Chapter 9
Numerical Drugs for Calcium-Induced Calcium Release

In the previous chapter, we developed models of calcium-induced calcium release (CICR) in terms of both a stochastic release model and a model of the probability density functions of the states involved in the stochastic release model. The models incorporated the effects of mutations in both the ryanodine receptors (RyRs) and the L-type calcium channels (LCCs). The purpose of the present chapter is to introduce theoretical drugs aimed at repairing the effect of mutations of both the LCCs and RyR channels. Model parameters used throughout this chapter are given in Table 9.1.

We have seen in previous chapters that, if we ignore the effect of the LCC, we can completely repair the effect of an RyR mutation using a closed state blocker if the mutation is of the CO type. In this chapter, we want to see if this result also holds when the effect of the LCCs is taken into account. Since the transmembrane potential V enters the model as a parameter, it is sufficient to control the effect of the LCCs for a number of different values of V. The next issue we want to address is how to repair the effect of LCC mutations. We will find optimal open and closed state blockers.

9.1 Markov Models for CICR, Including Drugs

We consider a situation where the RyR or the LCC may be affected by CO-mutations. Both effects are modeled by Markov models and in this section we introduce theoretical drugs in terms of open and closed state blockers for both the RyR and the LCC.

A. Tveito, G.T. Lines, *Computing Characterizations of Drugs for Ion Channels and Receptors Using Markov Models*, Lecture Notes in Computational Science and Engineering 111, DOI 10.1007/978-3-319-30030-6_9

Table 9.1 Values of parameters used in simulations in this chapter

v_d	1 ms^{-1}
v_r	0.1 ms^{-1}
v_s	0.01 ms^{-1}
c_0	0.1 μM
c_1	1,000 μM

9.1.1 Theoretical Blockers for the RyR

As discussed above, the gating of the release of calcium from the sarcoplasmic reticulum to the dyad is given by the stochastic variable $\bar{\gamma}_r = \bar{\gamma}_r(t)$ governed by the reaction scheme

$$C_r \underset{\mu k_{co}^r}{\overset{k_{oc}^r}{\leftrightarrows}} O_r. \tag{9.1}$$

Here μ is the mutation severity index, which is one in the wild type case. We have seen that open and closed state blockers can be added to the reaction as

$$B_c^r \underset{k_{bc}^r}{\overset{k_{cb}^r}{\leftrightarrows}} C_r \underset{\mu k_{co}^r}{\overset{k_{oc}^r}{\leftrightarrows}} O_r \underset{k_{ob}^r}{\overset{k_{bo}^r}{\leftrightarrows}} B_o^r, \tag{9.2}$$

where B_c^r and B_o^r denote the blocked states associated with the closed and open states, respectively. The characteristics of the drugs are given by the constants k_{cb}^r and k_{bc}^r (for the closed state blocker) and k_{ob}^r and k_{bo}^r (for the open state blocker).

9.1.2 Theoretical Blockers for the LCC

The Markov model governing the stochastic variable $\bar{\gamma}_l = \bar{\gamma}_l(t)$ of the LCC is given by

$$C_l \underset{\eta k_{co}^l}{\overset{k_{oc}^l}{\leftrightarrows}} O_l, \tag{9.3}$$

where we have introduced the parameter η to indicate a mutation of the LCC. The wild type case is again represented by $\eta = 1$ and any $\eta > 1$ denotes a leaky LCC. We introduce a theoretical representation of a drug as for the RyR channels:

$$B_c^l \underset{k_{bc}^l}{\overset{k_{cb}^l}{\leftrightarrows}} C_l \underset{\eta k_{co}^l}{\overset{k_{oc}^l}{\leftrightarrows}} O_l, \underset{k_{ob}^l}{\overset{k_{bo}^l}{\leftrightarrows}} B_o^l, \tag{9.4}$$

where, in line with the RyR case, B_c^l and B_o^l denote the blocked states associated with the closed and open states, respectively, and the characteristics of the LCC drugs are given by the constants k_{cb}^l and k_{bc}^l (for the closed state blocker) and k_{ob}^l and k_{bo}^l (for the open state blocker).

