A Mathematical Model for $\beta_1$-adrenergic Regulation of the Mouse Ventricular Myocyte Contraction

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A MATHEMATICAL MODEL FOR β₁-ADRENERGIC REGULATION OF THE MOUSE VENTRICULAR MYOCYTE CONTRACTION

by

PAULA MULLINS

Under the Direction of Vladimir E. Bondarenko, PhD

ABSTRACT

The β₁-adrenergic signaling system is one of the most important systems regulating heart function. Activation of this system leads to an increased heart rate, which can be beneficial during exercise, but can lead to cardiac hypertrophy and heart failure with continuous over-stimulation. In this dissertation, we have developed two comprehensive mathematical models of mouse ventricular myocyte contraction. The first model is based on a previously published mathematical model of action potential and Ca²⁺ handling mechanism of the mouse cardiac cell that are not modulated by the β₁-adrenergic signaling system. The model was verified with experimental data on mouse myocyte contraction at room temperature. In the model, we implement simplified sarcomere length variability and indirect modulation of the tropomyosin transition rates by Ca²⁺ and troponin. The resulting model describes well steady-state force-
calcium relationships, dependence of contraction force on sarcomere length, time course of
contraction force and myocyte shortening, frequency dependence of contraction force and
cellular contraction, and experimentally measured derivatives of myocyte length variation. We
emphasize the importance of including variable sarcomere length in the model for ventricular
myocyte contraction and investigate the differences in contraction force and cell shortening for
epicardial and endocardial ventricular myocytes. The second model of the mouse ventricular
myocyte contraction includes a more advanced description of the forces involved in myocyte
contraction (active, passive, viscous, and flexible forces) and the β1-adrenergic signaling system.
The model was verified by the simulation of major experimental protocols on measurements of
steady-state force-calcium relationships, crossbridge release rate (k_{rel}) and force development
rate (k_{df}), force-velocity relationship, and force redevelopment rate (k_{tr}). It also reproduces quite
well frequency and isoproterenol dependencies for [Ca^{2+}]i transients, total contraction force, and
sarcomere shortening. The resulting mathematical model reveals the mechanisms of increased
contraction force and myocyte shortening upon stimulation of β1-adrenergic receptors. The
developed mathematical models can be used further for simulations of contraction of ventricular
myocytes from genetically modified mice and myocytes from mice which have developed
chronic cardiac diseases.

INDEX WORDS: Contraction force, Sarcomere shortening, Crossbridge kinetics,
Phosphorylation, Troponin I, Myosin binding protein C
A MATHEMATICAL MODEL FOR β1-ADRENERGIC REGULATION OF THE MOUSE VENTRICULAR MYOCYTE CONTRACTION

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DEDICATION

To my loving and supportive parents, Joyce and Harold.
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1 INTRODUCTION

Heart disease is the number one cause of death in the United States [1]. A common way to treat heart disease is through pharmacological interventions and implanted devices. A comprehensive knowledge of the basic physiological processes that occur at the cellular level is required for proper treatment of cardiac disease states. While experimental studies of cardiac cells are the primary source of knowledge on cardiac physiology, mathematical models are useful supplementary tools in understanding the mechanisms behind heart function in health and disease. In this chapter, we review the basic physiology of cardiac cell contraction and the current state of mathematical modeling of cardiac cellular contraction.

![Diagram of the heart](image)

Figure 1.1 Diagram of the heart.

1.1 Physiological background

The heart is made up of several distinct regions, with different roles in the overall function of the organ. Because of their different roles, the regions have different types of cells. Some of the major components of the heart are the sinoatrial node, the left and right atrium, and the left and right ventricles (Fig. 1.1). The sinoatrial node, located on the right atrium, is the pacemaker of the heart. It sends electrical signals to the rest of the heart by means of Purkinje
fibers. The atria are the upper chambers of the heart, into which blood flows from the body. The blood is then pumped into the larger, lower chambers, called ventricles. From the ventricles, blood is pumped back out to the rest of the body. Due to their major role in heart contraction, the model presented in this paper is of contraction in ventricular cells.

**Figure 1.2 Schematic diagram of cardiac sarcomeres.**
Thick filaments are composed primarily of myosin, attached to the Z-line by titin. Thin filaments contain actin, tropomyosin, and troponin complex. When the myosin heads change conformation, the thin filaments move toward the M line, causing a contraction.

**1.1.1 Myofilaments and contraction**

Cellular contraction is achieved through the interaction of contractile proteins in myofilaments. Myofilaments account for a significant amount of the volume in mammalian cardiac cells. In mouse hearts, for example, they account for approximately half of the cell volume [2]. Each myofilaent is comprised of a series of thick and thin filaments (Fig. 1.2) which interact to generate cell movement and contraction. A sarcomere is a section of the myofilament between two consecutive Z-lines. The thick filaments are composed of myosin, titin, and myosin binding protein C (MyBP-C), while the thin filaments are composed of actin, tropomyosin (Tm), and troponin complex (TnI, TnC, and TnT) (Fig. 1.3). The globular heads of the myosin proteins protrude from the thick filament and bind to the actin on the thin filaments to form crossbridges. When myosin hydrolyzes ATP, the myosin head changes conformation, pulling the thin filament toward the M line and causing a contraction. In its resting state,
however, tropomyosin blocks the myosin binding sites on actin (Fig. 1.4A). When calcium (Ca\(^{2+}\)) binds to TnC, the tropomyosin protein shifts enough to uncover the binding sites and allow crossbridges to form (Fig. 1.4B). In this way, Ca\(^{2+}\) regulates cardiac contraction.

**Figure 1.3 Thin and thick filament structure.**

Tropomyosin and actin each form two strands which are interwoven to form the thin filament (top). The troponin complex consists of three subunits: troponin T (TnT), troponin C (TnC), and troponin I (TnI). The strand of the thick filament (bottom) is made primarily of the rod-like myosin tails (heavy chains). The myosin heads, which are attached to the heavy chains by the regulatory light chain (RLC) and essential light chain (ELC), protrude from the thick filament. Myosin binding protein C (MyBP-C) is typically spaced along the thick filament such that three pairs of myosin heads are located between consecutive MyBP-C molecules.

### 1.1.2 Phosphorylation of contractile proteins

In muscle cells, contractions are primarily regulated by intracellular Ca\(^{2+}\) levels, but there are other changes to contractile proteins which can affect the formation or disassociation of crossbridges. One such change is phosphorylation [3]. Phosphorylation is the addition of a negatively charged phosphate group to a protein. The addition of this group can change the structure of the protein, which can change the function of the protein [4]. While phosphorylation can occur to most of the contractile proteins, only TnI, MyBP-C, and the myosin regulatory light chain (RLC) are phosphorylated and dephosphorylated fast enough to influence contractions [3]. However, of these three, only TnI and MyBP-C are phosphorylated by protein kinase A (PKA), a
component of the $\beta_1$-adrenergic signaling system, so they are the only two whose phosphorylation is included in our contraction model.

**Figure 1.4 Two conformations of the thin filament.**

(A) In the nonpermissive state, tropomyosin is blocking the myosin binding sites on actin. (B) In the permissive state, Ca$^{2+}$ is bound to TnC, causing tropomyosin to shift so that the myosin binding sites are exposed.

1.1.2.1 Troponin I

Troponin I is the subunit of troponin complex which binds to actin and is a target of PKA [2]. Activation of the $\beta_1$-adrenergic signaling system increases the percentage of phosphorylated TnI from a baseline level of $\sim$40% to a saturation level of $\sim$80% [5, 6]. Multiple studies have shown that the phosphorylation of TnI decreases Ca$^{2+}$ sensitivity [7-9], but Robertson et al. [7] found that the major effect of TnI phosphorylation was on the unbinding rate of Ca$^{2+}$. While investigating the role of phosphorylation of TnI versus MyBP-C on crossbridge kinetics, Kentish et al. [8] found that it is TnI phosphorylation by PKA that increases relaxation rates.

1.1.2.2 Myosin binding protein C

Myosin binding protein C is a protein located on the thick filament of a sarcomere. MyBP-C molecules are spaced along the thick filament such that there are three sets of myosin
heads between them (Fig. 1.4) [10, 11]. MyBP-C’s role in crossbridge mechanics is still relatively unknown, but its phosphorylation has been found to be important in maintaining sarcomere structure and normal cardiac function [12]. Mutations of MyBP-C are the most common genetic cause of hypertrophic cardiomyopathies, with 150 different mutations of the MyBP-C gene having been found to be linked to cardiomyopathies [10].

PKA-activated phosphorylation of MyBP-C accelerates crossbridge kinetics, decreases Ca^{2+} sensitivity, and enhances relaxation [13]. Tong et al. [14] found that changes in stretch-activated contraction kinetics were due to phosphorylation of MyBP-C, not TnI, while the changes in the steady state force-Ca^{2+} relationship were primarily due to TnI phosphorylation. More recent experimental data, however, has shown that both MyBP-C and TnI make approximately equal contribution to the change in steady-state force-Ca^{2+} relationships [15].

1.1.3 The β1-adrenergic signaling system

The β1-adrenergic signaling system is one of the primary signaling systems in the body. Activation of this system sends epinephrine (adrenaline) and norepinephrine (noradrenaline) throughout the body initiating what is often called the “fight or flight” response, which includes increased heart rate, blood pressure, and cardiac contractility. In ventricular myocytes, stimulation of the β1-adrenoreceptors (β1-ARs) by a β1-adrenergic agonist (isoproterenol) sets off a sequence of events (see [16]) which leads downstream to the activation of PKA. PKA phosphorylates several cardiac proteins, including TnI and MyBP-C (see Section 1.1.2).

1.2 Mathematical models of cardiac cells

1.2.1 Modeling cardiac electrical activity and Ca^{2+} dynamics

The first cardiac cell models were of Purkinje cells. Because these cells have currents similar to neural cells (sodium and potassium currents), the first models were based on the 1952
Hodgkin-Huxley (H-H) model of a neuron [17]. Like the H-H model, the 1962 Noble model [18] included a differential equation for the membrane current ($I_m$) comprised of three ionic currents, sodium ($I_{Na}$), potassium ($I_K$), and the anion (leak) current ($I_{An}$):

$$I_m = C_m \frac{dE_m}{dt} + I_{Na} + I_K + I_{An}, \quad (1.1)$$

where $C_m$ is the membrane capacity, $t$ is the time, and $E_m$ is the membrane potential. Each individual ionic current was expressed as the ionic conductance ($g_{Na}$, $g_K$, and $g_{An}$) times the difference in the membrane potential and the ionic equilibrium potential ($E_{Na}$, $E_K$, and $E_{An}$):

$$I_{Na} = g_{Na} (E_m - E_{Na}) \quad (1.2)$$

$$I_K = g_K (E_m - E_K) \quad (1.3)$$

$$I_{An} = g_{An} (E_m - E_{An}) \quad (1.4)$$

An explanation of the non-linear differential equations of the gating variables related to the conductances, and how they have been modified from the H-H equations, can be found in [18].

At that time there was little experimental knowledge about the role of Ca$^{2+}$ in cardiac cells, therefore, the 1962 Noble model [18] did not include a Ca$^{2+}$ current. One important change from the H-H model was that Noble described potassium (K$^+$) dynamics using two currents, a fast inward and a slow outward current, each with their own conductances ($g_{K1}$ and $g_{K2}$, respectively). The addition of a slow outward current allowed the model to reproduce the long plateau in the action potential. Unfortunately, the model was flawed because it was based on flawed experimental data [19].

As experiments became more precise and more detail was discovered about the components of cardiac cells, the cardiac models became increasingly complex. In 1975, the McAllister-Noble-Tsien model of a Purkinje cell [20] extended the Noble model to include five
more currents. They introduced a secondary inward current \( (i_{si}) \) partially carried by \( \text{Ca}^{2+} \), a transient outward chloride current \( (i_{qr}) \), replaced the outward \( K^+ \) current \( (I_{K1}) \) with two \( K^+ \) currents \( (i_{x1} \text{ and } i_{x2}) \), and replaced the single leak (anion) current with three background ionic currents: an inward current \( (i_{Na,b}) \) and two outward currents \( (i_{K1} \text{ and } i_{Cl,b}) \).

The 1985 DiFrancesco-Noble Purkinje model [21] made several important additions to the modeling of cardiac cells. Among those improvements were the addition of time-dependent intracellular \( \text{Na}^+, \text{Ca}^{2+}, \text{and } K^+ \) concentrations, time-dependent extracellular \( K^+ \) concentration, the \( \text{Na}^+-\text{K}^+ \) exchange pump current \( (i_p) \), and the \( \text{Na}^+/\text{Ca}^{2+} \) exchange current \( (i_{NaCa}) \). It also modeled the movement of \( \text{Ca}^{2+} \) through the sarcoplasmic reticulum (SR) by the SR \( \text{Ca}-\text{ATPase (SERCA)} \) from the cytosol into the network sarcoplasmic reticulum (NSR), from the NSR to the junctional sarcoplasmic reticulum (JSR) through diffusion, and release from the JSR by \( \text{Ca}^{2+} \) induced \( \text{Ca}^{2+} \) release (CICR) [19]. This description of intracellular \( \text{Ca}^{2+} \) cycling becomes particularly important in the description of cellular contraction.

1.2.2 Modeling ventricular cells

Much of the current research on cardiac cells focuses on ventricular cells. Abnormalities in ventricular action potential duration (APD) are believed to be the leading cause of fatal cardiac arrhythmias. For this reason, modeling ventricular cells has become particularly important [22].

In 1977, Beeler and Reuter introduced the first model of a cardiac ventricular cell [23]. It was based primarily on the McAllister-Noble-Tsien Purkinje cell model, using H-H type descriptions for membrane currents. Like the McAllister-Noble-Tsien Purkinje cell model, they included currents \( i_{K1}, i_{x1}, i_{Na}, i_{Ca}, \text{and } i_{s} \), however, they did not believe the experimental evidence for ventricular cells supported the existence of two more time-activated outward currents or the
dynamic chloride current, so they did not include $i_k2$, $i_x2$, or $i_cl$ in their ventricular cell model. They also omitted the $i_{Na}$ current, including its effects in the $i_s$ current [23].

As cardiac cell modeling advanced, most of the models became species and region specific. One benefit of this specificity was that modelers could attempt to better fit types of data that varied between species (such as the APD) and make more reliable model predictions for cellular behavior. Despite being designed as species specific, most models could be modified to account for differences in species data. The Luo-Rudy (L-R) ventricular cardiac action potential (AP) models from the early 1990’s marked a significant step forward [24-26]. These guinea pig myocyte models were based on an extensive amount of data, including data from single cell and single channel experiments. This allowed the authors to update existing ion current descriptions, as well as introduce additional currents. The Luo-Rudy phase 2 dynamic AP model [24, 25] included many of the processes important to intracellular Ca$^{2+}$ transients, such as the Na$^+$/Ca$^{2+}$ exchanger ($I_{NaCa}$), a non-specific Ca$^{2+}$ activated current ($I_{ns(Ca)}$), a sarcolemmal Ca$^{2+}$ pump ($I_{p(Ca)}$), buffering of Ca$^{2+}$ ions in the myoplasm and SR, and movement of Ca$^{2+}$ through the SR ($I_{up}$, $I_{r}$, $I_{leak}$, and $I_{rel}$). The inclusion of these processes allowed the dynamic L-R 2 model to incorporate variable ionic concentrations, particularly Ca$^{2+}$, which they noted could be the basis for future excitation-contraction models [24]. In addition, Luo and Rudy published their model equations so others were able to implement their model. Because of these innovations, the L-R 2 model [24, 25] has become the most used ventricular myocyte model [19].

Other models which introduced important Ca$^{2+}$ handling processes were the 1998 Jafri-Rice-Winslow (JRW) model [27] and the 1999 Winslow et al. model [28]. Among other innovations, the JRW model introduced a subspace region for local control of CICR. The
Winslow et al. model, which was the first canine model, was able to model Ca\(^{2+}\) mediated AP prolongation in tachycardia-induced heart failure [19].

The 2004 Bondarenko et al. model [29] was the first mouse ventricular cell model. Mice and rats have a significantly shorter APD than larger species, with no plateau. This difference makes the electrophysiological models of other species more difficult to adapt to the mouse, the most used species in genetic research. The Bondarenko et al. model was the first to describe the short, “triangular” AP of mice, and included both apex and septum cells. This model was also the first to simulate Ca\(^{2+}\) fluxes and describe a comprehensive Markov model for the L-type Ca\(^{2+}\) channel.

### 1.2.3 Modeling the beta adrenergic signaling system

Early cardiac cell experiments and models, such as those discussed above, focused on electrical activity and Ca\(^{2+}\) dynamics. Recently there has been a research focus on protein signaling systems such as the \(\alpha\)- and \(\beta\)-adrenergic and CaMKII-mediated signaling systems, which modulate various cell activity [16]. The \(\beta_1\)-adrenergic signaling system has been of particular note as it causes the most prominent effects on cardiac cells and is a target for pharmacological interventions such as “beta-blockers”.

Comprehensive mathematical models of the \(\beta_1\)-adrenergic system in ventricular cells have been developed for various species [16, 30-33]. The 2003 Saucerman et al. model [30] of rat ventricular myocytes was the first such model. This model included two PKA targets, phospholamban and the L-type Ca\(^{2+}\) channel. The 2004 Saucerman-McCulloch model [31] for rabbit ventricular myocytes included additional PKA targets: slow delayed rectifier K\(^+\) current (\(I_{Kr}\)), ryanodine receptors, and troponin I. The Yang-Saucerman model [33] extended the
previous Saucerman models to mouse ventricular myocytes, focusing on $\text{Ca}^{2+}$ dynamics [16], but it did not describe the effects of $\beta_1$-adrenoreceptor activation on the mouse action potential.

Heijman et al. [34] developed a canine ventricular myocyte model which included three signaling systems: the $\beta_1$- and $\beta_2$-adrenergic and the CaMKII-mediated signaling systems. This compartmentalized model included both biochemical and electrophysiological parts and was extensively verified by experimental data. Like the Heijman et al. model [34], the Bondarenko mouse ventricular myocyte model [16] is compartmentalized, containing three subcellular compartments: caveolae, extracaveolae, and cytosol. Compartmentalization is important due to the localization of the components of the various signaling systems [35-38]. The Bondarenko model [16] contains the $\beta_1$-adrenergic signaling system, but has been extended in the Rozier-Bondarenko model [39] to include the $\beta_2$-adrenergic signaling system.

1.2.4  **Modeling cardiac contraction**

The basis of our current understanding of crossbridge kinetics can be traced back at least to Huxley [40]. He proposed the sliding of two filaments, one of myosin and one of actin, to cause a contraction. He mentioned “side-pieces”, now known to be myosin heads, which could slide along the actin filament, combining temporarily with the actin filament. In his mathematical model [40] of striated muscle contraction, he included two crossbridge states, attached and detached, which he described by partial differential equations. In addition, he included the role of ATP in his model, but not $\text{Ca}^{2+}$ activation.

However, it is now understood that $\text{Ca}^{2+}$ plays an integral role in crossbridge formation in cardiac muscle cells. With the advances in the modeling of $\text{Ca}^{2+}$ transients, more physiologically accurate contraction models were able to be developed. The 1996 Negroni-Lascoano contraction model [41], while based on the Huxley model, introduced the effects of $\text{Ca}^{2+}$ kinetics and
sarcomere dynamics on crossbridge structure and mechanics. The Ca^{2+} kinetics were described by a four state system: TnC without bound Ca^{2+} (T), TnC with bound Ca^{2+} but no crossbridges (TCa), TnC with bound Ca^{2+} and crossbridges (TCa*), and TnC without bound Ca^{2+} but with crossbridges (T*).

In 1999, Rice et al. [42] examined various Markov models for tropomyosin states based on the number of crossbridges and whether Ca^{2+} was bound to TnC. States with bound Ca^{2+} were considered permissive states (P), the states without Ca^{2+} were considered nonpermissive (N) (see Fig. 1.4). The models the authors considered ranged from four to six tropomyosin states. In three of the models, transitions from N to P were modulated by a two troponin states. Using the models with multiple crossbridges, Rice et al. [42] examined the effects of various mechanisms to describe crossbridge cooperativity.

A more comprehensive model of cardiac cell contraction, which included a description of active, passive, viscous, and flexible forces was developed by Rice et al. [43] in 2008. They introduced a four-state crossbridge model that included nonpermissive and permissive states, but distinguished between weakly bound and strongly bound crossbridge states. The model reproduced multiple experimental protocols on the steady-state force-Ca^{2+} relationship, force-velocity relationship, time behavior of force and sarcomere shortening, and rate of force redevelopment, k_{tr}, as a function of normalized force. The 2008 Rice et al. model [43] was species specific for rat and rabbit ventricular myocytes.

The Mullins-Bondarenko model [44] was developed in 2013 to describe mouse ventricular myocyte contraction (see Chapter 2). The model is based on the Bondarenko et al. [29] model of action potential and Ca^{2+} dynamics in mouse ventricular myocytes, but has a simplified description of sarcomere shortening using Hooke’s law. The model describes well the
contraction of ventricular myocytes from two heart regions, the epicardium and endocardium. It
emphasizes the importance of variable sarcomere length in the description of contraction force.
The results of the model simulations fit well the experimental data on the steady-state force-$\text{Ca}^{2+}$
relationship, time course of contraction force and sarcomere shortening, and frequency
dependence of contraction force and myocyte shortening.

The effects of the $\beta_1$-adrenergic signaling system on ventricular contraction was studied
by Land et al. [45] in 2013. The authors used modifications of the model parameters from their
previous mathematical model of mouse ventricular contraction [46] to include the effects of
stimulation of the $\beta_1$-adrenergic receptors parametrically, however, the biochemical part of the
signaling system was not incorporated. The resulting model was used to simulate tension
development without and with stimulation of $\beta_1$-ARs. The authors [45] concluded that in control
their model produced realistic tension development, while upon stimulation with isoproterenol
the simulated tension was greater than that measured experimentally.

More recently, Negroni et al. [47] developed a detailed mathematical model for the
$\beta_1$-adrenergic regulation of rabbit ventricular myocyte contraction. This model was based on the
Negroni-Lascano contraction model [48] and the Soltis-Saucerman model of $\beta_1$-adrenergic
signaling in rabbit ventricular myocytes [49]. The model described the effects of activation of
$\beta_1$-ARs on the steady-state force-$\text{Ca}^{2+}$ relationship, the stiffness-frequency relationship, force-
velocity dependence, and stretch-activation of the contraction force. The authors compared the
results of their simulations to the corresponding experimental data. While the Negroni et al. model [47]
described the effects of stimulation of $\beta_1$-ARs, it had limitations in that the model
was developed based on experimental data from multiple species, including frog, guinea pig,
rabbit, ferret, cat, and mouse.
1.3 Purpose of the study

While multiple models were developed for myocyte contraction, including mouse ventricular myocyte contraction [46], the models were not investigated with respect to stimulations of different frequencies, nor did they describe the effects of cellular heterogeneity or variable sarcomere length. The existing cardiac contraction models also have a limited ability to simulate the effects of $\beta_1$-adrenergic signaling on ventricular myocyte contraction. The $\beta_1$-adrenergic contraction models were only developed for rabbit ventricular myocytes, but a model for the mouse ventricular cell, which has much shorter action potential and different Ca$^{2+}$ dynamics, was absent.

Therefore, in this dissertation, we develop two mathematical models of mouse ventricular myocyte contraction. The first model is based on a comprehensive mathematical model of the action potential and Ca$^{2+}$ dynamics in mouse ventricular myocytes [29] and addresses the questions about the effects of stimulation frequencies, variable sarcomere lengths, and cellular heterogeneity on the myocyte contraction. The second model is designed to describe the $\beta_1$-adrenergic signaling system and its effects on mouse ventricular myocyte contraction. It also simulates a broad set of the experimental protocols for measurements of steady-state force-Ca$^{2+}$ relationships, crossbridge release rate ($k_{rel}$) and force development rate ($k_{dfr}$), force-velocity relationship, and force redevelopment rate ($k_{ftr}$).
2 A SIMPLIFIED MATHEMATICAL MODEL OF THE MOUSE VENTRICULAR MYOCYTE CONTRACTION

2.1 Introduction

Cardiac cell functions include the interaction of several major subsystems, including those responsible for the generation of electrical activity, Ca\(^{2+}\) dynamics, and cardiac contraction. Experimental data from diseased hearts or obtained at fast pacing rates show that the changes in one of the subsystems can lead to abnormal behavior in others. For example, dysfunction of the L-type Ca\(^{2+}\) channel, as in Timothy syndrome when the channel’s inactivation is significantly reduced, affects Ca\(^{2+}\) handling in cardiac cells [50, 51] resulting in cardiac arrhythmias. Heterogeneities in cellular electrical activities in the heart, dysfunction of K\(^+\) channels, or acidosis can also produce pro-arrhythmic behavior, such as action potential propagation block, re-entry, Ca\(^{2+}\) alternans, and irregular contractions [52, 53]. In particular, instability of Ca\(^{2+}\) dynamics (alternans) can lead to action potential alternans [54] and alternans in mechanical contraction [55]. Therefore, understanding interactions of the major cardiac cell subsystems and mechanisms of their pro-arrhythmic activity is of great importance.

Myocyte contraction is a complex process which involves activation of ionic currents (Fig. 2.1A), including L-type Ca\(^{2+}\) current (I\(_{\text{CaL}}\)), through which Ca\(^{2+}\) enters the cell and causes Ca\(^{2+}\) release (J\(_{\text{rel}}\)) from the intracellular Ca\(^{2+}\) store, the sarcoplasmic reticulum [56]. High intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{i}\)) leads to an increase in Ca\(^{2+}\) bound by intracellular proteins (troponin, calmodulin) and changes the myofilament configuration, resulting in force development. Force generation involves conformational changes in thick (myosin) and thin (actin, tropomyosin, and troponin) filaments resulting in an increase in their overlap. Myosin represents a polypeptide chain with globular heads, which constitute crossbridges that interact
Figure 2.1 Schematic diagram of the mouse model cell and Markov model for force generation.

(A) Mouse model ionic currents and Ca\(^{2+}\) fluxes as presented by Bondarenko et al. [29]. Transmembrane currents are the fast Na\(^{+}\) current (\(I_{\text{Na}}\)), the L-type Ca\(^{2+}\) current (\(I_{\text{CaL}}\)), the sarcolemmal Ca\(^{2+}\) pump (\(I_{\text{p(Ca)}}\)), the Na\(^{+}\)/Ca\(^{2+}\) exchanger (\(I_{\text{NaCa}}\)), the rapidly recovering transient outward K\(^{+}\) current (\(I_{\text{Kto,f}}\)), the slowly recovering transient outward K\(^{+}\) current (\(I_{\text{Kto,s}}\)), the rapid delayed rectifier K\(^{+}\) current (\(I_{\text{Kr}}\)), the ultrarapidly activating delayed rectifier K\(^{+}\) current (\(I_{\text{Kur}}\)), the noninactivating steady-state voltage activated K\(^{+}\) current (\(I_{\text{Kss}}\)), the time-independent K\(^{+}\) current (\(I_{\text{K1}}\)), the slow delayed rectifier K\(^{+}\) current (\(I_{\text{Ks}}\)), the Na\(^{+}\)/K\(^{+}\) pump (\(I_{\text{NaK}}\)), the Ca\(^{2+}\)-activated chloride current (\(I_{\text{Cl,Ca}}\)), the Ca\(^{2+}\) and Na\(^{+}\) background currents (\(I_{\text{ICab}}\) and \(I_{\text{INab}}\)). \(I_{\text{stim}}\) is the external stimulation current. The Ca\(^{2+}\) fluxes within the cell are uptake of Ca\(^{2+}\) from the cytosol to the network sarcoplasmic reticulum (SR) (\(J_{\text{up}}\)), Ca\(^{2+}\) release from the junctional SR (\(J_{\text{rel}}\)), Ca\(^{2+}\) flux from the network SR (NSR) to junctional SR (JSR) (\(J_{\text{J}}\)), Ca\(^{2+}\) leak from the SR to the cytosol (\(J_{\text{leak}}\)), Ca\(^{2+}\) flux from the subspace volume to the bulk myoplasm (\(J_{\text{trs}}\)), Ca\(^{2+}\) flux to troponin (\(J_{\text{trpn}}\)). The model includes Ca\(^{2+}\) buffering by troponin and calmodulin in the cytosol and by calsequestrin in the SR. Ca\(^{2+}\), Na\(^{+}\), and K\(^{+}\) concentrations in cytosol; Na\(^{+}\) and K\(^{+}\) concentrations in extracellular space. Contraction force (\(F_{\text{contr}}\)) develops due to interaction of thin and thick filaments in the cytosol. (B) State diagram of the Markov model for the force generation in mouse cardiac myofilaments [42]. Top states describe crossbridge formation, bottom states describe Ca\(^{2+}\) binding to troponin. P0, P1, P2, and P3 are the permissive states; N0 and N1 are the nonpermissive states. TCa is Ca\(^{2+}\) bound troponin; T is unbound troponin. (Figure reproduced from [44])

Thin filaments. Thin filaments are composed of long tropomyosin polypeptide chains, on which globular actin molecules aggregate in a double-stranded helix with crossbridge binding sites. In a non-active configuration, troponin blocks crossbridge binding sites (Fig. 1.4). Upon Ca\(^{2+}\) binding to troponin, troponin-tropomyosin complex exposes crossbridge binding sites
which interact with myosin globular heads, thereby creating weak bonds. ATP molecules bound to actin release a phosphate group and transform weak bonds into strong bonds. This transformation results in a change of crossbridge conformation to a bent position and forces thick filaments to slide relative to thin filaments.

Because of the complexity of the contraction mechanism, most mathematical models use a significantly simplified description of this process [57]. They explore the Huxley two-state crossbridge model [40], extend it to a larger number of crossbridge states, and include direct and indirect interaction with troponin and variable sarcomere lengths [42, 57]. Such simplified description, for example, does not involve energy metabolism and interaction with mitochondria. The crossbridge models are further incorporated into cellular models, which include electrical activity, comprehensive Ca$^{2+}$ dynamics [43, 46, 58], and energy metabolism [59, 60].

In this chapter, we developed a new electromechanical model for mouse ventricular myocyte contraction at room temperature (298$^\circ$K, or +25$^\circ$C) [44]. We employed previously published models for action potential and Ca$^{2+}$ dynamics in mouse ventricular myocytes [29, 61-63], which were also developed for room temperature (298$^\circ$K, or +25$^\circ$C), and incorporated a myocyte contraction model from Rice et al. [42]. These models were successfully employed for simulations of proarrhythmic activities in mouse cardiac cells and tissues [62, 63]. In addition, in the Rice et al. [42] model, we implemented a simplified sarcomere length variation during twitch. We also explored the effects of heterogeneity of the electrical activity and Ca$^{2+}$ dynamics in epicardial and endocardial cells on the contraction force generation and cell shortening. The resulting model was adjusted to fit experimental data on mouse ventricular cell contraction. Our model successfully reproduces steady-state force-calcium relationships for different sarcomere lengths; time courses of the Ca$^{2+}$ transients, developed force, and cellular shortening; peak force-
frequency and cell shortening-frequency relationships; and time-to-peak force and time-to-50% force relaxation. We also investigated and emphasized the importance of using variable sarcomere lengths in models of myocyte contraction. In the simulations, we compared both the absolute value of the contraction force and cellular shortening, and their normalized dependencies to fit existing experimental data.

2.2 Methods

A mathematical model for mouse ventricular myocyte contraction is a natural extension of the Bondarenko et al. model [29] for action potential and Ca\(^{2+}\) dynamics in mouse ventricular myocytes, with model improvements from [61-63] (Fig. 2.1A), developed for room temperature (298°K, or +25°C). In this chapter, we explored mouse ventricular myocyte models from the epicardial and endocardial regions of the heart [63]. Endocardial cells have more prolonged action potentials and larger intracellular [Ca\(^{2+}\)] transients compared to epicardial cells [63]. We incorporated the Rice et al. [42] contraction model 4 in our model of electrical activity and Ca\(^{2+}\) handling [29, 61-63] (See Appendix A) and adjusted model parameters to fit experimental data on myocyte contraction obtained for room temperatures.

The Rice et al. [42] model links Ca\(^{2+}\) dynamics and myocyte contraction (Fig. 2.1B). The model contains two nonpermissive tropomyosin states (N0 and N1) and four permissive tropomyosin states (P0, P1, P2, and P3). N0, N1, P0, P1, P2, and P3 are functions of time that describe probabilities of finding the model in that particular state. N0 is the rest state of the model, with no strongly bound crossbridges. When Ca\(^{2+}\) binds to the tropomyosin, it changes its conformation to a permissive state without strongly bound crossbridges (P0), which allows for strong binding of one (P1), two (P2), or three (P3) crossbridges. The model also includes one nonpermissive state with one strongly bound crossbridge even without a bound Ca\(^{2+}\) ion (N1).
All transition rates in the model are Ca\(^{2+}\)-independent, except for \(k_{NP}\), which depends on the concentration of troponin with Ca\(^{2+}\) bound to a low-affinity binding site. Detailed analysis of several contraction models and the plausibility of different cooperative mechanisms was performed in [42]. The model which we adopted for the mouse ventricular myocyte contraction (Model 4 from [42]) gave the best fit to the existing experimental data for mice. The contraction model parameters for epicardial and endocardial cells are presented in Appendix A.

Contraction force \(F_{\text{contr}}\) (in mN/mm\(^2\)) was calculated using the equation [42]:

\[
F_{\text{contr}} = -73.26 F_{\text{contr}}^* \tag{2.1}
\]

where

\[
F_{\text{contr}} = \frac{P_1 + N_1 + 2(P_2) + 3(P_3)}{F_{\text{max}}}, \tag{2.2}
\]

\[
F_{\text{max}} = P_{1_{\text{max}}} + 2(P_{2_{\text{max}}}) + 3(P_{3_{\text{max}}}), \tag{2.3}
\]

\[
P_{1_{\text{max}}} = \frac{f_{01}(2g_{\text{min},x}) (3g_{\text{min},x})}{\Sigma}, \tag{2.4}
\]

\[
P_{2_{\text{max}}} = \frac{f_{01}f_{12} (3g_{\text{min},x})}{\Sigma}, \tag{2.5}
\]

\[
P_{3_{\text{max}}} = \frac{f_{01}f_{12}f_{23}}{\Sigma}, \tag{2.6}
\]

\[
\Sigma = (g_{\text{min},x}) (2g_{\text{min},x}) (3g_{\text{min},x}) + f_{01}(2g_{\text{min},x}) (3g_{\text{min},x}) + f_{01}f_{12} (3g_{\text{min},x}) + f_{01}f_{12}f_{23}, \tag{2.7}
\]

\[
f_{01} = 3f_{XB}, f_{12} = 10f_{XB}, f_{23} = 7f_{XB}. \tag{2.8}
\]

In equation (2.1), \(F_{\text{contr}}\) is the normalized contraction force, and the coefficient \(-73.26\) was obtained from fitting absolute values of the steady-state and dynamic experimental forces. For simulating steady-state force-calcium relationships (F-Ca\(^{2+}\)), we used fixed values of the sarcomere lengths (SL), so that \(d(\text{SL})/dt = 0\), and changed intracellular Ca\(^{2+}\) concentration. We
simulated F-Ca\textsuperscript{2+} relationships for sarcomere lengths 1.9, 2.1, and 2.3 μm. In this case, F\textsubscript{contr} has time-independent magnitude.

For simulating twitch contraction, where F\textsubscript{contr} is time-dependent, we used Hooke’s law, the linear relationship between contraction/relaxation force and cell shortening/extension:

\[ SL = 0.8F_{\text{contr}} + SL_0 \]  

(2.9)

where SL\textsubscript{0} is the initial value of SL. In this case, sarcomere length becomes a function of time.

We estimated the variable cell length by

\[ L = L_0 \times \frac{SL}{SL_0} \]  

(2.10)

where initial cell length L\textsubscript{0} = 100 μm. For all simulations in this chapter, we used extracellular Ca\textsuperscript{2+} concentration [Ca\textsuperscript{2+}]\textsubscript{o} = 2 mM.

The electromechanical cardiac cell models were stimulated with different frequencies using a stimulus current (I\textsubscript{stim} = 80 pA/pF, \(\tau\text{\textsubscript{stim}} = 0.5\) ms) for at least 200,000 ms to reach a quasi-steady state. Simulated data of intracellular [Ca\textsuperscript{2+}]\textsubscript{i} transients, myocyte contraction force F\textsubscript{contr}, and sarcomere length SL on the interval from 192,000 to 200,000 ms were compared to extensive experimental data.

The model consists of 51 ordinary differential equations and multiple model parameters (see Appendix A). Differential equations were solved by fourth-order Runge-Kutta method with time step 0.0001 ms. The model was implemented as an original Intel FORTRAN 90 code, which was run under SUSE Linux on a Dell Precision Workstation T3500 (Intel Xeon Processor W3670, 3.2 GHz, 8 GB RAM). To determine the values of the model parameters, we ran simulations and compared key characteristics of myocyte [Ca\textsuperscript{2+}]\textsubscript{i} transients and contraction force to experimental data obtained from mice. We adjusted transition rates in the Markov model for tropomyosin until our simulations fit well the experimental data from multiple laboratories.
2.3 Results

2.3.1 Steady-state force-calcium relationships

We first simulated steady-state force-calcium relationships. Both epicardial and endocardial cell models demonstrated the same simulation data for the steady-state force, as the contraction model Rice et al. [42] depends on intracellular [Ca\textsuperscript{2+}]\textsubscript{i} concentration. Figure 2.2A shows the Ca\textsuperscript{2+}-dependence of the absolute value of contraction force obtained by Prabhakar et al. [64] for two different sarcomere lengths, 1.9 and 2.3 \( \mu \text{m} \), from skinned mouse ventricular myocytes. For both cases, the force represents an increasing sigmoid function of calcium concentration. There is a relatively small increase in the saturation force from 48.8 to 57.2 mN/mm\textsuperscript{2} when sarcomere length increases by about 20%, from 1.9 to 2.3 \( \mu \text{m} \). Figure 2.2B shows simulation of the steady-state force-calcium relationships for three sarcomere lengths, 1.9, 2.1, and 2.3 \( \mu \text{m} \). Our model is able to closely reproduce the saturating value of the force for corresponding sarcomere lengths. However, there are some differences between simulated and experimental data in sensitivity to external Ca\textsuperscript{2+}, as simulated force saturates at smaller values of Ca\textsuperscript{2+} concentrations. Such differences are due to a decrease in Ca\textsuperscript{2+} sensitivity of skinned compared to intact cardiac cells [2].

Our model is also able to reproduce a shift in Ca\textsuperscript{2+} sensitivity for steady-state force-calcium relationships shown for three sarcomere lengths (Fig. 2.2D). Such a shift can be clearly seen for normalized steady-state force-calcium relationships. Simulations show that an increase in sarcomere length leads to smaller half-saturation values of Ca\textsuperscript{2+} concentrations, demonstrating an increase in Ca\textsuperscript{2+} sensitivity (Fig. 2.2D). A similar shift in Ca\textsuperscript{2+} sensitivity is also observed experimentally for mouse cardiac cells (Fig. 2.2C) [64, 65].
Figure 2.2 The steady-state force-$[\text{Ca}^{2+}]_i$ relationship.

The steady-state absolute force-$[\text{Ca}^{2+}]_i$ relationship (A and B) and the steady-state normalized force-$[\text{Ca}^{2+}]_i$ relationship (C and D). Experimental data from Prabhakar et al. [64] (SL = 1.9 and 2.3 μm) and Konhilas et al. [65] (SL = 1.95 and 2.25 μm), obtained with skinned myocytes, are shown in (A) and (C) with filled symbols; experimental data for non-skinned myocytes from [66] is shown by unfilled circles in (C) and (D). The model’s simulations at various initial sarcomere lengths (SL = 1.9, 2.1, and 2.3 μm) are shown in (B) and (D). Simulated data for both epicardial and endocardial cells are the same. (Figure reproduced from [44])

In addition to the skinned mouse ventricular myocytes, our simulation data is also compared to the available experimental data on steady-state force-calcium relationships from intact cells, shown in Fig. 2.2 C and D with unfilled circles [66]. Figure 2.2D shows that our simulations are in good agreement with the experimental data. ICa50 and Hill coefficient $h$
obtained by fitting steady-state force-calcium relationships from McCloskey et al. [66] data with the function

$$F\left(\left[Ca^{2+}\right]_i\right) = F_{\text{min}} + \frac{F_{\text{max}} - F_{\text{min}}}{1 + \left(\left[Ca^{2+}\right]_i / ICa_{50}\right)^h}$$

(2.11)

are 0.4 µM [Ca2+]i and 3.05, respectively. Fitting our simulation data gives ICa50 0.68, 0.59, and 0.49 µM [Ca2+]i; and Hill coefficients 2.30, 2.33, and 2.25, for sarcomere lengths 1.9, 2.1, and 2.3 µM, respectively.

