# lem Sheet 1 Answers

1.

$$\begin{tikzcd}
 & & & \text{flux } J \text{ to maintain } S_e \arrow[d] \\
S_i + C_i \arrow[r, shift left, "k_+"] \arrow[r, bend left=60, "R_1"] \arrow[d] & P_i \arrow[l, shift left, "k_-"] \arrow[r, shift left, "k"] \arrow[r, bend left=60, "F"] & P_e \arrow[l, shift left, "k"] \arrow[r, shift left, "k_-"] \arrow[r, bend left=60, "R_2"] & S_e + C_e \arrow[l, shift left, "k_+"] \\
J & C_i \arrow[r, shift left, "k"] \arrow[r, bend right=60, "G"'] & C_e \arrow[l, shift left, "k"] &
\end{tikzcd}$$

Meaning, ~~not~~ see notes. i, e internal, external binding sites

concentrations {
$S$ substrate binding to
$C$ gate protein to form
$P$ complex which switches conformally between i & e states.

The overall reaction rates are

$$R_1 = k_+ S_i C_i - k_- P_i$$

$$R_2 = k_- P_e - k_+ S_e C_e$$

$$F = k P_i - k P_e$$

$$G = k C_i - k C_e$$

& then

$$\dot{S}_i = -R_1 - J$$

$$\dot{C}_i = -R_1 - G$$

$$\dot{P}_i = R_1 - F$$

$$\dot{P}_e = F - R_2$$

$$\dot{S}_e = R_2 + J$$

$$\dot{C}_e = R_2 + G$$

including fluxes

~~[Efflux to $C_e$ depletes $S_e$ etc~~]

In equilibrium $J = -R_1 = +G = -R_2 = -F$

& two conservation laws (substrate & gates)

$$P_i + P_e + C_i + C_e = C_0$$

$$P_i + P_e + S_i + S_e = S_0$$

So $J = k_- P_i - k_+ S_i C_i$ (1)

$= k C_i - k C_e$ (2)

$= k_+ S_e C_e - k_- P_e$ (3)

$= k P_e - k P_i$ (4)

So $P_e = P_i + \frac{J}{k}$ ~ (4)

$C_e = C_i - \frac{J}{k}$ ~ (2)

Substitute $2(P_i + C_i) = C_0 \Rightarrow P_i = \frac{C_0}{2} - C_i$

& $k_- P_i - k_+ S_i C_i = J$ from (1)

$\Rightarrow k_-\left(\frac{C_0}{2} - C_i\right) - k_+ S_i C_i = J$

$$\Rightarrow C_i = \frac{k_- \frac{C_0}{2} - J}{k_- + k_+ S_i} \quad \sim (1)$$

use (3): $J = k_+ S_e \left[C_i - \frac{J}{k}\right] - k_-\left[\frac{C_0}{2} - C_i + \frac{J}{k}\right]$

$$\Rightarrow J\left[1 + \frac{k_+ S_e}{k} + \frac{k_-}{k}\right] = -\frac{k_- C_0}{2} + (k_- + k_+ S_e)\frac{\left[k_- \frac{C_0}{2} - J\right]}{(k_- + k_+ S_i)}$$

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

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

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

So

$$J\left[\cancel{\frac{k_+}{k_-}}\ \frac{K_m+S_e}{K_d}\right] = \frac{k_-C_0}{2}\left[-1+\frac{K_m-K_d+S_e}{K_m-K_d+S_i}\right] \quad \cancel{\frac{k_+k_-C_0}{2k}}$$

$$-\left[\frac{K_m-K_d+S_e}{K_m-K_d+S_i}\right]J$$

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

$$J\left[\begin{aligned}&K_m^2-K_dK_m+K_mS_i+(K_m-K_d)S_e+S_iS_e\\&+K_dK_m\quad -K_d^2\qquad +K_dS_e\end{aligned}\right] = \frac{k_-C_0K_d}{2}(S_e-S_i)$$

$$\downarrow$$

$$= J\left[K_m^2+K_mS_i+K_mS_e+S_iS_e-K_d^2\right] = \frac{k_-C_0k}{2k_+}(S_e-S_i)$$

so $$J = \frac{k_-kC_0\,(S_e-S_i)}{2k_+\left[(K_m+S_i)(K_m+S_e)-K_d^2\right]}$$

ugly but...

