PHILOSOPHICAL TRANSACTIONS A

Phil. Trans. R. Soc. A.
doi:10.1098/not yet assigned

SUPPLEMENTAL MATERIALS

Afterdepolarizations and abnormal calcium handling in atrial myocytes with modulated SERCA uptake: A sensitivity analysis of calcium handling channels

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Keywords: *SERCA uptake, delayed afterdepolarizations, altered calcium handling, bifurcation analysis, TBX5, atrial fibrillation*

Supplemental Methods

To investigate if a bidirectional SERCA pump is a necessary component in capturing the phenoma where a reduction in SERCA activity initiates SDs, and a normalization or elevation instead suppresses them, we replaced the bidirectional SERCA pump in the full Maleckar et al. model with a unidirectional formulation taken from the Courtemanche-Ramirez-Nattel (CRN) model. Because the SERCA pump is now unidirectional, a generic leak from the CRN model was also introduced to the uptake compartment to ensure the model reaches steady state during diastole (53). We termed this hybrid model the 'Maleckar-CRN model' (Supplemental Materials Figure S6).

Using the Maleckar-CRN model, we conducted the same bifurcation analysis with SERCA-RyR, SERCA-I_{CaL}, and SERCA-I_{NaCa}, then compared the newly obtained SD threshold lines with that of the full Maleckar et al. model. For the unidirectional SERCA in all three bifurcations, from 80% SERCA to 40% SERCA, the minimum multiplier to trigger SDs for RyR and I_{CaL} was significantly higher and increased more steeply than in the bidirectional case. In comparison, the minimum multiplier for I_{NaCa} was significantly lower and decreased more sharply than in the bidirectional case in that parameter region. From 100% SERCA to 200%, the minimum multiplier was significantly lower and increased less steeply for RyR and I_{CaL}, while the minimum multiplier for I_{NaCa} was significantly higher and decreased less steeply than in the bidirectional case in that parameter region (Supplemental Materials Figure S7).

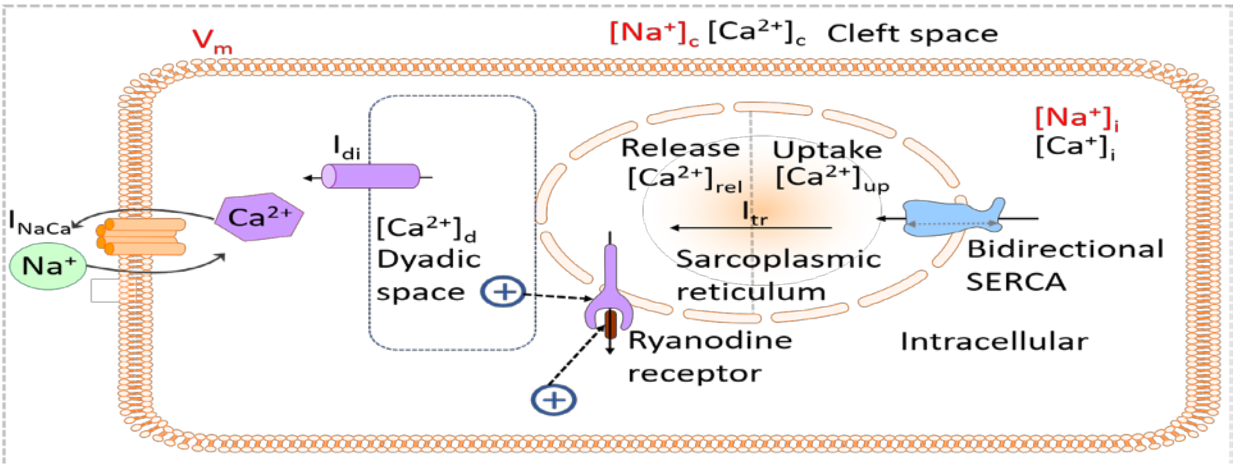

Figure S1. Schematic of the reduced Maleckar et al. model. V_m, $[Na^+]_i$, and $[Na^+]_c$ are set constant to their end-diastolic values after 3000 s pacing in the full Maleckar et al. model. A scalar multiplier is applied only to $[Na^+]_i$ to cause an elevation in total Ca^{2+} concentration and potentially trigger SDs.

