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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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Mathematical model of β_1-adrenergic signaling in mouse ventricular myocytes as an *in silico* tool for the cardiovascular drug test

24 March 2014

Vladimir E. Bondarenko
Department of Mathematics and Statistics,
Georgia State University,
Atlanta, GA 30303
E-mail: vbondarenko@gsu.edu

Can we actually use mathematical models to predict physiological phenomena?

Example 1: prediction of proline hinge in Kv1.4

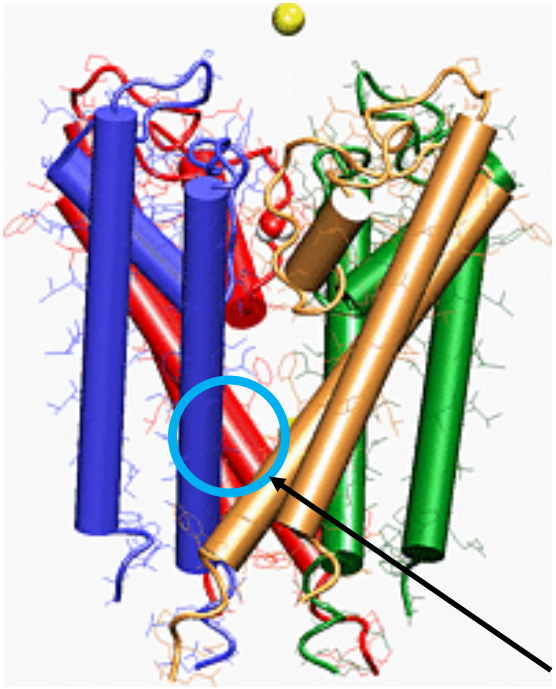
Am J Physiol Heart Circ Physiol 284: H71–H80, 2003.
First published August 29, 2002; 10.1152/ajpheart.00392.2002.

Regulation of N- and C-type inactivation of Kv1.4 by pH_o and K^+: evidence for transmembrane communication

XIAOYAN LI,[1,2] GLENNA C. L. BETT,[1] XUEJUN JIANG,[1] VLADIMIR E. BONDARENKO,[1]
MICHAEL J. MORALES,[1] AND RANDALL L. RASMUSSON[1]

Example 1: prediction of proline hinge in Kv1.4

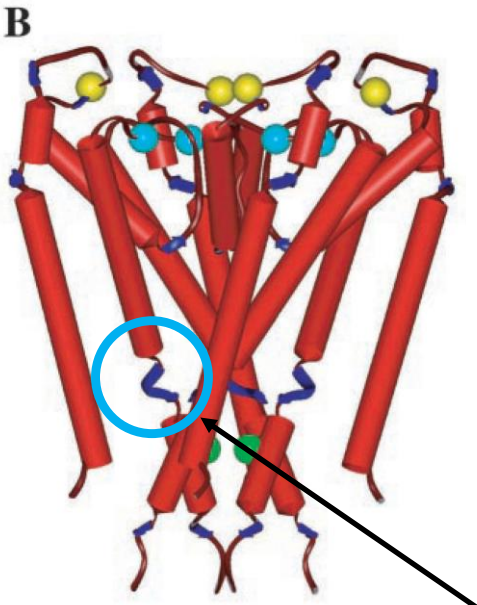
KcsA



no hinge

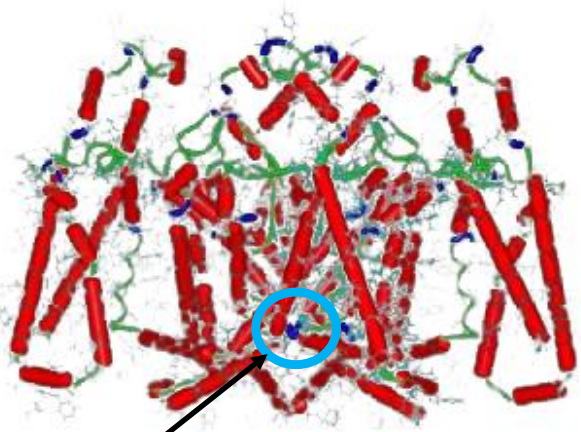
From:
http://www.ks.uiuc.edu/
Research/smd_imd/
Doyle et al. Science 280:
69-77, 1998.

Kv1.4



Homology model based
on KcsA from:
Li et al. Am J Physiol
284: H71-H80, 2003.

Kv1.2



hinge

From PDB file:
Long et al. Science
309: 897-903, 2005.

Example 2: mouse action potential shape and activation time constant for $I_{Kto,f}$

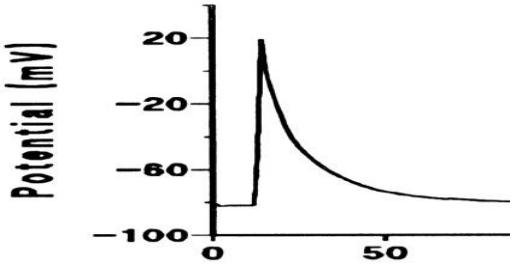
Am J Physiol Heart Circ Physiol 287: H1378–H1403, 2004.
First published May 13, 2004; 10.1152/ajpheart.00185.2003.

Computer model of action potential of mouse ventricular myocytes

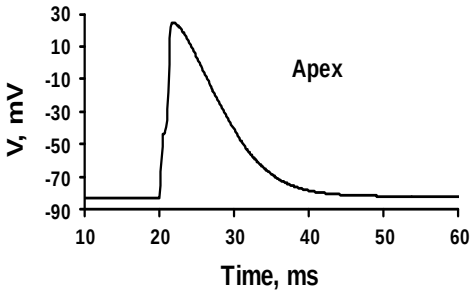
Vladimir E. Bondarenko,[1] Gyula P. Szigeti,[1] Glenna C. L. Bett,[1] Song-Jung Kim,[2] and Randall L. Rasmusson[1]

[1]*Department of Physiology and Biophysics, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York 14214-3078; and* [2]*Cell Biology and Molecular Medicine Cardiovascular Research Institute, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, New Jersey 07103*

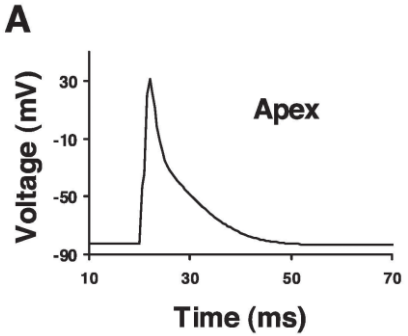
Example 2: mouse action potential shape and activation time constant for $I_{Kto,f}$

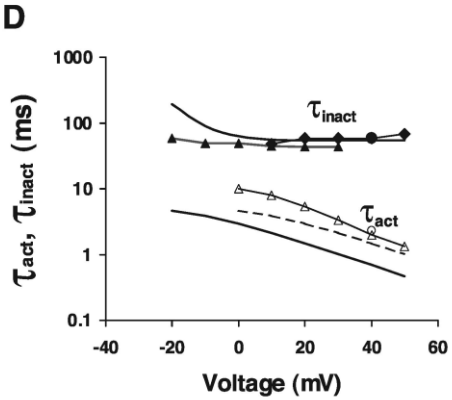


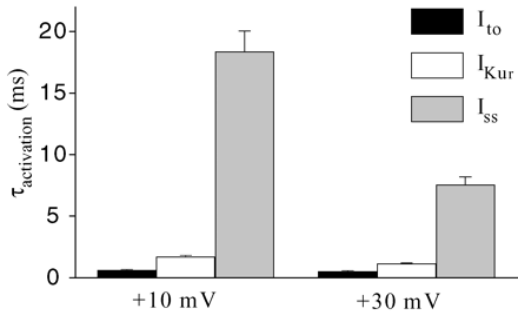
Experiment from:
Wang et al. Circ Res 79: 79-85, 1996.



Simulations with experimental activation time constant from
Xu et al. J Gen Physiol 113: 661-677, 1999



