Impact of Calcium Store Overload on Electrical Dynamics of Cardiac Myocytes

UMBC REU Site: Interdisciplinary Program in High Performance Computing
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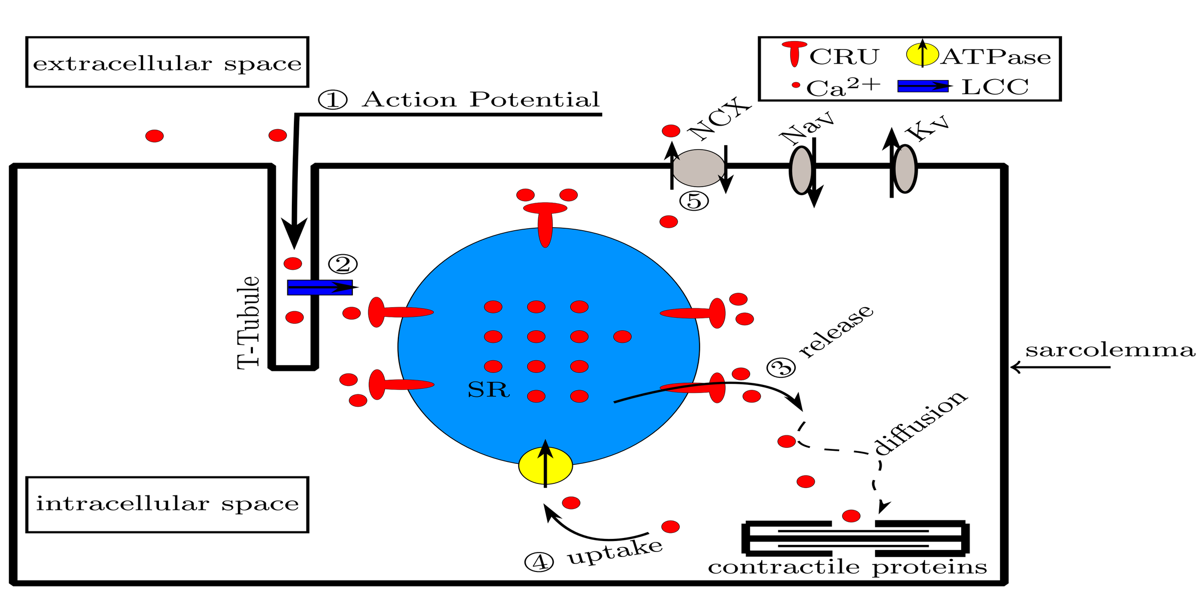
Objective

Electrical signaling in cardiac muscle cells triggers calcium (Ca^{2+}) release from the sarcoplasmic reticulum (SR) through Ca^{2+} release units (CRUs). CRU's can activate spontaneously under certain conditions, such as high SR load and increased CRU release probability, sometimes resulting in a large wave-like release. We use a mathematical model to explore the timing and organization of spontaneous Ca^{2+} release as this can lead to an irregular heart beat.

Biological Model

Changes in voltage differences across the cell membrane cause Ca^{2+} to enter the cytosol, triggering SR to release Ca^{2+} through CRU's. This begins the process of Ca^{2+}-induced-Ca^{2+}-release (CICR), which results in Ca^{2+} binding to contractile proteins and a contraction of the heart.