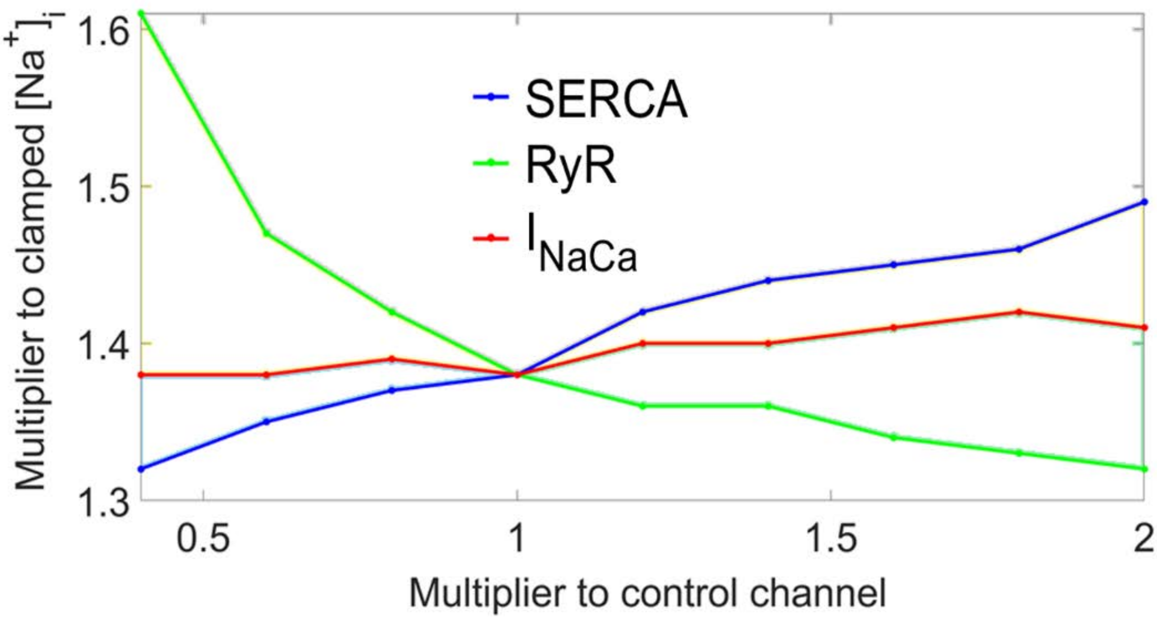

Figure S2. A calcium subsystem analysis of the reduced variant of the Maleckar et al. model illustrating how the minimum multiplier required for clamped $[Na^+]_i$ to generate calcium oscillations changes due to changes in SERCA, RyR, or I_{NaCa}.

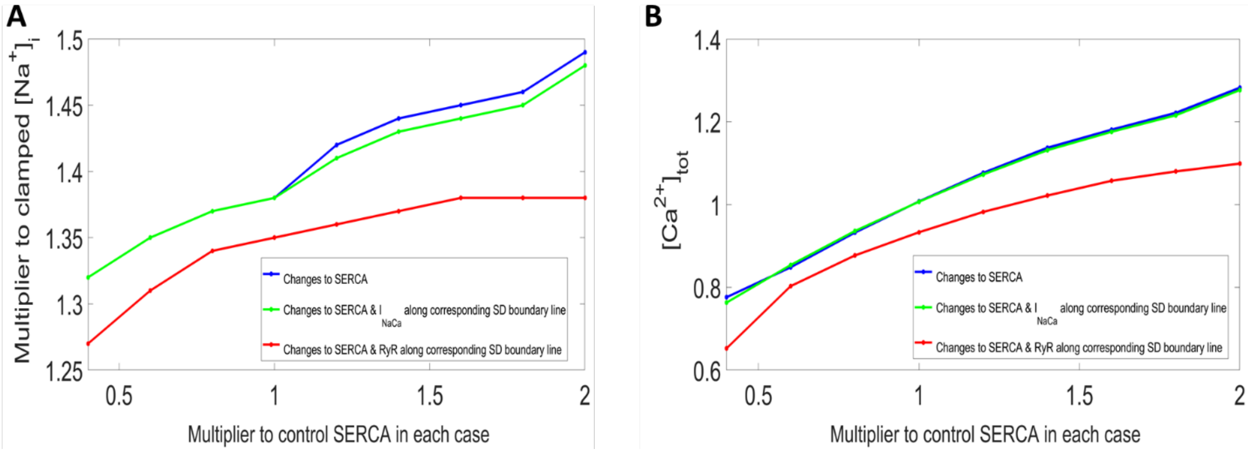

Figure S3: Comparing the multiplier to clamped $[Na^+]_i$ **A)** and corresponding minimum $[Ca^{2+}]_{tot}$ in the myocyte **B)** for Ca^{2+} oscillations in the reduced model due to changes in SERCA alone (blue line), and from changes in SERCA and I_{NaCa} (green line), and changes in SERCA and RyR (red line) based on those along the SD boundary in their respective bifurcations. SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; RyR, type 2 ryanodine receptor; SD, spontaneous depolarization.

