Chapter 12
A Simple Model of the Sodium Channel

In the previous two chapters, we studied a prototypical model of an ion channel. The model consisted of a differential equation involving a gating mechanism that could be either open or closed. A Markov model governed the gating and we derived a system giving the probability density functions of the states involved in the Markov model. We used the probability density approach to compute optimal theoretical drugs and noted that a mutation leading to an increase in the closed to open reaction rate could be completely repaired by an optimal closed state drug.

Next, we extended the prototypical model to also include an inactivated state. The inactivated state can also be affected by mutations and we studied the particular case in which the rates from inactivated to open and from inactivated to closed were increased by a factor μ referred to as the mutation severity index. In this case, we observed that an optimal drug was represented by a blocker associated with the inactivated state. We were again able to completely repair the effect of the mutation using the theoretical drug.

In this chapter, we shall move closer to realistic Markov models of sodium channels. These models tend to be somewhat more intricate than the prototypical model we have studied so far. Providing Markov models of the sodium channels has been a very active field of research for decades and a series of models are available. We have chosen to study models that seem to capture the basic structure applied in many models but are manageable from a mathematical point of view. We choose this approach for clarity of presentation and not for its ability to represent specific data. It is, hopefully, quite clear that the method we use to analyze the models is applicable to many other models.

Mutations of the sodium channel can lead to impaired inactivation. This may lead to leakage of the sodium current, which can again trigger arrhythmias. Here we will consider a model of the ΔKPQ mutation of the SCN5A gene. This mutation may lead to an arrhythmogenic disorder referred to as the long-QT syndrome, which can lead to sudden cardiac death in the worst case. There are several models representing

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the effect of the ΔKPQ mutation. One that is well known is provided by Clancy and Rudy [14]. Their approach to model the impaired inactivation is to introduce a burst mode in the model where no inactivation state is available. We will consider two ways of modeling the effect of the mutation.

In the first approach, we will use the method utilized above. We will simply increase the reaction rate from the inactivated to the closed state and from the inactivated to the open state by a factor $\mu \geq 1$, referred to as the mutation severity index. This change will clearly reduce the probability of being in the inactivated state. It is therefore a model of impaired inactivation.

The second approach is to introduce a burst mode in the model. When the channel is in the burst mode, there is no inactivated state. This model will be parameterized such that it is highly unlikely that the channel will enter the burst mode for the wild type case, but the probability of entering the burst mode is considerably higher in the mutant case.

12.1 Markov Model of a Wild Type Sodium Channel

Markov models have turned out to be a powerful tool in representing the physics of the sodium channel and a series of alternatives have been proposed by various authors. Since this is still a very active field of research, it is hard to claim one particular model as the definitive model. We shall therefore focus on a kind of model that has a structure that seems to be more or less agreed upon but, as usual, we attack this problem with simplicity in mind. This also holds true for the way we introduce the effect of a mutation.

We start by considering a simple model of the sodium channel, illustrated in Fig. 12.1. The actual functions used in our computations will be given below. However, we should note that the functions will always be chosen such that they satisfy the principle of detailed balance, which, for the model given in Fig. 12.1, means that the following relation holds:

$$k_{io}k_{oc}k_{ci} = k_{oi}k_{ic}k_{co}. \tag{12.1}$$

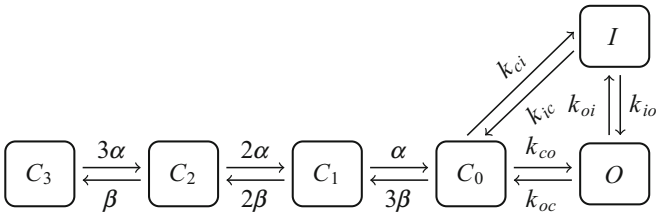

Fig. 12.1 Markov model of a wild type sodium channel consisting of an open state (O), an inactivated state (I), and four closed states (C_0, C_1, C_2, C_3)

The model of the closed states deserves a comment or two. Let us assume that a sodium channel consists of three subunits and these subunits may exist in two states: closed or permissible. The whole channel is in the state C_0 if all three units are in the permissible state. Over a brief period given by Δt, the channel can change from the state C_0 to the open state and the probability of this event is $\Delta t k_{co}$ or it can change to the inactivated state with probability $\Delta t k_{ci}$. However, the channel can also go from the permissible state C_0 to the state C_1 and the probability of doing this is $3\Delta t\beta$. The reason for the factor of three here is that it is sufficient that one of the three subunits closes. By assuming that the subunits act independently, we find that the probability is $3\Delta t\beta$. The same reasoning gives us the rest of the transitions between the different closed states.