Mathematical Model

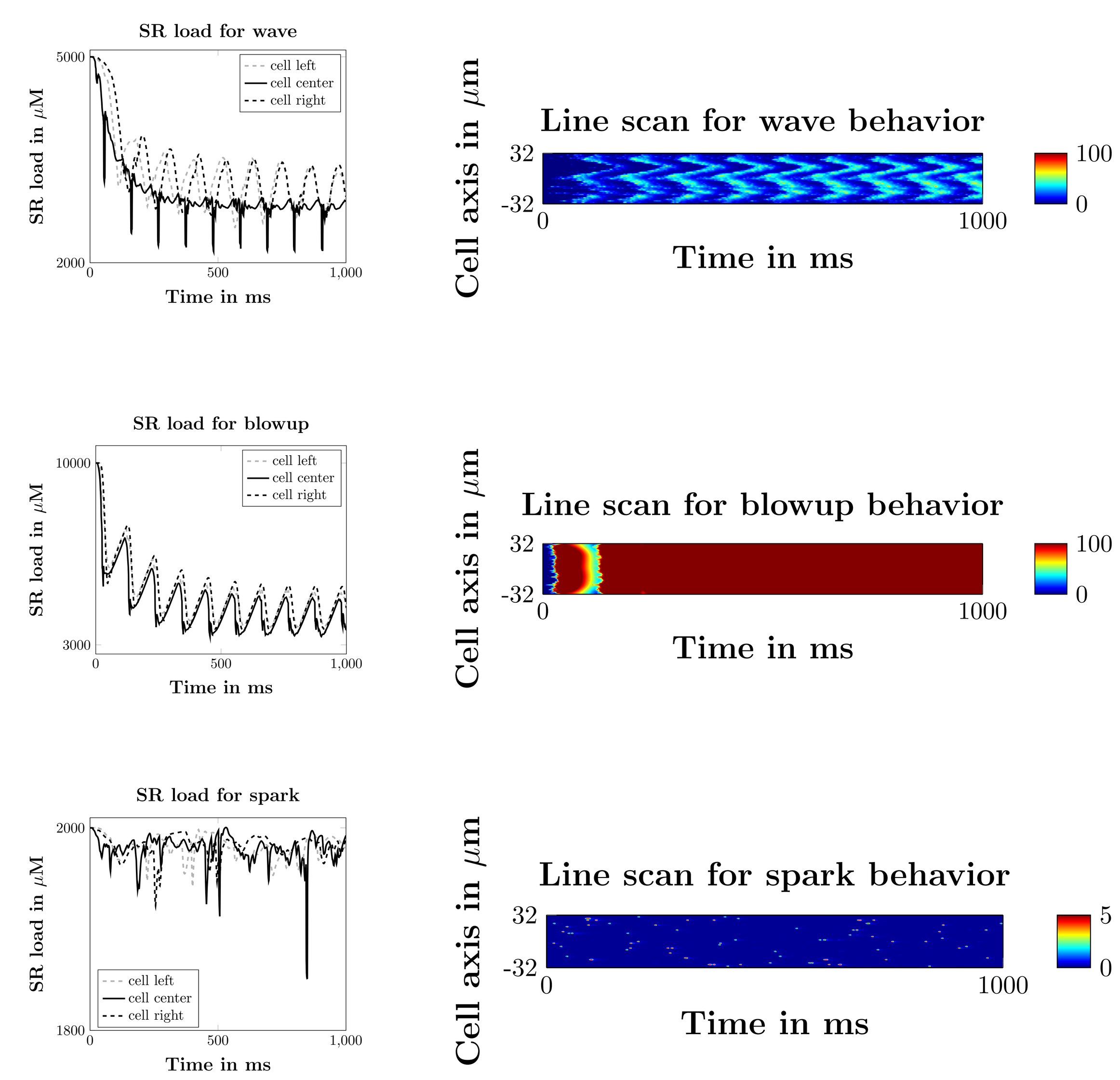
The following system of PDE's is solved using the Finite Volume Method.

$$c_t = \nabla \cdot (D_c \nabla c) + \Sigma R_i + (J_{CRU} + J_{leak} - J_{pump}),$$
$$b_{i_t} = \nabla \cdot (D_{b_i} \nabla b_i) + R_i,$$
$$s_t = \nabla \cdot (D_s \nabla s) + \Sigma R_j - \gamma(J_{CRU} + J_{leak} - J_{pump}),$$
$$b_{j_t} = \nabla \cdot (D_{b_j} \nabla b_j) + R_j,$$