2.

$$\begin{tikzcd}
S_0 \arrow[r, shift left, "N\alpha"] \arrow[r, bend left=60, "R_1"] & S_1 \arrow[l, shift left, "\beta"] \arrow[r, shift left, "(N-1)\alpha"] \arrow[r, bend left=60, "R_2"] & \cdots \arrow[l, shift left, "2\beta"] \arrow[r, shift left, "\alpha"] \arrow[r, bend left=60, "R_N"] & S_N \arrow[l, shift left, "N\beta"]
\end{tikzcd}$$

Define $R_i$ as shown, thus

$$R_1 = N\alpha S_0 - \beta S_1$$

$$R_2 = (N-1)\alpha S_1 - 2\beta S_2$$

$$\vdots$$

$$R_i = (N-i+1)\alpha S_{i-1} - i\beta S_i$$

$$\vdots$$

$$A_N = \alpha S_{N-1} - N\beta S_N$$

and

$$\dot{S}_0 = -R_1$$

$$\dot{S}_1 = R_1 - R_2$$

$$\vdots$$

$$\dot{S}_i \doteq R_i - R_{i-1}$$

$$\dot{S}_{N-1} = R_{N-1} - R_N$$

$$\dot{S}_N = R_N$$

Conservation $S_0 + S_1 + \dots + S_N = 1$

~~$S_1 = \frac{N\alpha S_0}{\beta}$~~

Ansatz $$S_j = \frac{N!}{(N-j)!\,j!} n^j (1-n)^{N-j}$$

$$R_j = (N-j+1)\,\alpha \frac{N!}{(N-j+1)!\,(j-1)!} n^{j-1}(1-n)^{N-j+1} - \frac{j\beta N!}{(N-j)!\,j!} n^j (1-n)^{N-j}$$

$$= \frac{N!\,\alpha\, n^{j-1}(1-n)^{N-j+1}}{(N-j)!\,(j-1)!} - \frac{\beta N!}{(N-j)!\,(j-1)!} n^j (1-n)^{N-j}$$

$$= \frac{N!\,n^{j-1}(1-n)^{N-j}}{(N-j)!\,(j-1)!} \left[\alpha(1-n) - \beta n\right]$$

Note

$$\dot{S}_j = \frac{N!}{(N-j)!\,j!}\left[ j n^{j-1}(1-n)^{N-j} - (N-j)\,n^j(1-n)^{N-j-1}\right]\dot{n}$$

$$= \frac{N!}{(N-j)!\,(j-1)!}\,n^{j-1}(1-n)^{N-j}\,\dot{n}$$

$$- \frac{N!}{(N-j-1)!\,j!}\,n^{j}(1-n)^{N-j-1}\,\dot{n}$$

recall $R_j = \frac{N!}{(N-j)!\,(j-1)!}\,n^{j-1}(1-n)^{N-j}\left[\alpha(1-n)-\beta n\right]$

thus $\dot{S}_j = \frac{R_j\,\dot{n}}{[\alpha(1-n)-\beta n]} - \frac{R_{j+1}\,\dot{n}}{[\alpha(1-n)-\beta n]}$

$$= (R_j - R_{j+1})\,\frac{\dot{n}}{[\alpha(1-n)-\beta n]}$$

$$= R_j - R_{j+1}$$

$\therefore$ <u>if</u> $S_j = \frac{N!}{(N-j)!\,j!}\,n^j(1-n)^{N-j}$

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

For $N = 2$

$$\dot{S}_0 = -R_1 \qquad R_1 = 2\alpha S_0 - \beta S_1$$

$$\dot{S}_2 = R_2 \qquad R_2 = \alpha S_1 - 2\beta S_2$$

& $S_0 + S_1 + S_2 = 1$

so $\dot{S}_0 = -2\alpha S_0 + \beta[1 - S_0 - S_2]$

$$\dot{S}_2 = \alpha[1 - S_0 - S_2] - 2\beta S_2$$

ie $\dot{S}_0 = \beta - (2\alpha+\beta)S_0 - \beta S_2$

$$\dot{S}_2 = \alpha - \alpha S_0 - (\alpha + 2\beta)S_2$$

We already know $S_0 = \overset{(1-n)^2}{\cancel{\alpha^2}}$, $S_2 = \overset{n^2}{\cancel{(1+n)^2}}$ is a solution with $\dot{n} = \alpha(1-n) - \beta n$

