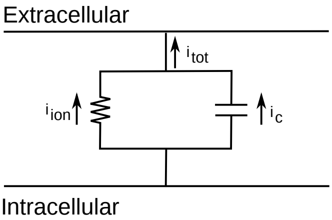
Electrical circuit model of the cell membrane



The membrane behaves like resistor and capacitor in parallel:

$$i_{tot} = i_{\text{ion}} + i_c$$

If no current escapes $i_{tot} = 0$ and all ions passing the membrane, i_{ion} accumulate and change the membrane potential according to

$$C_m \frac{dV}{dt} = i_c = -i_{\text{ion}}$$

Voltage gated Ion channels

Recall that ion currents across the membrane can be expressed as:

$$I = N\, p(V,t)\mathcal{I}(V)$$

Here $p(V,t)$ determines the portion of the N channels in the membrane that are open. This propensity function varies with time and membrane potential.

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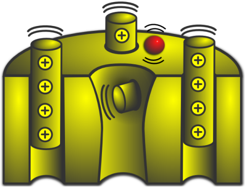
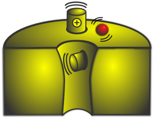


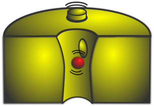
Next we will go through different expressions for how this propensity function can be derived for voltage gated ion channels.

Voltage gated channel with one gate

Assumes that a channel is gated by one gate that can exist in two states, closed(C) and open(O):



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



Applying law of mass action:

$$\frac{d[0]}{dt} = \alpha(V)[C] - \beta(V)[O]$$

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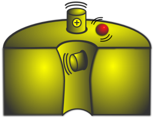

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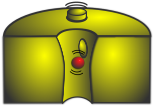


Applying law of mass action:

$$\frac{d[0]}{dt} = \alpha(V)[C] - \beta(V)[O]$$

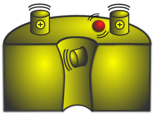
Dividing by the total amount of channels ([C]+[O]) yields

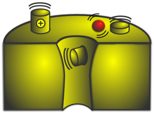
$$\frac{dp}{dt} = \alpha(V)(1-p) - \beta(V)p$$

where p is the portion of open channel ([O]/([C]+[O])).

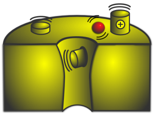
Voltage gated channel with two identical and independent gates

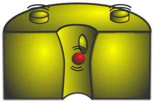
For some channels it is more appropriate to include several gates, which all need to be open for the channel to conduct. Example with two gates:





$$\begin{array}{ccc} S_{00} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & S_{10} \\ \alpha\downarrow\uparrow\beta & & \alpha\downarrow\uparrow\beta \\ S_{01} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & S_{11} \end{array}$$





Using the law of mass action we get a system of four equation. Will try to reduce this number to one!

First we make a reasonable claim: $p(V,t) = n^2$ where $\dot{n} = \alpha(1-n) - \beta n$

Further claim:

$$S_{11} = n^2; \quad S_{10} = S_{01} = n(1-n) = (1-n)n; \quad S_{00} = (1-n)^2$$

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Differentiate S_{11}

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From mass conservation and insertion:

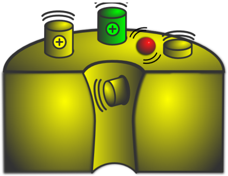
$$\begin{aligned}
\dot{S}_{11} &= \alpha\left(S_{01} + S_{10}\right) - 2\beta S_{11} \\
&= \alpha 2n(1-n) - 2\beta n^2 \\
&= 2n\left[\alpha(1-n) - \beta n\right]
\end{aligned}$$

Voltage gated channel with three gates, where two are identical and all are independent

Behavior of the Sodium conductance can not be described by a chain of two identical gates.