12.1.1 The Equilibrium Solution

The equilibrium probabilities of the model given in Fig. 12.1 are characterized by the equations

$$\begin{aligned} k_{ci}c_0 = k_{ic}i, \quad k_{oi}o = k_{io}i, \quad k_{co}c_0 = k_{oc}o, \\ 3\beta c_0 = \alpha c_1,\ 2\alpha c_2 = 2\beta c_1,\ 3\alpha c_3 = \beta c_2, \end{aligned}$$

where c_0 denotes the equilibrium probability of being in the state C_0. Similarly, the other variables are defined as the equilibrium probability of being in the states C_1, C_2, C_3, I, and O. We express all probabilities in terms of the open probability:

$$\begin{aligned} i = \frac{k_{oi}}{k_{io}}o,\ c_0 = \frac{k_{oc}}{k_{co}}o, \\ c_1 = \frac{3\beta}{\alpha}\frac{k_{oc}}{k_{co}}o,\ c_2 = \frac{3\beta^2}{\alpha^2}\frac{k_{oc}}{k_{co}}o,\ c_3 = \frac{\beta^3}{\alpha^3}\frac{k_{oc}}{k_{co}}o. \end{aligned}$$

Since $o + i + c_0 + c_1 + c_2 + c_3 = 1$, we find the following equilibrium probabilities:

$$\begin{aligned} o = \frac{1}{q_w},\ i = \frac{k_{oi}/k_{io}}{q_w},\ c_0 = \frac{k_{oc}/k_{co}}{q_w}, \\ c_1 = \frac{3\beta}{\alpha}\frac{k_{oc}/k_{co}}{q_w},\ c_2 = \frac{3\beta^2}{\alpha^2}\frac{k_{oc}/k_{co}}{q_w},\ c_3 = \frac{\beta^3}{\alpha^3}\frac{k_{oc}/k_{co}}{q_w}, \end{aligned} \tag{12.2}$$

where

$$q_w = 1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}}\left(1 + \beta/\alpha\right)^3.$$

Here the subscript w is used to indicate that q_w represents the wild type case.

12.2 Modeling the Effect of a Mutation Impairing the Inactivated State

The mutation impairs the inactivated state of the channel. In Sect. 11.3 we modeled this by increasing the probability of moving from the inactivated state to the open state or to the closed state. This was done by increasing the rates k_{io} and k_{ic}. We use the same approach here and define

$$\bar{k}_{ic} = \mu k_{ic}, \tag{12.3}$$

$$\bar{k}_{io} = \mu k_{io}, \tag{12.4}$$

where, as usual, μ is the mutation severity index. From (12.1), we have

$$k_{io}k_{oc}k_{ci} = k_{ic}k_{co}k_{oi}$$

and therefore

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

so

$$\bar{k}_{io}k_{oc}k_{ci} = \bar{k}_{ic}k_{co}k_{oi}$$

and thus the principle of detailed balance also holds for the mutant case, in which the rates are given by (12.3) and (12.4).

