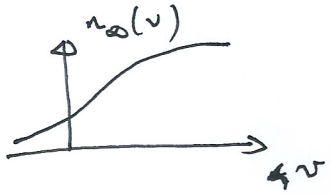
MP Lecture 4

FitzHugh - Nagumo (type) model

Phase plane analysis

$$\dot{n} = n_\infty(v) - n$$

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



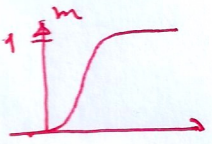
Start by taking $I^* = 0$.

Nullclines n-nullcline : $n = n_\infty(v)$

v-nullcline : $g(v,n) = 0$

$$g = \gamma_K (v + v_K^*) n^4 + \gamma_L (v - v_L^*) - (1-v)(\bar{h} - n) m^3(v)$$

$\gamma_K \sim 0.3$, $v_K^* \sim 0.1$, $\gamma_L \sim 0.003$, $v_L^* \sim 0.1$, $\bar{h} \sim 0.8$

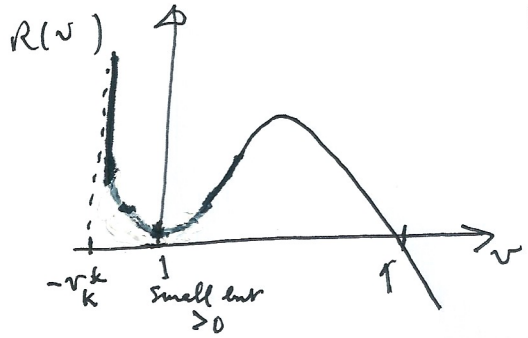


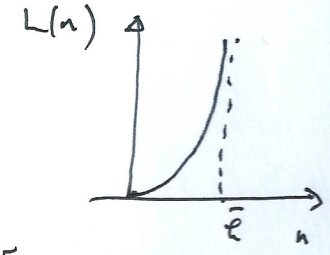
$\gamma_L \ll 1$ so $g = 0 \iff$

$$L(n) \equiv \frac{n^4}{\bar{h} - n} \simeq \frac{m^3(v)(1-v)}{\gamma_K (v + v_K^*)} \equiv R(v) \left[- \frac{\gamma_L (v - v_L^*)}{\gamma_K (v + v_K^*)(\bar{h} - n)} \right]$$

does this matter? — no

By inspection



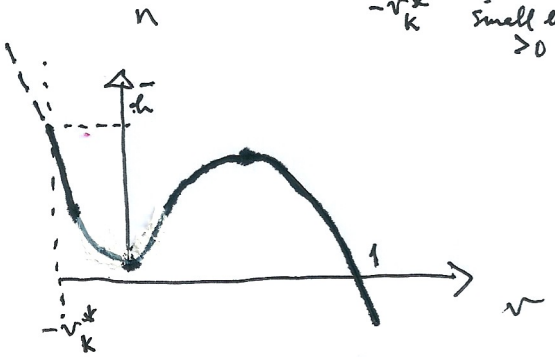


$n = L^{-1}[R(v)]$

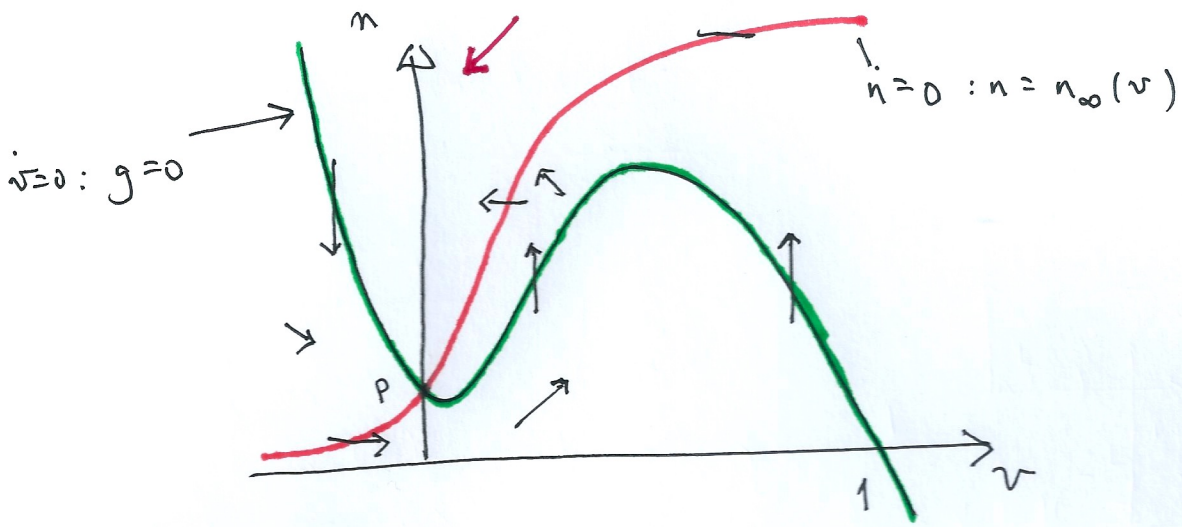
L^{-1} monotone increasing

$n \to \bar{h}$ when $R(v) \to \infty$

$\Rightarrow$



Note : by choice of scaling $g[0, n_\infty(0)] = 0$ (i.e. $V = V_{eq}$ when $v = 0$)



We assume only one fixed point as shown

1. Draw nullclines (intersections are fixed points)
   → horizontal + vertical directions on them
2. Find trajectory directions somewhere

e.g. $n \to \infty$ & $0 < v < 1$

then $\dot{n} = n_\infty(v) - n \to \dot{n} < 0$

$$C\dot{v} = -g = -\left[\gamma_K (v - v_K^*) n^4 + \gamma_L (v - v_L^*) - (1-v)(\bar{\epsilon} - n) m^3(v)\right]$$

$\to \dot{v} < 0$ (note $\Rightarrow g > 0$ above v-nullcline)

gives red arrow at top

3. Fill in rest of trajectories - each time crossing a nullcline, corresponding variable changes direction
   → gives arrows as shown

We see that the trajectories cycle round the fixed point

$\Rightarrow$ it is not a saddle, thus node or spiral.