9.1.3 Combined Theoretical Blockers for the LCC and the RyR

To use the probability density formalism, it is convenient to rewrite the two Markov models as one combined model of the form illustrated in Fig. 9.1.This model consists of 16 separate states given by

$$\begin{array}{cccc} B_c^l B_c^r & B_c^l C_r & B_c^l O_r & B_c^l B_o^r \\ C_l B_c^r & C_l C_r & C_l O_r & C_l B_o^r \\ O_l B_c^r & O_l C_r & O_l O_r & O_l B_o^r \\ B_o^l B_c^r & B_o^l C_r & B_o^l O_r & B_o^l B_o^r \end{array} \tag{9.5}$$

and the combined LCC and RyR drug is fully specified by

$$k_{cb}^r, k_{bc}^r, k_{bo}^r, k_{ob}^r, k_{cb}^l, k_{bc}^l, k_{bo}^l, \text{ and } k_{ob}^l. \tag{9.6}$$

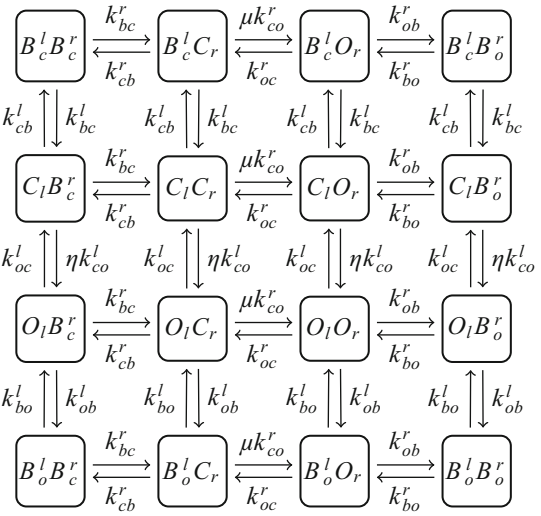

Fig. 9.1 The Markov model represented in Fig. 8.3 extended to account for blockers for the LCC and the RyR

9.2 Probability Density Functions Associated with the 16-State Model

As mentioned in Chap. 7 (see page 119), it is convenient to use a more compact notation to represent the system of partial differential equations governing the probability density functions when the Markov model consists of numerous states. By using the notation introduced in Chap. 7 , we can write the probability density system associated with the Markov model in Fig. 9.1 in the form

$$\frac{\partial \rho_{ij}}{\partial t} + \frac{\partial}{\partial x}\left(a_{ij}^{x}\rho_{ij}\right) + \frac{\partial}{\partial y}\left(a_{ij}^{y}\rho_{ij}\right) = R_{ij}, \tag{9.7}$$

where

$$\begin{aligned} R_{ij} = {} & K_{i,j+1}^{i,j}\rho_{i,j+1} + K_{i+1,j}^{i,j}\rho_{i+1,j} + K_{i,j-1}^{i,j}\rho_{i,j-1} + K_{i-1,j}^{i,j}\rho_{i-1,j} \\ & - \left(K_{i,j}^{i,j+1} + K_{i,j}^{i+1,j} + K_{i,j}^{i,j-1} + K_{i,j}^{i-1,j}\right)\rho_{i,j}. \end{aligned}$$

The flux terms are given by

$$\begin{aligned} a_{ij}^{x} &= \gamma_i^r v_r\,(y - x) + v_d\,(c_0 - x) - \gamma_j^l J_l, \\ a_{ij}^{y} &= \gamma_i^r v_r\,(x - y) + v_s\,(c_1 - y)\,, \end{aligned}$$

where $\gamma_i^r = 1$ when the RyR state is open and $\gamma_i^r = 0$ when the RyR state is closed and similarly for γ^l and the LCC.

9.3 RyR Mutations Under a Varying Transmembrane Potential

In this section, we assume that a mutation affects the RyR such that the mutation severity index is increased. This problem has been discussed several times above, but here we also need to take into account that the value of the transmembrane potential may change. In our computations, we use $\mu = 3$ and we try to repair the effect of the mutation by adding a closed state blocker to the Markov model of the RyR channel. The Markov model is shown in Fig. 9.2.

The closed state drug applied to the RyR channel is represented by the two parameters k_{cb}^r and k_{bc}^r. We have seen above that for closed state blockers of the RyR it is reasonable to define

$$k_{cb}^r = (\mu - 1)\,k_{bc}^r,$$

where the value of k_{bc}^r remains to be decided.

