Chapter 10
A Prototypical Model of an Ion Channel

So far we have been concerned with calcium-induced calcium release (CICR) as illustrated in Fig. 8.2 (page 126). To study CICR, we started by studying the development of the concentration of calcium ions in the dyad and kept everything else constant. The interesting part was then to see how the release mechanism of the ryanodine receptor RyR changes the dynamics of the dyad concentration. In particular, we were interested in RyR mutations and their theoretical effect on the dyad concentration through changes in the open probability of the RyR channel. We saw how theoretical blockers could be defined in order to repair the effect of the mutations, in the sense that we were able to restore essential properties of the process. We also introduced the effect of allowing the concentration of the junctional sarcoplasmic reticulum to change and we studied how the overall processes were affected by introducing the transmembrane potential and allowing the L-type calcium channel (LCC) to open and close.

Now we leave the RyR and Markov models based on concentrations of calcium ions and focus on voltage-gated channels. We touched upon this topic earlier, since the LCC is voltage gated, but now we will dynamically update the voltage and focus solely on how voltage develops and how it affects the transitions of the Markov model.

We will start by studying a very simple channel to explain the basics steps as carefully as possible. This channel does not have a name and probably does not exist in nature, but it provides a good example to get a handle on the steps involved in understanding much more complex (and more realistic) ion channels.

In the study of CICR, we examined what was going on in a very small part of the cell based on the tacit assumption that if we can repair what is going on in every tiny part of the cell, we will probably also do a decent job in repairing all of the cell. We will follow the same strategy in studying voltage-gated channels: We will study a single channel and see how mutations may affect the function of the channel and thereby how the transmembrane potential is changed. Again, we will

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derive theoretical drugs and see how they should be defined in order to repair the effect of the mutations. However, the assumption that small domains can be studied independently is less reliable for voltage-gated channels than for the CICR process in the vicinity of the dyad. The reason for this is that electrical diffusion waves travel much faster than concentration waves.

10.1 Stochastic Model of the Transmembrane Potential

The transmembrane potential is defined to be the difference between the intracellular potential v_i and the extracellular potential v_e:

$$v = v_i - v_e. \tag{10.1}$$

Let us consider a membrane consisting of a leakage current with conductance given by g_L and an ion channel with conductance given by g_i. The transmembrane potential of such a membrane is governed by the differential equation

$$Cv' = -g_L\,(v - V_L) - g_i(v - V_i), \tag{10.2}$$

where C is the capacitance of the membrane, V_L is the resting potential of the leakage current, and V_i is the resting potential of the ion channel. In our computations, we will consider an example[1] with the parameters listed in Table 10.1. We assume that the ion channel can be either open (O), with $g_i = 1$ mS/cm^2, or closed (C), with $g_i = 0$ mS/cm^2. The state of the stochastic ion channel is governed by a Markov model of the form

$$C \underset{k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O, \tag{10.3}$$

Table 10.1 Values of the parameters used in the model (10.2)

C	1 μF/cm^2
g_L	1/10 mS/cm^2
V_L	0 mV
V_i	11/10 mV

[1] Here, the choice of the parameter V_i may seem a bit strange, but we will see below that it will lead to a very simple computational domain for the probability density functions.

where the reactions rates will be specified below. With these definitions, the stochastic equation takes the form

$$v' = -\frac{1}{10}v - \gamma\left(v - \frac{11}{10}\right), \tag{10.4}$$

where γ is zero (closed) or one (open) depending on the state of the Markov model (10.3).

10.1.1 A Numerical Scheme

We compute numerical solutions of the model (10.4) using the scheme

$$v_{n+1} = v_n - \Delta t\left(\frac{1}{10}v_n + \gamma_n\left(v_n - \frac{11}{10}\right)\right), \tag{10.5}$$

where Δt denotes the time step and γ_n takes on values based on the state of the Markov model. Based on the Markov model, the value of γ_n is computed as described on page 28. We assume that the time step (in ms) satisfies the condition

$$\Delta t < \frac{10}{11}. \tag{10.6}$$

10.1.2 An Invariant Region

We discussed above that it is useful to derive an invariant region for the stochastic model since such a region can be used to define the computational domain of the probability density equation. We claim that, under the condition (10.6) for the time step, the solutions generated by scheme (10.5) will always remain in the interval given by

$$\Omega = (0, 1),$$

provided that the initial condition is in this region. To show that Ω is an invariant region for solutions generated by scheme (10.5), we write the scheme in the form

$$v_{n+1} = H(v_n, \gamma_n),$$

where

$$H(v, \gamma) = v - \Delta t\left(\frac{1}{10}v + \gamma\left(v - \frac{11}{10}\right)\right).$$

Since

$$\frac{\partial H(v,\gamma)}{\partial v} = 1 - \Delta t\left(\frac{1}{10} + \gamma\right) > 0$$

because of (10.6) and

$$\frac{\partial H(v,\gamma)}{\partial \gamma} = \Delta t\left(\frac{11}{10} - v\right) > 0$$

for any $v \in \Omega$, we have

$$v_{n+1} = H(v_n, \gamma_n) \leqslant H(1,1) = 1$$

and

$$v_{n+1} = H(v_n, \gamma_n) \geqslant H(0,0) = 0.$$

So, by induction, we have $v_n \in \Omega$ for all n.