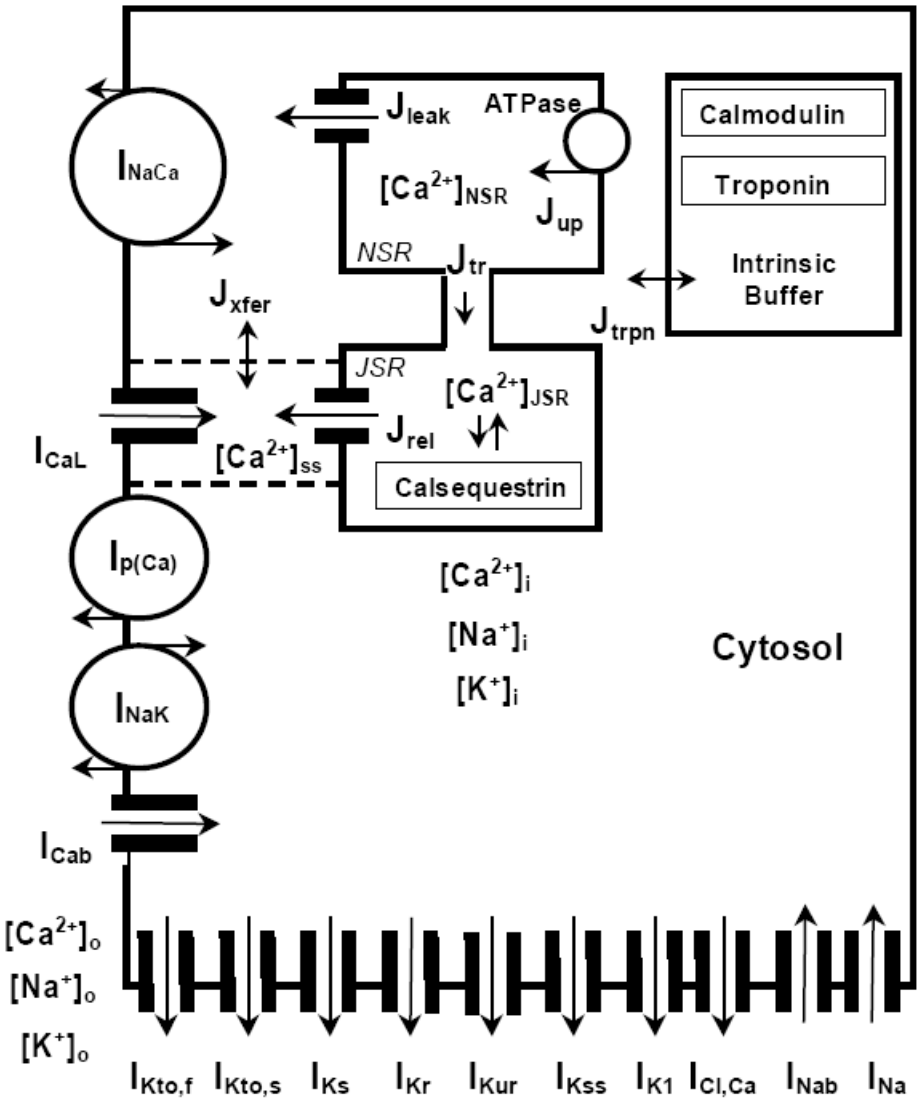




Experiment from:
Brouillette et al. J Physiol 559: 777-798, 2004.

Simulation from:
Bondarenko et al. Am J Physiol 287: H1378-H1403, 2004.

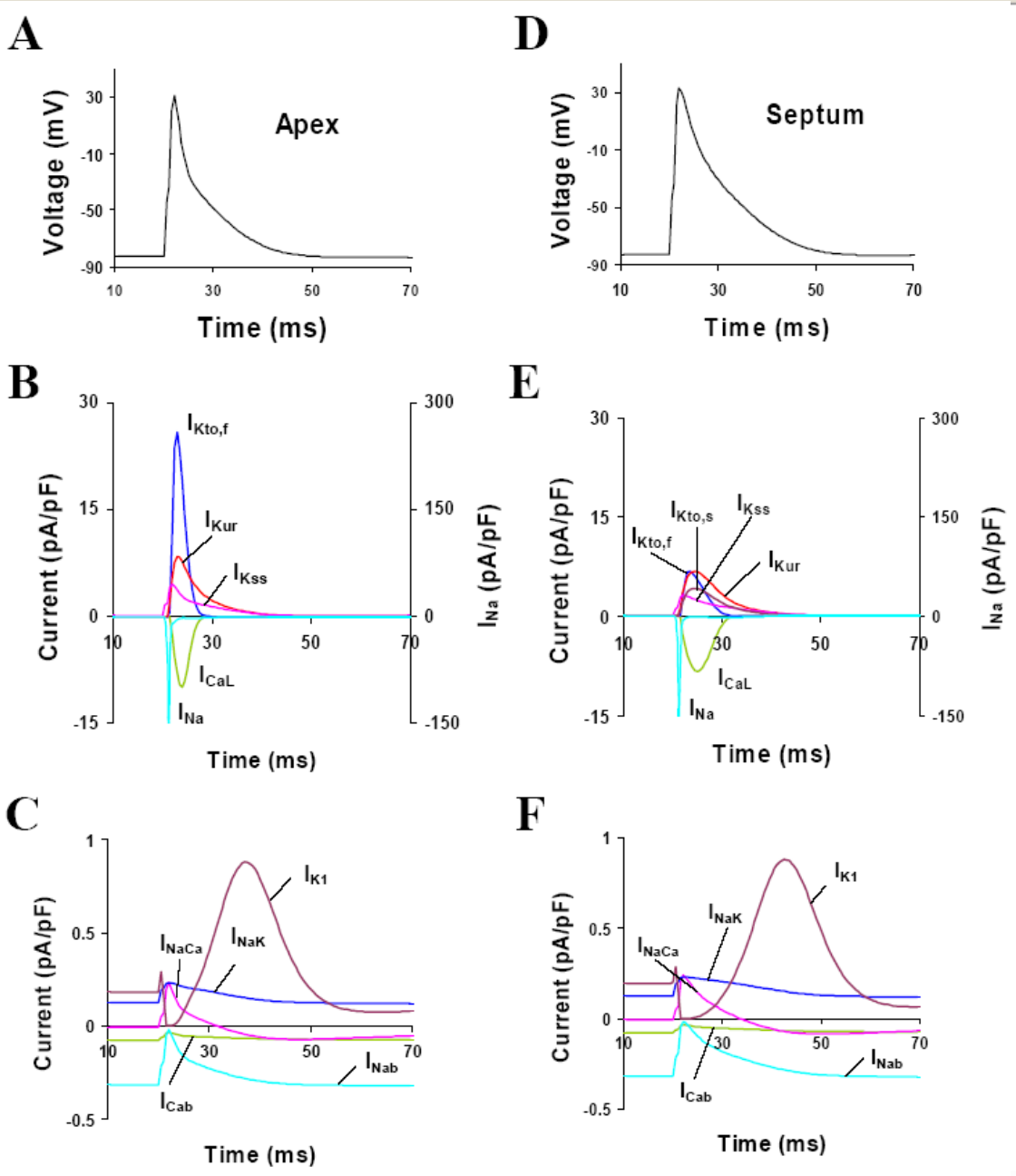
Model cell



$$dV/dt = -1/C_m(I_{Na} + I_{Nab} + I_{CaL} + I_{p(Ca)} + I_{Cab} + I_{NaCa} + I_{NaK} + I_{Kto,f} + I_{Kto,s} + I_{Kur} + I_{Kss} + I_{K1} + I_{Kr} + I_{Ks} + I_{Cl,Ca} + I_{stim})$$

Model cell is described by 44 ordinary differential equations.

Bondarenko et al., Am J Physiol Heart Circ Physiol 287: H1378-H1403, 2004.



The mouse action potentials

Simulated action potentials and underlying currents using the mouse ventricular myocyte model.

PANEL A: The apex action potential.
PANELS B,C: Currents underlying the apex action potential.
PANEL D: The septum action potential.
PANEL E,F: Currents underlying the septum action potential.

Bondarenko et al., Am J Physiol 287: H1378-H1403, 2004.

Next Generation Mathematical Models of Protein Signaling Systems in Cardiac Cells

Non-compartmentalized models

Saucerman JJ, Brunton LL, Michailova AP, McCulloch AD. Modeling β-adrenergic control of cardiac myocyte contractility *in silico*. *J Biol Chem* 278: 47997-48003, 2003.

Saucerman JJ, Healy SN, Belik ME, Puglisi JL, McCulloch AD. Proarrhythmic consequences of a KCNQ1 AKAP-binding domain mutation: computational models of whole cells and heterogeneous tissue. *Circ Res* 95: 1216-1224, 2004.

Yang JH, Saucerman JJ. Phospholemman is a negative feed-forward regulator of Ca^{2+} in β-adrenergic signaling, accelerating β-adrenergic inotropy. *J Mol Cell Cardiol* 52: 1048-1055, 2012.

A compartmentalized model

Heijman J, Volders PGA, Westra RL, Rudy Y. Local control of β-adrenergic stimulation: effects on ventricular myocyte electrophysiology and Ca^{2+} transient. *J Mol Cell Cardiol* 50: 863-871, 2011.

A Compartmentalized Mathematical Model of the β_1-Adrenergic Signaling System in Mouse Ventricular Myocytes

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Department of Mathematics and Statistics and Neuroscience Institute, Georgia State University, Atlanta, Georgia, United States of America

