Bifurcations, chaos, and sensitivity to parameter variations in the Sato cardiac cell model

Stefan Ottea,b, Sebastian Berga,b, Stefan Luthera,b,c, Ulrich Parlitza,b,c,∗

a Max Planck Institute for Dynamics and Self-Organization, Am Faßberg 17, 37077 Göttingen, Germany
b Institute for Nonlinear Dynamics, Georg-August-Universität Göttingen, Am Faßberg 17, 37077 Göttingen, Germany
c German Centre for Cardiovascular Research, Partner Site Göttingen, 37077 Göttingen, Germany

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The dynamics of a detailed ionic cardiac cell model proposed by Sato et al. (2009) is investigated in terms of periodic and chaotic action potentials, bifurcation scenarios, and coexistence of attractors. Starting from the model’s standard parameter values bifurcation diagrams are computed to evaluate the model’s robustness with respect to (small) parameter changes. While for some parameters the dynamics turns out to be practically independent from their values, even minor changes of other parameters have a very strong impact and cause qualitative changes due to bifurcations or transitions to coexisting attractors. Implications of this lack of robustness are discussed.

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1. Introduction

Mathematical modelling has become an important tool in the life sciences to address problems that are not approachable experimentally. For example, to investigate cardiac arrhythmias or sudden cardiac death, models have been developed to describe cardiac dynamics from gene to organ level [2,3]. Therefore, many models exist to describe the action potentials (AP) of single ventricular cells. For better comparison with experimental results, these models are often developed to represent dynamics of specific mammals: For example, the well-known Luo–Rudy model [4] can be used to model guinea pig ventricular cells, while the model used by Wang and Sobie [5] describes mouse ventricular action potentials, and the one used by Sato et al. [1] (first AP model, in the following referred to as the Sato model) models ventricular rabbit myocytes.

However, many of these models share the feature of consisting of a great number of equations and parameters. For example, the Sato model uses 27 variables whose calculation requires 118 equations and 177 parameters. Therefore, the exact implementation of these models as given in the original publications is quite error-prone, and since changes in parameters can dramatically alter the dynamics of the model, reproducing results from former studies can be a challenging task.

Studies analysing the parameter sensitivity of electrophysiological models are still rare [6,7]. Therefore, in this paper we use the Sato model to investigate the sensitivity of the dynamics to parameter variations. This cardiac cell model was used to provide an explanation for ventricular tachycardia and ventricular fibrillation originating from early afterdepolarisations at the cellular level by a chaos synchronization mechanism [1,8]. As will be shown in the following sections this model...
exhibits chaotic action potentials as well as coexistence of different types of periodic and chaotic attractors. To investigate the robustness of the dynamics given by the standard parameter set of this model [1], bifurcation diagrams are computed showing dynamical changes when going below or above the standard parameter values and it turns out that for some parameters already minor deviations from the standard value lead to qualitatively different dynamics.

2. Methods

The Sato model, which is given in detail in Appendix A, describes the action potentials in the membrane voltage \( V(t) \) of ventricular rabbit myocytes. It uses 27 variables that can be described by 118 equations involving 177 parameters. Besides ion concentrations, channel conductances or physical constants, many of these parameters are coefficients, obtained from fitting mathematical models to experimental data. Since the sensitivity of the model dynamics to changes of these fitted parameters is to be examined as well, all fit coefficients were labelled (see Tables A.3–A.6) and included in the total list of model parameters.

The cardiac cell model is given as a set of ordinary differential equations (ODE’s)

\[
\begin{align*}
\frac{dV(t)}{dt} &= -\frac{l_{\text{ion}}(h, t) + I_{\text{stim}}(t)}{C_m} \\
\frac{dh(t)}{dt} &= F(h, V, t)
\end{align*}
\]

where \( C_m \) is the membrane capacity and \( I_{\text{stim}} \) the external stimulation current with pulses of 1 ms duration and amplitudes of \(-40 \mu\text{A/cm}^2\). \( l_{\text{ion}} \) is the sum of all considered transmembrane or intracellular ionic currents. The state vector \( h \) includes all additionally needed, time dependent variables like gating variables or ionic concentrations. The ODE system (1) was solved in C++, using the Nordsieck BDF method with adaptive time steps implemented in the GNU Scientific Library [9]. The maximum absolute and relative error tolerances were set to \(10^{-8}\) with a maximum allowed time step of 0.5 s. Since this ODE solver requires the Jacobian matrix of the ODE system (1), the symbolic Jacobian was calculated using the GiNaC framework [10].

For the Sato model, no initial conditions were given in the original publications [1,11]. We obtained steady state initial conditions by setting all 27 variables to 0.1 prior to pacing the system with a constant PCL of 0.8 s until a steady state was reached, which took about 300 s of simulated cell activity. The initial conditions obtained by this procedure are given in Table A.2.

The model was originally designed to reproduce cardiac dynamics at fast pacing [11] and includes modifications to be capable of generating early afterdepolarisations (EADs) [1], which are known to be potential triggers of lethal cardiac arrhythmias [12,13]. A detailed description of EADs and the underlying ionic mechanisms can, for example, be found in Ref. [14]. Briefly, an EAD is an abnormal depolarisation during the plateau phase of an AP, which essentially prolongs the action potential duration (APD). The APD for each AP is defined here as the time duration where the shape and duration of the action potential are PCL-dependent, we defined the phase space point \( v_n^0 \) of the \( n \)th action potential of variable \( v \) as

\[
v_n^0 := v(t_0 + (n + 0.3)\Delta t)
\]

where \( t_0 \) is the time of the depolarisation of the first AP considered. Thus, the phase increases linearly with PCL. Furthermore, for calculating Lyapunov exponents, a discrete QR decomposition based method as described in [15] was implemented.

3. Results

3.1. Periodic and chaotic action potentials

Fig. 1 shows the temporal evolution of the membrane voltage \( V(t) \) for three different PCLs: For \( \text{PCL} = 1.100 \) s and \( \text{PCL} = 1.370 \) s, the APD is in each case constant for every AP. While for \( \text{PCL} = 1.100 \) s no EADs occur at all, however, for \( \text{PCL} = 1.370 \) s EADs occur at each beat. For intermediate PCLs, in this case \( \text{PCL} = 1.282 \) s, EADs occur irregularly on some beats.

Fig. 2 shows a three dimensional projection of the chaotic attractor underlying the time series shown in the middle panel of Fig. 1. Colours indicate the average concentration \( c_j \) of free \( \text{Ca}^{2+} \) in the sarcoplasmic reticulum (SR).

To investigate the occurrence of EADs for a larger PCL range, we calculated the APD for 200 APs for \( 1.1 \text{s} < \text{PCL} < 1.4 \text{s} \) with a step size of \( \Delta \text{PCL} = 0.5 \) ms. Prior to the APD calculation, we paced the system for 500 s of cell activity and for the \( n \)th PCL, we used the final state vector of the previous \( \text{PCL}_{n-1} = PCL_n - \Delta \text{PCL} \) as initial condition. The resulting bifurcation diagram in Fig. 3A shows that for a certain PCL range, the APD takes many different values, which shows the irregular behaviour in the appearance of EADs. Note that an APD value larger than about 0.5 s represents an EAD. For smaller and larger PCL values the APD does not vary, which indicates periodic behaviour. Furthermore, the irregular behaviour in the intermediate PCL range is interrupted by periodic windows. Fig. 3B shows a bifurcation diagram where instead of APDs
Membrane voltage $V$ for different PCLs: for small and large PCL, the shape and duration of the APs do not change, while for small PCLs no EADs occur at all and for large PCLs, EADs occur at every beat. For intermediate PCLs, EADs occur irregularly with some APs.

Chaotic attractor occurring for PCL $= 1.282$ s (see action potentials in the middle panel in Fig. 1). Plotted is a three dimensional projection into a subspace of the state space spanned by the membrane voltage $V$, the intracellular Na$^+$ concentration $[Na^+]$, and the average concentration $c_i$ of free Ca$^{2+}$ in the cytosol. The colour encodes the average concentration $c_j$ of free Ca$^{2+}$ in the sarcoplasmic reticulum (SR).

Values of the membrane voltage $V_p$ in the Poincaré section are plotted which are calculated according to Eq. (2). Note that a $V_p$ value larger than about $-30$ mV represents an EAD. While the shape of the two bifurcation diagrams shown in Fig. 3A and B differ due to the different quantities used, the same irregular behaviour in the intermediate PCL range is visible. Furthermore, in the bifurcation diagram using the membrane voltages $V_p$ in the Poincaré section the periodic windows are more clearly visible: a period-2, 3, 4 and 5 window can easily be identified, which is not the case in the APD bifurcation diagram. Since the latter contains no further information that the $V_p$ bifurcation diagram lacks, we will use the values $V_p$ in the Poincaré section for further analysis. We found that for $0.3 \text{s} < \text{PCL} < 4.0 \text{s}$, there is no other PCL range exhibiting irregular $V_p$ behaviour except for the one described above.

