Calcium Sparks and Homeostasis in a Minimal Model of Local and Global Calcium Responses in Quiescent Ventricular Myocytes

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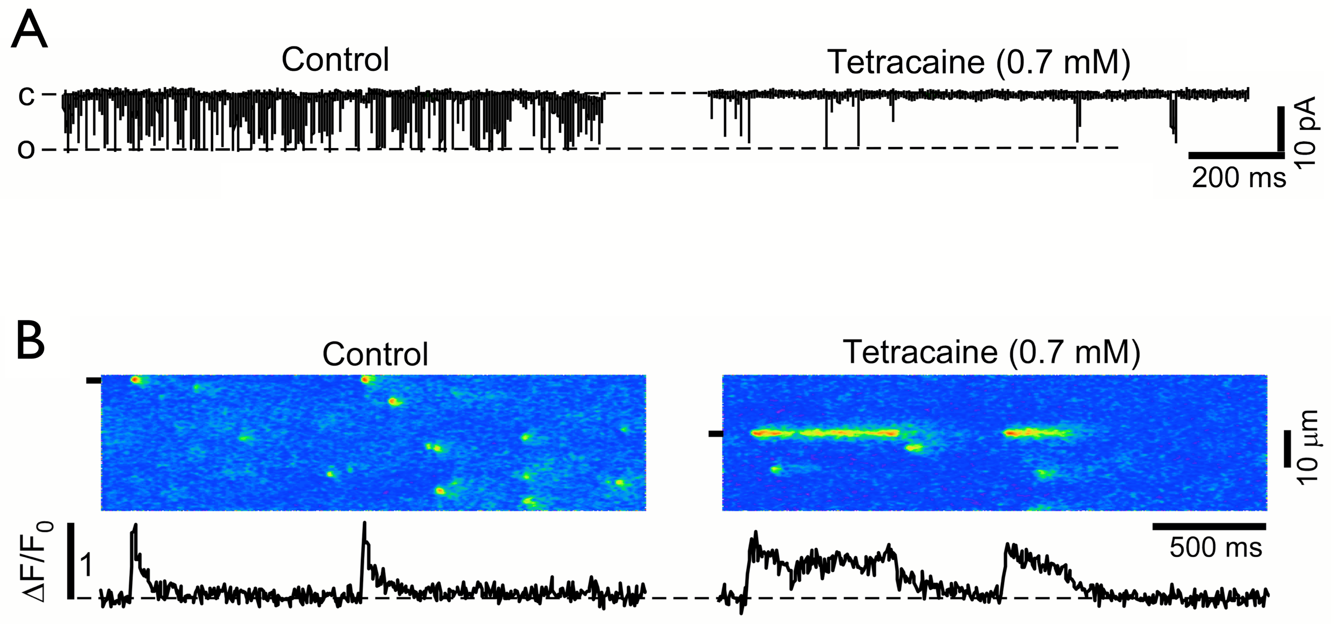
— Introduction —

We present a minimal whole cell model that accounts for both local and global aspects of Ca^{2+} signaling in quiescent ventricular myocytes. We correlate our modeling results with recent experiments showing that tetracaine, an inhibitor of RyRs, causes a transient suppression of Ca^{2+} sparks followed by an increase in SR [Ca^{2+}], partial recovery of spark frequency, and an increase in Ca^{2+} spark duration [1].