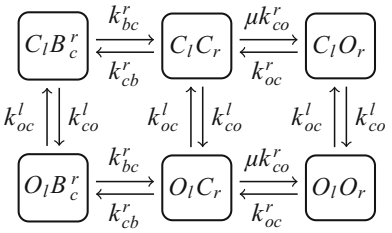

Fig. 9.2 The Markov model represented in Fig. 8.3 extended to include an RyR mutation and a closed state blocker for the RyR

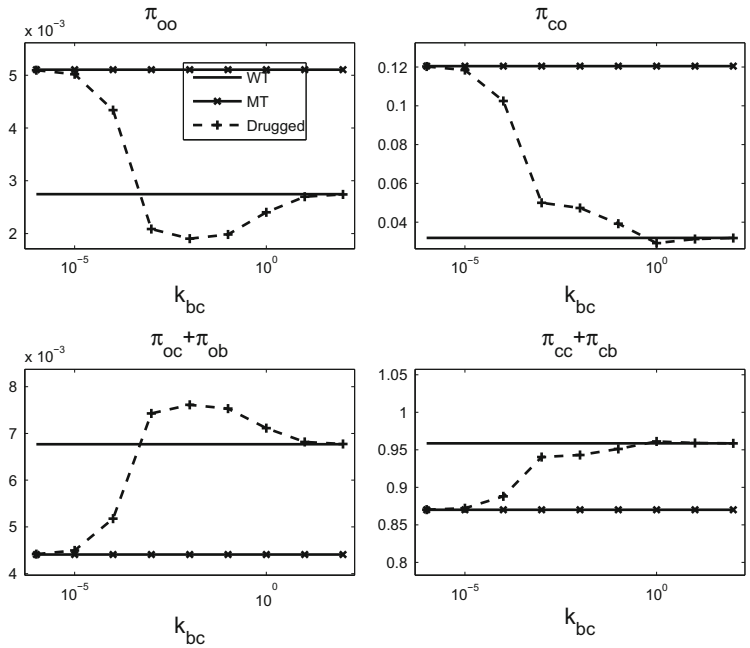

Fig. 9.3 Total probabilities based on the model for the probability density functions associated with the Markov model in Fig. 9.2. A closed state blocker is applied, the mutation severity index is $\mu = 3$, and the transmembrane potential is $V = 0$ mV. The *plots* show the total probability of being in the state OO, (OC+OB), CO, or (CC+CB) as a function of k_{bc}^r. In the *upper left plot*, the total probability of being in the OO state is higher for the mutant than for the wild type. This is repaired by the closed state drug. Similar results are shown for the other states

9.3.1 *Theoretical Closed State Blocker Repairs the Open Probabilities of the RyR CO-Mutation*

Numerical results using the closed state drug shown in Fig. 9.2 are given in Fig. 9.3. Note that we aim to repair the probability of being in the open state and are not

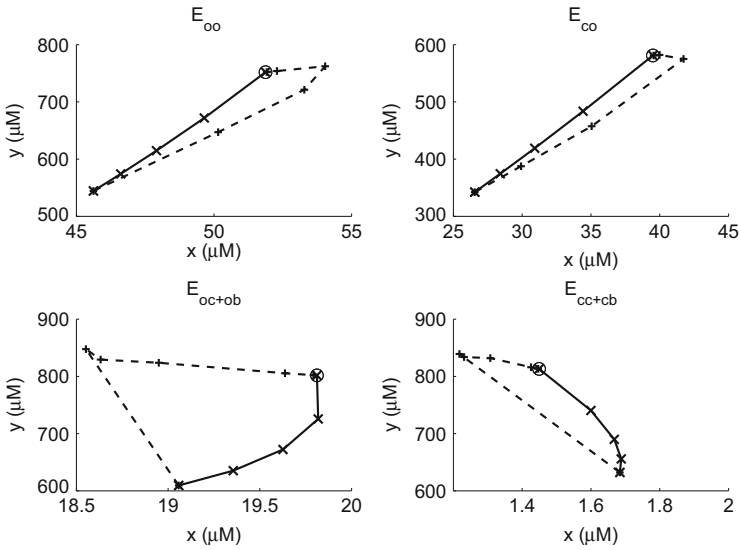

Fig. 9.4 Based on the probability density functions of the states OO, (OC+OB), CO, and (CC+CB), we can compute the expected concentrations of the dyad (x) and the JSR (y). The wild type is denoted by $\circ$ and the RyR mutation index μ increases from one to three along the *solid line*. In the *dashed line*, we keep $\mu = 3$ and increase the value of k_{bc}^r from 0 to 100 ms^{-1}. We observe that as k_{bc}^r increases, the expected concentrations are completely repaired. The experiment is carried out for the case of $V = 0$ mV

interested in whether the channel is in a blocked state or in a closed state. The probability of being in a closed or blocked state is therefore added in the graphs. We observe from the graphs that the mutant channel is completely repaired by the closed state blocker.

In Fig. 9.4, we show the development of the expected concentrations of the dyad (x) and the junctional sarcoplasmic reticulum (JSR) (y) and observe that the expected concentrations are repaired by a sufficiently strong version of the blocker associated with the closed state of the RyR channel.

