Appendix A. Equations for ”Modeling β-adrenergic control of cardiac myocyte contractility in silico”

1 β-adrenergic receptor module

$$[L_{tot}] - [LR] - [LRG] - [L] = 0$$

$$[\beta_1 AR_{act}] - [LR] - [LRG] - [RG] - [\beta_1 AR] = 0$$

$$[G_{stot}] - [RG] - [LRG] - [G_{s\beta\gamma}] - [G_s] = 0$$

$$\begin{aligned}\frac{d([\beta_1 AR_{act}])}{dt} = {} & \{k_{\beta ARK-}[\beta_1 AR\_S464] - k_{\beta ARK+}([LR] + [LRG])\} + \\ & \{k_{PKA-}[\beta_1 AR\_S301] - k_{PKA+}[PKAC_I][\beta_1 AR_{act}]\}\end{aligned}$$

$$\frac{d([\beta_1 AR\_S464])}{dt} = k_{\beta ARK+}([LR] + [LRG]) - k_{\beta ARK-}[\beta_1 AR\_S464]$$

$$\frac{d([\beta_1 AR\_S301])}{dt} = k_{PKA+}[PKAC_I][\beta_1 AR_{act}] - k_{PKA-}[\beta_1 AR\_S301]$$

where:

$[LR] = [L][\beta_1 AR]/K_L$; $[LRG] = [L][\beta_1 AR][G_s]/(K_L \cdot K_R)$; $[RG] = [\beta_1 AR][G_s]/K_C$

2 G$_s$ activation module

$$\frac{d([G_{s\alpha GTPtot}])}{dt} = k_{gact}([RG] + [LRG]) - k_{hyd}[G_{s\alpha GTPtot}]$$

$$\frac{d([G_{s\beta\gamma}])}{dt} = k_{gact}([RG] + [LRG]) - k_{reassoc}[G_{s\alpha GDP}][G_{s\beta\gamma}]$$

$$\frac{d([G_{s\alpha GDP}])}{dt} = k_{hyd}[G_{s\alpha GTPtot}] - k_{reassoc}[G_{s\alpha GDP}][G_{s\beta\gamma}]$$

3 cyclic AMP metabolism module

$$[G_{s\alpha GTPtot}] - [G_{s\alpha GTP}] - [G_{s\alpha GTP} : AC] = 0$$

$$[AC_{tot}] - [G_{s\alpha GTP} : AC] - [AC] = 0$$

$$[PDE_{tot}] - [PDE_{inhib}] - [PDE] = 0$$

$$[IBMX_{tot}] - [PDE_{inhib}] - [IBMX] = 0$$

$$\frac{d([cAMP_{tot}])}{dt} = \frac{k_{AC-basal}[AC][ATP]}{K_{m-basal} + [ATP]} + \frac{k_{AC-Gs\alpha}[G_{s\alpha GTP}:AC][ATP]}{K_{m-Gs\alpha GTP} + [ATP]} - \frac{k_{PDE}[PDE][cAMP]}{K_{m-PDE} + [cAMP]}$$

where $[G_{s\alpha GTP} : AC] = [G_{s\alpha GTP}][AC]/K_{Gs\alpha}$; $[PDE_{inhib}] = [PDE][IBMX]/K_{IBMX}$

4 PKA activation module

$$[cAMP_{tot}] - ([ARC_I] + 2[A_2RC_I] + 2[A_2R_I]) - ([ARC_{II}] + 2[A_2RC_{II}] + 2[A_2R_{II}]) - [cAMP] = 0$$

$2[PKA_{Itot}] - ([RC_I] + [ARC_I] + [A_2RC_I] + [PKAC_I : PKI]) - [PKAC_I] = 0$

$2[PKA_{IItot}] - ([RC_{II}] + [ARC_{II}] + [A_2RC_{II}] + [PKAC_{II} : PKI]) - [PKAC_{II}] = 0$

where:

$[RC_I] = \frac{K_A \cdot K_B}{[cAMP]^2} \frac{[PKAC_I]}{K_D}([PKAC_I] + [PKAC_I : PKI])$