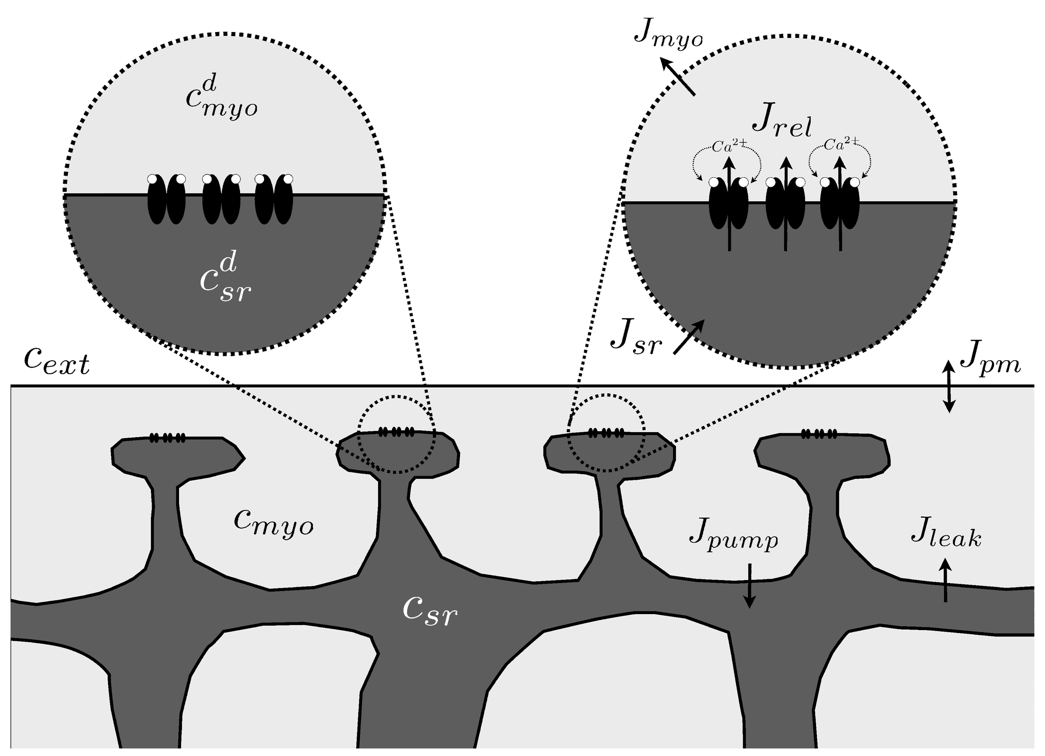


(Reproduced from Zima et al. 2008)

— Model Formulation —

The model represents two bulk compartments: the SR (c_{sr}) and the myoplasm (c_{myo}). The membrane of the SR contains multiple release sites, each of which includes a local Ca^{2+} domain on both sides of the membrane and is composed of N two-state RyRs with Ca^{2+} activation,

$$C \underset{k_{oc}}{\overset{k_{co}(c^d_{myo})^2}{\rightleftharpoons}} O \qquad (1)$$



By assuming mean-field coupling, the release site model becomes

$$0 \underset{k_{oc}}{\overset{Nk_{co}(c^{d,0}_{myo})^2}{\rightleftharpoons}} 1 \underset{2k_{oc}}{\overset{(N-1)k_{co}(c^{d,1}_{myo})^2}{\rightleftharpoons}} \cdots \underset{(N-1)k_{oc}}{\overset{2k_{co}(c^{d,N-2}_{myo})^2}{\rightleftharpoons}} N-1 \underset{Nk_{oc}}{\overset{k_{co}(c^{d,N-1}_{myo})^2}{\rightleftharpoons}} N \qquad (2)$$

The fluxes shown in the above figure are given by

$$J^T_{myo} = \sum_{n=0}^{N} f_n v^T_{myo}\left(c^{d,n}_{myo} - c_{myo}\right) \qquad (3)$$

$$J^T_{sr} = \sum_{n=0}^{N} f_n v^T_{sr}\left(c_{sr} - c^{d,n}_{sr}\right) \qquad (4)$$

$$J_{pm} = k_{pm}\left(c_{ext} - c_{myo}\right) \qquad (5)$$

$$J_{leak} = v_{leak}\left(c_{sr} - c_{myo}\right) \qquad (6)$$

$$J_{pump} = \frac{v_{pump} c^2_{myo}}{k^2_{pump} + c^2_{myo}}. \qquad (7)$$

Under the assumption of a very large number of release sites, we may write whole cell model equations (see below) where $\lambda_{sr} = V_{sr}/V_{myo}$, V_{myo} and V_{sr} are the effective myoplasmic and SR volumes (i.e., accounting for Ca^{2+} buffering capacity), J^T_{myo} and J^T_{sr} are total fluxes obtained by summing over all release sites, $Q = (q_{ij})$ is the infinitesimal generator matrix that corresponds to Eq. 2, and the elements of the row vector $\boldsymbol{\pi}(t)$ give the probability of finding a randomly sampled release site in each of $N+1$ possible states.