To test whether the irregular appearance of EADs is due to dynamical chaos, the three largest Lyapunov exponents $\lambda$ were calculated and are shown for $1.1 \text{s} < \text{PCLs} < 1.4 \text{s}$ in Fig. 3C: The PCL values where APD and $V_p$ show irregular behaviour correspond to a positive largest Lyapunov exponent $\lambda_{\text{max}}$, which shows that the irregularity is dynamical chaos.

All of the results above are similar to the results by Sato et al. [1] but the chaotic PCL ranges differ quantitatively. To the best of knowledge, the model was implemented exactly as described in [1,11]. Due to the number of equations and
parameters, the possibility of errors while transferring the equations from paper to computer or vice versa cannot fully be excluded. In the following, we therefore analyse the sensitivity of the model dynamics to parameter changes.

3.2. Bifurcations

A simple, but insightful approach to qualitatively analyse the parameter sensitivity of the model is to vary every model parameter independently and to examine and compare the resulting bifurcation diagrams. For our purposes, a variation for each parameter $P$ by up to 100 % around its standard value $\bar{P}$ as given in Tables A.3–A.6 is considered to be sufficient. More precisely, for every $P$, we calculated the membrane voltages $V^p$ for 200 APs for $(\bar{P}/100) < P < 2 \cdot \bar{P}$ with a step size of $\Delta P = (\bar{P}/100)$. Prior to the $V^p$ calculation, we paced the system for at least 300 APs and for the $n$th parameter value $P_n$, we used the final state vector of the previous $P_{n-1} = P_n - \Delta P$ as initial condition. For $P_0$ we used the initial conditions as given in Table A.2. This “upward” calculation for every $P$ (i.e. from small to large parameter values) was followed by an analogous “downward” calculation (i.e. from large to small parameter values) where again we used the final state vector of the $n$th parameter value calculation $P_n$ as initial condition for the following parameter value $P_{n+1}$. This calculation was carried out for PCL = 1.282 s such that the model should yield chaotic dynamics if $P = \bar{P}$ according to Figs. 2 and 3C.

In Fig. 4, a selection of the bifurcation diagrams is shown. The standard value $\bar{P}$ for each parameter is represented by a vertical line, and the differently coloured points representing the membrane voltage $V^p$ in the Poincaré section reflect the previously explained “upward” (light blue) and “downward” (dark red) calculation. Note that the “downward” calculation is plotted on top of the “upward” calculation, such that the dark red points can essentially hide the light blue points, meaning that the dynamics in the affected parts of the bifurcation diagram are equal for both calculations. The bifurcation diagrams show that a wide range of different behaviour can be observed under individual variation of different parameters:

- Fig. 4A shows that the chaotic dynamics, which is expected for PCL = 1.282 s according to Figs. 2 and 3, is stable under parameter variation of parameter eq48P1, independent of whether the variation occurs from small to large values or vice versa.
- Fig. 4B: For small values of the parameter eq92P1, the points indicate a period-6 orbit (with three nearby points at $V^p \approx -3$ mV) which for increasing values of eq92P1 undergoes period doubling bifurcations and subsequently shows chaotic dynamics for the standard value of eq92P1 = 20. The chaotic dynamics becomes unstable and changes over to a
Fig. 4. \(V_p\) over \(P\) for selected parameters \(P\) with PCL = 1.282 s and 200 APs per parameter value: the “upward” (from small to large \(P\); light) and “downward” (from large to small \(P\); dark) calculations as described in Section 3.2 are shown, as well as the standard parameter value (vertical line). For different \(P\), the diagrams reveal qualitatively very different behaviour under parameter variation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
period-5 orbit (with two nearby points at $V^P \approx -3$ mV) for a critical value of $eq92P1 \approx 33$. If now decreased again, the period-5 orbit does not become unstable at $eq92P1 \approx 33$ but remains stable up to $eq92P1 \approx 12.4$: In this parameter range, at least two attractors coexist with periodic and chaotic behaviour, respectively. Note that this range also includes the standard value of $eq92P1 = 20$. At $eq92P1 \approx 12.4$, the period-5 orbit becomes unstable and the dynamics of “upward” and “downward” calculation equal.

- **Fig. 4C:** The variation of $eq73P2$ shows that the “upward” variation of this parameter yields chaotic dynamics for almost all parameter values (with two exceptions for $eq73P2 \approx 3$ and $eq73P2 \approx 13$), while the “downward” variation yields periodic dynamics with period 5 (with two nearby points at $V^P \approx -3$ mV) except for very large values of $eq73P2$: Therefore, once the trajectory is bound to one of these attractors, both are relatively stable to parameter variations of $eq73P2$.

- **Fig. 4D:** Except for very small values of the dissociation constant $K_{mem}$, the dynamics is bound for both “upward” and “downward” calculation to the already mentioned periodic attractor with period 5: Once bound to this attractor, the dynamics is very stable to variations in $K_{mem}$ and chaotic motion is never observed in this case. For decreasing values of $K_{mem}$, the period-5 orbit becomes unstable and changes over to a period-3 orbit, while the “upward” calculation exhibited different behaviour in this regime.

- **Fig. 4E** shows that for increasing values of $eq89P1$ the dynamics follows periodic orbits of different periods and subsequently shows chaos for a fairly narrow parameter range around the standard value of $eq89P1 = 3$. This chaotic behaviour becomes unstable if $eq89P1$ is further increased and eventually leads to a period-2 orbit. Note that the chaotic behaviour does not occur for parameter values smaller than the standard value, meaning that the motion is highly sensitive to slightly decreased values of $eq89P1$. In this bifurcation diagram both “upward” and “downward” calculation yield the same dynamics for all parameter values larger than the standard value. However, for smaller parameter values it is clearly visible how the dynamics depends on the “direction” of parameter variation: For decreasing parameter values, the motion is bound to the respective periodic attractor longer than for the “upward” calculation before it becomes unstable and goes over to a different periodic attractor.

- **Fig. 4F:** The bifurcation diagram for $K_{mem,Na}$ shows that if this parameter is only slightly varied to either side around its standard value of $K_{mem,Na} = 87.5$, the dynamics becomes periodic. Several more chaotic regions exist for larger and smaller parameter values, respectively. Also, in the “downward” calculation, the motion is periodic even for the standard value. Therefore, the dynamics is highly sensitive to changes in $K_{mem,Na}$.

- **Fig. 4G:** For small values of the threshold for leak onset $k_j$, the motion exhibits chaotic behaviour which is interrupted by periodic windows for increasing values of $k_j$. Period doubling bifurcations are clearly visible within these periodic windows. Subsequently, chaotic motion also appears around the standard value of $k_j = 50$, but quickly becomes periodic on either side of this value. For even larger values of $k_j$, the motion goes over to the already mentioned period-5 attractor which is stable over a fairly broad parameter range. If decreased again, the dynamical behaviour is nearly identical with the exception that the period-5 attractor remains stable for values of $k_j$ even smaller than the standard value.

- **Fig. 4H** shows that the variation of $eq57P3$ yields a bifurcation diagram very similar to one of $k_j$: Although these parameters appear in equations describing different aspects of the cell dynamics, both have qualitatively very similar influence on the dynamics of the system. Also note that while $k_j$ can be interpreted biologically, $eq57P3$ was obtained by fitting a model equation to experimental data.

These examples illustrate that the model parameters can strongly influence the dynamics of the system and even small deviations from the given standard parameter values can lead to very different dynamical behaviour. In addition, for the standard parameter values a periodic attractor with period-5 coexists to the chaotic attractor which occurred for PCL = 1.282 s in Fig. 3. The possibility of more coexisting attractors cannot be excluded.