12.2.1 The Equilibrium Probabilities

The reaction scheme of the mutant is illustrated in Fig. 12.2. In the mutant case, the equilibrium probabilities are given by

$$o = \frac{1}{q_m},\ i = \frac{k_{oi}/\left(\mu k_{io}\right)}{q_m},\ c_0 = \frac{k_{oc}/k_{co}}{q_m}, \tag{12.5}$$

$$c_1 = \frac{3\beta}{\alpha}\frac{k_{oc}/k_{co}}{q_m},\ c_2 = \frac{3\beta^2}{\alpha^2}\frac{k_{oc}/k_{co}}{q_m},\ c_3 = \frac{\beta^3}{\alpha^3}\frac{k_{oc}/k_{co}}{q_m},$$

where

$$q_m = 1 + \frac{k_{oi}}{\mu k_{io}} + \frac{k_{oc}}{k_{co}}\left(1 + \beta/\alpha\right)^3.$$

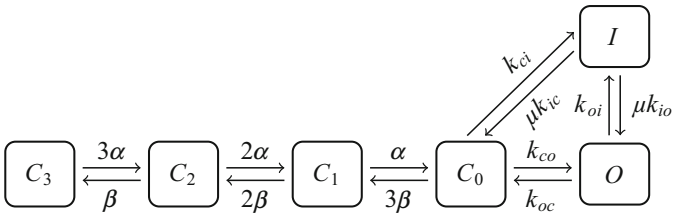

Fig. 12.2 Markov model of the mutant version of the sodium channel consisting of an open state (O), an inactivated state (I), and four closed states (C_0, C_1, C_2, C_3). Here μ is referred to as the mutation severity index

For the equilibrium state it is worth observing that, since

$$i = \frac{k_{oi}/k_{io}}{\frac{k_{oi}}{k_{io}} + \mu\left(1 + \frac{k_{oc}}{k_{co}}\left(1 + \beta/\alpha\right)^3\right)},$$

the probability of being in the inactivated state is reduced when μ is increased. Similarly, we observe that the associated open probability given by

$$o = \frac{1}{1 + \frac{k_{oi}}{\mu k_{io}} + \frac{k_{oc}}{k_{co}}\left(1 + \beta/\alpha\right)^3}$$

increases as μ increases. Although these calculations concern the equilibrium state, this is a pretty strong hint of an increased open probability in the dynamic case as well and an increased open probability is exactly the problem one observes when inactivation is impaired.

12.3 Stochastic Model of the Sodium Channel

We use the same model of the transmembrane potential as above (see (10.2) on page 154). Recall that the stochastic differential equation is given by

$$Cv' = -g_L\left(v - V_L\right) - \gamma g_{Na}(v - V_{Na}), \tag{12.6}$$

where C is the capacitance of the membrane, V_L is the resting potential of the leakage current, and V_{Na} is the resting potential of the sodium channel. The parameters are listed in Table 12.1.

The sodium channel can be either open (O), with $\gamma = 1$, or closed (C), with $\gamma = 0$, and, as usual, the state of the channel is determined by a Markov model.

Table 12.1 Values of the parameters used in model (12.6)

C	$1\,\mu\text{F/cm}^2$
g_L	$1/10\ \text{mS/cm}^2$
g_{Na}	$1\ \text{mS/cm}^2$
V_L	-85 mV
V_{Na}	45 mV

Since $C = 1$, we rewrite the equation in the more convenient form

$$v' = -g_L\,(v - V_L) - \gamma g_{Na}(v - V_{Na}), \tag{12.7}$$

where g_L and g_{Na} now have the unit[1] ms^{-1}.

12.3.1 A Numerical Scheme with an Invariant Region

A numerical scheme for the model (12.7) can be written in the form

$$v_{n+1} = v_n - \Delta t\,(g_L\,(v_n - V_L) + \gamma_n g_{Na}(v_n - V_{Na})), \tag{12.8}$$

where γ_n is either zero or one and where Δt denotes the time step. We assume that the condition

$$\Delta t < \frac{1}{g_L + g_{Na}} \tag{12.9}$$

holds and, under this condition, we will show that an invariant region for the solutions generated by the scheme (12.8) is given by

$$\Omega = (V_L, V_+)\,, \tag{12.10}$$

where

$$V_+ = \frac{g_L V_L + g_{Na} V_{Na}}{g_L + g_{Na}}$$

and, for the parameters we defined in (12.1), we have $V_+ \approx 33.18$ mV.