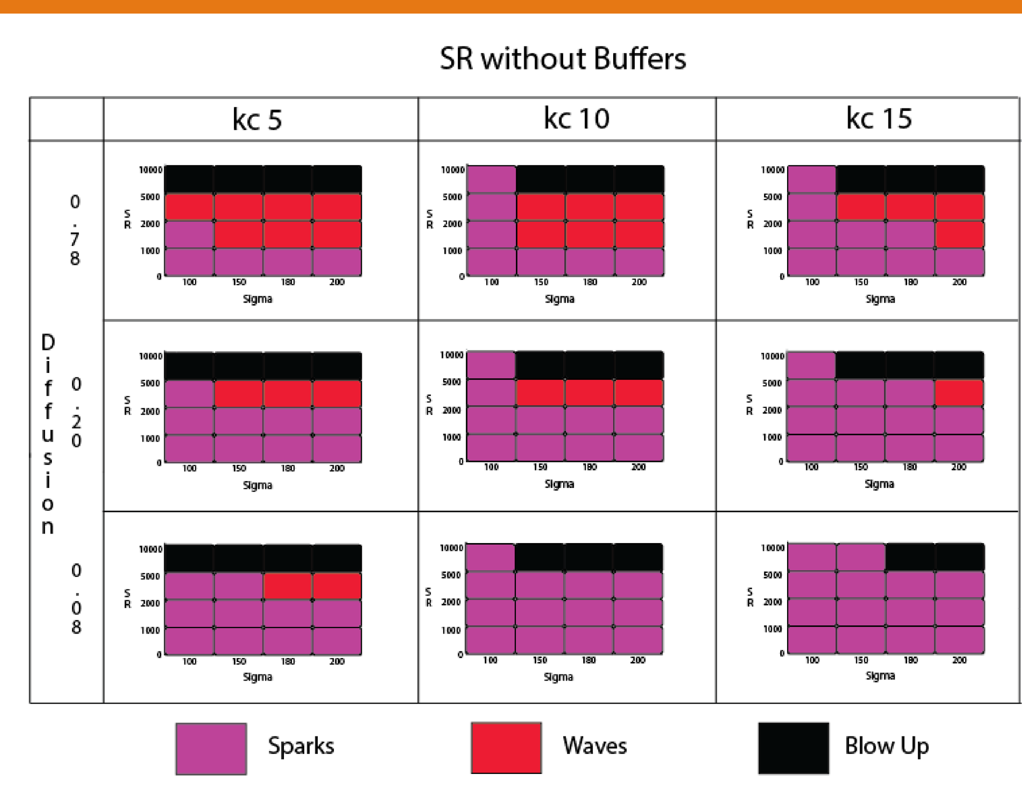
where the cell is modeled as a rectangular prism with a lattice mesh of CRU's.

Behavior Classification

Measurements of calcium concentration along a single line in space in the cell were measured versus time, allowing us to group a dynamic into one of the following three classifications:



