Parameter Sensitivity Analysis of Ca^{2+} Spark Using Stochastic Simulation and Regression

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A cardiac Ca^{2+} spark is the local release of Ca^{2+} from the sarcoplasmic reticulum (SR) through a cluster of ryanodine receptors (RyRs). The release is the elementary Ca^{2+} signaling event of excitation-contraction coupling in cardiac myocytes.

To study the parameter dependence of Ca^{2+} sparks, we used a combination of simulating stochastic model of Ca^{2+} sparks and the partial least squares (PLS) regression method to analyze the parameter sensitivity of 19 parameters which might influence the spark duration, area of total [Ca^{2+}] release, peak of spark, and the spark probability. We generated a stochastic simulation of 2000 trials as the population of Ca^{2+} sparks used for PLS regression.

The results of parameter sensitivity analysis showed that the volume of junction SR has the largest effect on the area of Ca^{2+} sparks, and RyR closing rate is the only parameter which contributes the duration of Ca^{2+} sparks significantly. Most significantly, Ca^{2+} concentration in the network SR significantly contributes on the area, peak, and probability of Ca^{2+} sparks, while Ca^{2+} diffusion rate through RyRs has a large effect on both peak and probability of Ca^{2+} spark. The PLS regression analysis also suggested that generating a simulation of 200 trials is sufficient to find parameter sensitivity.