To derive the invariant region, we proceed along the lines used on page 155 and thus start by defining

$$H(v, \gamma) = v - \Delta t\,(g_L\,(v - V_L) + \gamma g_{Na}(v - V_{Na})).$$

[1]The use of the odd units for g_L and g_{Na} stems from the fact that we have, for notational convenience, incorporated the capacitance of the membrane in these constants.

For values of v in the region Ω and for values of Δt satisfying condition (12.9), we have the properties

$$\frac{d}{dv}H(v,\gamma) = 1 - \Delta t\,(g_L + \gamma g_{Na}) \geqslant 1 - \Delta t\,(g_L + g_{Na}) > 0$$

and

$$\frac{d}{d\gamma}H(v,\gamma) = -\Delta t\,(g_{Na}(v - V_{Na})) > 0.$$

Using these observations, we obtain

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

and

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

So, by induction, it holds that $\Omega = (V_L, V_+)$ is an invariant region for scheme (12.8).

12.4 Probability Density Functions for the Voltage-Gated Channel

The systems modeling the probability density functions in the wild type and mutant cases are of exactly the same form; the only difference is given by the mutation severity index. The probability density functions of the states of the Markov model given in Fig. 12.2 are given by

$$\begin{aligned}
\frac{\partial \rho_o}{\partial t} + \frac{\partial}{\partial v}(a_o\rho_o) &= k_{co}\rho_0 - (k_{oc} + k_{oi})\,\rho_o + \mu k_{io}\rho_i,\\
\frac{\partial \rho_i}{\partial t} + \frac{\partial}{\partial v}(a_c\rho_i) &= k_{oi}\rho_o - \mu\,(k_{io} + k_{ic})\,\rho_i + k_{ci}\rho_0,\\
\frac{\partial \rho_0}{\partial t} + \frac{\partial}{\partial v}(a_c\rho_0) &= k_{oc}\rho_o - (k_{ci} + k_{co} + 3\beta)\,\rho_0 + \mu k_{ic} i + \alpha\rho_1,\\
\frac{\partial \rho_1}{\partial t} + \frac{\partial}{\partial v}(a_c\rho_1) &= 2\alpha\rho_2 - (\alpha + 2\beta)\,\rho_1 + 3\beta\rho_0,\\
\frac{\partial \rho_2}{\partial t} + \frac{\partial}{\partial v}(a_c\rho_2) &= 3\alpha\rho_3 - (2\alpha + \beta)\,\rho_2 + 2\beta\rho_1,\\
\frac{\partial \rho_3}{\partial t} + \frac{\partial}{\partial v}(a_c\rho_3) &= -3\alpha\rho_3 + \beta\rho_2,
\end{aligned} \tag{12.11}$$

where

$$a_o = -g_L\,(v - V_L) - g_{Na}(v - V_{Na}), \qquad (12.12)$$
$$a_c = -g_L\,(v - V_L)\,,$$

with ρ_o denoting the probability density function of being in the open state, ρ_0 denoting the probability density function of being in the state C_0, and so on.

12.4.1 Model Parameterization

To carry out numerical computations comparing the properties of the wild type and the mutant sodium channel, we need to define the rates involved in the model described in Fig. 12.2. We use the rates

$$k_{ab}(v) = k_{ab}^{\infty}(v)/\tau_{ab}, \quad k_{ba}(v) = (1 - k_{ab}^{\infty}(v))/\tau_{ab},$$

with

$$k_{ab}^{\infty} = \frac{1}{1 + e^{s_{ab}(V_{ab} - v)}}.$$

Furthermore, the rates α and β in Fig. 12.2 are given by

$$\alpha = k_{cp}^{\infty}/\tau_{cp} \text{ and } \beta = (1 - k_{cp}^{\infty})/\tau_{cp}.$$

With this parameterization, the principle of detailed balance is satisfied, provided that

$$s_{co} + s_{ic} + s_{oi} = 0 \text{ and } s_{co}V_{co} + s_{oi}V_{oi} + s_{ic}V_{ic} = 0.$$

The parameters are given in Table 12.2 and we introduce the mutation as we did in the previous chapter: We increase the probability of going from the inactivated state to either the open or the closed state. More specifically, we define

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

where, as usual, the wild type case is given by $\mu = 1$.