Thus linearising $S_0 = (1-n)^2 + y_0$ $S_2 = \overset{n^2}{\cancel{(1-n)^2}} + y_2$

$$\Rightarrow \quad \dot{y}_0 = -(2\alpha+\beta)y_0 - \beta y_2$$

$$\dot{y}_2 = -\alpha y_0 - (\alpha + 2\beta)y_2$$

$$\dot{\begin{pmatrix} y_0 \\ y_2 \end{pmatrix}} = -\underbrace{\begin{pmatrix} 2\alpha+\beta & \beta \\ \alpha & \alpha+2\beta \end{pmatrix}}_{M}$$

$$\det(-M) = \det M = 2(\alpha+\beta)^2 > 0$$

$$\operatorname{tr}(-M) = -3(\alpha+\beta) < 0$$

Solutions $\propto e^{\lambda t}$ $\quad \lambda^2 + 3(\alpha+\beta) + 2(\alpha+\beta)^2 = 0$

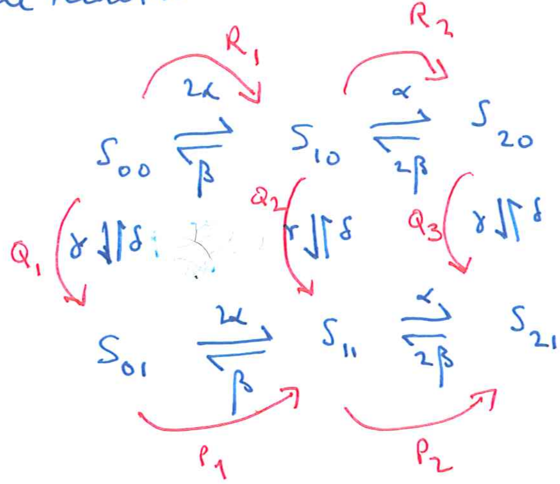
$$\lambda = -2(\alpha+\beta), -(\alpha+\beta)$$

$\Rightarrow$ Stable.

3. [optional depending on time]

(7

The reaction scheme is



Reaction rates are

$$R_1 = 2\alpha S_{00} - \beta S_{10}$$
$$R_2 = \alpha S_{10} - 2\beta S_{20}$$
$$Q_1 = \gamma S_{00} - \delta S_{01}$$
$$Q_2 = \gamma S_{10} - \delta S_{11}$$
$$Q_3 = \gamma S_{20} - \delta S_{21}$$
$$P_1 = 2\alpha S_{01} - \beta S_{11}$$
$$P_2 = \alpha S_{11} - 2\beta S_{21}$$

& then

$$\dot{S}_{00} = -R_1 - Q_1$$
$$\dot{S}_{10} = R_1 - R_2 - Q_2$$
$$\dot{S}_{20} = R_2 - Q_3$$
$$\dot{S}_{01} = Q_1 - P_1$$
$$\dot{S}_{11} = P_1 - P_2 + Q_2$$
$$\dot{S}_{21} = P_2 + Q_3$$

$\sum S_{ij} = 1$ Suppose $S_{21} = m^2 h$

$S_{11} = 2m(1-m)h$

$S_{20} = m^2(1-h)$

$$\left.\right\} \to \quad P_2 = 2\alpha m(1-m)h - \overset{2\beta m^2 h}{\cancel{2\beta m(1-m)}}$$
$$Q_3 = \gamma m^2(1-h) - \delta m^2 h$$