9.3.2 The Open State Blocker Does Not Work as Well as the Closed State Blocker for CO-Mutations in RyR

In Table 9.2, we report on the performance of the open and closed state blockers for the RyR mutation. Recall that the probability π_{oo}, the expected dyad concentration (E_{oo}^x), and the expected JSR concentration (E_{oo}^y) are defined on page 72. The closed blocker clearly is best suited to repair this mutation.

Table 9.2 Properties of the probability density function (ρ_{oo}) of being in the state OO with $\mu = 3$ (and $\eta = 1$). The closed state blocker works fine in the sense that it is well suited for repairing a CO-mutation of the RyR. The open state blocker is unable to completely repair the effect of the mutation. The open state blocker is found using Matlab's *Fminsearch*, with a cost function defined to minimize the difference between the wild type and the mutation when the drug is applied. In this table, WT and MT mean wild type and mutant, respectively, and $V = 0$ mV is used in the simulations

	WT	MT	Optimal closed blocker	Optimal open blocker
$10^3 \times \pi_{oo}$	2.75	5.11	2.74	0.81
E^x_{oo}	51.87	45.62	51.92	52.46
E^y_{oo}	751.76	544.30	751.99	713.89

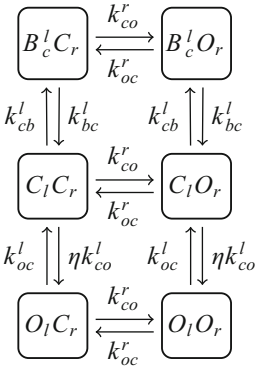

Fig. 9.5 The Markov model represented in Fig. 8.3 extended to include an LCC mutation and a closed state blocker for the LCC

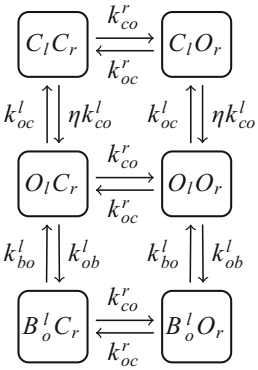

Fig. 9.6 The Markov model represented in Fig. 8.3 extended to include an LCC mutation and an open state blocker for the LCC

9.4 LCC Mutations Under a Varying Transmembrane Potential

Next, we address the problem of defining a theoretical drug for LCC mutations. We consider closed state LCC blockers of the form given in Fig. 9.5 and open state blockers of the form given in Fig. 9.6.

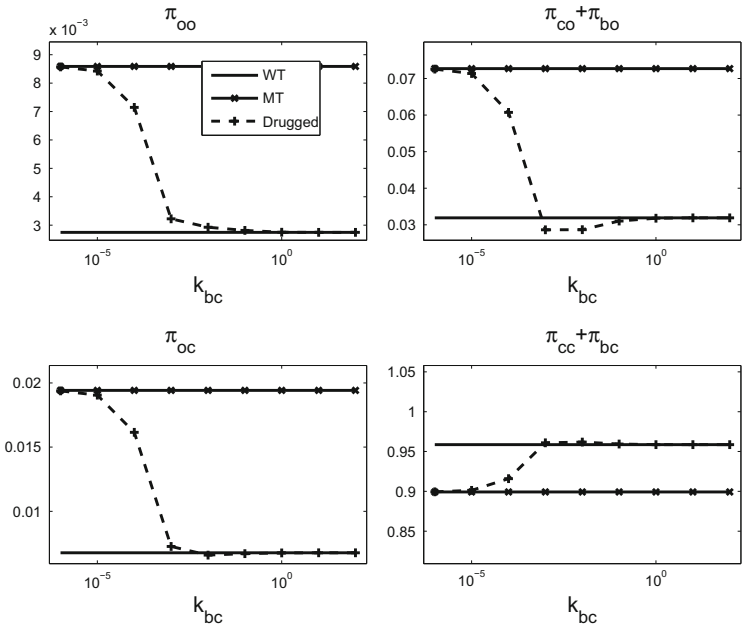

Fig. 9.7 Total probabilities based on the model for the probability density functions associated with the Markov model in Fig. 9.5, where an LCC-type closed state blocker is included. The LCC mutation severity index is $\eta = 3$ and the transmembrane potential is $V = 0$ mV. The *plots* show the total probability of being in the state OO, OC, (CO+BO), or (CC+BC) as a function of k^l_{bc}. In the *upper left plot*, the total probability of being in the OO state is higher for the mutant than for the wild type. This is repaired by the closed state drug. Similar results are shown for the other states

For the closed state blockers, we need to determine the two parameters k^l_{bc} and k^l_{cb} and for the open state blockers we must determine k^l_{bo} and k^l_{ob}. For the closed state blockers we define

$$k^l_{cb} = (\eta - 1)\, k^l_{bc}$$

and we consider various values of k^l_{bc}.

