Optimizing Cardiac Excitation-Metabolic Model By Using Parallel Grid Computing

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INTRODUCTION

The enzymatically isolated cardiac cells from epicardial and endocardial regions differ primarily with respect to their repolarization characteristics and Ca^{2+} activity[1,2,5]. The epicardial myocytes display **(a)** shorter action potential duration due to differences in variant ionic currents (I_{Na}, I_{to}, I_{Kr}, I_{Ks}), and **(b)** shorter time to peak and duration of the global Ca^{2+} transient due to variations in SERCA expression. The epicardial myocytes respond also differently to pathophysiological states. It has been suggested that changes in ATP-sensitive K^+ channel (K_{ATP}) sensitivity to ATP among the cell sub-types might be partially responsible for the greater action potential shortening in the epicardial region during ischemia[4]. However, little is known (**a**) how local Ca^{2+} transients in the juctional, subsarcolemmal and cytosolic spaces are regulated among the cell sub-types, and (**b**) how the distribution of K_{ATP} channels may affect the cell excitability and contractility under pathological conditions. To investigate further these mechanisms we extended the Shannon-Bers ionic model in rabbits[3] to incorporate (**a**) the regional variations in ion channel densities and SERCA pump expression, and (**b**) equations for Mg^{2+}-nucleotide regulation of K_{ATP} channel, L-type Ca^{2+} channel, sarcolemmal and sarcoplasmic Ca^{2+}-ATPases, and Na^+/K^+ pump[4]. We used a distributed parameter optimization tool (Nimrod)[6] to stabilize the epi- and endocardial Ca^{2+} transients in the juctional, subsarcolemmal and cytosolic compartments under normal conditions for time interval of 3 min at 0.5Hz.

MODEL

The model currently includes (see Figure 1)

- The Shannon-Bers model, describing ion channel currents and Ca^{2+} transport in rabbit ventricular myocytes
- The regional variations in ion channel densities (G_i) and SERCA pump expression
- K_{ATP} channel regulation by free ATP and MgADP
- MgATP and MgADP regulation of L-type Ca^{2+} channel, SR Ca^{2+} ATPase, Na^+/K^+ pump and sarcolemmal Ca^{2+} pump
- The realistic ATP, ADP, P_i, creatine (Cr), creatine phosphate (PCr) concentrations and extra- and intracellular diastolic ionic levels (Na^+, K^+, Mg^{2+}, H^+) in normal rabbit cells

Assumptions

- Among the cell sub-types total metabolite (ATP, ADP, AMP), P_i, Cr, PCr, Mg^{2+}, and pH levels are equal and spatially uniform

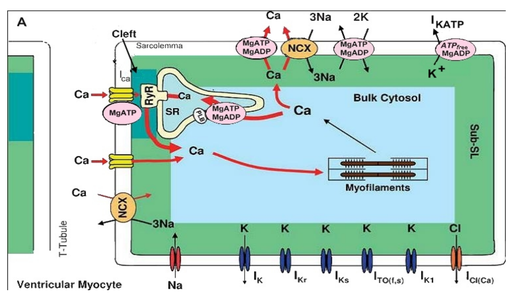


Figure 1: Ionic-metabolic model in rabbit ventricular myocytes

	Epi	Endo
G_{Na} (ms/μF)	6.0	7.0
G_{to}(ms/μF)	0.06	0.025
G_{Kr} (ms/μF)	0.04	0.03
G_{Ks}(ms/μF)	0.75	0.3
SERCA	2	1

Table: Ion channel conductance and scaling term for SERCA pump among the cell sub-types

MgATP/MgADP kinetic equations

L-type Ca^{2+} current

$$I^*_{Ca}(t) = \frac{1}{1+\left(\frac{k_{MgATP\_ICa}}{[MgATP]_i}\right)^{2.6}} I_{Ca}(t)$$

SERCA pump

$$J^*_{up}(t) = \left(\frac{K_{MgATP\_SERCA}}{[MgATP]_i}\left(1+\frac{[MgADP\ ]_i}{K_{MgADP\_SERCA1}}\right)+\left(1+\frac{[MgADP\ ]_i}{K_{MgADP\_SERCA2}}\right)\right)^{-1} J_{up}(t)$$