$[ARC_I] = \frac{K_A}{[cAMP]} \frac{[PKAC_I]}{K_D}([PKAC_I] + [PKAC_I : PKI])$

$[A_2RC_I] = \frac{[PKAC_I]}{K_D}([PKAC_I] + [PKAC_I : PKI])$

$[A_2R_I] = [PKAC_I] + [PKAC_I : PKI]$

$[RC_{II}] = \frac{K_A \cdot K_B}{[cAMP]^2} \frac{[PKAC_{II}]}{K_D}([PKAC_{II}] + [PKAC_{II} : PKI])$

$[ARC_{II}] = \frac{K_A}{[cAMP]} \frac{[PKAC_{II}]}{K_D}([PKAC_{II}] + [PKAC_{II} : PKI])$

$[A_2RC_{II}] = \frac{[PKAC_{II}]}{K_D}([PKAC_{II}] + [PKAC_{II} : PKI])$

$[A_2R_{II}] = [PKAC_{II}] + [PKAC_{II} : PKI]$

$[PKI] = \frac{K_{PKI}[PKI_{tot}]}{K_{PKI}+[PKAC_I]+[PKAC_{II}]}$

$[PKAC_I : PKI] = \frac{[PKAC_I][PKI_{tot}]}{K_{PKI}+[PKAC_I]+[PKAC_{II}]}$

$[PKAC_{II} : PKI] = \frac{[PKAC_{II}][PKI_{tot}]}{K_{PKI}+[PKAC_I]+[PKAC_{II}]}$

5 Phospholamban regulation module

$\frac{d([PLBp])}{dt} = \frac{k_{PKA-PLB}[PKAC_I][PLB]}{K_{mPKA-PLB}+[PLB]} - \frac{k_{PP1-PLB}[PP1][PLBp]}{K_{mPP1-PLB}+[PLBp]}$

$\frac{d([PLB])}{dt} = \frac{k_{PP1-PLB}[PP1][PLBp]}{K_{mPP1-PLB}+[PLBp]} - \frac{k_{PKA-PLB}[PKAC_I][PLB]}{K_{mPKA-PLB}+[PLB]}$

$\frac{d([Inhib1p_{tot}])}{dt} = \frac{k_{PKA-Inhib1}[PKAC_I][Inhib1p_{tot}]}{K_{mPKA-Inhib1}+[Inhib1p_{tot}]} - \frac{V_{\max PP2A-Inhib1}[Inhib1p_{tot}]}{K_{mPP2A-Inhib1}+[Inhib1p_{tot}]}$

$\frac{d([Inhib1])}{dt} = \frac{V_{\max PP2A-Inhib1}[Inhib1p_{tot}]}{K_{mPP2A-Inhib1}+[Inhib1p_{tot}]} - \frac{k_{PKA-Inhib1}[PKAC_I][Inhib1p_{tot}]}{K_{mPKA-Inhib1}+[Inhib1p_{tot}]}$

$[Inhib1p_{tot}] - [PP1 : Inhib1p] - [Inhib1p] = 0$

$\varepsilon[PP1_{tot}] - [PP1 : Inhib1p] - [PP1] = 0$

where: $[PP1 : Inhib1p] = [PP1][Inhib1p]/K_{Inhib1}$

6 L-type Calcium Channel regulation module

6.1 β_2 subunit

$\frac{d([LCC\beta_2p])}{dt} = \frac{\varepsilon k_{PKA-LCC}[PKAC_{II}][LCC\beta_2]}{K_{mPKA-LCC}+\varepsilon[LCC\beta_2]} - \frac{\varepsilon k_{PP1-LCC}[PP1_{LCC}][LCC\beta_2p]}{K_{mPP1-LCC}+\varepsilon[LCC\beta_2p]}$

$\frac{d([LCC\beta_2])}{dt} = \frac{\varepsilon k_{PP1-LCC}[PP1_{LCC}][LCC\beta_2p]}{K_{mPP1-LCC}+\varepsilon[LCC\beta_2p]} - \frac{\varepsilon k_{PKA-LCC}[PKAC_{II}][LCC\beta_2]}{K_{mPKA-LCC}+\varepsilon[LCC\beta_2]}$

