Chapter 11
Inactivated Ion Channels: Extending the Prototype Model

Experimental evidence suggests that some ion channels can take on three main states: open (O), closed (C), or inactivated (I). Here both C and I mean that the channel is non-conducting, but when the channel is inactivated, it is harder to open again than when the channel is in the closed state. This feature is useful in modeling an action potential. In the action potential of a cardiac cell, the upstroke is driven mainly by the sodium current. When the upstroke is completed, the sodium channels are inactivated to avoid spurious new upstrokes before the cell has undergone a restitution period. Certain mutations impair the ability of the channel to deactivate, which may lead to arrhythmias. We will return to this topic below. Here, it suffices to state that we need to introduce an inactivated state in the prototype model discussed above.

The stochastic model considered in this chapter is the same as in Chap. 10

$$Cv' = -g_L\,(v - V_L) - g_i(v - V_i), \tag{11.1}$$

with the parameters given in Table 10.1 on page 154.

11.1 Three-State Markov Model

The reaction scheme of an ion channel taking on the three states O, C, and I is given in Fig. 11.1. To model the properties of the action potential in the way we described above, we need to introduce reaction rates that depend on the transmembrane potential v. At this point, we just want to derive a prototypical model and we

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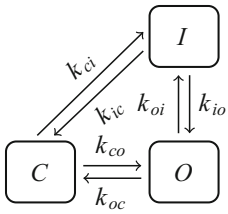

Fig. 11.1 Markov model including three possible states: open (O), closed (C), and inactivated (I)

therefore, admittedly somewhat arbitrarily, define the following rates:

$$\begin{aligned} k_{co} &= \tfrac{k_{co}^{\infty}}{\tau_{co}}, \quad & k_{oc} &= \tfrac{1-k_{co}^{\infty}}{\tau_{co}}, \\ k_{oi} &= 1, & k_{io} &= \tfrac{k_{co}k_{oi}k_{ic}}{k_{oc}k_{ci}}, \\ k_{ic} &= e^{-30v}, & k_{ci} &= \tfrac{1}{100}, \end{aligned} \tag{11.2}$$

where

$$k_{co}^{\infty} = \frac{1}{1+e^{6-16v}}$$

and

$$\tau_{co} = \frac{1}{10}.$$

By the definition of k_{io}, these rates satisfy the principle of detailed balance (see page 10 and the notes of Chap. 1).

11.1.1 Equilibrium Probabilities

We saw above (see page 8) that the equilibrium state of the reaction shown in Fig. 11.1 is given by

$$o = \frac{1}{1+\frac{k_{oc}}{k_{co}}+\frac{k_{oi}}{k_{io}}},$$

$$c = \frac{\frac{k_{oc}}{k_{co}}}{1+\frac{k_{oc}}{k_{co}}+\frac{k_{oi}}{k_{io}}},$$

$$i = \frac{\frac{k_{oi}}{k_{io}}}{1+\frac{k_{oc}}{k_{co}}+\frac{k_{oi}}{k_{io}}}.$$

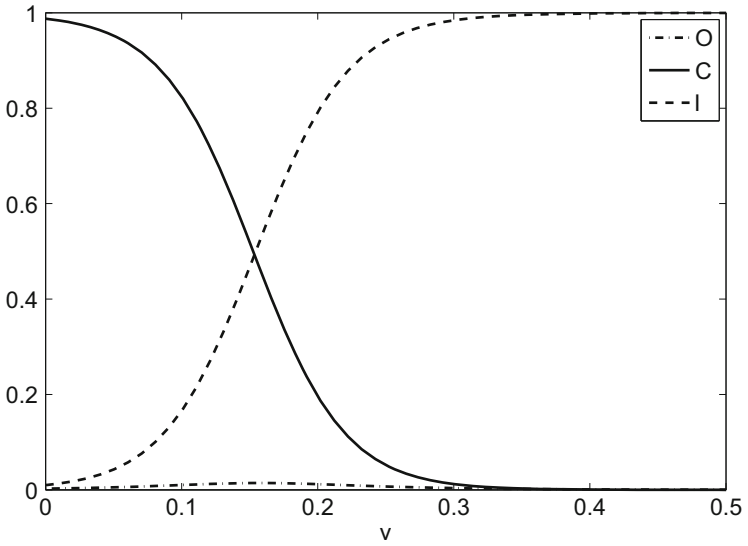

Fig. 11.2 Equilibrium probabilities of the open, closed, and inactivated states as functions of the transmembrane potential v

These probabilities are graphed as functions of the transmembrane potential in Fig. 11.2. Note that the open probability in equilibrium is quite small; the channel is basically closed for v close to zero and it is inactivated for large values of v.