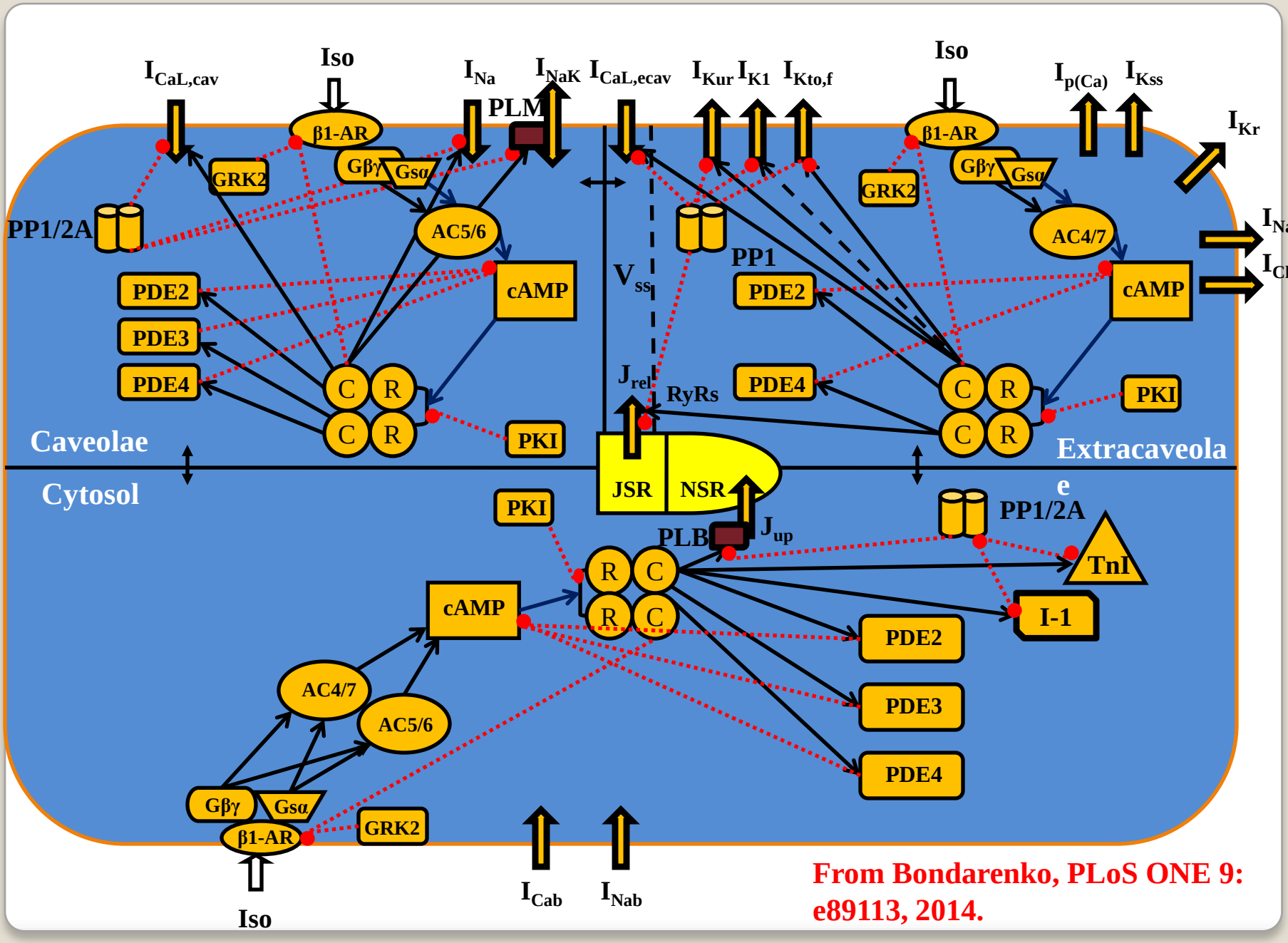
Abstract

The β_1-adrenergic signaling system plays an important role in the functioning of cardiac cells. Experimental data shows that the activation of this system produces inotropy, lusitropy, and chronotropy in the heart, such as increased magnitude and relaxation rates of $[Ca^{2+}]_i$ transients and contraction force, and increased heart rhythm. However, excessive stimulation of β_1-adrenergic receptors leads to heart dysfunction and heart failure. In this paper, a comprehensive, experimentally based mathematical model of the β_1-adrenergic signaling system for mouse ventricular myocytes is developed, which includes major subcellular functional compartments (caveolae, extracaveolae, and cytosol). The model describes biochemical reactions that occur during stimulation of β_1-adrenoceptors, changes in ionic currents, and modifications of Ca^{2+} handling system. Simulations describe the dynamics of major signaling molecules, such as cyclic AMP and protein kinase A, in different subcellular compartments; the effects of inhibition of phosphodiesterases on cAMP production; kinetics and magnitudes of phosphorylation of ion channels, transporters, and Ca^{2+} handling proteins; modifications of action potential shape and duration; magnitudes and relaxation rates of $[Ca^{2+}]_i$ transients; changes in intracellular and transmembrane Ca^{2+} fluxes; and $[Na^+]_i$ fluxes and dynamics. The model elucidates complex interactions of ionic currents upon activation of β_1-adrenoceptors at different stimulation frequencies, which ultimately lead to a relatively modest increase in action potential duration and significant increase in $[Ca^{2+}]_i$ transients. In particular, the model includes two subpopulations of the L-type Ca^{2+} channels, in caveolae and extracaveolae compartments, and their effects on the action potential and $[Ca^{2+}]_i$ transients are investigated. The presented model can be used by researchers for the interpretation of experimental data and for the developments of mathematical models for other species or for pathological conditions.

Citation: Bondarenko VE (2014) A Compartmentalized Mathematical Model of the β_1-Adrenergic Signaling System in Mouse Ventricular Myocytes. PLoS ONE 9(2): e89113. doi:10.1371/journal.pone.0089113

Editor: Xun Ai, Loyola University Chicago, United States of America

Received September 29, 2013; **Accepted** January 14, 2014; **Published** February 21, 2014

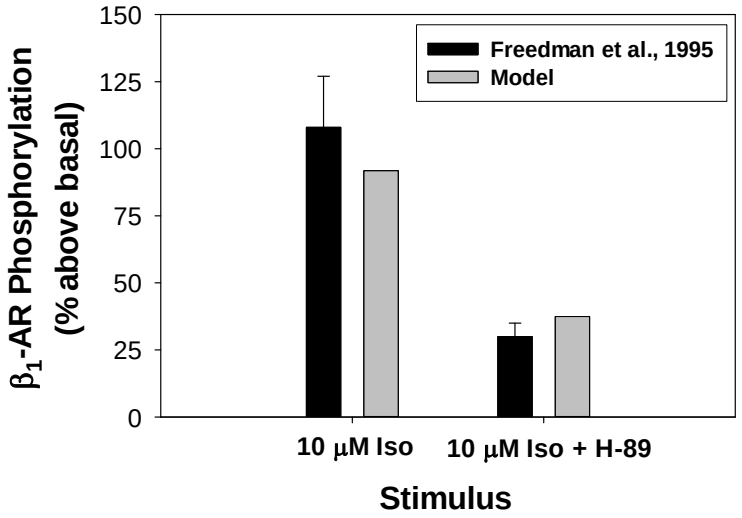

I_CaL,cav
Iso
I_Na
I_NaK
I_CaL,ecav
I_Kur
I_K1
I_Kto,f
Iso
I_p(Ca)
I_Kss
I_Kr
PLM
β1-AR
Gβγ
Gsα
GRK2
PP1/2A
AC5/6
AC4/7
cAMP
PDE2
PDE3
PDE4
C
R
PKI
V_ss
PP1
J_rel
RyRs
I_NaCa
I_Cl,Ca
Caveolae
Cytosol
Extracaveolae
JSR
NSR
J_up
PLB
PP1/2A
TnI
I-1
I_Cab
I_Nab
Iso
From Bondarenko, PLoS ONE 9: e89113, 2014.

β_1-adrenergic Signaling System in Mouse Ventricular Myocytes

This is a virtual cell model, which allows for testing at least the following drugs:

Isoproterenol
Epinephrine
Norepinephrine
H-89
Forskolin
IBMX
Nifedipine
Calyculin A
Cilostamide
Milrione
Rolipram
Ro 20-1724
Propranolol
Esmolol
Bretylium
Amiodarone
Tetrodotoxin
Dofetilide
Quinidine
Verapamil
Lidocaine
Flecainide
Sotalol
E-4031

Reproducing the experimental data



β_1-adrenoceptors phosphorylation above basal level upon application of 10 μM isoproterenol or 10 μM isoproterenol + PKA inhibitor H-89. Experimental data from Freedman et al. (1995) are shown with black bars with errors, simulation data are shown with gray bars. Effect of H-89 was simulated by setting $[PKA]_{tot}$ = 0 μM.

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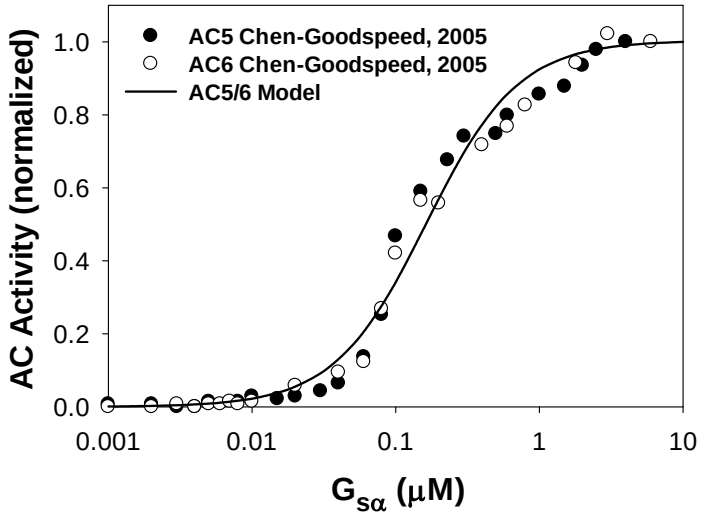
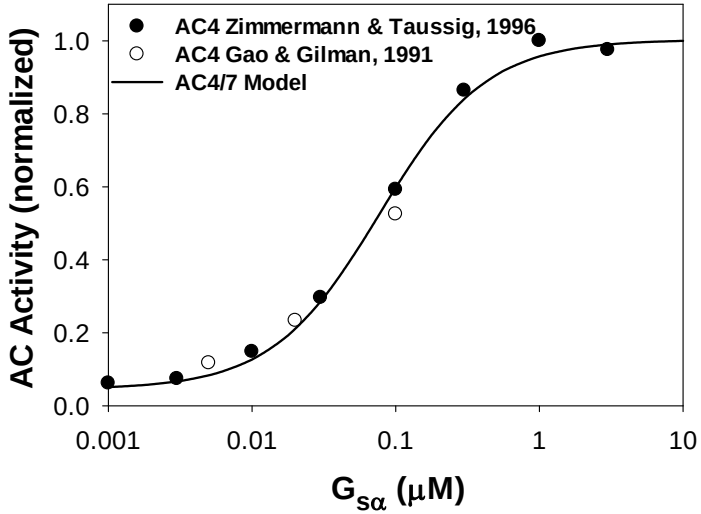
Reproducing the experimental data

A



B



Normalized activity of adenylyl cyclases as functions of $G_{s\alpha}$.