**Table 2.1 Experimental conditions for measurements of contraction force, cell shortening, and [Ca2+]i transients and corresponding simulated conditions.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Temperature, °C</th>
<th>Sarcomere length, µm</th>
<th>[Ca2+]o-mM</th>
<th>Stimulation freq., Hz</th>
<th>[Ca2+]i indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al. [67]</td>
<td>20-22</td>
<td>2.1-2.2</td>
<td>2.0</td>
<td>0.5</td>
<td>Fura-2</td>
</tr>
<tr>
<td>Kirchhefer et al. [68]</td>
<td>Room</td>
<td>No data</td>
<td>2.0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Kogler et al. [69]</td>
<td>22-23</td>
<td>2.1-2.2</td>
<td>2.0</td>
<td>0.5</td>
<td>Fura-2</td>
</tr>
<tr>
<td>McCloskey et al. [70]</td>
<td>22</td>
<td>2.1</td>
<td>2.0</td>
<td>0.5</td>
<td>Fura-2</td>
</tr>
<tr>
<td>Stuyvers et al. [71]</td>
<td>25</td>
<td>2.0-2.1</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Fentzke et al. [72]</td>
<td>22-23</td>
<td>2.3</td>
<td>2.0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Huang et al. [73]</td>
<td>Room</td>
<td>2.3</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Jones et al. [74]</td>
<td>25</td>
<td>2.1</td>
<td>2.0</td>
<td>0.5</td>
<td>Fluo-3</td>
</tr>
<tr>
<td>Simulation, this chapter</td>
<td>25</td>
<td>2.1</td>
<td>2.0</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Table reproduced from [44]

### 2.3.2 Dynamic behavior of contraction force

To test the ability of our model to reproduce time behavior of the contraction force developed by mouse ventricular myocytes, we first stimulated the model cells with a constant frequency of 0.5 Hz. The time course of force in epicardial and endocardial cell simulations is plotted in Fig. 2.3A by red solid and dashed lines, respectively. As endocardial cells show larger [Ca2+]i transients than epicardial cells, we obtained that the former develops stronger contraction force and larger shortening than the latter. The time behavior of the contraction forces obtained experimentally is shown by black solid lines with symbols [67, 69-71]. There are significant
Figure 2.3 Contraction force, myocyte shortening, and [Ca\textsuperscript{2+}].

The time course force (in mN/mm\textsuperscript{2}) (A) and normalized force (B) simulated by the model for epicardial (red solid lines) and endocardial (red dashed lines) cells are compared with experimental data from Stuyvers et al. [71], Gao et al. [67], Kirchhefer et al. [68], Kogler et al. [69], and McCloskey et al. [70]. (C) Normalized shortening as a function of time. Simulation data is shown by red solid (epicardial cell) and red dashed (endocardial cell) lines, experimental data from Fentzke et al. [72] and Huang et al. [73] are shown by lines with symbols. (D) Normalized [Ca\textsuperscript{2+}] transients as functions of time. The model simulation (red solid and red dashed lines for epicardial and endocardial cells, respectively) is compared to experimental data from Gao et al. [67], Jones et al. [74], Kogler et al. [69], and McCloskey et al. [70] (lines with symbols). For comparison, the initial sarcomere length in the model simulation is set to 2.1 µm, extracellular [Ca\textsuperscript{2+}] concentration is 2 mM, and the frequency is 0.5 Hz, the frequency used most in the experimental data (see Table 2.1). (Figure reproduced from [44])

differences in the experimental data obtained from different experimental groups on the time behavior of force, both in peak values and residual forces (Table 2.1). Comparison of the time behavior of normalized simulated and experimental forces, both for epicardial and endocardial
cells, shows a clear similarity in the time-to-peak values and relaxation of the simulated forces (Fig. 2.3B) [67-71].

Our model includes changes in sarcomere length during myocyte contraction. The time behavior of normalized sarcomere shortening for simulated cells is shown in Fig. 2.3C by red solid and dashed lines for epicardial and endocardial cells, respectively. The models did not show large differences in time-to-peak shortening and relaxation times. They closely reproduced myocyte shortening obtained in different experiments with mice (solid lines with symbols in Fig. 2.3C) [72, 73]. For comparison of the time scales of contraction force and Ca\textsuperscript{2+} dynamics, we also plotted the time courses of the simulated and experimental intracellular Ca\textsuperscript{2+} transients by red lines and black solid lines with symbols in Fig. 2.3D, respectively. In each case, there is a delay in force development following the peak of the Ca\textsuperscript{2+} transient (compare times to peaks in Fig. 2.3 B and D).

### 2.3.3 Force-frequency relationships

In order to investigate force-frequency relationships, we also stimulated model cells with different frequencies ranging from 0.25 to 2.0 Hz. Frequency dependencies of intracellular Ca\textsuperscript{2+} transients, contraction force, and cell shortening are shown in Fig. 2.4. Our simulated peak [Ca\textsuperscript{2+}]-frequency relationship (red solid and dashed lines in Fig. 2.4A) is within the variability of experimental data (solid lines with symbols in Fig. 2.4A) [70, 71, 75, 76]. Note that the simulated amplitudes of [Ca\textsuperscript{2+}]\textsubscript{i} transients for epicardial and endocardial cells are verified by the experimental data obtained by Dilly et al. [77] (Fig. 2.4D). The models were able to reproduce peak contraction force-frequency relationships for mouse ventricular myocytes in the frequency range from 0.5 to 2.0 Hz (Fig. 2.4B). The experimental data shows biphasic behavior of the peak force, with a decrease from 0.25 to 0.5-1.0 Hz, followed by an increase from 1.0 to 2.0 Hz [70],
Figure 2.4 Stimulation frequency dependence.

(A) Peak [Ca\(^{2+}\)]. (B) Peak force. (C) Cell shortening. The simulation data is shown by red solid (epicardial cell) and red dashed (endocardial cell) lines. The modeling results are compared to data from Ito et al. [75, 76] (A), McCloskey et al. [70] (A and B), and Huang et al. [73] (C). The initial SL for the simulation is 2.1 µm. (D) Experimental (black bars [77]) and simulated (gray bars) intracellular [Ca\(^{2+}\)] transients obtained for epicardial and endocardial cells at stimulation frequency 1 Hz. (Figure reproduced from [44])

with a clear minimum in force-frequency relationships (however, see data of Ito et al. [76] where the minimum is less apparent). Our model reproduced such biphasic behavior of the force-frequency relationships for epicardial cells. Peak contraction force for endocardial cells increases with stimulation frequency.

Finally, we were able to simulate peak lengthening-frequency relationships (red lines in Fig. 2.4C). While some experimental data shows consistent decrease in cellular shortening
Figure 2.5 Time course of the contraction force, sarcomere length, and percentage of shortening for epicardial and endocardial cells for different sarcomere lengths.

Simulations with different resting sarcomere lengths (SL0 = 1.9, 2.1, and 2.3 μm) show a significant difference in the magnitude of the contraction force (A, D), sarcomere length (B, E) and percentage of sarcomere length shortening (C, F). The stimulation frequency for each simulation is 1 Hz. Simulations are performed for epicardial (A, B, C) and endocardial (D, E, F) cells. (Figure reproduced from [44])
with frequency [73], other data follows biphasic behavior [75, 76] (solid lines with symbols in Fig. 2.4C). Our modeling data demonstrates biphasic behavior in cell shortening for epicardial cells, which is consistent with the biphasic behavior of the contraction force and \([\text{Ca}^{2+}]_i\) transients (red solid lines in Fig. 2.4 A, B and C). Model endocardial cells show only an increase in cell shortening as well as in \([\text{Ca}^{2+}]_i\) (red dashed lines in Fig. 2.4 A and C, respectively).

Simulated time courses for contraction forces, sarcomere lengths, and sarcomere shortenings for three different resting sarcomere lengths (1.9, 2.1, and 2.3 \(\mu\)m) for epicardial and endocardial cells are shown in Fig. 2.5. As seen from the figure, an increase in the resting sarcomere length increases twitch force and relative sarcomere shortening. Similar behavior is also observed experimentally and from simulation of others [43, 46]. At comparable sarcomere lengths, the endocardial cells develop larger contraction force and sarcomere shortening than the epicardial cells (Fig. 2.5).

### 2.3.4 Constant versus variable sarcomere length

While steady-state simulations show that peak force is dependent on the initial sarcomere length, there is also a dynamic relationship between force and sarcomere length. Our models use a variable SL when calculating the transition rate from non-permissive to permissive states, as well as in the detachment rates in permissive states. To see the effect of using a variable SL in the transition rate equations, we ran simulations in which a constant SL replaced the variable SL in the calculation of the normalized sarcomere length

\[
SL_{\text{norm}} = \frac{SL - 1.3\mu m}{2.3\mu m - 1.3\mu m}
\]

(2.12)

which is used in the detachment rates and transition rates in the Markov model (Fig. 2.1B)

\[
g_{10SL} = g_{xSL}, \quad g_{21SL} = 2g_{xSL}, \quad g_{32SL} = 3g_{xSL}
\]

(2.13)
\[ k_{NP} = k_{PN} \left( \frac{\left[ \text{LTRPNCa} \right]}{\text{LTRPNCa}_{\text{half}}} K_{\text{half}} \right)^{Ntm}, \]  
\[ g_{\text{hSL}} = g_{\text{minch}} \left( 2 - \left( SL_{\text{norm}} \right)^{1.6} \right), \]  
\[ K_{\text{half}} = \frac{1}{1 + \frac{K_{Ca}}{1.5 \mu M - SL_{\text{norm}} \times 1.0 \mu M}}, \]  
\[ Ntm = 5 + 3 SL_{\text{norm}}, \]

where \( K_{Ca} = k_{-\text{trpn}}/k_{\text{trpn}}^+, \) and the constants can be found in Appendix A.

Figure 2.6A shows force development in epicardial cells at a stimulation rate of 1 Hz in the simulation using a constant SL (dashed line) versus the simulation using a variable SL (solid line) (see also Fig. 2.6B). Data for endocardial cells displays similar behavior and is shown in Fig. 2.6 C and D. The peak force when using a constant SL is clearly higher, while the residual force appears to be about the same. However, simulations run at various frequencies show that the peak and residual force when using a constant SL (Fig. 2.7E) is always higher than corresponding forces when a variable SL is used (Fig. 2.7C). Even though there is a difference in the magnitude of force, the frequency dependence of peak force when using a constant SL (black dashed line in Fig. 2.7F) is similar to the frequency dependence when a variable SL is used (black solid line in Fig. 2.7F). For comparison, Fig. 2.7 B and D show simulated data on cell shortening and contraction force at different stimulation frequencies for endocardial cells, using variable sarcomere length (data on constant SL is not shown). As seen from the figures, both peak contraction force and cell shortening are larger for the endocardial cells than the epicardial cells. In both cases, constant and variable SL, we observed a decrease in time-to-peak and time to 50% relaxation rate for the contraction force with an increase of stimulation frequency starting
Figure 2.6 The effects of constant and variable sarcomere lengths on the contraction force development and myocyte shortening.

(A) Force development for the models with variable (solid line) and constant (dashed line) sarcomere lengths. Changing the SL from variable to a constant (B, D) does not change \([\text{Ca}^{2+}]\) transients, but changes contraction force (A, C). The initial SL for each simulation is 2.1 \(\mu\)m with a stimulation frequency of 1 Hz. Simulation data shows an increase in force, both for epicardial (A) and endocardial (C) cells, when variable SL is replaced by constant SL. (Figure reproduced from [44])

from 0.5 Hz. A similar increase in the residual contraction force at the larger stimulation frequencies is also observed experimentally [78].

2.3.5 Frequency dependence of \(dL/dt\) and \(dF/dt\)

The frequency dependencies of the peak force and cell shortening are shown in Fig. 2.4. As might be expected, \(dL/dt\) and \(dF/dt\) also showed frequency dependence. Simulated time
Figure 2.7 The effects of stimulation frequency on the time behavior of sarcomere length and contraction force for epicardial and endocardial cells.

The time courses of the SL (A and B) and contraction force (C, D, and E) over a four second interval are shown at different stimulation frequencies for epicardial (A, C, and E) and endocardial (B and D) cells. The simulation data with constant SL is shown only for epicardial cells, as the data for endocardial cells is similar. The frequency dependence of force for an epicardial cell when a variable SL parameter is used is not as pronounced as the frequency dependence of force when a constant SL parameter is used (C and E). The initial SL for each simulation is 2.1 µm, but the residual force for higher frequencies leads to significant shortening (A and B). Frequency dependence of peak force for epicardial and endocardial cells with variable SL and for epicardial cell with constant SL is shown in (F). (Figure reproduced from [44])
courses for dL/dt (Fig. 2.8 A and B) and dF/dt (Fig. 2.8 C and D) are shown for various frequencies from 0.25 Hz to 4.0 Hz, both for epicardial (Fig. 2.8 A and C) and endocardial (Fig. 2.8 B and D) cells. A negative dL/dt value indicates cell shortening during a contraction, while a positive dL/dt corresponds to relaxation. A positive dF/dt indicates the increase in force during a contraction, while a negative dF/dt corresponds to relaxation. The epicardial cell demonstrated a monotonic increase in the magnitudes of peak values for dL/dt and dF/dt in the frequency range from 0.25 to 4 Hz (Fig. 2.8 A and C). In contrast, the endocardial cell showed biphasic behavior in the peak magnitudes of the derivatives: an increase when the stimulation frequency changes from 0.25 to 2 Hz, and a decrease in the frequency range from 2 to 4 Hz (Fig. 2.8 B and D).

The frequency relationship for +dL/dt_{max} (solid lines) and −dL/dt_{max} (dashed lines) is shown in Fig. 2.9A. Both values showed biphasic behavior. For the epicardial cell, +dL/dt_{max} and −dL/dt_{max} decreased at stimulation frequencies from 0.25 to 0.5 Hz, and then increased for stimulation frequencies up to 4 Hz. For the endocardial cell, +dL/dt_{max} and −dL/dt_{max} increased at stimulation frequencies from 0.25 to 2 Hz, and then decreased for stimulations frequencies up to 4 Hz. When compared to the experimental data, our model tended to show, on average, peak contraction rates approximately equal to experimental data (open symbols). However, the model showed somewhat slower relaxation, thus lower values of +dL/dt_{max}, than experimental data (solid symbols) [73, 79, 80].

Figure 2.9B shows the frequency relationship for +dF/dt_{max} (solid lines) and −dF/dt_{max} (dashed lines). As with corresponding values for +dL/dt_{max} and −dL/dt_{max}, the +dF/dt_{max} and −dF/dt_{max} showed biphasic behavior for both epicardial and endocardial cells.

To compare experimental and simulated data quantitatively, we plotted experimental and simulated results on time-to-peak and time-to-50% relaxation of the contraction force and
Figure 2.8 Time behavior of $\frac{dL}{dt}$ and $\frac{dF}{dt}$ for different stimulation frequencies.

Simulated time course of the rates of cellular shortening $\frac{dL}{dt}$ (A, B) and contraction force $\frac{dF}{dt}$ (C, D) during twitches for epicardial (A, C) and endocardial (B, D) cells. For epicardial cells, the largest values of $\pm \frac{dL}{dt_{\text{max}}}$ and $\pm \frac{dF}{dt_{\text{max}}}$ are observed at a relatively fast stimulation frequency of 4 Hz (solid lines in (A) and (C)). For endocardial cells, the largest values of $\pm \frac{dL}{dt_{\text{max}}}$ and $\pm \frac{dF}{dt_{\text{max}}}$ occur in the frequency interval from 1 to 4 Hz (dashed lines in (B) and (D)). (Figure reproduced from [44])

intracellular $[\text{Ca}^{2+}]$ transients in Fig. 2.10. Simulated data are shown for both epicardial and endocardial cells (black and red, respectively, in Fig. 2.10 B and D). Simulated data for time-to-peak force showed good agreement with the experimental data (compare Fig. 2.10 B and A), while time-to-50% relaxation were somewhat longer in the simulated data than those obtained in the experiments (compare Fig. 2.10 D and C). Experimental data for time-to-peak and time-to-50% relaxation of $[\text{Ca}^{2+}]$ transients were somewhat longer than those from simulations, but the
Figure 2.9 Frequency dependence of $dL/dt_{\text{max}}$ and $dF/dt_{\text{max}}$.

(A) The simulated frequency dependencies of $(+dL/dt)_{\text{max}}$ (solid lines) and $(-dL/dt)_{\text{max}}$ (dashed lines). Experimental data from Chu et al. [80], Flagg et al. [79], and Huang et al. [73] are shown by symbols. We consider $(-dL/dt)$ to correspond to cell shortening. (B) The simulated frequency dependence of $(+dF/dt)_{\text{max}}$ (solid lines) and $(-dF/dt)_{\text{max}}$ (dashed lines). We consider $(+dF/dt)$ to correspond to contraction. The initial SL for the simulations in (A) and (B) is 2.1 µm. Data for epicardial and endocardial cells are shown in black and red, respectively. (Figure reproduced from [44])

50% relaxation of $[Ca^{2+}]_i$ transients were somewhat longer than those from simulations, but the simulated time-to-50% relaxations approached the experimental values at larger frequencies. Epicardial and endocardial cells showed similar simulated values for time-to-peak and time-to-50% relaxation of $[Ca^{2+}]_i$ transients, and for time-to-50% relaxation of contraction force. However, there were moderate differences between the cells for time-to-peak of the contraction force (Fig. 2.10B).
2.4 Discussion

In this chapter, we developed a new model for mouse ventricular myocyte contraction. This model is based on previously published models for epicardial and endocardial cells [29, 61-63], which include a comprehensive description of action potential, ionic currents, and Ca\(^{2+}\) dynamics. For a description of myocyte contraction, we adopted Model 4 developed by Rice \textit{et al.} [42] by fitting experimental data on contraction for mice.

Figure 2.10 Time-to-peak and time-to-50% relaxation of the contraction force and [Ca\(^{2+}\)]\text{\textsubscript{i}} transients as function of stimulation frequency.

Experimental (A) and simulated (B) frequency dependencies of time-to-peaks for intracellular [Ca\(^{2+}\)]\text{\textsubscript{i}} transients and contraction force, and experimental (C) and simulated (D) frequency dependencies of time-to-50% relaxations for intracellular [Ca\(^{2+}\)]\text{\textsubscript{i}} transients and contraction force. Experimental data are obtained by Gao \textit{et al.} ([67], triangles) and Ramirez-Correa \textit{et al.} ([81], circles). Unfilled and filled symbols are used for intracellular [Ca\(^{2+}\)]\text{\textsubscript{i}} transients and contraction force, respectively. Simulation data for contraction force and intracellular [Ca\(^{2+}\)]\text{\textsubscript{i}} transients are shown by solid and dashed lines, respectively, and data for epicardial and endocardial cells are shown in black and red, respectively. (Figure reproduced from [44])
Mice demonstrate much faster heartbeats than many other species. Their contraction rate is about 10 beats per second [82], which is, for example, faster than the rabbit (4 Hz, [83]) and human (1 Hz, [84]) heart contraction rates. In addition, the action potential duration in mouse ventricular myocytes is also much shorter (APD50 ~ 4.5 ms in mice [29] versus ~200 ms in rabbits [43] and ~300-400 ms in humans [85]). These differences suggest different time characteristics for contraction in mouse, compared to human or rabbit, ventricular myocytes.

In a mouse cardiac cell, at moderate stimulation rates, an increase in action potential is followed by an increase in [Ca\textsuperscript{2+}]; and a delayed increase in force. The peak value of Ca\textsuperscript{2+} transient occurs after almost complete repolarization of action potential. In addition, peak contraction force appears after a significant decline of [Ca\textsuperscript{2+}]. Our model replicates this relationship. Figure 2.11 shows normalized values for epicardial action potential (solid line), [Ca\textsuperscript{2+}]; (dashed line), and force (dotted line) over a 0.5 second interval for a simulation at 1 Hz. In larger species, such as rabbit, time scaling of the action potential, [Ca\textsuperscript{2+}]; and contraction force transients is different (Fig. 9 in [43]). For rabbits, [Ca\textsuperscript{2+}]; transient, in significant part, overlaps with the action potential and contraction force transient, while the peak sequence is the same as in mice.

Mouse ventricular myocytes, unlike other species, demonstrate biphasic frequency dependence of intracellular [Ca\textsuperscript{2+}]; transient and peak force [70, 71] (however, see data of Ito et al. [76] where biphasic behavior is less apparent). Stuyvers et al. [71] suggested a qualitative mechanism which explains this biphasic behavior based on frequency-dependent Ca\textsuperscript{2+} dynamics. The minimum occurs at the crossroad of the descending frequency trend of the Ca\textsuperscript{2+} load into the sarcoplasmic reticulum during diastole and ascending trend in Ca\textsuperscript{2+} entry into the cell through L-type Ca\textsuperscript{2+} channels. They used a simplified description of Ca\textsuperscript{2+} dynamics for mouse ventricular
Figure 2.11 Scaling action potential, \([\text{Ca}^{2+}]_i\), transient, and force in the model for mouse ventricular myocyte contraction.

The simulation used an initial SL of 2.1 µm and a stimulation frequency of 1 Hz. In mouse ventricular myocytes, \(\text{Ca}^{2+}\) transient develops after action potential repolarization is almost complete. After that, the contraction force develops with time delay due to \(\text{Ca}^{2+}\) binding to troponin and troponin-induced changes in contractile proteins. (Figure reproduced from [44])

myocytes. Our model for an epicardial cell, which includes a comprehensive description of the electrical activity and \(\text{Ca}^{2+}\) dynamics in mouse ventricular myocytes during cell twitch, was also able to reproduce this physiological phenomenon. In our model, myocyte contraction force is related to \(\text{Ca}^{2+}\) dynamics through the Markov model for crossbridge kinetics. While both peak \([\text{Ca}^{2+}]_i\) transients and peak contraction force show minimum values as functions of stimulation frequency, these minimum frequency values are slightly different (Fig. 2.4). This trend is also confirmed by the experimental data of McCloskey et al. [66].

However, our model for the endocardial cell does not show biphasic behavior in the frequency-dependence of both peak \([\text{Ca}^{2+}]_i\) transients and peak contraction force. There is also some experimental data in which non-monotonic increase in peak \([\text{Ca}^{2+}]_i\) transients and myocyte shortening in mice is less apparent: even saturation and decrease in myocyte shortening amplitude at relatively large stimulation frequencies occurred [76]. Our model for the endocardial cell, at least qualitatively, reproduced saturation and even decrease in sarcomere
shortening and contraction force amplitude at 4 Hz stimulation (Fig. 2.7 B and D). This effect can be explained by the larger peak and diastolic values of [Ca\(^{2+}\)] transients in endocardial cells compared to epicardial cells, which shift the operation interval of intracellular Ca\(^{2+}\) towards a smaller slope in force-calcium relationships (Fig. 2.2D).

While there are no specific experimental studies of contraction force and cell shortening in mouse epicardial and endocardial ventricular myocytes, there are a few studies of the differences in action potentials and Ca\(^{2+}\) handling in these cells [77, 86]. The studies show that the endocardial cells demonstrate significantly larger [Ca\(^{2+}\)] transients, and our modeling predicts larger contraction force and shortening in these ventricular myocytes.

Our electromechanical model for mouse ventricular myocyte contraction includes a variable sarcomere length during cell contraction, the effect that occurs in most experiments. Simulations with variable sarcomere length produced significantly smaller contraction force than the simulations with constant sarcomere length despite the same time course and amplitude of [Ca\(^{2+}\)] transient during twitch. This suggests the importance of the inclusion of cell shortening in the model for cardiac myocyte contraction. Note that a similar result was obtained with a more complex model of Rice et al. [43], developed for rabbit ventricular myocytes, who also studied the effects of variable and fixed sarcomere length on the force development.

Several models for cardiac myocyte contraction have been developed to date [42, 43, 46, 58, 60] (see also review [57]). Earlier models did not include sarcomere shortening during twitch [42, 58, 60]. They are primarily focused on simplification of the description of crossbridge kinetics, their dependence on Ca\(^{2+}\) dynamics, and careful reproduction of the existing experimental data on steady-state and dynamic force-calcium relationships. Most of these models have limitations due to this and other simplifications.
Rice et al. [42] investigated five Markov models describing contraction mechanisms in cardiac myocytes. Two of the models consisted of four tropomyosin states and transitions between them (N0, N1, P0, and P1, see Fig. 2.1B). These models differed by the mechanisms of modulation of the transition rates (in Fig. 2.1B they are defined as $k_{NP}$ and $k_{PN}$). In Model 1, rates $k_{NP}$ and $k_{PN}$ were independent of the developed force, while in Model 2 the rates depended on the developed force. In both models, Ca$^{2+}$ binding to troponin directly affected tropomyosin shifting, i.e., rates $k_{NP}$ and $k_{PN}$. Model 3 included an indirect connection of the Ca$^{2+}$ binding to troponin and tropomyosin shifting, as shown by dashed arrows in Fig. 2.1B (see also [42]), and only four states (N0, N1, P0, and P1). Models 4 and 5 were extended to up to three crossbridge bindings, which resulted in four permissive tropomyosin states, P0, P1, P2, and P3, (Fig. 2.1B and [42]). The only difference between Models 4 and 5 was the modulation of the $k_{\text{impn}}$ rate by generated force. Because Model 4 and Model 5 yielded an approximately equal description of myocyte contraction, we implemented Model 4 in our electrophysiological model, as Model 5 led to unstable solutions.

Our model of mouse ventricular myocyte contraction also has some limitations due to the simplification of the biophysical mechanism of contraction. In particular, the model uses a simplified description of the relationships between contraction force and cellular shortening in the form of Hooke’s law, while the real dependence is more complicated [43]. It does not describe the effects of cellular shortening on Ca$^{2+}$ transients, as does the 2008 model of Rice et al. [43]; however, this effect is relatively small. Also, our model, as most other models, does not take into account intracellular spatial inhomogeneities of Ca$^{2+}$ concentration and crossbridge binding sites.
Nevertheless, despite the limitations, our electromechanical model of mouse ventricular myocyte contraction was extensively verified by experimental data obtained for mice. It reproduced reasonably well a significant amount of the existing experimental data. The model can be used for cells from two different regions of the heart (epicardium and endocardium). As with most other models, it uses a simplified description of the contraction force generation. We employed a six-state Markov model for tropomyosin dynamics and separate Ca$^{2+}$ binding to troponin to describe force development. More comprehensive models will be necessary to develop a better simulation of more extended experimental data sets.

For supporting information, see the model summary in Appendix A.
3 A MATHEMATICAL MODEL OF β1-ADRENERGIC REGULATION OF MOUSE VENTRICULAR MYOCYTE CONTRACTION

3.1 Introduction

Multiple experimental protocols have been developed to study mechanisms of cardiac myocyte contraction and isolate the stages of this process. These include measurements of steady-state force-calcium relationships, the crossbridge release rate ($k_{rel}$), force development rate ($k_{df}$), force-velocity relationship, and force redevelopment rate ($k_{tr}$), which were performed with skinned cardiac cells [15, 87, 88]. In addition, frequency and isoproterenol dependencies for $[\text{Ca}^{2+}]_i$ transients, total contraction force, and sarcomere shortening were measured with non-skinned cardiac cells [67, 70, 75, 76, 81, 89-95].

Cardiac myocyte contraction is modulated by the β1-adrenergic signaling system and its components, the activation of which significantly increases contraction force, sarcomere shortening, and speeds up contraction relaxation [91, 92]. Experimental data demonstrate that it is the phosphorylation of two contractile proteins, TnI and MyBP-C, that causes the major effects of β1-adrenoreceptor activation on myocyte contraction [15, 87]. While the experimental investigations have led to the development of mathematical models that allow for detailed description of myocyte contraction, only a few models include the effects of activation of β1-adrenergic signaling. Land et al. [45] used modifications of their model parameters to include the effects of stimulation of the β1-adrenergic receptors, however, there was no detailed description of the biochemical reactions involved in the β1-adrenergic signaling system. More recently, a detailed mathematical model was developed for the β1-adrenergic regulation of rabbit ventricular myocytes [47] that included modeling of biochemical reactions. However, the model gave qualitative, rather than quantitative, agreement with the experimental data, perhaps because...
the model was developed based on data from multiple species, including mice, which have a significantly different repolarization mechanism and different Ca\textsuperscript{2+} dynamics.

In this chapter, we developed a new comprehensive mathematical model of the β\textsubscript{1}-adrenergic regulation of mouse ventricular myocyte contraction, which was verified by experimental data obtained from mice. Our model is based on a model of the β\textsubscript{1}-adrenergic signaling system in mouse ventricular cells [16] and models for myocyte contraction [42-44]. In this new model, we incorporated phosphorylation of MyBP-C, as well as the effect of phosphorylation of TnI and MyBP-C on crossbridge attachment and detachment rates and on the viscosity coefficient. With the resulting model, we were able to simulate major experimental protocols without and with stimulation of the β\textsubscript{1}-adrenergic signaling system. These protocols included measurements of steady-state force-calcium relationships, force-velocity relationship, and rates k\textsubscript{rel}, k\textsubscript{df}, and k\textsubscript{fr}. We also simulated frequency and isoproterenol dependencies for [Ca\textsuperscript{2+}]\textsubscript{i} transients, total contraction force, and sarcomere shortening. The fit of the simulations to the experimental data suggests that the increased contraction force and myocyte shortening upon stimulation of β\textsubscript{1}-ARs is primarily due to the increased [Ca\textsuperscript{2+}]\textsubscript{i} transients and phosphorylation of TnI and MyBP-C resulting from activation of the β\textsubscript{1}-adrenergic signaling system. The new mathematical model can also be modified to simulate ventricular myocyte contraction in genetically modified mice modeling chronic cardiac diseases.

3.2 Methods

3.2.1 Model development

To develop this model, we modified the Bondarenko model [16], which describes action potential, Ca\textsuperscript{2+} dynamics, and the biochemical part of the β\textsubscript{1}-adrenergic signaling system (Fig. 3.1), to include active contraction force from [42, 44], passive and flexible contraction forces
from [43], and modified viscous force based on the description by Rice et al. [43]. A detailed description of the Bondarenko model is given elsewhere [16, 96]. In this chapter we focused on the model development for myocyte contraction.

Our mathematical model is based exclusively on experimental data obtained from mice. During model development we used data from multiple laboratories so that our model would fall within the range of an “average” set of experimental data. Due to the modular structure of the original Bondarenko model [16], we were able to add modules for MyBP-C phosphorylation and myocyte contraction without affecting the parameters for existing modules. First we added the MyBP-C module, and fit parameters to experimental data for MyBP-C phosphorylation. Next we added the contraction module, and fit parameters to match experimental contraction data for control conditions. As we simulated new protocols (described in the remainder of Section 3.2) and compared the results to the corresponding experimental data, we were able to identify the contributions of active, passive, viscous, and flexible force and refine the parameters accordingly. To account for changes in contraction characteristics due to stimulation of the β1-adrenergic system, we introduced factors to adjust several rates and constants due to TnI and MyBP-C phosphorylation. We repeated the parameter fitting process for the contraction module, focusing only on parameters for the introduced factors. When experimental data was available for the independent effects of TnI versus MyBP-C phosphorylation in a particular protocol, we adjusted the parameters accordingly; otherwise we adjusted the parameters such that TnI and MyBP-C affected the rate equally.

### 3.2.2 Active contraction force

The active force portion of the model is based on force generated from crossbridges. We used our previous Markov model of six tropomyosin states (see Chapter 2, Fig. 2.1B), with
modifications of the rate constants and the equation for active contraction force. Time behavior of the tropomyosin states is described by the same differential equations as in Chapter 2 [44]. These equations and the contraction model parameters are presented in Appendix B.

Figure 3.1 Schematic diagram of the β₁-adrenergic regulation of the mouse ventricular myocyte contraction.

The model cell contains three intracellular compartments in the β₁-adrenergic signaling system: caveolae, extracaveolae, and cytosol. The subspace volume (Vₙs) is located in the caveolae domain. Transmembrane currents are the time-independent K⁺ current (Iₖ₁), the L-type Ca²⁺ current (IₐCa₂⁺,cav and IₐCa₂⁺,ecav), the fast Na⁺ current (IₐNa), the Na⁺/K⁺ pump [IₐNaK, regulated by phospholemman(PLM)], the ultrarapidly activating delayed rectifier K⁺ current (IₐKur), the rapidly recovering transient outward K⁺ current (IₐKto,f), the sarcolemmal Ca²⁺ pump (Iₚ(Ca)), the noninactivating steady-state voltage activated K⁺ current (IₐKs), the Na⁺/Ca²⁺ exchanger (IₐNaCa), the Ca²⁺-activated chloride current (IₐCl₂Ca), the Ca²⁺ and Na⁺ background currents (IₐCa and IₐNa). The Ca²⁺ fluxes within the cell are uptake of Ca²⁺ from the cytosol to the network sarcoplasmic reticulum (NSR) by the SERCA pump (Jₚ(Ca)) and the Ca²⁺ release from the junctional sarcoplasmic reticulum (JSR) through the ryanodine receptors (RyRs) (Jₚ(Ca)). The components of the β₁-adrenergic signaling system are the β₁-adrenergic receptors (β₁-AR); α- and βγ-subunits of stimulatory G-protein (Gs and Gβγ); G-protein-coupled receptor kinase of type 2 (GRK2); adenylyl cyclases of type 5/6 or 4/7 (AC₅/₆ or AC₄/₇, respectively); cyclic AMP (cAMP); regulatory (R) and catalytic (C) subunit of protein kinase A (PKA) holoenzyme; phosphodiesterases of type 2, 3, or 4 (PDE₂, PDE₃, or PDE₄, respectively); inhibitor-1 (I₁); protein kinase A inhibitor (PKI); and protein phosphatases of type 1 and 2A (PP₁ and PP₂A). Stimulatory links are shown by black arrows and inhibitory links are shown by red dashed lines with circles. The contractile proteins are actin; myosin; myosin binding protein C (MyBP-C); troponin I, C and T (Tnl, TnC and TnT, respectively); and tropomyosin (Tm). They are localized in the cytosolic compartment. Two of these (Tnl and MyBP-C) are substrates of the β₁-adrenergic signaling system.
Active contraction force $F_{\text{contr}}$ (in mN/mm²) was calculated using the equation:

$$F_{\text{contr}} = 58.0 \frac{F_{\text{contrn}}}{F_{\text{max}}}, \quad (3.1)$$

where

$$F_{\text{contrn}} = \frac{P1 + N1 + 2(P2) + 3(P3)}{F_{\text{max}}}, \quad (3.2)$$

$$F_{\text{max}} = P1_{\text{max}} + 2(P2_{\text{max}}) + 3(P3_{\text{max}}), \quad (3.3)$$

$$P1_{\text{max}} = \frac{f_{01}(2g_{min,xb})(3g_{min,xb})}{\Sigma}, \quad (3.4)$$

$$P2_{\text{max}} = \frac{f_{01}f_{12}(3g_{min,xb})}{\Sigma}, \quad (3.5)$$

$$P3_{\text{max}} = \frac{f_{01}f_{12}f_{23}}{\Sigma}, \quad (3.6)$$

$$\Sigma = (g_{min,xb})(2g_{min,xb})(3g_{min,xb}) + f_{01}(2g_{min,xb})(3g_{min,xb}) + f_{01}f_{12}(3g_{min,xb}) + f_{01}f_{12}f_{23}, \quad (3.7)$$

$$f_{01} = 15f_{XB}, f_{12} = 30f_{XB}, f_{23} = 7f_{XB}. \quad (3.8)$$

In equation (3.1), $F_{\text{contrn}}$ is the normalized contraction force, and the coefficient 58.0 was obtained from fitting absolute values of the steady-state and dynamic experimental forces.

Experimental data show that active contraction force is regulated by Ca²⁺ transients and activation of the β₁-adrenergic signaling system. Two major proteins are involved in the force modulation, TnI and MyBP-C. Activation of β₁-ARs results in an increased level of phosphorylation of TnI and MyBP-C which changes the transition rates between tropomyosin states.

TnI phosphorylation is described by a differential equation developed by Bondarenko [16]:

$$\frac{df_{Tnl,p}^{\text{cyt}}}{dt} = \frac{k_{Tnl-PKA} \cdot [C]^{\text{cyt}} \cdot (1 - f_{Tnl,p}^{\text{cyt}})}{K_{Tnl-PKA} + (1 - f_{Tnl,p}^{\text{cyt}})} - \frac{k_{Tnl-PP2A} \cdot [PP2A]^{\text{cyt}} \cdot f_{Tnl,p}^{\text{cyt}}}{K_{Tnl-PP2A} + f_{Tnl,p}^{\text{cyt}}}, \quad (3.9)$$
where \( f^{\text{cyt}}_{\text{TnI}_{p}} \) is the fraction of phosphorylated TnI, \( k_{\text{TnI}_{pPKA}} \) is the rate of TnI phosphorylation by PKA, \( k_{\text{TnI}_{PP2A}} \) is the rate of TnI dephosphorylation by PP2A, \( K_{\text{TnI}_{PKA}} \) is the relative affinity for TnI phosphorylation by PKA, \( K_{\text{TnI}_{PP2A}} \) is the relative affinity for TnI dephosphorylation by PP2A, \([C]^{\text{cyt}}\) is the cytosolic concentration of catalytic subunit of PKA, and \([PP2A]^{\text{cyt}}\) is the cytosolic concentration of protein phosphatase of type 2A (see Appendix B).

Similarly, we describe phosphorylation of MyBP-C by the following differential equation:

\[
\frac{df^{\text{cyt}}_{\text{MyBP-C}_{p}}}{dt} = \frac{k_{\text{MyBP-C}_{PKA}} \cdot [C]^{\text{cyt}} \cdot (1 - f^{\text{cyt}}_{\text{MyBP-C}_{p}})}{K_{\text{MyBP-C}_{PKA}} + (1 - f^{\text{cyt}}_{\text{MyBP-C}_{p}})} - \frac{k_{\text{MyBP-C}_{PP}} \cdot ([PP1]^{\text{cyt}} + [PP2A]^{\text{cyt}}) \cdot f^{\text{cyt}}_{\text{MyBP-C}_{p}}}{K_{\text{MyBP-C}_{PP}} + f^{\text{cyt}}_{\text{MyBP-C}_{p}}},
\] (3.10)

where \( f^{\text{cyt}}_{\text{MyBP-C}_{p}} \) is the fraction of phosphorylated MyBP-C, \( k_{\text{MyBP-C}_{PKA}} \) is the rate of MyBP-C phosphorylation by PKA, \( k_{\text{MyBP-C}_{PP}} \) is the rate of MyBP-C dephosphorylation by PP1 and PP2A, \( K_{\text{MyBP-C}_{PKA}} \) is the relative affinity for MyBP-C phosphorylation by PKA, \( K_{\text{MyBP-C}_{PP}} \) is the relative affinity for MyBP-C dephosphorylation by PP1 and PP2A, and \([PP1]^{\text{cyt}}\) is the cytosolic concentration of protein phosphatase of type 1, (see Appendix B).

Model parameters for equation (3.10) were adjusted to fit experimental data on phosphorylation of MyBP-C. Figure 3.2A demonstrates simulated and experimental increases of phosphorylation levels of MyBP-C due to an activation of \( \beta_1 \)-ARs. Experimental data [97-99] show a significant level of phosphorylation of MyBP-C (~55-60%) without stimulation of \( \beta_1 \)-ARs, which is in line with our modeling value of 57.5% phosphorylation. Upon activation of \( \beta_1 \)-ARs, the experimental phosphorylation level of MyBP-C increased 1.65-1.8 fold [97-99], which is close to our simulated 1.64 fold. In addition, we simulated kinetics of MyBP-C
phosphorylation, shown in Fig. 3.2B. Our simulation data fits well the experimental data of Verduyn et al. [99].

![Figure 3.2 MyBP-C phosphorylation levels.](image)

(A) Maximum MyBP-C phosphorylation levels of model simulations and experimental data [97-99] without (Control) and with (PKA) β₁-adrenergic stimulation. Values have been normalized to control values for comparison. Simulation data was obtained by stimulation with 10 μM isoproterenol to achieve maximum effect. (B) The time-course of MyBP-C phosphorylation by fold increase. The model simulation was obtained by stimulation with 10 μM isoproterenol (shown by the solid line) and is compared to experimental data from Verduyn et al. [99] (shown by symbols).

Activation of the β₁-adrenergic system increases detachment rates and decreases attachment rates. In our model this effect is accomplished by the modulation of rate constants, \( f_{XB} \) and \( g_{minxb} \), using the level of phosphorylation of TnI and MyBP-C, as shown below:

\[
f_{XB} = f_{XB0} \left( 1 + 0.45 \left( f^{cyst}_{TnI,p} - 0.364 \right) \right)^{-1} \left( 1 + 1.5 \left( f^{cyst}_{MyBP_C,p} - 0.575 \right) \right)^{-1}, \tag{3.11}
\]

\[
g_{minxb} = g_{minxb0} \left( 1 + 0.3 \left( f^{cyst}_{TnI,p} - 0.364 \right) \right) \left( 1 + 1.0 \left( f^{cyst}_{MyBP_C,p} - 0.575 \right) \right), \tag{3.12}
\]

where the numbers 0.364 and 0.575 reflect the unstimulated phosphorylation levels of TnI and MyBP-C, respectively, and \( f_{XB0} \) and \( g_{minxb0} \) are given in Appendix B.