As can be seen from the bifurcation diagrams, some parameters influence the dynamics of the system while others do not. Also, the sensitivity of the dynamics to changes in the parameters varies from parameter to parameter. We therefore heuristically defined five parameter classes in order to group parameters with similar influence on the dynamics: The first class contains parameters which do not alter the dynamics of the system if varied by up to 100%, as $eq48P1$ in Fig. 4A. The second and third class contain parameters which qualitatively influence the dynamics if varied by more (as $eq92P1$ in Fig. 4B) or less (as $eq89P1$ in Fig. 4E) than 10 %, respectively. All parameters of Table A.7 are excluded from this grouping as they consist of physical constants or other physical parameters like the cell volume or the temperature. These parameters form the fourth class. The fifth class contains all those parameters where numerical difficulties (e.g., divergence of solutions) occurred for parameter values $P_i$ far from $P$ and the “upward” or “downward” calculation of the bifurcation diagrams failed at some point.1 The parameter classes, together with a short description and the number of parameters per class are shown in Table 1. Here, three PCLs (PCL = 1.1 s, PCL = 1.282 s, and PCL = 1.37 s) are considered and the corresponding parameter bifurcation diagrams (similar to Fig. 4) are used to classify the model parameters. Furthermore, we grouped the parameters into different categories: $Ca^{2+}$, $Na^+$, $K^+$, and the rest. This categorisation was motivated by the hypothesis that the impact of each parameter may depend on the ion dynamics it is involved in.

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1 As an alternative for those parameter values that lead to numerical difficulties if they become too small or too large one can compute bifurcation diagrams where the respective parameter is not varied from small to large values, but is being increased or decreased from the standard value.
Table 1
Parameter classes and number of parameters per class. For each PCL, the number of parameters in class 0 is the number of parameters needed to give a grand total of 177 parameters (including the constants).

| Class   | Definition                                                                 |
|---------|-----------------------------------------------------------------------------|
| 0: not grouped | Parameters that caused numerical difficulties and were not grouped with this procedure |
| 1: non sensitive | Parameters whose variation up to 100 % does not effect the qualitative dynamics (periodic, chaotic,...) of the system |
| 2: mildly sensitive | Parameters whose variation of more than 10 % and less than 100 % does effect the dynamics of the system qualitatively |
| 3: highly sensitive | Parameters whose variation of less or equal than 10 % does effect the dynamics of the system qualitatively |
| 4: constants | Physical constants and ionic concentrations (11 parameters) |

| PCL     | 1.1 s | 1.282 s | 1.37 s |
|---------|-------|---------|--------|
| Parameter group/class | 1 2 3 | 1 2 3 | 1 2 3 |
| Ca²⁺-related | 23 18 6 | 0 7 44 | 3 9 37 |
| Na⁺-related | 15 11 0 | 5 7 14 | 9 11 6 |
| K⁺-related | 28 22 5 | 5 12 38 | 11 14 30 |
| Others | 5 7 3 | 0 0 15 | 0 1 14 |
| Total | 71 58 14 | 10 26 111 | 23 35 87 |

Fig. 5. Class membership of all parameters for different PCLs (the parameters corresponding to each number are given in Tables A.3–A.6). Parameters are grouped according to the ion dynamics they are involved in.

For PCL = 1.1 s 72 parameters belong to classes 2 or 3 and therefore qualitatively alter the dynamics if varied by less than 100 %. From these, 14 are “highly sensitive” parameters, i.e. a variation of less than 10 % of their values changes the dynamics qualitatively. For PCLs 1.282 s, resulting in chaotic dynamics, and 1.37 s the number of sensitive parameters is even larger (137 and 122, respectively). To address the question whether particular parameters exhibit for all three PCLs (high) sensitivity and a major impact on the dynamics of the model Fig. 5 shows the class membership of all parameters and all three PCLs (differently coloured symbols). There are only 23 parameters in classes 1, 2, or 3 which belong for all three PCLs to the same group (see parameters marked with an asterisk in Tables A.3–A.6). In most cases, the class membership changes with the PCL and physiological factors determining the class membership (for arbitrary PCLs) are very difficult to identify. Even when grouping the parameters according to their role in modelling the dynamics of different ions (see Fig. 5) no direct relation between ion type and sensitivity class is visible. Therefore, we conclude that the observed bifurcation scenarios and the impact of parameter variations are not governed by biophysical or physiological effects but mainly due to the very large number of parameters (and model terms). From Statistical Learning Theory [16] it is known that overly detailed models (“overfitting”) may suffer from adverse features like low generalisation ability and poor prediction properties. This is a general phenomenon that does not rely on the particular (physical) context of the model and appears to be relevant for cardiac cell modelling, too.

4. Conclusion

Many ionic cardiac cell models aim at detailed “realistic” modelling taking into account any known biophysical detail. As a consequence these models consist of a large number of variables and an even larger number of parameters. A large number of variables implies a large dimension of the state space. This is a priori not a problem but perhaps not necessary, because even the chaotic attractors of such cell models are usually quite low dimensional and therefore, a four or five dimensional state space, for example, would be sufficient to “host” the relevant attractors. Much more problematic is the very large number of parameters. The values of some parameters can be precisely measured but others are difficult to determine or are just imported from previous research (under partly different conditions or with different species). In any case, there may be limited information about the true and proper values of parameters and this raises the question of what happens if these
parameters vary within a small interval (enclosing the conjectured but unknown “true” value)? The bifurcation diagrams obtained for the parameters of the Sato model clearly demonstrate that this is a severe issue. While some parameters have practically no influence on the dynamics others have to be known very precisely to achieve the expected or desired dynamics. This (extreme) sensitivity reduces the robustness of the model and its ability to generalise. These findings are in good agreement with results from statistical learning theory and machine learning where overfitting leads to strong degradation of regression and classification results [16]. Our attempt to interpret the class membership of each parameter in a physiologically meaningful sense failed, because most parameters occur in different classes depending on the PCL applied. There is also no evidence that parameters determining a specific ion dynamics are more (or less) sensitive than others. We conjecture that this feature of low robustness is a general “overfitting effect” and not due to some physiological or biophysical processes. In this sense we expect that it is shared by many (if not all) high dimensional ionic cell models and has to be taken into account when using these models for simulating or even predicting dynamical events like the onset of arrhythmias.

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Appendix A. The Sato model

The following section contains the equations, parameters and initial conditions of the cardiac myocyte model investigated in this article. It is based on a model developed and described by Mahajan et al. [11], which is also available online as a cellML implementation [17]. As these versions differ slightly, the equations from [17] were adopted. Furthermore, the model is modified as described by Sato et al. [1] (first AP model), and further ambiguities where eliminated after correspondence with the authors. Thus, some of the following model equations contain terms that are not given or differ from the ones in the original publications. In the following, these terms are boxed. Furthermore, for parameter eq6P2 a value of 0.5 was used instead of 0.05 [1], to avoid very large derivatives $dP_r/dV$ when computing and applying the Jacobian matrix of the model.

### A.1. Variables and initial conditions of the model

| Variable | Definition | Initial value |
|----------|------------|---------------|
| $c_i$ | Average concentration of free Ca$^{2+}$ in the submembrane space | 0.137483 μM |
| $c_l$ | Average concentration of free Ca$^{2+}$ in the cytosol | 0.130489 μM |
| $c_s$ | Average concentration of free Ca$^{2+}$ in the SR | 127.498 μM/1 cytosol |
| $c_j$ | Average free Ca$^{2+}$ concentration available for release in the JSR | 125.711 μM/1 cytosol |
| $I_{rel}$ | Total release flux out of the SR via RyR channels | 0.0046091 μM/ms |
| $C_{L}$ | L-type Ca$^{2+}$ channel state | 0.991324 |
| $C_{j}$ | L-type Ca$^{2+}$ channel state | 1.63521 $10^{-6}$ |
| $I_{CaL}$ | L-type Ca$^{2+}$ channel state | 3.32817 $10^{-7}$ |
| $I_{CaA}$ | L-type Ca$^{2+}$ channel state | 1.43069 $10^{-5}$ |
| $I_{Na}$ | L-type Ca$^{2+}$ channel state | 5.28378 $10^{-7}$ |
| $I_{to}$ | L-type Ca$^{2+}$ channel state | 0.00865914 |
| $[\text{CaT}]_i$ | Concentration of Troponin C binding sites | 12.7657 μM/1 cytosol |
| $[\text{CaT}]_s$ | Concentration of Troponin C binding sites | 13.2176 μM/1 cytosol |
| $c_p$ | Average Ca$^{2+}$ concentration in active dyadic clefts | 0.597462 μM |
| $V$ | Membrane potential | −87.4094 mV |
| $h$ | Gating variable for $I_{to}$ | 0.991187 |
| $j$ | Gating variable for $I_{to}$ | 0.994210 |
| $m$ | Gating variable for $I_{to}$ | 0.00103212 |
| $s_0$ | Gating variable for $I_{to}$ | 0.00677880 |
| $s_1$ | Gating variable for $I_{to}$ | 0.019339 |
| $s_2$ | Gating variable for $I_{to}$ | 0.0664083 |
| $X_{to}$, $f$ | Gating variable for $I_{to}$ | 0.00358546 |
| $Y_{to}$, $f$ | Gating variable for $I_{to}$ | 0.00358546 |
| $X_{to}$, $s$ | Gating variable for $I_{to}$ | 0.297391 |
| $Y_{to}$, $s$ | Gating variable for $I_{to}$ | 0.417681 |
| $R_s$ | Variable needed for $I_{to}$ | 0.00358546 |
A.2. Model equations