6.2 Mode Normal

$$\frac{d(P[1])}{dt} = \beta_{LCC}P[2] + \omega_{LCC}P[7] - (4\alpha_{LCC} + \gamma_{LCC})P[1] - PHOSPH[1]$$

$$\frac{d(P[2])}{dt} = 4\alpha_{LCC}P[1] + 2\beta_{LCC}P[3] + \frac{\omega_{LCC}}{2}P[8] - (\beta_{LCC} + 3\alpha_{LCC} + 2\gamma_{LCC})P[2] - PHOSPH[2]$$

$$\frac{d(P[3])}{dt} = 3\alpha_{LCC}P[2] + 3\beta_{LCC}P[4] + \frac{\omega_{LCC}}{2^2}P[9] - (2\beta_{LCC} + 2\alpha_{LCC} + 2^2\gamma_{LCC})P[3] - PHOSPH[3]$$

$$\frac{d(P[4])}{dt} = 2\alpha_{LCC}P[3] + 4\beta_{LCC}P[5] + \frac{\omega_{LCC}}{2^3}P[10] - (3\beta_{LCC} + \alpha_{LCC} + 2^3\gamma_{LCC})P[4] - PHOSPH[4]$$

$$\frac{d(P[5])}{dt} = \alpha_{LCC}P[4] + g_{nLCC}P[6] + \frac{\omega_{LCC}}{2^4}P[11] - (4\beta_{LCC} + f_{nLCC} + 2^4\gamma_{LCC})P[5] - PHOSPH[5]$$

$$\frac{d(P[6])}{dt} = f_{nLCC}P[5] - g_{nLCC}P[6] - PHOSPH[6]$$

6.3 Mode Ca

$$\frac{d(P[7])}{dt} = \frac{\beta_{LCC}}{2}P[8] + \gamma_{LCC}P[1] - (4 \cdot 2\alpha_{LCC} + \omega_{LCC})P[7] - PHOSPH[7]$$

$$\frac{d(P[8])}{dt} = 4 \cdot 2\alpha_{LCC}P[7] + \beta_{LCC}P[9] + 2\gamma_{LCC}P[2] - (\frac{\beta_{LCC}}{2} + 3 \cdot 2\alpha_{LCC} + \frac{\omega_{LCC}}{2})P[8] - PHOSPH[8]$$

$$\frac{d(P[9])}{dt} = 3 \cdot 2\alpha_{LCC}P[8] + \frac{3\beta_{LCC}}{2}P[10] + 2^2\gamma_{LCC}P[3] - (\beta_{LCC} + 2 \cdot 2\alpha_{LCC} + \frac{\omega_{LCC}}{2^2})P[9] - PHOSPH[9]$$

$$\frac{d(P[10])}{dt} = 2 \cdot 2\alpha_{LCC}P[9] + 2\beta_{LCC}P[11] + 2^3\gamma_{LCC}P[4] - (\frac{3\beta_{LCC}}{2} + 2\alpha_{LCC} + \frac{\omega_{LCC}}{2^3})P[10] - PHOSPH[10]$$

$$\frac{d(P[11])}{dt} = 2\alpha_{LCC}P[10] + g_{cLCC}P[12] + 2^4\gamma_{LCC}P[5] - (\frac{4\beta_{LCC}}{2} + f_{cLCC} + \frac{\omega_{LCC}}{2^4})P[11] - PHOSPH[11]$$

$$\frac{d(P[12])}{dt} = f_{cLCC}P[11] - g_{cLCC}P[12] - PHOSPH[12]$$

6.4 Mode P

$$\frac{d(P[13])}{dt} = \beta_{LCC}P[14] + \omega_{LCC}P[19] - (4\alpha_{LCC} + \gamma_{LCC})P[13] + PHOSPH[1]$$

$$\frac{d(P[14])}{dt} = 4\alpha_{LCC}P[13] + 2\beta_{LCC}P[15] + \frac{\omega_{LCC}}{2}P[20] - (\beta_{LCC} + 3\alpha_{LCC} + 2\gamma_{LCC})P[14] + PHOSPH[2]$$