11.2 Probability Density Functions in the Presence of the Inactivated State

When the inactivated state is included in the model, as indicated in Fig. 11.1, the system governing the associated probability density functions is given by

$$\frac{\partial \rho_o}{\partial t} + \frac{\partial}{\partial v}(a_o \rho_o) = k_{co}\rho_c - (k_{oc} + k_{oi})\rho_o + k_{io}\rho_i, \tag{11.3}$$

$$\frac{\partial \rho_c}{\partial t} + \frac{\partial}{\partial v}(a_c \rho_c) = k_{oc}\rho_o - (k_{co} + k_{ci})\rho_c + k_{ic}\rho_i, \tag{11.4}$$

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial}{\partial v}(a_c \rho_i) = k_{oi}\rho_o - (k_{io} + k_{ic})\rho_i + k_{ci}\rho_c, \tag{11.5}$$

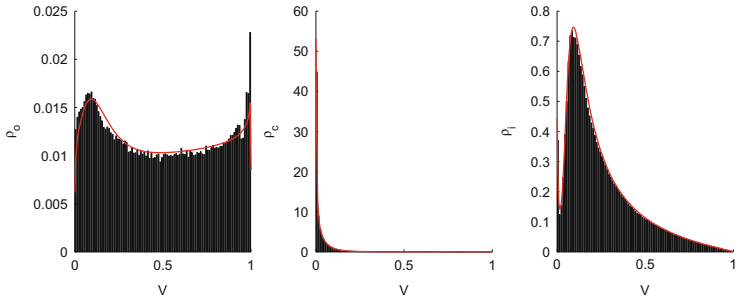

Fig. 11.3 Probability density functions of the open, closed, and inactivated states (*red lines*) computed as numerical solutions of the system (11.3)–(11.5) and histograms based on Monte Carlo simulations using the stochastic differential equation (11.1)

where

$$a_o = -g_L\,(v - V_L) - (v - V_i) = \frac{11}{10}\,(1 - v)\,, \tag{11.6}$$

$$a_c = -g_L\,(v - V_L) = -\frac{1}{10}v.$$

11.2.1 Numerical Simulations

Again, we want to compare the solution computed by Monte Carlo simulations based on the stochastic differential equation given in (11.1) and the probability density functions defined by the system (11.3)–(11.5). The numerical results are given in their usual form in Fig. 11.3. As expected, the histograms computed using Monte Carlo simulations and the numerical solution of the system (11.3)–(11.5) are quite similar. In these computations, the stochastic simulation ran for 100 s, with $\Delta t = 0.01$ ms, and we used the mesh size $\Delta v = 0.01$ in the numerical solution of the system (11.3)–(11.5). It is particularly interesting to see that the tiny boundary layer close to $v = 0$ for the probability density function of the inactivated state is captured using both the Monte Carlo and the probability density function approaches.

11.3 Mutations Affecting the Inactivated State of the Ion Channel

Certain mutations of the sodium channel are known to impair the channel's ability to deactivate. We introduce a mutation severity index μ and assume that the reaction rates of the mutant are changed such that both the probabilities of moving from