Model of the L-type Ca\(^{2+}\) current

\[ p_0^\infty = (1 + \exp((-V + \text{eq1P1})/\text{eq1P2}))^{-1} \]  (A.1)

\[ \alpha = \frac{p_0^\infty}{\tau_{po}} \]  (A.2)

\[ \beta = \frac{1 - p_0^\infty}{\tau_{po}} \]  (A.3)

\[ f = (1 + (k_p^0/c_p)^3)^{-1} \]  (A.4)

\[ R_1 = \text{eq5P1} + \text{eq5P2} \cdot \exp(V/\text{eq5P3}) \]  (A.5)

\[ P_t = (\exp((V + \text{eq6P1})/\text{eq6P2}) + 1)^{-1} \]  (A.6)

\[ P_3 = (1 + \exp(-(V + \text{eq7P1})/\text{eq7P2}))^{-1} \]  (A.7)

\[ T_{Ca} = \frac{\text{eq8P1}}{1 + (c_p/c_p)^4} + \text{eq8P2} \]  (A.8)

\[ \tau_{Ca} = (R_1 - T_{Ca}) \cdot P_t + T_{Ca} \]  (A.9)

\[ \tau_{Ba} = (R_1 - T_{Ba}) \cdot P_t + T_{Ba} \]  (A.10)

\[ k_5 = \frac{1 - P_t}{\tau_{Ca}} \]  (A.11)

\[ k_6 = \frac{f \cdot P_t}{\tau_{Ca}} \]  (A.12)

\[ k'_6 = \frac{1 - P_t}{\tau_{Ba}} \]  (A.13)

\[ k'_6 = \frac{P_t}{\tau_{Ba}} \]  (A.14)

\[ s_1 = \text{eq15} \cdot f \]  (A.15)

\[ k_1 = \text{eq16} \cdot f \]  (A.16)

\[ k_2 = k_1 \cdot \frac{s_2}{s_1} \cdot \frac{r_2}{r_1} \]  (A.17)

\[ k'_2 = k'_1 \cdot \frac{s'_2}{s'_1} \cdot \frac{r_2}{r_1} \]  (A.18)

\[ k_3 = \frac{\exp(-(V + \text{eq19P1})/\text{eq19P2})}{\text{eq19P3} \cdot (1 + \exp(-(V + \text{eq19P1})/\text{eq19P2}))} \]  (A.19)

\[ k'_3 = k_3 \]  (A.20)

\[ k_4 = k_3 \cdot \frac{\alpha}{\beta} \cdot \frac{k_1}{k_2} \cdot \frac{k_5}{k_6} \]  (A.21)

\[ k'_4 = k'_3 \cdot \frac{\alpha}{\beta} \cdot \frac{k'_1}{k'_2} \cdot \frac{k'_5}{k'_6} \]  (A.22)

\[ p_0 = 1 - (C_1 + C_2 + I_{1Ca} + I_{2Ca} + I_{1Ba} + I_{2Ba}) \]  (A.23)

\[ \frac{dC_2}{dt} = \beta \cdot C_1 + k_5 \cdot I_{2Ca} + k'_5 \cdot I_{2Ba} - (k_6 + k_6 + \alpha) \cdot C_2 \]  (A.24)

\[ \frac{dC_1}{dt} = \alpha \cdot C_2 + k_2 \cdot I_{1Ca} + k'_2 \cdot I_{1Ba} + r_2 \cdot P_t - (r_1 + \beta + k_1 + k'_1) \cdot C_1 \]  (A.25)

\[ \frac{di_{1Ca}}{dt} = k_1 \cdot C_1 + k_4 \cdot I_{2Ca} + s_1 \cdot P_t - (k_2 + k_3 + s_2) \cdot I_{1Ca} \]  (A.26)

\[ \frac{di_{2Ca}}{dt} = k_3 \cdot I_{1Ca} + k_6 \cdot C_2 - (k_4 + k_5) \cdot I_{2Ca} \]  (A.27)

\[ \frac{di_{1Ba}}{dt} = k'_1 \cdot C_1 + k'_4 \cdot I_{2Ba} + s'_1 \cdot P_t - (k'_2 + k'_3 + s'_2) \cdot I_{1Ba} \]  (A.28)

\[ \frac{di_{2Ba}}{dt} = k'_3 \cdot I_{1Ba} + k'_6 \cdot C_2 - (k'_4 + k'_5) \cdot I_{2Ba} \]  (A.29)
The SERCA (uptake) pump

\[ J_{\text{up}} = \frac{v_{\text{up}} \cdot C^2_l}{C^2_l + C^2_{\text{up}}} \]  
(A.30)

Diffusive flux

\[ J_d = \frac{C_s - C_i}{\tau_d} \]  
(A.31)

The L-type Ca\(^{2+}\) current

\[ a = \frac{V \cdot F}{RT} \]  
(A.32)

\[ c_{s,mM} = \frac{C_s}{1000} \]  
(A.33)

\[ J_{\text{L}} = \frac{4P_{\text{Ca}} \cdot (c_{s,mM} \cdot \exp(2a)) - eq34 \cdot [\text{Ca}^{2+}]_o}{RT \cdot (\exp(a) - 1)} \]

if \[ |a| < 0.001 \]

\[ J_{\text{Ca}} = g_{\text{Ca}} \cdot p_0 \cdot i_{\text{Ca}} \]  
(A.35)

Nonlinear buffering

\[ \beta_s = \left( 1 + \frac{B_{\text{SR}} \cdot K_{\text{SR}}}{(C_s + K_{\text{SR}})^2} + \frac{B_{\text{Cd}} \cdot K_{\text{Cd}}}{(C_s + K_{\text{Cd}})^2} + \frac{B_{\text{mem}} \cdot K_{\text{mem}}}{(C_s + K_{\text{mem}})^2} + \frac{B_{\text{sat}} \cdot K_{\text{sat}}}{(C_s + K_{\text{sat}})^2} + \frac{B_{\text{ATP}} \cdot K_{\text{ATP}}}{(C_s + K_{\text{ATP}})^2} \right)^{-1} \]  
(A.36)

\[ \beta_i = \left( 1 + \frac{B_{\text{SR}} \cdot K_{\text{SR}}}{(C_i + K_{\text{SR}})^2} + \frac{B_{\text{Cd}} \cdot K_{\text{Cd}}}{(C_i + K_{\text{Cd}})^2} + \frac{B_{\text{mem}} \cdot K_{\text{mem}}}{(C_i + K_{\text{mem}})^2} + \frac{B_{\text{sat}} \cdot K_{\text{sat}}}{(C_i + K_{\text{sat}})^2} + \frac{B_{\text{ATP}} \cdot K_{\text{ATP}}}{(C_i + K_{\text{ATP}})^2} \right)^{-1} \]  
(A.37)

\[ j_{\text{trpn}} = k_{\text{on}} \cdot C_i \cdot (B_T - [\text{CaT}]_i) - k_{\text{off}} \cdot [\text{CaT}]_i \]  
(A.38)

\[ \frac{d[\text{CaT}]_i}{dt} = j_{\text{trpn}} \]  
(A.40)

\[ \frac{d[\text{CaT}]_s}{dt} = f_{\text{trpn}} \]  
(A.41)

Na\(^{+}/\text{Ca}^{2+}\) exchange flux

\[ K_o = \left( 1 + \frac{c_{\text{NaCa}}}{c_s} \right)^{-3} \]  
(A.42)

\[ H = K_{\text{mCaO}} \cdot [\text{Na}^+]^3 + K_{\text{mNaO}}^3 \cdot C_{s,mM} + K_{\text{mNaCa}} \cdot [\text{Ca}^{2+}]_o \cdot \left( C_s + C_{s,mM} \right) \]  
(A.43)

\[ + K_{\text{mCa}} \cdot [\text{Na}^+]^3 \cdot \left( 1 + \frac{[\text{Na}^+]_o}{K_{\text{mNaO}}} \right)^3 + \frac{[\text{Na}^+]_o^3 \cdot [\text{Ca}^{2+}]_o}{K_{\text{mNaCa}}^3} + [\text{Na}^+]_o^3 \cdot C_{s,mM} \]  
(A.44)

\[ J_{\text{NaCa}} = g_{\text{NaCa}} \cdot K_o \cdot \exp(\xi - a) \cdot [\text{Na}^+] \cdot [\text{Ca}^{2+}]_o - \exp((\xi - 1) \cdot a) \cdot [\text{Na}^+]_o^3 \cdot C_{s,mM} \]  
(A.45)