Panel A: Experimental normalized activity of AC5 (filled circles) and AC6 (unfilled circles) [Chen-Goodspeed et al., 2005]. Simulated data for normalized activity of AC5/6 is shown by a solid line.

Panel B: Experimental normalized activity of AC4 (filled circles from [Zimmermann and Taussig, 1996] and unfilled circles from [Gao and Gilman, 1991]). Simulated data for normalized activity of AC4/7 is shown by a solid line.

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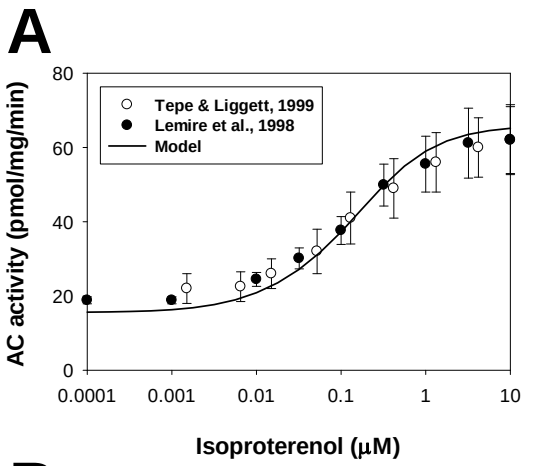
Reproducing the experimental data

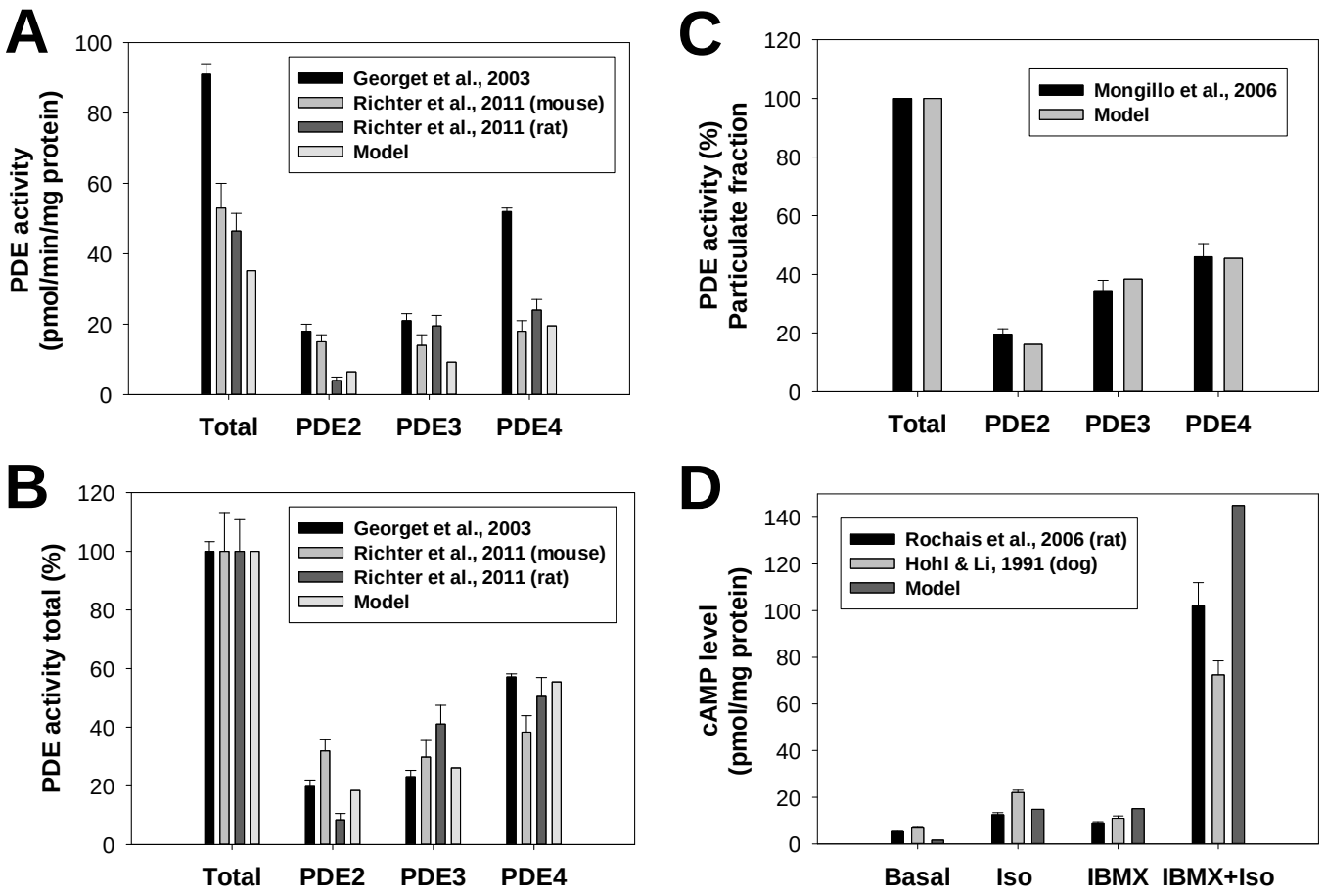


Panel A: Adenylyl cyclase activity as a function of isoproterenol. Experimental data on AC activity (in pmol/mg/min) in mouse hearts and ventricular myocytes obtained after 10-minutes exposure to isoproterenol are shown by unfilled circles [Tepe and Liggett, 1999] and filled circles [Lemire et al., 1998]. The solid line shows corresponding simulated AC activities at different concentrations of isoproterenol.

Panel B: Desensitization of β_1-ARs. Increase in adenylyl cyclase activities above basal level (in %) are measured at maximum (control, filled circles) and at two time moments (5 min and 30 min, unfilled circles and unfilled squares, respectively) after exposure to different concentrations of isoproterenol [Freedman et al., 1995]. Corresponding simulated data for the maximum, 5-minute, and 30-minute delays are shown by solid, dashed, and dash-dotted lines, respectively.

From Bondarenko, PLoS ONE 9: e89113, 2014.

Reproducing the experimental data



Absolute (A) and relative (B) PDE activity in mouse ventricular myocytes. (C) PDE activity in particulate fraction. (D) Effect of Iso and IBMX on cAMP level.

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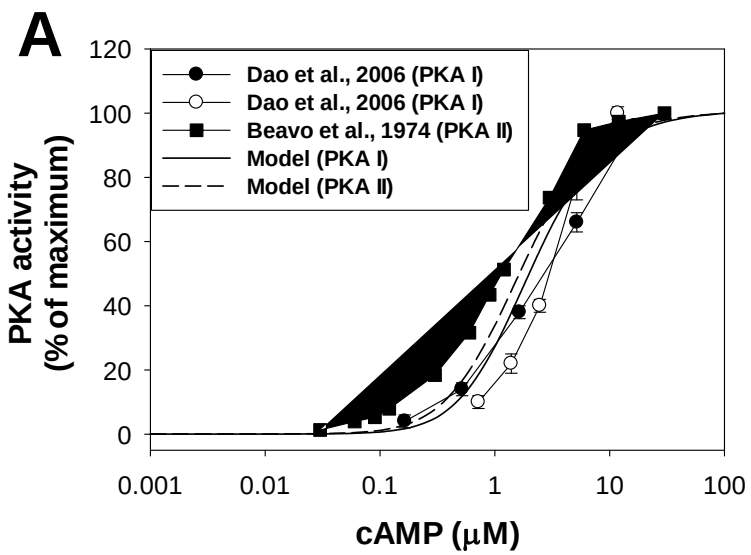
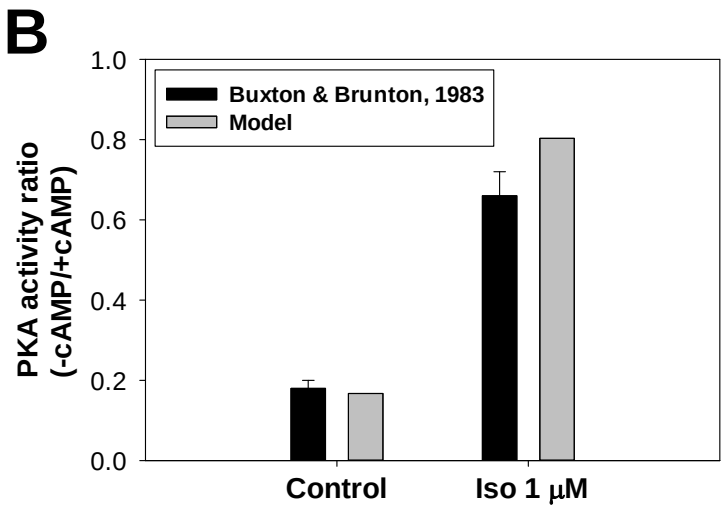
Reproducing the experimental data





Protein kinase A activation.