### 3.2.3 Passive contraction force

Passive contraction force is similar to that developed by Rice et al. [43]. It includes titin- and collagen-related components:
\[
F_{\text{passive}}(SL) = F_{\text{titin}}(SL) + F_{\text{collagen}}(SL),
\]

where

\[
F_{\text{titin}}(SL) = \begin{cases} 
PCon_{\text{titin}} \left( \exp \left( PExp_{\text{titin}}(SL - SL_{\text{rest}}) \right) - 1 \right) & \text{if } SL \geq SL_{\text{rest}} \\
-PCon_{\text{titin}} \left( \exp \left( PExp_{\text{titin}}(SL_{\text{rest}} - SL) \right) - 1 \right) & \text{if } SL < SL_{\text{rest}} 
\end{cases}
\] (3.14)

\[
F_{\text{collagen}}(SL) = \begin{cases} 
PCon_{\text{collagen}} \left( \exp \left( PExp_{\text{collagen}}(SL - SL_{\text{collagen}}) \right) - 1 \right) & \text{if } SL \geq SL_{\text{collagen}} \\
0 & \text{if } SL < SL_{\text{collagen}} 
\end{cases}
\] (3.15)

Constants in Eqs. (3.14) and (3.15) are given in Appendix B.

Because experimental data by Najafi et al. [100] shows that passive contraction force is very weakly modulated by PKA, and the magnitude of the passive force is relatively small compared to the active force, we did not include the effects of stimulation of β\textsubscript{1}-ARs on the passive force in this model.

### 3.2.4 Viscous force

In our model, we implemented viscous force, which contains two terms, one with linear and one with quadratic dependence on the sarcomere shortening velocity \( v \):

\[
F_{\text{visc}} = -v \cdot \text{visc} \cdot \left( 1 - a_{\text{fx}} \cdot v \right),
\]

where \( v \) is the linear viscosity coefficient and \( a_{\text{fx}} \) is the additional parameter responsible for nonlinearity.

This form of the viscous force can be derived from the Hill equation relating force and muscle velocity [101] (see Appendix C for details):

\[
(v + b)(F + a) = b(F_0 + a).
\] (3.17)

Solution of this equation with respect to \( F/F_0 \) gives:
In equation (3.18), the numerator is a linear function of $v$, which reflects a decrease in $F/F_0$ with shortening velocity. The term $v/b$ in the denominator changes this behavior to hyperbolic.

Experimental data on the dependence of shortening velocity on the relative force for mice [88] demonstrates that the deviation from linearity is quite small, which suggests that the ratio $v/b$ in the denominator is also small. Using the Taylor expansion of the denominator, we obtain:

$$
\frac{F}{F_0} \approx \left(1 - \frac{av}{bF_0}\right)\left(1 - \frac{v}{b}\right).
$$

Equation (3.19) can be presented in the form

$$
\frac{F}{F_0} \approx 1 - \left(\frac{a}{bF_0} + \frac{1}{b}\right)v + \left(\frac{a}{b^2F_0}\right)v^2,
$$

which includes both linear and quadratic dependence of the force on the muscle shortening velocity, which was implemented in our model.

Experimental data by Sadayappan et al. [88] also shows that the shortening velocity increases upon stimulation of the $\beta_1$-adrenergic signaling system. To simulate these effects, we implemented modulation of $visc$ and $a_{fx}$ by phosphorylated fractions of TnI and MyBP-C:

$$
visc = visc_0 \left(1 + 0.33\left(f_{TnI,p}^{cryt} - 0.364\right)\right)^{-1} \left(1 + 1.1\left(f_{MyBPC,p}^{cryt} - 0.575\right)\right)^{-1},
$$

$$
a_{fx} = a_{fx0} \left(1 + 0.2\left(f_{TnI,p}^{cryt} - 0.364\right)\right)^{-1} \left(1 + 0.6\left(f_{MyBPC,p}^{cryt} - 0.575\right)\right)^{-1},
$$

in which parameters were obtained to fit the experimental data by Sadayappan et al. [88] ($visc_0$ and $a_{fx0}$ are given in Appendix B).
3.2.5 **Flexible force**

We used the expression of the flexible forces as proposed by Rice *et al.* [43]

\[
F_{\text{flex}} = KSE (SL - SL_0),
\]

(3.23)

where parameter KSE = 1.0.

3.2.6 **Sarcomere shortening**

Unlike our Chapter 2 model, where sarcomere shortening was calculated using Hooke’s law and active contraction force only, sarcomere (SL) shortening in this model is described using Newton’s second law represented in the form of two first-order differential equations:

\[
\frac{dv}{dt} = \frac{F_{\text{contr}} + F_{\text{passive}} + F_{\text{visc}} + F_{\text{flex}}}{\text{mass}},
\]

(3.24)

\[
\frac{dSL}{dt} = -v.
\]

(3.25)

Here, \( \text{mass} \) is the model parameter related to sarcomere mass.

3.2.7 **Method of simulation**

The cardiac cell model was stimulated with different frequencies using a stimulus current \((I_{\text{stim}} = 80 \text{ pA/pF}, \tau_{\text{stim}} = 1.0 \text{ ms})\) for at least 300,000 ms to reach a quasi-steady state. Simulated data of intracellular \([\text{Ca}^{2+}]_i\) transients, myocyte contraction force, and sarcomere length SL on the interval from 296,000 to 300,000 ms were compared to extensive experimental data.

The model consists of 150 ordinary differential equations (see Appendix B), which were solved by the fourth-order Runge-Kutta method. In order to decrease computing time, the differential equations for four “fast” variables \([\text{Ca}^{2+}]_{\text{ss}}\) and RyR states \(P_{O1}, P_{C1p},\) and \(P_{O1p}\) were solved with a time step of 0.000002 ms, but the differential equations for all remaining variables were solved with two different time steps. The 0.000002 ms time step was used during the first 10 milliseconds after the initiation of the stimulus current, but a larger time step, 0.0001 ms, was
used otherwise. For the force-velocity simulations with isoproterenol and frequency dependence simulations with isoproterenol, all time steps were decreased by a factor of 10. The model was implemented as an original Intel FORTRAN 90 code, which was run under SUSE Linux on a Dell Precision Workstation T3500 (Intel Xeon Processor W3670, 3.20 GHz, 8 GB RAM).

3.3 Results

We used several mathematical models as templates for the development of our model of the $\beta_1$-adrenergic regulation of mouse ventricular myocyte contraction. These included a model of the $\beta_1$-adrenergic signaling system in mouse ventricular cells [16] and models for myocyte contraction [42-44]. The resulting model allowed for simulation of major experimental protocols designed for studying cardiac myocyte contraction without and with stimulation of the $\beta_1$-adrenergic signaling system.

Experimental data demonstrated that the phosphorylation of two contractile proteins, TnI and MyBP-C, cause the major effects of $\beta_1$-AR stimulation on cardiac myocyte contraction [15, 102]. The Bondarenko model of the $\beta_1$-adrenergic signaling system in mouse ventricular myocytes [16] included a description of phosphorylation of TnI, as it was involved in the modulation of Ca$^{2+}$ dynamics. In the current model, we developed equations to describe phosphorylation of MyBP-C (see Appendix B). Figure 3.2 shows simulated and experimental data on MyBP-C phosphorylation upon stimulation of the $\beta_1$-adrenergic signaling system. Experimental data shows that the MyBP-C phosphorylation level increased 1.6-1.8 fold after application of PKA. Our model replicated this increase well when stimulated with a maximum concentration (10 $\mu$M) of isoproterenol (Fig. 3.2A). In addition, we were able to simulate the time course of MyBP-C phosphorylation, which is shown in Fig. 3.2B. Simulated phosphorylation kinetics are consistent with the experimental data from Verduyn et al. [99].
The first protocol we simulated using our model was the steady-state active force-[Ca$^{2+}$]$_i$ relationship for differing SL lengths (Fig. 3.3). Sarcomeres with a larger resting length show both an increase in absolute force and an increase in [Ca$^{2+}$]$_i$ sensitivity. These increases can be seen in both the experimental data and model simulations (Fig. 3.3 A and B, respectively). Our simulations model well the maximum absolute force for a 2.3 µm sarcomere, but the reduction in maximum force for shorter sarcomeres is not as large as the experimental data for Prabhakar et al. [64]. Figure 3.3 C and D show the normalized force-[Ca$^{2+}$]$_i$ relationship. The experimental
data for Prabhakar et al. [64] and Konhilas et al. [65], which are from skinned myocytes, show a lower \([\text{Ca}^{2+}]_i\) sensitivity than the model simulations. However, the \([\text{Ca}^{2+}]_i\) sensitivity in our model matches well the data for McCloskey et al. [66], which are from non-skinned myocytes. In addition, our model matches well the experimental increase in \([\text{Ca}^{2+}]_i\) sensitivity when sarcomere length increases. The ratio of half-activation \([\text{Ca}^{2+}]_i\) concentrations estimated from the experimental data by Prabhakar et al. [64] is equal to 1.31 when sarcomere length changes from 1.9 to 2.3 \(\mu\)m. The ratio estimated from the experimental data by Konhilas et al. [65] is equal to 1.29 when sarcomere length changes from 1.95 to 2.25 \(\mu\)m. Our simulations give the ratio 1.33 when sarcomere length changes from 1.9 to 2.3 \(\mu\)m, which is close to the experimental ratios (Fig. 3.3 C and D).

Activation of the \(\beta_1\)-adrenergic signaling system decreases \([\text{Ca}^{2+}]_i\) sensitivity of the active force. Experimental data for the normalized force-[\(\text{Ca}^{2+}]_i\), relationship without and with activation with PKA (Fig. 3.4A) show this decrease in \([\text{Ca}^{2+}]_i\) sensitivity. The experimental ratio of the half-activation \([\text{Ca}^{2+}]_i\) values for the active force with and without application of PKA is estimated as 1.47±0.05 (mean±SE) based on the experimental data sets [15, 72, 88, 103, 104]. Experimental data were obtained for the sarcomere lengths ranging from 2.1 to 2.3 \(\mu\)m. Our corresponding simulated half-activation \([\text{Ca}^{2+}]_i\) ratios obtained upon stimulation with and without 10 \(\mu\)M isoproterenol are equal to 1.66, 1.51, and 1.36 for sarcomere lengths 1.9, 2.1, and 2.3 \(\mu\)m, respectively (Fig. 3.4B).

Our model was able to reproduce a second experimental protocol: stretch-activated force kinetics in response to a small (~1%) stretch of the sarcomere (Fig. 3.5). This protocol was designed to determine two critical rates, \(k_{rel}\) and \(k_{df}\), that characterize contraction force [87]. The rate \(k_{rel}\) characterizes the rate of crossbridges detachment during phase 2 and the rate \(k_{ar}\)
Figure 3.4 The effect of β1-adrenergic stimulation on the normalized steady-state force-[Ca2+]i relationship.

(A) Experimental data for controls are shown with solid lines and symbols. Experimental data using stimulation with PKA are shown with dashed lines and unfilled symbols [15, 88, 103, 104]. (B) Model simulations without and with β1-adrenergic stimulation (10 µM isoproterenol) are shown with solid and dashed lines, respectively. The model replicates the decrease in calcium sensitivity, which results from β1-adrenergic stimulation. Simulated sarcomere length is 2.1 µm.

represents the rate of the force development after the stretch (phase 3 in Fig. 3.5B) [87]. To simulate this experiment, we first applied a [Ca2+]i to achieve about 50% of maximum active force. Then, at time moment 3000 ms, we stretched the sarcomere length by 1%, from 2.1 µm to 2.12 µm. To simulate the crossbridge detachment during abrupt stretch, we multiplied parameter g_{minxb} by the factor

\[ 1 + 1.4 \exp[-(t - 3000.0)(1 + 0.3(f_{TnI,p}^{cyt} - 0.364))(1 + 1.0(f_{MyBP-C,p}^{cyt} - 0.575))/6.0]. \]

This factor determines an abrupt increase in the g_{minxb} rate at t = 3000 ms that decreases exponentially in time with characteristic time constant 6.0 ms to ensure almost complete crossbridges detachment within approximately 20 ms. In addition, this time constant is modulated by phosphorylation of TnI and MyBP-C, as it is observed experimentally.

As a result of this stretch, the force sharply increased (phase 1) and decreased (phase 2), and then redeveloped to a larger steady-state value (phase 3) (Fig. 3.5 A and B). This kind of behavior is also observed experimentally [87]. In the experiments, application of PKA resulted in
an increase of both $k_{rel}$ and $k_{df}$. Our simulations were able to reproduce these changes (dashed lines in Fig. 3.5 A and B). Simulated and experimental values of $k_{rel}$ and $k_{df}$ without and with stimulation of the $\beta_1$-adrenergic signaling system are shown in Fig. 3.5 C and D. Our model reproduced well the rate of crossbridge detachment $k_{rel}$ in stimulated and unstimulated cardiac cells (Fig. 3.5C), as well as the rate of force development $k_{df}$ in the stimulated cell; however, the simulated value of $k_{df}$ in the unstimulated cell was lower than the experimental value (Fig. 3.5D).

**Figure 3.5 The stretch activation protocol.**

In this protocol, contraction force was activated by 0.361 and 0.545 µM of [Ca$^{2+}$], for control and 10 µM isoproterenol, respectively, which approximately corresponds to ~50% of the maximum active force. Then the sarcomere was stretched by 1% of its length from the 3rd to 5th seconds. (A) The simulated time courses of the absolute force without and with $\beta_1$-adrenergic stimulation are shown with solid and dashed lines, respectively. Initial sarcomere length is 2.1 µm. (B) Time behavior of the force as fraction of pre-stretched force. (C) The simulated (black bars) crossbridge release rate $k_{rel}$ without (Control) and with (PKA) stimulation of $\beta_1$-adrenergic signaling system is compared to the experimental data Stelzer et al. [87] (gray bars). (D) The simulated (black bars) force development rate $k_{df}$ without (Control) and with (PKA) stimulation of $\beta_1$-adrenergic signaling system is compared to the experimental data Stelzer et al. [87] (gray bars).
The third major experimental protocol we simulated with our model was a force-velocity protocol. In this protocol, the active force was first maximally activated with 2 µM of [Ca$^{2+}$]$_i$. At 1000 ms the [Ca$^{2+}$]$_i$ was changed to simulate an afterload ranging from 0.0 to 1.0 of the maximum force. The afterload force was increased from 0.0 to 1.0 of the maximum force in 0.1 steps during successive trials. The velocity of sarcomere shortening was determined on the interval from 1005 to 1020 ms, where the change in sarcomere length is approximately linear as a function of time. Figure 3.6 A and B show the changes in sarcomere length during the force-velocity protocol as a function of time for the afterload forces from 0.0 to 1.0 of the maximum force for control conditions (Fig. 3.6A) and after stimulation with 10 µM isoproterenol (Fig. 3.6B). It can be seen that isoproterenol accelerated sarcomere shortening at all values of afterload force. The comparison of the simulated and experimental sarcomere shortening velocity at different afterloads without and with stimulation of the β$_1$-adrenergic signaling system is shown in Fig. 3.6C. The simulated data fit well the experimental data obtained by Sadayappan et al. [88] for mouse ventricular myocytes. In addition, the model was able to reproduce the experimental data on the effects of PKA on the cardiac muscle power output defined as the product of the force and the sarcomere shortening velocity [88] (Fig. 3.6D).

Finally, we simulated ventricular myocyte behavior during a fourth major experimental protocol, one which determines the rate of force redevelopment, k$_{fr}$. For this purpose, the myocyte was activated with different concentrations of [Ca$^{2+}$]$_i$ from 0.1 to 8.0 µM. The cell was first held at a sarcomere length of 2.1 µm for 2000 ms. At time moment 2000 ms the sarcomere length was reduced to the steady-state sarcomere length for that [Ca$^{2+}$]$_i$ concentration. After 20 ms, the sarcomere was stretched back to 2.1 µm. The time course of force was then fitted with an exponential function to obtain k$_{fr}$. (The steady-state sarcomere length for each [Ca$^{2+}$]$_i$)
Figure 3.6 The force-velocity protocol.

The time courses of SL are shown during the force-velocity protocol without and with beta adrenergic stimulation (A and B, respectively). During this protocol, the active force was maximally activated with 2 µM of [Ca\textsuperscript{2+}]. The afterload force was changed from 0.0 to 1.0 of the maximum force in 0.1 steps at 1000 ms. The velocity of sarcomere shortening is determined on the interval from 1005 to 1020 ms, where the change in sarcomere length is approximately linear as a function of time. The force-velocity relationship (C) and power output (D) from the model simulations (shown by lines) are compared to data from Sadayappan et al. [88] (shown by symbols). Model simulations without and with \( \beta_1 \)-adrenergic stimulation are shown in (C) and (D) by solid and dashed lines, respectively. Experimental data without and with \( \beta_1 \)-adrenergic stimulation are shown by filled and unfilled symbols, respectively.

was obtained by a separate simulation of the model behavior for 4000 ms at that [Ca\textsuperscript{2+}].) Figure 3.7 shows the absolute and normalized values of \( k_r \) as functions of the relative force, which was determined by [Ca\textsuperscript{2+}]\textsubscript{i} concentration. Experimental data shows that \( k_r \) increased with relative force up to a maximum value both without and with application of PKA. Application of PKA
increased the magnitudes of $k_{tr}$ at all relative forces. Our simulations reproduced these dependencies in general. Simulations of $k_{tr}$ without $\beta_1$-adrenergic stimulation demonstrated good agreement with the experimental data. However, our simulations with $\beta_1$-adrenergic stimulation by 10 $\mu$M isoproterenol showed somewhat higher values for $k_{tr}$.

**Figure 3.7 $k_{tr}$ and normalized $k_{tr}$ values as a function of relative force.**

The $k_{tr}$ and normalized $k_{tr}$ values are shown as a function of relative force (A and B, respectively) without and with $\beta_1$-adrenergic stimulation (solid and dashed lines, respectively). The myocyte was activated with different concentrations of [Ca$^{2+}$]$_i$ from 0.1 to 8.0 $\mu$M. At time moment 2000 ms the sarcomere length was reduced from 2.1 $\mu$m to the steady-state value for a given [Ca$^{2+}$]$_i$ concentration for 20 ms and then stretched back to 2.1 $\mu$m. Time course of the force was fitted with an exponential function to obtain $k_{tr}$. Model simulations without and with stimulation with 10 $\mu$M isoproterenol are shown in red. Experimental data without and with PKA stimulation [15, 105] are shown in black with filled and unfilled symbols, respectively.

To investigate the effects of $\beta_1$-adrenergic stimulation on [Ca$^{2+}$]$_i$ transients, total contraction force, and sarcomere shortening, we simulated electrical stimulation of the ventricular myocyte model with $I_{stim} = 80$ pA/pF and $\tau_{stim} = 1.0$ ms at 1 Hz without and with application of 1 $\mu$M isoproterenol (Fig. 3.8). Simulations showed a significant increase in the magnitude of [Ca$^{2+}$]$_i$ transients, total contraction force, and sarcomere shortening after stimulation of $\beta_1$-adrenoceptors (Fig. 3.8 A-C). In addition, they showed faster rates of activation and relaxation. We compared the increases of model cell activities stimulated at 0.5 Hz to experimental data obtained at stimulation frequencies ranging from 0.5 to 4.0 Hz (Fig. 3.8 D-F).
Figure 3.8 Time course of \([\text{Ca}^{2+}]_i\), contraction force, and sarcomere length.

The simulated time course of \([\text{Ca}^{2+}]_i\) (A), contraction force (B), and sarcomere length (C) without and with \(\beta_1\)-adrenergic stimulation by 1 \(\mu\text{M}\) isoproterenol are shown by solid and dashed lines, respectively. The simulated increases in peak \([\text{Ca}^{2+}]_i\) (D), peak force (E), and percentage shortening (F) resulting from \(\beta_1\)-adrenergic stimulation are compared to experimental data \([89, 92, 94, 95, 102, 106, 107]\) without and with \(\beta_1\)-adrenergic stimulation. The values for \([\text{Ca}^{2+}]_i\) and force are normalized to control peak values. The model stimulation frequency for (A), (B), and (C) is 1 Hz. The model stimulation frequency for (D), (E), and (F) is 0.5 Hz. Experimental measurements were obtained at 0.5 Hz for Brickson \textit{et al.} \[102\] and Nakayama \textit{et al.} \[92\]; 1 Hz for Wang \textit{et al.} \[107\]; 2 Hz for Despa \textit{et al.} \[106\] and Ackers-Johnson \textit{et al.} \[89\]; and 4 Hz for Vandecasteele \textit{et al.} \[95\] and Takimoto \textit{et al.} \[94\].
Upon activation of the $\beta_1$-adrenergic signaling system, simulated $[\text{Ca}^{2+}]_i$ transients increased by 2.7 fold, while the increases in the experimental data ranged from 1.9 to 5.8 fold (Fig. 3.8D). Similarly, the simulated increase in the total force was 4.1, which is similar to the experimental data, which ranged from 2.3 to 3.5 fold (Fig. 3.8E). Finally, our model showed an increase in fractional sarcomere shortening from 3.6% to 14.0% before and after application of 1 $\mu$M isoproterenol, respectively. Simulation data with $\beta_1$-adrenergic stimulation is in line with the experimental data (ranging from 12.2% to 17.5%), but sarcomere shortening for control is somewhat smaller than in this set of experimental data (6.7% to 8.6%). Better agreement was obtained with another set of experimental data for control (ranging from 2.3% to 5.5% at 0.5 Hz, Fig. 3.9B), but those experiments did not include measurements of the effects of $\beta_1$-adrenergic stimulation.

Our model reproduced quite well the frequency dependencies of the peak $[\text{Ca}^{2+}]_i$ transients, peak total force, and sarcomere shortening (Fig. 3.9). Both simulations and experimental data showed bi-phasic frequency dependence of $[\text{Ca}^{2+}]_i$ transients (Fig. 3.9A). Simulations of the peak force demonstrated biphasic behavior, as well; however, some experimental data showed bi-phasic frequency dependence with saturation in contraction force at frequencies from 2 to 4 Hz (Fig. 3.9B). Finally, our simulations of sarcomere shortening showed tri-phasic behavior as stimulation frequency increased from 0.25 to 4.0 Hz (Fig. 3.9C). These simulation results are close to the experimental data in terms of shortening magnitude, but some experimental data demonstrated only bi-phasic dependencies.

Finally, we simulated the behavior of peak $[\text{Ca}^{2+}]_i$ transients, peak total force, and sarcomere shortening as functions of isoproterenol (Fig. 3.10). Our simulations showed a somewhat larger increase in peak $[\text{Ca}^{2+}]_i$ transients with isoproterenol concentration than the
Figure 3.9 Frequency dependence of peak \([\text{Ca}^{2+}]_i\), peak force, and cell shortening.

The simulated frequency dependence of peak \([\text{Ca}^{2+}]_i\) (A), peak force (B), and cell shortening (C) (shown in red) are compared to experimental data [67, 70, 75, 76, 81, 90-92, 94] (shown in black). The initial SL for the model simulation is 1.9 \(\mu\text{m}\).

Experimental values (Fig. 3.10A). However, we have only one experiment available in which isoproterenol dependence of peak \([\text{Ca}^{2+}]_i\) transients was measured; other experimental data obtained specifically at 1 \(\mu\text{M}\) isoproterenol shows better agreement with our simulations (Fig. 3.8D). Our simulation of the isoproterenol dependence of peak force is also quite close to the experimental data (Fig. 3.10B), taking into account the accuracy of the force measurements. Simulated sarcomere shortening is within the range of the experimental data (Fig. 3.10C).
Figure 3.10 Isoproterenol dependence of peak $[\text{Ca}^{2+}]_i$, peak force, and cell shortening.

The simulated isoproterenol dependence of peak $[\text{Ca}^{2+}]_i$ (A), peak force (B), and cell shortening (C) (shown in red) are compared to experimental data [89, 91-95] (shown in black). The values for peak $[\text{Ca}^{2+}]_i$ (A) and peak force (B) are normalized to control values. The initial SL for the model simulation is 1.9 $\mu$m with a stimulation frequency of 0.5 Hz. Experimental measurements were obtained at 0.5 Hz for Nakayama et al. [92], Kirchhefer et al. [91] and Ramirez-Correa et al. [93]; 2 Hz for Ackers-Johnson et al. [89]; and 4 Hz for Takimoto et al. [94] and Vandecasteele et al. [95].

Thus, in this chapter, we developed a new mathematical model of the $\beta_1$-adrenergic regulation of mouse ventricular myocyte contraction that was able to simulate major experimental protocols on measurements of steady-state force-calcium relationships, crossbridge release rates ($k_{rel}$) and force development ($k_{df}$), force-velocity relationship, and force...
redevelopment (ktr). It also reproduced quite well frequency and isoproterenol dependencies for [Ca^{2+}]_i transients, total contraction force, and sarcomere shortening.

3.4 Discussion

3.4.1 Recent progress in mathematical modeling of cardiac myocyte contraction

Mathematical modeling of cardiac myocyte contraction has a long history. Multiple cardiac contraction models have been developed since the early work of Huxley [40]. The most popular models were developed by Negroni and Lascano [41], Rice et al. [42], and Rice et al. [43]. Many of these are implemented in cellular contraction models that include a description of action potential and Ca^{2+} dynamics.

The 1999 Rice et al. model [42] was implemented in several cardiac cellular models, including one for guinea pig ventricular myocytes [58] and one for mouse ventricular myocytes [44]. The 2000 Rice et al. model [58] focused mostly on modeling short-term interval-force relations, which was found to result from the interplay of the ryanodine receptor adaptation and the SR Ca^{2+} load, with additional contributions of the membrane currents and myofilament activation. Mullins and Bondarenko [44] adopted Rice et al. [42] Model 4 to simulate mouse ventricular myocyte contraction with the inclusion of sarcomere shortening. They were able to reproduce steady-state force-Ca^{2+} relationships, dependence of contraction force on the sarcomere length, time course of contraction force and myocyte shortening, and frequency dependence of contraction force and myocyte shortening. The 2008 Rice et al. model [43] was implemented in rat and rabbit ventricular myocyte models, and in a canine ventricular myocyte model by Campbell et al. [108].

Our new mathematical model of mouse ventricular myocyte contraction synthesizes several previously developed models of mouse ventricular myocytes [16, 96] and cardiac
myocyte contraction [42-44]. We used a recent mouse ventricular myocyte model that includes descriptions of action potential, Ca\(^{2+}\) dynamics, and the \(\beta_1\)-adrenergic signaling system [16, 96] to incorporate a modified three-crossbridge model from Rice et al. [42], and passive and flexible forces from Rice et al. [43]. In this paper, we also proposed a new description of viscous force that includes both linear and nonlinear viscosity. The resulting model reproduced quantitatively major experimental data on ventricular myocyte contraction obtained from mice.

### 3.4.2 The effects of \(\beta_1\)-adrenergic stimulation on cardiac cell contraction

Experimental data demonstrates that activation of the \(\beta_1\)-adrenergic signaling system results in stronger active contraction force, decrease in Ca\(^{2+}\)-sensitivity of the steady-state force-Ca\(^{2+}\) relationship, and accelerated force development and relaxation [89, 103]. These effects are mostly due to phosphorylation of troponin I and myosin binding protein C, which affect Ca\(^{2+}\) sensitivity of the contraction force, crossbridge attachment and detachment rates, viscosity, rate of force redevelopment, and the power of cardiac output [88, 105].

Previously, a mathematical model of the \(\beta_1\)-adrenergic regulation of the rabbit ventricular myocyte contraction was developed [47], which was based on the contraction model of Negroni and Lascano [48] and the Soltis-Saucerman model of \(\beta_1\)-adrenergic signaling [49]. The model described the effects of \(\beta_1\)-adrenergic stimulation on myocyte contraction mostly qualitatively, to demonstrate the direction of its effects rather than their magnitude. In addition, the simulation data were compared not only to those obtained from rabbit cardiac cells, but also from ventricular myocytes of other species [47].

Our mathematical model of the \(\beta_1\)-adrenergic regulation of the mouse ventricular myocyte contraction was developed based on data obtained from a single species (mouse). We simulated major experimental contraction protocols for measurements of steady-state force-
calcium relationships, crossbridge release rate \( (k_{rel}) \) and force development rate \( (k_{df}) \), force-velocity relationship, and force redevelopment rate \( (k_{tr}) \). Most of the simulation data compares quite well with the experiments (e.g., steady-state force-Ca\(^{2+}\) relationship, force-velocity relationship, power output as a function of the relative force). Our model implements the effects of \( \beta_1 \)-adrenergic signaling through the phosphorylation of TnI and MyBP-C, and their effects on the transition rates between tropomyosin states and on viscous force. These modulations allowed for the simulation of all experimental protocols described in this study.

### 3.4.3 Model limitations

Although our mathematical model of the \( \beta_1 \)-adrenergic regulation of mouse ventricular myocyte contraction describes well a number of experimental protocols, it has several limitations. One limitation is that we used the model of an epicardial ventricular cell, however, the experimental data used for the model development does not discriminate between the epicardial and endocardial cell types. We also used data obtained from different laboratories which varied significantly in the magnitude of force, Ca\(^{2+}\) sensitivity, and sensitivity to isoproterenol. Lastly, in our model we only implemented the \( \beta_1 \)-adrenergic signaling system, which can potentially interact with \( \beta_2 \)-adrenergic and CaMKII-mediated signaling systems.

For supplemental information, see the model summary in Appendix B.
4 CONCLUSIONS

Thus, in this dissertation, we developed two mathematical models of mouse ventricular myocyte contraction. The first model was based on a comprehensive model of the action potential and Ca\textsuperscript{2+} dynamics in mouse ventricular myocytes that is not modulated by the \(\beta_1\)-adrenergic signaling system. In the model, we used a simplified description of the contraction force and sarcomere shortening. The resulting model fit well experimental data on steady-state force-calcium relationships, dependence of the contraction force on the sarcomere length, time course of the contraction force and myocyte shortening, frequency dependence of the contraction force and cellular contraction, and experimentally measured derivatives of the myocyte length variation. We emphasized the importance of the inclusion of variable sarcomere length into a model for ventricular myocyte contraction, and we investigated the differences in contraction force and cell shortening for epicardial and endocardial ventricular myocytes.

The second, more comprehensive mathematical model of the mouse ventricular myocyte contraction included regulation of the contraction by the \(\beta_1\)-adrenergic signaling system through phosphorylation of troponin I and myosin binding protein C. The model was based on experimental data obtained from mice and described well major experimental protocols on ventricular contraction (steady-state force-Ca\textsuperscript{2+} relationship, stretch-activated force development, force-velocity relationship, power output as a function of relative force, the rate of force redevelopment as a function of relative force, the effects of isoproterenol on the magnitude of contraction force and sarcomere shortening, and frequency and isoproterenol-dependence of contraction force and sarcomere shortening). The model can be used as a template for mathematical models of \(\beta_1\)-adrenergic regulation of contraction in other cell types and cells from other species, as well as for the interpretation of experimental data obtained from mice.
REFERENCES


APPENDICES

Appendix A  Chapter 2 Model Summary

Membrane Potential

\[
\frac{dV}{dt} = -\frac{1}{C_m} (I_{CaL} + I_{p(Ca)} + I_{NaCa} + I_{CaH} + I_{Na} + I_{NaK} + I_{Kto,f} \\
+ I_{Kto,s} + I_{K1} + I_{Ks} + I_{Kur} + I_{Kss} + I_{Kr} + I_{Cl,Ca} - I_{stim})
\]  

(A.1)

Calcium Dynamics

Calcium Concentration

\[
\frac{d[Ca^{2+}]_i}{dt} = B_i \left( J_{\text{leak}} + J_{\text{sfer}} - J_{up} - J_{\text{trpm}} - \left( I_{CaH} - 2I_{NaCa} + I_{p(Ca)} \right) \frac{A_{\text{cap}} C_m}{2 V_{\text{myo}} F} \right)
\]  

(A.2)

\[
\frac{d[Ca^{2+}]_{ss}}{dt} = B_{ss} \left( J_{rel} \frac{V_{\text{JSR}}}{V_{ss}} - J_{\text{sfer}} \frac{V_{\text{myo}}}{V_{ss}} - I_{CaL} \frac{A_{\text{cap}} C_m}{2 V_{ss} F} \right) 
\]  

(A.3)

\[
\frac{d[Ca^{2+}]_{\text{JSR}}}{dt} = B_{\text{JSR}} \left( J_{tr} - J_{rel} \right) 
\]  

(A.4)

\[
\frac{d[Ca^{2+}]_{\text{NSR}}}{dt} = \left( J_{\text{up}} - J_{\text{leak}} \right) \frac{V_{\text{myo}}}{V_{\text{NSR}}} - J_{\text{tr}} \frac{V_{\text{JSR}}}{V_{\text{NSR}}} 
\]  

(A.5)

\[
B_i = \left( 1 + \frac{[CMDN]_{\text{tot}} K_{m}^{CMDN}}{(K_{m}^{CMDN} + [Ca^{2+}]_i)^2} \right)^{-1}
\]  

(A.6)

\[
B_{ss} = \left( 1 + \frac{[CMDN]_{\text{tot}} K_{m}^{CMDN}}{(K_{m}^{CMDN} + [Ca^{2+}]_{ss})^2} \right)^{-1}
\]  

(A.7)

\[
B_{\text{JSR}} = \left( 1 + \frac{[CSQN]_{\text{tot}} K_{m}^{CSQN}}{(K_{m}^{CSQN} + [Ca^{2+}]_{\text{JSR}})^2} \right)^{-1}
\]  

(A.8)
**Calcium Fluxes**

\[ J_{rel} = v_1(P_{O1} + P_{O2})\left([Ca^{2+}]_{SR} - [Ca^{2+}]_{ss}\right)P_{RyR} \]  \hspace{1cm} (A.9)

\[ J_{tr} = \frac{[Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR}}{\tau_{tr}} \]  \hspace{1cm} (A.10)

\[ J_{xfer} = \frac{[Ca^{2+}]_{in} - [Ca^{2+}]_{out}}{\tau_{xfer}} \]  \hspace{1cm} (A.11)

\[ J_{leak} = v_2([Ca^{2+}]_{NSR} - [Ca^{2+}]_{in}) \]  \hspace{1cm} (A.12)

\[ J_{up} = \frac{[Ca^{2+}]_{in}^2}{K_{m,up} + [Ca^{2+}]_{in}^2} \]  \hspace{1cm} (A.13)

\[ J_{trpn} = k_{trpn}^{+}[Ca^{2+}]_i\left([HTRPN]_{out} - [HTRPNCa]\right) - k_{trpn}^{-}[HTRPNCa] \]
\[ + k_{trpn}^{+}[Ca^{2+}]_i\left([LTRPN]_{out} - [LTRPNCa]\right) - k_{trpn}^{-}[LTRPNCa] \]  \hspace{1cm} (A.14)

\[ \frac{dP_{RyR}}{dt} = -0.04P_{RyR} - 0.1\frac{I_{Cal}}{I_{Cal,\max}} e^{-\frac{(V+5.0)^2}{648.0}} \]  \hspace{1cm} (A.15)

**Calcium Buffering**

\[ \frac{d[LTRPNCa]}{dt} = k_{trpn}^{+}[Ca^{2+}]_i\left([LTRPN]_{out} - [LTRPNCa]\right) - k_{trpn}^{-}[LTRPNCa] \]  \hspace{1cm} (A.16)

\[ \frac{d[HTRPNCa]}{dt} = k_{trpn}^{-}[Ca^{2+}]_i\left([HTRPN]_{out} - [HTRPNCa]\right) - k_{trpn}^{-}[HTRPNCa] \]  \hspace{1cm} (A.17)

**Ryanodine Receptors**

\[ \frac{dP_{O1}}{dt} = k_a^{+}[Ca^{2+}]_{ss}P_{C1} - k_a^{-}P_{O1} - k_b^{+}[Ca^{2+}]_{ss}P_{O1} + k_b^{-}P_{O2} - k_c^{-}P_{O1} + k_c^{+}P_{C2} \]  \hspace{1cm} (A.18)

\[ P_{C1} = 1 - (P_{C2} + P_{O1} + P_{O2}) \]  \hspace{1cm} (A.19)
\[
\frac{dP_{o2}}{dt} = k^+_b [Ca^{2+}]_{ss} P_{o1} - k^-_b P_{o2}
\]  \hspace{1cm} (A.20)

\[
\frac{dP_{c2}}{dt} = k^+_c P_{o1} - k^-_c P_{c2}
\]  \hspace{1cm} (A.21)

**Calcium Currents**

**L-type Calcium Current**

\[
I_{Cal} = G_{Cal} O(V - E_{Cal})
\]  \hspace{1cm} (A.22)

\[
\frac{dO}{dt} = \alpha C_4 - 4\beta O + K_{pcb} I_1 - \gamma O + 0.001(\alpha I_2 - K_{pbf} O)
\]  \hspace{1cm} (A.23)

\[
C_1 = 1 - (O + C_2 + C_3 + C_4 + I_1 + I_2 + I_3)
\]  \hspace{1cm} (A.24)

\[
\frac{dC_2}{dt} = 4\alpha C_1 - \beta C_2 + 2\beta C_3 - 3\alpha C_2
\]  \hspace{1cm} (A.25)

\[
\frac{dC_3}{dt} = 3\alpha C_2 - 2\beta C_3 + 3\beta C_4 - 2\alpha C_3
\]  \hspace{1cm} (A.26)

\[
\frac{dC_4}{dt} = 2\alpha C_3 - 3\beta C_4 + 4\beta O - \alpha C_4 + 0.01(4K_{pcb}\beta I_1 - \alpha\gamma C_4)
\]
\[+ 0.002(4\beta I_2 - K_{pbf} C_4) + 4\beta K_{pcb} I_3 - \gamma K_{pbf} C_4
\]  \hspace{1cm} (A.27)

\[
\frac{dI_1}{dt} = \gamma O - K_{pcb} I_1 + 0.001(\alpha I_3 - K_{pbf} I_1) + 0.01(\alpha\gamma C_4 - 4\beta K_{pcb} I_1)
\]  \hspace{1cm} (A.28)

\[
\frac{dI_2}{dt} = 0.001(K_{pbf} O - \alpha I_2) + K_{pcb} I_3 - \gamma I_2 + 0.002(K_{pbf} C_4 - 4\beta I_2)
\]  \hspace{1cm} (A.29)

\[
\frac{dI_3}{dt} = 0.001(K_{pbf} I_1 - \alpha I_3) + \gamma I_2 - K_{pcb} I_3 + \gamma K_{pbf} C_4 - 4\beta K_{pcb} I_3
\]  \hspace{1cm} (A.30)

\[
\alpha = 0.4e^{(V+15.0)/15.0}
\]  \hspace{1cm} (A.31)

\[
\beta = 0.13 e^{-(V+15.0)/18.0}
\]  \hspace{1cm} (A.32)
\[ \gamma = \frac{K_{pc,max} [Ca^{2+}]_i}{K_{pc,Half} + [Ca^{2+}]_i} \]  
(A.33)

\[ K_{pc} = 2.5 \text{ ms}^{-1} \]  
(A.34)

**Calcium Pump Current**

\[ I_{p(Ca)} = I_{p(Ca)}^{\text{max}} \frac{[Ca^{2+}]_i^2}{K_{m,p(Ca)}^2 + [Ca^{2+}]_i^2} \]  
(A.35)

**Na\(^+\)-Ca\(^{2+}\) Exchange Current**

\[ I_{NaCa} = k_{NaCa} \frac{1}{K_{m,Na} + [Na^+]_0} \frac{1}{K_{m,Ca} + [Ca^{2+}]_0} \frac{1}{1 + k_{sat} e^{(\eta-1)RT/F}} \times (e^{\eta RT/F} [Na^+]_0 [Ca^{2+}]_0 - e^{(\eta-1)RT/F} [Na^+]_0 [Ca^{2+}]_i) \]  
(A.36)

**Calcium Background Current**

\[ I_{Cab} = G_{Cab} (V - E_{CaN}) \]  
(A.37)

\[ E_{CaN} = \frac{RT}{2F} \ln \left( \frac{[Ca^{2+}]_0}{[Ca^{2+}]_i} \right) \]  
(A.38)

**Sodium Dynamics**

**Sodium Concentration**

\[ \frac{d[Na^+]_i}{dt} = -(I_Na + I_{Na} + 3I_{NaCa} + 3I_{Nak}) \frac{A_{cap} C_m}{V_{myo} F} \]  
(A.39)