Table 12.2 Parameters of the Markov model illustrated in Figs. 12.1 and 12.2

ab	V_{ab} (mV)	s_{ab} (1/mV)	τ_{ab} (ms)
co	−60	0.1	0.01
oi	−120	0.05	3
ic	−80	−0.15	10
cp	−60	0.1	0.1

12.4.2 Numerical Experiments Comparing the Properties of the Wild Type and the Mutant Sodium Channel

In Fig. 12.3, we show the probability density functions of the open state, the inactivated state, and the sum of the closed states for the wild type case ($\mu = 1$) and two mutations ($\mu = 10$ and $\mu = 30$). The properties of the solutions are summarized in Table 12.3, which presents the expected values of the open state, the inactivated state, and the sum of the closed states.

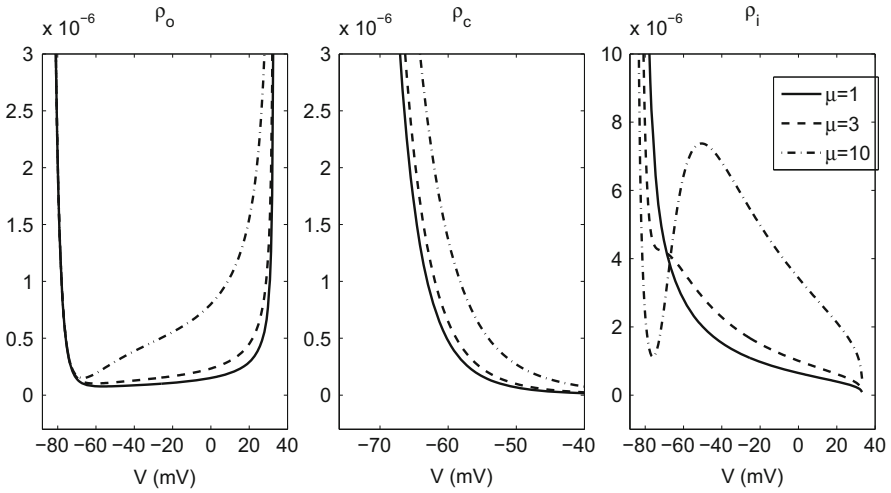

Fig. 12.3 The probability density functions of the open state (*left*), the sum of the closed states (*center*), and the inactivated state (*right*) for the wild type case (*solid line*) and two values of the mutation severity index: $\mu = 10$ and $\mu = 30$. The strongest mutation differs the most from the wild type solution

Table 12.3 Probability of being in the open, closed, or inactivated states and the expected value of the transmembrane potential, provided that the channel is open, closed, or inactivated

μ	$\pi_o \times 100$	π_c	$\pi_i \times 100$	E_o	E_c	E_i
1	0.0067	0.9951	0.4834	−50.8	−84.9	−83.5
3	0.0080	0.9982	0.1765	−41.1	−84.9	−79.6
10	0.0162	0.9989	0.0942	−13.4	−84.9	−57.0

12.4.3 Stochastic Simulations Illustrating the Late Sodium Current in the Mutant Case

Impaired inactivation of the sodium channel leads to a late sodium current, which is illustrated in Fig. 12.4. The figure also includes experimental data of the sodium current taken from Bennett et al. [2]. We observe that, by using $\mu = 30$, the model fits the experimental data fairly well.