10.2 Probability Density Functions for the Voltage-Gated Channel

We can now follow exactly the same steps as in Sect. 2.2 (see page 30) to derive a model of the probability density functions of the open state and the closed state. The probability of the channel being in the open state for voltages between v and $v + \Delta v$ is given by

$$P_o\{v < V(t) < v + \Delta v\} = \int_v^{v+\Delta v} \rho_o(w,t)dw,$$

where ρ_o is the probability density function of the open state. Similarly, we have

$$P_c\{v < V(t) < v + \Delta v\} = \int_v^{v+\Delta v} \rho_c(w,t)dw$$

where ρ_c is the probability density function of the closed state. By the arguments given in Sect. 2.2, we find that the probability density functions must be solutions

of the system

$$\begin{aligned} \frac{\partial \rho_o}{\partial t} + \frac{\partial}{\partial v}(a_o \rho_o) &= k_{co}\rho_c - k_{oc}\rho_o, \\ \frac{\partial \rho_c}{\partial t} + \frac{\partial}{\partial v}(a_c \rho_c) &= k_{oc}\rho_o - k_{co}\rho_c, \end{aligned} \tag{10.7}$$

where the flux terms are given by

$$\begin{aligned} a_o &= -g_L(v - V_L) - (v - V_i) = \frac{11}{10}(1 - v), \\ a_c &= -g_L(v - V_L) = -\frac{1}{10}v \end{aligned} \tag{10.8}$$

As usual, the boundary conditions are set up to avoid a probability leak across the boundary. Hence we need the fluxes $a_o\rho_o$ and $a_c\rho_c$ to be zero for $v = 0$ and $v = 1$. Note that $a_o(1) = a_c(0) = 0$; so we require $\rho_o(0) = 0$ and $\rho_c(1) = 0$. In the numerical simulations presented below, we use the scheme described in Sect. 2.3. Stationary solutions of the numerical scheme are computed as described on page 44.

10.3 Analytical Solution of the Stationary Case

We showed in Sect. 2.6 how an analytical solution can be derived for a stationary system of the form (10.7). Here we shall repeat this derivation for a voltage-gated channel. For simplicity we shall consider a channel where the reaction scheme of the Markov model is independent of the voltage; we choose

$$k_{oc} = 1 \text{ ms}^{-1} \text{ and } k_{co} = \mu \text{ ms}^{-1}.$$

So, we will again focus on CO-mutations. Here μ, referred to as the mutation severity index, will be specified in the computations below. In all computations, $\mu = 1$ will be referred to as the wild type case. Increased values of k_{co} will increase the open probability of the ion channel in (10.2) and therefore bring the transmembrane potential closer to the maximum value (given by $V_+ = 1$ mV).

The first step in the derivation of the analytical solution is to observe that, in the steady state, the sum of the equations of (10.7) results in the equation

$$\frac{\partial}{\partial v}(a_o\rho_o + a_c\rho_c) = 0.$$

The second step is to observe that the boundary conditions imply that

$$a_o\rho_o + a_c\rho_c = 0.$$

Therefore, for the present model, we find that

$$\rho_c = -\frac{a_o}{a_c}\rho_o = \frac{11}{v}(1-v)\,\rho_o$$

and, from (10.7), we have

$$\frac{\partial}{\partial v}(a_o\rho_o) = \mu\rho_c - \rho_o = \left(11\mu\frac{1-v}{v} - 1\right)\rho_o.$$