Stability of fixed point $(0, n^*)$ resp

Linearise $n = n^* + N$

$$\dot{N} \simeq n_\infty'(0)\, v - N$$
$$\varepsilon \dot{v} \simeq -g_v v - g_n N$$

$$\Rightarrow \begin{pmatrix} \dot{N} \\ \dot{v} \end{pmatrix} = M \begin{pmatrix} N \\ v \end{pmatrix}, \quad M = \begin{pmatrix} -1 & n_\infty' \\ -\frac{g_n}{\varepsilon} & -\frac{g_v}{\varepsilon} \end{pmatrix}$$

(partial derivatives $g_v = \frac{\partial g}{\partial v}$, $g_n = \frac{\partial g}{\partial n}$ evaluated at $(0, n^*)$)

$$T = \mathrm{tr}\, M = -1 - \frac{g_v}{\varepsilon}, \quad D = \det M = \frac{1}{\varepsilon}(g_v + g_n n_\infty')$$

[we already know $D > 0$ (trajectories cycle round) but in case not

slope of n-nullcline $= n_\infty' >$ slope of v-nullcline $= -\frac{g_v}{g_n}$

Also 

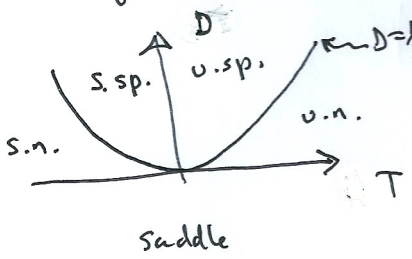
$g_n > 0 \Rightarrow n_\infty' g_n > -g_v \Rightarrow D > 0$]

So fixed point is stable if $-1 - \frac{g_v}{\varepsilon} < 0$ i.e. $g_v > -\varepsilon$

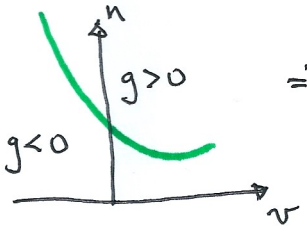
$\Delta \varepsilon \ll 1$ so essentially if $g_v > 0$

$\Leftrightarrow$ v-nullcline has $-$ve slope at $v = 0$

& we will assume this.



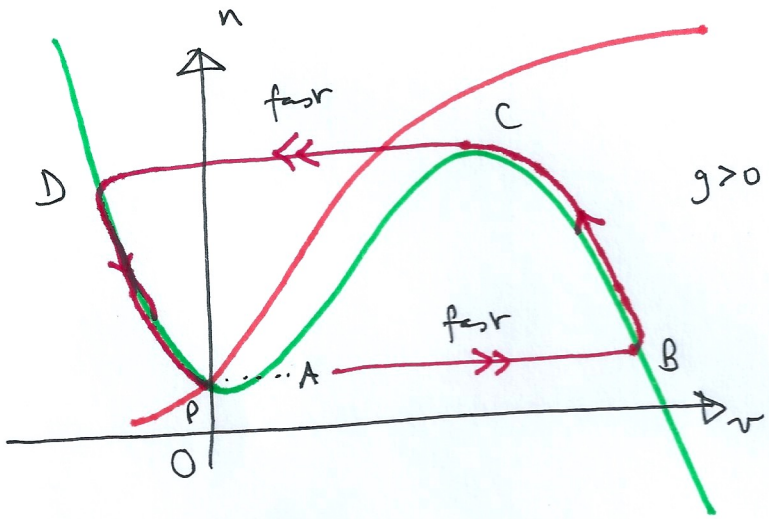
[Note $T \sim \frac{1}{\varepsilon^2}$ $D \sim \frac{1}{\varepsilon}$ so $D \ll T^2$ $\Rightarrow$ stable node]



$\Rightarrow g_v > 0$ at fixed point

Excitability

The steady state P is excitable, bearing in mind $\varepsilon \ll 1$



[, or too]

Perturb to A : the trajectory follows the action potential trajectory

ABCDP

Because $\varepsilon \ll 1$ v relaxes rapidly to $g = 0$

then BC is slow (n increases towards $n_\infty(v)$)

then CD is fast, DP is slow.

Comments

1. If $I^* > 0$ (applied current) the v-nullcline is $g(v,n) = I^*$ and is shifted upwards — limit cycles can occur (ex.)
2. As commonly referred to the FitzHugh-Nagumo equations have the form

$$\varepsilon \dot{v} = I^* + f(v) - w \quad , \quad f(v) = v(v-a)(1-v) \quad , \quad 0 < a < 1$$

$$\dot{w} = \gamma v - w \quad ,$$

— dynamics are the same.