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COMPUTER MODELLING ON CARDIAC FUNCTION

Akinori Noma, Satoshi Matsuoka and Nobuaki Sarai

Cell/Biodynamics Simulation Project Kyoto University, Department of Physiology, Faculty of Medicine Kyoto University, Kyoto, Japan

The magnitude and time course of developed tension is regulated by multiple functional units, such as $[Ca^{2+}]_i$, the molecular machinery of contraction, the membrane excitation, the ion homeostasis within the cell, the excitation-contraction coupling, the neural regulation, the cell volume regulation and the energy metabolism in the cardiac myocytes. So far, a huge amount of experimental findings on each issue has been accumulated, and now it is possible to develop a comprehensive cardiac cell model to analyze the interactions of many molecular functional units underlying the regulation of the cardiac contraction. Starting from the models of cardiac membrane excitation (DiFrancesco and Noble, 1985), we developed a comprehensive cell model, Kyoto Model (Matsuoka et al, 2003).

The Kyoto model can respond to various experimental interventions in a reversible manner. Increasing $[Ca^{2+}]_o$ results in a positive inotropy accompanied with the slight shortening of the action potential duration. Decreasing $[Na^+]_o$ increases the force of contraction through the accumulation of Ca^{2+} within the sarcoplasmic reticulum by modulating the Na/Ca exchange. Varying $[K^+]_o$ affects both the action potential shape and the resting membrane potential. The force of contraction increases with decreasing $[K^+]_o$. The Ca^{2+} stored within the sarcoplasmic reticulum (2～4 mM) is released by the activation of the RyR channel through the influx of Ca^{2+} via L-type Ca^{2+} channels. $[Ca^{2+}]_i$ is determined by the intracellular Ca^{2+} buffer as well as the binding to troponin C. The contraction model is based on the Negroni and Lascano (2001), but is improved for the positive cooperativity for Ca^{2+}-mediated activation by combining with the model of Robinson et al (2002). The ATP homeostasis is established between the consumption by the myofilament, Na/K pump and CERCA and the production by mitochondria. Removing oxygen results in shortening of the action potential and loss of contraction.

Quantitative dynamic computer models, which integrate a variety of molecular functions into a cell model, provide a powerful tool to create and test working hypotheses. Our new modeling tool, the *simBio* package (freely available from http://www.sim-bio.org/) is used for constructing cell models such as cardiac cells, epithelial cells and pancreatic β cells. The *simBio* package is written in Java, uses XML and solves ordinary differential equations.

References

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