Density of open channels as gates are independent & an open channel needs

M open
M open
H open

& the probability of M open is $m$, of H open is $h$

so prob of open channel is $m^2h$

[ A bit subtle – we identify probability with a realisation ]

$$
\begin{aligned}
\text{Put } S_{00} &= (1-m)^2(1-h)\\
S_{10} &= 2m(1-m)(1-h)\\
S_{20} &= m^2(1-h)\\
S_{01} &= (1-m)^2 h\\
S_{11} &= 2m(1-m)h\\
S_{21} &= m^2 h \;\rightarrow\; \dot S_{21} = P_2 + Q_3 = \alpha S_{11} - 2\beta S_{21} + \gamma S_{20} - \delta S_{21}
\end{aligned}
$$

& for example

$$
\begin{aligned}
\dot{(m^2h)} &= 2mh\dot m + m^2\dot h\\
&= \overset{\alpha S_{11}}{2\alpha m(1-m)h} \overset{-2\beta S_{21}}{- 2\beta m^2 h} + \overset{\gamma S_{20}}{\gamma m^2(1-h)} - \overset{\delta S_{21}}{\delta m^2 h}\\
&= 2mh[\alpha(1-m) - \beta m] + m^2[\gamma(1-h) - \delta h]
\end{aligned}
$$

is clearly satisfied if

$$\dot m = \alpha(1-m) - \beta m$$
$$\dot h = \gamma(1-h) - \delta h$$

& can check others □

(*) For $r$ proteins controlling $S$ gates

ie proteins $M_1 \dots M_r$ with $m_k$ gates of $M_k$ s.t. $\sum m_k = S$

If $S_{i_1 \dots i_r}$ is density of gates with $i_j$ open $M_j$ gates and $n_j$ is fraction of open $M_j$ gates then we expect in equilibrium

$$S_{i_1 \dots i_r} = \prod_{j=1}^{r} {}^{m_j}C_{i_j}\, n_j^{i_j} (1-n_j)^{m_j - i_j}$$

where ${}^{m}C_i = \frac{m!}{i!(m-i)!}$ is the binomial coefficient.

~~P.S. 2 answers~~

4.

H-H model is

$$C_m \dot{V} = I_{app} - I_i$$

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

~~Scale~~

$$\tau_m \dot{m} = m_\infty(V) - m$$

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

$$\tau_h \dot{h} = h_\infty(V) - h$$

take V relative to resting potential $V_{eq}$

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

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

$t \sim \tau_n$

then $\varepsilon \dot{v} = I^* - g$, $\varepsilon = \frac{C_m}{\tau_n} \frac{v_{Na}}{g_{Na} v_{Na}} = \frac{C_m}{\tau_n g_{Na}}$

$$g = m^3 h (v - 1) + \frac{g_K}{g_{Na}} n^4 \left(v - \frac{v_K}{v_{Na}}\right) + \frac{g_L}{g_{Na}} \left(v - \frac{v_L}{v_{Na}}\right)$$

& $\dot{n} = n_\infty - n$

$\frac{\tau_m}{\tau_n} \dot{m} = m_\infty - m$

$\frac{\tau_h}{\tau_n} \dot{h} = h_\infty - h$

Now assume $\tau_m \ll \tau_n \Rightarrow m \simeq m_\infty(v)$ or just $m(v)$

$\tau_n \simeq \tau_h$, $n_\infty + h_\infty \simeq \bar{h}$

$\Rightarrow n + h \to \bar{h}$, take $h = \bar{h} - n$

then we have

$$\dot{n} = n_\infty - n$$

$$\varepsilon \dot{v} = I^* - g$$

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

$$\gamma_K = \frac{g_K}{g_{Na}} \qquad \gamma_L = \frac{g_L}{g_{Na}} \qquad v_K^* = -\frac{v_K}{v_{Na}} \qquad v_L^* = \frac{v_L}{v_{Na}}$$

$$\gamma_K = \frac{36}{120} \sim 0.3 \qquad \gamma_L = \frac{0.3}{120} \sim 0.003$$

$$v_K^k = -\frac{(-12)}{\underset{115}{\cancel{120}}} \sim 0.1 \qquad v_L^* = \frac{10.6}{115} \sim 0.1$$