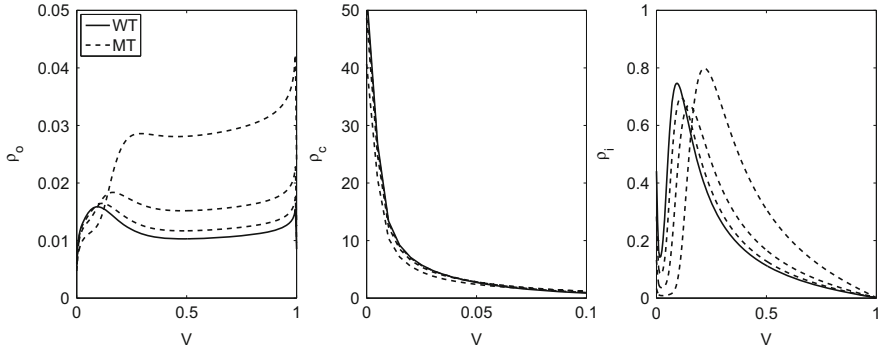

Fig. 11.4 Probability density functions of the open, closed, and inactivated states for the wild type and for three values of the mutation severity index: $\mu = 1.5,\ 3,\ 10$. Larger values of μ give solutions farther away from the wild type solution (*solid line*). The probability density of the closed state is only shown for v between 0 and 0.1 to magnify very small differences

the inactivated to the closed state and from the inactivated to the open state are increased. The effect of these changes will clearly be to lower the probability of the channel being in the inactivated state.

In mathematical terms, we define

$$\bar{k}_{ic} = \mu k_{ic}, \tag{11.7}$$
$$\bar{k}_{io} = \mu k_{io},$$

where $\mu \geqslant 1$ and where k_{ic} and k_{io} are the wild type reaction rates given by (11.2). It should be noted that the new reaction rates still satisfy the principle of detailed balance. In Fig. 11.4, we show the equilibrium probability density functions of the open, closed, and inactivated states for the wild type and for three values of the mutation severity index μ.

11.4 A Theoretical Drug for Mutations Affecting the Inactivation

We want to derive a theoretical drug repairing the effect of the mutation described in (11.7). In the Markov model illustrated in Fig. 11.5, we have introduced a blocked state associated with the open, closed, and inactivated state and we now want to figure out what the best choice might be. The equilibrium solution of the reaction

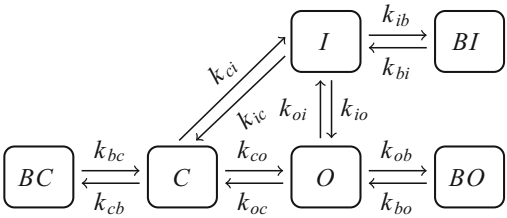

Fig. 11.5 The model represented in Fig. 11.1 extended to account for blockers associated with the closed state (BC), the open state (BO), and inactivated state (BI)

represented in Fig. 11.5 is characterized by the equations

$$k_{co}c = k_{oc}o,\ k_{ci}c = k_{ic}i,$$
$$k_{oi}o = k_{io}i,\ k_{bc}b_c = k_{cb}c,$$
$$k_{bo}b_o = k_{ob}o,\ k_{bi}b_i = k_{ib}i.$$

It is useful to define

$$r_{xy} = \frac{k_{xy}}{k_{yx}}$$

and to note that

$$r_{xy} = \frac{1}{r_{yx}}.$$

With this notation, the principle of detailed balance stating that

$$\frac{k_{co}k_{oi}k_{ic}}{k_{oc}k_{io}k_{ci}} = 1$$

can be written as

$$r_{co}r_{oi}r_{ic} = r_{oc}r_{io}r_{ci} = 1.$$

The equations above can now be written as

$$c = r_{oc}o,\ c = r_{ic}i,$$
$$o = r_{io}i,\ b_c = r_{cb}c,$$
$$b_o = r_{ob}o,\ b_i = r_{ib}i.$$

It is convenient to express all probabilities in terms of the open probability:

$$\begin{aligned} c &= r_{oc} o, \\ i &= r_{oi} o, \\ b_c &= r_{cb} c = r_{cb} r_{oc} o, \\ b_o &= r_{ob} o, \\ b_i &= r_{ib} i = r_{ib} r_{oi} o. \end{aligned}$$