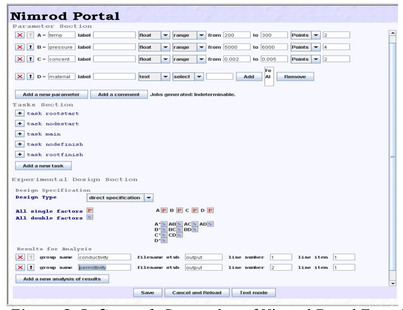
Na^+/K^+ pump

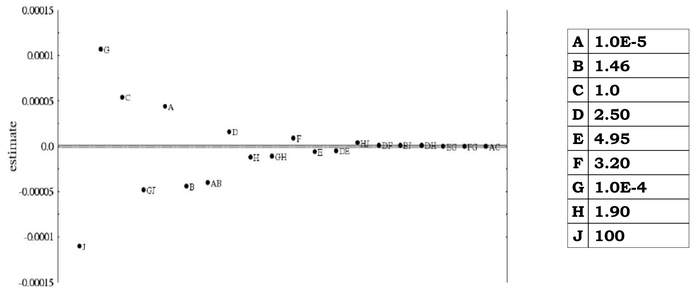
$$I^*_{NaK}(t) = \left(1+\frac{K_{MgATP\_NaK}}{[MgATP]_i}\left(1+\frac{[MgADP]_i}{K_{MgADP\_NaK}}\right)\right)^{-1} I_{NaK}(t)$$

Sarcolemmal Ca^{2+} pump

$$I^*_{pCa}(t) = \left(1+\frac{K_{MgATP\_IpCa1}}{[MgATP]_i}\left(1+\frac{[MgADP\ ]_i}{K_{MgADP\_IpCa}}\right)\right)^{-1}+\left(1+\frac{K_{MgATP\_IpCa2}}{[MgATP]_i}\right)^{-1} I_{p(Ca)}(t)$$

RESULTS





A	1.0E-5
B	1.46
C	1.0
D	2.50
E	4.95
F	3.20
G	1.0E-4
H	1.90
J	100

Figure 2: Left panel: Screenshot of Nimrod Portal Experimental Design Planning Page. **Right panel:** Length plot for Nimrod/E Experiment: **A**-K_MgATP_NaK; **B**-K_MgADP_NaK; **C**-K_MgATP_ICa; **D**-K_MgATP_IpCa1; **E**-K_MgADP_IpCa; **F**-K_MgATP_IpCa2; **G**-K_MgATP_SERCA; **H**-K_MgADP_SERCA1; **J**- K_MgADP_SERCA2

