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Supplemental information

Voltage-mediated mechanism for calcium wave synchronization and arrhythmogenesis in atrial tissue

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Online supplement

Phenomenological model describing the population of Ca sparks in atrial myocytes

A limitation of the detailed spatial model shown in Figure 1 is that it is computationally expensive to model cardiac tissue composed of tens of thousands of cells. Thus, we will apply a phenomenological model of subcellular Ca that captures the main features of the detailed model. This model was developed in a previous publication, and it is based on experimental linescan imaging of Ca release in atrial myocytes(1). In this approach, we keep track only on the total number of Ca sparks at the cell boundary, denoted as $n_b(t)$, as well as the cell interior $n_i(t)$. The number of sparks at the boundary obeys a simple reaction scheme

$$0 \underset{\beta_b}{\overset{\alpha_b}{\rightleftharpoons}} 1 \ , \tag{1}$$

where 0 denotes an RyR2 cluster which is shut, and 1 denotes a cluster where Ca is released due to a spark. The nucleation and extinction rate of sparks is given by α_b and β_b respectively, which are taken to be phenomenological functions of the Ca concentration in the cell. The population of active sparks is then updated according to

$$n_b(t + \Delta t) = n_b(t) + B(\alpha_b \Delta t, N_b - n_b) - B(\beta_b \Delta t, n_b), \tag{2}$$

where $B(p, n)$ is a random number picked from a binomial distribution with success probability p and number of trails n, and where N_b denotes the total number of RyR2 clusters at the cell boundary. Similarly in the cell interior we model Ca spark recruitment with the same reaction scheme given in Eq. (1), with a spark recruitment rate α_i, and extinction rate β_i. To model generation of Ca waves propagating into the cell interior we note that α_i will depend on the number of Ca sparks ignited at the cell boundary and the SR load. This dependence can be captured by a simple phenomenological function of the form $\alpha_i = \big(a_i F(p_b) + b_i G(p_i)\big)\phi(c_{sr})$, where $p_b = n_b/N_b$ and $p_i = n_i/N_i$, and where N_i is the number of RyR2 clusters in the cell interior. Here, a_i and b_i are adjustable constants and the nonlinear dependence on the number of fraction of boundary sparks is taken to have the form $F(p_b) = 1/(1 + (p_b^*/p_b)^{\gamma_b})$, where p_b^* is the threshold for Ca wave nucleation at the cell boundary, and γ_b is the Hill coefficient. Also, the nucleation rate of Ca sparks in the interior will depend on p_i according to $G(p_i) = 1/(1 + (p_i^*/p_i)^{\gamma_i})$, where p_i^* is the nucleation threshold. Using this approach, a Ca wave in the interior is initiated when $p_i > p_i^*$, so that the nucleaton rate of sparks increases in a nonlinear fashion once the threshold is exceeded. When this occurs, the internal Ca concentration rises to $c_i > 2 - 3\mu M$, and is substantially smaller ($< 1\mu M$) when a wave does not occur. By tuning the magnitude and rate of these events we can then reproduce the qualitative features of Ca wave nucleation and propagation during pacing, as observed using the detailed spatial model, and experimentally. Full details of the computational model are given in our previous publication(1).

References

1. Shiferaw, Y., G. L. Aistrup, and J. A. Wasserstrom. 2018. Synchronization of triggered waves in atrial tissue. Biophysical journal 115:1130-1141.