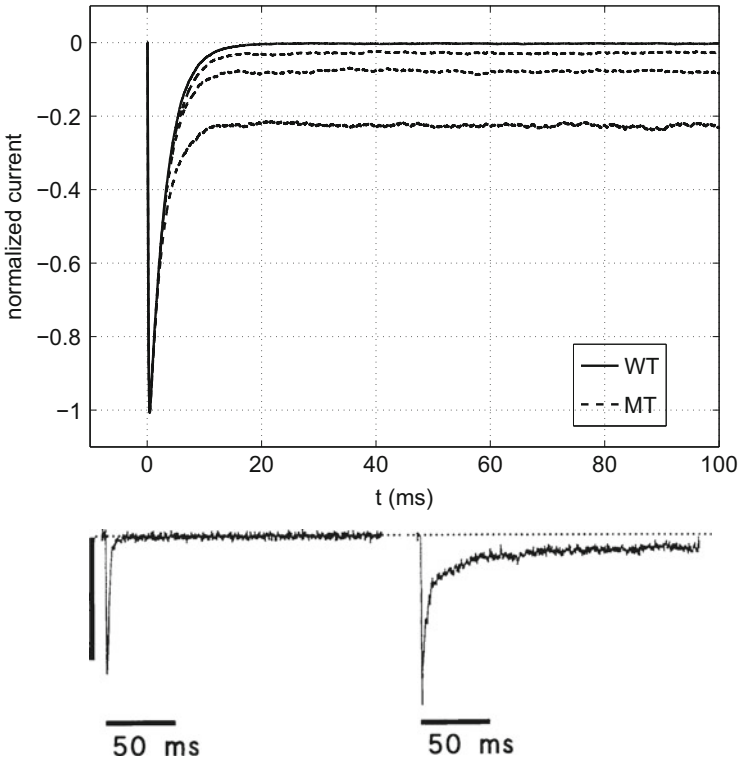

Fig. 12.4 Currents computed using the Markov model given in Fig. 12.2. *Top panel*: Currents based on numerical simulations for $\mu = 1, 10, 30, 100$. Each trace is an average of 10,000 Monte Carlo runs. The current is given by $I = g_{Na}P_o(v - V_{Na})$, with the transmembrane potential clamped at $v = 0$. The currents are normalized so that the wild type case peaks at -1. The parameters are given by $V_{Na} = 45$ and $g_{Na} = 1$ and P_o is the average ratio of open channels over 10,000 runs, computed at each time step. The lower graphs are from Bennett et al. [2], for the wild type case (*left*) and mutant case (*right*)

12.5 A Theoretical Drug Repairing the Sodium Channel Mutation

We introduce a theoretical drug for the sodium channel of the form given in Fig. 12.5. The equilibrium probabilities of the model are characterized by the equations

$$\begin{gathered}
k_{ci}c_0 = \mu k_{ic} i, \quad k_{oi} o = \mu k_{io} i, \quad k_{co} c_0 = k_{oc} o, \\
3\beta c_0 = \alpha c_1, \quad 2\alpha c_2 = 2\beta c_1, \quad 3\alpha c_3 = \beta c_2, \\
k_{bc} b_0 = k_{cb} c_0, \; k_{bc} b_1 = k_{cb} c_1, \; k_{bc} b_2 = k_{cb} c_2, \\
k_{bc} b_3 = k_{cb} c_3, \quad k_{bi} b_i = k_{ib} i, \quad k_{bo} b_o = k_{ob} o.
\end{gathered}$$

As usual, we express all probabilities in terms of the open state probability,

$$\begin{aligned}
i &= \frac{k_{oi}}{\mu k_{io}} o, \; c_0 = \frac{k_{oc}}{k_{co}} o, \\
c_1 &= \frac{3\beta}{\alpha} \frac{k_{oc}}{k_{co}} o, \; c_2 = \frac{3\beta^2}{\alpha^2} \frac{k_{oc}}{k_{co}} o, \; c_3 = \frac{\beta^3}{\alpha^3} \frac{k_{oc}}{k_{co}} o, \\
b_0 &= \delta_c \frac{k_{oc}}{k_{co}} o, \; b_1 = \delta_c \frac{3\beta}{\alpha} \frac{k_{oc}}{k_{co}} o, \; b_2 = \delta_c \frac{3\beta^2}{\alpha^2} \frac{k_{oc}}{k_{co}} o, \\
b_3 &= \delta_c \frac{\beta^3}{\alpha^3} \frac{k_{oc}}{k_{co}} o, \; b_i = \delta_i \frac{k_{oi}}{\mu k_{io}} o, \; b_o = \delta_o o,
\end{aligned}$$

where we have introduced the following parameters characterizing the drug:

$$\delta_o = \frac{k_{ob}}{k_{bo}}, \; \delta_i = \frac{k_{ib}}{k_{bi}}, \; \delta_c = \frac{k_{cb}}{k_{bc}}.$$