The SR leak flux

\[ L = \frac{C^2_j}{C^2_j + C^2_j} \]  
(A.46)

\[ J_{\text{leak}} = g_1 \cdot L \cdot (v_t / v_{\text{leak}}) \cdot (C_j - C_i) \]  
(A.47)

The fast sodium current \((I_{\text{Na}})\)

\[ \alpha_m = \frac{eq48P1}{eq48P2} \cdot \frac{V + eq48P3}{1 - \exp(-0.1 \cdot (V + eq48P3))} \]  
if \[ |V + eq48P3| > 0.001 \]

\[ \beta_m = eq49P1 \cdot \exp(-V/eq49P2) \]  
(A.49)

\[ E_{\text{Na}} = \frac{RT}{F} \cdot \log \left( \frac{[\text{Na}^+]_o}{[\text{Na}^+]_i} \right) \]  
(A.50)

\[ I_{\text{Na}} = g_{\text{Na}} \cdot m^3 \cdot h \cdot j \cdot (V - E_{\text{Na}}) \]  
(A.51)

\[ \frac{dh}{dt} = \alpha_h \cdot (1 - h) - \beta_h \cdot h \]  
(A.52)
\[ \frac{dj}{dt} = \alpha_j \cdot (1 - j) - \beta_j \cdot j \quad (A.53) \]
\[ \frac{dm}{dt} = \alpha_m \cdot (1 - m) - \beta_m \cdot m \quad (A.54) \]

For \( V \leq -40 \text{ mV} \):
\[ \alpha_h = 0 \quad (A.55) \]
\[ \alpha_j = 0 \quad (A.56) \]
\[ \beta_h = (1 + \exp((V + eq57P2)/-eq57P3))^{-1} \quad (A.57) \]
\[ \beta_j = \frac{eq58P1 \cdot \exp(eq58P2 \cdot 10^{-7} \cdot V)}{1 + \exp(-0,1 \cdot (V + eq58P3))} \quad (A.58) \]

For \( V < -40 \text{ mV} \):
\[ \alpha_h = eq59P1 \cdot \exp((V + eq59P2)/-eq59P3) \quad (A.59) \]
\[ \beta_h = eq60P1 \cdot \exp(eq60P2 \cdot V) + eq60P3 \cdot 10^5 \cdot \exp(eq60P4 \cdot V) \quad (A.60) \]
\[ \alpha_j = -eq61P1 \cdot 10^5 \cdot \exp(eq61P2 \cdot V) - eq61P3 \cdot 10^{-5} \cdot \exp(-eq61P4 \cdot V) \]
\[ \times \frac{(V + eq61P5)}{1 + \exp(eq61P6 \cdot (V + eq61P7))} \exp(-eq62P2 \cdot V) \quad (A.61) \]
\[ \beta_j = eq62P1 \frac{eq62P2}{1 + \exp(-eq62P3 \cdot (V + eq62P4))} \quad (A.62) \]

Na⁺ dynamics
\[ \alpha' = \frac{1000 \cdot F \cdot v_i}{C_m} \quad (A.63) \]
\[ \frac{d[Na^+]i}{dt} = -\left( \frac{hNa + 3 \cdot hNCa + 3 \cdot hNAK}{\alpha'} \right) \quad (A.64) \]

Averaged Ca²⁺ dynamics in the dyadic space
\[ Q = \begin{cases} 0 & \text{if } 0 < \tau_f' < 50 \\ \tau_f' - 50 & \text{if } 50 \leq \tau_f' \leq c_{sr} \\ u \cdot \tau_f' + s & \text{if } \tau_f' > c_{sr} \end{cases} \quad (A.65) \]
\[ g_{SR} = g_{SR} \cdot \frac{\exp(-eq66P1 \cdot (V + eq66P2))}{1 + \exp(-eq66P1 \cdot (V + eq66P2))} \quad (A.66) \]
\[ f_{SR} = g_{SR} \cdot Q \cdot P_0 \cdot |i_{Ca}| \quad (A.67) \]
\[ f_{Ca} = g_{Ca} \cdot P_0 \cdot |i_{Ca}| \quad (A.68) \]

Inward rectifier K⁺ current (\( I_K1 \))
\[ E_K = \frac{RT}{F} \log \left( \frac{[K^+]_{lo}}{[K^+]_{hi}} \right) \quad (A.69) \]
\[ B_{K1} = \frac{eq70P1 \cdot \exp(eq70P2 \cdot (V - E_K + eq70P3)) + \exp(eq70P4 \cdot (V - E_K - eq70P5))}{1 + \exp(-eq70P6 \cdot (V - E_K + eq70P7))} \quad (A.70) \]
\[ A_{K1} = \frac{1 + \exp(eq71P1 \cdot (V - E_K - eq71P3))}{eq71P1} \quad (A.71) \]
\[ I_{K1} = g_{K1} \cdot \sqrt{[K^+]_{lo} \cdot A_{K1} \cdot V - E_K} \frac{eq72}{A_{K1} + B_{K1}} \quad (A.72) \]

The rapid component of the delayed rectifier K⁺ current (\( I_{Kr} \))
\[ \tau_{Kr} = \left( \frac{eq73P1 \cdot (V + eq73P2)}{1 - \exp(-eq73P3 \cdot (V + eq73P2))} + \frac{eq73P4 \cdot (V + eq73P5)}{-1 + \exp(eq73P6 \cdot (V + eq73P5))} \right)^{-1} \quad (A.73) \]
\[ x_{Kr} = (1 + \exp((-V + eq74P1)/eq74P2))^{-1} \quad (A.74) \]
\[ R_2 = (1 + \exp((V + eq75P1)/eq75P2))^{-1} \quad (A.75) \]
\[ I_{Kr} = g_{Kr} \cdot \sqrt{[K^+]_{lo} \cdot x_{Kr} \cdot R_2 \cdot (V - E_K)} \quad (A.76) \]
\[
\frac{dx_{Kr}}{dt} = \frac{x_{Kr}^\infty - x_{Kr}}{\tau_{Kr}} \tag{A.77}
\]

**The slow component of the delayed rectifier K⁺ current** \((I_{Ks})\)

\[
E_{Ks} = \frac{RT}{F} \log \left( \frac{[K^+]_o + eq78 \cdot [Na^+]_o}{[K^+]_r + eq78 \cdot [Na]_r} \right) \tag{A.78}
\]

\[
\tau_{s1} = \left( \frac{1}{1 - \exp(-(eq79P1 \cdot (V + eq79P2)) + eq79P4 \cdot (V + eq79P5))} \right) \tag{A.79}
\]

\[
\tau_{s2} = 4 \cdot \tau_{s1} \tag{A.80}
\]

\[
x_{s1}^\infty = (1 + \exp(-(V - eq81P1)/eq81P2))^{-1} \tag{A.81}
\]

\[
q_{Ks} = 1 + \frac{eq82P1}{1 + (eq82P2/eq3)} \tag{A.82}
\]

\[
I_{Ks} = g_{Ks} \cdot x_{s1} \cdot x_{s2} \cdot q_{Ks} \cdot (V - E_{Ks}) \tag{A.83}
\]

\[
\frac{dx_{s1}}{dt} = \frac{x_{s1}^\infty - x_{s1}}{\tau_{s1}} \tag{A.84}
\]

\[
\frac{dx_{s2}}{dt} = \frac{x_{s2}^\infty - x_{s2}}{\tau_{s2}} \tag{A.85}
\]

**The Na⁺/K⁺ pump current** \((I_{Nak})\)

\[
\sigma = \frac{\exp([Na^+]_o/eq86P1) - 1}{eq86P2} \tag{A.86}
\]

\[
f_{Nak} = (1 + eq87P1 \cdot \exp(-0.1 \cdot VF/(RT))) + eq87P2 \cdot \sigma \cdot \exp(-(VF/(RT)))^{-1} \tag{A.87}
\]

\[
I_{Nak} = g_{Nak} \cdot f_{Nak} \cdot \frac{1}{1 + (eq88P1/[Na]_o))} \cdot \frac{[K^+]_o + eq88P2}{[K^+]_r + eq88P2} \tag{A.88}
\]

