Gating and Conductance

Definition 7. *We will use the following notation:*

$P_i := \frac{\#open\ channels}{\#total\ channels}$
$\bar{g}_i$: *maximum conductance*
$g_i := \overline{g_i} \cdot P_i$ *(conductance)*

3.1.4 Membrane channel dynamics

We will differentiate between persistent and transient channels.

(A) Persistent channels

$P_K(V_m)$ increases with depolarization, and decreases with hyperpolarization.
Persistent channels can be interpreted as a swinging door. This door, representing the gating properties (governed by conformational changes) of an ion channel, is modeled by k artificial subunits. We assign the open probability n to each of the k subunits. Therefore, the probability that a channels is open is

$$P_K = n^k \quad n \in [0,1] \tag{3.10}$$

k needs be be estimated from experimental data (in the case of K^+ channels $k = 4$).

Definition 8. *Activation and deactivation rates are denoted by* $\alpha_n(V)$ *and* $\beta_n(V)$*.*

How does n change?

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n \tag{3.11}$$

$$\Leftrightarrow \quad \tau_n(V)\frac{dn}{dt} = n_\infty(V) - n \tag{3.12}$$

$$\text{with} \quad \tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)} \tag{3.13}$$

$$n_\infty = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)} \tag{3.14}$$

Computing α_n and β_n

Activation: The energy barrier $qB_\alpha V$ needs to be overcome. B_α depends on the charge and membrane thickness. The energy barrier is overcome with $\exp(-qB_\alpha/k_BT)$.

$$\Rightarrow \alpha_n(V) := A_\alpha \exp\left(-qB_\alpha/k_BT\right)(\equiv A_\alpha \exp\left(-B_\alpha V/V_T\right) \tag{3.15}$$

A_α needs to be fitted using experimental data.

Analogously:

$$\beta_n(V) := A_\beta \exp\left(-qB_\beta V/k_B T\right) \tag{3.16}$$

$$\Rightarrow \quad n_\infty(V) = \frac{1}{1 + \frac{\beta_n}{\alpha_n}(V)} = \frac{1}{1 + \left(\frac{A_\beta}{A_\alpha} \cdot \exp\left(\frac{(B_\alpha - B_\beta)\cdot V}{V_T}\right)\right)}$$

(B) Transient channels

Transient channels are governed by two individual processes. The two are oppositely voltage dependent.
Open probability (e.g. Na^+ channels)
1. **Swinging door** In analogy to persistent channels: m^k (e.g. $k = 3$) → activation
2. **Ball:** Inactivation with probability h^i (e.g. $i = 1$)
$\Rightarrow P_{Na^+} = m^3 h$

Temporal changes of m and h:

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)\cdot m \tag{3.17}$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)\cdot h \tag{3.18}$$

$\alpha_{m,h}$, $\beta_{m,h}$ are computed like α_n and β_n.

$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m \tag{3.19}$$

$$\tau_m(V) = \frac{1}{\alpha_m(V) + \beta_m(V))} \tag{3.20}$$

$$m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)} \tag{3.21}$$

3.2 The Hodgkin-Huxley model

The Hodgkin-Huxley model describes Na^+ and K^+ conductances and the corresponding membrane currents.

3.2.1 Model equations

1.

$$i_m = \overline{g}_i\,(V - E_L) + g_K\, n^4\,(V - E_K) + \overline{g}_{Na}\, m^3 h\,(V - E_{Na}) \tag{3.22}$$

$$\overline{g}_i = 0.003\,\mathrm{mS/mm^2} \qquad E_L = -54.387\,\mathrm{mV} \tag{3.23}$$

$$\overline{g}_K = 0.36\,\mathrm{mS/mm^2} \qquad E_K = -77\,\mathrm{mV} \tag{3.24}$$

$$\overline{g}_{Na} = 1.2\,\mathrm{mS/mm^2} \qquad E_{Na} = 50\,\mathrm{mV} \tag{3.25}$$

2.

$$C_m \frac{dV}{dt} = -i_m + \frac{I_e}{A} \tag{3.26}$$

3.