Since $c + i + o + b_c + b_o + b_i = 1$, we have

$$o = p^{-1},$$

where

$$p = 1 + r_{oc}\,(1 + r_{cb}) + r_{oi}\,(1 + r_{ib}) + r_{ob}.$$

We refer to p as the inverse open probability and we note that for the wild type it is given by

$$p = 1 + r_{oc} + r_{oi}.$$

11.4.1 Open Probability in the Mutant Case

As discussed above, we are interested in understanding how to define a theoretical drug for mutations affecting the inactivation of the ion channel. We assume that the mutation affects the inactivation in a way that reduces the probability of being in the inactivated state. As mentioned above, this can be modeled by increasing the reaction rates from the inactivated state to both the closed and the open states. We assume that

$$\bar{k}_{ic} = \mu k_{ic},\ \bar{k}_{io} = \mu k_{io},$$

where $\mu \geqslant 1$ is the mutation severity index. This gives

$$\bar{r}_{ic} = \frac{\bar{k}_{ic}}{k_{ci}} = \mu r_{ic}$$

and

$$\bar{r}_{io} = \frac{\bar{k}_{io}}{k_{oi}} = \mu r_{io}.$$

We assume that the reaction rates between the closed and open states are unaffected by the mutation and therefore

$$\bar{r}_{oc} = r_{oc}.$$

Detailed balance dictates that we should have

$$(\mu k_{ic})k_{co}k_{oi} = (\mu k_{io})k_{oc}k_{ci},$$

which holds regardless of the choice of μ, since the wild type rates satisfy the principle of detailed balance.

The inverse open probability in the presence of the mutations is given by

$$\bar{p} = 1 + r_{oc} + \bar{r}_{oi} = 1 + r_{oc} + 1/\bar{r}_{io} = 1 + r_{oc} + \frac{1}{\mu r_{io}} = 1 + r_{oc} + \frac{r_{oi}}{\mu}.$$

11.4.2 The Open Probability in the Presence of the Theoretical Drug

When the drug given in Fig. 11.5 is applied, the inverse open probability is

$$p_b = 1 + r_{oc}\,(1 + r_{cb}) + \frac{r_{oi}}{\mu}\,(1 + r_{ib}) + r_{ob}$$

where r_{cb}, r_{ib}, and r_{ob} are used to characterize the drug. Our aim is to now use these parameters to tune the drug such that

$$p_b \approx p,$$

where p is the inverse open probability of the wild type. More precisely, we want to determine the constants r_{cb}, r_{ib}, and r_{ob} such that

$$1 + r_{oc}\,(1 + r_{cb}) + \frac{r_{oi}}{\mu}\,(1 + r_{ib}) + r_{ob} \approx 1 + r_{oc} + r_{oi}$$

holds for all relevant values of the transmembrane potential v. We observe that if we put $r_{cb} = r_{ob} = 0$, we obtain the condition

$$\frac{r_{oi}}{\mu}\,(1 + r_{ib}) \approx r_{oi}$$

and therefore we set

$$r_{ib} = \mu - 1.$$

We conclude that we can repair the equilibrium state of the mutation completely by applying a drug consisting of a blocker of the inactivated state, provided that the reaction rates of the drug satisfy

$$\frac{k_{ib}}{k_{bi}} = \mu - 1,$$

where μ is the severity index of the mutation. This means that we have reduced the problem of finding a drug to a single parameter given by k_{bi}. This remaining degree of freedom will be addressed below.

11.5 Probability Density Functions Using the Blocker of the Inactivated State

In Sect. 11.2 above, we derived a system governing the probability density functions of the open, closed, and inactivated states. Here, we want to extend the system to account for the theoretical drug represented by a blocker of the inactivated state. The Markov model of the drug is given in Fig. 11.6. The drug will completely repair the equilibrium state of the Markov model, provided that

$$k_{ib} = (\mu - 1)\, k_{bi}, \tag{11.8}$$

where μ is the mutation severity index of the mutation (see (11.7)). The stationary probability density functions of the states in the Markov model of Fig. 11.6 are governed by the system

$$\frac{\partial}{\partial v}\left(a_o \rho_o\right) = k_{co}\rho_c - \left(k_{oc} + k_{oi}\right)\rho_o + \mu k_{io}\rho_i, \tag{11.9}$$

$$\frac{\partial}{\partial v}\left(a_c \rho_c\right) = k_{oc}\rho_o - \left(k_{co} + k_{ci}\right)\rho_c + \mu k_{ic}\rho_i, \tag{11.10}$$