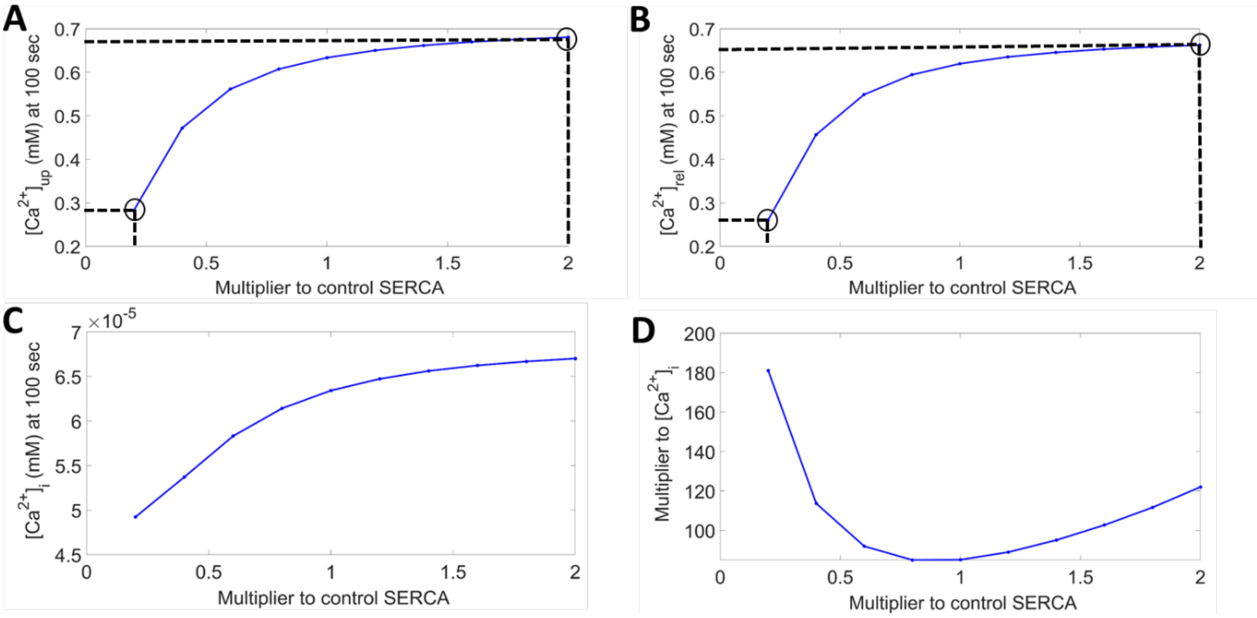

Figure S4: A-C: Values of $[Ca^{2+}]_{up}$, $[Ca^{2+}]_{rel}$, and $[Ca^{2+}]_i$ obtained at 100 s for various levels of SERCA under intracellular Ca^{2+} injection protocol 1. The indicated points for A and B show the values for $[Ca^{2+}]_{up}$ and $[Ca^{2+}]_{rel}$ from 200% and 20% SERCA which were used for intracellular Ca^{2+} injection protocol 2 to test how increasing or decreasing $[Ca^{2+}]_{up}$ and $[Ca^{2+}]_{rel}$ affects the $[Ca^{2+}]_i$ SD threshold for various levels of SERCA. **D:** The minimum multiplier applied to $[Ca^{2+}]_i$ to reach the $[Ca^{2+}]_i$ SD threshold for various levels of SERCA.