Two subunits of type *m* and one of type *h*.

$$
\begin{array}{ccccc}
S_{00} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{10} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{20} \\
\gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\
S_{01} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{11} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{21}
\end{array}
$$



Arguments similar to the one used above leads to these equations for m and h:

$$\dot{m} = \alpha(1-m) - \beta m, \quad \dot{h} = \gamma(1-h) - \delta h, \quad p(V,t) = m^2 h$$

Coupled dynamic model of membrane voltage and gates

An ODE system with three states:

$$C_m \frac{dV}{dt} = -g_{\mathrm{Na}} m h (V - E_{\mathrm{Na}}) - g_{\mathrm{K}} (V - E_{\mathrm{K}})$$

$$\frac{dm}{dt} = \alpha(V)(1-m) - \beta(V) m$$

$$\frac{dh}{dt} = \gamma(V)(1-h) - \delta(V) h$$

Assuming the m gate is fast we approximate:

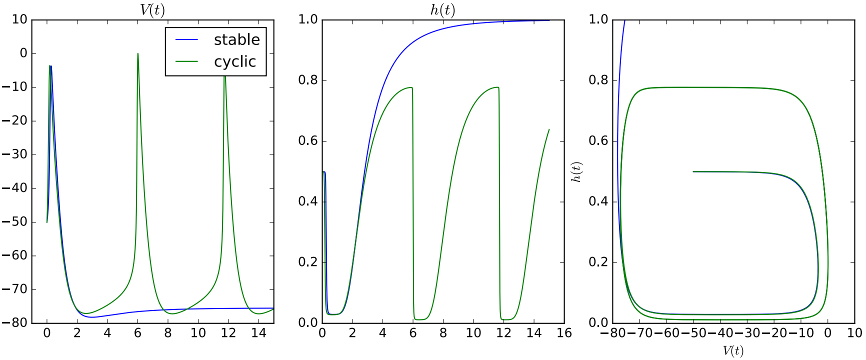
$$m(t) \approx m_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)}$$

to obtain a two state model:

$$C_m \frac{dV}{dt} = -g_{\mathrm{Na}} m_\infty(V) h (V - E_{\mathrm{Na}}) - g_{\mathrm{K}} (V - E_{\mathrm{K}})$$

$$\frac{dh}{dt} = \gamma(V)(1-h) - \delta(V) h$$

Solutions with two different parameter sets



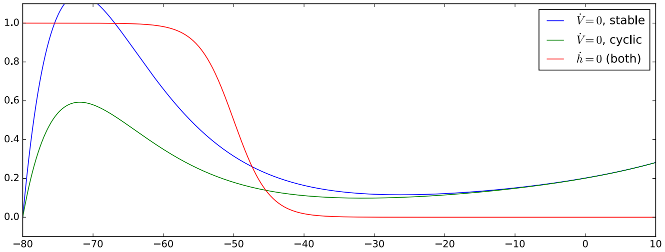
Nullclines

We can analyse the behavior of the system by seeing where the derivatives are zero and changes sign:

$$\frac{dh}{dt} = 0 \rightarrow h(V) = \frac{\gamma(V)}{\gamma(V) + \delta(V)}$$

$$\frac{dV}{dt} = 0 \rightarrow h(V) = \frac{g_{\mathrm{K}}(V - E_{\mathrm{K}})}{C_m g_{\mathrm{Na}} m_\infty(V)(E_{\mathrm{Na}} - V)}$$

Nullclines

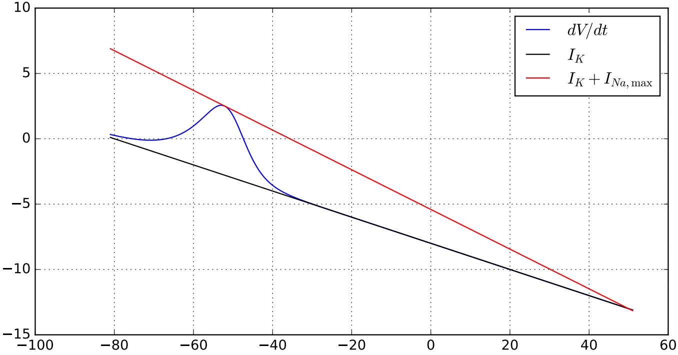


$\dot{V}=0$, stable
$\dot{V}=0$, cyclic
$\dot{h}=0$ (both)
1.0
0.8
0.6
0.4
0.2
0.0
−80
−70
−60
−50
−40
−30
−20
−10
0
10