Panel A: PKA I and PKA II activities as functions of cAMP. Experimental data for PKA I obtained by two methods are shown by filled and unfilled circles [Dao et al., 2006]; data for PKA II obtained by Beavo et al. [1974]. Corresponding simulated data are shown by a solid (PKA I) and a dashed (PKA II) line.

Panel B: PKA activity ratio. Experimental data were obtained without (−cAMP) and with (+cAMP) externally applied 3 μM cAMP, both without and with 1 μM isoproterenol (black bars [Buxton and Brunton, 1983]). We also performed four simulations: no isoproterenol/basic level cAMP (−cAMP), no isoproterenol/3 μM cAMP (+cAMP), 1 μM isoproterenol/no externally applied cAMP (−cAMP), and 1 μM isoproterenol/3 μM cAMP (+cAMP). Then, the corresponding PKA ratios were calculated.

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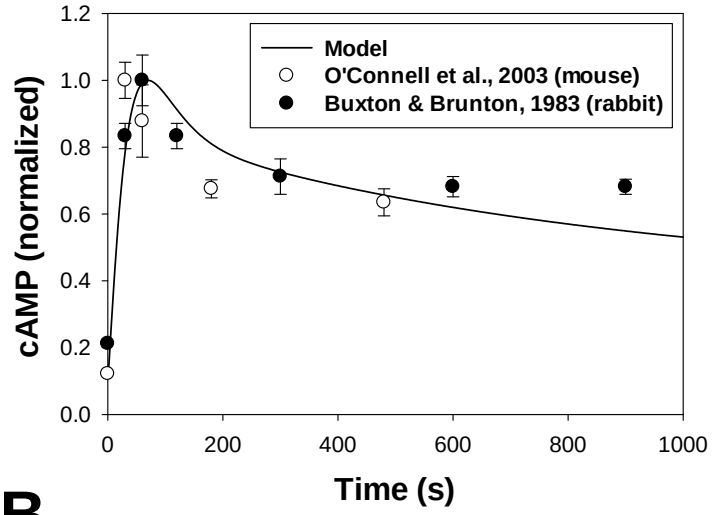
Reproducing the experimental data

A



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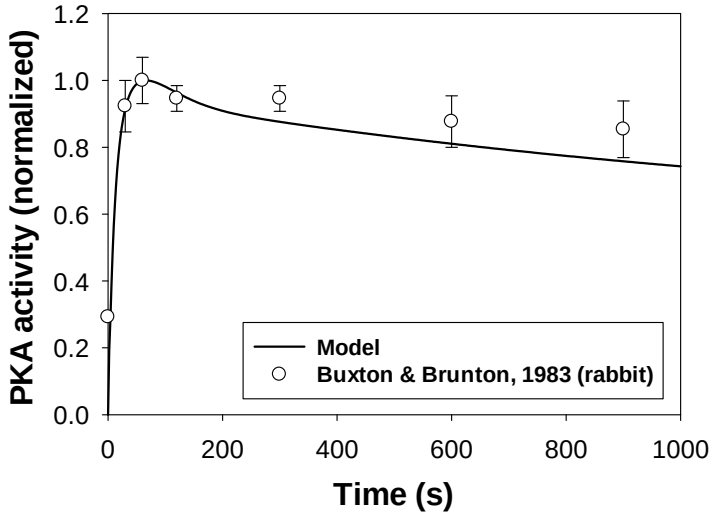

Panel A: cAMP dynamics in ventricular myocytes. Experimental data of normalized cAMP in mouse [O'Connell et al., 2003] and rabbit [Buxton & Brunton, 1983] ventricular myocytes are shown by unfilled and filled circles, respectively; simulation data is shown by a solid line.

Panel B: PKA dynamics in ventricular myocytes. Experimental data of normalized PKA activity in rabbit [Buxton & Brunton, 1983] ventricular myocytes are shown by unfilled circles; simulation data is shown by a solid line.

Data in **Panels A** and **B** were obtained upon application of 1 μM isoproterenol.

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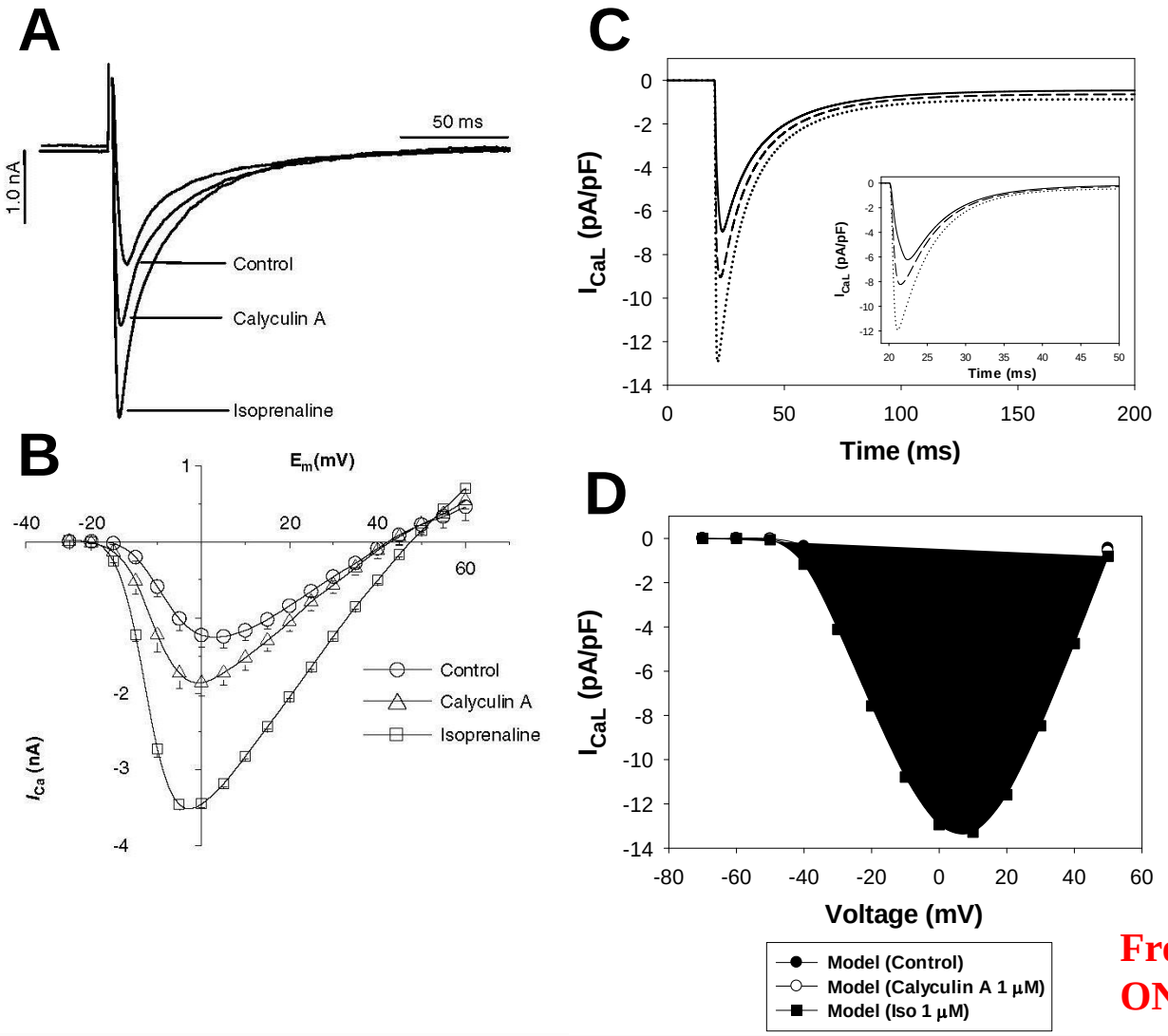
Reproducing the experimental data



The effects of Iso and Calyculin A on the L-type Ca^{2+} current. (A) and (B) Experimental data by Bracken et al., 2006. (C) and (D) simulated data. (A) and (C) Current traces. (B) and (D) I-V relationships.