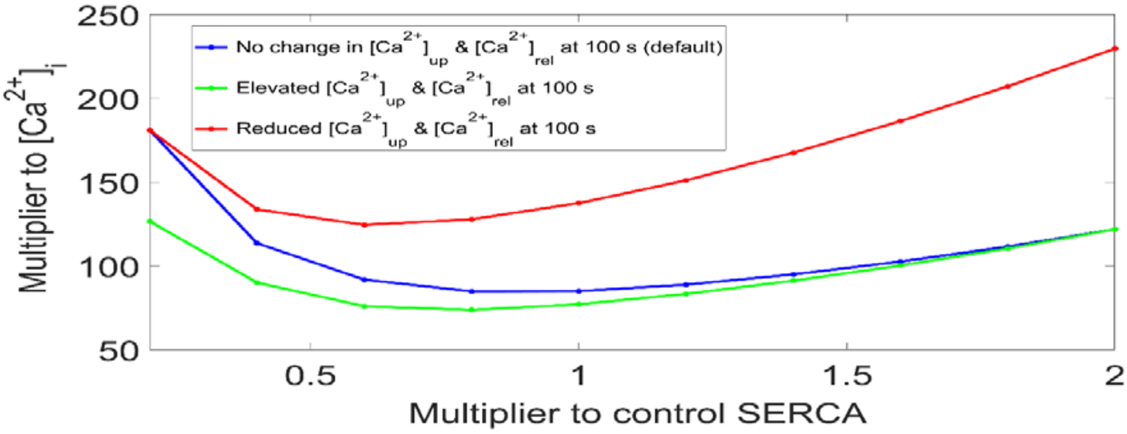

Figure S5: The minimum multiplier needed to raise $[Ca^{2+}]_i$ to the $[Ca^{2+}]_i$ SD threshold for various levels of SERCA for three different cases. The default case is when no change was made to $[Ca^{2+}]_{up}$ and $[Ca^{2+}]_{rel}$ at 100 s into the simulation, prior to intracellular Ca^{2+} injection (blue). The other two cases are when at 100 s into the simulation, prior to intracellular Ca^{2+} injection, $[Ca^{2+}]_{up}$ and $[Ca^{2+}]_{rel}$ were elevated and reduced to their values at 200% SERCA (green) and 20% SERCA (red) at 100 s respectively(see Figure S4A and B).

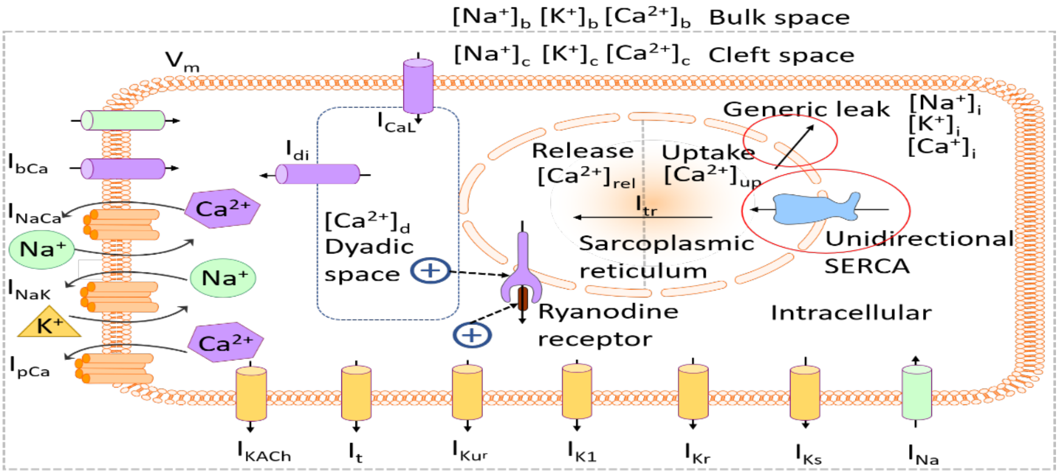

Figure S6: Schematic of the Maleckar-CRN model. Circled in red are the components taken from the CRN model.