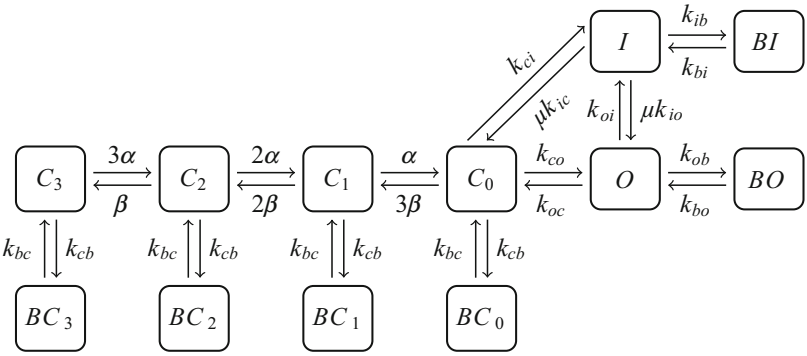

Fig. 12.5 Markov model for a theoretical drug of the sodium channel. The model consists of the usual states O, I, C_0, C_1, C_2, and C_3 and the blocked states BO, BI, BC_0, BC_1, BC_2, and BC_3

Since the sum of the probabilities is one, we obtain

$$o_{m,d} = \frac{1}{q_{m,d}},$$

where the subscript indicates the mutant case in the presence of a drug. Here,

$$q_{m,d} = 1 + \frac{k_{oi}}{\mu k_{io}} + \frac{k_{oc}}{k_{co}} (1 + \beta/\alpha)^3 (1 + \delta_c) + \delta_i \frac{k_{oi}}{\mu k_{io}} + \delta_o$$

and we recall that the wild type open probability is given by

$$o_w = \frac{1}{q_w},$$

where

$$q_w = 1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} (1 + \beta/\alpha)^3 .$$

Obviously, we obtain $o_{m,d} \approx o_w$, provided that $q_{m,d} \approx q_w$. If we choose a drug characterized by

$$\delta_o = \delta_c = 0, \text{and } \delta_i = \mu - 1 \tag{12.13}$$

we find that

$$q_{m,d} = 1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} (1 + \beta/\alpha)^3 = q_w$$

and therefore, with the drug specified by (12.13), we have $o_{m,d} = o_w$, so the open probability at equilibrium is repaired.

12.5.1 Numerical Experiments Using the Blocker of the Inactivated State

We have seen that a blocker of the inactivated state is a promising candidate for repairing the mutation described in Fig. 12.2. The drug is characterized by (12.13), so we have

$$k_{ib} = \delta_i k_{bi} = (\mu - 1)\, k_{bi} \tag{12.14}$$

and the parameter k_{bi} remains to be determined. In Table 12.4, we show that the blocker is more efficient the larger k_{bi} is. In fact, the blocker is able to repair all the

Table 12.4 The open probability, π_o, the expected value of the transmembrane potential, E_o, and the standard deviation, σ_o, for increasing values of k_{bi}. For large values of k_{bi}, the statistical properties of the mutant are completely repaired by the drug

k_{bi}	$\pi_o \times 10^3$	E_o	σ_o
WT	0.067	−50.794	46.828
MT	1.534	12.991	26.831
10^{-6}	1.341	12.940	26.913
10^{-5}	1.180	12.487	27.634
10^{-4}	0.556	8.240	33.343
10^{-3}	0.135	−16.903	49.326
0.01	0.070	−47.563	48.205
0.1	0.067	−50.729	46.869
1	0.067	−50.791	46.830