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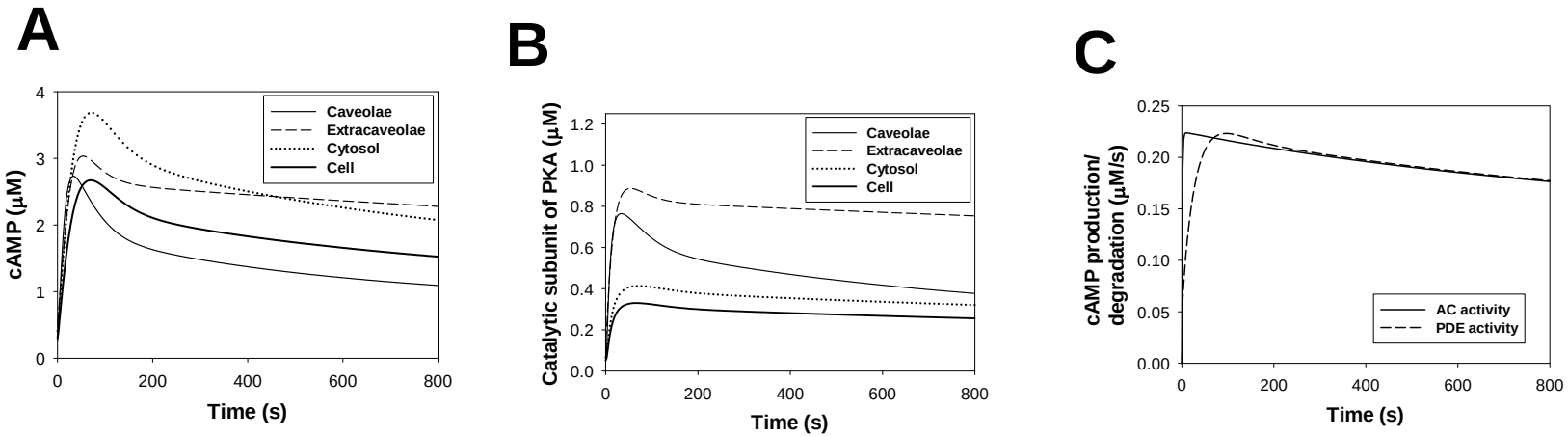
Simulation results



Panel A: Simulated time courses of cAMP concentrations in caveolae (thin solid line), extracaveolae (dashed line), and cytosolic compartments (dotted line), and in the whole cell volume (bold solid line) after application of 1 μM isoproterenol.

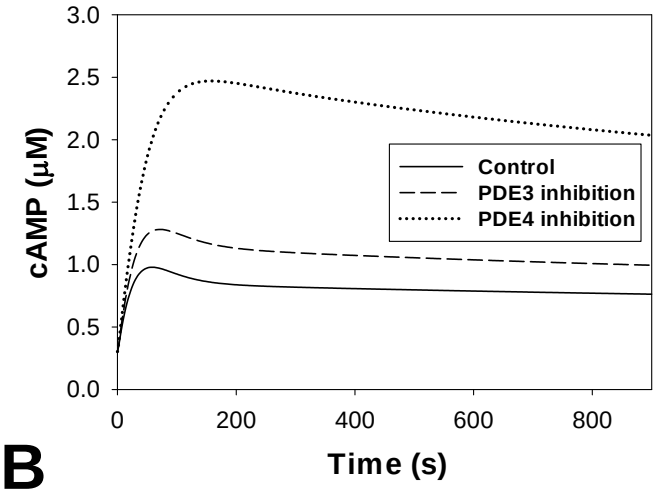
Panel B: Simulated time courses of PKA catalytic subunit concentrations in caveolae (thin solid line), extracaveolae (dashed line), and cytosolic compartments (dotted line), and in the whole cell volume (bold solid line) after application of 1 μM isoproterenol.

Panel C: Simulated cellular activities of ACs and PDEs after application of 1 μM isoproterenol.

From Bondarenko, PLoS ONE 9: e89113, 2014.

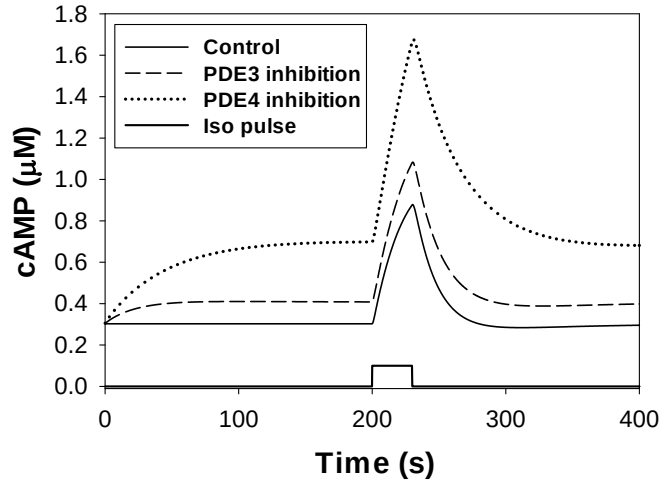
Simulation results

A



Panel A: Simulated time courses of cellular cAMP concentrations for control conditions (solid line), upon inhibition of PDE3 (dashed line), and upon inhibition of PDE4 (dotted line) after sustained application of 0.1 μM isoproterenol at time moment *t* = 0 s. Activities of PDE3 or PDE4 are inhibited by 90% to simulate the effects of corresponding selective inhibitors, cilostamide or milrione for PDE3, or rolipam or Ro 20-1724 for PDE4.

B



Panel B: Simulated time courses of cellular cAMP concentrations for control conditions (solid line), upon inhibition of PDE3 (dashed line), and upon inhibition of PDE4 (dotted line) after pulsed application of 0.1 μM isoproterenol at time moment *t* = 200 s for 30 s (thick solid line). The degrees of inhibition of PDE3 and PDE4 are the same as in **Panel A**.

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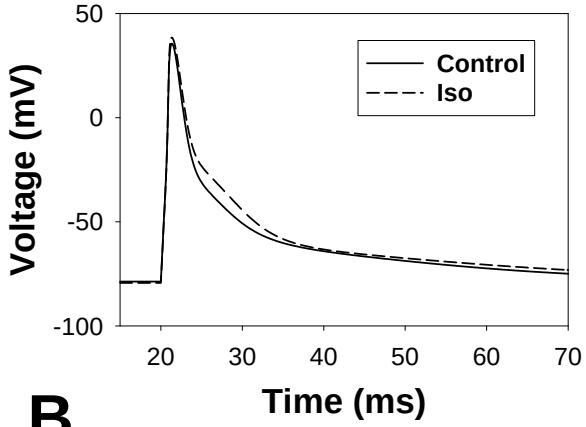
Simulation results

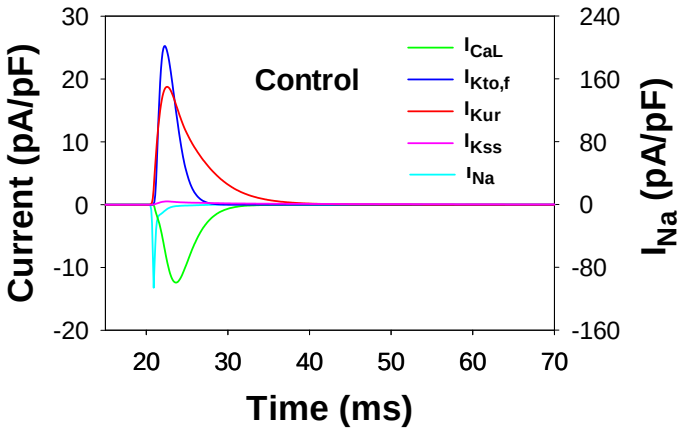
1 Hz

A

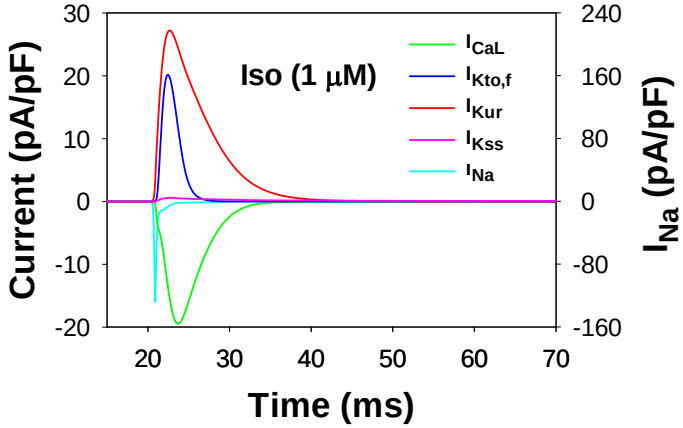


Simulated action potentials (Panel A) and underlying ionic currents of the isolated ventricular cell model for control conditions (Panel B) and after application of 1 μM isoproterenol (Panel C).