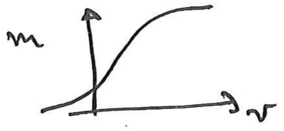
$$\varepsilon = \frac{C_m}{\tau_n g_{Na}} \sim \frac{10^{-6}}{5\,10^{-3}\,\underset{10^{-3}}{120}} \; \frac{F}{cm^2\, s\; S}\, cm^2 = \frac{1}{600} = 1.6 \times 10^{-3}$$

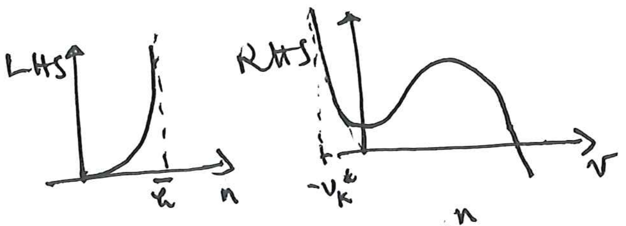
Form of $g$

$\gamma_L \ll 1$, ignore,

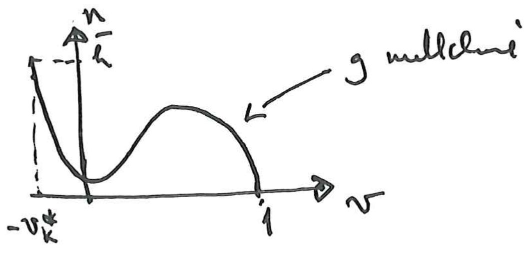
$$g = 0 \text{ if } \gamma_K (v + v_K^*) n^4 \simeq (1-v)(\bar{h} - n)\, m^3(v)$$

$$\text{viz} \quad \frac{\gamma_K n^4}{\bar{h} - n} = \frac{(1-v)\, m^3(v)}{v + v_K^*}$$





$\Rightarrow$



but do it in class

[wouldn't expect this ↓, I didn't do it in lecture!]

[The neglect of $\gamma_L$ is ok till $n \approx \bar{h}$. When $n = \bar{h}$,

then $\gamma_K (v + v_K^*) \bar{h}^4 + \gamma_L (v - v_L^*) = 0$

$$\Rightarrow (\gamma_K \bar{h}^4 + \gamma_L) v = -\gamma_K v_K^* \bar{h}^4 + \gamma_L v_L^*$$

ie $v \approx \dfrac{-\gamma_K v_K^* \bar{h}^4 + \gamma_L v_L^*}{\gamma_K \bar{h}^4 + \gamma_L} = \dfrac{-\left[v_K^* - \dfrac{\gamma_L v_L^*}{\gamma_K \bar{h}^4}\right]}{1 + \dfrac{\gamma_L}{\gamma_K \bar{h}^4}} \approx -v_K^*$

is ok.

For $n > \bar{h}$ the $\gamma_L$ term is required,

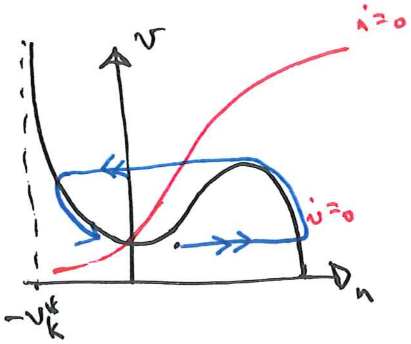
$$\gamma_K (v + v_K^*) n^4 + \underset{>0}{(1-v)(n-\bar{h}) m^3(v)} \approx \gamma_L (v_L^* - v) > 0$$

In practice $m^3$ becomes very small ($\sim 10^{-6}$ for $v \approx -0.1$)

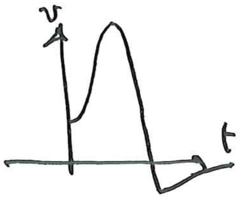
So in fact $\gamma_K n^4 \approx \dfrac{\gamma_L (v_L^* - v)}{v + v_K^*} \sim \dfrac{\gamma_L (v_L^* + v_K^*)}{v + v_K^*}$ as $v \to -v_K^*$

So the asymptote does work ]

Thus



If $n'(0)$ large enough (so $n$ nullcline clears $g = 0$) fixed point is excitable as shown.



excitable : excursion before returning to rest state.