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Supplemental information

Mechanistic link between CaM-RyR2 interactions and the genesis of cardiac arrhythmia

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Online Supplement

The role of the second closed state C_2

The computational approach developed in this study can be used to explore how the Markov state scheme for an RyR2 subunit determines macroscopic Ca cycling behavior. In this section we will evaluate specifically how the presence of the second closed state C_2 determines the time course of a Ca spark, the waiting time to a spontaneous Ca spark, and the Ca wave propagation velocity. To accomplish this we will consider a model in which the C_2 state is eliminated, so that the RyR2 subunit transitions between C_1 and O in Eq. 13. In Figure S1A we compute the full RyR2 open probability as a function of $[Ca]$ in the absence of the state C_2. Here, we find that eliminating C_2 induces a leftward shift of the RyR2 open probability P_o, along with an increase in the plateau open probability for large $[Ca]$. This increase in P_o is a direct consequence of the fact that at high $[Ca]$ the RyR2 subunit must reside in the open state. Thus, the half maximum of the P_o will occur at a smaller $[Ca]$ and the open probability at high $[Ca]$ approaches $P_o = 1$. This is in contrast to the model considered in Eq. 13 where $P_o < 1$ since the subunit can transition to the state C_2 at high $[Ca]$. To evaluate the effect of this change on the macroscopic behavior of the system we have also computed the time course of a Ca spark (Figure S1B), the mean time to a spontaneous Ca spark $\langle T_{spon} \rangle$ (Figure S1C), and finally the Ca wave speed V_{wave} (Figure S1D). Our numerical simulations show that the time course of a Ca spark is only modestly dependent on the presence of the C_2 state. In particular, we find that eliminating C_2 increases the amount of Ca released during a Ca spark by a modest 10%. We have also computed the mean time to a spontaneous Ca spark $\langle T_{spon} \rangle$ and found that removing C_2 decreases the mean open time. This effect increases with $[CaM]$ and we find almost a 20% reduction of $\langle T_{spon} \rangle$ at $[CaM] = 0.4\mu M$. Thus, as $[CaM]$ is increased the effect of the C_2 state becomes more pronounced. Also, our simulations reveal that the dependence of the Ca wave speed on the SR load is highly dependent on the presence of the C_2 state. In particular we find that removing C_2 decreases the threshold for Ca wave propagation and increases the Ca wave speed by roughly 30% (Figure S1D). These simulation results indicate that removing the state C_2 effectively increases the excitability of an RyR2 cluster but has little effect on the time course of a Ca spark once it is triggered.

The dependence of RyR2 open probability on SR load

To complete our computational model of RyR2 we have also computed the dependence of the RyR2 open probability on the JSR load $[Ca]_{jsr}$. In Figure S2 we plot P_O vs $[Ca]_{jsr}$ for diastolic Ca levels $[Ca]_i = 2\mu M$ (black line), $[Ca]_i = 5\mu M$ (red line), and $[Ca]_i = 10\mu M$ (blue line).