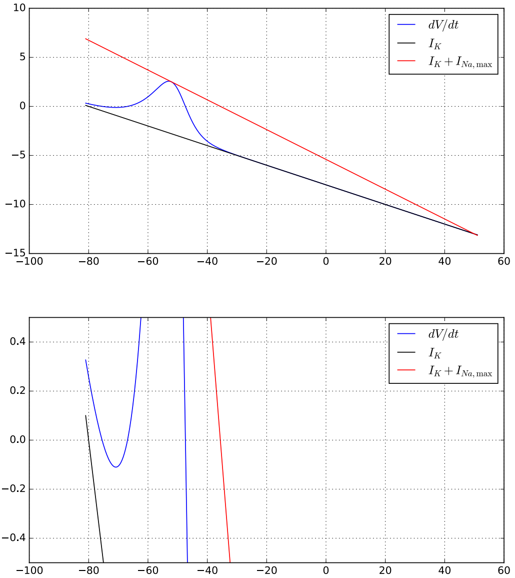
Finding the equlibrium points

In order to find the equilibrium points we can reduce the 2x2 system into a scalar equation by using the equilibrium for h:

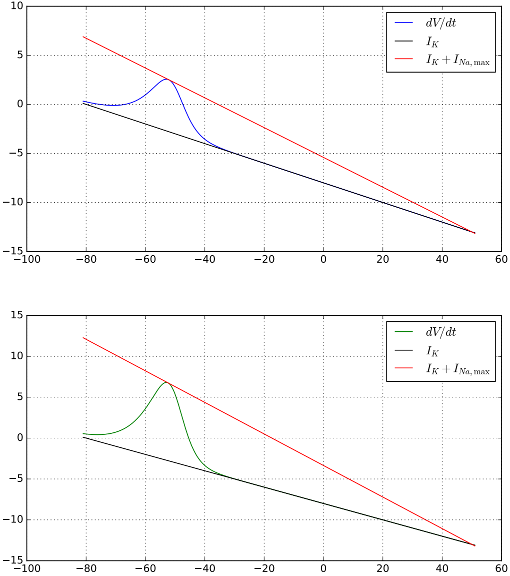
$$\frac{dh}{dt} = 0 \; \& \; \frac{dV}{dt} = 0 \rightarrow g_{\mathrm{Na}} m_\infty(V) h_\infty(V)(V - E_{\mathrm{Na}}) + g_{\mathrm{K}}(V - E_{\mathrm{K}}) = 0$$



The stable case, zoomed



The stable vs cyclic case



Rate constants as probabilities

Consider again the following model:

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

Probabilistic interpretation of α and β:

$$\alpha : P(C \rightarrow O \text{ in } dt) \simeq \alpha dt$$

$$\beta : P(O \rightarrow C \text{ in } dt) \simeq \beta dt$$

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

Probabilistic interpretation of α and β:

$$\alpha : P(C \rightarrow O \text{ in } dt) \simeq \alpha dt$$

$$\beta : P(O \rightarrow C \text{ in } dt) \simeq \beta dt$$

Probability that the channel is open at time $t + dt$:

$$\begin{aligned} P(O, t + dt) &= P(C, t) \cdot P(C \rightarrow O \text{ in } dt) \\ &\quad + P(O, t) \cdot P(\text{not} \quad O \rightarrow C \text{ in } dt) \\ &= P(C, t) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt) \end{aligned}$$

$$
\begin{aligned}
P(O, t+dt) &= P(C, t) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt) \\
&= (1 - P(O, t)) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt).
\end{aligned}
$$

Divide by dt and rearranges:

$$
\frac{P(O, t+dt) - P(O, t)}{dt} = \alpha \cdot (1 - P(O, t)) - \beta \cdot P(O, t)
$$

Going to the limit:

$$
\frac{dP(O, t)}{dt} = \alpha \cdot (1 - P(O, t)) - \beta \cdot P(O, t)
$$

Which we recognize as the familiar gating equation:

$$
\frac{dp}{dt} = \alpha(V)(1 - p) - \beta(V)p
$$

The general case with N different states

Let $S(t) \in [1, 2, \dots, N]$ be the state of the system at time t. We define:

$$\phi_j(t) = P(S(t) = j).$$

k_{ij} is the probability rate going from $S = i$ to $S = j$:

$$k_{ij}dt \simeq P(S(t + dt) = j | S(t) = i)$$

Probability of staying $S = i$:

$$P(S(t + dt) = i | S(t) = i) = 1 - \sum_{j}^{j \neq i} k_{ij}dt = 1 - K_i dt$$

where $K_i = \sum_j^{i \neq j} k_{ij}$, total escape rate.