B

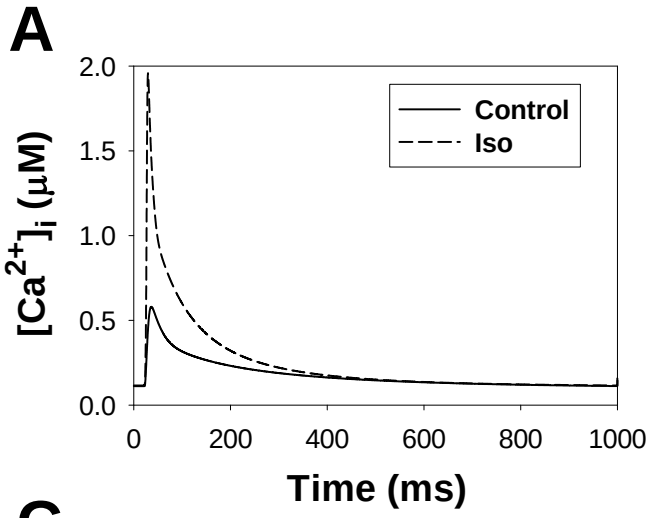


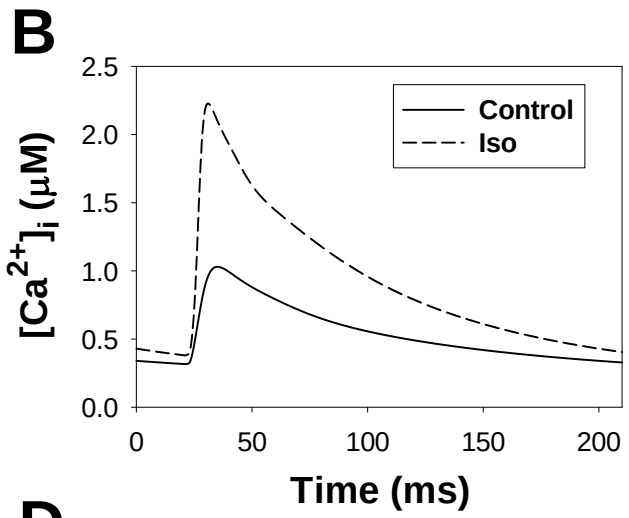
C

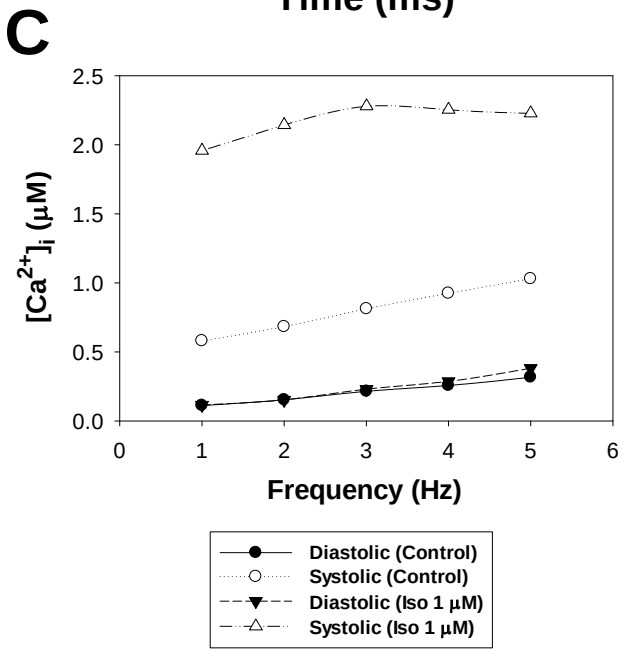


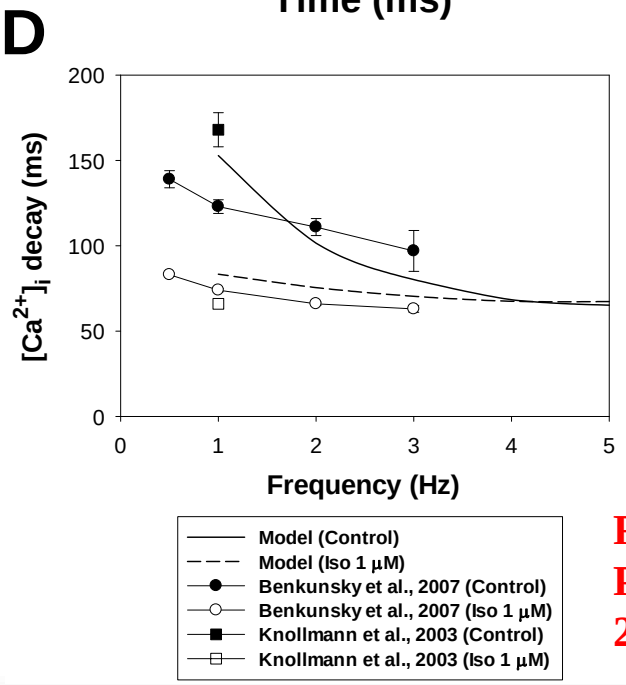
From Bondarenko, PLoS ONE 9: e89113, 2014.

Simulation results



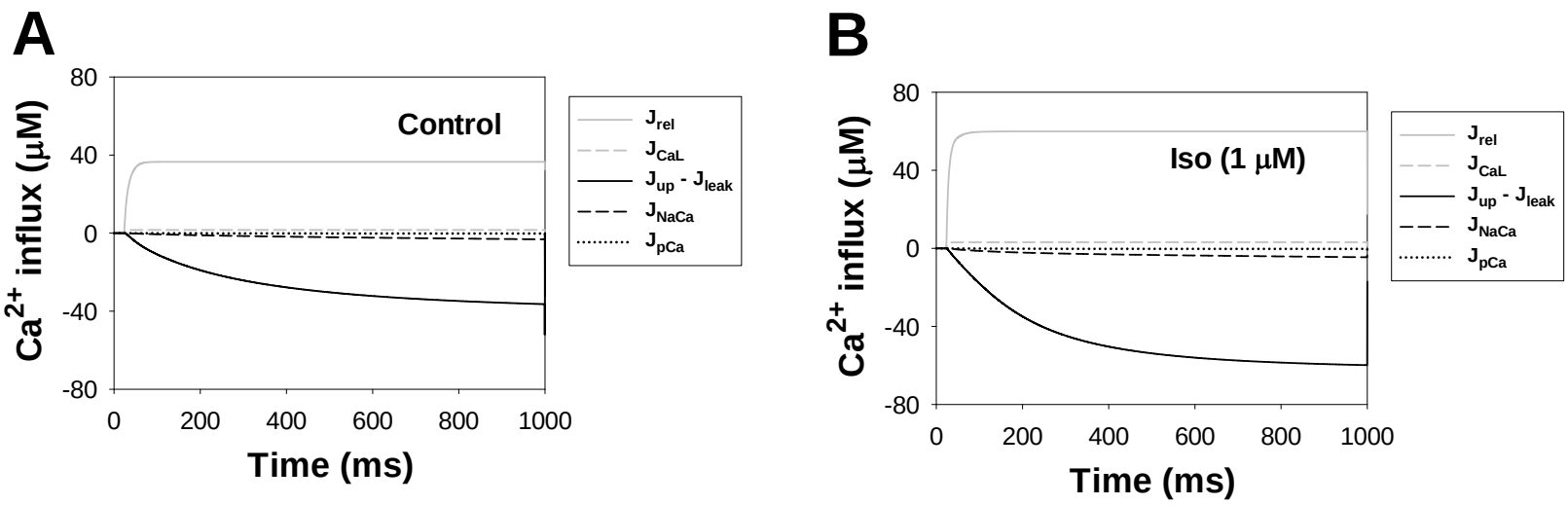






From Bondarenko, PLoS ONE 9: e89113, 2014.

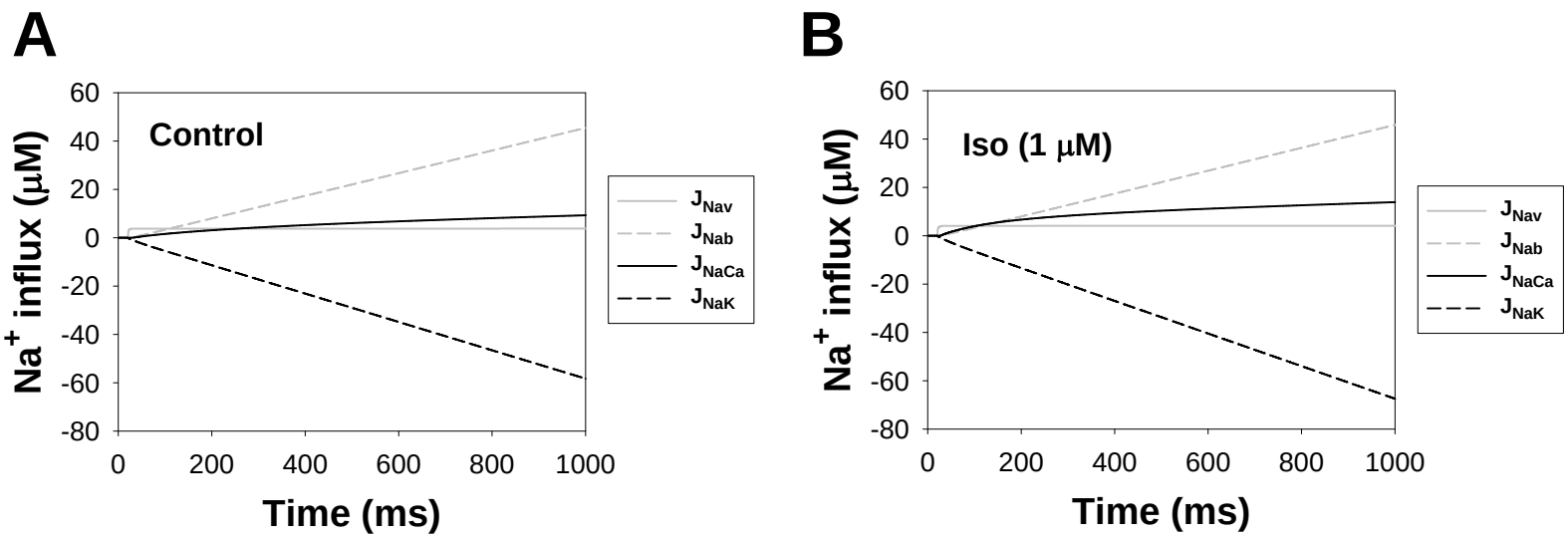
Simulation results



Simulated major integral Ca^{2+} fluxes during one cardiac cycle in the isolated ventricular cell model for control conditions (Panel A) and after application of 1 μM isoproterenol (Panel B). Pacing frequency is 1 Hz. Major integral Ca^{2+} fluxes are shown after 300 s of stimulation. In Panel B 1 μM isoproterenol is applied at time *t* = 0 s.