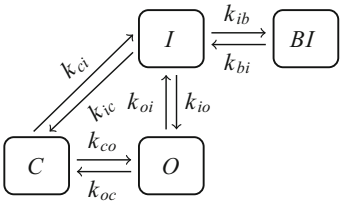

Fig. 11.6 Markov model of the prototype ion channel with a blocker associated with the inactivated state

$$\frac{\partial}{\partial v}\left(a_c\rho_i\right) = k_{oi}\rho_o - \left(\mu k_{io} + \mu k_{ic} + (\mu - 1)\, k_{bi}\right)\rho_i + k_{ci}\rho_c + k_{bi}\rho_b, \tag{11.11}$$

$$\frac{\partial}{\partial v}\left(a_c\rho_b\right) = (\mu - 1)\, k_{bi}\rho_i - k_{bi}\rho_b, \tag{11.12}$$

where ρ_o, ρ_c, ρ_i, and ρ_b denote the probability density functions of the open, closed, inactivated, and blocked states, respectively, and where the flux terms are given by

$$a_o = -g_L\left(v - V_L\right) - \left(v - V_i\right) = \frac{11}{10}\left(1 - v\right),$$

$$a_c = -g_L\left(v - V_L\right) = -\frac{1}{10}v.$$

The associated model of the wild type is given by

$$\frac{\partial}{\partial v}\left(a_o\rho_o\right) = k_{co}\rho_c - \left(k_{oc} + k_{oi}\right)\rho_o + k_{io}\rho_i, \tag{11.13}$$

$$\frac{\partial}{\partial v}\left(a_c\rho_c\right) = k_{oc}\rho_o - \left(k_{co} + k_{ci}\right)\rho_c + k_{ic}\rho_i, \tag{11.14}$$

$$\frac{\partial}{\partial v}\left(a_c\rho_i\right) = k_{oi}\rho_o - \left(k_{io} + k_{ic}\right)\rho_i + k_{ci}\rho_c. \tag{11.15}$$

All the reactions rates used in the computations are given in (11.2); the computational domain is given by $\Omega = [0, 1]$ and we used 201 mesh points. In Fig. 11.7, we show the difference between the open state probability density function of the wild type, denoted by ρ_o, computed by solving the system (11.13)–(11.15), and the mutant where the drug is applied, computed by solving (11.9)–(11.12), denoted by ρ_o^*. The difference is defined by the norm

$$\|\rho_o - \rho_o^*\| = \frac{\left\|\rho_o - \rho_o^*\right\|_{L^2(\Omega)}}{\|\rho_o\|_{L^2(\Omega)} + \left\|\rho_o^*\right\|_{L^2(\Omega)}}, \tag{11.16}$$

where, as usual,

$$\|\rho\|_{L^2(\Omega)} = \left(\int_\Omega \rho^2 dv\right)^{1/2}.$$

We observe that, as k_{bi} increases, the drug defined by (11.8) completely repairs the effect of the mutation.

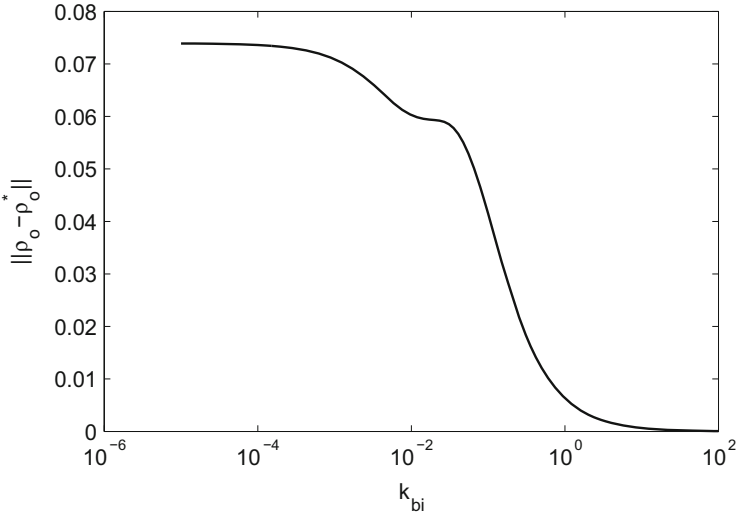

Fig. 11.7 The difference between the open probability density function of the wild type (ρ) and the open probability density function (ρ^*) of the mutant using the drug defined by (11.8), measured by the norm $\|\rho_o - \rho_o^*\|$ defined in (11.16). The difference goes to zero as the parameter k_{bi} is increased