Time evolution of $\phi_j(t)$

$$
\begin{aligned}
\phi_j(t+dt) &= \phi_j(t)\cdot P(\text{staying in } j \text{ for } dt) \\
&\quad + \sum_{i\neq j} \phi_i(t) P(\text{enter } j \text{ from } i \text{ in } dt) \\
&= \phi_j(t)\cdot(1 - K_j dt) + \sum_{i}^{i\neq j} \phi_i(t) k_{ij} dt
\end{aligned}
$$

Divide by dt and rearrange:

$$
\frac{\phi_j(t+dt) - \phi_j(t)}{dt} = -K_j\phi_j(t) + \sum_{i}^{i\neq j} \phi_i(t) k_{ij}
$$

And in the limit:

$$
\frac{d\phi_j(t)}{dt} = \sum_{i=1}^{n} k_{ij}\phi_i(t), \quad k_{ii} = -K_j
$$

Time evolution of $\phi_j(t)$

$$\frac{d\phi_j(t)}{dt} = \sum_{i=1}^{n} k_{ij}\phi_i(t), \quad k_{ii} = -K_j$$

can be expressed as a matrix-vector multiplication:

$$\frac{d\phi(t)}{dt} = K\phi(t)$$

Here K is called a *transition matrix* and multiplied with the probability vector ϕ provides the right hand side function of a system of ODEs.

Example with a four state Markov model

$$
\begin{array}{ccc}
C & \overset{(Ca/Ko_d)^4}{\underset{k\_}{\overrightarrow{\overleftarrow{\quad}}}} & O \\
(Ca/Ki_d)^2 \downarrow\uparrow ki\_ & & (Ca/Ki_d)^2 \downarrow\uparrow ki\_ \\
I & \overset{(Ca/Ko_d)^4}{\underset{k\_}{\overrightarrow{\overleftarrow{\quad}}}} & R
\end{array}
$$

Example with a four state Markov model

$$\begin{array}{ccc} C & \underset{k\_}{\overset{(Ca/Ko_d)^4}{\rightleftarrows}} & O \\ (Ca/Ki_d)^2 \downarrow\uparrow ki\_ & & (Ca/Ki_d)^2 \downarrow\uparrow ki\_ \\ I & \underset{k\_}{\overset{(Ca/Ko_d)^4}{\rightleftarrows}} & R \end{array} \Longrightarrow \begin{array}{ccc} \boxed{0} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & \boxed{1} \\ \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\ \boxed{2} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & \boxed{3} \end{array}$$

$$\begin{bmatrix} \frac{\phi_0}{dt} \\ \frac{\phi_1}{dt} \\ \frac{\phi_2}{dt} \\ \frac{\phi_3}{dt} \end{bmatrix} = \begin{bmatrix} -(\alpha+\gamma) & \beta & \delta & 0 \\ \alpha & -(\beta+\gamma) & 0 & \delta \\ \gamma & 0 & -(\alpha+\delta) & \beta \\ 0 & \gamma & \alpha & -(\beta+\delta) \end{bmatrix} \begin{bmatrix} \phi_0 \\ \phi_1 \\ \phi_2 \\ \phi_3 \end{bmatrix}$$

Stochastic simulation

```python
def advance(state, A, dt):

    P = A[:,state]*dt;
    P[state] = 0;
    CP = np.cumsum(P);

    random_number = np.random.rand();
    for i in range(len(CP)):

        if random_number < CP[i]:
            state = i;
            return state

    return state
```

How long time a state either stays open or stay closed tells us something about the rates

How long time (T_i) does the system spend in a state S_i before leaving? We define $P_i(t) := P(T_i < t)$.
Note $P(\text{leaving } S_i \text{ during } dt) \simeq K_i dt$

$$\begin{aligned} P_i(t+dt) &= P(\text{transition has already occurred at } t) \\ &\quad + P(\text{not occurred yet}) \cdot P(\text{it takes place in this interval}) \\ &= P_i(t) + (1 - P_i(t)) \cdot K_i dt \end{aligned}$$

Rearrange, divide and go to the limit:

$$\frac{dP_i(t)}{dt} = K_i(1 - P_i(t))$$

Which has the solution:

$$P_i(t) = 1 - e^{-K_i t}$$

Waiting time

$P_i(t)$ is the cumulative distribution. The probability density function is found by differentiation:

$$p_i(t) = \frac{dP_i(t)}{dt} = K_i e^{-K_i t}$$

The mean waiting time is the expected value of T_i:

$$E(T_i) = \int_0^\infty t p_i(t) dt = \frac{1}{K_i}$$

(If K_i does not depend on t)