9.4.1 *The Closed State Blocker Repairs the Open Probabilities of the LCC Mutant*

The results of applying the theoretical closed state blocker associated with the closed state (see Fig. 9.5) of the LCC are given in Figs. 9.7, 9.8, and 9.9. In the first figure, we show how the closed state blocker repairs the total probabilities and in the

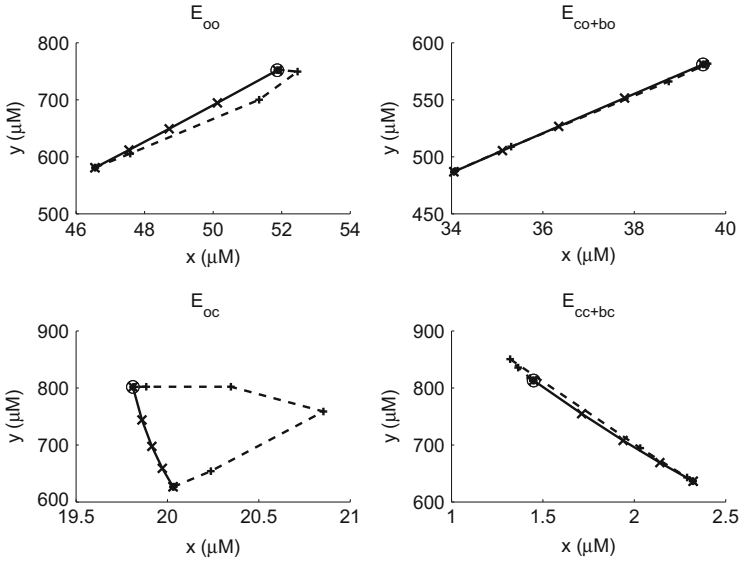

Fig. 9.8 Using the probability density functions of the states OO, OC, (CO+BO), and (CC+BC), we compute the expected concentrations of the dyad (x) and the JSR (y). The wild type is denoted by $\circ$ and the LCC mutation index η increases from one to three along the *solid line*. In the *dashed line*, we keep $\eta = 3$ and increase the value of k_{bc}^{l} from 0 to 100 ms^{-1}. We observe that as k_{bc}^{l} increases, the expected concentrations are completely repaired. The simulations are performed using $V = 0$ mV

second figure we consider the expected concentrations. In Fig. 9.9, we show how the expected concentrations are repaired for six values of the transmembrane potential.

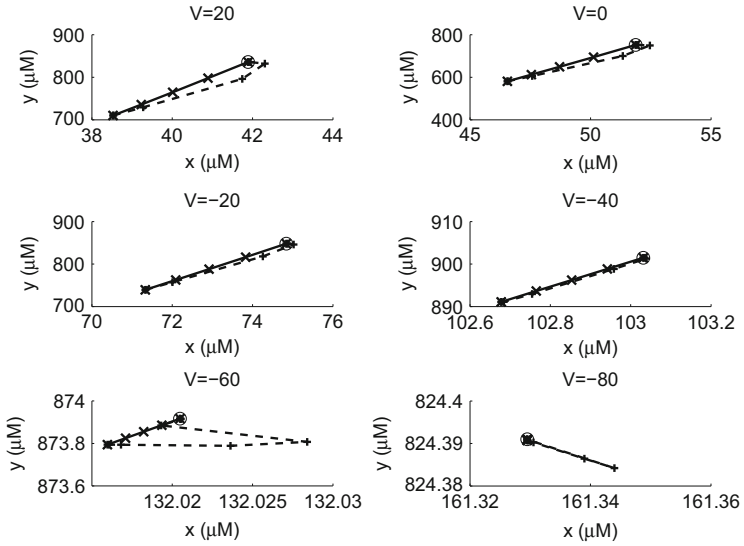

Fig. 9.9 The expected concentration of the dyad (x) and the JSR (y) for the OO state for the transmembrane potential changing from −80 to 20 mV. The wild type is denoted by ∘ and the LCC mutation index η increases from one to three along the *solid line*. In the *dashed line*, we keep $\eta = 3$ and increase the value of k_{bc}^{l} from 0 to 100 ms^{-1}. In all cases, the closed state blocker repairs the effect of the mutation