**The fast component of the rapid inward K⁺ current** \((I_{to,f})\)

\[
X_{to,f}^\infty = (1 + \exp(-(V + eq89P1)/eq89P2))^{-1} \tag{A.89}
\]

\[
Y_{to,f}^\infty = (1 + \exp((V + eq90P1)/eq90P2))^{-1} \tag{A.90}
\]

\[
\tau_{Xtof} = eq91P1 \cdot \exp(-(V/eq91P2)^2) + eq91P3 \tag{A.91}
\]

\[
\tau_{Ytof} = \frac{eq92P1}{1 + \exp((V + eq92P2)/eq92P3)} + eq92P4 \tag{A.92}
\]

\[
I_{to,f} = g_{tof} \cdot X_{to,f} \cdot Y_{to,f} \cdot (V - E_K) \tag{A.93}
\]

\[
\frac{dX_{to,f}}{dt} = \frac{X_{to,f}^\infty - X_{to,f}}{\tau_{Xtof}} \tag{A.94}
\]

\[
\frac{dY_{to,f}}{dt} = \frac{Y_{to,f}^\infty - Y_{to,f}}{\tau_{Ytof}} \tag{A.95}
\]

**The slow component of the rapid outward K⁺ current** \((I_{to,s})\)

\[
R_{s}^\infty = Y_{to,f}^\infty \tag{A.96}
\]

\[
X_{to,s}^\infty = X_{to,f}^\infty \tag{A.97}
\]

\[
Y_{to,s}^\infty = R_{s}^\infty \tag{A.98}
\]

\[
\tau_{Xtos} = \frac{eq99P1}{1 + \exp((V + eq99P2)/eq99P3)} + eq99P4 \tag{A.99}
\]

\[
\tau_{Ytos} = \frac{eq100P1}{1 + \exp((V + eq100P2)/eq100P3)} + eq100P4 \tag{A.100}
\]

\[
\tau_{Rs} = \frac{eq101P1}{1 + \exp((V + eq101P2)/eq101P3)} + eq101P4 \tag{A.101}
\]

\[
I_{to,s} = g_{tos} \cdot X_{to,s} \cdot (Y_{to,s} + 0.5 \cdot R_{s}) \cdot (V - E_K) \tag{A.102}
\]

\[
\frac{dX_{to,s}}{dt} = \frac{X_{to,s}^\infty - X_{to,s}}{\tau_{Xtos}} \tag{A.103}
\]
\[
\frac{dY_{10.5}}{dt} = \frac{Y_{10.5}^\infty - Y_{10.5}}{\tau_{Y10.5}} \\
\frac{dR_s}{dr} = \frac{R_s^\infty - R_s}{\tau_{Rs}}
\]

(A.104) (A.105)

**Equations for Ca\(^{2+}\) cycling**

\[
I_{Ca} = \frac{2 \cdot F \cdot v_i \cdot J_{Ca}}{C_m}
\]

(A.106)

\[
l_{NaCa} = \frac{F \cdot v_i \cdot J_{NaCa}}{C_m}
\]

(A.107)

\[
g_{RyR} = \frac{g_{RyR} \cdot \exp(-eq108P1 \cdot (V + eq108P2))}{1 + \exp(-eq108P1 \cdot (V + eq108P2))}
\]

(A.108)

\[
N_s' = g_{RyR} \cdot P_0 \cdot |I_{Ca}|
\]

(A.109)

\[
\bar{T} = \frac{\tau_r}{1 - \tau_r \cdot \frac{dc}{dr} / c_j}
\]

(A.110)

\[
\frac{dc_s}{dr} = \beta_s \cdot ((v_i/v_s) \cdot (J_{rel} - J_d - J_{Ca} + J_{NaCa}) - J_{trpn}^i)
\]

(A.111)

\[
\frac{dc_i}{dr} = \beta_i \cdot (J_d - J_{up} + J_{leak} - J_{trpn})
\]

(A.112)

\[
\frac{dc_j}{dr} = -J_{rel} + J_{up} - J_{leak}
\]

(A.113)

\[
\frac{dc_j'}{dr} = \frac{c_j - c_j'}{\tau_a}
\]

(A.114)

\[
\frac{dl_{rel}}{dt} = \frac{N_s' \cdot c_j \cdot Q_{csr}}{c_{sr}} - \frac{J_{rel}}{\bar{T}}
\]

(A.115)

\[
\frac{dc_p}{dt} = \frac{f_{SR} + f_{Ca} - (c_p - c_j)}{\tau_s}
\]

(A.116)

**Ionic currents**

\[
I_{ion} = I_{Na} + I_{NaK} + I_{Ca} + I_{NaCa} + I_{K1}
\]

(A.117)

\[
\frac{dV}{dt} = -(I_{ion} + I_{stim})
\]

(A.118)
### A.3. Model parameters

#### Table A.3

Ca\(^{2+}\)-related parameters, including class memberships (Table 1) for three PCLs.