**Fast Sodium Current**

\[ I_{Na} = G_{Na} O_{Na} (V - E_{Na}) \]  
(A.40)

\[ E_{Na} = \frac{RT}{F} \ln \left( \frac{0.9[Na^+]_0 + 0.1[K^+]_0}{0.9[Na^+]_i + 0.1[K^+]_i} \right) \]  
(A.41)
\[ C_{Na3} = 1 - (O_{Na} + C_{Na1} + C_{Na2} + IF_{Na} + I1_{Na} + I2_{Na} + IC_{Na2} + IC_{Na3}) \]  
(A .42)

\[ \frac{dC_{Na2}}{dt} = \alpha_{Na1} C_{Na3} - \beta_{Na1} C_{Na2} + \beta_{Na12} C_{Na1} - \alpha_{Na12} C_{Na2} + \alpha_{Na3} IC_{Na2} - \beta_{Na3} C_{Na2} \]  
(A .43)

\[ \frac{dC_{Na}}{dt} = \alpha_{Na2} C_{Na2} - \beta_{Na2} C_{Na} + \beta_{Na3} O_{Na} - \alpha_{Na3} C_{Na} + \alpha_{Na1} IF_{Na} - \beta_{Na} C_{Na} \]  
(A .44)

\[ \frac{dO_{Na}}{dt} = \alpha_{Na13} C_{Na1} - \beta_{Na13} O_{Na} + \beta_{Na2} IF_{Na} - \alpha_{Na2} O_{Na} \]  
(A .45)

\[ \frac{dIF_{Na}}{dt} = \alpha_{Na2} O_{Na} - \beta_{Na2} IF_{Na} + \beta_{Na3} C_{Na1} - \alpha_{Na3} IF_{Na} + \beta_{Na} I_{Na} - \alpha_{Na4} IF_{Na} \]  
\[ + \alpha_{Na12} IC_{Na2} - \beta_{Na12} IF_{Na} \]  
(A .46)

\[ \frac{dI1_{Na}}{dt} = \alpha_{Na4} IF_{Na} - \beta_{Na4} I1_{Na} + \beta_{Na5} I2_{Na} - \alpha_{Na5} I1_{Na} \]  
(A .47)

\[ \frac{dI2_{Na}}{dt} = \alpha_{Na5} I1_{Na} - \beta_{Na5} I2_{Na} \]  
(A .48)

\[ \frac{dIC_{Na2}}{dt} = \alpha_{Na11} IC_{Na3} - \beta_{Na11} IC_{Na2} + \beta_{Na12} IF_{Na} - \alpha_{Na12} IC_{Na2} + \beta_{Na3} C_{Na2} - \alpha_{Na3} IC_{Na2} \]  
(A .49)

\[ \frac{dIC_{Na3}}{dt} = \beta_{Na11} IC_{Na2} - \alpha_{Na11} IC_{Na3} + \beta_{Na3} C_{Na3} - \alpha_{Na3} IC_{Na3} \]  
(A .50)

\[ \alpha_{Na11} = \frac{3.802}{0.1027e^{-(V+2.5)/17.0} + 0.2e^{-(V+2.5)/150.0}} \]  
(A .51)

\[ \alpha_{Na12} = \frac{3.802}{0.1027e^{-(V+2.5)/15.0} + 0.23e^{-(V+2.5)/150.0}} \]  
(A .52)

\[ \alpha_{Na13} = \frac{3.802}{0.1027e^{-(V+2.5)/12.0} + 0.25e^{-(V+2.5)/150.0}} \]  
(A .53)

\[ \beta_{Na11} = 0.1917e^{-(V+2.5)/20.3} \]  
(A .54)

\[ \beta_{Na12} = 0.2e^{-(V-2.5)/20.3} \]  
(A .55)

\[ \beta_{Na13} = 0.22e^{-(V-7.5)/20.3} \]  
(A .56)
\[ \alpha_{Na3} = 7.0 \times 10^{-7} e^{-(V + 7.0)/7.7} \] (A.57)

\[ \beta_{Na3} = 0.0084 + 0.00002(V + 7.0) \] (A.58)

\[ \alpha_{Na2} = \frac{1.0}{0.188495e^{-(V + 7.0)/16.6} + 0.393956} \] (A.59)

\[ \beta_{Na2} = \alpha_{Na1} \alpha_{Na2} \alpha_{Na3} \beta_{Na3} / (\beta_{Na1} \beta_{Na3}) \] (A.60)

\[ \alpha_{Na4} = \alpha_{Na2} / 1000.0 \] (A.61)

\[ \beta_{Na4} = \alpha_{Na3} \] (A.62)

\[ \alpha_{Na5} = \alpha_{Na2} / 95000 \] (A.63)

\[ \beta_{Na5} = \alpha_{Na3} / 50.0 \] (A.64)

**Background Sodium Current**

\[ I_{Na0} = G_{Na0}(V - E_{Na}) \] (A.65)

**Potassium Dynamics**

**Potassium Concentration**

\[ \frac{d[K^+]}{dt} = -(I_{Kto,f} + I_{Kto,s} + I_{K1} + I_{Ks} + I_{Kss} + I_{Kap} + I_{Kr} - 2I_{NaK}) \frac{A_{cap} C_m}{V_{myo} F} \] (A.66)

**Transient Outward Potassium Current** \[ I_{Kto,f} \]

\[ I_{Kto,f} = G_{Kto,f} a_{lo,f}^3 i_{lo,f}(V - E_K) \] (A.67)

\[ E_K = \frac{RT}{F} \ln \left( \frac{[K^+]_0}{[K^+]_i} \right) \] (A.68)

\[ \frac{da_{lo,f}}{dt} = \alpha_a (1 - a_{lo,f}) - \beta_a a_{lo,f} \] (A.69)
\[
\frac{di_{i_{to,f}}}{dt} = \alpha_i (1 - i_{i_{to,f}}) - \beta_i i_{i_{to,f}} \tag{A.70}
\]

\[
\alpha_a = 0.18064 e^{0.03577(V + 30.0)} \tag{A.71}
\]

\[
\beta_a = 0.3956 e^{-0.06237(V + 30.0)} \tag{A.72}
\]

\[
\alpha_i = \frac{0.000152 e^{-(V + 13.5)/7.0}}{0.067083 e^{-(V + 33.5)/7.0} + 1} \tag{A.73}
\]

\[
\beta_i = \frac{0.00095 e^{(V + 33.5)/7.0}}{0.051335 e^{(V + 33.5)/7.0} + 1} \tag{A.74}
\]

**Transient Outward Potassium Current** \(I_{K_{to,s}}\)

\[
I_{K_{to,s}} = G_{K_{to,s}} a_{to,s} i_{to,s} (V - E_K) \tag{A.75}
\]

\[
\frac{da_{i_{to,s}}}{dt} = \frac{a_s - a_{i_{to,s}}}{\tau_{i_{to,s}}} \tag{A.76}
\]

\[
\frac{di_{i_{to,s}}}{dt} = \frac{i_s - i_{i_{to,s}}}{\tau_{i_{to,s}}} \tag{A.77}
\]

\[
a_s = 1/(1 + e^{-(V + 22.5)/7.7}) \tag{A.78}
\]

\[
i_s = 1/(1 + e^{(V + 45.2)/5.7}) \tag{A.79}
\]

\[
\tau_{i_{to,s}} = 0.493 e^{-0.0629V} + 2.058 \tag{A.80}
\]

\[
\tau_{i_{to,s}} = 270.0 + \frac{1050.0}{1 + e^{(V + 45.2)/5.7}} \tag{A.81}
\]

**Time-independent Potassium Current**

\[
I_{K1} = 0.3397 \left( \frac{[K^+]_0}{[K^+]_0 + 210.0} \right) \left( \frac{V - E_K}{1 + e^{0.0448(V - E_K)}} \right) + 0.0193V \tag{A.82}
\]
**Slow Delayed-Rectifier Potassium Current**

\[ I_{Ks} = G_{Ks} n_{Ks}^2 (V - E_K) \]  \hspace{1cm} (A.83)

\[ \frac{dn_{Ks}}{dt} = \alpha_n (1 - n_{Ks}) - \beta_n n_{Ks} \]  \hspace{1cm} (A.84)

\[ \alpha_n = \frac{0.00000481333(V + 26.5)}{1 - e^{-0.128(V + 26.5)}} \]  \hspace{1cm} (A.85)

\[ \beta_n = 0.0000953333 e^{-0.038(V + 26.5)} \]  \hspace{1cm} (A.86)

**Ultra-Rapidly Activating Delayed-Rectifier Potassium Current**

\[ I_{kur} = G_{kur} a_w i_w (V - E_K) \]  \hspace{1cm} (A.87)

\[ \frac{da_{ur}}{dt} = \frac{a_{ss} - a_{ur}}{\tau_{aur}} \]  \hspace{1cm} (A.88)

\[ \frac{di_{ur}}{dt} = \frac{i_{ss} - i_{ur}}{\tau_{iur}} \]  \hspace{1cm} (A.89)

\[ \tau_{aur} = \frac{6.1}{e^{0.0629(V + 40.0)} + e^{-0.0629(V + 40.0)}} + 2.058 \]  \hspace{1cm} (A.90)

\[ \tau_{iur} = 1200.0 - \frac{170.0}{1 + e^{(V + 45.2)/5.7}} \]  \hspace{1cm} (A.91)

**Non-Inactivating Steady-State Potassium Current**

\[ I_{Kss} = G_{Kss} a_{Kss} (V - E_K) \]  \hspace{1cm} (A.92)

\[ \frac{da_{Kss}}{dt} = \frac{a_{ss} - a_{Kss}}{\tau_{Kss}} \]  \hspace{1cm} (A.93)

\[ \frac{di_{Kss}}{dt} = 0 \]  \hspace{1cm} (A.94)

\[ \tau_{Kss} = \frac{1235.5}{e^{0.0862(V + 40.0)} + e^{-0.0862(V + 40.0)}} + 13.17 \]  \hspace{1cm} (A.95)
Rapid Delayed Rectifier Potassium Current (mERG)

\[ I_{Kr} = O_K \cdot G_K \cdot \left[ V - \frac{RT}{F} \ln \left( \frac{0.98[K^+]_o + 0.02[Na^+]_o}{0.98[K^+]_i + 0.02[Na^+]_i} \right) \right] \]  

(A .96)

\[ C_{K0} = 1 - (C_{K1} + C_{K2} + O_K + I_K) \]  

(A .97)

\[ \frac{dC_{K1}}{dt} = \alpha_{a0} C_{K0} - \beta_{a0} C_{K1} + k_b C_{K2} - k_f C_{K1} \]  

(A .98)

\[ \frac{dC_{K2}}{dt} = k_f C_{K1} - k_b C_{K2} + \beta_{a1} O_K - \alpha_{a1} C_{K2} \]  

(A .99)

\[ \frac{dO_K}{dt} = \alpha_{a1} C_{K2} - \beta_{a1} O_K + \beta_i I_K - \alpha_i O_K \]  

(A .100)

\[ \frac{dI_K}{dt} = \alpha_i O_K - \beta_i I_K \]  

(A .101)

\[ \alpha_{a0} = 0.022348^e^{0.01176V} \]  

(A .102)

\[ \beta_{a0} = 0.047002^e^{-0.0631V} \]  

(A .103)

\[ \alpha_{a1} = 0.013733 \cdot e^{0.038198V} \]  

(A .104)

\[ \beta_{a1} = 0.0000689 \cdot e^{-0.04178V} \]  

(A .105)

\[ \alpha_i = 0.090821 \cdot e^{0.02339(V + 5.0)} \]  

(A .106)

\[ \beta_i = 0.006497 \cdot e^{-0.0326(V + 5.0)} \]  

(A .107)

Sodium-Potassium Pump Current

\[ I_{NaK} = \int_{NaK}^{max} f_{NaK} \frac{1}{1 + (K_{m,Na} / [Na^+]_i)^{3/2}} \left[ K^+ \right]_o \]  

(A .108)

\[ f_{NaK} = \frac{1}{1 + 0.1245 e^{-0.1VF/RT} + 0.0365 e^{-VF/RT}} \]  

(A .109)
\[
\sigma = \frac{1}{7}(e^{[\text{Na}^+]_0/67300} - 1) \tag{A.110}
\]

**Calcium-Activated Chloride Current**

\[
I_{\text{Cl,Ca}} = \frac{G_{\text{Cl,Ca}}}{O_{\text{Cl,Ca}}} \frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_i + K_{m,\text{Cl}}} (V - E_{\text{Cl}}) \tag{A.111}
\]

\[
O_{\text{Cl,Ca}} = \frac{0.2}{1 + \exp[-(V - 46.7)/7.8]} \tag{A.112}
\]

**Contraction**

**Permissive states**

\[
\frac{dN0}{dt} = k_{PN} P0 + g_{10SL} N1 - k_{NP} N0 \tag{A.113}
\]

\[
\frac{dN1}{dt} = k_{PN} P1 - (k_{NP} + g_{10SL}) N1 \tag{A.114}
\]

\[
\frac{dP0}{dt} = g_{10SL} P1 + k_{NP} N0 - (k_{PN} + f_{01}) P0 \tag{A.115}
\]

\[
\frac{dP1}{dt} = g_{21SL} P2 + f_{01} P0 + k_{NP} N1 - (f_{12} + g_{10SL} + k_{PN}) P1 \tag{A.116}
\]

\[
\frac{dP2}{dt} = g_{32SL} P3 + f_{12} P1 - (f_{23} + g_{21SL}) P2 \tag{A.117}
\]

\[
\frac{dP3}{dt} = f_{23} P2 - g_{32SL} P3 \tag{A.118}
\]

\[
f_{01} = 3 f_{XB} \tag{A.119}
\]

\[
f_{12} = 10 f_{XB} \tag{A.120}
\]

\[
f_{23} = 7 f_{XB} \tag{A.121}
\]
\[ g_{10SL} = g_{sbSL} \]  
(A .122)

\[ g_{21SL} = 2g_{sbSL} \]  
(A .123)

\[ g_{32SL} = 3g_{sbSL} \]  
(A .124)

\[ g_{sbSL} = g_{mixb} \left( 2 - (SL_{norm})^{1.6} \right) \]  
(A .125)

\[ SL_{norm} = \frac{SL - 1.3 \mu m}{2.3 \mu m - 1.3 \mu m} \]  
(A .126)

\[ SL = 0.8F_{contr} + SL_0 \]

\[ k_{NP} = k_{PN} \left( \frac{[LTRPNCa]}{[LTRPNCa]_{tot} \times K_{half}} \right)^{Ntm} \]  
(A .128)

\[ Ntm = 5 + 3 SL_{norm} \]  
(A .129)

\[ K_{half} = 1 \left( 1 + \frac{K_{Ca}}{1.5 \mu M - SL_{norm} \times 1.0 \mu M} \right) \]  
(A .130)

\[ K_{Ca} = \frac{k^-_{trpm}}{k^+_{trpm}} \]  
(A .131)

**Contraction Force**

\[ F_{contr} = -73.26 F_{contr} \]  
(A .132)

\[ F_{contr} = - \frac{P1 + N1 + 2(P2) + 3(P3)}{F_{max}} \]  
(A .133)

\[ F_{max} = P1_{max} + 2(P2_{max}) + 3(P3_{max}) \]  
(A .134)

\[ P1_{max} = \sum f_{01} \left( 2g_{min\ b} \right) \left( 3g_{min\ b} \right) \]  
(A .135)
\[ P_{2\text{max}} = \frac{f_{01} f_{12} (3g_{\text{min,xy}})}{\Sigma} \quad (A.136) \]

\[ P_{3\text{max}} = \frac{f_{01} f_{12} f_{23}}{\Sigma} \quad (A.137) \]

\[ \Sigma = (g_{\text{min,xy}}) (2g_{\text{min,xy}}) (3g_{\text{min,xy}}) + f_{01} (2g_{\text{min,xy}}) (3g_{\text{min,xy}}) + f_{01} f_{12} (3g_{\text{min,xy}}) + f_{01} f_{12} f_{23} \quad (A.138) \]

**Model parameters**

**Cell Geometry Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_{\text{cap}} )</td>
<td>Capacitive membrane area</td>
<td>( 1.53 \times 10^{-4} \text{ cm}^2 )</td>
</tr>
<tr>
<td>( V_{\text{myo}} )</td>
<td>Myoplasmic volume</td>
<td>( 25.84 \times 10^{-6} \text{ ( \mu )l} )</td>
</tr>
<tr>
<td>( V_{\text{JSR}} )</td>
<td>Junctional SR volume</td>
<td>( 0.12 \times 10^{-6} \text{ ( \mu )l} )</td>
</tr>
<tr>
<td>( V_{\text{NSR}} )</td>
<td>Network SR volume</td>
<td>( 2.098 \times 10^{-6} \text{ ( \mu )l} )</td>
</tr>
<tr>
<td>( V_{\text{ss}} )</td>
<td>Subspace volume</td>
<td>( 1.485 \times 10^{-9} \text{ ( \mu )l} )</td>
</tr>
</tbody>
</table>

**Extracellular Ion Concentrations**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( [K^+]_o )</td>
<td>Extracellular K(^+) concentration</td>
<td>4,000 ( \mu \text{M} )</td>
</tr>
<tr>
<td>( [Na^+]_o )</td>
<td>Extracellular Na(^+) concentration</td>
<td>136,000 ( \mu \text{M} )</td>
</tr>
<tr>
<td>( [Ca^{2+}]_o )</td>
<td>Extracellular Ca(^{2+}) concentration</td>
<td>2,000 ( \mu \text{M} )</td>
</tr>
</tbody>
</table>

**SR Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_1 )</td>
<td>Maximum RyR channel Ca(^{2+}) permeability (epicardial cell)</td>
<td>4.0 ms(^{-1})</td>
</tr>
<tr>
<td>( v_1 )</td>
<td>Maximum RyR channel Ca(^{2+}) permeability (endocardial cell)</td>
<td>2.9 ms(^{-1})</td>
</tr>
<tr>
<td>( v_2 )</td>
<td>Ca(^{2+}) leak rate constant from the NSR</td>
<td>( 1.74 \times 10^{-5} \text{ ms}^{-1} )</td>
</tr>
<tr>
<td>( v_3 )</td>
<td>SR Ca(^{2+})-ATPase maximum pump rate</td>
<td>( 0.315 \mu \text{M} \text{ ms}^{-1} )</td>
</tr>
<tr>
<td>( K_{m,up} )</td>
<td>Half-saturation constant for SR Ca(^{2+})-ATPase pump</td>
<td>0.5 ( \mu \text{M} )</td>
</tr>
<tr>
<td>( \tau_r )</td>
<td>Time constant for transfer from NSR to JSR</td>
<td>20.0 ms</td>
</tr>
<tr>
<td>( \tau_{xfer} )</td>
<td>Time constant for transfer from subspace to myoplasm</td>
<td>8.0 ms</td>
</tr>
<tr>
<td>( k_a^+ )</td>
<td>RyR ( P_{CI} - P_{O1} ) rate constant</td>
<td>0.006075 ( \mu \text{M}^{-4} \text{ ms}^{-1} )</td>
</tr>
<tr>
<td>( k_a^- )</td>
<td>RyR ( P_{O1} - P_{CI} ) rate constant</td>
<td>0.07125 ms(^{-1})</td>
</tr>
<tr>
<td>( k_b^- )</td>
<td>RyR ( P_{O1} - P_{O2} ) rate constant</td>
<td>0.00405 ( \mu \text{M}^{-3} \text{ ms}^{-1} )</td>
</tr>
</tbody>
</table>
\( k_c^i \)  & RyR \( P_{O2} - P_{O1} \) rate constant & 0.965 ms\(^{-1}\) \\
\( k_c^e \)  & RyR \( P_{O1} - P_{C2} \) rate constant & 0.009 ms\(^{-1}\) \\
\( k_c^c \)  & RyR \( P_{C2} - P_{O1} \) rate constant & 0.0008 ms\(^{-1}\) \\
n  & RyR \( \text{Ca}^{2+} \) cooperativity parameter \( P_{C1} - P_{O1} \) & 4 \\
m  & RyR \( \text{Ca}^{2+} \) cooperativity parameter \( P_{O1} - P_{O2} \) & 3 \\

### L-type \( \text{Ca}^{2+} \) Channel Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( G_{CaL} )</td>
<td>Specific maximum conductivity for L-type ( \text{Ca}^{2+} ) channel</td>
<td>0.2342 mS ( \mu )F(^{-1})</td>
</tr>
<tr>
<td>( E_{Ca,L} )</td>
<td>Reversal potential for L-type ( \text{Ca}^{2+} ) channel</td>
<td>52.0 mV</td>
</tr>
<tr>
<td>( K_{pc,max} )</td>
<td>Maximum time constant for ( \text{Ca}^{2+} )-induced inactivation</td>
<td>0.11662 ms(^{-1})</td>
</tr>
<tr>
<td>( K_{pc,\text{half}} )</td>
<td>Half-saturation constant for ( \text{Ca}^{2+} )-induced inactivation</td>
<td>10.0 ( \mu )M</td>
</tr>
<tr>
<td>( K_{pct} )</td>
<td>Voltage-insensitive rate constant for inactivation</td>
<td>0.0005 ms(^{-1})</td>
</tr>
<tr>
<td>( I_{CaL,max} )</td>
<td>Normalization constant for L-type ( \text{Ca}^{2+} ) current</td>
<td>7.0 pA ( \text{pF}^{-1})</td>
</tr>
</tbody>
</table>

### Buffering Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>([LTRPN]_{\text{tot}})</td>
<td>Total myoplasmic troponin low-affinity site concentration</td>
<td>70.0 ( \mu )M</td>
</tr>
<tr>
<td>([HTRPN]_{\text{tot}})</td>
<td>Total myoplasmic troponin high-affinity site concentration</td>
<td>140.0 ( \mu )M</td>
</tr>
<tr>
<td>( k^{+}\text{trpn} )</td>
<td>( \text{Ca}^{2+} ) on rate constant for troponin high-affinity sites</td>
<td>0.00237 ( \mu )M(^{-1}) ms(^{-1})</td>
</tr>
<tr>
<td>( k^{-}\text{trpn} )</td>
<td>( \text{Ca}^{2+} ) off rate constant for troponin high-affinity sites</td>
<td>3.2 ( \times 10^{-5} ) ms(^{-1})</td>
</tr>
<tr>
<td>( k^{+}\text{tlrpn} )</td>
<td>( \text{Ca}^{2+} ) on rate constant for troponin low-affinity sites</td>
<td>0.0327 ( \mu )M(^{-1}) ms(^{-1})</td>
</tr>
<tr>
<td>( k^{-}\text{tlrpn} )</td>
<td>( \text{Ca}^{2+} ) off rate constant for troponin low-affinity sites</td>
<td>0.0196 ms(^{-1})</td>
</tr>
<tr>
<td>([CMDN]_{\text{tot}})</td>
<td>Total myoplasmic calmodulin concentration</td>
<td>50.0 ( \mu )M</td>
</tr>
<tr>
<td>([CSQN]_{\text{tot}})</td>
<td>Total junctional SR calsequestrin concentration</td>
<td>15,000 ( \mu )M</td>
</tr>
<tr>
<td>( K_m^{CMDN} )</td>
<td>( \text{Ca}^{2+} ) half saturation constant for calmodulin</td>
<td>0.238 ( \mu )M</td>
</tr>
<tr>
<td>( K_m^{CSQN} )</td>
<td>( \text{Ca}^{2+} ) half saturation constant for calsequestrin</td>
<td>800.0 ( \mu )M</td>
</tr>
</tbody>
</table>

### Membrane Current Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_m )</td>
<td>Specific membrane capacitance</td>
<td>1.0 ( \mu )F cm(^{-2})</td>
</tr>
<tr>
<td>( F )</td>
<td>Faraday’s constant</td>
<td>96.5 C mmol(^{-1})</td>
</tr>
<tr>
<td>( T )</td>
<td>Absolute temperature</td>
<td>298 K</td>
</tr>
<tr>
<td>( R )</td>
<td>Ideal gas constant</td>
<td>8.314 J mol(^{-1}) K(^{-1})</td>
</tr>
<tr>
<td>( k_{NaCa} )</td>
<td>Scaling factor of ( \text{Na}^+\text{-Ca}^{2+} ) exchange (epicardial cell)</td>
<td>234.24 pA ( \text{pF}^{-1})</td>
</tr>
<tr>
<td>( k_{NaCa} )</td>
<td>Scaling factor of ( \text{Na}^+\text{-Ca}^{2+} ) exchange (endocardial cell)</td>
<td>131.76 pA ( \text{pF}^{-1})</td>
</tr>
<tr>
<td>( K_m^{Na} )</td>
<td>( \text{Na}^+ ) half saturation constant for ( \text{Na}^+\text{-Ca}^{2+} ) exchange</td>
<td>87,500 ( \mu )M</td>
</tr>
<tr>
<td>Parameter</td>
<td>Definition</td>
<td>Value</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>$K_{m,Na}$</td>
<td>Sodium half saturation constant for Na+ - Na+ exchange</td>
<td>21,000 $\mu M$</td>
</tr>
<tr>
<td>$K_{m,Ko}$</td>
<td>Potassium half saturation constant for Na+ - K+ exchange</td>
<td>1,500 $\mu M$</td>
</tr>
<tr>
<td>$I_{max,NaK}$</td>
<td>Maximum Na+ - K+ exchange current (epicardial cell)</td>
<td>0.704 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$I_{max,NaK}$</td>
<td>Maximum Na+ - K+ exchange current (endocardial cell)</td>
<td>0.6952 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$I_{max,p(Ca)}$</td>
<td>Maximum Ca$^{2+}$ pump current (epicardial cell)</td>
<td>0.085 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$I_{max,p(Ca)}$</td>
<td>Maximum Ca$^{2+}$ pump current (endocardial cell)</td>
<td>0.0595 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$K_{m,p(Ca)}$</td>
<td>Ca$^{2+}$ half saturation constant for Ca$^{2+}$ pump current</td>
<td>0.5 $\mu M$</td>
</tr>
<tr>
<td>$G_{Cab}$</td>
<td>Maximum background Ca$^{2+}$ current conductance (epicardial cell)</td>
<td>0.000033 mS $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Cab}$</td>
<td>Maximum background Ca$^{2+}$ current conductance (endocardial cell)</td>
<td>0.000017 mS $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Na}$</td>
<td>Maximum fast Na+ current conductance</td>
<td>13.0 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Ko}$</td>
<td>Maximum background K$^{+}$ current conductance</td>
<td>0.0026 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Ko,f}$</td>
<td>Maximum transient outward K$^{+}$ current conductance (epicardial cell)</td>
<td>0.3846 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Ko,f}$</td>
<td>Maximum transient outward K$^{+}$ current conductance (endocardial cell)</td>
<td>0.1939 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Ks}$</td>
<td>Maximum slow delayed rectifier K$^{+}$ current conductance</td>
<td>0.00575 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Ko,s}$</td>
<td>Maximum transient outward K$^{+}$ current conductance (epicardial cell)</td>
<td>0.0 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>Maximum ultra-rapidly delayed rectifier K$^{+}$ current conductance (epicardial cell)</td>
<td>0.3424 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>Maximum ultra-rapidly delayed rectifier K$^{+}$ current conductance (endocardial cell)</td>
<td>0.1405 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Kr,s}$</td>
<td>Maximum non-inactivating steady-state K$^{+}$ current conductance (apex)</td>
<td>0.0611 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>Maximum rapid delayed rectifier K$^{+}$ current conductance</td>
<td>0.078 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$k_f$</td>
<td>Rate constant for rapid delayed rectifier K$^{+}$ current</td>
<td>0.023761 ms$^{-1}$</td>
</tr>
<tr>
<td>$k_o$</td>
<td>Rate constant for rapid delayed rectifier K$^{+}$ current</td>
<td>0.036778 ms$^{-1}$</td>
</tr>
<tr>
<td>$G_{Cl,Cl}$</td>
<td>Maximum calcium-activated chloride current conductance</td>
<td>10.0 $\mu S$ $\mu F^{-1}$</td>
</tr>
<tr>
<td>$K_{m,Cl}$</td>
<td>Half saturation constant for Ca$^{2+}$-activated chloride current</td>
<td>10.0 $\mu M$</td>
</tr>
<tr>
<td>$E_{Cl}$</td>
<td>Reversal potential for calcium-activated chloride current</td>
<td>$-40.0$ mV</td>
</tr>
</tbody>
</table>

**Contraction Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$SL_0$</td>
<td>Initial sarcomere length</td>
<td>2.1 $\mu m$</td>
</tr>
<tr>
<td>$k_{PN}$</td>
<td>Transition rate from permissive to non-permissive state</td>
<td>0.045 ms$^{-1}$</td>
</tr>
<tr>
<td>$f_{XB}$</td>
<td>Basic transition rate from weak to strong crossbridge</td>
<td>0.10 ms$^{-1}$</td>
</tr>
<tr>
<td>$g_{minXB}$</td>
<td>Minimum detachment rate from strong to weak crossbridge</td>
<td>0.14 ms$^{-1}$</td>
</tr>
</tbody>
</table>
### Initial Conditions (epicardial cell)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t )</td>
<td>Time</td>
<td>0.0 ms</td>
</tr>
<tr>
<td>( V )</td>
<td>Membrane potential</td>
<td>(-76.3108 ) mV</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{i})</td>
<td>Myoplasmic Ca(^{2+}) concentration</td>
<td>0.128703 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{\text{ss}})</td>
<td>Subspace SR Ca(^{2+}) concentration</td>
<td>0.128703 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{\text{JSR}})</td>
<td>Junctional SR Ca(^{2+}) concentration</td>
<td>1125.08 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{\text{NSR}})</td>
<td>Network SR Ca(^{2+}) concentration</td>
<td>1125.08 (\mu)M</td>
</tr>
<tr>
<td>([L\text{TRPN}Ca])</td>
<td>Concentration Ca(^{2+}) bound low-affinity troponin-binding sites</td>
<td>12.3737 (\mu)M</td>
</tr>
<tr>
<td>([H\text{TRPN}Ca])</td>
<td>Concentration Ca(^{2+}) bound high-affinity troponin-binding sites</td>
<td>126.707 (\mu)M</td>
</tr>
<tr>
<td>( O )</td>
<td>L-type Ca(^{2+}) channel conducting state</td>
<td>(0.854831 \times 10^{-11})</td>
</tr>
<tr>
<td>( C_1 )</td>
<td>L-type Ca(^{2+}) channel closed state</td>
<td>0.993178</td>
</tr>
<tr>
<td>( C_2 )</td>
<td>L-type Ca(^{2+}) channel closed state</td>
<td>(6.80457 \times 10^{-2})</td>
</tr>
<tr>
<td>( C_3 )</td>
<td>L-type Ca(^{2+}) channel closed state</td>
<td>(0.174826 \times 10^{-4})</td>
</tr>
<tr>
<td>( C_4 )</td>
<td>L-type Ca(^{2+}) channel closed state</td>
<td>(0.199631 \times 10^{-7})</td>
</tr>
<tr>
<td>( I_1 )</td>
<td>L-type Ca(^{2+}) channel inactivated state</td>
<td>(0.253348 \times 10^{-10})</td>
</tr>
<tr>
<td>( I_2 )</td>
<td>L-type Ca(^{2+}) channel inactivated state</td>
<td>(0.318339 \times 10^{-8})</td>
</tr>
<tr>
<td>( I_3 )</td>
<td>L-type Ca(^{2+}) channel inactivated state</td>
<td>(0.943466 \times 10^{-8})</td>
</tr>
<tr>
<td>( P_{C1} )</td>
<td>Fraction of RyR channels in state ( P_{C1} )</td>
<td>0.999714</td>
</tr>
<tr>
<td>( P_{C2} )</td>
<td>Fraction of RyR channels in state ( P_{C2} )</td>
<td>(2.63112 \times 10^{-3})</td>
</tr>
<tr>
<td>( P_{O1} )</td>
<td>Fraction of RyR channels in state ( P_{O1} )</td>
<td>(2.33877 \times 10^{-4})</td>
</tr>
<tr>
<td>( P_{O2} )</td>
<td>Fraction of RyR channels in state ( P_{O2} )</td>
<td>(2.09256 \times 10^{-9})</td>
</tr>
<tr>
<td>( C_{Na3} )</td>
<td>Closed state of fast Na(^+) channel</td>
<td>0.420023</td>
</tr>
<tr>
<td>( C_{Na2} )</td>
<td>Closed state of fast Na(^+) channel</td>
<td>0.0267137</td>
</tr>
<tr>
<td>( C_{Na1} )</td>
<td>Closed state of fast Na(^+) channel</td>
<td>(0.723752 \times 10^{-3})</td>
</tr>
<tr>
<td>( O_{Na} )</td>
<td>Open state of fast Na(^+) channel</td>
<td>(4.14576 \times 10^{-5})</td>
</tr>
<tr>
<td>( I_{FNa} )</td>
<td>Fast inactivated state of fast Na(^+) channel</td>
<td>(0.893687 \times 10^{-3})</td>
</tr>
<tr>
<td>( I_{IIaNa} )</td>
<td>Slow inactivated state 1 of fast Na(^+) channel</td>
<td>(0.124299 \times 10^{-4})</td>
</tr>
<tr>
<td>( I_{IIbNa} )</td>
<td>Slow inactivated state 2 of fast Na(^+) channel</td>
<td>(0.909901 \times 10^{-7})</td>
</tr>
<tr>
<td>( I_{ICNa2} )</td>
<td>Close-inactivated state of fast Na(^+) channel</td>
<td>(0.0329860)</td>
</tr>
<tr>
<td>( I_{ICNa3} )</td>
<td>Close-inactivated state of fast Na(^+) channel</td>
<td>(0.518643)</td>
</tr>
<tr>
<td>([\text{Na}^+]_{i})</td>
<td>Myoplasmic Na(^+) concentration</td>
<td>(14,564.6 \mu)M</td>
</tr>
<tr>
<td>([\text{K}^+]_{i})</td>
<td>Myoplasmic K(^+) concentration</td>
<td>(143,419 \mu)M</td>
</tr>
<tr>
<td>( a_{iof} )</td>
<td>Gating variable for transient outward K(^+) current</td>
<td>(0.482630 \times 10^{-2})</td>
</tr>
<tr>
<td>( i_{iof} )</td>
<td>Gating variable for transient outward K(^+) current</td>
<td>(0.999945)</td>
</tr>
<tr>
<td>( n_{ks} )</td>
<td>Gating variable for slow delayed rectifier K(^+) current</td>
<td>(0.645626 \times 10^{-3})</td>
</tr>
<tr>
<td>( a_{ios} )</td>
<td>Gating variable for transient outward K(^+) current</td>
<td>(0.921658 \times 10^{-3})</td>
</tr>
<tr>
<td>( i_{ios} )</td>
<td>Gating variable for transient outward K(^+) current</td>
<td>(0.995756)</td>
</tr>
<tr>
<td>( a_{u} )</td>
<td>Gating variable for ultra-rapidly activating delayed rectifier K(^+) current</td>
<td>(0.921658 \times 10^{-3})</td>
</tr>
<tr>
<td>( i_{u} )</td>
<td>Gating variable for ultra-rapidly activating delayed rectifier K(^+) current</td>
<td>(0.995756)</td>
</tr>
<tr>
<td>Variable</td>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>$a_{Kss}$</td>
<td>Gating variable for non-inactivating steady-state K⁺ current</td>
<td>0.921658×10⁻³</td>
</tr>
<tr>
<td>$i_{Kss}$</td>
<td>Gating variable for non-inactivating steady-state K⁺ current</td>
<td>1.0</td>
</tr>
<tr>
<td>$C_{k0}$</td>
<td>mERG channel closed state</td>
<td>0.996856</td>
</tr>
<tr>
<td>$C_{k1}$</td>
<td>mERG channel closed state</td>
<td>0.156600×10⁻²</td>
</tr>
<tr>
<td>$C_{k2}$</td>
<td>mERG channel closed state</td>
<td>0.101174×10⁻²</td>
</tr>
<tr>
<td>$O_k$</td>
<td>mERG channel open state</td>
<td>0.450855×10⁻³</td>
</tr>
<tr>
<td>$I_k$</td>
<td>mERG channel inactivated state</td>
<td>0.115611×10⁻³</td>
</tr>
<tr>
<td>$P_{RyR}$</td>
<td>Ca²⁺ release modulation factor</td>
<td>0.358438×10⁻¹³</td>
</tr>
<tr>
<td>SL</td>
<td>Sarcomere length</td>
<td>2.096593 μm</td>
</tr>
<tr>
<td>N0</td>
<td>Nonpermissive tropomyosin with 0 crossbridges</td>
<td>0.998770</td>
</tr>
<tr>
<td>N1</td>
<td>Nonpermissive tropomyosin with 1 crossbridge</td>
<td>0.367612×10⁻⁴</td>
</tr>
<tr>
<td>P0</td>
<td>Permissive tropomyosin with 0 crossbridges</td>
<td>0.112735×10⁻³</td>
</tr>
<tr>
<td>P1</td>
<td>Permissive tropomyosin with 1 crossbridge</td>
<td>0.148856×10⁻³</td>
</tr>
<tr>
<td>P2</td>
<td>Permissive tropomyosin with 2 crossbridges</td>
<td>0.408484×10⁻³</td>
</tr>
<tr>
<td>P3</td>
<td>Permissive tropomyosin with 3 crossbridges</td>
<td>0.523108×10⁻³</td>
</tr>
</tbody>
</table>
Appendix B  Chapter 3 Model Summary

Biochemical part

Cell compartments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{cap}$</td>
<td>Capacitive membrane area</td>
<td>$1.534 \times 10^{-4}$ cm$^2$</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{cell}$</td>
<td>Cell volume</td>
<td>$38.00 \times 10^{-6}$ μl</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{cyt}$</td>
<td>Cytosolic volume</td>
<td>$25.84 \times 10^{-6}$ μl</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{JSR}$</td>
<td>Junctional SR volume</td>
<td>$0.12 \times 10^{-6}$ μl</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{NSR}$</td>
<td>Network SR volume</td>
<td>$2.098 \times 10^{-6}$ μl</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{ss}$</td>
<td>Subspace volume</td>
<td>$1.485 \times 10^{-9}$ μl</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$V_{cav}$</td>
<td>Caveolar volume</td>
<td>$0.02 \times V_{cell}$</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$V_{ecav}$</td>
<td>Extracaveolar volume</td>
<td>$0.04 \times V_{cell}$</td>
<td>Heijman et al. [34]</td>
</tr>
</tbody>
</table>

The protein $P$ concentrations in the cell ($[P]_{cell}$), caveolae, extracaveolae, and cytosol

$$[P]_{cav} = f_p^{cav} \cdot [P]_{cell} \cdot \frac{V_{cell}}{V_{cav}}$$  \hspace{1cm} (B.1)

$$[P]_{ecav} = f_p^{ecav} \cdot [P]_{cell} \cdot \frac{V_{cell}}{V_{ecav}}$$  \hspace{1cm} (B.2)

$$[P]_{cyt} = (1 - f_p^{cav} - f_p^{ecav}) \cdot [P]_{cell} \cdot \frac{V_{cell}}{V_{cyt}}$$  \hspace{1cm} (B.3)

$\beta_1$-adrenergic receptor module

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[L]$</td>
<td>Ligand concentration</td>
<td>$0...100$ μM</td>
<td>Hilal-Dandan et al. [109]</td>
</tr>
<tr>
<td>$[R_{\beta 1}]_{tot}$</td>
<td>Total $\beta_1$-adrenoceptor concentration</td>
<td>$0.0103$ μM</td>
<td>Rybin et al. [37] Balijepalli et al. [35]</td>
</tr>
<tr>
<td>$f_{\beta 1}^{cav}$</td>
<td>Fraction of $\beta_1$-adrenoceptors located in caveolae</td>
<td>$0.01$</td>
<td>Rybin et al. [37] Balijepalli et al. [35]</td>
</tr>
<tr>
<td>$f_{\beta 1}^{ecav}$</td>
<td>Fraction of $\beta_1$-adrenoceptors located in extracaveolae</td>
<td>$0.5$</td>
<td>Rybin et al. [37] Balijepalli et al. [35]</td>
</tr>
<tr>
<td>$f_{\beta 1}^{cyt}$</td>
<td>Fraction of $\beta_1$-adrenoceptors located in cytosol</td>
<td>$f_{\beta 1}^{cyt} = 1 - f_{\beta 1}^{cav} - f_{\beta 1}^{ecav}$</td>
<td>Rybin et al. [37] Balijepalli et al. [35]</td>
</tr>
<tr>
<td>$[G_S]_{tot}$</td>
<td>Total concentration of $G_S$ protein</td>
<td>$2.054$ μM</td>
<td>Post et al. [110]</td>
</tr>
<tr>
<td>$f_{G_S}^{cav}$</td>
<td>Fraction of $G_S$ protein located in caveolae</td>
<td>$0.4$</td>
<td>Rybin et al. [37]</td>
</tr>
<tr>
<td>Parameter</td>
<td>Description</td>
<td>Value</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>( f_{G_s}^{\text{cav}} )</td>
<td>Fraction of G_s protein located in extracaveolae</td>
<td>0.4</td>
<td>Rybin et al. [37]</td>
</tr>
<tr>
<td>( f_{G_s}^{\text{cyt}} )</td>
<td>Fraction of G_s protein located in cytosol</td>
<td>( 1 - f_{G_s}^{\text{cav}} )</td>
<td></td>
</tr>
<tr>
<td>( K_{\beta_1,L} )</td>
<td>Low affinity constant of ( \beta_1 )-adrenoceptor for isoproterenol</td>
<td>0.567 ( \mu )M</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( K_{\beta_1,H} )</td>
<td>High affinity constant of ( \beta_1 )-adrenoceptor for isoproterenol</td>
<td>0.0617 ( \mu )M</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( K_{\beta_1,C} )</td>
<td>Affinity constant of ( \beta_1 )-adrenoceptor for G_s protein</td>
<td>2.86 ( \mu )M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{\text{PKA}^+} )</td>
<td>Rate of PKA phosphorylation of ( \beta_1 )-adrenoceptor</td>
<td>0.00081 ( \mu )M(^{-1})s(^{-1})</td>
<td>Freedman et al. [111]</td>
</tr>
<tr>
<td>( k_{\text{PKA}^-} )</td>
<td>Rate of PKA dephosphorylation of ( \beta_1 )-adrenoceptor</td>
<td>0.000205 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{\text{GRK2}^+} )</td>
<td>Rate of GRK2 phosphorylation of ( \beta_1 )-adrenoceptor</td>
<td>0.000243 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{\text{GRK2}^-} )</td>
<td>Rate of GRK2 dephosphorylation of ( \beta_1 )-adrenoceptor</td>
<td>( k_{\text{PKA}^-} )</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{\text{act1,Gs}} )</td>
<td>Activation rate for G_s by high affinity complex</td>
<td>4.9 s(^{-1})</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( k_{\text{act2,Gs}} )</td>
<td>Activation rate for G_s by low affinity complex</td>
<td>0.26 s(^{-1})</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( k_{\text{hyd,Gs}} )</td>
<td>Hydrolysis rate of G_s-GTP</td>
<td>0.8 s(^{-1})</td>
<td>Saucerman et al. [30]</td>
</tr>
<tr>
<td>( k_{\text{reas,Gs}} )</td>
<td>Re-association rate for G_s</td>
<td>1200 ( \mu )M(^{-1})s(^{-1})</td>
<td>Saucerman et al. [30]</td>
</tr>
</tbody>
</table>