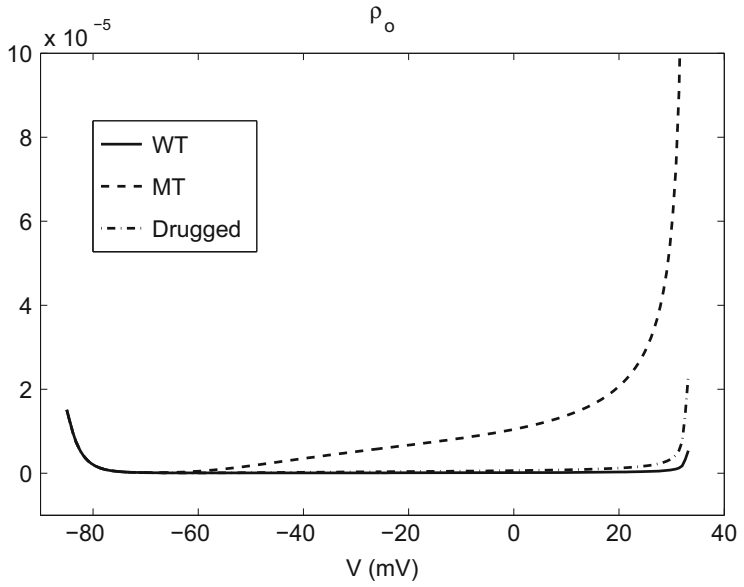

Fig. 12.6 The open probability density function for the wild type (WT) case and the mutant (MT) case using the mutation severity index $\mu = 30$ and, finally, the mutant case with the drug given by (12.14) with $k_{bi} = 0.001$ ms^{-1}. A small value of k_{bi} was used to see a difference between the drugged case and the WT case

relevant statistical properties of the solution. The statistical properties presented in the table are introduced in Sect. 4.2 on page 72.

In Fig. 12.6, we show the open state probability density functions of the wild type, the mutant, and the drugged version of the mutant. Again, we see that the drug completely repairs the open state probability density function.

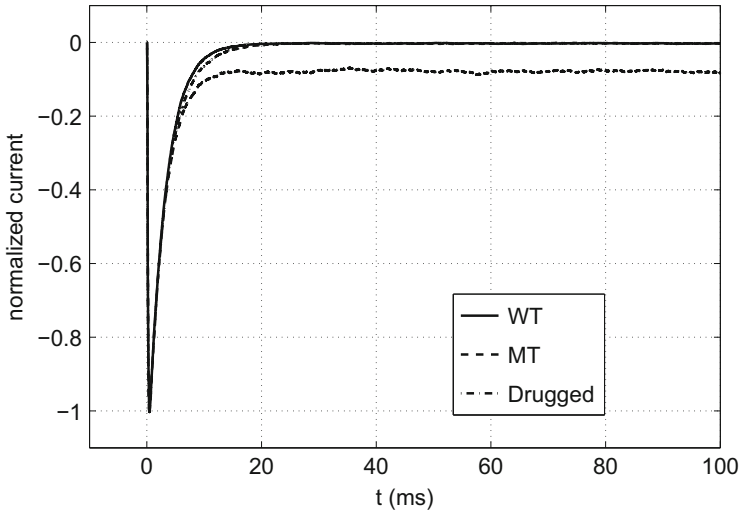

Fig. 12.7 The sodium current for the wild type (WT) and the mutant (MT) with the mutation severity index $\mu = 30$. The drug given by (12.14) with $k_{bi} = 0.01\ \text{ms}^{-1}$ almost completely removes the late sodium current

12.5.2 The Late Sodium Current Is Removed by the Inactivated State Blocker

In Fig. 12.4 above, we demonstrated, using Monte Carlo simulations, that the mutation under consideration leads to a significant late sodium current comparable to the current observed in experiments. By using the drug described in (12.13) with $k_{bi} = 0.01\ \text{ms}^{-1}$, we see that the late current more or less completely disappears (see Fig. 12.7).

12.6 Notes

1. The basic structure of the Markov model in Fig. 12.1 is taken from Patlak [65], who discusses and evaluates several possible models in relation to experimental data.
2. Modeling the effects of a drug on the sodium channel is motivated by the paper of Clancy et al. [16].