By differentiation, we obtain

$$a_o\frac{\partial}{\partial v}\rho_o = \left(11\mu\frac{1-v}{v} - 1 - \frac{\partial}{\partial v}a_o\right)\rho_o$$

and thus

$$\rho_o' = a(v)\rho_o, \tag{10.9}$$

where

$$a(v) = \left(\frac{10\mu}{v} + \frac{1}{11(1-v)}\right).$$

The solution of (10.9) is given by

$$\rho_o = c\frac{v^{10\mu}}{(1-v)^{1/11}} \tag{10.10}$$

and then

$$\rho_c = 11c\,(1-v)^{10/11}\,v^{10\mu-1}.$$

Here the constant c must be chosen such that

$$\int_\Omega (\rho_o + \rho_c)\,dv = 1.$$

It is interesting to note here that, even if both ρ_o and ρ_c depend heavily on the mutation severity index μ, the relation between these functions is independent of μ since

$$\frac{\rho_o}{\rho_c} = \frac{v}{11(1-v)}.$$

10.4 Comparison of Monte Carlo Simulations and Probability Density Functions

In previous chapters we gave many examples showing that the probability density functions faithfully represent the frequency distributions that can be computed using Monte Carlo simulations. We will briefly show that this also holds for the ion channel model considered here. In Fig. 10.1, we compare the open probability density function given by (10.10) and a histogram computed using Monte Carlo simulations based on the numerical scheme given by (10.5). We observe again—and by now we are starting to get used to it—that the probability density functions more or less coincide with the histograms computed using Monte Carlo simulations.[2]

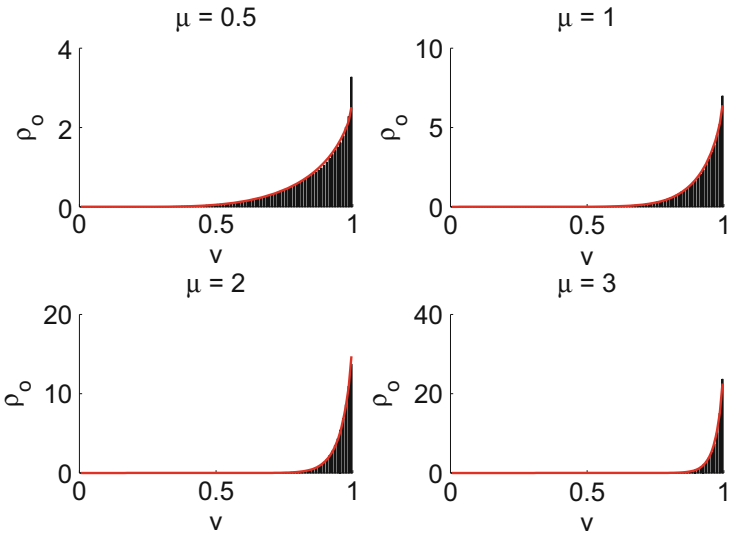

Fig. 10.1 Comparison of the results of Monte Carlo simulations (histogram) and analytical solutions of the system governing the probability density functions for four values of the mutation severity index μ. The unit interval is divided into 100 sub-intervals where the number of occurrences is counted in the Monte Carlo simulations. The analytical solutions are evaluated in the center of these sub-intervals. Each case was simulated for 10 s, with $\Delta t = 0.01$ ms

[2] At this point it feels appropriate to remind the reader of one of the many great quotes by John von Neumann: "In mathematics you don't understand things. You just get used to them."

10.5 Mutations and Theoretical Drugs

In our analysis of the RyR, we studied the effect of mutations increasing the open probability of the channel. In addition, for voltage-gated ion channels, mutations may affect the open probability of the channel and thereby change the dynamics of the transmembrane potential. We will study specific examples of this below, where we present actual mutations and their effect on actual ion channels, such as the sodium channel. However, for the time being, we will stick to our not so realistic but rather cute model. We will assume that the stochastic dynamics of the transmembrane potential are governed by (10.2), that the probability density functions are governed by (10.7), and that the Markov model is given by

$$C \underset{k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O, \tag{10.11}$$

where $k_{oc} = 1\ \mathrm{ms}^{-1}$ and $k_{co} = \mu\ \mathrm{ms}^{-1}$. As usual, μ is the mutation severity index and $\mu = 1$ denotes the wild type case. Motivated by the results for the RyR mutations, we will try to repair the effect of the mutation using an open or a closed state blocker. This will prove to be quite efficient, since we are dealing with a CO-mutation.