### Caveolae

\[
[R_{\beta_1}]_{\text{cav, tot}} = f_{\beta_1}^{\text{cav}, \text{tot}} \cdot \frac{V_{\text{cell}}}{V_{\text{cav}}}
\]

(B.4)

\[
[G_s]_{\beta_1, \text{cav, tot}} = f_{G_s}^{\text{cav}, \text{tot}} \cdot \left[ G_s \right]_{\text{tot, GTP}} \cdot \frac{V_{\text{cell}}}{V_{\text{cav}}} - [G_s]_{\alpha, \text{tot, GDP}}^{\text{cav}}
\]

(B.5)

\[
[R_{\beta_1}]_{\text{cav, ap, tot}} = [R_{\beta_1}]_{\text{cav, tot}} - [R_{\beta_1}]_{\text{cav, PKA, tot}}^{\text{cav}} - [R_{\beta_1}]_{\text{cav, GRK2, tot}}^{\text{cav}}
\]

(B.6)

\[
d_{\beta_1}^{\text{cav}} = \frac{1}{K_{\beta_1,L}} \cdot (K_{\beta_1,L} + [L]) \cdot (K_{\beta_1,H} + [L])
\]

(B.7)

\[
b_{\beta_1}^{\text{cav}} = [G_s]_{\beta_1, \text{cav}} \cdot (K_{\beta_1,H} + [L]) - [R_{\beta_1}]_{\text{cav, ap, tot}} \cdot (K_{\beta_1,H} + [L]) + K_{\beta_1,C} \cdot K_{\beta_1,H} \left(1 + \frac{[L]}{K_{\beta_1,L}}\right)
\]

(B.8)

\[
c_{\beta_1}^{\text{cav}} = -[R_{\beta_1}]_{\text{cav, ap, tot}} \cdot K_{\beta_1,C} \cdot K_{\beta_1,H}
\]

(B.9)
\[
[R_{\beta_1}]_{\text{hap}, f}^{\text{cav}} = -\frac{b_{\beta_1}^{\text{cav}} + \sqrt{[b_{\beta_1}^{\text{cav}}]^2 - 4 \cdot a_{\beta_1}^{\text{cav}} \cdot c_{\beta_1}^{\text{cav}}}}{2 \cdot a_{\beta_1}^{\text{cav}}}
\]  
(B.10)

\[
[G_s]_{f}^{\text{cav}} = \frac{[G_s]_{\text{r}, \text{Gyr}}^{\text{cav}}}{1 + [R_{\beta_1}]_{\text{hap}, f}^{\text{cav}} \left( \frac{1}{K_{\beta_1, C}} + \frac{[L]}{K_{\beta_1, C} \cdot K_{\beta_1, H}} \right)}
\]  
(B.11)

\[
[LR_{\beta_1}]_{\text{hap}}^{\text{cav}} = \frac{[L] \cdot [R_{\beta_1}]_{\text{hap}, f}^{\text{cav}}}{K_{\beta_1, L}}
\]  
(B.12)

\[
[R_{\beta_1}]_{\text{hap}, f}^{\text{cav}} = \frac{[R_{\beta_1}]_{\text{hap}, f}^{\text{cav}} \cdot [G_s]_{f}^{\text{cav}}}{K_{\beta_1, C}}
\]  
(B.13)

\[
[LR_{\beta_1}G_s]_{\text{hap}}^{\text{cav}} = \frac{[L] \cdot [R_{\beta_1}]_{\text{hap}, f}^{\text{cav}} \cdot [G_s]_{f}^{\text{cav}}}{K_{\beta_1, C} \cdot K_{\beta_1, H}}
\]  
(B.14)

\[
\frac{d[R_{\beta_1}]_{\text{PKA,tot}}^{\text{cav}}}{dt} = k_{\text{PKA}+} \cdot [C]^{\text{cav}} \cdot [R_{\beta_1}]_{\text{hap,tot}}^{\text{cav}} - k_{\text{PKA}-} \cdot [R_{\beta_1}]_{\text{PKA,tot}}^{\text{cav}}
\]  
(B.15)

\[
\frac{d[R_{\beta_1}]_{\text{GRK2,tot}}^{\text{cav}}}{dt} = k_{\text{GRK2}+} \cdot \left( [LR_{\beta_1}]_{\text{hap}}^{\text{cav}} + [LR_{\beta_1}G_s]_{\text{hap}}^{\text{cav}} \right) - k_{\text{GRK2}-} \cdot [R_{\beta_1}]_{\text{GRK2,tot}}^{\text{cav}}
\]  
(B.16)

\[
\frac{d[G_s]_{\text{r}, \text{GTP}}^{\text{cav}}}{dt} = k_{\text{act}, \text{Gs}} \cdot [R_{\beta_1}]_{\text{hap}}^{\text{cav}} + k_{\text{act1}, \text{Gt}} \cdot [LR_{\beta_1}G_s]_{\text{hap}}^{\text{cav}} - k_{\text{hyd}, \text{Gt}} \cdot [G_s]_{\text{r}, \text{GTP}}^{\text{cav}}
\]  
(B.17)

\[
\frac{d[G_s]_{\text{r}, \text{GDP}}^{\text{cav}}}{dt} = k_{\text{act}, \text{Gs}} \cdot [R_{\beta_1}]_{\text{hap}}^{\text{cav}} + k_{\text{act1}, \text{Gt}} \cdot [LR_{\beta_1}G_s]_{\text{hap}}^{\text{cav}} - k_{\text{reas}, \text{Gt}} \cdot [G_s]_{\text{r}, \text{GDP}}^{\text{cav}} \cdot [G_s]_{\text{r}, \text{GTP}}^{\text{cav}}
\]  
(B.18)

\[
\frac{d[G_s]_{\text{r}, \text{GDP}}^{\text{cav}}}{dt} = k_{\text{hyd}, \text{Gt}} \cdot [G_s]_{\text{r}, \text{GTP}}^{\text{cav}} - k_{\text{reas}, \text{Gt}} \cdot [G_s]_{\text{r}, \text{GDP}}^{\text{cav}} \cdot [G_s]_{\text{r}, \text{GTP}}^{\text{cav}}
\]  
(B.19)

**Extracaveolae**

\[
[R_{\beta_1}]_{\text{tot}}^{\text{cav}} = f_{\text{cav}}^{\text{r,cav}} \cdot [R_{\beta_1}]_{\text{tot}} \cdot \frac{V_{\text{cell}}}{V_{\text{cav}}}
\]  
(B.20)

\[
[G_s]_{\text{r}, \gamma}^{\text{cav}} = f_{\text{cav}}^{\text{r,cav}} \cdot [G_s]_{\text{tot}} \cdot \frac{V_{\text{cell}}}{V_{\text{cav}}} - [G_s]_{\text{r}, \text{GTP}}^{\text{cav}} - [G_s]_{\text{r}, \text{GDP}}^{\text{cav}}
\]  
(B.21)
\[
\begin{align*}
[R_{\beta 1}]_{\text{np,tot}}^{\text{ecav}} &= [R_{\beta 1}]_{\text{tot}}^{\text{ecav}} - \frac{1}{K_{\beta 1,L}} \cdot (K_{\beta 1,H} + [L]) \cdot (K_{\beta 1,L} + [L]) \\
d_{\beta 1}^{\text{ecav}} &= \frac{1}{K_{\beta 1,L}} \cdot (K_{\beta 1,H} + [L]) \cdot (K_{\beta 1,L} + [L]) \\
b_{\beta 1}^{\text{ecav}} &= [G_s]_{\text{scav}} \cdot (K_{\beta 1,H} + [L]) - [R_{\beta 1}]_{\text{np,tot}}^{\text{ecav}} \cdot (K_{\beta 1,H} + [L]) + K_{\beta 1,C} \cdot K_{\beta 1,H} \left( 1 + \frac{[L]}{K_{\beta 1,L}} \right) \\
c_{\beta 1}^{\text{ecav}} &= -[R_{\beta 1}]_{\text{np,tot}}^{\text{ecav}} \cdot K_{\beta 1,C} \cdot K_{\beta 1,H} \\
[R_{\beta 1}]_{\text{np,f}}^{\text{ecav}} &= \frac{-b_{\beta 1}^{\text{ecav}} + \sqrt{[b_{\beta 1}^{\text{ecav}}]^2 - 4 \cdot a_{\beta 1}^{\text{ecav}} \cdot c_{\beta 1}^{\text{ecav}}}}{2 \cdot a_{\beta 1}^{\text{ecav}}} \\
[G_s]_{f}^{\text{scav}} &= \frac{-b_{\beta 1}^{\text{ecav}} + \sqrt{[b_{\beta 1}^{\text{ecav}}]^2 - 4 \cdot a_{\beta 1}^{\text{ecav}} \cdot c_{\beta 1}^{\text{ecav}}}}{2 \cdot a_{\beta 1}^{\text{ecav}}} \\
LR_{\beta 1}^{\text{ecav}} &= \frac{[L] \cdot [R_{\beta 1}]_{\text{np,f}}^{\text{scav}}}{K_{\beta 1,L}} \\
[R_{\beta 1}G_s]_{np}^{\text{ecav}} &= \frac{[R_{\beta 1}]_{\text{np,f}}^{\text{ecav}} \cdot [G_s]_{f}^{\text{scav}}}{K_{\beta 1,C}} \\
LR_{\beta 1}G_s^{\text{ecav}} &= \frac{[L] \cdot [R_{\beta 1}]_{\text{np,f}}^{\text{ecav}} \cdot [G_s]_{f}^{\text{ecav}}}{K_{\beta 1,C} \cdot K_{\beta 1,H}} \\
\frac{d[R_{\beta 1}]_{PKA,tot}^{\text{ecav}}}{dt} &= k_{PKA^+} \cdot [C]^{\text{ecav}} \cdot [R_{\beta 1}]_{\text{np,tot}}^{\text{ecav}} - k_{PKA^-} \cdot [R_{\beta 1}]_{PKA,tot}^{\text{ecav}} \\
\frac{d[R_{\beta 1}]_{GRK2,tot}^{\text{ecav}}}{dt} &= k_{GRK2^+} \cdot (LR_{\beta 1}^{\text{scav}} + LR_{\beta 1}G_s^{\text{scav}}) - k_{GRK2^-} \cdot LR_{\beta 1}^{\text{ecav}} \\
\frac{d[G_s]_{\text{act}_{\beta 2,GTP}}^{\text{ecav}}}{dt} &= k_{act_{2,Gs}} \cdot [R_{\beta 1}G_s]_{np}^{\text{ecav}} + k_{act_{1,Gs}} \cdot LR_{\beta 1}G_s^{\text{ecav}} - k_{hyd_{GS}} \cdot [G_s]_{\text{act}_{\beta 2,GTP}}^{\text{ecav}} \\
\frac{d[G_s]_{\text{act}_{\beta 2,GDP}}^{\text{ecav}}}{dt} &= k_{act_{2,Gs}} \cdot [R_{\beta 1}G_s]_{np}^{\text{ecav}} + k_{act_{1,Gs}} \cdot LR_{\beta 1}G_s^{\text{ecav}} - k_{hyd_{GPP}} \cdot [G_s]_{\text{act}_{\beta 2,GDP}}^{\text{ecav}} \\
\end{align*}
\]
\[
\frac{d[G_s]_{cav}}{dt} = k_{hyd,cs} \cdot [G_s]_{cav} - k_{react,cs} \cdot [G_s]_{cav} \cdot [G_s]_{lo,GDP}
\] (B.35)

**Cytosol**

\[
[R_{\beta_1}]_{c} = f_{\beta_1}^c \cdot [R_{\beta_1}]_{c} \cdot \frac{V_{cell}}{V_{cyt}}
\] (B.36)

\[
[G_s]_{c} = f_{G_s}^c \cdot [G_s]_c \cdot \frac{V_{cell}}{V_{cyt}} - [G_s]_{c} + [G_s]_{c}
\] (B.37)

\[
[R_{\beta_1}]_{c} = [R_{\beta_1}]_{c} - [R_{\beta_1}]_p \cdot [R_{\beta_1}]_{c} - [R_{\beta_1}]_{GRK2,2,ot}
\] (B.38)

\[
\phi_{\beta_1}^c = \frac{1}{K_{\beta_1,c}} \cdot \left( K_{\beta_1,c} + [L] \right) \cdot \left( K_{\beta_1,H} + [L] \right)
\] (B.39)

\[
b_{\beta_1}^c = [G_s]_c \cdot \left( K_{\beta_1,H} + [L] \right) - [R_{\beta_1}]_p \cdot \left( K_{\beta_1,H} + [L] \right) + K_{\beta_1,c} \cdot K_{\beta_1,H} \left( 1 + \frac{[L]}{K_{\beta_1,c}} \right)
\] (B.40)

\[
c_{\beta_1}^c = -[R_{\beta_1}]_p \cdot K_{\beta_1,c} \cdot K_{\beta_1,H}
\] (B.41)

\[
[R_{\beta_1}]_{c} = \frac{-b_{\beta_1}^c + \sqrt{b_{\beta_1}^c} - 4 \cdot a_{\beta_1}^c \cdot c_{\beta_1}^c}{2 \cdot a_{\beta_1}^c}
\] (B.42)

\[
[G_s]_f = \frac{[G_s]_c}{1 + [R_{\beta_1}]_p \cdot \left( \frac{1}{K_{\beta_1,c}} + \frac{[L]}{K_{\beta_1,c} \cdot K_{\beta_1,H}} \right)}
\] (B.43)

\[
[LR_{\beta_1}]_p = \frac{[L] \cdot [R_{\beta_1}]_p}{K_{\beta_1,L}}
\] (B.44)

\[
[R_{\beta_1}G_s]_p = \frac{[R_{\beta_1}]_p \cdot [G_s]_f}{K_{\beta_1,c}}
\] (B.45)

\[
[LR_{\beta_1}G_s]_p = \frac{[L] \cdot [R_{\beta_1}]_p \cdot [G_s]_f}{K_{\beta_1,c} \cdot K_{\beta_1,H}}
\] (B.46)
\[
d\frac{[R_{j\alpha}]^{\text{tot}}}{dt} = k_{PKA+} \cdot [C]^{\text{tot}} \cdot [R_{j\alpha}]_{\text{np, tot}}^{\text{tot}} - k_{PKA-} \cdot [R_{j\alpha}]^{\text{tot}}^{\text{PKA, tot}} \\
\]

\[
d\frac{[R_{j\alpha}]^{\text{tot}}}{dt} = k_{GRK2+} \cdot \left( [LR_{j\alpha}]_{\text{np}}^{\text{tot}} + [LR_{j\alpha}G_s]_{\text{np}}^{\text{tot}} \right) - k_{GRK2-} \cdot [R_{j\alpha}]^{\text{tot}}^{GRK2, \text{tot}} \\
\]

\[
d\frac{[G_s]_{\text{GTP}}^{\text{tot}}}{dt} = k_{a} \cdot [R_{j\alpha}G_s]_{\text{np}}^{\text{tot}} + k_{c} \cdot [LR_{j\alpha}G_s]_{\text{np}}^{\text{tot}} - k_{\text{hyd},G_s} \cdot [G_s]^{\text{tot}}^{\text{GTP}} \\
\]

\[
d\frac{[G_s]_{\text{GDP}}^{\text{tot}}}{dt} = k_{\text{hyd},G_s} \cdot [G_s]^{\text{tot}}^{\text{GTP}} - k_{\text{hyd},G_s} \cdot [G_s]^{\text{tot}}^{\text{GDP}} \\
\]

### Adenylyl cyclase module

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\text{m,ATP}}$</td>
<td>Adenylyl cyclase affinity for ATP</td>
<td>340 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>[ATP]</td>
<td>ATP concentration</td>
<td>5000 μM</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>[AC]$_{\text{tot}}$</td>
<td>Total cellular AC concentration</td>
<td>0.02622 μM</td>
<td>Post et al. [110]</td>
</tr>
<tr>
<td>$f_{AC56,AC47}$</td>
<td>Fraction of AC that is of type 5 or 6</td>
<td>0.74</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$f_{AC56}$</td>
<td>Fraction of AC5/6 located in caveolae</td>
<td>0.0875</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$f_{AC47}$</td>
<td>Fraction of AC4/7 located in extracaveolae space</td>
<td>0.1648</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$K_{AC56_{m,Gsa}}$</td>
<td>AC5/6 affinity for Gsa</td>
<td>0.0852 μM</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$h_{AC56, Gsa}$</td>
<td>Hill coefficient for AC5/6 activation by Gsa</td>
<td>1.357</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$V_{AC56_{m,Gsa}}$</td>
<td>Maximum amplification of AC5/6 by Gsa</td>
<td>1.430</td>
<td>Gao et al. [112]</td>
</tr>
<tr>
<td>$K_{AC56_{m,Gsa}}$</td>
<td>Affinity constant for Gsa modulation of AC5/6</td>
<td>0.003793 μM</td>
<td>Gao et al. [112]</td>
</tr>
<tr>
<td>$h_{AC56, Gsa}$</td>
<td>Hill coefficient for Gsa modulation of AC5/6</td>
<td>1.0842</td>
<td>Gao et al. [112]</td>
</tr>
<tr>
<td>$AC56_{basal}$</td>
<td>Basal AC5/6 activity</td>
<td>0.0377</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$AF_{AC56}$</td>
<td>Amplification factor for AC5/6</td>
<td>51.1335 s$^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{AC47_{m,Gsa}}$</td>
<td>AC4/7 affinity for Gsa</td>
<td>0.05008 μM</td>
<td>Zimmermann and Taussig [113]</td>
</tr>
<tr>
<td>$h_{AC47, Gsa}$</td>
<td>Hill coefficient for AC4/7 activation by Gsa</td>
<td>1.1657</td>
<td>Zimmermann and Taussig [113]</td>
</tr>
<tr>
<td>$V_{AC47_{Gsa}}$</td>
<td>Maximum amplification of AC4/7 by Gsa</td>
<td>1.3500</td>
<td>Zimmermann and Taussig [113]</td>
</tr>
<tr>
<td>$K_{AC47}$</td>
<td>Affinity constant for $G_{q\beta}$ modulation of AC4/7</td>
<td>0.004466 μM</td>
<td>Zimmermann and Taussig [113]</td>
</tr>
<tr>
<td>$h_{AC47, G_{q\beta}}$</td>
<td>Hill coefficient for $G_{q\beta}$ modulation of AC4/7</td>
<td>0.8700</td>
<td>Zimmermann and Taussig [113]</td>
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<tr>
<td>$AC47_{basal}$</td>
<td>Basal AC4/7 activity</td>
<td>0.04725</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$AF_{47}$</td>
<td>Amplification factor for AC4/7</td>
<td>9.283 s$^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

**Caveolae**

\[
[AC56]_{cav} = f_{AC56,cav}^cav \cdot f_{AC56,AC47} \cdot [AC]_{tot} \cdot \frac{V_{cell}}{V_{cav}} \quad \text{(B.52)}
\]

\[
k_{AC56}^{cav} = AF_{56} \cdot \left( AC56_{basal} + \frac{[G_s]_{47,GTP}^{cav} h_{AC56,Gs}^{AC56,Gs}}{K_{m,Gs}^{AC56} + [G_s]_{47,GTP}^{cav} h_{AC56,Gs}^{AC56,Gs}} \right) \left( 1 + \frac{V_{AC56}^{cav} G_{q\beta} \cdot ([G_s]_{47,GTP}^{cav} h_{AC56,Gs}^{AC56,Gs})}{K_{m,Gs}^{AC56} + [G_s]_{47,GTP}^{cav} h_{AC56,Gs}^{AC56,Gs}} \right) \quad \text{(B.53)}
\]

\[
\frac{d[cAMP]_{AC56}}{dt} = k_{AC56}^{cav} \cdot \frac{[AC56]_{cav} \cdot [ATP]}{K_{m,ATP} + [ATP]} \quad \text{(B.54)}
\]

**Extracaveolae**

\[
[AC47]_{cav} = f_{AC47}^{cav} \cdot (1 - f_{AC56,AC47}) \cdot [AC]_{tot} \cdot \frac{V_{cell}}{V_{cav}} \quad \text{(B.55)}
\]

\[
k_{AC47}^{cav} = AF_{47} \cdot \left( AC47_{basal} + \frac{[G_s]_{47,GTP}^{cav} h_{AC47,Gs}^{AC47,Gs}}{K_{m,Gs}^{AC47} + [G_s]_{47,GTP}^{cav} h_{AC47,Gs}^{AC47,Gs}} \right) \left( 1 + \frac{V_{AC47}^{cav} G_{q\beta} \cdot ([G_s]_{47,GTP}^{cav} h_{AC47,Gs}^{AC47,Gs})}{K_{m,Gs}^{AC47} + [G_s]_{47,GTP}^{cav} h_{AC47,Gs}^{AC47,Gs}} \right) \quad \text{(B.56)}
\]

\[
\frac{d[cAMP]_{AC47}}{dt} = k_{AC47}^{cav} \cdot \frac{[AC47]_{cav} \cdot [ATP]}{K_{m,ATP} + [ATP]} \quad \text{(B.57)}
\]

**Cytosol**

\[
[AC56]_{cyt} = (1 - f_{AC56}^{cav}) \cdot f_{AC56,AC47} \cdot [AC]_{tot} \cdot \frac{V_{cell}}{V_{cyt}} \quad \text{(B.58)}
\]

\[
[AC47]_{cyt} = (1 - f_{AC47}^{cav}) \cdot (1 - f_{AC56,AC47}) \cdot [AC]_{tot} \cdot \frac{V_{cell}}{V_{cyt}} \quad \text{(B.59)}
\]
\[ k_{AC56}^{cyst} = AF_{56} \cdot \left( AC56_{basal} + \frac{[G_{i}^{cyst}]_{AC56,56}}{K_{m,AC56} + [G_{i}^{cyst}]_{AC56,56}} \right) \left( 1 + \frac{V_{AC56}^{cyst}}{K_{m,AC56} + [G_{i}^{cyst}]_{AC56,56}} \right) \]  

\[ \frac{d[cAMP]_{AC56}^{cyst}}{dt} = k_{AC56}^{cyst} \cdot \frac{[AC56]^{cyst} \cdot [ATP]}{K_{m,ATP} + [ATP]} \]  

\[ k_{AC47}^{cyst} = AF_{47} \cdot \left( AC47_{basal} + \frac{[G_{i}^{cyst}]_{AC47,47}}{K_{m,AC47} + [G_{i}^{cyst}]_{AC47,47}} \right) \left( 1 + \frac{V_{AC47}^{cyst}}{K_{m,AC47} + [G_{i}^{cyst}]_{AC47,47}} \right) \]  

\[ \frac{d[cAMP]_{AC47}^{cyst}}{dt} = k_{AC47}^{cyst} \cdot \frac{[AC47]^{cyst} \cdot [ATP]}{K_{m,ATP} + [ATP]} \]

### Phosphodiesterase module

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[IBMX]</td>
<td>Concentration of IBMX</td>
<td>0…100 μM</td>
<td></td>
</tr>
<tr>
<td>( h_{IBMX,PDE2} )</td>
<td>Hill coefficient for inhibition of PDE2 by IBMX</td>
<td>1.000</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{IBMX,PDE2} )</td>
<td>Affinity of IBMX for PDE2</td>
<td>29.50 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( h_{IBMX,PDE3} )</td>
<td>Hill coefficient for inhibition of PDE3 by IBMX</td>
<td>1.000</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{IBMX,PDE3} )</td>
<td>Affinity of IBMX for PDE3</td>
<td>5.100 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( h_{IBMX,PDE4} )</td>
<td>Hill coefficient for inhibition of PDE4 by IBMX</td>
<td>1.000</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{IBMX,PDE4} )</td>
<td>Affinity of IBMX for PDE4</td>
<td>16.200 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{PDEp} )</td>
<td>Rate of phosphorylation of PDE3/4 by PKA</td>
<td>0.0196 μM⁻¹ s⁻¹</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( k_{d,PDEp} )</td>
<td>Rate of dephosphorylation of PDE3/4 by PKA</td>
<td>0.0102 s⁻¹</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( \Delta k_{PDE3/4} )</td>
<td>Increase in PDE3/4 activity after phosphorylation</td>
<td>3.0</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( k_{PDE2} )</td>
<td>Rate of cAMP hydrolysis by PDE2</td>
<td>20 s⁻¹</td>
<td>Iancu et al. [114]</td>
</tr>
<tr>
<td>( K_{m,PDE2} )</td>
<td>Affinity of PDE2 for cAMP</td>
<td>33 μM</td>
<td>Bode et al. [115]</td>
</tr>
<tr>
<td>( k_{PDE3} )</td>
<td>Rate of cAMP hydrolysis by PDE3</td>
<td>2.5 s⁻¹</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( K_{m,PDE3} )</td>
<td>Affinity of PDE3 for cAMP</td>
<td>0.44 μM</td>
<td>Bode et al. [115]</td>
</tr>
<tr>
<td>( k_{PDE4} )</td>
<td>Rate of cAMP hydrolysis by PDE4</td>
<td>3.5 s⁻¹</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{m,PDE4} )</td>
<td>Affinity of PDE4 for cAMP</td>
<td>1.4 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( f_{PDE,part} )</td>
<td>Fraction of total PDE located in the particulate fraction</td>
<td>0.2</td>
<td>Osadchii [116]</td>
</tr>
<tr>
<td>( r_{part,PDE2,PDE3} )</td>
<td>Ratio of PDE2 and PDE3 activities in particulate fraction</td>
<td>0.570</td>
<td>Mongillo et al. [117]</td>
</tr>
<tr>
<td>$r_{part,PDE3,PDE4}$</td>
<td>Ratio of PDE3 and PDE4 activities in particulate fraction</td>
<td>0.748</td>
<td>Mongillo et al. [117]</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------</td>
<td>--------</td>
<td>---------------------</td>
</tr>
<tr>
<td>$[PDE2]_{tot}$</td>
<td>Total cellular concentration of PDE2</td>
<td>0.034610 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$[PDE3]_{tot}$</td>
<td>Total cellular concentration of PDE3</td>
<td>0.010346 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$[PDE4]_{tot}$</td>
<td>Total cellular concentration of PDE4</td>
<td>0.026687 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE2}^{cav}$</td>
<td>Fraction of PDE2 located in caveolae</td>
<td>0.06608</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE2}^{ecav}$</td>
<td>Fraction of PDE2 located in extracaveolae</td>
<td>2 · $f_{PDE2}^{cav}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE2}^{cyt}$</td>
<td>Fraction of PDE2 located in cytosol</td>
<td>1 − $f_{PDE2}^{cav} − f_{PDE2}^{ecav}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE3}^{cav}$</td>
<td>Fraction of PDE3 located in caveolae</td>
<td>0.29814</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE3}^{ecav}$</td>
<td>Fraction of PDE3 located in extracaveolae</td>
<td>0.0</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE3}^{cyt}$</td>
<td>Fraction of PDE3 located in cytosol</td>
<td>1 − $f_{PDE3}^{cav} − f_{PDE3}^{ecav}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE4}^{cav}$</td>
<td>Fraction of PDE4 located in caveolae</td>
<td>0.05366</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE4}^{ecav}$</td>
<td>Fraction of PDE4 located in extracaveolae</td>
<td>2 · $f_{PDE4}^{cav}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{PDE4}^{cyt}$</td>
<td>Fraction of PDE4 located in cytosol</td>
<td>1 − $f_{PDE4}^{cav} − f_{PDE4}^{ecav}$</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

**Caveolae**

\[
[PDE2]_{tot}^{cav} = \left( 1 - \frac{[IBMX]_{hIBMX,PDE2}^{IBMX,PDE2}}{K_{m,PDE2}^{IBMX} + [IBMX]_{hIBMX,PDE2}^{IBMX}} \right) \cdot f_{PDE2}^{cav} \cdot [PDE2]_{tot} \cdot \frac{V_{cell}}{V_{cav}} \tag{B.64}
\]

\[
[PDE3]_{tot}^{cav} = \left( 1 - \frac{[IBMX]_{hIBMX,PDE3}^{IBMX,PDE3}}{K_{m,PDE3}^{IBMX} + [IBMX]_{hIBMX,PDE3}^{IBMX}} \right) \cdot f_{PDE3}^{cav} \cdot [PDE3]_{tot} \cdot \frac{V_{cell}}{V_{cav}} \tag{B.65}
\]

\[
[PDE4]_{tot}^{cav} = \left( 1 - \frac{[IBMX]_{hIBMX,PDE4}^{IBMX,PDE4}}{K_{m,PDE4}^{IBMX} + [IBMX]_{hIBMX,PDE4}^{IBMX}} \right) \cdot f_{PDE4}^{cav} \cdot [PDE4]_{tot} \cdot \frac{V_{cell}}{V_{cav}} \tag{B.66}
\]

\[
\frac{d[PDE3]_{p}^{cav}}{dt} = k_{f,PDEP} \cdot [C]^{cav} \cdot ([PDE3]_{tot}^{cav} - [PDE3]_{p}^{cav}) - k_{b,PDEP} \cdot [PDE3]_{p}^{cav} \tag{B.67}
\]

\[
\frac{d[PDE4]_{p}^{cav}}{dt} = k_{f,PDEP} \cdot [C]^{cav} \cdot ([PDE4]_{tot}^{cav} - [PDE4]_{p}^{cav}) - k_{b,PDEP} \cdot [PDE4]_{p}^{cav} \tag{B.68}
\]

\[
\frac{d[cAMP]_{PDE2}^{cav}}{dt} = k_{PDE2} \cdot [PDE2]_{tot}^{cav} \cdot [cAMP]^{cav} \tag{B.69}
\]

\[
\frac{d[cAMP]_{PDE3}^{cav}}{dt} = k_{PDE3} \cdot [PDE3]_{tot}^{cav} \cdot [cAMP]^{cav} \tag{B.70}
\]

\[
\frac{d[cAMP]_{PDE4}^{cav}}{dt} = k_{PDE4} \cdot [PDE4]_{tot}^{cav} \cdot [cAMP]^{cav} \tag{B.71}
\]

\[
\frac{d[cAMP]_{tot}^{cav}}{dt} = k_{PDE2} \cdot [PDE2]_{tot}^{cav} \cdot [cAMP]^{cav} \tag{B.72}
\]
\[
\frac{dcAMP_{PDE3}^{rev}}{dt} = \frac{k_{PDE3} \cdot ([PDE3]_{tot}^{rev} - [PDE3]_{p}^{rev}) \cdot [cAMP]^{rev} + \Delta_{A,PDE3/4} \cdot k_{PDE3} \cdot [PDE3]_{p}^{rev} \cdot [cAMP]^{rev}}{K_{m,PDE3} + [cAMP]^{rev}}
\]

(B.70)

\[
\frac{dcAMP_{PDE4}^{rev}}{dt} = \frac{k_{PDE4} \cdot ([PDE4]_{tot}^{rev} - [PDE4]_{p}^{rev}) \cdot [cAMP]^{rev} + \Delta_{A,PDE3/4} \cdot k_{PDE4} \cdot [PDE4]_{p}^{rev} \cdot [cAMP]^{rev}}{K_{m,PDE4} + [cAMP]^{rev}}
\]

(B.71)

**Extracaveolae**

\[
[PDE2]_{tot}^{rev} = \left(1 - \frac{[IBMX]^{bmax,rev2}}{K_{m,PDE2}^{IBMX} + [IBMX]^{bmax,rev2}}\right) \cdot \frac{g_{PDE2}^{rev} \cdot [PDE2]_{tot}^{rev} \cdot V_{cell}^{rev}}{V_{PDE2}^{rev}}
\]

(B.72)

\[
[PDE4]_{tot}^{rev} = \left(1 - \frac{[IBMX]^{bmax,rev4}}{K_{m,PDE4}^{IBMX} + [IBMX]^{bmax,rev4}}\right) \cdot \frac{g_{PDE4}^{rev} \cdot [PDE4]_{tot}^{rev} \cdot V_{cell}^{rev}}{V_{PDE4}^{rev}}
\]

(B.73)

\[
\frac{d[PDE4]_{p}^{rev}}{dt} = k_{f,PDEp} \cdot [C]^{rev} \cdot ([PDE4]_{tot}^{rev} - [PDE4]_{p}^{rev}) - k_{b,PDEp} \cdot [PDE4]_{p}^{rev}
\]

(B.74)

\[
\frac{dcAMP_{PDE2}^{rev}}{dt} = \frac{k_{PDE2} \cdot ([PDE2]_{tot}^{rev} \cdot [cAMP]^{rev})}{K_{m,PDE2} + [cAMP]^{rev}}
\]

(B.75)

\[
\frac{dcAMP_{PDE4}^{rev}}{dt} = \frac{k_{PDE4} \cdot ([PDE4]_{tot}^{rev} - [PDE4]_{p}^{rev}) \cdot [cAMP]^{rev} + \Delta_{A,PDE3/4} \cdot k_{PDE4} \cdot [PDE4]_{p}^{rev} \cdot [cAMP]^{rev}}{K_{m,PDE4} + [cAMP]^{rev}}
\]

(B.76)

**Cytosol**

\[
[PDE2]_{tot}^{y} = \left(1 - \frac{[IBMX]^{bmax,rev2}}{K_{m,PDE2}^{IBMX} + [IBMX]^{bmax,rev2}}\right) \cdot \frac{g_{PDE2}^{y} \cdot [PDE2]_{tot} \cdot V_{cell}^{y}}{V_{PDE2}^{y}}
\]

(B.77)

\[
[PDE3]_{tot}^{y} = \left(1 - \frac{[IBMX]^{bmax,rev3}}{K_{m,PDE3}^{IBMX} + [IBMX]^{bmax,rev3}}\right) \cdot \frac{g_{PDE3}^{y} \cdot [PDE3]_{tot} \cdot V_{cell}^{y}}{V_{PDE3}^{y}}
\]

(B.78)

\[
[PDE4]_{tot}^{y} = \left(1 - \frac{[IBMX]^{bmax,rev4}}{K_{m,PDE4}^{IBMX} + [IBMX]^{bmax,rev4}}\right) \cdot \frac{g_{PDE4}^{y} \cdot [PDE4]_{tot} \cdot V_{cell}^{y}}{V_{PDE4}^{y}}
\]

(B.79)

\[
\frac{d[PDE3]_{p}^{y}}{dt} = k_{f,PDEp} \cdot [C]^{y} \cdot ([PDE3]_{tot}^{y} - [PDE3]_{p}^{y}) - k_{b,PDEp} \cdot [PDE3]_{p}^{y}
\]

(B.80)

\[
\frac{d[PDE4]_{p}^{y}}{dt} = k_{f,PDEp} \cdot [C]^{y} \cdot ([PDE4]_{tot}^{y} - [PDE4]_{p}^{y}) - k_{b,PDEp} \cdot [PDE4]_{p}^{y}
\]

(B.81)
\[
\frac{d[cAMP]_{PDE2}^{\text{tot}}}{dt} = k_{PDE2} \cdot [PDE2]_{\text{tot}}^{\text{tot}} \cdot [cAMP]^{\text{tot}} + \frac{K_{m,PDE2} + [cAMP]^{\text{tot}}}{K_{m,PDE2} + [cAMP]^{\text{tot}}}
\]  
(B.82)

\[
\frac{d[cAMP]_{PDE3}^{\text{tot}}}{dt} = k_{PDE3} \cdot (\{PDE3\}_{\text{tot}}^{\text{tot}} - [PDE3]_{\text{tot}}^{\text{tot}}) \cdot [cAMP]^{\text{tot}} + \Delta_{\text{PDE3}} \cdot k_{PDE3} \cdot [PDE3]_{\text{tot}}^{\text{tot}} \cdot [cAMP]^{\text{tot}}
\]  
(B.83)

\[
\frac{d[cAMP]_{PDE4}^{\text{tot}}}{dt} = k_{PDE4} \cdot (\{PDE4\}_{\text{tot}}^{\text{tot}} - [PDE4]_{\text{tot}}^{\text{tot}}) \cdot [cAMP]^{\text{tot}} + \Delta_{\text{PDE4}} \cdot k_{PDE4} \cdot [PDE4]_{\text{tot}}^{\text{tot}} \cdot [cAMP]^{\text{tot}}
\]  
(B.84)

**cAMP-PKA module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[PKA]_{\text{tot}}</td>
<td>Total cellular concentration of PKA holoenzyme</td>
<td>0.5176 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>f_{\text{cav,PKA}}</td>
<td>Fraction of PKA located in caveolae</td>
<td>0.08</td>
<td>Bondarenko [16]</td>
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<tr>
<td>f_{\text{ecav,PKA}}</td>
<td>Fraction of PKA located in extracaveolae</td>
<td>0.20</td>
<td>Bondarenko [16]</td>
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<tr>
<td>f_{\text{cyt,PKA}}</td>
<td>Fraction of PKA located in cytosol</td>
<td>1 - f_{\text{cav,PKA}} - f_{\text{ecav,PKA}}</td>
<td></td>
</tr>
<tr>
<td>[PKI]_{\text{tot}}</td>
<td>Total cellular concentration of PKA inhibitor</td>
<td>2 \cdot 0.2 \cdot [PKA]_{\text{tot}}</td>
<td>Beavo et al. [118]</td>
</tr>
<tr>
<td>f_{\text{cav,PKI}}</td>
<td>Fraction of PKI located in caveolae</td>
<td>f_{\text{cav,PKA}}</td>
<td></td>
</tr>
<tr>
<td>f_{\text{ecav,PKI}}</td>
<td>Fraction of PKI located in extracaveolae</td>
<td>f_{\text{ecav,PKA}}</td>
<td></td>
</tr>
<tr>
<td>f_{\text{cyt,PKI}}</td>
<td>Fraction of PKI located in cytosol</td>
<td>f_{\text{cyt,PKA}}</td>
<td></td>
</tr>
<tr>
<td>k_{\text{PKAI,f1}}</td>
<td>Forward rate for binding of the first cAMP to PKA</td>
<td>5.6 μM⁻¹ s⁻¹</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>K_{\text{PKAI,1}}</td>
<td>Equilibrium value for the binding of the first cAMP to PKA</td>
<td>2.9 μM</td>
<td>Dao et al. [119]</td>
</tr>
<tr>
<td>k_{\text{PKAI,f2}}</td>
<td>Forward rate for binding of the second cAMP to PKA</td>
<td>k_{\text{PKAI,f1}}</td>
<td>Bondarenko [16]</td>
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<tr>
<td>K_{\text{PKAI,2}}</td>
<td>Equilibrium value for binding of the second cAMP to PKA</td>
<td>2.9 μM</td>
<td>Dao et al. [119]</td>
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<tr>
<td>k_{\text{PKAI,f3}}</td>
<td>Forward rate for dissociation of C subunit</td>
<td>2.6 s⁻¹</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>K_{\text{PKAI,3}}</td>
<td>Equilibrium value for dissociation of C subunit</td>
<td>1.3 μM</td>
<td>Bondarenko [16]</td>
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<tr>
<td>k_{\text{PKI,f}}</td>
<td>Forward rate for inhibition of C subunit by PKI</td>
<td>50 μM⁻¹ s⁻¹</td>
<td>Heijman et al. [34]</td>
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<tr>
<td>K_{\text{PKI}}</td>
<td>Equilibrium value for inhibition of C subunit by PKI</td>
<td>2.6 \cdot 10⁻⁴ μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>k_{\text{PKAIH,f1}}</td>
<td>Forward rate for binding of the first cAMP to PKA</td>
<td>k_{\text{PKAI,f1}}</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>K_{\text{PKAIH,3}}</td>
<td>Equilibrium value for the binding of the first cAMP to PKA</td>
<td>2.5 μM</td>
<td>Heijman et al. [34]</td>
</tr>
</tbody>
</table>
**Caveolae**

\[
[PKA]_{f}^{\text{cav}} = f_{PKA}^{\text{cav}} \cdot [PKA]_{\text{tot}}^{\text{cav}} \cdot \frac{V_{\text{cell}}^{\text{cav}}}{V_{\text{cav}}} 
\]

(B.85)

\[
[RC]_{f}^{\text{cav}} = 2 \cdot [PKA]_{f}^{\text{cav}} - [ARC]_{f}^{\text{cav}} - [A_{2}RC]_{f}^{\text{cav}} - [A_{2}R]_{f}^{\text{cav}}
\]

(B.86)

\[
[PKI]_{f}^{\text{cav}} = f_{PKI}^{\text{cav}} \cdot [PKI]_{\text{tot}}^{\text{cav}} \cdot \frac{V_{\text{cell}}^{\text{cav}}}{V_{\text{cav}}} - [PKIC]_{f}^{\text{cav}}
\]