$$\frac{dc_{myo}}{dt} = J^T_{myo} + J_{leak} - J_{pump} + J_{pm} \qquad (8)$$

$$\frac{dc_{sr}}{dt} = \frac{1}{\lambda_{sr}}\left(J^T_{sr} - J_{leak} + J_{pump}\right) \qquad (9)$$

$$\frac{d\boldsymbol{\pi}}{dt} = \boldsymbol{\pi} Q \qquad (10)$$

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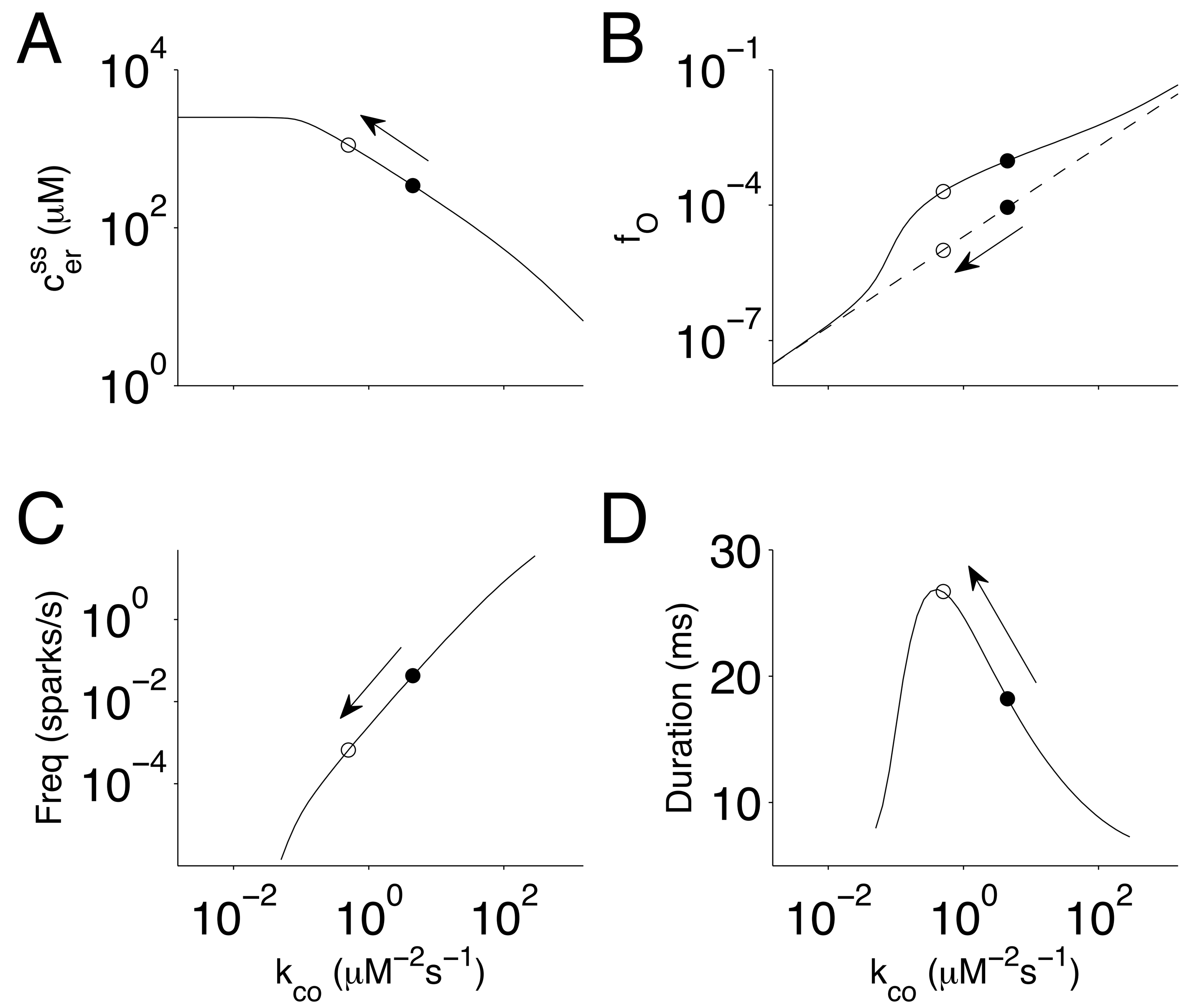
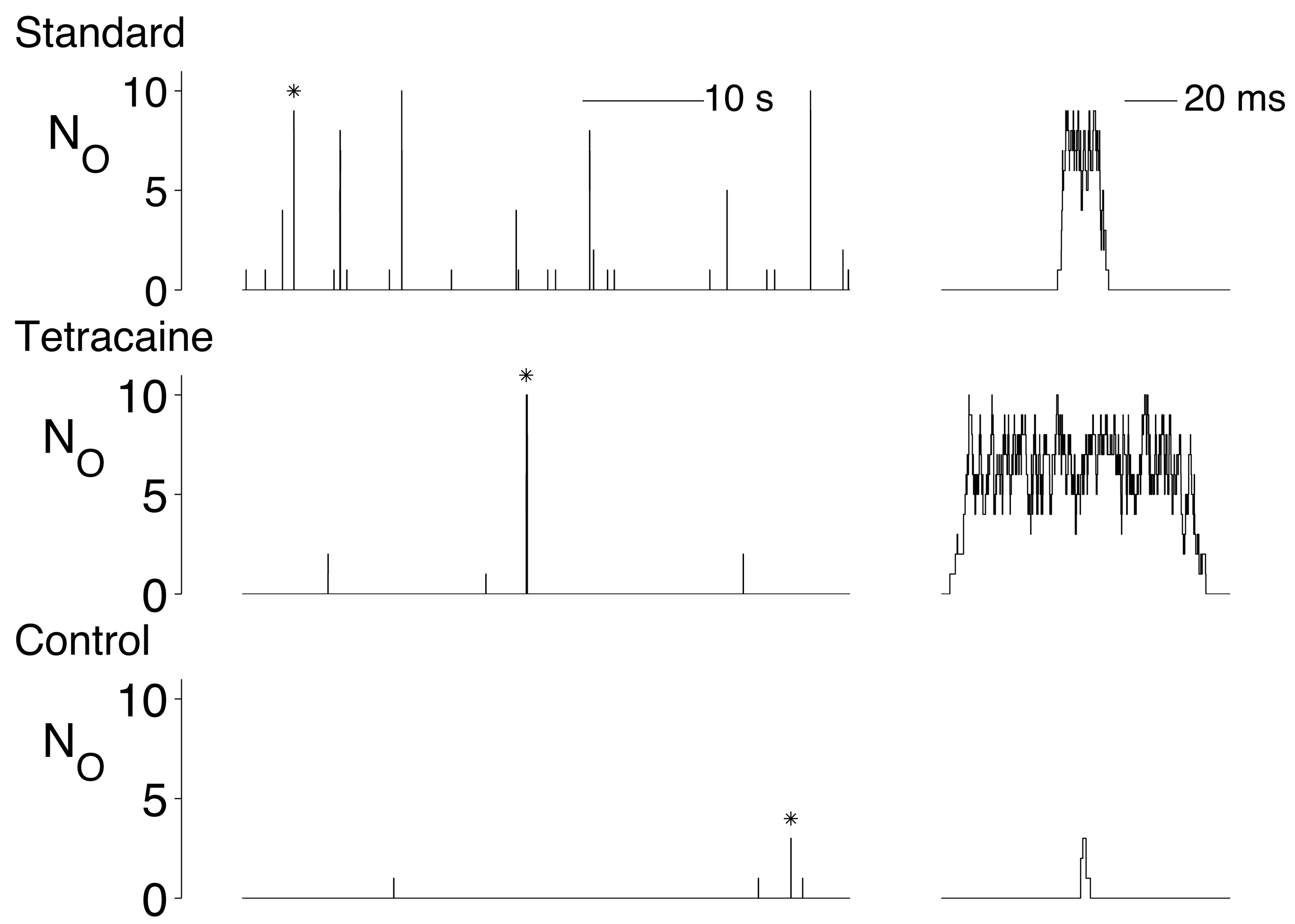
— Simulated Application of Tetracaine —