10.5.1 Theoretical Open State Blocker

The Markov model of the theoretical open state blocker is

$$C \underset{k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O \underset{k_{ob}}{\overset{k_{bo}}{\leftrightarrows}} B, \tag{10.12}$$

where the parameters k_{bo} and k_{ob} need to be determined. The associated steady state version of the probability density system is given by

$$\begin{aligned}
\frac{\partial}{\partial v}\left(a_o \rho_o\right) &= k_{co}\rho_c - \left(k_{oc} + k_{ob}\right)\rho_o + k_{bo}\rho_b, \\
\frac{\partial}{\partial v}\left(a_c \rho_c\right) &= k_{oc}\rho_o - k_{co}\rho_c, \\
\frac{\partial}{\partial v}\left(a_c \rho_b\right) &= k_{ob}\rho_o - k_{bo}\rho_b,
\end{aligned} \tag{10.13}$$

where ρ_o, ρ_c, and ρ_b denote the probability density functions of the open (O), closed (C), and blocked (B) states, respectively. We compute optimal values of the parameters k_{bo} and k_{ob} using the *Fminsearch* function in Matlab applied to the difference between the open probability density function computed by

solving (10.13) and the wild type solution given by system (10.7), with $\mu = 1$. The function used in the minimization is given by

$$\frac{\sqrt{\int |\rho_{o,\mathrm{mt+d}} - \rho_{o,\mathrm{wt}}|^2 dv}}{\sqrt{\int \rho_{o,\mathrm{wt}}^2 dv}},$$

where $\rho_{o,\mathrm{wt}}$ is the wild type open probability density function and $\rho_{o,\mathrm{mt+d}}$ is the mutant open probability density function where the theoretical drug is applied.

10.5.2 Theoretical Closed State Blocker

The Markov model of the theoretical closed state blocker is

$$B \underset{k_{bc}}{\overset{k_{cb}}{\leftrightarrows}} C \underset{k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O, \tag{10.14}$$

where the parameters k_{cb} and k_{bc} must be computed. Following the arguments on page 58, we find that these parameters must be related as

$$k_{cb} = (\mu - 1)\, k_{bc} \tag{10.15}$$

and thus we are left with the task of finding a proper value for only one parameter: k_{bc}. Of course, based on what we learned for the RyR channel, we suspect that k_{bc} should be as large as possible. The computations reported below will verify this suspicion.

The steady state version of the probability density system associated with the Markov model (10.14) is given by

$$\begin{aligned}
\frac{\partial}{\partial v}(a_o \rho_o) &= k_{co}\rho_c - k_{oc}\rho_o, \\
\frac{\partial}{\partial v}(a_c \rho_c) &= k_{oc}\rho_o - (k_{co} + (\mu - 1)\, k_{bc})\, \rho_c + k_{bc}\rho_b, \\
\frac{\partial}{\partial v}(a_c \rho_b) &= (\mu - 1)\, k_{bc}\rho_c - k_{bc}\rho_b,
\end{aligned} \tag{10.16}$$

where, again, ρ_o, ρ_c, and ρ_b denote the probability density functions of the open (O), closed (C), and blocked (B) states, respectively. Here, the value of k_{bc} characterizing the drug remains to be determined and will be discussed below.

10.5.3 Numerical Computations Using the Theoretical Blockers

Let us start by showing that the closed state blocker is improved by increasing values of k_{bc}. In Fig. 10.2, we show the numerical solutions of system (10.16) with increasing values of k_{bc} for four values of the mutation severity index μ. We observe, as expected, that the drug is improved as k_{bc} is increased.

In Fig. 10.3, we compare a good theoretical closed state blocker (using $k_{bc} = 100\ \text{ms}^{-1}$) and the best open state blocker for four values of the mutation severity index μ. This figure does not reveal much difference between the two alternative blockers, but we will see below that the statistical properties of the solutions show that there is a significant difference.

10.5.4 Statistical Properties of the Theoretical Drugs

To further compare the properties of the drugs, it is useful to use the statistical properties introduced above. We recall that the probability of being in state i is

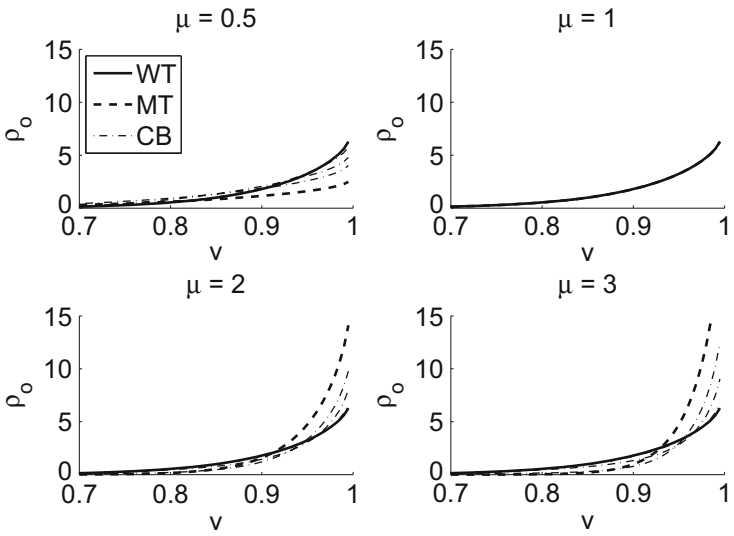

Fig. 10.2 The open probability density functions of the wild type (WT), mutants (MT) and mutants in the presence of the closed state blocker (CB) for four values of the mutation severity index μ. We use k_{bc} = 0.1, 1, 10, 100 ms^{-1} and observe that, for the largest value of k_{bc}, the drugged solutions are virtually indistinguishable from the wild type solution