(B.87)

\[
k_{PKAI,b,1} = k_{PKAI,f,1} \cdot K_{PKAI,3}
\]

(B.88)

\[
k_{PKAI,b,2} = k_{PKAI,f,2} \cdot K_{PKAI,2}
\]

(B.89)

\[
k_{PKAI,b,3} = k_{PKAI,f,3} / K_{PKAI,3}
\]

(B.90)

\[
k_{PKI,b} = k_{PKI,f} \cdot K_{PKI}
\]

(B.91)

\[
\frac{d[cAMP]_{PKAI}^{\text{cav}}}{dt} = -k_{PKAI,f,1} \cdot [RC]_{f}^{\text{cav}} \cdot [cAMP]_{f}^{\text{cav}} + k_{PKAI,b,1} \cdot [ARC]_{f}^{\text{cav}}
\]

\[
- k_{PKAI,f,2} \cdot [ARC]_{f}^{\text{cav}} \cdot [cAMP]_{f}^{\text{cav}} + k_{PKAI,b,2} \cdot [A_{2}RC]_{f}^{\text{cav}}
\]

(B.92)

\[
\frac{d[ARC]_{f}^{\text{cav}}}{dt} = k_{PKAI,f,1} \cdot [RC]_{f}^{\text{cav}} \cdot [cAMP]_{f}^{\text{cav}} - k_{PKAI,b,1} \cdot [ARC]_{f}^{\text{cav}}
\]

\[
- k_{PKAI,f,2} \cdot [ARC]_{f}^{\text{cav}} \cdot [cAMP]_{f}^{\text{cav}} + k_{PKAI,b,2} \cdot [A_{2}RC]_{f}^{\text{cav}}
\]

(B.93)

\[
\frac{d[A_{2}RC]_{f}^{\text{cav}}}{dt} = k_{PKAI,f,2} \cdot [ARC]_{f}^{\text{cav}} \cdot [cAMP]_{f}^{\text{cav}} - (k_{PKAI,b,2} + k_{PKAI,f,3}) \cdot [A_{2}RC]_{f}^{\text{cav}}
\]

\[
+ k_{PKAI,b,3} \cdot [A_{2}R]_{f}^{\text{cav}} \cdot [C]_{f}^{\text{cav}}
\]

(B.94)

\[
\frac{d[A_{2}R]_{f}^{\text{cav}}}{dt} = k_{PKAI,f,3} \cdot [A_{2}RC]_{f}^{\text{cav}} - k_{PKAI,b,3} \cdot [A_{2}R]_{f}^{\text{cav}} \cdot [C]_{f}^{\text{cav}}
\]

(B.95)
\[
\frac{d[C]^{\text{cav}}}{dt} = k_{\text{PKAII},f_3} \cdot [A_2RC]^{\text{cav}} - k_{\text{PKAII},b_3} \cdot [A_2R]^{\text{cav}} \cdot [C]^{\text{cav}} + k_{\text{PKI},b} \cdot [PKIC]^{\text{cav}} \tag{B.96}
\]
\[
- k_{\text{PKI},f} \cdot [PKI]_f^{\text{cav}} \cdot [C]^{\text{cav}}
\]
\[
\frac{d[PKIC]^{\text{cav}}}{dt} = -k_{\text{PKI},b} \cdot [PKIC]^{\text{cav}} + k_{\text{PKI},f} \cdot [PKI]_f^{\text{cav}} \cdot [C]^{\text{cav}} \tag{B.97}
\]

**Extracaveolae**

\[
[PKA]^{\text{ecav}} = \tau_{\text{PKA}}^{\text{ecav}} \cdot [PKA]_{\text{tot}} \cdot \frac{V_{\text{cell}}}{V_{\text{ecav}}} \tag{B.98}
\]
\[
[RC]_f^{\text{ecav}} = 2 \cdot [PKA]^{\text{ecav}} - [ARC]^{\text{ecav}} - [A_2RC]^{\text{ecav}} - [A_2R]^{\text{ecav}} \tag{B.99}
\]
\[
[PKI]_f^{\text{ecav}} = \tau_{PKI}^{\text{ecav}} \cdot [PKI]_{\text{tot}} \cdot \frac{V_{\text{cell}}}{V_{\text{ecav}}} - [PKIC]^{\text{ecav}} \tag{B.100}
\]
\[
k_{\text{PKAII},b_1} = k_{\text{PKAII},f_1} \cdot K_{\text{PKAII},3} \tag{B.101}
\]
\[
k_{\text{PKAII},b_2} = k_{\text{PKAII},f_2} \cdot K_{\text{PKAII},2} \tag{B.102}
\]
\[
k_{\text{PKAII},b_3} = k_{\text{PKAII},f_3} / K_{\text{PKAII},3} \tag{B.103}
\]
\[
k_{\text{PKI},b} = k_{\text{PKI},f} \cdot K_{\text{PKI}} \tag{B.104}
\]
\[
\frac{d[cAMP]^{\text{PKA}}}{dt} = -k_{\text{PKAII},f_1} \cdot [RC]_f^{\text{ecav}} \cdot [cAMP]^{\text{ecav}} + k_{\text{PKAII},b_1} \cdot [ARC]^{\text{ecav}} \tag{B.105}
\]
\[- k_{\text{PKAII},f_2} \cdot [ARC]^{\text{ecav}} \cdot [cAMP]^{\text{ecav}} + k_{\text{PKAII},b_2} \cdot [A_2RC]^{\text{ecav}}
\]
\[
\frac{d[ARC]^{\text{ecav}}}{dt} = k_{\text{PKAII},f_1} \cdot [RC]_f^{\text{ecav}} \cdot [cAMP]^{\text{ecav}} - k_{\text{PKAII},b_1} \cdot [ARC]^{\text{ecav}} \tag{B.106}
\]
\[- k_{\text{PKAII},f_2} \cdot [ARC]^{\text{ecav}} \cdot [cAMP]^{\text{ecav}} + k_{\text{PKAII},b_2} \cdot [A_2RC]^{\text{ecav}}
\]
\[
\frac{d[A_2RC]^{\text{ecav}}}{dt} = k_{\text{PKAII},f_2} \cdot [ARC]^{\text{ecav}} \cdot [cAMP]^{\text{ecav}} - (k_{\text{PKAII},b_2} + k_{\text{PKAII},f_3}) \cdot [A_2RC]^{\text{ecav}} \tag{B.107}
\]
\[+ k_{\text{PKAII},b_3} \cdot [A_2R]^{\text{ecav}} \cdot [C]^{\text{ecav}}
\]
\[
\frac{d[A_2R]^{\text{ecav}}}{dt} = k_{\text{PKAII},f_3} \cdot [A_2RC]^{\text{ecav}} - k_{\text{PKAII},b_3} \cdot [A_2R]^{\text{ecav}} \cdot [C]^{\text{ecav}} \tag{B.108}
\]
\[
\frac{d[C]_{cav}^{\text{ecav}}}{dt} = k_{PKAI,b3} \cdot [A_2RC]^{\text{ecav}} - k_{PKAI,b3} \cdot [A_2R]^{\text{ecav}} \cdot [C]^{\text{ecav}} + k_{PKI,b} \cdot [PKIC]^{\text{ecav}} - k_{PKI,f} \cdot [PKI_f]^{\text{ecav}} \cdot [C]^{\text{ecav}}
\]

(B.109)

\[
\frac{d[PKIC]^{\text{ecav}}}{dt} = -k_{PKI,b} \cdot [PKIC]^{\text{ecav}} + k_{PKI,f} \cdot [PKI_f]^{\text{ecav}} \cdot [C]^{\text{ecav}}
\]

(B.110)

**Cytosol**

\[
[PKA]^{\text{cyt}} = f_{PKA}^{\text{cyt}} \cdot [PKA]_{tot}^{\text{cyt}} \cdot \frac{V^{\text{cell}}_{cyt}}{V^{\text{cell}}_{cyt}}
\]

(B.111)

\[
[RC]^{\text{cyt}}_f = 2 \cdot [PKA]^{\text{cyt}} - [ARC]^{\text{cyt}} - [A_2RC]^{\text{cyt}} - [A_2R]^{\text{cyt}}
\]

(B.112)

\[
[PKI]^{\text{cyt}}_f = f_{PKI}^{\text{cyt}} \cdot [PKI]_{tot}^{\text{cyt}} \cdot \frac{V^{\text{cell}}_{cyt}}{V^{\text{cell}}_{cyt}} - [PKIC]^{\text{cyt}}
\]

(B.113)

\[
k_{PKAI,b1} = k_{PKAI,f1} \cdot K_{PKAI,3}
\]

(B.114)

\[
k_{PKAI,b2} = k_{PKAI,f2} \cdot K_{PKAI,2}
\]

(B.115)

\[
k_{PKAI,b3} = k_{PKAI,f3} / K_{PKAI,3}
\]

(B.116)

\[
k_{PKI,b} = k_{PKI,f} \cdot K_{PKI}
\]

(B.117)

\[
\frac{d[cAMP]^{\text{cyt}}_{PKA}}{dt} = -k_{PKAI,f1} \cdot [RC]^{\text{cyt}}_f \cdot [cAMP]^{\text{cyt}} + k_{PKAI,b1} \cdot [ARC]^{\text{cyt}} - k_{PKAI,f2} \cdot [ARC]^{\text{cyt}} \cdot [cAMP]^{\text{cyt}} + k_{PKAI,b2} \cdot [A_2RC]^{\text{cyt}}
\]

(B.118)

\[
\frac{d[ARC]^{\text{cyt}}}{dt} = k_{PKAI,f1} \cdot [RC]^{\text{cyt}}_f \cdot [cAMP]^{\text{cyt}} - k_{PKAI,b1} \cdot [ARC]^{\text{cyt}} - k_{PKAI,f2} \cdot [ARC]^{\text{cyt}} \cdot [cAMP]^{\text{cyt}} + k_{PKAI,b2} \cdot [A_2RC]^{\text{cyt}}
\]

(B.119)

\[
\frac{d[A_2RC]^{\text{cyt}}}{dt} = k_{PKAI,f2} \cdot [ARC]^{\text{cyt}} \cdot [cAMP]^{\text{cyt}} - (k_{PKAI,b2} + k_{PKAI,f3}) \cdot [A_2RC]^{\text{cyt}} + k_{PKAI,b3} \cdot [A_2R]^{\text{cyt}} \cdot [C]^{\text{cyt}}
\]

(B.120)

\[
\frac{d[A_2R]^{\text{cyt}}}{dt} = k_{PKAI,f3} \cdot [A_2RC]^{\text{cyt}} - k_{PKAI,b3} \cdot [A_2R]^{\text{cyt}} \cdot [C]^{\text{cyt}}
\]

(B.121)
\[
\frac{d[C]^{\text{cyt}}}{dt} = k_{\text{PKAI},f3} \cdot [A_{2}RC]^{\text{cyt}} - k_{\text{PKAI},b3} \cdot [A_{2}R]^{\text{cyt}} \cdot [C]^{\text{cyt}} + k_{\text{PKI},b} \cdot [PKIC]^{\text{cyt}} \\
- k_{\text{PKI},f} \cdot [PKI]_{f}^{\text{cyt}} \cdot [C]^{\text{cyt}}
\]  
\[
\frac{d[PKIC]^{\text{cyt}}}{dt} = -k_{\text{PKI},b} \cdot [PKIC]^{\text{cyt}} + k_{\text{PKI},f} \cdot [PKI]_{f}^{\text{cyt}} \cdot [C]^{\text{cyt}}
\]

**Protein phosphatases and inhibitor-1 module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>([PP1]_{\text{tot}}^{\text{cyt}})</td>
<td>Total concentration of PP1 in the cytosolic compartment</td>
<td>0.2 (\mu)M</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>([PP1]^{\text{cyt}})</td>
<td>Cytosolic concentration of PP1</td>
<td>0.0607843 (\mu)M</td>
<td>This paper</td>
</tr>
<tr>
<td>([PP2A]^{\text{cyt}})</td>
<td>Cytosolic concentration of PP2A</td>
<td>0.0607843 (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>([PP1]_{\text{cav}}^{\text{cyt}})</td>
<td>Concentration of PP1 in the caveolae compartment</td>
<td>0.1 (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>([PP2A]_{\text{cav}}^{\text{cyt}})</td>
<td>Concentration of PP2A in the caveolae compartment</td>
<td>0.1 (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>([PP]_{\text{cav}}^{\text{cyt}})</td>
<td>Total phosphatase concentration in caveolae compartment ([PP1]<em>{\text{cav}}^{\text{cyt}} + [PP2A]</em>{\text{cav}}^{\text{cyt}})</td>
<td>0.2 (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>([PP1]_{\text{cav}}^{\text{cyt}})</td>
<td>Concentration of PP1 in the extracaveolae compartment</td>
<td>0.1 (\mu)M</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>([Inhib1]_{\text{tot}}^{\text{cyt}})</td>
<td>Total concentration of inhibitor 1 in the cytosolic compartment</td>
<td>0.08543 (\mu)M</td>
<td>El-Armouche et al. [120]</td>
</tr>
<tr>
<td>(K_{\text{inhib1}})</td>
<td>Affinity for PP1 – Inhibitor 1 binding</td>
<td>1.0(\cdot10^{-3}) (\mu)M</td>
<td>Saucerman et al. [30]</td>
</tr>
<tr>
<td>(k_{\text{PKA,Inhib1}})</td>
<td>Rate of phosphorylation of inhibitor 1 by PKA</td>
<td>1080.0 (\mu)M(^{-1}) (s^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{m,PKA,Inhib1})</td>
<td>Affinity of inhibitor 1 for PKA catalytic subunit</td>
<td>1.5 (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{\text{PP2A,Inhib1}})</td>
<td>Rate of dephosphorylation of inhibitor 1</td>
<td>50.67 (\mu)M(^{-1}) (s^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{m,PP2A,Inhib1})</td>
<td>Affinity for PP2A – Inhibitor 1 binding</td>
<td>1.0(\cdot10^{-3}) (\mu)M</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

\[
[\text{Inhib1}]_{f}^{\text{cyt}} = [\text{Inhib1}]_{\text{tot}}^{\text{cyt}} - [\text{Inhib1}]_{p,\text{tot}}^{\text{cyt}}
\]

\[
a_{\text{Inhib1}} = 1.0
\]

\[
b_{\text{Inhib1}} = K_{\text{Inhib1}} + [PP1]_{\text{tot}}^{\text{cyt}} - [\text{Inhib1}]_{p,\text{tot}}^{\text{cyt}}
\]

\[
c_{\text{Inhib1}} = -[\text{Inhib1}]_{p,\text{tot}}^{\text{cyt}} \cdot K_{\text{Inhib1}}
\]
\[
[I_{\text{Inhib}}]^{\text{ctf}}_p = \frac{-b_{\text{Inhib}} + \sqrt{[b_{\text{Inhib}}]^2 - 4 \cdot a_{\text{Inhib}} \cdot c_{\text{Inhib}}}}{2 \cdot a_{\text{Inhib}}}
\]  
(B.128)

\[
[PPI]^{\text{ctf}}_p = \frac{[PPI]^{\text{ctf}} \cdot K_{\text{Inhib}}}{K_{\text{Inhib}} + [I_{\text{Inhib}}]^{\text{ctf}}}
\]  
(B.129)

\[
d[I_{\text{Inhib}}]^{\text{ctf}}_{p,\text{tot}} = \frac{k_{\text{PKA, Inhib}} \cdot [C]^{\text{ctf}} \cdot [I_{\text{Inhib}}]^{\text{ctf}} + k_{\text{PP2A, Inhib}} \cdot [PP2A]^{\text{ctf}} \cdot [I_{\text{Inhib}}]^{\text{ctf}}}{K_{\text{mPKA, Inhib}} + [I_{\text{Inhib}}]^{\text{ctf}} + K_{\text{mPP2A, Inhib}} + [I_{\text{Inhib}}]^{\text{ctf}}}
\]  
(B.130)

### cAMP fluxes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( J_{\text{cav/ecav}} )</td>
<td>Rate of cAMP diffusion between caveolae and extracaveolea compartments</td>
<td>5.000 \cdot 10^{-9} \text{ \scriptsize \mu L s}^{-1}</td>
<td>Iancu et al. [114]</td>
</tr>
<tr>
<td>( J_{\text{cav/cyt}} )</td>
<td>Rate of cAMP diffusion between caveolae and cytosolic compartments</td>
<td>7.500 \cdot 10^{-8} \text{ \scriptsize \mu L s}^{-1}</td>
<td>Iancu et al. [114]</td>
</tr>
<tr>
<td>( J_{\text{ecav/cyt}} )</td>
<td>Rate of cAMP diffusion between extracaveolae and cytosolic compartments</td>
<td>9.000 \cdot 10^{-9} \text{ \scriptsize \mu L s}^{-1}</td>
<td>Iancu et al. [114]</td>
</tr>
</tbody>
</table>

\[
d[cAMP]^{\text{cav}} = \frac{d[cAMP]^{\text{cav}}_{\text{PKA}} + d[cAMP]^{\text{cav}}_{\text{AC56}} - d[cAMP]^{\text{cav}}_{\text{PDE2}} - d[cAMP]^{\text{cav}}_{\text{PDE3}}}{dt}
\]  
(B.131)

\[
d[cAMP]^{\text{ecav}} = \frac{d[cAMP]^{\text{ecav}}_{\text{PKA}} + d[cAMP]^{\text{ecav}}_{\text{AC47}} - d[cAMP]^{\text{ecav}}_{\text{PDE2}} - d[cAMP]^{\text{ecav}}_{\text{PDE4}}}{dt}
\]  
(B.132)

\[
d[cAMP]^{\text{ctf}} = \frac{d[cAMP]^{\text{ctf}}_{\text{PKA}} + d[cAMP]^{\text{ctf}}_{\text{AC56}} + d[cAMP]^{\text{ctf}}_{\text{AC47}} - d[cAMP]^{\text{ctf}}_{\text{PDE2}} - d[cAMP]^{\text{ctf}}_{\text{PDE4}}}{dt}
\]  
(B.133)
Electrophysiological part: PKA substrates

**L-type \( \text{Ca}^{2+} \) current module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>([I_{\text{Cal}]}_{\text{tot}})</td>
<td>Total cellular concentration of the L-type ( \text{Ca}^{2+} ) channels</td>
<td>0.0273 µM</td>
<td>Chu et al. [121] Bers and Stiffel [122]</td>
</tr>
<tr>
<td>(f_{\text{cav}}^{\text{ICaL}})</td>
<td>Fraction of the L-type ( \text{Ca}^{2+} ) channels located in caveolae</td>
<td>0.2</td>
<td>Scriven et al. [38]</td>
</tr>
<tr>
<td>(f_{\text{ecav}}^{\text{ICaL}})</td>
<td>Fraction of the L-type ( \text{Ca}^{2+} ) channels located in extracaveolae</td>
<td>(1 - f_{\text{cav}}^{\text{ICaL}})</td>
<td>Scriven et al. [38]</td>
</tr>
<tr>
<td>(G_{\text{Cal}})</td>
<td>Specific maximum conductivity for L-type ( \text{Ca}^{2+} ) channel (non-phosphorylated)</td>
<td>0.3772 mS/µF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(G_{\text{Cal,p}})</td>
<td>Specific maximum conductivity for L-type ( \text{Ca}^{2+} ) channel (phosphorylated)</td>
<td>0.7875 mS/µF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(E_{\text{Cal}})</td>
<td>Reversal potential for L-type ( \text{Ca}^{2+} ) channel</td>
<td>52.0 mV</td>
<td>Petkova-Kirova et al. [61]</td>
</tr>
<tr>
<td>(K_{p_{c,\text{max}}})</td>
<td>Maximum rate constant for ( \text{Ca}^{2+} )-induced inactivation</td>
<td>233.24 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{p_{c,\text{half}}})</td>
<td>Half-saturation constant for ( \text{Ca}^{2+} )-induced inactivation</td>
<td>10.0 µM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{p_{cf}})</td>
<td>Forward voltage-insensitive rate constant for inactivation</td>
<td>40,000 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{p_{cb}})</td>
<td>Backward voltage-insensitive rate constant for inactivation</td>
<td>2.4 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{co})</td>
<td>Forward voltage-insensitive rate constant for activation (non-phosphorylated)</td>
<td>1.000 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{cop})</td>
<td>Forward voltage-insensitive rate constant for activation (phosphorylated)</td>
<td>4,000 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{ac})</td>
<td>Backward voltage-insensitive rate constant for activation</td>
<td>1,000 s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(I_{\text{Cal,max}})</td>
<td>Normalization constant for L-type ( \text{Ca}^{2+} ) current</td>
<td>7.0 pA/pF</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{f\text{Cal}_PKA})</td>
<td>Phosphorylation rate of the L-type ( \text{Ca}^{2+} ) channel by PKA</td>
<td>(1.74 \cdot 10^{-2}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{f\text{Cal}_PP})</td>
<td>Dephosphorylation rate of the L-type ( \text{Ca}^{2+} ) channel by PP1 and PP2A</td>
<td>(2.325 \cdot 10^{-4}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{f\text{Cal}_PKA})</td>
<td>Affinity of the L-type ( \text{Ca}^{2+} ) channel for PKA</td>
<td>0.5 µM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{f\text{Cal}_PP})</td>
<td>Affinity of the L-type ( \text{Ca}^{2+} ) channel for PP1 and PP2A</td>
<td>0.2 µM</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

\[
I_{\text{Cal}} = I_{\text{ICaL}}^{\text{cav}} + I_{\text{ICaL}}^{\text{ecav}} \quad \text{(B.134)}
\]

\[
\alpha = 0.4 e^{(V+15.0)/15.0} \quad \text{(B.135)}
\]
\[ \alpha_p = 0.4e^{(F+15.0+20.0)/15.0} \]  
(B.136)

\[ \beta = 0.13e^{-(F+15.0)/18.0} \]  
(B.137)

**Caveolae**

\[ [I_{CaL\ tot}]_{cav} = f_{cav}^i[I_{CaL\ tot}]_{cav} \frac{V_{cell}}{V_{cav}} \]  
(B.138)

\[ I_{CaL}^{cav} = f_{cav}^i(G_{CaL} \cdot O_{cav}^{cav} + G_{CaL,p} \cdot O_{p}^{cav}) (V - E_{CaL}) \]  
(B.139)

\[ \gamma_{cav}^{cav} = \frac{K_{pc,max}[Ca^{2+}]}{K_{pc,half} + [Ca^{2+}]} \]  
(B.140)

\[ \frac{dO_{cav}^{cav}}{dt} = k_{co} C_{cav}^{cav} - k_{oc} O_{cav}^{cav} + k_{pc} I_{cav}^{cav} - \gamma_{cav}^{cav} O_{cav}^{cav} + 0.001(\alpha I_{cav}^{cav} - K_{pcf} O_{cav}^{cav}) \]  
(B.141)

\[ C_{1}^{cav} = 1 - (O_{cav}^{cav} + C_{2}^{cav} + C_{3}^{cav} + C_{4}^{cav} + C_{p}^{cav} + I_{1}^{cav} + I_{2}^{cav} + I_{3}^{cav} + O_{p}^{cav} + C_{1p}^{cav} + C_{2p}^{cav} + C_{3p}^{cav} + C_{4p}^{cav} + I_{1p}^{cav} + I_{2p}^{cav} + I_{3p}^{cav}) \]  
(B.142)

\[ \frac{dC_{2}^{cav}}{dt} = 4\alpha C_{1}^{cav} - \beta C_{2}^{cav} + 2\beta C_{3}^{cav} - 3\alpha C_{2}^{cav} \]  
(B.143)

\[ \frac{dC_{3}^{cav}}{dt} = 4\alpha C_{1}^{cav} - \beta C_{2}^{cav} + 2\beta C_{3}^{cav} - 3\alpha C_{2}^{cav} \]  
(B.144)

\[ \frac{dC_{4}^{cav}}{dt} = 4\alpha C_{1}^{cav} - \beta C_{2}^{cav} + 2\beta C_{3}^{cav} - 3\alpha C_{2}^{cav} \]  
(B.145)
\[
\frac{dC_{p}^{\text{cav}}}{dt} = \alpha C_{1}^{\text{cav}} - 4\beta C_{p}^{\text{cav}} + k_{\text{oc}} O_{p}^{\text{cav}} - k_{\text{co}} C_{p}^{\text{cav}} \quad \text{(B.146)}
\]

\[
\frac{dI_{1}^{\text{cav}}}{dt} = \gamma_{1}^{\text{cav}} O_{p}^{\text{cav}} - K_{\text{pcb}} I_{1}^{\text{cav}} + 0.001(\alpha I_{1}^{\text{cav}} - K_{\text{pcb}} I_{1}^{\text{cav}}) + 0.01(\frac{k_{\text{co}}}{k_{\text{oc}}} \gamma_{1}^{\text{cav}} C_{4}^{\text{cav}} - 4\beta K_{\text{pcb}} I_{1}^{\text{cav}}) \quad \text{(B.147)}
\]

\[
\frac{dI_{2}^{\text{cav}}}{dt} = 0.001(K_{\text{pcf}} O_{p}^{\text{cav}} - \alpha I_{2}^{\text{cav}}) + K_{\text{pcb}} I_{3}^{\text{cav}} - \gamma_{2}^{\text{cav}} I_{2}^{\text{cav}} + 0.002(\frac{k_{\text{co}}}{k_{\text{oc}}} K_{p_{\text{pcf}}} C_{4}^{\text{cav}} - 4\beta I_{2}^{\text{cav}}) \quad \text{(B.148)}
\]

\[
\frac{dI_{3}^{\text{cav}}}{dt} = 0.001(K_{\text{pcf}} I_{2}^{\text{cav}} - \alpha I_{3}^{\text{cav}}) + \gamma_{3}^{\text{cav}} I_{2}^{\text{cav}} - K_{\text{pcb}} I_{3}^{\text{cav}} + \frac{k_{\text{co}}}{k_{\text{oc}}} K_{p_{\text{pcf}}} C_{4}^{\text{cav}} - 4\beta K_{\text{pcb}} I_{3}^{\text{cav}} \quad \text{(B.149)}
\]

\[
\frac{dO_{p}^{\text{cav}}}{dt} = k_{\text{cop}} C_{p}^{\text{cav}} - k_{\text{oc}} O_{p}^{\text{cav}} + K_{\text{pcb}} I_{1}^{\text{cav}} - \gamma_{2}^{\text{cav}} O_{p}^{\text{cav}} + 0.001(\alpha_{p} I_{2}^{\text{cav}} - K_{\text{pcf}} O_{p}^{\text{cav}}) \quad \text{(B.150)}
\]

\[
\frac{dC_{p}^{\text{cav}}}{dt} = \beta C_{1}^{\text{cav}} - 4\alpha_{p} C_{1}^{\text{cav}} + \frac{k_{\text{ICaL_PK}}[C_{1}^{\text{cav}}]}{K_{\text{ICaL_PK}} + [I_{\text{ICaL}}]_{\text{cav}} C_{1}^{\text{cav}}} - \alpha_{p}^{3} k_{\text{cop}} \frac{k_{\text{ICaL_PP}}[PP]^{\text{cav}}}{K_{\text{ICaL_PP}} + [I_{\text{ICaL}}]_{\text{cav}} C_{1}^{\text{cav}} C_{p}^{\text{cav}}} \quad \text{(B.151)}
\]

\[
\frac{dC_{p}^{\text{cav}}}{dt} = 4\alpha_{p} C_{1}^{\text{cav}} - \beta C_{2}^{\text{cav}} + 2\beta C_{3}^{\text{cav}} - 3\alpha_{p} C_{3}^{\text{cav}} \quad \text{(B.152)}
\]

\[
\frac{dC_{p}^{\text{cav}}}{dt} = 3\alpha_{p} C_{2}^{\text{cav}} - 2\beta C_{3}^{\text{cav}} + 3\beta C_{4}^{\text{cav}} - 2\alpha_{p} C_{3}^{\text{cav}} \quad \text{(B.153)}
\]
\[
\frac{dC_{cav}^{4p}}{dt} = 2\alpha_p C_{cav}^{4p} - 3\beta C_{cav}^{4p} + 4\beta C_{cav}^{4p} - \alpha_p C_{cav}^{4p} + 0.01(4K_{pcb}\beta I_{cav}^{1p} - \frac{k_{cav}}{k_{oc}}\gamma_{cav} C_{cav}^{4p})
\] (B.154)

\[
+ 0.002(4\beta I_{cav}^{1p} - \frac{k_{cav}}{k_{oc}} K_{p_{cf}} C_{cav}^{4p}) + 4\beta K_{p_{cb}} I_{cav}^{3p} - \frac{k_{cav}}{k_{oc}}\gamma_{cav} K_{p_{cf}} C_{cav}^{4p}
\]

\[
+ \frac{k_{ICal_{PKA}}[C_{cav}^{4p}]}{K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]} = \frac{k_{cav} k_{ICal_{PKA}}}{} + \frac{k_{ICal_{PP}}[PP_{cav}]}{k_{cav} K_{ICal_{PP}} + [I_{Cal_{tot}} C_{cav}^{4p}]}
\]

\[
\frac{dC_{cav}^{4p}}{dt} = \alpha_p C_{cav}^{4p} - 4\beta C_{cav}^{4p} + k_{oc} O_{cav} - k_{cav} C_{cav}^{4p}
\] (B.155)

\[
+ \frac{k_{ICal_{PKA}}[C_{cav}^{4p}]}{K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]} = \alpha_p k_{cav} K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]
\]

\[
\frac{dI_{cav}^{1p}}{dt} = \gamma_{cav} O_{cav} - K_{p_{cb}} I_{cav}^{1p} + 0.001(\alpha_p I_{cav}^{1p} - K_{p_{cf}} I_{cav}^{1p}) + 0.01(\frac{k_{cav}}{k_{oc}}\gamma_{cav} C_{cav}^{4p} - 4\beta K_{p_{cb}} I_{cav}^{1p})
\] (B.156)

\[
+ \frac{k_{ICal_{PKA}}[C_{cav}^{4p}]}{K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]} = \alpha_p k_{cav} K_{ICal_{PP}} + [I_{Cal_{tot}} C_{cav}^{4p}]
\]

\[
\frac{dI_{cav}^{2p}}{dt} = 0.001(K_{p_{cf}} O_{cav} - \alpha_p I_{cav}^{2p}) + K_{p_{cb}} I_{cav}^{3p} - \gamma_{cav} I_{cav}^{2p} + 0.002(\frac{k_{cav}}{k_{oc}} K_{p_{cf}} C_{cav}^{4p} - 4\beta I_{cav}^{2p})
\] (B.157)

\[
+ \frac{k_{ICal_{PKA}}[C_{cav}^{4p}]}{K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]} = \frac{k_{ICal_{PP}}[PP_{cav}]}{K_{ICal_{PP}} + [I_{Cal_{tot}} C_{cav}^{4p}]}
\]

\[
\frac{dI_{cav}^{3p}}{dt} = 0.001(K_{p_{cf}} I_{cav}^{1p} - \alpha_p I_{cav}^{3p}) + \gamma_{cav} I_{cav}^{2p} - K_{p_{cb}} I_{cav}^{3p} + \frac{k_{cav}}{k_{oc}}\gamma_{cav} K_{p_{cf}} C_{cav}^{4p} - 4\beta K_{p_{cb}} I_{cav}^{3p}
\] (B.158)

\[
+ \frac{k_{ICal_{PKA}}[C_{cav}^{4p}]}{K_{ICal_{PKA}} + [I_{Cal_{tot}} C_{cav}^{4p}]} = \frac{k_{ICal_{PP}}[PP_{cav}]}{K_{ICal_{PP}} + [I_{Cal_{tot}} C_{cav}^{4p}]}
\]

**Extractacaveolae**

\[
[I_{Cal_{tot}}]_{ecav} = f_{ICal_{tot}}[I_{Cal_{tot}}]_{tot} V_{cell} \frac{V_{cell}}{V_{ecav}}
\] (B.159)

\[
I_{Cal}^{ecav} = f_{ICal}^{ecav}(G_{Cal} \cdot O_{cav} + G_{Cal_{tot}} \cdot O_{cav})(V - E_{Cal})
\] (B.160)

\[
\gamma_{ecav} = \frac{K_{pc_{max}}[Ca^{2+}]_{ss}}{K_{pc_{half}} + [Ca^{2+}]_{ss}}
\] (B.161)
\[
\frac{dO^\text{ecav}}{dt} = k_{oc} C_p^\text{ecav} - k_{oc} O^\text{ecav} + K_{p_{cb}} I_1^\text{ecav} - \gamma^\text{ecav} O^\text{ecav} + 0.001(\alpha I_2^\text{ecav} - K_{p_{cf}} O^\text{ecav}) 
\]

\[
C_1^\text{ecav} = 1 - (O^\text{ecav} + C_2^\text{ecav} + C_3^\text{ecav} + C_4^\text{ecav} + C_p^\text{ecav} + I_1^\text{ecav} + I_2^\text{ecav} + I_3^\text{ecav} + O_p^\text{ecav} + C_{1p}^\text{ecav} + C_{2p}^\text{ecav} + C_{3p}^\text{ecav} + C_{4p}^\text{ecav} + C_p^\text{ecav} + I_{1p}^\text{ecav} + I_{2p}^\text{ecav} + I_{3p}^\text{ecav}) 
\]

\[
\frac{dC_2^\text{ecav}}{dt} = 4\alpha C_1^\text{ecav} - \beta C_2^\text{ecav} + 2\beta C_3^\text{ecav} - 3\alpha C_2^\text{ecav} 
\]

\[
\frac{dC_3^\text{ecav}}{dt} = 3\alpha C_2^\text{ecav} - 2\beta C_3^\text{ecav} + 3\beta C_4^\text{ecav} - 2\alpha C_3^\text{ecav} 
\]

\[
\frac{dC_4^\text{ecav}}{dt} = 2\alpha C_3^\text{ecav} - 3\beta C_4^\text{ecav} + 4\beta C_p^\text{ecav} - \alpha C_4^\text{ecav} + 0.01(4K_{p_{cb}} \beta I_1^\text{ecav} - \frac{k_{co}}{k_{oc}} \alpha \gamma^\text{ecav} C_4^\text{ecav}) + 0.002(4\beta I_2^\text{ecav} - \frac{k_{co}}{k_{oc}} K_{p_{cf}} C_4^\text{ecav}) + 4\beta K_{p_{cb}} I_3^\text{ecav} - \frac{k_{co}}{k_{oc}} \gamma^\text{ecav} K_{p_{cf}} C_4^\text{ecav} 
\]

\[
\frac{dC_p^\text{ecav}}{dt} = \alpha C_4^\text{ecav} - 4\beta C_p^\text{ecav} + k_{oc} O^\text{ecav} - k_{cs} C_p^\text{ecav} 
\]

\[
\frac{dI_1^\text{ecav}}{dt} = \gamma^\text{ecav} O^\text{ecav} - K_{p_{cb}} I_1^\text{ecav} + 0.001(\alpha I_3^\text{ecav} - K_{p_{cf}} I_1^\text{ecav}) + 0.01(\frac{k_{co}}{k_{oc}} \alpha \gamma^\text{ecav} C_4^\text{ecav} - 4\beta K_{p_{cb}} I_1^\text{ecav}) 
\]
\[
\frac{dI_2^\text{ecav}}{dt} = 0.001(K_{\text{pcf}} O_\text{ecav} - \alpha I_2^\text{ecav}) + K_{\text{pcb}} I_3^\text{ecav} - \gamma I_2^\text{ecav} + 0.002\left(\frac{k_{\text{ecav}}}{k_{oc}} K_{\text{pcf}} C_4 - 4\beta I_2^\text{ecav}\right) \tag{B.169}
\]

\[
- \frac{k_{I_{\text{Cal}, PKA}} [C] I_2^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] I_2^\text{ecav}} + \frac{k_{I_{\text{Cal}, PP}} [PP] I_2^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] I_2^\text{ecav}}
\]

\[
\frac{dI_3^\text{ecav}}{dt} = 0.001(K_{\text{pcf}} I_1^\text{ecav} - \alpha I_3^\text{ecav}) + \gamma I_2^\text{ecav} - K_{\text{pcb}} I_3^\text{ecav} + \frac{k_{\text{ecav}}}{k_{oc}} \gamma_{\text{ecav}} K_{\text{pcf}} C_4 - 4\beta K_{\text{pcb}} I_3^\text{ecav} \tag{B.170}
\]

\[
- \frac{k_{I_{\text{Cal}, PKA}} [C] I_3^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] I_3^\text{ecav}} + \frac{k_{I_{\text{Cal}, PP}} [PP] I_3^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] I_3^\text{ecav}}
\]

\[
\frac{dO_p^\text{ecav}}{dt} = k_{\text{cop}} C_{1p}^\text{ecav} - k_{oc} O_p^\text{ecav} + K_{\text{pcb}} I_p^\text{ecav} - \gamma O_p^\text{ecav} + 0.001(\alpha_p I_p^\text{ecav} - K_{\text{pcf}} O_p^\text{ecav}) \tag{B.171}
\]

\[
+ \frac{k_{I_{\text{Cal}, PKA}} [C] O_p^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] O_p^\text{ecav}} - \frac{\alpha}{\alpha_p} \frac{k_{I_{\text{Cal}, PP}} [PP] O_p^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] O_p^\text{ecav}}
\]

\[
\frac{dC_{1p}^\text{ecav}}{dt} = \beta C_{2p}^\text{ecav} - 4\alpha_p C_{1p}^\text{ecav} + \frac{k_{I_{\text{Cal}, PKA}} [C] C_1^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] C_1^\text{ecav}} - \frac{\alpha_p^2 k_{\text{cop}}}{\alpha_p^2 k_{oc}} \frac{k_{I_{\text{Cal}, PP}} [PP] C_{1p}^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] C_{1p}^\text{ecav}} \tag{B.172}
\]

\[
\frac{dC_{2p}^\text{ecav}}{dt} = 4\alpha_p C_{1p}^\text{ecav} - \beta C_{2p}^\text{ecav} + 2\beta C_{3p}^\text{ecav} - 3\alpha_p C_{2p}^\text{ecav} \tag{B.173}
\]

\[
+ \frac{k_{I_{\text{Cal}, PKA}} [C] C_{2p}^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] C_{2p}^\text{ecav}} - \frac{\alpha_p^2 k_{\text{cop}}}{\alpha_p^2 k_{oc}} \frac{k_{I_{\text{Cal}, PP}} [PP] C_{2p}^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] C_{2p}^\text{ecav}}
\]

\[
\frac{dC_{3p}^\text{ecav}}{dt} = 3\alpha_p C_{2p}^\text{ecav} - 2\beta C_{3p}^\text{ecav} + 3\beta C_{4p}^\text{ecav} - 2\alpha_p C_{3p}^\text{ecav} \tag{B.174}
\]

\[
+ \frac{k_{I_{\text{Cal}, PKA}} [C] C_{3p}^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] C_{3p}^\text{ecav}} - \frac{\alpha_p^2 k_{\text{cop}}}{\alpha_p^2 k_{oc}} \frac{k_{I_{\text{Cal}, PP}} [PP] C_{3p}^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] C_{3p}^\text{ecav}}
\]

\[
\frac{dC_{4p}^\text{ecav}}{dt} = 2\alpha_p C_{3p}^\text{ecav} - 3\beta C_{4p}^\text{ecav} + 4\beta C_{pp}^\text{ecav} - \alpha_p C_{4p}^\text{ecav} + 0.01(4K_{\text{pcb}} \beta I_1^\text{ecav} = \frac{k_{\text{cop}}}{k_{oc}} \alpha_{\text{ecav}} C_{4p}^\text{ecav}) \tag{B.175}
\]

\[
+ 0.002(4I_2^\text{ecav} - \frac{k_{\text{cop}}}{k_{oc}} K_{\text{pcf}} C_{4p}^\text{ecav}) + 4\beta K_{\text{pcb}} I_3^\text{ecav} - \frac{k_{\text{cop}}}{k_{oc}} \gamma_{\text{ecav}} K_{\text{pcf}} C_{4p}^\text{ecav} \]

\[
+ \frac{k_{I_{\text{Cal}, PKA}} [C] C_{4p}^\text{ecav}}{K_{I_{\text{Cal}, PKA}} + [I_{\text{Cal}, \text{lost}}] C_{4p}^\text{ecav}} - \frac{k_{\text{cop}}}{k_{oc}} \frac{k_{I_{\text{Cal}, PP}} [PP] C_{4p}^\text{ecav}}{K_{I_{\text{Cal}, PP}} + [I_{\text{Cal}, \text{lost}}] C_{4p}^\text{ecav}}
\]
\[
\frac{dC^\text{ecav}_{Pp}}{dt} = \alpha_p C^\text{ecav}_{4p} - 4\beta C^\text{ecav}_{Pp} + k_\text{oc} O^\text{ecav}_{Pp} - k_\text{cop} C^\text{ecav}_{Pp} \\
+ \frac{k_{I\text{cal} \_PKA} [C]^\text{ecav}_{Pp} C^\text{ecav}_{Pp}}{K_{I\text{cal} \_PKA} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{Pp} C^\text{ecav}_{Pp}} - \frac{\alpha k_{I\text{cal} \_PP} [PPI]^\text{ecav}_{Pp} C^\text{ecav}_{Pp}}{\alpha P^\text{ecav}_{Pp} + k_{I\text{cal} \_PP} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{Pp}} 
\] (B.176)

\[
\frac{dI^\text{ecav}_{1p}}{dt} = \gamma^\text{ecav} O^\text{ecav}_{Pp} - K_{pca} I^\text{ecav}_{1p} + 0.001(\alpha_p I^\text{ecav}_{1p} - K_{pca} I^\text{ecav}_{1p}) + 0.01(\frac{k_{I\text{cal} \_PKA}}{k_{oc}} \alpha_p \gamma^\text{ecav} C^\text{ecav}_{4p} - 4\beta K_{pca} I^\text{ecav}_{1p}) \\
+ \frac{k_{I\text{cal} \_PKA} [C]^\text{ecav}_{1p} I^\text{ecav}_{1p}}{K_{I\text{cal} \_PKA} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{1p} I^\text{ecav}_{1p}} - \frac{\alpha_p k_{I\text{cal} \_PP} [PPI]^\text{ecav}_{1p} I^\text{ecav}_{1p}}{\alpha P^\text{ecav}_{1p} + k_{I\text{cal} \_PP} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{1p}} 
\] (B.177)

\[
\frac{dI^\text{ecav}_{2p}}{dt} = 0.001(K_{pca} O^\text{ecav}_{2p} - \alpha_p I^\text{ecav}_{2p}) + K_{pca} I^\text{ecav}_{2p} - \gamma^\text{ecav} I^\text{ecav}_{2p} + 0.002(\frac{k_{I\text{cal} \_PKA}}{k_{oc}} \alpha_p \gamma^\text{ecav} C^\text{ecav}_{4p} - 4\beta K_{pca} I^\text{ecav}_{2p}) \\
+ \frac{k_{I\text{cal} \_PKA} [C]^\text{ecav}_{2p} I^\text{ecav}_{2p}}{K_{I\text{cal} \_PKA} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{2p} I^\text{ecav}_{2p}} - \frac{k_{I\text{cal} \_PP} [PPI]^\text{ecav}_{2p} I^\text{ecav}_{2p}}{K_{I\text{cal} \_PP} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{2p}} 
\] (B.178)

\[
\frac{dI^\text{ecav}_{3p}}{dt} = 0.001(K_{pca} I^\text{ecav}_{3p} - \alpha_p I^\text{ecav}_{3p}) + \gamma^\text{ecav} I^\text{ecav}_{3p} - K_{pca} I^\text{ecav}_{3p} + \frac{k_{I\text{cal} \_PKA}}{k_{oc}} \gamma^\text{ecav} K_{pca} C^\text{ecav}_{4p} - 4\beta K_{pca} I^\text{ecav}_{3p} \\
+ \frac{k_{I\text{cal} \_PKA} [C]^\text{ecav}_{3p} I^\text{ecav}_{3p}}{K_{I\text{cal} \_PKA} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{3p} I^\text{ecav}_{3p}} - \frac{k_{I\text{cal} \_PP} [PPI]^\text{ecav}_{3p} I^\text{ecav}_{3p}}{K_{I\text{cal} \_PP} + [I_{\text{cal} \_\text{tot}}]^\text{ecav}_{3p}} 
\] (B.179)