$$\frac{d(P[15])}{dt} = 3\alpha_{LCC}P[14] + 3\beta_{LCC}P[16] + \frac{\omega_{LCC}}{2^2}P[21] - (2\beta_{LCC} + 2\alpha_{LCC} + 2^2\gamma_{LCC})P[15] + PHOSPH[3]$$

$$\frac{d(P[16])}{dt} = 2\alpha_{LCC}P[15] + 4\beta_{LCC}P[17] + \frac{\omega_{LCC}}{2^3}P[22] - (3\beta_{LCC} + \alpha_{LCC} + 2^3\gamma_{LCC})P[16] + PHOSPH[4]$$

$$\frac{d(P[17])}{dt} = \alpha_{LCC}P[16] + g_{pLCC}P[18] + \frac{\omega_{LCC}}{2^4}P[23] - (4\beta_{LCC} + f_{pLCC} + 2^4\gamma_{LCC})P[17] + PHOSPH[5]$$

$$\frac{d(P[18])}{dt} = f_{pLCC}P[17] - g_{pLCC}P[18] + PHOSPH[6]$$

6.5 Mode CaP

$$\frac{d(P[19])}{dt} = \frac{\beta_{LCC}}{2}P[20] + \gamma_{LCC}P[13] - (4 \cdot 2\alpha_{LCC} + \omega_{LCC})P[19] + PHOSPH[7]$$

$$\frac{d(P[20])}{dt} = 4 \cdot 2\alpha_{LCC}P[19] + \beta_{LCC}P[21] + 2\gamma_{LCC}P[14] - (\frac{\beta_{LCC}}{2} + 3 \cdot 2\alpha_{LCC} + \frac{\omega_{LCC}}{2})P[20] + PHOSPH[8]$$

$$\frac{d(P[21])}{dt} = 3 \cdot 2\alpha_{LCC}P[18] + \frac{3\beta_{LCC}}{2}P[20] + 2^2\gamma_{LCC}P[15] - (\beta_{LCC} + 2 \cdot 2\alpha_{LCC} + \frac{\omega_{LCC}}{2^2})P[21] + PHOSPH[9]$$

$$\frac{d(P[22])}{dt} = 2 \cdot 2\alpha_{LCC}P[17] + 2\beta_{LCC}P[19] + 2^3\gamma_{LCC}P[16] - (\frac{3\beta_{LCC}}{2} + 2\alpha_{LCC} + \frac{\omega_{LCC}}{2^3})P[22] + PHOSPH[10]$$

$$\frac{d(P[23])}{dt} = 2\alpha_{LCC}P[16] + g_{cLCC}P[24] + 2^4\gamma_{LCC}P[17] - (\frac{4\beta_{LCC}}{2} + f_{cLCC} + \frac{\omega_{LCC}}{2^4})P[23] + PHOSPH[11]$$

$$\frac{d(P[24])}{dt} = f_{cLCC}P[23] - g_{cLCC}P[24] + PHOSPH[12]$$

where: $PHOSPH[i] = \frac{\varepsilon k_{PKA-LCC}[PKAC_{II}]P[i]}{K_{mPKA-LCC} + \varepsilon[LCC_{tot}]P[i]} - \frac{\varepsilon k_{PP2A-LCC}[PP2A_{LCC}]P[i+12]}{K_{mPP2A-LCC} + \varepsilon[LCC_{tot}]P[i+12]}$;

$\alpha_{LCC} = 400e^{(V_m+12)/10}$; $\beta_{LCC} = 50e^{-(V_m+12)/13}$; $\gamma_{LCC} = \gamma_{oLCC}[Cai]$;

Appendix B. Parameters for ”Modeling β-adrenergic control of cardiac myocyte contractility in silico”

7 β-adrenergic receptor module

Parameter	*Value*	*Units*	*Source*
$[L_{tot}]$	0..100	μM	[1]
$[\beta_1 AR_{tot}]$	0.0132	μM	[1],[2],[3]
$[G_{stot}]$	3.83	μM	[1]
K_L	0.285	μM	[4]
K_R	0.062	μM	[4]
K_C	33	μM	[5]
$k_{\beta ARK+}$	0.0011	sec^{--1}	[5]
$k_{\beta ARK-}$	$2k_{\beta ARK+}$	sec^{-1}	[5]
k_{PKA+}	0.0036	sec $^{-1}\cdot\mu$M^{-1}	[5],[6]
k_{PKA-}	$0.62k_{PKA+}$	sec^{-1}	[5],[6]