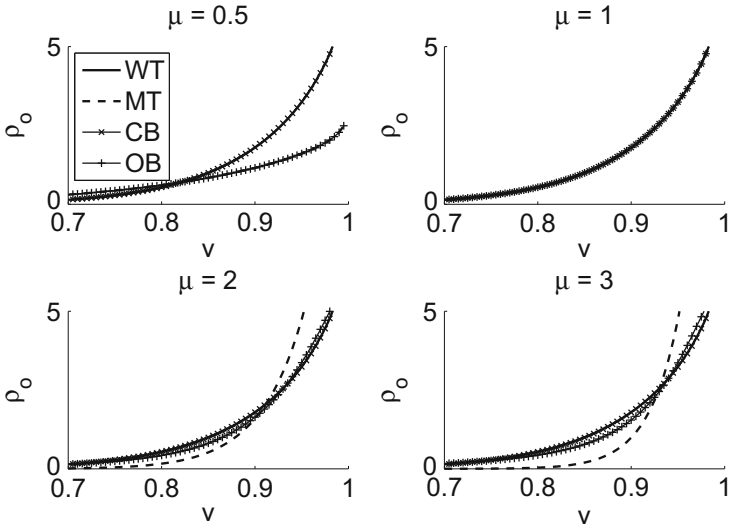

Fig. 10.3 Comparison of the best closed and open state blockers for four values of the mutation severity index. For the case $\mu = 0.5$ the optimization did not find any open state blockers that helped (the solution for the mutant in the presence of the open state blocker (OB) is superimposed on the solution for the mutant (MT) in the lower trace.) We found the following specifications of the open state blockers to be optimal: For $\mu = 2$, we used $k_{bo} = 0.37$ ms^{-1} and $k_{ob} = 0.21$ ms^{-1} and, for $\mu = 3$, we used $k_{bo} = 0.45$ ms^{-1} and $k_{ob} = 0.35$ ms^{-1}. In all cases, we used the closed state blocker characterized by $k_{bc} = 100$ ms^{-1} and $k_{cb} = (\mu - 1)\, k_{bc}$

given by

$$\pi_i = \int_\Omega \rho_i dv,$$

where $i = o, c$, or b for the open, closed, or blocked state, respectively. The expected value of the transmembrane potential under the condition that the channel is open, closed, or blocked is given by

$$E_i = \frac{1}{\pi_i} \int_\Omega v \rho_i dv,$$

for $i = o, c$, or b, respectively. Finally, for $i = o, c$, or b, the standard deviations are given by

$$\sigma_i^2 = \frac{1}{\pi_i} \int_\Omega v^2 \rho_i dv - E_i^2.$$

Table 10.2 Statistics of the open probability density functions in the case of $\mu = 3$. The closed state blocker is given by $k_{bc} = 100\ \text{ms}^{-1}$ and $k_{cb} = (\mu - 1)\, k_{bc}$ and the open state blocker is given by $k_{bo} = 0.45\ \text{ms}^{-1}$ and $k_{ob} = 0.35\ \text{ms}^{-1}$

	WT	MT	CB	OB
π_o	0.500	0.750	0.500	0.478
E_o	0.922	0.969	0.922	0.919
σ_o	0.076	0.031	0.076	0.088

In Table 10.2, we compare the statistical properties of the solutions based on different theoretical blockers. We see that the mutation significantly increases the open probability but leaves the expected value of the transmembrane potential more or less unchanged. The standard deviation, however, is significantly reduced by the mutation.

Both the open and closed state blockers are able to significantly reduce the effect of the mutations, as illustrated in Fig. 10.3. However, the closed state blocker is slightly better at this than the optimal open state blocker.

10.6 Notes

1. The equation

$$Cv' = -g_L\,(v - V_L) - g_i(v - V_i) \tag{10.17}$$

(see (10.2)) underpins this chapter and most of the rest of these lecture notes. It is a classical equation and derivations are found in numerous places. A thorough discussion is given in the classical text by Plonsey and Barr [66]. The basic idea of the derivation is to equate the flux of ions through the membrane with the associated change of the charge in the extracellular and intracellular domains.