We simulate the application of tetracaine by decreasing the association rate constant k_{co} in the single channel RyR model (Eq. 1). The filled circles (•) indicate the standard value ($k_{co} = 4.5\ \mu\mathrm{M}^{-2}s^{-1}$); the open circles (○) correspond to the simulated addition of tetracaine ($k_{co} = 0.5\ \mu\mathrm{M}^{-2}s^{-1}$).



— Spark Frequency and Duration —

Below are representative Ca^{2+} sparks in the minimal whole cell model under three different steady-state conditions. In order to confirm that the decreased spark frequency and increased mean spark duration are due to overloading of bulk SR [Ca^{2+}], the figure below (Control) shows a simulation with bulk SR [Ca^{2+}] "clamped," RyR parameters that correspond to the addition of tetracaine and bulk SR [Ca^{2+}] that results from the standard parameters.



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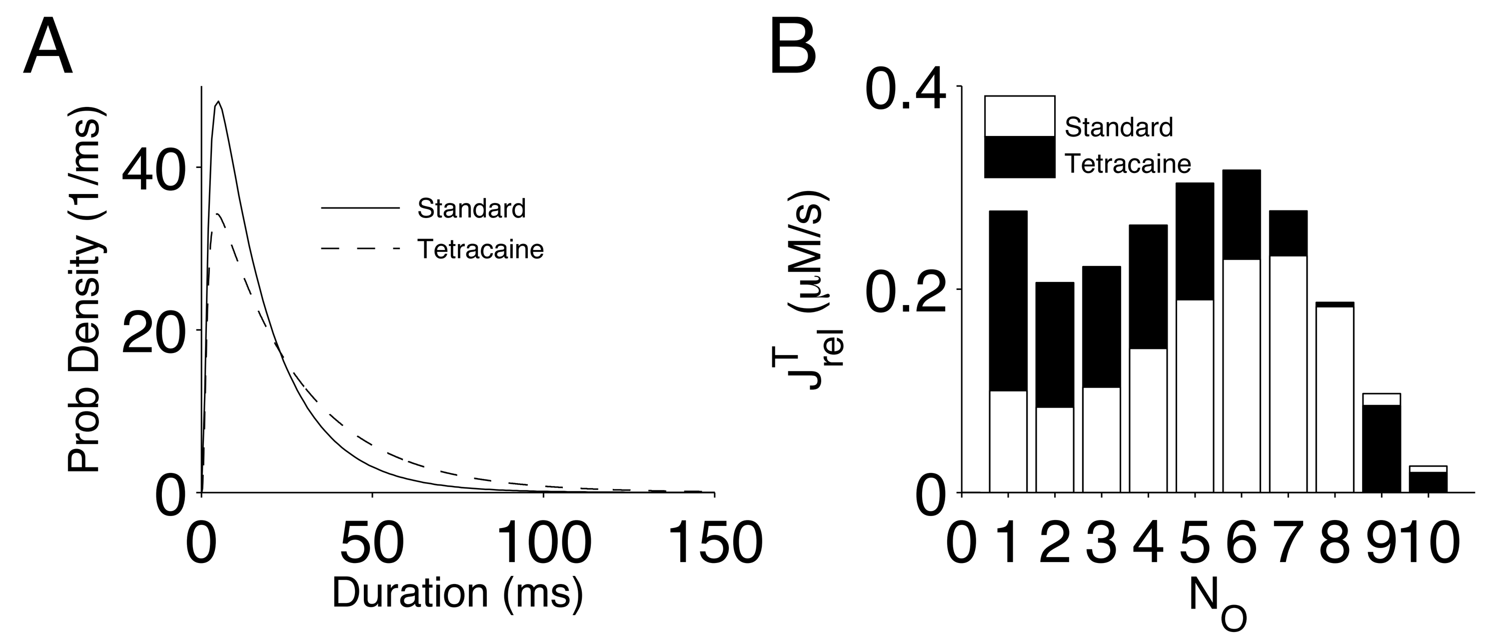
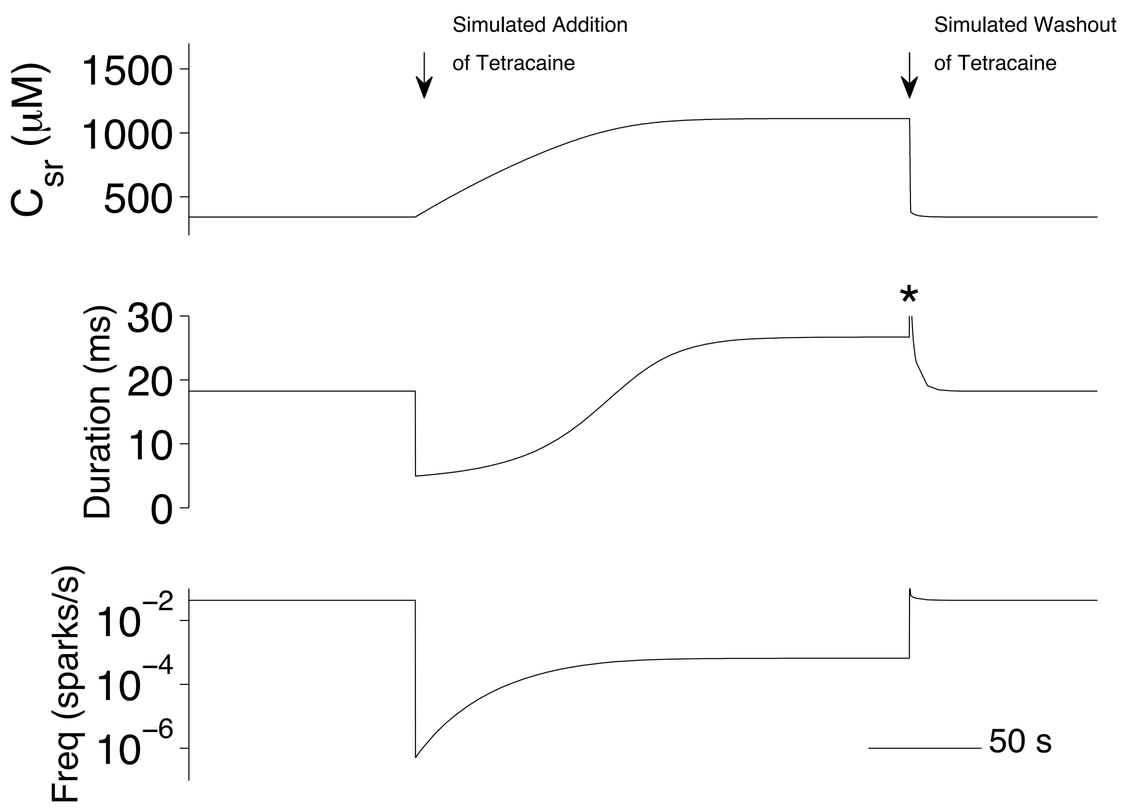
— Aggregate Release Flux —