8 G$_s$ activation module

Parameter	*Value*	*Units*	*Source*
k_{gact}	16	sec^{-1}	[7],[8]
k_{hyd}	0.8	sec^{-1}	[7],[8]
$k_{reassoc}$	1.2e3	sec$^{-1}\cdot\mu$M^{-1}	[9]

9 cyclic AMP metabolism module

Parameter	*Value*	*Units*	*Source*
$[AC_{tot}]$	0.0497	μM	[1]
$[ATP]$	5.0e3	μM	[10]
$[PDE_{tot}]$	0.039	μM	[11],[12]
$[IBMX_{tot}]$	0..1e3	μM	[13]
$K_{Gs\alpha}$	315	μM	[14]
K_{IBMX}	30	μM	[15]
$k_{AC-basal}$	0.2	sec^{-1}	[16]
$K_{m-basal}$	1.03e3	μM	[16]
$k_{AC-Gs\alpha}$	8.5	sec^{-1}	[16]
$K_{m-Gs\alpha GTP}$	315	μM	[16]
k_{PDE}	5	sec^{-1}	[11]
K_{m-PDE}	1.3	μM	[11]

10 PKA activation module

Parameter	*Value*	*Units*	*Source*
$[PKA_{Itot}]$	0.59	μM	[17],[18]
$[PKA_{IItot}]$	0.025	μM	[10]
$[PKI_{tot}]$	0.18	μM	[19],[20]
K_A	9.14	μM	[21],[22]
K_B	1.64	μM	[21],[22]
K_D	4.375	μM	[23]
K_{PKI}	2e-4	μM	[19],[20]

11 Phospholamban regulation module

Parameter	*Value*	*Units*	*Source*
$[PLB_{Itot}]$	106	μM	[10],[24]
$[PP1_{tot}]$	0.89	μM	[25],[26]
$[Inhib1_{tot}]$	0.3	μM	[25]
ε	10	none	[27]
$k_{PKA-PLB}$	54	sec^{-1}	[28],[29]
$K_{mPKA-PLB}$	21	μM	[29]
$k_{PP1-PLB}$	8.5	sec^{-1}	[26],[30]
$K_{mPP1-PLB}$	7.0	μM	[26],[30]
$k_{PKA-Inhib1}$	60	sec^{-1}	[31]
$K_{mPKA-Inhib1}$	1.0	μM	[31]
$V_{\max PP2A-Inhib1}$	14	$\mu\text{M} \cdot \text{sec}^{-1}$	[25],[30]
$K_{mPP2A-Inhib1}$	1.0	μM	[25],[30]
K_{Inhib1}	1e-3	μM	[25]

12 L-type Calcium Channel regulation module

Parameter	*Value*	*Units*	*Source*
$[LCC_{tot}]$	0.025	μM	[10]
$[PP1_{LCC}]$	0.025	μM	[10]
$[PP2A_{LCC}]$	0.025	μM	[10]
ε	10	none	[27]
$k_{PKA-LCC}$	54	sec^{-1}	[28],[29]
$K_{mPKA-LCC}$	21	μM	[29]
$k_{PP1-LCC}$	8.5	sec^{-1}	[26],[30]
$K_{mPP1-LCC}$	3.0	μM	[30]
$k_{PP2A-LCC}$	10.1	sec^{-1}	[30]
$K_{mPP2A-LCC}$	3.0	μM	[30]
ω_{LCC}	10	sec^{-1}	[32]
γ_{oLCC}	2.8e3	sec^{-1}	[32]
f_{nLCC}	200	sec^{-1}	[32],[33],[34]
g_{nLCC}	2.0e3	sec^{-1}	[32]
f_{cLCC}	5.0	sec^{-1}	[32]
g_{cLCC}	7.0e3	sec^{-1}	[32]
f_{pLCC}	800	sec^{-1}	[33],[34]
g_{pLCC}	2.0e3	sec^{-1}	[32]

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