Figure S1

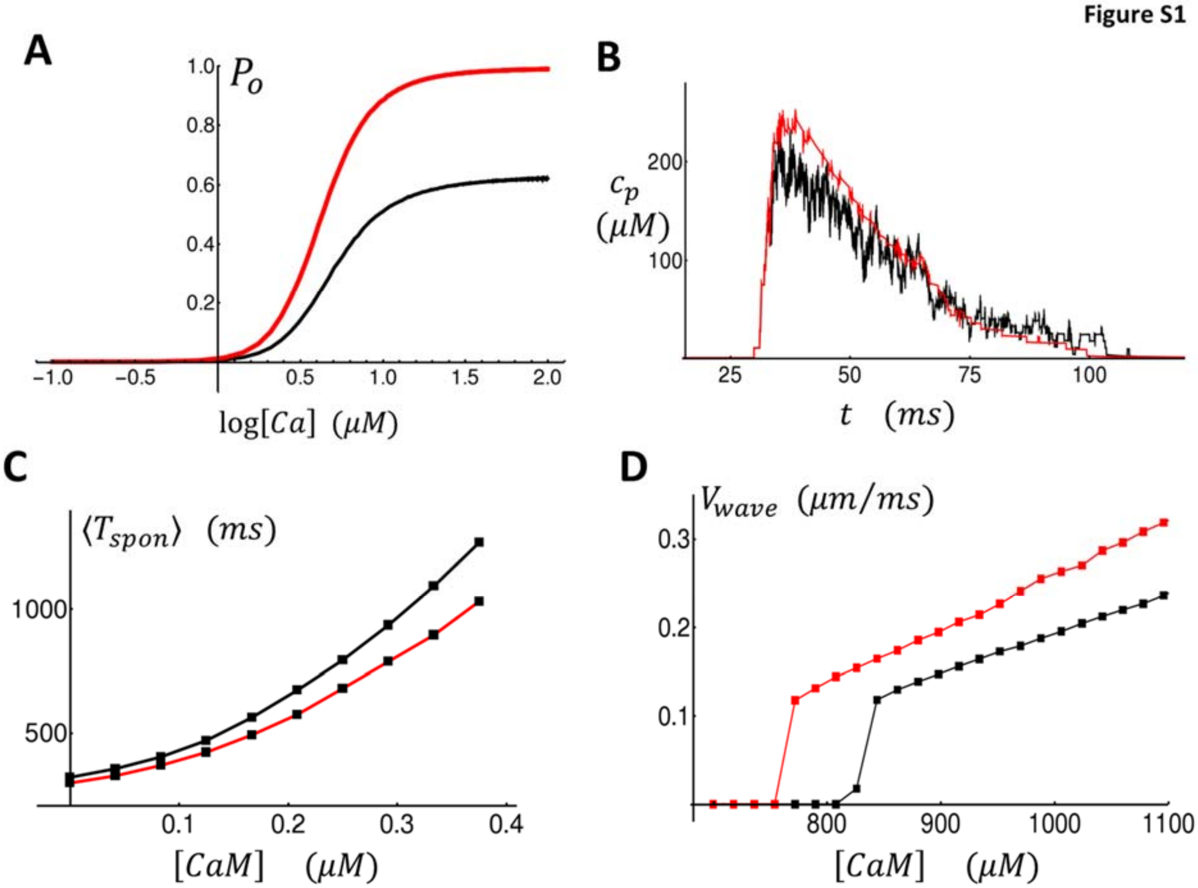

Figure S1. Model properties in the presence (black) and absence (red) of the state state C_2. (A) RyR2 open probability. In this simulation the Calmodulin concentration is fixed at $[CaM] = 0.2\mu M$. (B) Dyadic junction Ca concentration c_p as a function of time. The initial NSR load is set at $c_{nsr} = 1000\mu M$. (C) $\langle T_{spon} \rangle$ vs $[CaM]$. (D) The Ca wave velocity V_{wave} as a function of the network SR load c_{nsr}.

Figure S2

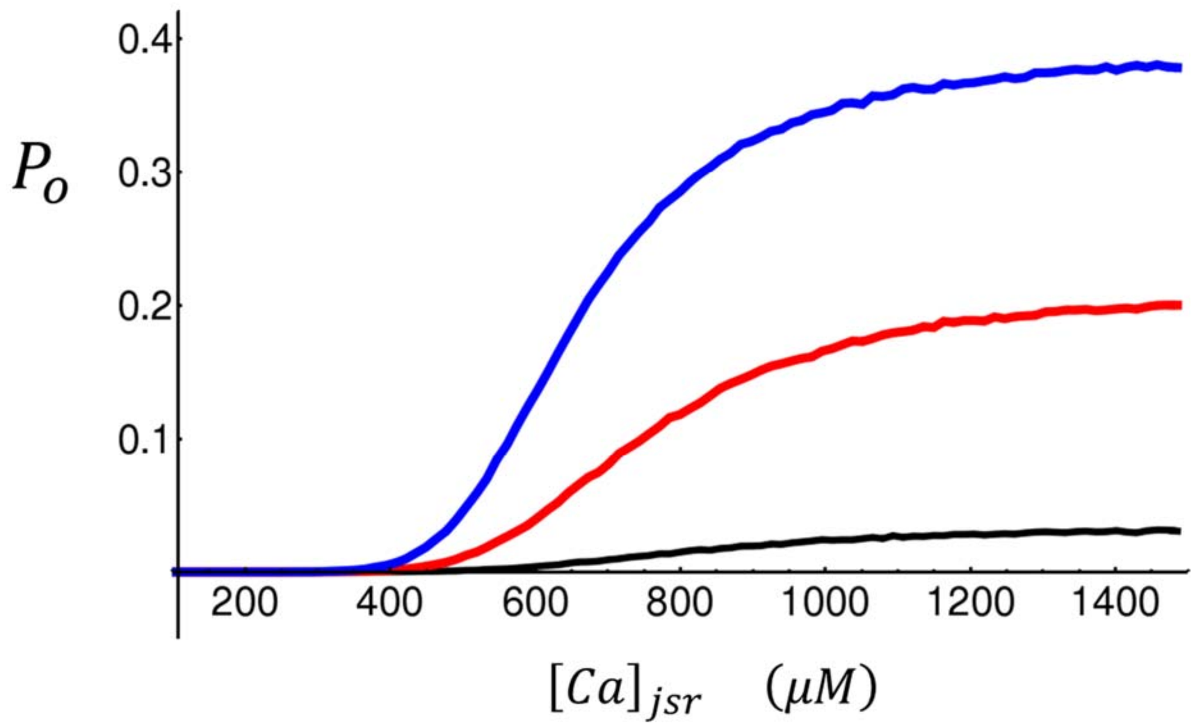

Figure S2. P_O vs $[Ca]_{jsr}$ for diastolic Ca levels $[Ca]_i = 2\mu M$ (black line), $[Ca]_i = 5\mu M$ (red line), and $[Ca]_i = 10\mu M$ (blue line). For all simulations we have fixed $[CaM] = 0.5\mu M$.