| # | Name | Definition | Value 1.1 s | Value 1.282 s | Value 1.37 s |
|---|------|------------|-------------|---------------|--------------|
| SR release parameters | | | | | |
| 1 | \( \tau_s \) | Spark lifetime | 30 ms | 2 | 3 | 3 |
| 2 | \( \tau_a \) | NSR-JSR relaxation time | 100 ms | 3 | 3 | 3* |
| 3 | \( \text{Ryr} \) | Release current strength | 3.0 sparks cm\(^2\)/mA | 0 | 3 | 3 |
| 4 | \( u \) | Release slope | 11.3 ms\(^{-1}\) | 3 | 3 | 3* |
| 5 | \( c_{sr} \) | Threshold for steep release function | 90 \( \mu \)M/1 cytosol | 0 | 0 | 0 |
| 6 | \( s \) | Release function parameter | \((1 - u)c_{sr} - 50 = -977 \mu \text{M}/\text{ms}\) | 3 | 3 | 3* |
| 7 | \( \tau_d \) | Submembrane-myoplasm diffusion time constant | 4 ms | 2 | 3 | 2 |
| 8 | \( \tau_s \) | Dyadic junction-submembrane diffusion time constant | 0.5 ms | 1 | 3 | 3 |
| Cytosolic buffering parameters | | | | | |
| 9 | \( B_T \) | Total conc. of Troponin C | 70.0 \( \mu \)mol/1 cytosol | 1 | 3 | 3 |
| 10 | \( B_{SR} \) | Total conc. of SR binding sites | 47.0 \( \mu \)mol/1 cytosol | 1 | 3 | 3 |
| 11 | \( B_{CG} \) | Total conc. of calmodulin binding sites | 24.0 \( \mu \)mol/1 cytosol | 1 | 3 | 2 |
| 12 | \( B_{mem} \) | Total conc. of membrane binding sites | 15.0 \( \mu \)mol/1 cytosol | 1 | 3 | 3 |
| 13 | \( B_{sar} \) | Total conc. of sarcolemma binding sites | 42.0 \( \mu \)mol/1 cytosol | 1 | 3 | 2 |
| 14 | \( B_{ATP} \) | Total conc. of ATP binding sites | 500.0 \( \mu \)mol/1 cytosol | 1 | 3 | 3 |
| 15 | \( k_f \) | On rate for Troponin C binding | 0.0327 (\( \mu \)M ms\(^{-1}\)) | 1 | 3 | 3 |
| 16 | \( k_{off} \) | Off rate for Troponin C binding | 0.0196 ms\(^{-1}\) | 0 | 3 | 3 |
| 17 | \( K_{SR} \) | Dissociation constant for SR binding sites | 0.6 \( \mu \)M | 1 | 3 | 3 |
| 18 | \( K_{CG} \) | Dissoc. const. for Calmodulin binding sites | 7.0 \( \mu \)M | 0 | 2 | 0 |
| 19 | \( K_{mem} \) | Dissoc. const. for membrane binding sites | 0.3 \( \mu \)M | 0 | 2 | 0 |
| 20 | \( K_{sar} \) | Dissoc. const. for sarcolemma binding sites | 13.0 \( \mu \)M | 1 | 3 | 2 |
| 21 | \( K_{ATP} \) | Dissoc. const. for ATP binding sites | 200.0 \( \mu \)M | 2 | 3 | 3 |
| Uptake and SR leak parameters | | | | | |
| 22 | \( c_{up} \) | Uptake threshold | 0.5 \( \mu \)M | 2 | 3 | 3 |
| 23 | \( v_{up} \) | Strength of uptake | 0.8 \( \mu \)M/ms | 2 | 3 | 3 |
| 24 | \( g_s \) | Strength of leak current | 2.07 \( \times 10^{-6} \) ms\(^{-1}\) | 2 | 3 | 2 |
| 25 | \( k_l \) | Threshold for leak onset | 50 \( \mu \)M | 1 | 3 | 2 |
| L-type \Ca^{2+}\ current parameters | | | | | |
| 26 | \( P_{Ca} \) | Constant | 0.00054 cm/s | 2 | 3 | 3 |
| 27 | \( g_{Ca} \) | Strength of \Ca^{2+}\ current flux | 546 mmol/(cm C) | 3 | 3 | 3* |
| 28 | \( g_{Ca} \) | Strength of local \Ca^{2+}\ flux due to L-type \Ca^{2+}\ channels | 9998.6 mmol/(cm C) | 1 | 3 | 3 |
| 29 | \( g_{Ca} \) | Strength of local \Ca^{2+}\ flux due to RyR channels | 23692 mmol/(cm C) | 1 | 3 | 2 |
| 30 | \( k_{in} \) | Threshold for \Ca^{2+}\-induced inactivation | 5.0117 \( \mu \)M | 1 | 3 | 3 |
| 31 | \( \tau_{Ca} \) | Time constant of \Ca^{2+}\ dependence of transition rate \( k_{Ca} \) | 4 \( \mu \)M | 2 | 3 | 3 |
| 32 | \( \tau_{in} \) | Time constant of activation | 0.35 ms | 1 | 3 | 3 |
| 33 | \( r_{in} \) | Opening rate | 0.41 ms\(^{-1}\) | 2 | 3 | 3 |
| 34 | \( r_{out} \) | Closing rate | 2.7 ms\(^{-1}\) | 2 | 0 | 3 |
| 35 | \( s_{in} \) | Inactivation rate | 0.00175 ms\(^{-1}\) | 0 | 0 | 0 |
| 36 | \( k_{in} \) | Inactivation rate | 0.00413 ms\(^{-1}\) | 0 | 0 | 0 |
| 37 | \( s_{out} \) | Inactivation rate | 0.000377 ms\(^{-1}\) | 2 | 3 | 3 |
| 38 | \( s_{out} \) | Inactivation rate | 0.000687 ms\(^{-1}\) | 0 | 0 | 0 |
| 39 | \( \tau_{Ca} \) | Time constant | 671.082 ms | 1 | 3 | 3 |
| Fit constants | | | | | |
| 40 | eqP1 | for L-type \Ca^{2+}\ current | 4.36 | 2 | 3 | 3 |
| 41 | eqP2 | for L-type \Ca^{2+}\ current | 6.8 | 0 | 0 | 0 |
| 42 | eqP1 | for L-type \Ca^{2+}\ current | 10 | 1 | 2 | 1 |
| 43 | eqP2 | for L-type \Ca^{2+}\ current | 10 | 1 | 2 | 1 |
| 44 | eqP3 | for L-type \Ca^{2+}\ current | 4954 | 1 | 2 | 2 |
| 45 | eqP2 | for L-type \Ca^{2+}\ current | 15.6 | 1 | 3 | 3 |
| 46 | eqP2 | for L-type \Ca^{2+}\ current | 50 | 2 | 3 | 3 |
| 47 | eqP1 | for L-type \Ca^{2+}\ current | 40 | 2 | 3 | 3 |
| 48 | eqP2 | for L-type \Ca^{2+}\ current | 10 | 0 | 0 | 0 |
| 49 | eqP1 | for L-type \Ca^{2+}\ current | 190 | 2 | 2 | 1 |
| 50 | eqP2 | for L-type \Ca^{2+}\ current | 10 | 1 | 2 | 1 |
| 51 | eqP1 | for L-type \Ca^{2+}\ current | 0.367 | 1 | 3 | 3 |
| 52 | eqP2 | for L-type \Ca^{2+}\ current | 0.0298 | 2 | 3 | 3 |
| 53 | eqP1 | for L-type \Ca^{2+}\ current | 50 | 2 | 3 | 3 |
| 54 | eqP2 | for L-type \Ca^{2+}\ current | 10 | 0 | 0 | 0 |
| 55 | eqP3 | for L-type \Ca^{2+}\ current | 3 | 0 | 0 | 0 |
| 56 | eqP3 | for L-type \Ca^{2+}\ current | 0.341 | 2 | 3 | 3 |
| 57 | eqP1 | for averaged \Ca^{2+}\ dynamics in dyadic space | 0.346 | 1 | 3 | 3 |
| 58 | eqP2 | for averaged \Ca^{2+}\ dynamics in dyadic space | 30 | 1 | 3 | 3 |
| 59 | eqP1 | for \Ca^{2+}\-cycling | 0.05 | 3 | 3 | 3* |
| 60 | eqP2 | for \Ca^{2+}\-cycling | 30 | 3 | 3 | 3* |
| #  | Name                  | Definition                        | Value     | 1.1 s | 1.282 s | 1.37 s |
|----|-----------------------|-----------------------------------|-----------|-------|---------|--------|
| 61 | $g_{sa}$              | Peak $h_{sa}$ conductance         | 12.0 mS/μF |       |         |        |
| 62 | $g_{48}$              | for fast Sodium current $h_{sa}$  | 3.2       | 2     | 1       | 1      |
| 63 | $g_{48}$              | for fast Sodium current $h_{sa}$  | 0.32      | 2     | 3       | 3      |
| 64 | $g_{48}$              | for fast Sodium current $h_{sa}$  | 47.13     | 2     | 3       | 3      |
| 65 | $g_{49}$              | for fast Sodium current $h_{sa}$  | 0.08      | 2     | 3       | 3      |
| 66 | $g_{49}$              | for fast Sodium current $h_{sa}$  | 11        | 0     | 0       | 0      |
| 67 | $g_{57}$              | for fast Sodium current $h_{sa}$  | 0.13      | 2     | 3       | 3      |
| 68 | $g_{57}$              | for fast Sodium current $h_{sa}$  | 10.66     | 1     | 3       | 3      |
| 69 | $g_{57}$              | for fast Sodium current $h_{sa}$  | 11.1      | 1     | 3       | 2      |
| 70 | $g_{58}$              | for fast Sodium current $h_{sa}$  | 0.3       | 1     | 3       | 2      |
| 71 | $g_{58}$              | for fast Sodium current $h_{sa}$  | 2.535     | 1     | 1       | 1*     |
| 72 | $g_{58}$              | for fast Sodium current $h_{sa}$  | 32        | 2     | 3       | 3      |
| 73 | $g_{59}$              | for fast Sodium current $h_{sa}$  | 0.135     | 1     | 2       | 1      |
| 74 | $g_{59}$              | for fast Sodium current $h_{sa}$  | 80        | 2     | 3       | 2      |
| 75 | $g_{60}$              | for fast Sodium current $h_{sa}$  | 6.8       | 0     | 0       | 0      |
| 76 | $g_{60}$              | for fast Sodium current $h_{sa}$  | 3.56      | 1     | 3       | 2      |
| 77 | $g_{60}$              | for fast Sodium current $h_{sa}$  | 0.079     | 2     | 3       | 2      |
| 78 | $g_{60}$              | for fast Sodium current $h_{sa}$  | 3.1       | 1     | 2       | 1      |
| 79 | $g_{60}$              | for fast Sodium current $h_{sa}$  | 0.35      | 2     | 3       | 2      |
| 80 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 1.2714    | 1     | 1       | 1*     |
| 81 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 0.2444    | 1     | 1       | 1*     |
| 82 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 3.474     | 2     | 2       | 1      |
| 83 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 0.04391   | 0     | 0       | 0      |
| 84 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 37.78     | 1     | 2       | 1      |
| 85 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 0.311     | 1     | 1       | 1*     |
| 86 | $g_{61}$              | for fast Sodium current $h_{sa}$  | 79.23     | 1     | 2       | 2      |
| 87 | $g_{62}$              | for fast Sodium current $h_{sa}$  | 0.1212    | 1     | 2       | 2      |
| 88 | $g_{62}$              | for fast Sodium current $h_{sa}$  | 0.01052   | 0     | 0       | 0      |
| 89 | $g_{62}$              | for fast Sodium current $h_{sa}$  | 0.1378    | 2     | 3       | 2      |
| 90 | $g_{62}$              | for fast Sodium current $h_{sa}$  | 40.14     | 2     | 3       | 2      |

| #  | Name                  | Definition                        | Value     | 1.1 s | 1.282 s | 1.37 s |
|----|-----------------------|-----------------------------------|-----------|-------|---------|--------|
| 91 | $g_{ks}$              | Peak $h_{ks}$ conductance         | 0.055 mS/μF |       |         |        |
| 92 | $g_{ks}$              | Peak $h_{ks}$ conductance         | 0.08 mS/μF  |       |         |        |
| 93 | $g_{ks}$              | Peak $h_{ks}$ conductance         | 0.36 mS/μF  |       |         |        |
| 94 | $g_{ks}$              | Peak $h_{ks}$ conductance         | 0.006 mS/μF |       |         |        |
| 95 | $g_{ks}$              | Peak $h_{ks}$ conductance         | 0.153 mS/μF |       |         |        |

