In cardiac cells, the contraction is driven by the release of Ca\(^{2+}\) ions from the sarcoplasmic reticulum (SR). This happens across the cell in thousands of calcium release units (CaRU), which are sets of clusters of different proteins occupying a volume of about 1 \(\mu\)m\(^2\) and that release the Ca\(^{2+}\) ions as a response to a signal (an action potential) through a positive-feedback process known as Calcium Induced Calcium Release (CICR).

The objective of this project is to build a stochastic model of a CaRU to compute how the probability for a calcium spark to occur depends on a variety of biophysical parameters and then use this information in a simplified cardiac cell model to study the onset of pulsus alternans, characterized by a beat-to-beat alternation in the strength of the heart contraction; it is a condition linked with a higher risk of arrhythmia, fibrillation and sudden death.

**CALCIUM RELEASE UNIT MODEL**

The model couples the Ca\(^{2+}\) concentrations via both diffusive and stochastic fluxes, which take into account the random configuration transitions of the protein channels (membrane LCC and RyR on the SR) via Markov chains.

- For small values of the opening rate (small constant \(k_0\)) corresponding to slower RyR opening, the probability curves are well fitted by a simple formula accounting for effective cooperativities. For faster opening rates, the model yields a sharper probability distribution and switch-like curves, for which the probability is very close to zero below certain values of the load and active RyR fraction.

The stochastic nature of the transitions together with the low number of proteins within a unit requires the results to be analyzed statistically. Computing the probability of a calcium spark to occur shows a consistent sigmoid dependency on both the SR Ca\(^{2+}\) load and the initial fraction of active RyR, which implies a cooperative behavior in the opening of the RyR channels.

- The effective cooperativity is lost for large diffusion times (slow diffusion).
- Decreasing the opening rate \(k_0\) also lowers the cooperativity dramatically.

**COUPLED RETURN MAPS SYSTEM**

A network of coupled CaRUs is simulated as \(L \times L\) arrays in which each node registers variables representing the beat-to-beat change in SR Ca\(^{2+}\) concentration and active RyR channels. The sparking probability used is obtained from fitting the data via both a probability-based release phase, an averaging (equilibration) phase (only for the load), and a recovery phase.

The minimum value for the effective cooperativities \((\gamma_x \text{ and } \gamma_y)\) that produces alternans is \(\gamma_x = \gamma_y = 12\). Notably, both cooperativities are needed to observe alternans in the system.

- The diffusion (equilibration) is necessary, since it's the mechanism through which the CaRU coordinate to produce a global calcium alternans.

**CONCLUSIONS**

- The higher effective cooperativity in the CaRU model is found for fast calcium diffusion in the dyadic space, together with a high value of the RyR opening rate (fast RyR opening).
- The inactivation of the RyR doesn’t seem to play a crucial role. Neither does the SR diffusion time scale.
- A high value for the diffusion time scale on the dyadic space dramatically lowers the cooperativities.

Despite of its simplicity, the stochastic coupled maps system is capable of reproducing the alternating behavior seen in more complex models.

Calcium alternans is sustained by both an alternation in the pre-systolic calcium load and an alternation in the pre-systolic recovered RyR2.