Wave propagtion in Excitable Systems, chapter 6

- The bistable equation
- Properties of traveling wave solution
- Analytical solution (for cubic reaction term)

The bistable equation

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + f(V) \tag{1}$$

Where $f(V)$ has three zeros, say at $V = 0, \alpha, 1$. For example:

$$f(V) = aV(V-1)(\alpha - V)$$

The solution will be a travelling wave.

Traveling wave

Assume a solution on the form:

$$V(x,t) = U(x+ct) = U(\xi)$$

Inserting this into the bistable equation yields a 2. order ODE:

$$U_{\xi\xi} - cU_\xi + f(U) = 0$$

Or equivalently a system of two 1. order ODEs:

$$\begin{aligned} U_\xi &= W \\ W_\xi &= cW - f(U) \end{aligned}$$

We seek solutions where

$$(U, U_\xi) \stackrel{\xi\to-\infty}{\longrightarrow} (0,0), \quad \text{and} \quad (U, U_\xi) \stackrel{\xi\to\infty}{\longrightarrow} (1,0).$$

Analytical solution in the cubic case

With

$$f(V) = A^2 V(V-1)(\alpha - V)$$

the solution is given as

$$U(\xi) = \frac{1}{2}\left[1 + \tanh\left(\frac{A}{2\sqrt{2}}\xi\right)\right]$$

with

$$c = \frac{A}{\sqrt{2}}(1-2\alpha)$$

Rate constants as probabilities, chapter 3.6

- Alternative derivation of gate variable equations - from probability theory
- Generalization to multi-state Markov models
- Waiting time
- Single channel experiments for estimating rate constants

Rate constants as probabilities

Consider again the following model:

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

Probabilistic interpretation of α and β:

$$\alpha : P(C \to O \text{ in } dt) = \alpha dt$$

$$\beta : P(O \to C \text{ in } dt) = \beta dt$$

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

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

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

since $P(C, t) + P(O, t) = 1$.
Divides 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 this as the usual gating equation!

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

The general case with N different states

Let $S = [1, \ldots, N]$. We write $S(t) = j$ if the system is in state j at time t, and define:

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

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

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

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 $K_i = \sum_j^{i \neq j} k_{ij}$

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:

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

Time evolution of $\phi_j(t)$

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

can be expressed as a matrix-vector expression:

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

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

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

Example with a four state Markov model

$$
\begin{array}{ccccccccc}
C & \underset{k_-}{\overset{(c/Ko_d)^4}{\rightleftarrows}} & O & & \boxed{0} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & \boxed{1} \\
(c/Ki_d)^2 \downarrow\uparrow ki_- & & (c/Ki_d)^2 \downarrow\uparrow ki_- & \Longrightarrow & \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\
I & \underset{k_-}{\overset{(c/Ko_d)^4}{\rightleftarrows}} & R & & \boxed{2} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & \boxed{3}
\end{array}
$$

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

Waiting time

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 $K_i dt = P(\text{leaving } S_i \text{ during } dt)$

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

Divides, and goes 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:

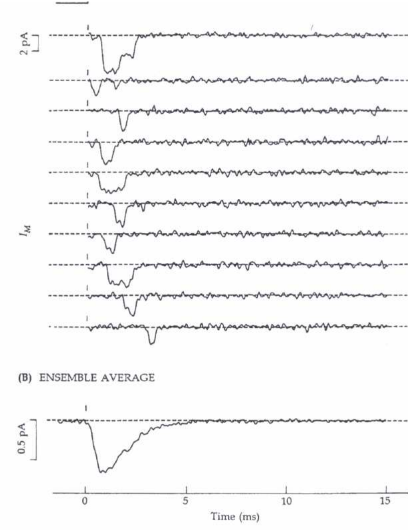
$$p_i(t) = \frac{dP_i(t)}{dt} = K_i e^{-K_i t}$$

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)

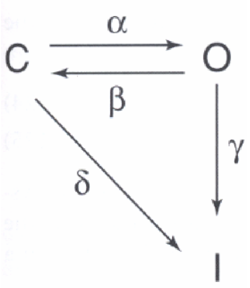
Single channel recordings can be used to fit rates in Markov models



Single channel analysis

Single channel recordings contain statistical information that can be used to estimate transition rate:

- Ratio of experiments where channel directly inactivates
- Distribution of the number of times the channel re-opens before finally inactivating
- Mean open time
- Mean close time



1: If first (and final) transition is $C \to I$

The channel is initially in the closed state.
As the transmembrane potential is elevated two things can happen:

$$P(C \to O) = A = \alpha/(\alpha + \delta)$$

$$P(C \to I) = \delta/(\alpha + \delta) = (\delta - \alpha + \alpha)/(\alpha + \delta) = 1 - A$$

Estimation of $1 - A$: The ratio of experiments where the channel fail to open.

2 & 3: Time spent in C and O

In the experiments where channels do open, record the time spent in C.
The distribution is described by: $P(t) = 1 - \exp(-\alpha)$
The average waiting time will be $E(T) = 1/\alpha$.

Record the duration the channel is open. The distribution is described by: $P(t) = 1 - \exp(-\beta - \gamma)$
The average waiting time will be $E(T) = 1/(\beta + \gamma)$.

4: Number of re-openings

Probability that the channels opens k times before inactivating:

$$
\begin{aligned}
P[N = k] &= P[N = k \text{ and finally } O \to I] + P[N = k \text{ and finally } C \to I] \\
&= A^k B^{k-1}(1 - B) + A^k B^k (1 - A) \\
&= (AB)^k \left(\frac{1 - AB}{B} \right)
\end{aligned}
$$

Where $A = \alpha/(\alpha + \delta)$ and $B = \beta/(\beta + \gamma)$
B can be estimated by fitting to the observed data.