| #  | Name                  | Definition                        | Value     | 1.1 s | 1.282 s | 1.37 s |
|----|-----------------------|-----------------------------------|-----------|-------|---------|--------|
| 96 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 0.49124 |       |         |        |
| 97 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 0.08032 |       |         |        |
| 98 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 5476     |       |         |        |
| 99 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 0.06175 |       |         |        |
|100 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 594.31   |       |         |        |
|101 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 0.5143   |       |         |        |
|102 | $g_{70}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 4.753    |       |         |        |
|103 | $g_{71}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 1.02     |       |         |        |
|104 | $g_{71}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 0.2385   |       |         |        |
|105 | $g_{71}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 59.215   |       |         |        |
|106 | $g_{72}$              | for Inward rectifier $K^+$ current $h_{ks}$ | 5.4      |       |         |        |
|107 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 0.01381 |       |         |        |
|108 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 7        |       |         |        |
|109 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 123      |       |         |        |
|110 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 0.000611 |       |         |        |
|111 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 10       |       |         |        |
|112 | $g_{72}$              | for fast comp. of delayed rectifier current $h_{ks}$ | 0.145    |       |         |        |
Table A.5 (continued)

| #  | Name      | Definition                                                      | Value   | 1.1 s | 1.282 s | 1.37 s |
|----|-----------|-----------------------------------------------------------------|---------|-------|---------|-------|
| 113| eq74P1    | for rapid comp. of delayed rectifier current $I_K$              | 50      | 1     | 2       | 1     |
| 114| eq74P2    | for rapid comp. of delayed rectifier current $I_K$              | 7.5     | 1     | 2       | 1     |
| 115| eq75P1    | for rapid comp. of delayed rectifier current $I_K$              | 33      | 2     | 3       | 3     |
| 116| eq75P2    | for rapid comp. of delayed rectifier current $I_K$              | 22.4    | 2     | 3       | 3     |
| 117| eq76      | for rapid comp. of delayed rectifier current $I_K$              | 5.4     | 1     | 3       | 3     |
| 118| eq78      | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.01833 | 2     | 3       | 3     |
| 119| eq79P1    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.0000719 | 0 | 0     | 0     |
| 120| eq79P2    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 30      | 3     | 3       | 3*    |
| 121| eq79P3    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.148   | 2     | 3       | 3     |
| 122| eq79P4    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.000131 | 0 | 0     | 0     |
| 123| eq79P5    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 30      | 1     | 3       | 3     |
| 124| eq79P6    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.0687  | 2     | 3       | 3     |
| 125| eq81P1    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 1.5     | 1     | 3       | 3     |
| 126| eq81P2    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 16.7    | 2     | 3       | 3     |
| 127| eq82P1    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.8     | 2     | 3       | 3     |
| 128| eq82P2    | for slow comp. of delayed rectifier K⁺ current $I_{i,(f)}$      | 0.5     | 2     | 3       | 3     |
| 129| eq95P1    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 3       | 2     | 3       | 3     |
| 130| eq95P2    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 15.2    | 2     | 3       | 3     |
| 131| eq90P1    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 33.5    | 3     | 3       | 3*    |
| 132| eq90P2    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 10      | 3     | 3       | 3*    |
| 133| eq91P1    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 3.5     | 1     | 3       | 2     |
| 134| eq91P2    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 30      | 1     | 3       | 3     |
| 135| eq91P3    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 1.5     | 1     | 3       | 3     |
| 136| eq92P1    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 20      | 1     | 2       | 2     |
| 137| eq92P2    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 33.5    | 1     | 2       | 1     |
| 138| eq92P3    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 10      | 1     | 2       | 1     |
| 139| eq92P4    | for fast comp. of rapid inward K⁺ current $I_{i,(f)}$            | 20      | 2     | 3       | 3     |
| 140| eq99P1    | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 9       | 1     | 2       | 2     |
| 141| eq99P2    | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 3       | 1     | 2       | 1     |
| 142| eq99P3    | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 15      | 1     | 3       | 2     |
| 143| eq99P4    | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 0.5     | 1     | 3       | 2     |
| 144| eq100P1   | for fast comp. of rapid out. K⁺ current $I_{o,(s)}$              | 3000    | 2     | 3       | 3     |
| 145| eq100P2   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 60      | 2     | 3       | 3     |
| 146| eq100P3   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 10      | 2     | 3       | 2     |
| 147| eq100P4   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 30      | 2     | 3       | 3     |
| 148| eq101P1   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 2300    | 2     | 3       | 3     |
| 149| eq101P2   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 60      | 2     | 3       | 3     |
| 150| eq101P3   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 10      | 1     | 3       | 3     |
| 151| eq101P4   | for slow comp. of rapid out. K⁺ current $I_{o,(s)}$              | 720     | 2     | 3       | 3     |

Table A.6
Other parameters, including class memberships (Table 1) for three PCLs.

| #  | Name     | Definition                                                                 | Value     | 1.1 s | 1.282 s | 1.37 s |
|----|----------|-----------------------------------------------------------------------------|-----------|-------|---------|-------|
| 152| $g_{NaCx}$ | Strength of exchange current                                                | 0.84 μM/ms | 2     | 3       | 3     |
| 153| $k_{sat}$ | Constant                                                                    | 0.2       | 1     | 3       | 3     |
| 154| $\xi$    | Constant                                                                    | 0.35      | 1     | 3       | 3     |
| 155| $K_{NaCa}$| Constant                                                                    | 12.3 mM   | 1     | 3       | 3     |
| 156| $K_{NaCl}$| Constant                                                                    | 87.5 mM   | 2     | 3       | 3     |
| 157| $K_{CaCx}$| Constant                                                                    | 0.0036 mM | 2     | 3       | 3     |
| 158| $K_{CaCl}$| Constant                                                                    | 1.3 mM    | 1     | 3       | 2     |
| 159| $c_{NaCa}$| Constant                                                                    | 0.3 μM    | 1     | 3       | 3     |
| 160| $g_{NaK}$ | Peak $I_{NaK}$ conduction                                                   | 1.5 mS/μF | 3     | 3       | 3*    |

Fit constants

| #  | Name     | Definition                                                                 | Value     | 1.1 s | 1.282 s | 1.37 s |
|----|----------|-----------------------------------------------------------------------------|-----------|-------|---------|-------|
| 161| eq86P1   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 67.3      | 3     | 3       | 3*    |
| 162| eq86P2   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 7         | 2     | 3       | 3     |
| 163| eq87P1   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 0.1245    | 2     | 3       | 3     |
| 164| eq87P2   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 0.0365    | 2     | 3       | 3     |
| 165| eq88P1   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 12        | 3     | 3       | 3*    |
| 166| eq88P2   | for Na⁺/K⁺ pump current $I_{NaK}$                                           | 1.5       | 2     | 3       | 3     |
Table A.7
Physical constants and ionic concentrations, including class memberships (Table 1) for three PCLs.

| #  | Name     | Definition                        | Value   | 1.1 s | 1.282 s | 1.37 s |
|----|----------|-----------------------------------|---------|-------|---------|--------|
| 167| $C_m$    | Cell capacitance                  | $3.1 \times 10^{-4}$ μF | 4      | 4       | 4      |
| 168| $v_i$    | Cell volume                       | $2.58 \times 10^{-5}$ μl | 4      | 4       | 4      |
| 169| $v_s$    | Submembrane volume                | $0.02 \, v_i$            | 4      | 4       | 4      |
| 170| $v_{SR}$ | SR volume                          | $0.06 \, v_i$            | 4      | 4       | 4      |
| 171| $F$      | Faraday constant                   | 96.5 C/mmol              | 4      | 4       | 4      |
| 172| $R$      | Universal gas constant             | $8.315 \, \text{J mol}^{-1}\text{K}^{-1}$ | 4 | 4 | 4 |
| 173| $T$      | Temperature                        | 308 K                | 4      | 4       | 4      |
| 174| $\left[\text{Na}^+\right]_o$ | External sodium concentration   | 136 mM          | 4      | 4       | 4      |
| 175| $\left[\text{K}^+\right]_i$    | Internal potassium concentration | 140 mM          | 4      | 4       | 4      |
| 176| $\left[\text{K}^+\right]_o$    | External potassium concentration | 5.4 mM           | 4      | 4       | 4      |
| 177| $\left[\text{Ca}^{2+}\right]_o$ | External calcium concentration   | 1.8 mM           | 4      | 4       | 4      |

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