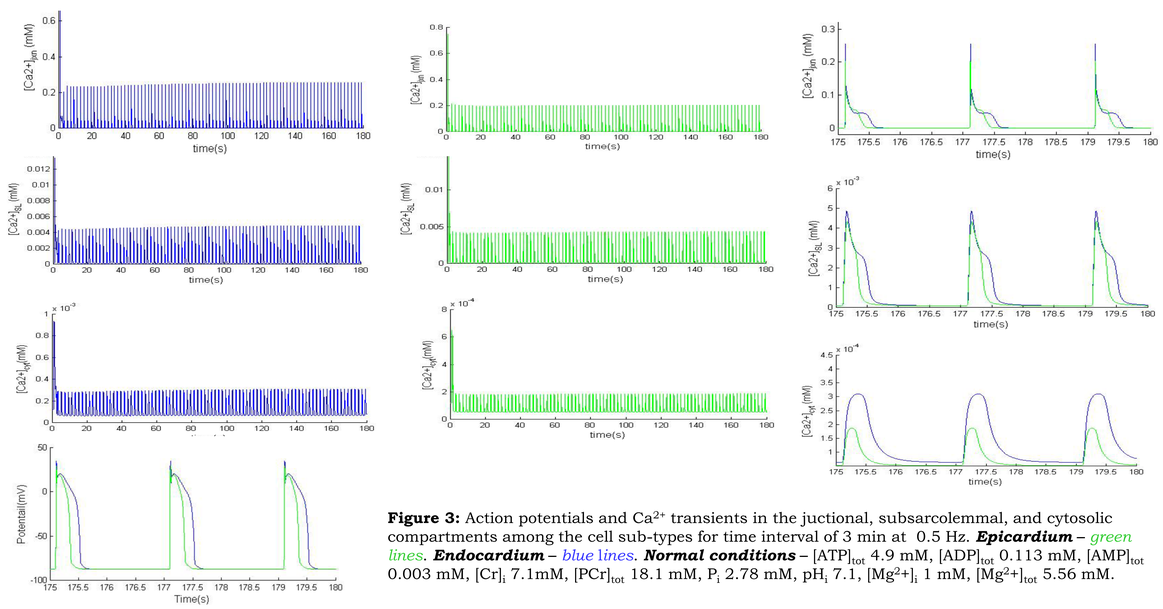


Figure 3: Action potentials and Ca^{2+} transients in the juctional, subsarcolemmal, and cytosolic compartments among the cell sub-types for time interval of 3 min at 0.5 Hz. ***Epicardium*** – *green lines*. ***Endocardium*** – *blue lines*. ***Normal conditions*** – $[ATP]_{tot}$ 4.9 mM, $[ADP]_{tot}$ 0.113 mM, $[AMP]_{tot}$ 0.003 mM, $[Cr]_i$ 7.1mM, $[PCr]_{tot}$ 18.1 mM, P_i 2.78 mM, pH_i 7.1, $[Mg^{2+}]_i$ 1 mM, $[Mg^{2+}]_{tot}$ 5.56 mM.

CONCLUSIONS

- **Nimrod/E experiment suggests: (1) the model outputs will be highly sensitive to SERCA parameter changes, less sensitive to I_{Ca} and I_{NaK} parameter changes while I_{pCa} parameter changes are expected to have insignificant impact; (2) MgATP and MgADP-dependent parameter changes alone will have opposite effects on the simulated curves; (3) the simultaneous changes in SERCA (G, J) or I_{NaK} (A,B) parameter values will have the most pronounced effect on the model outputs.**

- **In rabbit epicardial myocytes model predicts (a) faster Ca^{2+} transient decay and shorter time to peak in the bulk cytosol, (b) faster Ca^{2+} transient decay in the juctional and subsarcolemmal spaces, (c) shorter action potential duration.**

- **Model provides good basis for further studies of how the distribution of K_{ATP} channels may regulate the excitation-contraction coupling under pathological conditions when I_{KATP} current is activated.**

ABSTRACT

We have extended the Shannon-Bers model in order to investigate excitation-contraction coupling in rabbit epicardial and endocardial ventricular myocytes[3]. We couple cytosolic metabolism to the cell electrical activity and include rate expressions for Mg^{2+}-nucleotide regulation of ATP-sensitive K^+ channel, L-type Ca^{2+} channel, sarcolemmal and sarcoplasmic Ca^{2+}-ATPases, and Na^+/K^+ pump[4]. The work was performed with a distributed parameter optimization tool (Nimrod) to search for stable model solutions[6]. The Nimrod experiment involved validation of the updated model by varying (a) input current parameters to stabilize the normal epi- and endocardial Ca^{2+} transients for time interval of 3 min at 0.5Hz, (b) input metabolic constants to fit the predicted normal ionic currents to be as close as possible to the experimentally suggested. The results suggest that the distribution of ATP-sensitive K^+ channels might be important mechanism regulating the excitation-contraction coupling during ischemia.

REFEREENCES

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[4] Michailova *et al.*, (2007) *AJP Cell Physiol* 293: C542-57.
[5] Flaim *et al.*, (2006) *AJP Heart Circ Physiol* 291: H2617-29.
[6] Nimrod Portal
http://www.csse.monash.edu.au/~davida/nimrod/portal.htm