Dynamic Classification Results



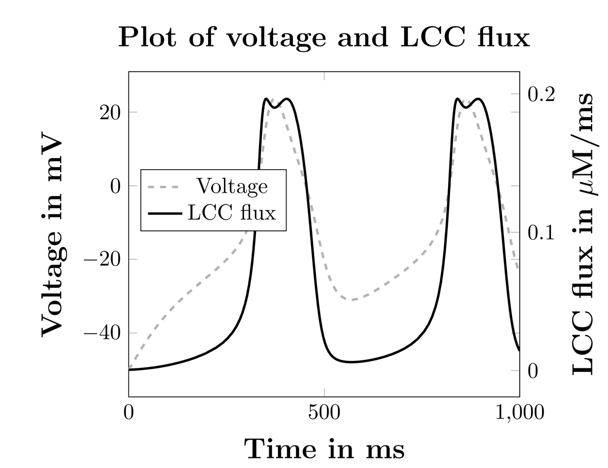
Including Voltage

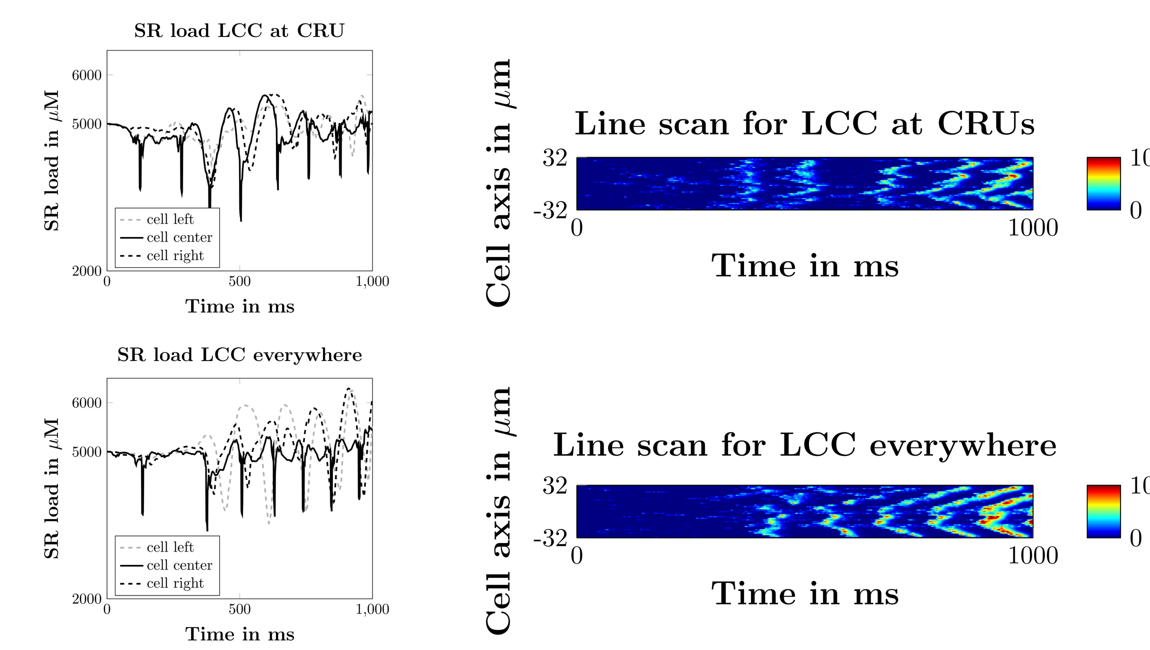
We implemented voltage by using a simplified version of the Morris-Lecar model scaled to oscillate with a period ~500ms.

$$c_t = \cdots + J_{LCC} + J_{mleak} - J_{mpump},$$
$$V_t = \frac{\tau}{C}(I - g_L(V - V_L) - g_{ca} m_\infty (V - V_{Ca}) - g_K n(V - V_K)),$$
$$n_t = \tau \cdot \lambda_n(V)[n_\infty(V) - n],$$
$$J_{LCC} = \frac{\kappa \cdot \mathsf{SA} \cdot g_{ca} m_\infty (V - V_{Ca})}{2F}.$$

Voltage Simulation Results

Voltage triggered Ca^{2+} influx from the extracellular space shifts the original spark dynamic to a wave dynamic.





Conclusions

- Increasing SR calcium load leads to more calcium waves, with blowout when SR concentration is too high with higher SR calcium diffusion coefficient and CRU probability of release sensitivity.
- Adding buffers to the SR model makes waves less likely to occur when all other parameters are kept consistent.
- Increased depolarization of the plasma membrane leads to increased Ca^{2+} influx into the cell and thus triggers greater SR calcium release into the intracellular space.

References

- Full technical report: HPCF–2015–25 `hpcf.umbc.edu` > Publications
- Gobbert, M.K., (2008). *SIAM J. Sci.Comput.*.
- Izu, L.T., W.G. Wier, C.W. Balke, (2011). *Biophys.J.*.

Acknowledgments

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