**Fast Na\(^+\) current module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G_{Na})</td>
<td>Specific maximum conductivity for the fast Na(^+) channel (non-phosphorylated)</td>
<td>14.4 mS/(\mu)F</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(G_{Nap})</td>
<td>Specific maximum conductivity for the fast Na(^+) channel (phosphorylated)</td>
<td>18.0 mS/(\mu)F</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{I\text{Na} _PKA})</td>
<td>Phosphorylation-trafficking rate of the fast Na(^+) channel by PKA</td>
<td>6.8400 (\cdot) 10(^{-3}) (\mu)M(^{-1}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{I\text{Na} _PP})</td>
<td>Dephosphorylation rate of the fast Na(^+) channel by PP1 and PP2A</td>
<td>1.9804 (\cdot) 10(^{-2}) (\mu)M(^{-1}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{I\text{Na} _PKA})</td>
<td>Affinity of the fast Na(^+) channel for PKA</td>
<td>5.49415 (\cdot) 10(^{-3})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{I\text{Na} _PP})</td>
<td>Affinity of the fast Na(^+) channel for PP1 and PP2A</td>
<td>0.393025</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>
\[ E_{Na} = \frac{RT}{F} \ln \left( \frac{0.9[Na^+]_o + 0.1[K^+]_o}{0.9[Na^+]_i + 0.1[K^+]_i} \right) \]  
(B.180)

\[ I_{Na} = (G_{Na} \cdot O_{Na} + G_{Na_{ap}} \cdot O_{Na_{ap}})(V - E_{Na}) \]  
(B.181)

\[ C_{Na3} = 1 - (O_{Na} + C_{Na2} + C_{Na1} + IF_{Na} + I1_{Na} + I2_{Na} + IC_{Na2} + IC_{Na3} + O_{Na_{ap}} + C_{Na3_{ap}} + C_{Na2_{ap}} + C_{Na1p} + IF_{Na_{ap}} + I1_{Na_{ap}} + I2_{Na_{ap}} + IC_{Na2_{ap}} + IC_{Na3_{ap}}) \]  
(B.182)

\[ \frac{dC_{Na2}}{dt} = \alpha_{Na1} C_{Na3} - \beta_{Na1} C_{Na2} + \beta_{Na2} C_{Na1} - \alpha_{Na2} C_{Na2} + \alpha_{Na3} IC_{Na2} - \beta_{Na3} C_{Na2} \]  
\[ - \frac{k_{Na_{PKA}} [C]_{Na2}^{ca} C_{Na2}}{K_{Na_{PKA}} + C_{Na2}} + \frac{k_{Na_{PP}} [PP]_{Na2}^{ca} C_{Na2}}{K_{Na_{PP}} + C_{Na2}} \]  
(B.183)

\[ \frac{dC_{Na1}}{dt} = \alpha_{Na1} C_{Na2} - \beta_{Na1} C_{Na1} + \beta_{Na3} O_{Na} - \alpha_{Na1} C_{Na1} + \alpha_{Na3} IC_{Na1} - \beta_{Na3} C_{Na1} \]  
\[ - \frac{k_{Na_{PKA}} [C]_{Na1}^{ca} C_{Na1}}{K_{Na_{PKA}} + C_{Na1}} + \frac{k_{Na_{PP}} [PP]_{Na1}^{ca} C_{Na1}}{K_{Na_{PP}} + C_{Na1}} \]  
(B.184)

\[ \frac{dO_{Na}}{dt} = \alpha_{Na1} C_{Na1} - \beta_{Na1} O_{Na} + \beta_{Na2} IF_{Na} - \alpha_{Na2} O_{Na} \]  
\[ - \frac{k_{Na_{PKA}} [C]_{Na1}^{ca} O_{Na}}{K_{Na_{PKA}} + O_{Na}} + \frac{k_{Na_{PP}} [PP]_{Na1}^{ca} O_{Na}}{K_{Na_{PP}} + O_{Na}} \]  
(B.185)

\[ \frac{dIF_{Na}}{dt} = \alpha_{Na2} O_{Na} - \beta_{Na2} IF_{Na} + \beta_{Na3} C_{Na1} - \alpha_{Na3} IF_{Na} + \beta_{Na4} I1_{Na} - \alpha_{Na4} IF_{Na} \]  
\[ + \alpha_{Na2} IC_{Na2} - \beta_{Na2} IC_{Na2} - \beta_{Na3} IF_{Na} - \frac{k_{Na_{PKA}} [C]_{Na2}^{ca} IF_{Na}}{K_{Na_{PKA}} + IF_{Na}} + \frac{k_{Na_{PP}} [PP]_{Na2}^{ca} IF_{Na}}{K_{Na_{PP}} + IF_{Na}} \]  
(B.186)

\[ \frac{dI1_{Na}}{dt} = \alpha_{Na4} IF_{Na} - \beta_{Na4} I1_{Na} + \beta_{Na5} I2_{Na} - \alpha_{Na5} I1_{Na} \]  
\[ - \frac{k_{Na_{PKA}} [C]_{Na3}^{ca} I1_{Na}}{K_{Na_{PKA}} + I1_{Na}} + \frac{k_{Na_{PP}} [PP]_{Na3}^{ca} I1_{Na}}{K_{Na_{PP}} + I1_{Na}} \]  
(B.187)

\[ \frac{dI2_{Na}}{dt} = \alpha_{Na5} I1_{Na} - \beta_{Na5} I2_{Na} - \frac{k_{Na_{PKA}} [C]_{Na5}^{ca} I2_{Na}}{K_{Na_{PKA}} + I2_{Na}} + \frac{k_{Na_{PP}} [PP]_{Na5}^{ca} I2_{Na}}{K_{Na_{PP}} + I2_{Na}} \]  
(B.188)
\[
\frac{dIC_{Na2}}{dt} = \alpha_{Na11}IC_{Na3} - \beta_{Na11}IC_{Na2} + \beta_{Na12}IF_{Na} - \alpha_{Na12}IC_{Na2} + \beta_{Na3}C_{Na2} - \alpha_{Na3}IC_{Na2} \\
= \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}IC_{Na2}}{K_{Ina_{\text{PKA}}} + IC_{Na2}} + \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}IC_{Na2}}{K_{Ina_{\text{PP}}} + IC_{Na2}}
\]

(B.189)

\[
\frac{dIC_{Na3}}{dt} = \beta_{Na11}IC_{Na2} - \alpha_{Na11}IC_{Na3} + \beta_{Na3}C_{Na3} - \alpha_{Na3}IC_{Na3} \\
= \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}IC_{Na3}}{K_{Ina_{\text{PKA}}} + IC_{Na3}} + \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}IC_{Na3}}{K_{Ina_{\text{PP}}} + IC_{Na3}}
\]

(B.190)

\[
\frac{dC_{Na3p}}{dt} = \beta_{Na11}C_{Na2p} - \alpha_{Na11}C_{Na3p} + \alpha_{Na3}IC_{Na3p} - \beta_{Na3}C_{Na3p} \\
+ \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}C_{Na3p}}{K_{Ina_{\text{PP}}} + C_{Na3p}} - \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}C_{Na3p}}{K_{Ina_{\text{PKA}}} + C_{Na3p}}
\]

(B.191)

\[
\frac{dC_{Na2p}}{dt} = \alpha_{Na11}C_{Na3p} - \beta_{Na11}C_{Na2p} + \beta_{Na12}C_{Na1p} - \alpha_{Na12}C_{Na2p} + \alpha_{Na3}IC_{Na2p} - \beta_{Na3}C_{Na2p} \\
+ \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}C_{Na2p}}{K_{Ina_{\text{PKA}}} + C_{Na2p}} - \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}C_{Na2p}}{K_{Ina_{\text{PP}}} + C_{Na2p}}
\]

(B.192)

\[
\frac{dC_{Na1p}}{dt} = \alpha_{Na12}C_{Na2p} - \beta_{Na12}C_{Na1p} + \beta_{Na13}C_{Na1p} - \alpha_{Na13}C_{Na1p} + \alpha_{Na3}IC_{Na1p} - \beta_{Na3}C_{Na1p} \\
+ \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}C_{Na1p}}{K_{Ina_{\text{PP}}} + C_{Na1p}} - \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}C_{Na1p}}{K_{Ina_{\text{PKA}}} + C_{Na1p}}
\]

(B.193)

\[
\frac{dO_{Nap}}{dt} = \alpha_{Na13}C_{Na1p} - \beta_{Na13}O_{Nap} + \beta_{Na2}IF_{Nap} - \alpha_{Na2}O_{Nap} \\
+ \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}O_{Nap}}{K_{Ina_{\text{PKA}}} + O_{Nap}} - \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}O_{Nap}}{K_{Ina_{\text{PP}}} + O_{Nap}}
\]

(B.194)

\[
\frac{dIF_{Nap}}{dt} = \alpha_{Na2}O_{Nap} - \beta_{Na2}IF_{Nap} + \beta_{Na3}C_{Na1p} - \alpha_{Na3}IC_{Na1p} + \beta_{Na4}I_{Nap} - \alpha_{Na4}IF_{Nap} \\
+ \alpha_{Na12}IC_{Na2p} - \beta_{Na12}IF_{Nap} + \frac{k_{Ina_{\text{PKA}}}[C]^{\text{cav}}IF_{Na}}{K_{Ina_{\text{PKA}}} + IF_{Na}} - \frac{k_{Ina_{\text{PP}}}[PP]^{\text{cav}}IF_{Nap}}{K_{Ina_{\text{PP}}} + IF_{Nap}}
\]

(B.195)
\[
\frac{dI_{Nap}^1}{dt} = \alpha_{Nap} I_{I_{Nap}}^1 - \beta_{Nap} I_{Nap}^1 + \beta_{Nap} I_{Nap}^2 - \alpha_{Nap} I_{Nap}^1 \\
+ \frac{k_{Ina,PKA}[C]^{cav} I_{Na} - k_{Ina,PP}[PP]^{cav} I_{Nap}}{K_{Ina,PKA} + I_{Nap}}
\]
(B.196)

\[
\frac{dI_{Nap}^2}{dt} = \alpha_{Nap} I_{I_{Nap}}^2 - \beta_{Nap} I_{Nap}^2 + \frac{k_{Ina,PKA}[C]^{cav} I_{Na} - k_{Ina,PP}[PP]^{cav} I_{Nap}}{K_{Ina,PKA} + I_{Nap}}
\]
(B.197)

\[
\frac{dI_{Na2p}}{dt} = \alpha_{Na1} I_{I_{Na3p}} - \beta_{Na1} I_{Na2p} + \beta_{Na1} I_{Nap} - \alpha_{Na3} I_{Na2p} + \beta_{Na3} I_{Na2p} \\
- \alpha_{Na3} I_{Na2p} + \frac{k_{Ina,PKA}[C]^{cav} I_{Na2} - k_{Ina,PP}[PP]^{cav} I_{Na2p}}{K_{Ina,PKA} + I_{Na2}}
\]
(B.198)

\[
\frac{dI_{Na3p}}{dt} = \beta_{Na1} I_{I_{Na3p}} - \alpha_{Na1} I_{I_{Na3p}} + \beta_{Na3} I_{Na3p} - \alpha_{Na3} I_{Na3p} \\
+ \frac{k_{Ina,PKA}[C]^{cav} I_{Na3} - k_{Ina,PP}[PP]^{cav} I_{Na3p}}{K_{Ina,PKA} + I_{Na3}}
\]
(B.199)

\[
\alpha_{Na1} = \frac{3.802}{0.1027 e^{-(V-2.5)/17.0} + 0.20 e^{-(V-2.5)/150.0}}
\]
(B.200)

\[
\alpha_{Na2} = \frac{3.802}{0.1027 e^{-(V-2.5)/15.0} + 0.23 e^{-(V-2.5)/150.0}}
\]
(B.201)

\[
\alpha_{Na3} = \frac{3.802}{0.1027 e^{-(V-2.5)/12.0} + 0.25 e^{-(V-2.5)/150.0}}
\]
(B.202)

\[
\beta_{Na1} = 0.1917 e^{-(V-2.5)/20.3}
\]
(B.203)

\[
\beta_{Na2} = 0.20 e^{-(V-7.5)/20.3}
\]
(B.204)

\[
\beta_{Na3} = 0.22 e^{-(V-12.5)/20.3}
\]
(B.205)

\[
\alpha_{Na3} = 7.0 \times 10^{-7} e^{-(V+7.0)/7.7}
\]
(B.206)

\[
\beta_{Na3} = 0.0084 + 0.00002(V + 7.0)
\]
(B.207)
\[ \alpha_{Na2} = \frac{1.0}{0.188495e^{-(R+7.0)/16.6} + 0.393956} \quad \text{(B.208)} \]

\[ \beta_{Na2} = \alpha_{Na3} \alpha_{Na2} \alpha_{Na3} / (\beta_{Na3} \beta_{Na3}) \quad \text{(B.209)} \]

\[ \alpha_{Na4} = \alpha_{Na2} / 100.0 \quad \text{(B.210)} \]

\[ \beta_{Na4} = \alpha_{Na3} \quad \text{(B.211)} \]

\[ \alpha_{Na5} = \alpha_{Na2} / 95000 \quad \text{(B.212)} \]

\[ \beta_{Na5} = \alpha_{Na3} / 50.0 \quad \text{(B.213)} \]

**Ryanodine receptor module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>([RyR]_{\text{tot}})</td>
<td>Total cellular concentration of ryanodine receptors</td>
<td>0.1993 µM</td>
<td>Chu et al. [121]</td>
</tr>
<tr>
<td>(v_1)</td>
<td>Maximum RyR channel Ca(^{2+}) permeability</td>
<td>4,500 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(n)</td>
<td>RyR Ca(^{2+}) cooperativity parameter (P_{C1} - P_{O1})</td>
<td>4</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(m)</td>
<td>RyR Ca(^{2+}) cooperativity parameter (P_{O1} - P_{O2})</td>
<td>3</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^+_{a})</td>
<td>RyR (P_{C1} - P_{O1}) rate constant</td>
<td>6.075 µM(^{-4}) s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^-_{a})</td>
<td>RyR (P_{O1} - P_{C1}) rate constant</td>
<td>71.25 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^+_{b})</td>
<td>RyR (P_{O1} - P_{O2}) rate constant</td>
<td>4.05 µM(^{-3}) s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^-_{b})</td>
<td>RyR (P_{O2} - P_{O1}) rate constant</td>
<td>965.0 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^+_{c})</td>
<td>RyR (P_{O1} - P_{C2}) rate constant</td>
<td>9.0 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^-_{c})</td>
<td>RyR (P_{C2} - P_{O1}) rate constant</td>
<td>0.8 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k^+_{ap})</td>
<td>RyR (P_{C1}p - P_{O1p}) rate constant</td>
<td>5(k^+_{a})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k^-_{ap})</td>
<td>RyR (P_{O1p} - P_{C1p}) rate constant</td>
<td>3(k^-_{a})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k^+_{hp})</td>
<td>RyR (P_{O1p} - P_{O2p}) rate constant</td>
<td>5(k^+_{b})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k^-_{hp})</td>
<td>RyR (P_{O2p} - P_{O1p}) rate constant</td>
<td>3(k^-_{b})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$k^+_{cp}$</td>
<td>RyR $P_{O1p} - P_{C2p}$ rate constant</td>
<td>$50k^+_{c}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$k^-_{cp}$</td>
<td>RyR $P_{C2p} - P_{O1p}$ rate constant</td>
<td>$30k^-_{c}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$f_{RyR}$</td>
<td>Allosteric factor for RyR</td>
<td>0.001</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$k_{RyR_PKA}$</td>
<td>Phosphorylation rate of ryanodine receptors by PKA</td>
<td>$5.775 \cdot 10^{-2} \mu M^{-1} s^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$k_{RyR_PP}$</td>
<td>Dephosphorylation rate of ryanodine receptors by PP1</td>
<td>$0.28875 \mu M^{-1} s^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{RyR_PKA}$</td>
<td>Affinity of ryanodine receptors for PKA</td>
<td>0.5 μM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{RyR_PP}$</td>
<td>Affinity of ryanodine receptors for PP1</td>
<td>0.05 μM</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

\[
[RyR]^{ecav} = [RyR]_{oitr} \frac{V_{cell}}{V_{ecav}} 
\]  
\[C_1 = 1 - (C_2 + O_1 + O_2 + C_{1p} + C_{2p} + O_{1p} + O_{2p})
\]

\[
\frac{dP_{O1}}{dt} = k^+_a [Ca^{2+}]_a^{n} P_{C1} - k^-_a P_{O1} - k^+_b [Ca^{2+}]_b^{m} P_{O1} + k^-_b P_{O2} - k^+_b P_{O1} + k^-_b P_{C2}
\]

\[
\frac{dP_{O2}}{dt} = k^+_b [Ca^{2+}]_b^{m} P_{O1} - k^-_b P_{O2}
\]

\[
\frac{dP_{C2}}{dt} = k^+_c P_{O1} - k^-_c P_{C2}
\]

\[
\frac{dP_{C1p}}{dt} = -k^-_{ap} [Ca^{2+}]_a^{n} P_{C1p} + k^-_{ap} P_{O1p}
\]
\[
\frac{dP_{O1,p}}{dt} = k^+_a [Ca^{2+}]_{o1} P_{C1,p} - k^-_{bp} P_{O1,p} - k^+_b [Ca^{2+}]_{o1} P_{O1,p} + k^-_{bp} P_{O2,p} - k^+_a P_{O1,p} + k^-_{ap} P_{C2,p} 
\]
(B.220)

\[
+ \frac{f_{RyR} k_{RyR,PKA} [C]^{ecav} P_{O1}}{K_{RyR,PKA} + [RyR]^{ecav} P_{O1}} - k^+_a k^-_{ap} f_{RyR} k_{RyR,PP}[PP]^{ecav} P_{O1,p} 
\]

\[
\frac{dP_{O2,p}}{dt} = k^+_b [Ca^{2+}]_{o1} P_{C1,p} - k^-_{bp} P_{O2,p} 
\]
(B.221)

\[
+ \frac{f_{RyR} k_{RyR,PKA} [C]^{ecav} P_{O2}}{K_{RyR,PKA} + [RyR]^{ecav} P_{O2}} - k^+_a k^-_{ap} f_{RyR} k_{RyR,PP}[PP]^{ecav} P_{O2,p} 
\]

\[
\frac{dP_{C2,p}}{dt} = k^+_c P_{O1,p} - k^-_{cp} P_{C2,p} 
\]
(B.222)

\[
+ \frac{f_{RyR} k_{RyR,PKA} [C]^{ecav} P_{C2}}{K_{RyR,PKA} + [RyR]^{ecav} P_{C2}} - k^+_a k^-_{ap} k^+_c k^-_{cp} f_{RyR} k_{RyR,PP}[PP]^{ecav} P_{C2,p} 
\]

\[
\frac{dP_{C2,p}}{dt} = k^+_c P_{O1,p} - k^-_{cp} P_{C2,p} 
\]

\[
\frac{dP_{O2,p}}{dt} = k^+_b [Ca^{2+}]_{o1} P_{C1,p} - k^-_{bp} P_{O2,p} 
\]
(B.223)

**Na⁺-K⁺ pump module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( I_{max}^{NaK} )</td>
<td>Maximum Na⁺-K⁺ pump current</td>
<td>4.0 pA/pF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{np}^{m,Nai} )</td>
<td>Na⁺ half-saturation constant for Na⁺-K⁺ pump current (non-phosphorylated PLM)</td>
<td>18,800 µM</td>
<td>Despa et al. [123]</td>
</tr>
<tr>
<td>( K_{np}^{m,Nai} )</td>
<td>Na⁺ half-saturation constant for Na⁺-K⁺ pump current (phosphorylated PLM)</td>
<td>13,600 µM</td>
<td>Despa et al. [123]</td>
</tr>
<tr>
<td>( K_{m,Ko} )</td>
<td>K⁺ half-saturation constant Na⁺-K⁺ pump current</td>
<td>1,500 µM</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>( k_{PLM,PKA} )</td>
<td>Rate of PLM phosphorylation by PKA</td>
<td>3.053 \cdot 10^{-3} µM⁻¹ s⁻¹</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{PLM,PKA} )</td>
<td>Relative affinity for PLM phosphorylation by PKA</td>
<td>0.0011001</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>( k_{PLM,PP} )</td>
<td>Rate of PLM dephosphorylation by PP1 and PP2A</td>
<td>1.8491 \cdot 10⁻² µM⁻¹ s⁻¹</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{PLM,PP} )</td>
<td>Relative affinity for PLM dephosphorylation by PP1 and PP2A</td>
<td>5.7392</td>
<td>Heijman et al. [34]</td>
</tr>
</tbody>
</table>

\[
\frac{df_{PLM,p}^{ecav}}{dt} = \frac{k_{PLM,PKA} [C]^{ecav} (1 - f_{PLM,p}^{ecav})}{K_{PLM,PKA} + (1 - f_{PLM,p}^{ecav})} - \frac{k_{PLM,PP}[PP]^{ecav} f_{PLM,p}^{ecav}}{K_{PLM,PP} + f_{PLM,p}^{ecav}} 
\]
(B.223)
\[
I_{NaK} = f_{NaK}^{\text{max}} \frac{1}{1 + (K_{m,Na} / [Na^+]_0)^3 [K^+]_0 + K_{m,Ko}}
\]  
\[f_{NaK} = \frac{1}{1 + 0.1245e^{-0.1\psi / RT} + 0.0365\sigma e^{-\psi / RT}}\]  
\[\sigma = \frac{1}{7}(e^{[Na^+]_0/67300} - 1)\]

\[
K_{m,Na} = K_{m,Na}^{\text{np}} (1 - f_{\text{PLM,p}}^c) + K_{m,Na}^p f_{\text{PLM,p}}^c
\]

**Ultra-rapidly activating delayed rectifier K\(^+\) current module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G_{Kur})</td>
<td>Specific maximum conductivity for the ultra-rapidly activating delayed rectifier (K^+) current (non-phosphorylated)</td>
<td>0.3424 pA/pF</td>
<td>Petkova-Kirova et al. [61]</td>
</tr>
<tr>
<td>(G_{Kurp})</td>
<td>Specific maximum conductivity for the ultra-rapidly activating delayed rectifier (K^+) current (phosphorylated)</td>
<td>0.53307 pA/pF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{IKur_{-PKA}})</td>
<td>Rate of (I_{Kur}) phosphorylation by PKA</td>
<td>(6.9537 \cdot 10^{-3}) (\mu\text{M}^{-1}\text{s}^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{IKur_{-PKA}})</td>
<td>Relative affinity for (I_{Kur}) phosphorylation by PKA</td>
<td>0.138115</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(k_{IKur_{-PP}})</td>
<td>Rate of (I_{Kur}) dephosphorylation by PP1</td>
<td>(3.170 \cdot 10^{-2}) (\mu\text{M}^{-1}\text{s}^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{IKur_{-PP}})</td>
<td>Relative affinity for (I_{Kur}) dephosphorylation by PP1</td>
<td>0.23310</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

\[
E_K = \frac{RT}{F} \ln \left( \frac{[K^+]_0}{[K^+]_t} \right)
\]

\[
I_{Kur} = (G_{Kur} a_{ur} i_{ur} f_{IKur}^c + G_{Kurp} a_{urp} i_{urp} (1 - f_{IKur}^c))(V - E_K)
\]

\[
\frac{df_{IKur}^c}{dt} = \frac{k_{IKur_{-PP}}[PP]}{K_{IKur_{-PP}} + (1 - f_{IKur}^c)} - \frac{k_{IKur_{-PKA}}[C]}{K_{IKur_{-PKA}} + f_{IKur}^c}
\]
\[ a_{ss} = \frac{1}{1 + e^{-(V+22.5)/7.7}} \tag{B.231} \]

\[ i_{ss} = \frac{1}{1 + e^{(V+45.2)/5.7}} \tag{B.232} \]

\[ \tau_{aur} = \frac{6.1}{e^{0.0629(V+40.0)} + e^{-0.0629(V+40.0)}} + 2.058 \tag{B.233} \]

\[ \tau_{iur} = 1200.0 - \frac{170.0}{1 + e^{(V+45.2)/5.7}} \tag{B.234} \]

\[ \frac{da_{ur}}{dt} = \frac{a_{ss} - a_{ur}}{\tau_{aur}} \tag{B.235} \]

\[ \frac{di_{ur}}{dt} = \frac{i_{ss} - i_{ur}}{\tau_{aur}} \tag{B.236} \]

\[ \frac{da_{arp}}{dt} = \frac{a_{ss} - a_{arp}}{\tau_{aur}} \tag{B.237} \]

\[ \frac{di_{arp}}{dt} = \frac{i_{ss} - i_{arp}}{\tau_{iur}} \tag{B.238} \]

**Rapidly inactivating transient outward \( K^+ \) current module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( G_{Kto,f} )</td>
<td>Specific maximum conductivity for the rapidly inactivating transient outward ( K^+ ) current (non-phosphorylated)</td>
<td>0.3846 pA/pF</td>
<td>Petkova-Kirova et al. [61]</td>
</tr>
<tr>
<td>( G_{Kto,fp} )</td>
<td>Specific maximum conductivity for the rapidly inactivating transient outward ( K^+ ) current (phosphorylated)</td>
<td>( G_{Kto,f} )</td>
<td>Petkova-Kirova et al. [61]</td>
</tr>
<tr>
<td>( k_{IKto,f _PKA} )</td>
<td>Rate of ( I_{Kto,f} ) phosphorylation by PKA</td>
<td>4.38983 ( \cdot ) 10(^{-2} ) ( \mu M )(^{-1} ) s(^{-1} )</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{IKto,f _PKA} )</td>
<td>Relative affinity for ( I_{Kto,f} ) phosphorylation by PKA</td>
<td>0.27623</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( k_{IKto,f _PP} )</td>
<td>Rate of ( I_{Kto,f} ) dephosphorylation by PP1</td>
<td>9.09678 ( \cdot ) 10(^{-2} ) ( \mu M )(^{-1} ) s(^{-1} )</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>( K_{IKto,f _PP} )</td>
<td>Relative affinity for ( I_{Kto,f} ) dephosphorylation by PP1</td>
<td>0.23310</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>
\[ I_{Kio,f} = (G_{Kio,f}a_{i_{io,f}}^3 + f_{Kio,f}^{\text{ecav}} + G_{Kio,f}a_{i_{io,f}}^3 i_{io,f} f_{Kio,f}^{\text{ecav}})(V - E_K) \] (B.239)

\[ \frac{df_{Kio,f}^{\text{ecav}}}{dt} = \frac{k_{i_{Kio,f}PP}}{K_{i_{Kio,f}PP} (1 - f_{Kio,f}^{\text{ecav}})} - \frac{k_{i_{Kio,f}PKA}f_{Kio,f}^{\text{ecav}}}{K_{i_{Kio,f}PKA} + f_{Kio,f}^{\text{ecav}}} \] (B.240)

\[ \frac{da_{i_{io,f}}}{dt} = \alpha_a (1 - a_{i_{io,f}}) - \beta_a a_{i_{io,f}} \] (B.241)

\[ \frac{di_{i_{io,f}}}{dt} = \alpha_i (1 - i_{i_{io,f}}) - \beta_i i_{i_{io,f}} \] (B.242)

\[ \frac{da_{i_{io,fp}}}{dt} = \alpha_{ap} (1 - a_{i_{io,fp}}) - \beta_{ap} a_{i_{io,fp}} \] (B.243)

\[ \frac{di_{i_{io,fp}}}{dt} = \alpha_{ip} (1 - i_{i_{io,fp}}) - \beta_{ip} i_{i_{io,fp}} \] (B.244)

\[ \alpha_a = 0.18064e^{0.03577(V+33.0)} \] (B.245)

\[ \beta_a = 0.3956e^{-0.06237(V+33.0)} \] (B.246)

\[ \alpha_i = \frac{0.000152e^{-(V+15.5)/7.0}}{0.067083e^{-(V+35.5)/7.0} + 1} \] (B.247)

\[ \beta_i = \frac{0.00095e^{(V+35.5)/7.0}}{0.051335e^{(V+35.5)/7.0} + 1} \] (B.248)

\[ \alpha_{ap} = 0.18064e^{0.03577(V+17.0)} \] (B.249)

\[ \beta_{ap} = 0.3956e^{-0.06237(V+17.0)} \] (B.250)

\[ \alpha_{ip} = \frac{0.000152e^{-(V+7.5)/7.0}}{0.067083e^{-(V+27.5)/7.0} + 1} \] (B.251)

\[ \beta_{ip} = \frac{0.00095e^{(V+27.5)/7.0}}{0.051335e^{(V+27.5)/7.0} + 1} \] (B.252)
Time-independent $K^+$ current module

$$\alpha_{K_1} = \frac{1.02}{1 + \exp(0.2385(V - E_K - 59.215))} \quad (B.253)$$

$$\beta_{K_1} = \frac{0.8\exp(0.08032(V - E_K + 5.476)) + \exp(0.06175(V - E_K - 594.31))}{1 + \exp(-0.5143(V - E_K + 4.753))} \quad (B.254)$$

$$I_{K_1} = 0.27 \sqrt{\frac{[K^+]_o}{5400}} \frac{\alpha_{K_1}}{\alpha_{K_1} + \beta_{K_1}} (V - E_K) \quad (B.255)$$

Phospholamban module

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^p_{m,\mu p}$</td>
<td>Half-saturation constant for SR Ca$^{2+}$-ATPase pump (non-phosphorylated)</td>
<td>0.41 µM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K^p_{m,\mu p}$</td>
<td>Half-saturation constant for SR Ca$^{2+}$-ATPase pump (phosphorylated)</td>
<td>0.37 µM</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$v_3$</td>
<td>SR Ca$^{2+}$-ATPase maximum pump rate</td>
<td>306.0 µM s$^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$k_{PLB _PKA}$</td>
<td>Rate of PLB phosphorylation by PKA</td>
<td>0.108917 µM$^{-1}$ s$^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{PLB _PKA}$</td>
<td>Relative affinity for PLB phosphorylation by PKA</td>
<td>4.90970 · 10$^{-4}$</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>$k_{PLB _PP1}$</td>
<td>Rate of PLB dephosphorylation by PP1</td>
<td>4.41956 · 10$^{-2}$ µM$^{-1}$ s$^{-1}$</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{PLB _PP1}$</td>
<td>Relative affinity for PLB dephosphorylation by PP1</td>
<td>1.69376 · 10$^{-2}$</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

$$K_{m,\mu p} = K^p_{m,\mu p}(1 - f_{PLB,p}^{\text{cyt}}) + K^p_{m,\mu p} f_{PLB,p}^{\text{cyt}} \quad (B.256)$$

$$\frac{df_{PLB,p}^{\text{cyt}}}{dt} = \frac{k_{PLB \_PKA} \cdot [C]^{\text{cyt}} \cdot (1 - f_{PLB,p}^{\text{cyt}}) - k_{PLB \_PP1} \cdot [PP1]^{\text{cyt}} \cdot f_{PLB,p}^{\text{cyt}}}{K_{PLB \_PKA} + (1 - f_{PLB,p}^{\text{cyt}}) + K_{PLB \_PP1} + f_{PLB,p}^{\text{cyt}}} \quad (B.257)$$
### Troponin I Module

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{LTRPN}]_{\text{tot}})</td>
<td>Total cytosolic troponin low-affinity site concentration</td>
<td>70.0 µM</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>([\text{HTRPN}]_{\text{tot}})</td>
<td>Total cytosolic troponin high-affinity site concentration</td>
<td>140.0 µM</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{\text{lirpn}}^+)</td>
<td>Ca(^{2+}) on rate constant for troponin high-affinity sites</td>
<td>2.37 µM s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{\text{lirpn}}^-)</td>
<td>Ca(^{2+}) off rate constant for troponin high-affinity sites</td>
<td>0.032 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{\text{lirpn},np}^+)</td>
<td>Ca(^{2+}) on rate constant for troponin low-affinity sites (non-phosphorylated)</td>
<td>32.7 µM s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{\text{lirpn},p}^-)</td>
<td>Ca(^{2+}) off rate constant for troponin low-affinity sites (phosphorylated)</td>
<td>19.6 s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(k_{\text{TnI,PKA}})</td>
<td>Rate of TnI phosphorylation by PKA</td>
<td>0.0247254 µM(^{-1}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{\text{TnI,PKA}})</td>
<td>Relative affinity for TnI phosphorylation by PKA</td>
<td>2.71430 (\cdot) 10(^{-5})</td>
<td>Heijman et al. [34]</td>
</tr>
<tr>
<td>(k_{\text{TnI,PP2A}})</td>
<td>Rate of TnI dephosphorylation by PP2A</td>
<td>0.0865898 µM(^{-1}) s(^{-1})</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>(K_{\text{TnI,PP2A}})</td>
<td>Relative affinity for TnI dephosphorylation by PP2A</td>
<td>0.801420</td>
<td>Bondarenko [16]</td>
</tr>
</tbody>
</table>

\[
k_{\text{lirpn}}^- = k_{\text{lirpn},np}^- (1 - f_{\text{TnI},p}^{\text{cyt}}) + k_{\text{lirpn},p}^- f_{\text{TnI},p}^{\text{cyt}} \tag{B.258}
\]

\[
\frac{df_{\text{TnI},p}^{\text{cyt}}}{dt} = \frac{k_{\text{TnI,PKA}} \cdot [C]^{\text{cyt}} \cdot (1 - f_{\text{TnI},p}^{\text{cyt}}) + k_{\text{TnI,PP2A}} \cdot [PP2A]^{\text{cyt}} \cdot f_{\text{TnI},p}^{\text{cyt}}}{K_{\text{TnI,PKA}} + (1 - f_{\text{TnI},p}^{\text{cyt}}) + K_{\text{TnI,PP2A}} + f_{\text{TnI},p}^{\text{cyt}}} \tag{B.259}
\]

\[
\frac{d[\text{LTRPN}Ca]}{dt} = k_{\text{lirpn}}^+ [Ca^{2+}]_i ([\text{LTRPN}]_{\text{tot}} - [\text{LTRPN}Ca]) - k_{\text{lirpn}}^- [\text{LTRPN}Ca] \tag{B.260}
\]

\[
\frac{d[\text{HTRPN}CA]}{dt} = k_{\text{lirpn}}^+ [Ca^{2+}]_i ([\text{HTRPN}]_{\text{tot}} - [\text{HTRPN}CA]) - k_{\text{lirpn}}^- [\text{HTRPN}CA] \tag{B.261}
\]
**MyBP-C module**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{MyBPC}]_{\text{tot}}$</td>
<td>Total cytosolic myosin binding protein C concentration</td>
<td>50.0 μM</td>
<td>This paper</td>
</tr>
<tr>
<td>$k_{\text{MyBPC}_{-}\text{PKA}}$</td>
<td>Rate of MyBP-C phosphorylation by PKA</td>
<td>$7.0 \cdot 10^{-3}$ μM$^{-1}$ s$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$K_{\text{MyBPC}_{-}\text{PKA}}$</td>
<td>Relative affinity for MyBP-C phosphorylation by PKA</td>
<td>0.5</td>
<td>This paper</td>
</tr>
<tr>
<td>$k_{\text{MyBPC}_{-}\text{PP}}$</td>
<td>Rate of MyBP-C dephosphorylation by PP1 and PP2A</td>
<td>$1.3985 \cdot 10^{-3}$ μM$^{-1}$ s$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$K_{\text{MyBPC}_{-}\text{PP}}$</td>
<td>Relative affinity for MyBP-C dephosphorylation by PP1 and PP2A</td>
<td>0.4</td>
<td>This paper</td>
</tr>
</tbody>
</table>

\[
\frac{df_{\text{MyBPC}_{-}p}^{\text{cyst}}}{dt} = \frac{k_{\text{MyBPC}_{-}\text{PKA}}}{{K}_{\text{MyBPC}_{-}\text{PKA}} + (1 - f_{\text{MyBPC}_{-}p}^{\text{cyst}})} \cdot \left(1 - f_{\text{MyBPC}_{-}p}^{\text{cyst}}\right) \cdot \left(\frac{[PP1]^{\text{cyst}} + [PP2A]^{\text{cyst}}}{K_{\text{MyBPC}_{-}\text{PP}} + f_{\text{MyBPC}_{-}p}^{\text{cyst}}}\right)
\]  

(B.262)

**Electrophysiological part: unaffected by PKA**

**Membrane potential**

\[
\frac{dV}{dt} = -\frac{1}{C_m} \left( I_{\text{Cal}} + I_{p(Ca)} + I_{\text{NaCa}} + I_{\text{Cab}} + I_{\text{Na}} + I_{\text{NaK}} + I_{K_{so.f}} ight. \\
+ I_{K_1} + I_{K_{ur}} + I_{K_{sx}} + I_{K_r} + I_{Cl,Ca} - I_{\text{stim}}
\]

(B.263)

**Calcium dynamics: Calcium concentrations**

\[
\frac{d[Ca^{2+}]_i}{dt} = B_i \left\{ J_{\text{leak}} + J_{xfer} - J_{up} - J_{\text{rpm}} - (I_{\text{Cab}} - 2I_{\text{NaCa}} + I_{p(Ca)} + J_{\text{cav}}) \frac{A_{\text{cap}} C_m}{2 V_{\text{cyst}} F} \right\}
\]

(B.264)

\[
\frac{d[Ca^{2+}]_s}{dt} = B_s \left\{ J_{\text{rel}} \frac{V_{\text{JSR}}}{V_{ss}} - J_{\text{sf}} \frac{V_{\text{cyst}}}{V_{ss}} - I_{\text{cav}} \frac{A_{\text{cap}} C_m}{2 V_{ss} F} \right\}
\]

(B.265)

\[
\frac{d[Ca^{2+}]_{\text{JSR}}}{dt} = B_{\text{JSR}} \left( J_{\text{ur}} - J_{\text{rel}} \right)
\]

(B.266)

\[
\frac{d[Ca^{2+}]_{\text{NSR}}}{dt} = \left( J_{\text{up}} - J_{\text{leak}} \right) \frac{V_{\text{cyst}}}{V_{\text{NSR}}} - J_{\text{ur}} \frac{V_{\text{JSR}}}{V_{\text{NSR}}}
\]