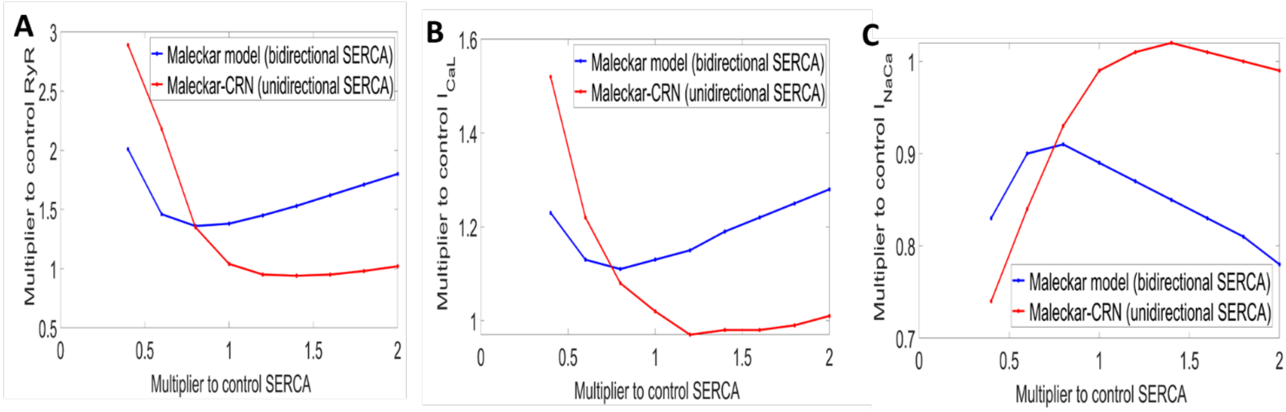

Figure S7: Bifurcation diagrams of **A)** SERCA-RyR **B)** SERCA-I_{CaL} and **C)** SERCA-I_{NaCa} from the full Maleckar et al. model (blue) and the Maleckar-CRN model (red).

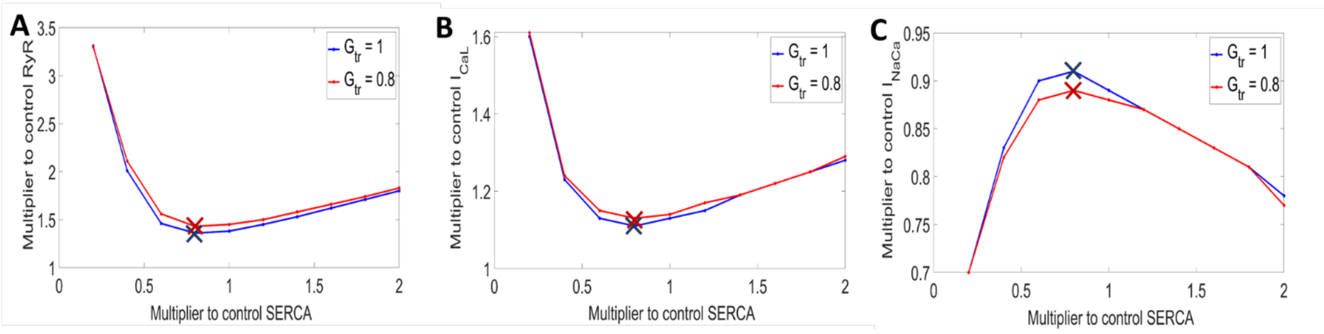

Figure S8: Bifurcation analysis of **A)** SERCA-RyR **B)** SERCA-I_{CaL}, and **C)** SERCA-I_{NaCa} under normal I_{tr} transfer (blue) and 80% of control I_{tr} transfer (red).

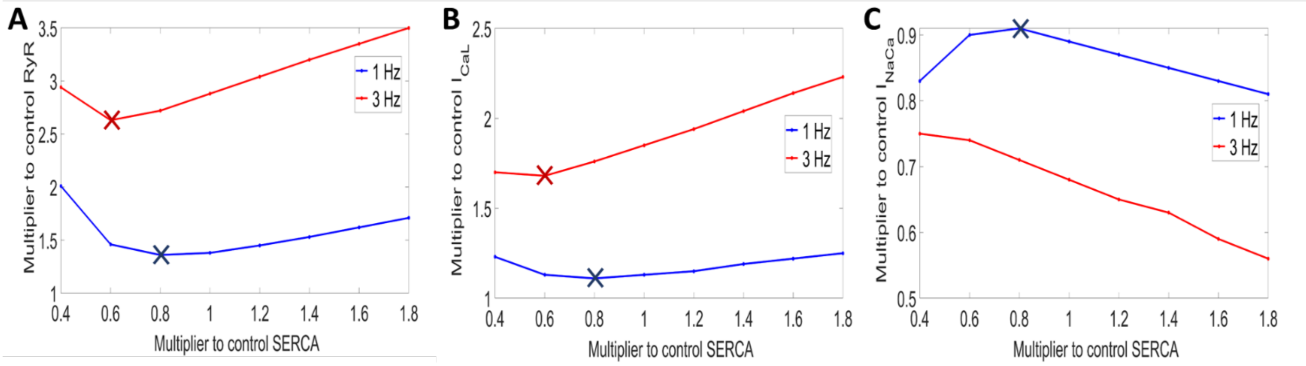

Figure S9. Bifurcation analysis of **A)** SERCA-RyR **B)** SERCA-I_{CaL}, and **C)** SERCA-I_{NaCa} under a 1 Hz (blue) and 3 Hz pacing (red) pacing protocol.