$$\text{a)} \quad \tau_m(V) \frac{dm}{dt} = m_\infty(V) - m \tag{3.27}$$

$$\text{b)} \quad \tau_n(V) \frac{dn}{dt} = n_\infty(V) - n \tag{3.28}$$

$$\text{c)} \quad \tau_h(V) \frac{dh}{dt} = h_\infty(V) - h \tag{3.29}$$

3.2.2 Parameters

$$\alpha_n = \frac{0.01(V+55)}{1 - \exp\left(-0.1\,(V+55)\right)} \tag{3.30}$$

$$\beta_n = 0.125\,\exp\left(-0.0125\,(V+65)\right) \tag{3.31}$$

$$\alpha_m = \frac{0.1(V+40)}{1 - \exp\left(-0.1\,(V+40)\right)} \tag{3.32}$$

$$\beta_m = 4\,\exp\left(-0.0556\,(V+65)\right) \tag{3.33}$$

$$\alpha_h = 0.07\,\exp\left(-0.05\,(V+65)\right) \tag{3.34}$$

$$\beta_h = \frac{1}{1 + \exp\left(-0.1\,(V+35)\right)} \tag{3.35}$$

3.2.3 Summary

- Good description of active membrane properties (Na^+ and K^+ channels)
- Entire membrane potential trace can be modeled (not just subthreshold dynamics)
- Still no spatial description of cells and the membrane potential
- Still no detailed description of the intra- and extracellular space (i.e. no coupling of electrical and biochemical processes)

3.3 Modeling synapses

1. Action potential reaches the synapse (Na^+, K^+)
2. Change of the membrane potential leads to opening of Ca^{2+} channels
3. Fusion of vesicles leads to neurotransmitter release into the cleft

4. Activation of postsynaptic receptors leads to Na^+, K^+ currents

Points (1-3) are presynaptic processes that will be subject to later investigation, and (4) is a postsynaptic process.

3.3.1 Modeling postsynaptic receptors

Markov models: Describe the conformational changes of a receptors.

Definition 9. *Let S_i, $i = 1 \ldots n$ denote the discrete protein conformation states.* $S_1 \rightleftarrows S_2 \rightleftarrows S_3 \rightleftarrows \ldots S_n$

Definition 10. *$P(S_i, t)$ is the probability that a receptor is in state S_i at time t.*

Temporal changes of $P(S_i, t)$

$$\frac{dP(S_i,t)}{dt} = \sum_{j=1}^{n} P(S_j,t)P(S_j \to S_i) - \sum_{j=1}^{n} P(S_i,t)P(S_i \to S_j) \tag{3.36}$$

Definition 11. *Let $P(S_j \to S_i)$ denote the transition probability from state S_j to S_i.*

From one channel to many

Let s_i denote the fraction of channels in state S_i.

With $S_i \underset{r_{ji}}{\overset{r_{ij}}{\rightleftarrows}} S_j$ follows

$$\frac{ds_i}{dt} = \sum_{j=1}^{n} s_j r_{ji} - \sum_{j=1}^{n} s_i r_{ij} \quad \text{(Markov kinetics)} \tag{3.37}$$

3.3.2 Special Markov models

1. **Two-state models**

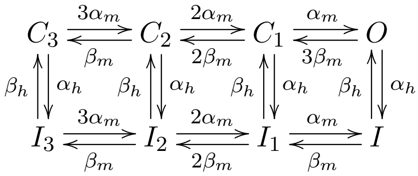
$$C \underset{r_2(V)}{\overset{r_1(V)}{\rightleftarrows}} O \tag{3.38}$$

Example: Hodgkin-Huxley

$$m \underset{\beta_m(V)}{\overset{\alpha_m(V)}{\rightleftarrows}} m^* \tag{3.39}$$

$$h \underset{\beta_h(V)}{\overset{\alpha_h(V)}{\rightleftarrows}} h^* \tag{3.40}$$

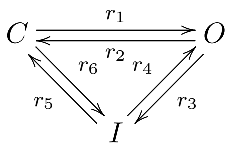
Channel conductances $O = m^3 h$
$\Rightarrow$ Three identical m-subunits + h-subunit



(3.41)

$\Rightarrow$ Hodgkin-Huxley model is part of Markov models.

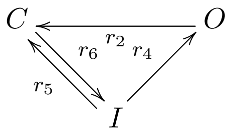
2. **Three-state models**
   a) C closed
   b) I inactivated
   c) O open



(3.42)

Examples:

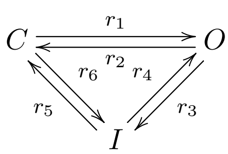
(a) **NMDA receptors**



(3.43)

$r_1 = 0$
$r_2 = 6,9\, S^{-1}$
$r_3 = 0$
$r_4 = 160\, S^{-1}$
$r_5 = 4,7\, S^{-1}$
$r_6 = 190\, S^{-1}\text{mM}^{-1}$

(b) **GABA receptors**



(3.44)

$r_1 = 150\, S^{-1}\text{mM}^{-1}$
$r_2 = 200\, S^{-1}$
$r_3 = 22\, S^{-1}$