(B.267)
\[ B_i = \left\{ 1 + \frac{[CMDN]_{tot} K_{m}^{CMDN}}{(K_{m}^{CMDN} + [Ca^{2+}]_i)^2} \right\}^{-1} \]  
(B.268)

\[ B_{ss} = \left\{ 1 + \frac{[CMDN]_{tot} K_{m}^{CMDN}}{(K_{m}^{CMDN} + [Ca^{2+}]_{ss})^2} \right\}^{-1} \]  
(B.269)

\[ B_{JSR} = \left\{ 1 + \frac{[CSQN]_{tot} K_{m}^{CSQN}}{(K_{m}^{CSQN} + [Ca^{2+}]_{JSR})^2} \right\}^{-1} \]  
(B.270)

**Calcium dynamics: Calcium fluxes**

\[ J_{rel} = v_1 (P_{O1} + P_{O2} + P_{O1p} + P_{O2p})([Ca^{2+}]_{JSR} - [Ca^{2+}]_{ss} P_{RyR}) \]  
(B.271)

\[ J_{tr} = \frac{[Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR}}{\tau_{tr}} \]  
(B.272)

\[ J_{sfer} = \frac{[Ca^{2+}]_{ss} - [Ca^{2+}]_{i}}{\tau_{sfer}} \]  
(B.273)

\[ J_{leak} = v_2 ([Ca^{2+}]_{NSR} - [Ca^{2+}]_{i}) \]  
(B.274)

\[ J_{up} = v_3 \frac{[Ca^{2+}]_i^2}{K_{m,up}^2 + [Ca^{2+}]_i^2} \]  
(B.275)

\[ J_{rpn} = k_{htrpn}^+ [Ca^{2+}]_i ([HTRPN]_{tot} - [HTRPNCa]) - k_{ltrpn}^- [HTRPNCa] \]  
(B.276)

\[ + k_{ltrpn}^- [Ca^{2+}]_i ([LTRPN]_{tot} - [LTRPNCa]) - k_{ltrpn}^- [LTRPNCa] \]

\[ \frac{dP_{RyR}}{dt} = -0.04 P_{RyR} - 0.1 \frac{I_{Cal}^{cav}}{I_{Cal,\text{max}}} e^{-\frac{(v+5.0)^2}{648.0}} \]  
(B.277)

**Calcium pump current**

\[ I_{p(Ca)} = I_{p(Ca)}^{max} \frac{[Ca^{2+}]_i^2}{K_{m,p(Ca)}^2 + [Ca^{2+}]_i^2} \]  
(B.278)
**Na\(^+\)/Ca\(^{2+}\) exchanger current**

\[
I_{NaCa} = k_{NaCa} \frac{1}{K_{m,Na}^3 + [Na^+]^3_o} \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \frac{1}{1 + k_{sat} e^{(e-1)V/RT}} \times (e^{eV/RT} [Na^+]_o [Ca^{2+}]_o - 2.0 e^{eV/RT} [Na^+]_o [Ca^{2+}]_o)
\]  

(B.279)

**Calcium background current**

\[
I_{Cab} = G_{Cab} (V - E_{CaN})
\]  

(B.280)

\[
E_{CaN} = \frac{RT}{2F} \ln \left( \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \right)
\]  

(B.281)

**Sodium dynamics: Sodium concentration**

\[
\frac{d[Na^+]}{dt} = -(I_Na + I_{NaCa} + 3I_{NaK} + 3I_{NaK}) \frac{A_{cap} C_m}{V_{cyt} F}
\]  

(B.282)

**Sodium background current**

\[
I_{NaB} = G_{NaB} (V - E_{Na})
\]  

(B.283)

**Potassium dynamics: Potassium concentration**

\[
\frac{d[K^+]}{dt} = -(I_{Ko,f} + I_{Ko,s} + I_{Kur} + I_{Kur} + I_{Kr} + I_{Ks} - 2I_{NaK}) \frac{A_{cap} C_m}{V_{cyt} F}
\]  

(B.284)

**Non-inactivating steady-state K\(^+\) current**

\[
I_{Kss} = G_{Kss} a_{Kss} (V - E_K)
\]  

(B.285)

\[
\frac{da_{Kss}}{dt} = \frac{a_{ss} - a_{Kss}}{\tau_{Kss}}
\]  

(B.286)

\[
\tau_{Kss} = \frac{1235.5}{e^{0.0862(V + 40.0)} + e^{-0.0862(V + 40.0)}} + 13.17
\]  

(B.287)
Rapid delayed rectifier $K^+$ current

\[ I_{Kr} = G_{Kr} O_{Kr} (V - E_{Kr}) \]  \hfill (B.288)

\[ E_{Kr} = \frac{RT}{F} \ln \left( \frac{0.98[K^+]_o + 0.02[Na^+]_o}{0.98[K^+]_i + 0.02[Na^+]_i} \right) \]  \hfill (B.289)

\[ C_{Kr0} = 1 - (C_{Kr1} + C_{Kr2} + O_{Kr} + I_{Kr1}) \]  \hfill (B.290)

\[ \frac{dC_{Kr1}}{dt} = \alpha_{a0} C_{Kr0} - \beta_{a0} C_{Kr1} + k_b C_{Kr2} - k_f C_{Kr1} \]  \hfill (B.291)

\[ \frac{dC_{Kr2}}{dt} = k_f C_{Kr1} - k_b C_{Kr2} + \beta_{a1} O_{Kr} - \alpha_{a1} C_{Kr2} \]  \hfill (B.292)

\[ \frac{dO_{Kr}}{dt} = \alpha_{a1} C_{Kr2} - \beta_{a1} O_{Kr} + \beta_{ir} I_{Kr1} - \alpha_{ir} O_{Kr} \]  \hfill (B.293)

\[ \frac{dI_{Kr1}}{dt} = \alpha_{ir} O_{Kr} + \beta_{ir} I_{Kr1} \]  \hfill (B.294)

\[ \alpha_{a0} = 0.022348 e^{0.01176 V} \]  \hfill (B.295)

\[ \beta_{a0} = 0.047002 e^{-0.0631 V} \]  \hfill (B.296)

\[ \alpha_{a1} = 0.013733 e^{0.038198 V} \]  \hfill (B.297)

\[ \beta_{a1} = 0.0000689 e^{-0.04178 V} \]  \hfill (B.298)

\[ \alpha_{ir} = 0.090821 e^{0.023391(V+5.0)} \]  \hfill (B.299)

\[ \beta_{ir} = 0.006497 e^{-0.03268(V+5.0)} \]  \hfill (B.300)
**Ca\textsuperscript{2+}-activated Cl\textsuperscript{-} current**

\[
I_{Cl,\text{Ca}} = G_{Cl,\text{Ca}} O_{Cl,\text{Ca}} \frac{[Ca^{2+}]_{i}}{[Ca^{2+}]_{i} + K_{m,Cl}} (V - E_{Cl}) \tag{B.301}
\]

\[
O_{Cl,\text{Ca}} = \frac{0.2}{1 + e^{-(V-46.7)/7.8}} \tag{B.302}
\]

**Extracellular ion concentrations**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[K^+]_o$</td>
<td>Extracellular K\textsuperscript{+} concentration</td>
<td>5,400 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$[Na^+]_o$</td>
<td>Extracellular Na\textsuperscript{+} concentration</td>
<td>140,000 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$[Ca^{2+}]_o$</td>
<td>Extracellular Ca\textsuperscript{2+} concentration</td>
<td>1,800 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
</tbody>
</table>

**Sarcoplasmic reticulum parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(v_2)</td>
<td>Ca\textsuperscript{2+} leak rate constant from the NSR</td>
<td>(1.74 \cdot 10^{-2}) s(^{-1})</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(\tau_{tr})</td>
<td>Time constant for transfer from NSR to JSR</td>
<td>0.02 s</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(\tau_{xfer})</td>
<td>Time constant for transfer from subspace to cytosol</td>
<td>0.008 s</td>
<td>Bondarenko et al. [29]</td>
</tr>
</tbody>
</table>

**Calmodulin and calsequestrin parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[CMDN]_{\text{tot}}$</td>
<td>Total cytosolic calmodulin concentration</td>
<td>50.0 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$[CSQN]_{\text{tot}}$</td>
<td>Total JSR calsequestrin concentration</td>
<td>15,000.0 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(K_m^{CMDN})</td>
<td>Ca\textsuperscript{2+} half-saturation constant for calmodulin</td>
<td>0.238 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>(K_m^{CSQN})</td>
<td>Ca\textsuperscript{2+} half-saturation constant for calsequestrin</td>
<td>800.0 (\mu)M</td>
<td>Bondarenko et al. [29]</td>
</tr>
</tbody>
</table>
**Membrane current parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m$</td>
<td>Specific membrane capacitance</td>
<td>1.0 $\mu$F/cm$^2$</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant</td>
<td>96.5 C/mmol</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$T$</td>
<td>Absolute temperature</td>
<td>298 K</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$R$</td>
<td>Ideal gas constant</td>
<td>8.314 J mol$^{-1}$K$^{-1}$</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$k_{NaCa}$</td>
<td>Scaling factor for Na$^+$/Ca$^{2+}$ exchanger</td>
<td>275 pA/pF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{m,Na}$</td>
<td>Na$^+$ half-saturation constant for Na$^+/Ca^{2+}$ exchanger</td>
<td>87,500 $\mu$M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$K_{m,Ca}$</td>
<td>Ca$^{2+}$ half-saturation constant for Na$^+/Ca^{2+}$ exchanger</td>
<td>1,380 $\mu$M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$k_{sat}$</td>
<td>Na$^+/Ca^{2+}$ exchanger saturation factor at very negative potentials</td>
<td>0.27</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Controls voltage dependence of Na$^+/Ca^{2+}$ exchanger</td>
<td>0.35</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$I_{p(Ca)}^{max}$</td>
<td>Maximum sarcolemmal Ca$^{2+}$ pump current</td>
<td>0.051</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$K_{m,p(Ca)}$</td>
<td>Ca$^{2+}$ half-saturation constant for sarcolemmal Ca$^{2+}$ pump current</td>
<td>0.5 $\mu$M</td>
<td>Bondarenko et al. [29]</td>
</tr>
<tr>
<td>$G_{Cab}$</td>
<td>Maximum background Ca$^{2+}$ current conductance</td>
<td>0.000284 mS/µF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$G_{Nab}$</td>
<td>Maximum background Na$^+$ current conductance</td>
<td>0.0063 mS/µF</td>
<td>Bondarenko [16]</td>
</tr>
<tr>
<td>$G_{Klo,s}$</td>
<td>Specific maximum conductivity for the slowly inactivating transient outward K$^+$ current</td>
<td>0.0 mS/µF</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$G_{Kss}$</td>
<td>Specific maximum conductivity for the noninactivating steady-state K$^+$ current</td>
<td>0.0611 mS/µF</td>
<td>Petkova-Kirova et al. [61]</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>Specific maximum conductivity for the slow delayed rectifier K$^+$ current</td>
<td>0.00575 mS/µF</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$G_{Kr}$</td>
<td>Specific maximum conductivity for the rapid delayed rectifier K$^+$ current</td>
<td>0.078 mS/µF</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$k_f$</td>
<td>Rate constant for the rapid delayed rectifier K$^+$ current</td>
<td>23.761 s$^{-1}$</td>
<td>Bondarenko et al. [29]</td>
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<td>$k_b$</td>
<td>Rate constant for the rapid delayed rectifier K$^+$ current</td>
<td>36.778 s$^{-1}$</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$G_{Cl,Ca}$</td>
<td>Specific maximum conductivity for the Ca$^{2+}$-activated Cl$^-$ current</td>
<td>10.0 mS/µF</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$K_{m,Cl}$</td>
<td>Half-saturation constant for the Ca$^{2+}$-activated Cl$^-$ current</td>
<td>10.0 $\mu$M</td>
<td>Bondarenko et al. [29]</td>
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<tr>
<td>$E_{Cl}$</td>
<td>Reversal potential for the Ca$^{2+}$-activated Cl$^-$ current</td>
<td>−40 mV</td>
<td>Bondarenko et al. [29]</td>
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</tbody>
</table>
Contraction part

**Contraction Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$SL_0$</td>
<td>Initial sarcomere length</td>
<td>1.9 – 2.3 $\mu$m</td>
<td></td>
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<tr>
<td>$SL_{rest}$</td>
<td>Resting sarcomere length</td>
<td>1.9 $\mu$m</td>
<td>Rice et al. [43]</td>
</tr>
<tr>
<td>$k_{PN}$</td>
<td>Transition rate from permissive to non-permissive state</td>
<td>1,350 s$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$PC_{titin}$</td>
<td>Titin passive force amplitude</td>
<td>0.002</td>
<td>Rice et al. [43]</td>
</tr>
<tr>
<td>$P_{Ex_{titin}}$</td>
<td>Titin passive force exponent</td>
<td>10.0</td>
<td>Rice et al. [43]</td>
</tr>
<tr>
<td>$SL_{collagen}$</td>
<td>Collagen sarcomere length</td>
<td>2.25 $\mu$m</td>
<td>Rice et al. [43]</td>
</tr>
<tr>
<td>$P_{Con_{collagen}}$</td>
<td>Collagen passive force amplitude</td>
<td>0.0005</td>
<td>This paper</td>
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<tr>
<td>$P_{Ex_{collagen}}$</td>
<td>Collagen passive force exponent</td>
<td>14.0</td>
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<tr>
<td>$m_{ass}$</td>
<td>Sarcomere mass</td>
<td>$15.0 \cdot 10^{-6}$ s$^2$ $\mu$m$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$K_{SE}$</td>
<td>Stiffness</td>
<td>1.0 $\mu$m$^{-1}$</td>
<td>This paper</td>
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<tr>
<td>$f_{XB0}$</td>
<td>Basic transition rate from weak to strong crossbridge</td>
<td>18.0 s$^{-1}$</td>
<td>This paper</td>
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<tr>
<td>$g_{min_{xb0}}$</td>
<td>Minimum detachment rate from strong to weak crossbridge</td>
<td>12.348 s$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$v_{isc0}$</td>
<td>Effective viscosity without $\beta_1$-adrenergic stimulation</td>
<td>0.0141 s $\mu$m$^{-1}$</td>
<td>This paper</td>
</tr>
<tr>
<td>$a_{fx0}$</td>
<td>Non-linear correction to effective viscosity without $\beta_1$-adrenergic stimulation</td>
<td>0.040 s $\mu$m$^{-1}$</td>
<td>This paper</td>
</tr>
</tbody>
</table>

**Permissive states**

\[
\frac{dN_0}{dt} = k_{PN} P_0 + g_{10SL} N_1 - k_{NP} N_0 \tag{B.303}
\]

\[
\frac{dN_1}{dt} = k_{PN} P_1 - (k_{NP} + g_{10SL}) N_1 \tag{B.304}
\]

\[
\frac{dP_0}{dt} = g_{10SL} P_1 + k_{NP} N_0 - (k_{PN} + f_{01}) P_0 \tag{B.305}
\]

\[
\frac{dP_1}{dt} = g_{21SL} P_2 + f_{01} P_0 + k_{NP} N_1 - (f_{12} + g_{10SL} + k_{PN}) P_1 \tag{B.306}
\]

\[
\frac{dP_2}{dt} = g_{32SL} P_3 + f_{12} P_1 - (f_{23} + g_{21SL}) P_2 \tag{B.307}
\]

\[
\frac{dP_3}{dt} = f_{23} P_2 - g_{32SL} P_3 \tag{B.308}
\]
\[ f_{XB} = f_{XBO} \left(1 + 0.45 \left(f_{TnI,p}^{\text{cyl}} - 0.364\right)\right)^{-1} \left(1 + 1.5 \left(f_{MyBPC,p}^{\text{cyl}} - 0.575\right)\right)^{-1} \]  
(B.309)

\[ g_{\text{minb}} = g_{\text{minb}0} \left(1 + 0.3 \left(f_{TnI,p}^{\text{cyl}} - 0.364\right)\right) \left(1 + 1.0 \left(f_{MyBPC,p}^{\text{cyl}} - 0.575\right)\right) \]  
(B.310)

\[ f_{01} = 15 f_{XB} \]  
(B.311)

\[ f_{12} = 30 f_{XB} \]  
(B.312)

\[ f_{23} = 7 f_{XB} \]  
(B.313)

\[ g_{10\text{SL}} = g_{\text{shSL}} \]  
(B.314)

\[ g_{21\text{SL}} = 2 g_{\text{shSL}} \]  
(B.315)

\[ g_{32\text{SL}} = 3 g_{\text{shSL}} \]  
(B.316)

\[ g_{\text{shSL}} = g_{\text{minb}} \left(2 - \left(SL_{\text{norm}}\right)^{1.6}\right) \]  
(B.317)

\[ SL_{\text{norm}} = \frac{SL - 1.3 \mu m}{2.5 \mu m - 1.3 \mu m} \]  
(B.318)

\[ k_{NP} = k_{PN} \left(\frac{[LTRPNCa]}{[LTRPNCa]_{\text{tot}} \times K_{\text{half}}}\right)^{Nim} \]  
(B.319)

\[ Nim = 5 + 3 SL_{\text{norm}} \]  
(B.320)

\[ K_{\text{half}} = \frac{1}{1 + \frac{K_{Ca}}{1.5 \mu M - SL_{\text{norm}} \times 1.0 \mu M}} \]  
(B.321)

\[ K_{Ca} = \frac{k_{\text{ltpm}}^{-}}{k_{\text{ltpm}}^{+}} \]  
(B.322)

**Active Contraction Force**

\[ F_{\text{contr}} = 58.0 F_{\text{contr}} \]  
(B.323)

\[ F_{\text{contr}} = \frac{P1 + N1 + 2(P2) + 3(P3)}{F_{\text{max}}} \]  
(B.324)
\[ F_{\text{max}} = P1_{\text{max}} + 2(P2_{\text{max}}) + 3(P3_{\text{max}}) \] (B.325)

\[ P1_{\text{max}} = \frac{f_{01}(2g_{\text{min},xh})(3g_{\text{min},xh})}{\Sigma} \] (B.326)

\[ P2_{\text{max}} = \frac{f_{01}f_{12}(3g_{\text{min},xh})}{\Sigma} \] (B.327)

\[ P3_{\text{max}} = \frac{f_{01}f_{12}f_{23}}{\Sigma} \] (B.328)

\[ \Sigma = (g_{\text{min},xh})(2g_{\text{min},xh})(3g_{\text{min},xh}) + f_{01}(2g_{\text{min},xh})(3g_{\text{min},xh}) + f_{01}f_{12}(3g_{\text{min},xh}) + f_{01}f_{12}f_{23} \] (B.329)

**Passive Contraction Force**

\[ F_{\text{passive}}(SL) = F_{\text{titin}}(SL) + F_{\text{collagen}}(SL) \] (B.330)

\[ F_{\text{titin}}(SL) = \begin{cases} PCon_{\text{titin}}(\exp(PExp_{\text{titin}}(SL - SL_{\text{rest}})) - 1) & \text{if } SL \geq SL_{\text{rest}} \\ -PCon_{\text{titin}}(\exp(PExp_{\text{titin}}(SL_{\text{rest}} - SL)) - 1) & \text{if } SL < SL_{\text{rest}} \end{cases} \] (B.331)

\[ F_{\text{collagen}}(SL) = \begin{cases} PCon_{\text{collagen}}(\exp(PExp_{\text{collagen}}(SL - SL_{\text{collagen}})) - 1) & \text{if } SL \geq SL_{\text{collagen}} \\ 0 & \text{if } SL < SL_{\text{collagen}} \end{cases} \] (B.332)

**Viscous and flexible forces**

\[ F_{\text{visc}} = -v_{\text{isc}} \cdot v(1 - a_{\text{fs}} \cdot v) \] (B.333)

\[ v_{\text{isc}} = v_{\text{isc},0} \left(1 + 0.33(f_{\text{Tnl},p}^{\text{cryt}} - 0.364)\right)^{-1} \left(1 + 1.1(f_{\text{MyBPC},p}^{\text{cryt}} - 0.575)\right)^{-1} \] (B.334)

\[ a_{\text{fs}} = a_{\text{fs},0} \left(1 + 0.2(f_{\text{Tnl},p}^{\text{cryt}} - 0.364)\right)^{-1} \left(1 + 0.6(f_{\text{MyBPC},p}^{\text{cryt}} - 0.575)\right)^{-1} \] (B.335)

\[ F_{\text{flex}} = KSE(SL - SL_{\text{0}}) \] (B.336)
Sarcomere length

\[ \frac{dSL}{dt} = -v \]  

(B.337)

\[ \frac{dv}{dt} = \frac{F_{\text{con} \, n} + F_{\text{passive}} + F_{\text{visc}} + F_{\text{flex}}}{\text{mass}} \]  

(B.338)

Initial Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t )</td>
<td>Time</td>
<td>0.0 ms</td>
</tr>
<tr>
<td>( V )</td>
<td>Membrane potential</td>
<td>-78.2807 mV</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{i})</td>
<td>Myoplasmic Ca(^{2+}) concentration</td>
<td>0.100156 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{ss})</td>
<td>Subspace SR Ca(^{2+}) concentration</td>
<td>0.100156 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{JSR})</td>
<td>Junctional SR Ca(^{2+}) concentration</td>
<td>1025.35 (\mu)M</td>
</tr>
<tr>
<td>([\text{Ca}^{2+}]_{NSR})</td>
<td>Network SR Ca(^{2+}) concentration</td>
<td>1025.35 (\mu)M</td>
</tr>
<tr>
<td>([\text{LTRPN}Ca])</td>
<td>Concentration Ca(^{2+}) bound low-affinity troponin-binding sites</td>
<td>8.66973 (\mu)M</td>
</tr>
<tr>
<td>([\text{HTRPN}Ca])</td>
<td>Concentration Ca(^{2+}) bound high-affinity troponin-binding sites</td>
<td>123.369 (\mu)M</td>
</tr>
<tr>
<td>(O_{\text{cav}})</td>
<td>L-type Ca(^{2+}) channel conducting state (non-phosphorylated, caveolae)</td>
<td>0.319908\times10^{-11}</td>
</tr>
<tr>
<td>(C_{1\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (non-phosphorylated, caveolae)</td>
<td>0.973686</td>
</tr>
<tr>
<td>(C_{2\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (non-phosphorylated, caveolae)</td>
<td>0.524361\times10^{2}</td>
</tr>
<tr>
<td>(C_{3\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (non-phosphorylated, caveolae)</td>
<td>0.105895\times10^{4}</td>
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<tr>
<td>(C_{4\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (non-phosphorylated, caveolae)</td>
<td>0.950461\times10^{8}</td>
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<tr>
<td>(C_{p\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (non-phosphorylated, caveolae)</td>
<td>0.319909\times10^{-11}</td>
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<tr>
<td>(I_{1\text{cav}})</td>
<td>L-type Ca(^{2+}) channel inactivated state (non-phosphorylated, caveolae)</td>
<td>0.308287\times10^{-11}</td>
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<tr>
<td>(I_{2\text{cav}})</td>
<td>L-type Ca(^{2+}) channel inactivated state (non-phosphorylated, caveolae)</td>
<td>0.217361\times10^{-7}</td>
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<td>(I_{3\text{cav}})</td>
<td>L-type Ca(^{2+}) channel inactivated state (non-phosphorylated, caveolae)</td>
<td>0.209470\times10^{-7}</td>
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<td>(O_{p\text{cav}})</td>
<td>L-type Ca(^{2+}) channel conducting state (phosphorylated, caveolae)</td>
<td>0.561698\times10^{-10}</td>
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<tr>
<td>(C_{1p\text{cav}})</td>
<td>L-type Ca(^{2+}) channel closed state (phosphorylated, caveolae)</td>
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<td>(C_{2p\text{cav}})</td>
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<td>0.421569\times10^{-3}</td>
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<td>(C_{3p\text{cav}})</td>
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<td>$I_{cav}^{1,p}$</td>
<td>L-type Ca$^{2+}$ channel inactivated state (phosphorylated, caveolae)</td>
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<td>L-type Ca$^{2+}$ channel conducting state (non-phosphorylated, extracaveolae)</td>
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<td>L-type Ca$^{2+}$ channel closed state (non-phosphorylated, extracaveolae)</td>
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<td>$C_{3cav}$</td>
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<tr>
<td>$C_{1p}$</td>
<td>L-type Ca$^{2+}$ channel closed state (phosphorylated, extracaveolae)</td>
<td>$0.120548$</td>
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<tr>
<td>$C_{2p}$</td>
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<td>$0.246280 \times 10^{-2}$</td>
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<td>$C_{3p}$</td>
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<td>$C_{4p}$</td>
<td>L-type Ca$^{2+}$ channel closed state (phosphorylated, extracaveolae)</td>
<td>$0.642469 \times 10^{-7}$</td>
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<td>$C_{p}$</td>
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<tr>
<td>$C_{Na3}$</td>
<td>Fast Na$^+$ channel closed state (non-phosphorylated)</td>
<td>$0.436281$</td>
</tr>
<tr>
<td>$C_{Na2}$</td>
<td>Fast Na$^+$ channel closed state (non-phosphorylated)</td>
<td>$0.132239 \times 10^{-1}$</td>
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<tr>
<td>$C_{Na1}$</td>
<td>Fast Na$^+$ channel closed state (non-phosphorylated)</td>
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<tr>
<td>$O_{Na}$</td>
<td>Fast Na$^+$ channel open state (non-phosphorylated)</td>
<td>$0.367578 \times 10^{-6}$</td>
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<td>$IF_{Na}$</td>
<td>Fast Na$^+$ channel inactivated state (non-phosphorylated)</td>
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<td>$I_{2Na}$</td>
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<td>$IC_{Na2}$</td>
<td>Fast Na$^+$ channel inactivated state (non-phosphorylated)</td>
<td>$0.125719 \times 10^{-1}$</td>
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<tr>
<td>Symbol</td>
<td>Description</td>
<td>Value</td>
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<td>--------</td>
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<td>IC\textsubscript{Na3}</td>
<td>Fast Na\textsuperscript{+} channel inactivated state (non-phosphorylated)</td>
<td>0.414772</td>
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<td>Fast Na\textsuperscript{+} channel closed state (phosphorylated)</td>
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<tr>
<td>C\textsubscript{Na2p}</td>
<td>Fast Na\textsuperscript{+} channel closed state (phosphorylated)</td>
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<tr>
<td>C\textsubscript{Na1p}</td>
<td>Fast Na\textsuperscript{+} channel closed state (phosphorylated)</td>
<td>0.225622 \times 10^{-4}</td>
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<tr>
<td>O\textsubscript{Nap}</td>
<td>Fast Na\textsuperscript{+} channel open state (phosphorylated)</td>
<td>0.514708 \times 10^{-7}</td>
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<tr>
<td>IF\textsubscript{Nap}</td>
<td>Fast Na\textsuperscript{+} channel inactivated state (phosphorylated)</td>
<td>0.214505 \times 10^{-4}</td>
</tr>
<tr>
<td>I\textsubscript{Nap}</td>
<td>Fast Na\textsuperscript{+} channel inactivated state (phosphorylated)</td>
<td>0.216956 \times 10^{-5}</td>
</tr>
<tr>
<td>IC\textsubscript{Na2p}</td>
<td>Fast Na\textsuperscript{+} channel inactivated state (phosphorylated)</td>
<td>0.301417 \times 10^{-7}</td>
</tr>
<tr>
<td>IC\textsubscript{Na3p}</td>
<td>Fast Na\textsuperscript{+} channel inactivated state (phosphorylated)</td>
<td>0.580768 \times 10^{-1}</td>
</tr>
<tr>
<td>P\textsubscript{C1}</td>
<td>RyR channel closed state (non-phosphorylated)</td>
<td>0.996216</td>
</tr>
<tr>
<td>P\textsubscript{C2}</td>
<td>RyR channel closed state (non-phosphorylated)</td>
<td>0.961523 \times 10^{-4}</td>
</tr>
<tr>
<td>P\textsubscript{O1}</td>
<td>RyR channel open state (non-phosphorylated)</td>
<td>0.854703 \times 10^{-5}</td>
</tr>
<tr>
<td>P\textsubscript{O2}</td>
<td>RyR channel open state (non-phosphorylated)</td>
<td>0.360387 \times 10^{-10}</td>
</tr>
<tr>
<td>P\textsubscript{C1p}</td>
<td>RyR channel closed state (phosphorylated)</td>
<td>0.367832 \times 10^{-2}</td>
</tr>
<tr>
<td>P\textsubscript{C2p}</td>
<td>RyR channel closed state (phosphorylated)</td>
<td>0.986391 \times 10^{-6}</td>
</tr>
<tr>
<td>P\textsubscript{O1p}</td>
<td>RyR channel open state (phosphorylated)</td>
<td>0.526043 \times 10^{-7}</td>
</tr>
<tr>
<td>P\textsubscript{O2p}</td>
<td>RyR channel open state (phosphorylated)</td>
<td>0.369679 \times 10^{-12}</td>
</tr>
<tr>
<td>[Na\textsuperscript{+}]\textsubscript{i}</td>
<td>Myoplasmic Na\textsuperscript{+} concentration</td>
<td>10,508.7 \mu M</td>
</tr>
<tr>
<td>[K\textsuperscript{+}]\textsubscript{i}</td>
<td>Myoplasmic K\textsuperscript{+} concentration</td>
<td>145,411 \mu M</td>
</tr>
<tr>
<td>a\textsubscript{ur}</td>
<td>Activation gate of non-phosphorylated I\textsubscript{Kur}</td>
<td>0.713766 \times 10^{-3}</td>
</tr>
<tr>
<td>i\textsubscript{ur}</td>
<td>Inactivation gate of non-phosphorylated I\textsubscript{Kur}</td>
<td>0.996992</td>
</tr>
<tr>
<td>f\textsubscript{ecav}</td>
<td>Fraction of phosphorylated I\textsubscript{Ko,f}</td>
<td>0.252661</td>
</tr>
<tr>
<td>a\textsubscript{o,f}</td>
<td>Activation gate of non-phosphorylated I\textsubscript{Ko,f}</td>
<td>0.533700 \times 10^{-2}</td>
</tr>
<tr>
<td>i\textsubscript{o,f}</td>
<td>Inactivation gate of non-phosphorylated I\textsubscript{Ko,f}</td>
<td>0.999945</td>
</tr>
<tr>
<td>a\textsubscript{o,fp}</td>
<td>Activation gate of phosphorylated I\textsubscript{Ko,f}</td>
<td>0.111478 \times 10^{-2}</td>
</tr>
<tr>
<td>i\textsubscript{o,fp}</td>
<td>Inactivation gate of phosphorylated I\textsubscript{Ko,f}</td>
<td>0.999983</td>
</tr>
<tr>
<td>f\textsubscript{PLB,p}</td>
<td>Fraction of phosphorylated phospholamban</td>
<td>0.186637</td>
</tr>
<tr>
<td>f\textsubscript{TnI,p}</td>
<td>Fraction of phosphorylated troponin I</td>
<td>0.364102</td>
</tr>
<tr>
<td>f\textsubscript{MyBPC,p}</td>
<td>Fraction of phosphorylated myosin binding protein C</td>
<td>0.572184</td>
</tr>
<tr>
<td>P\textsubscript{RyR}</td>
<td>RyR modulation factor</td>
<td>0.253809 \times 10^{-11}</td>
</tr>
<tr>
<td>a\textsubscript{Kss}</td>
<td>Activation gate of I\textsubscript{Kss}</td>
<td>0.921658 \times 10^{-3}</td>
</tr>
<tr>
<td>C\textsubscript{k0}</td>
<td>mERG channel closed state</td>
<td>0.997366</td>
</tr>
<tr>
<td>C\textsubscript{k1}</td>
<td>mERG channel closed state</td>
<td>0.135199 \times 10^{-2}</td>
</tr>
<tr>
<td>C\textsubscript{k2}</td>
<td>mERG channel closed state</td>
<td>0.873471 \times 10^{-3}</td>
</tr>
<tr>
<td>( O_k )</td>
<td>( I_k )</td>
<td>( \left[ R_{\beta_1}^{\text{cav}} \right]^{\text{cav}}_{\text{PKA,tot}} )</td>
</tr>
<tr>
<td>mERG channel open state</td>
<td>mERG channel inactivated state</td>
<td>Concentration of total ( \beta_1 )-ARs phosphorylated by PKA (caveolae)</td>
</tr>
<tr>
<td>( 0.332502 \times 10^{-3} )</td>
<td>( 0.763460 \times 10^{-4} )</td>
<td>( 0.799452 \times 10^{-3} ) µM</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE4&lt;/sub&gt;&lt;sup&gt;cav&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE4 (caveolae)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>PDE4&lt;sub&gt;P&lt;/sub&gt;&lt;sup&gt;cav&lt;/sup&gt;</td>
<td>Concentration of phosphorylated PDE4 (extracaveolae)</td>
<td>0.158226×10⁻¹ µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE2&lt;/sub&gt;&lt;sup&gt;cav&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE2 (extracaveolae)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE4&lt;/sub&gt;&lt;sup&gt;cav&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE4 (extracaveolae)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>PDE3&lt;sub&gt;p&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>Concentration of phosphorylated PDE3 (cytosol)</td>
<td>0.120998×10⁻² µM</td>
</tr>
<tr>
<td>PDE4&lt;sub&gt;p&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>Concentration of phosphorylated PDE4 (cytosol)</td>
<td>0.373102×10⁻² µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE2&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE2 (cytosol)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE3&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE3 (cytosol)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PDE4&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>cAMP concentration degraded by PDE4 (cytosol)</td>
<td>0.1 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PKA&lt;/sub&gt;&lt;sup&gt;cav&lt;/sup&gt;</td>
<td>cAMP concentration change due to binding to PKA (caveolae)</td>
<td>7.92317 µM</td>
</tr>
<tr>
<td>ARC&lt;sub&gt;cav&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 1 cAMP molecule bound (caveolae)</td>
<td>0.299288 µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;RC&lt;sub&gt;cav&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 2 cAMP molecules bound (caveolae)</td>
<td>0.303358×10⁻¹ µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;cav&lt;/sub&gt;</td>
<td>Concentration of PKA R subunit with 2 cAMP molecules bound (caveolae)</td>
<td>0.858440 µM</td>
</tr>
<tr>
<td>C&lt;sub&gt;cav&lt;/sub&gt;</td>
<td>Concentration of free PKA catalytic subunit (caveolae)</td>
<td>0.459397×10⁻¹ µM</td>
</tr>
<tr>
<td>PKIC&lt;sub&gt;cav&lt;/sub&gt;</td>
<td>Concentration of PKI inactivated PKA catalytic subunit (caveolae)</td>
<td>0.823499 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PKA&lt;/sub&gt;&lt;sup&gt;ex cav&lt;/sup&gt;</td>
<td>cAMP concentration change due to binding to PKA (extracaveolae)</td>
<td>6.74029 µM</td>
</tr>
<tr>
<td>ARC&lt;sub&gt;ex cav&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 1 cAMP molecule bound (extracaveolae)</td>
<td>0.653988 µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;RC&lt;sub&gt;ex cav&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 2 cAMP molecules bound (extracaveolae)</td>
<td>0.132861 µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;ex cav&lt;/sub&gt;</td>
<td>Concentration of PKA R subunit with 2 cAMP molecules bound (extracaveolae)</td>
<td>1.17000 µM</td>
</tr>
<tr>
<td>C&lt;sub&gt;ex cav&lt;/sub&gt;</td>
<td>Concentration of free PKA catalytic subunit (extracaveolae)</td>
<td>0.147623 µM</td>
</tr>
<tr>
<td>PKIC&lt;sub&gt;ex cav&lt;/sub&gt;</td>
<td>Concentration of PKI inactivated PKA catalytic subunit (extracaveolae)</td>
<td>1.03338 µM</td>
</tr>
<tr>
<td>cAMP&lt;sub&gt;PKA&lt;/sub&gt;&lt;sup&gt;cyt&lt;/sup&gt;</td>
<td>cAMP concentration change due to binding to PKA (cytosol)</td>
<td>9.32461 µM</td>
</tr>
<tr>
<td>ARC&lt;sub&gt;cyt&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 1 cAMP molecule bound (cytosol)</td>
<td>0.996350×10⁻¹ µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;RC&lt;sub&gt;cyt&lt;/sub&gt;</td>
<td>Concentration of PKA RC dimer with 2 cAMP molecules bound (cytosol)</td>
<td>0.140099×10⁻¹ µM</td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;cyt&lt;/sub&gt;</td>
<td>Concentration of PKA R subunit with 2 cAMP molecules bound (cytosol)</td>
<td>0.273868 µM</td>
</tr>
<tr>
<td>C&lt;sub&gt;cyt&lt;/sub&gt;</td>
<td>Concentration of free PKA catalytic subunit (cytosol)</td>
<td>0.665022×10⁻¹ µM</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>([PKIC])_{\text{cyt}}</td>
<td>Concentration of PKI inactivated PKA catalytic subunit (cytosol)</td>
<td>0.218365 µM</td>
</tr>
<tr>
<td>([Inhibi])_{p,\text{tot}}</td>
<td>Concentration of total phosphorylated PP1 inhibitor 1 (cytosol)</td>
<td>0.213571×10⁻¹ µM</td>
</tr>
<tr>
<td>([cAMP])_{\text{cav}}</td>
<td>Concentration of cAMP in caveolae</td>
<td>0.253399 µM</td>
</tr>
<tr>
<td>([cAMP])_{\text{ecav}}</td>
<td>Concentration of cAMP in extracaveolae</td>
<td>0.507889 µM</td>
</tr>
<tr>
<td>([cAMP])_{\text{cyt}}</td>
<td>Concentration of cAMP in cytosol</td>
<td>0.407775 µM</td>
</tr>
<tr>
<td>(SL)</td>
<td>Sarcomere length</td>
<td>1.89958 µm</td>
</tr>
<tr>
<td>(\nu)</td>
<td>Shortening velocity</td>
<td>0.110974×10⁻¹⁴ μm s⁻¹</td>
</tr>
<tr>
<td>(N0)</td>
<td>Nonpermissive tropomyosin with 0 crossbridges</td>
<td>0.999236</td>
</tr>
<tr>
<td>(N1)</td>
<td>Nonpermissive tropomyosin with 1 crossbridge</td>
<td>0.447564×10⁻³</td>
</tr>
<tr>
<td>(P0)</td>
<td>Permissive tropomyosin with 0 crossbridges</td>
<td>0.344737×10⁻⁴</td>
</tr>
<tr>
<td>(P1)</td>
<td>Permissive tropomyosin with 1 crossbridge</td>
<td>0.683798×10⁻⁵</td>
</tr>
<tr>
<td>(P2)</td>
<td>Permissive tropomyosin with 2 crossbridges</td>
<td>0.901321×10⁻⁴</td>
</tr>
<tr>
<td>(P3)</td>
<td>Permissive tropomyosin with 3 crossbridges</td>
<td>0.184806×10⁻³</td>
</tr>
</tbody>
</table>
Appendix C  Derivation of $F_{\text{visc}}$

We start from Hill’s Equation [101] (see equation (3.17)):

\[(v + b)(F + a) = b(F_o + a)\]

Using algebraic manipulations, we can obtain an equation for $F/F_0$:

\[v + b = b \frac{F_o + a}{F + a}\]

\[v = b \left( \frac{F_o + a}{F + a} - b \frac{F + a}{F + a} \right)\]

\[v = b \left( \frac{F_o + a - F - a}{F + a} \right)\]

\[v = b \left( \frac{F_0 - F}{F + a} \right)\]

\[v = b \left( 1 - \frac{F}{F_0} \right) \left( \frac{F}{F_0} + \frac{a}{F} \right)\]

\[\frac{v}{b} = \frac{1 - \frac{F}{F_0}}{\frac{a}{F_0} + \frac{F}{F_0}}\]

\[\frac{v}{b} \left( \frac{a}{F_0} + \frac{F}{F_0} \right) = 1 - \frac{F}{F_0}\]

\[\frac{av}{bF_0} + \frac{v F}{b F_0} = 1 - \frac{F}{F_0}\]

\[\frac{F}{F_0} \left( 1 + \frac{v}{b} \right) = 1 - \frac{av}{bF_0}\]
With the assumption that the ratio \( v/b \) is small, we can use the Taylor Expansion of 

\[
f(v) = \left( 1 + \frac{v}{b} \right)^{-1}
\]

at \( v = 0 \):

\[
f(v) = \left( 1 + \frac{v}{b} \right)^{-1}, \quad f'(v) = -\frac{1}{b} \left( 1 + \frac{v}{b} \right)^{-2},\quad f''(v) = \frac{2}{b^2} \left( 1 + \frac{v}{b} \right)^{-3}, \quad f'''(v) = -\frac{6}{b^3} \left( 1 + \frac{v}{b} \right)^{-3}
\]

\[
f(0) = 1, \quad f'(0) = -\frac{1}{b}, \quad f''(0) = \frac{2}{b^2}, \quad f'''(0) = -\frac{6}{b^3}
\]

Therefore

\[
f(v) = f(0) + f'(0)v + \frac{1}{2} f''(0)v^2 + \frac{1}{6} f'''(0)v^3 + \cdots
\]

\[
= 1 - \frac{v}{b} + \frac{v^2}{2b^2} - \frac{v^3}{6b^3} + \cdots
\]

Since \( \frac{v}{b} \) is small, \( \left( 1 + \frac{v}{b} \right)^{-1} \approx \frac{1}{1 + \frac{v}{b}} \), and we obtain equation (3.19):

\[
\frac{F}{F_0} \approx \left( 1 - \frac{av}{bF_0} \right) \left( 1 - \frac{v}{b} \right).
\]