From Bondarenko, PLoS ONE 9: e89113, 2014.

Simulation results



Simulated major integral Na^+ fluxes during one cardiac cycle in the isolated ventricular cell model for control conditions (Panel A) and after application of 1 μM isoproterenol (Panel B). Pacing frequency is 1 Hz. Major integral Na^+ fluxes are shown after 300 s of stimulation. In Panel B 1 μM isoproterenol is applied at time *t* = 0 s.

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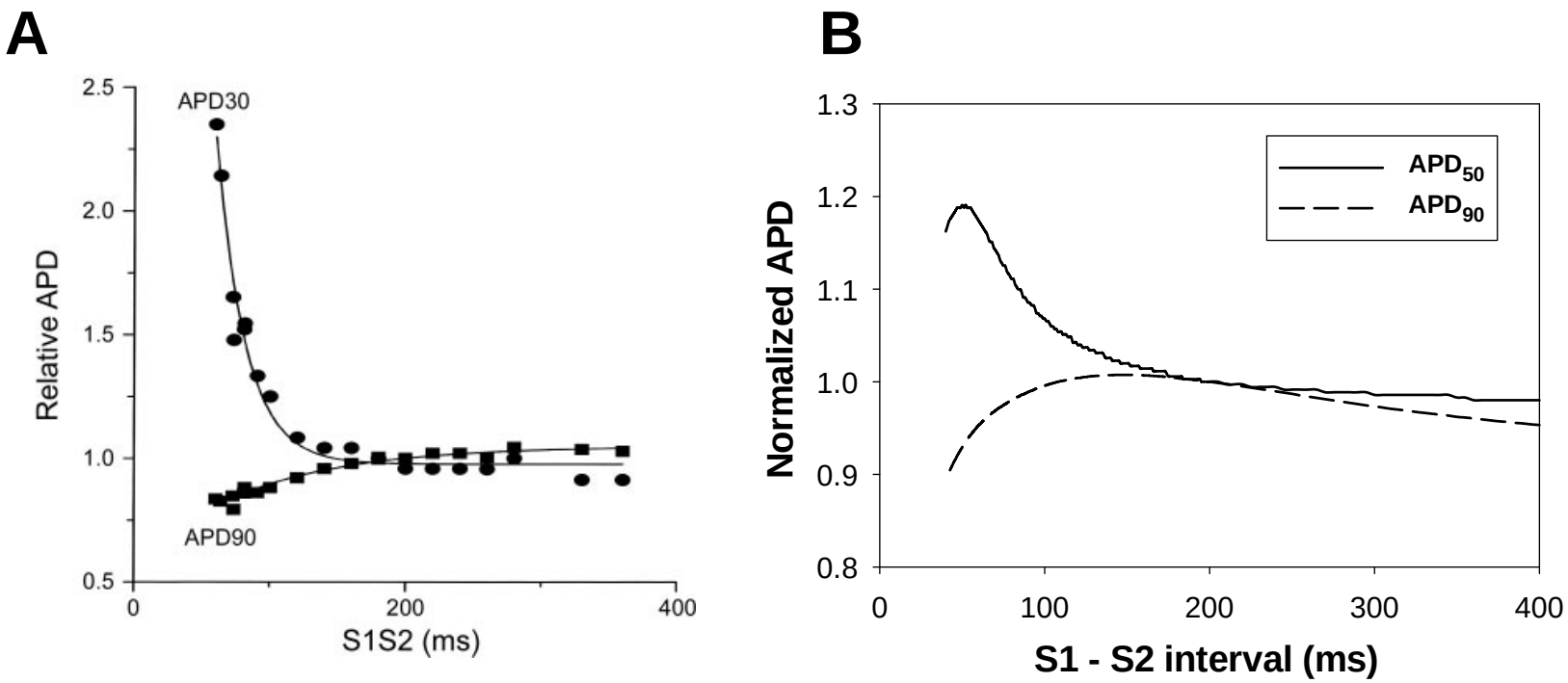
Simulation results



Experimental (Panel A) and simulated (Panel B) normalized APD as functions of S1-S2 interval obtained for control conditions. Experimental data [Knollmann et al., 2007] are shown for APD_{30} and APD_{90}, simulation data - for APD_{50} and APD_{90}. APDs are normalized to the corresponding values for S1-S2 interval of 200 ms.

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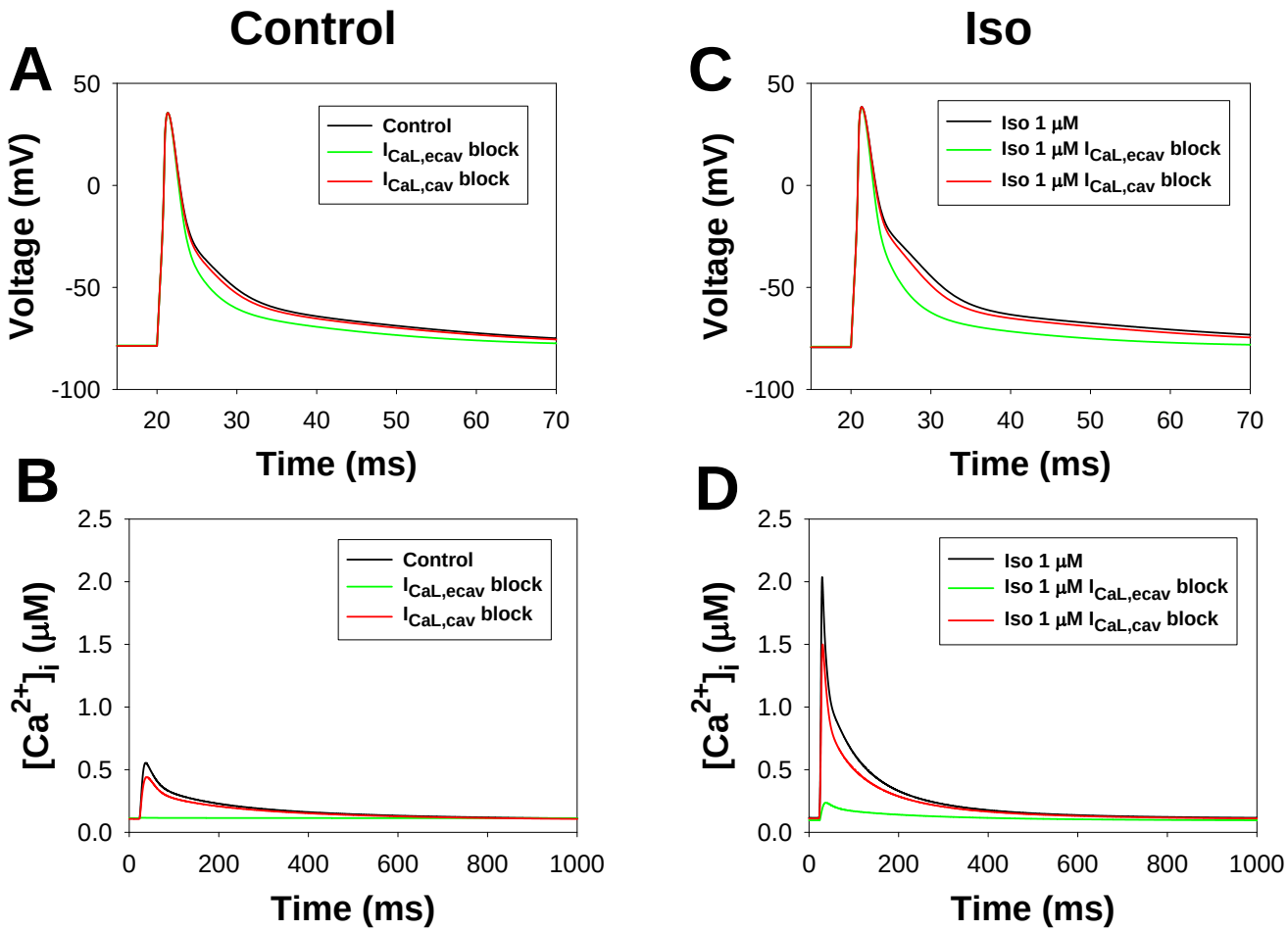
Simulation results



The effects of caveolae and extracaveolae I_{CaL} block on action potential and Ca^{2+} transients. Control conditions (Panel A, B) and after application of 1 μM isoproterenol (Panels C, D).

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Acknowledgments

University at Buffalo, SUNY

Glenna C. L. Bett

Michael J. Morales

Randall L. Rasmusson

Harold C. Strauss

Georgia State University

Igor V. Belykh

Gennady S. Cymbalyuk

Andrey L. Shilnikov

Wuhan University

Xuejun Jiang

Xiaoyan Li

University of Debrecen

Gyula P. Szigeti

Graduate Students

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Vladislav V. Zarayskiy

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Paula Mullins

Kelvin Rozier

Konstantin Kapustin

Rachid Marsli

Financial support: B&B and RIG (GSU) and AHA

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