Because small amplitude events may not be detectable experimentally, it is of interest to dissect the aggregate release flux to determine the fraction of spontaneous release due to sparks vs. quarks. The following figure shows that tetracaine suppresses release mediated by sites with a small number of open channels more effectively than release mediated by sites with a large number of open channels.



— Transient Effects of Tetracaine Application —

Consistent with experimental observations [1,2], the figure below shows that the initial application of tetracaine causes spark frequency to decrease, resulting in a slow increase in SR load that ultimately increases the mean spark duration. Upon simulated washout of tetracaine there is a transient increase in spark frequency and a rapid depletion of SR [Ca^{2+}] from elevated to baseline values.



— RyR Inhibition Mechanism —

The open probability of the RyR can also be reduced by increasing the rate constant k_{oc}, analogous to the action of the pharmacological agent flecainide, which has been shown to reduce the dwell time in open states of the RyR [3]. When the same level of RyR inhibition is modeled as a decrease in open dwell time, the mean spark duration and frequency change, but other whole cell dynamics remain consistent.

	standard	tetracaine $\tau_C\uparrow$	flecainide $\tau_O\downarrow$	dual mechanism $\tau_C\uparrow$ & $\tau_O\downarrow$
k_{co} ($\mu\mathrm{M}^{-2}s^{-1}$)	4.5	0.5	4.5	1.5
k_{oc} (s^{-1})	500	500	4500	1500
f_O	9.6×10^{-4}	2.0×10^{-4}	-	-
$score$	0.51	0.59	-	-
c_{sr} (μM)	342	1112	-	-
duration (ms)	18.2	26.7	2.97	8.90
frequency (sparks/s)	0.043	6.5×10^{-4}	0.053	0.0059

— References —

1. Zima, A., E. Picht, D. Bers, and L. Blatter. 2008. Partial inhibition of sarcoplasmic reticulum Ca^{2+}release evokes long-lasting Ca^{2+}release events in ventricular myocytes: Role of luminal Ca^{2+}in termination of Ca^{2+}release. *Biophys. J.* 94:1867-79.

2. Györke, S., V. Lukyanenko, and I. Györke. 1997. Dual effects of tetracaine on spontaneous calcium release in rat ventricular myocytes. *Journal of Physiology*. 500 Pt 2:297-309.

3. Watanabe, H., N. Chopra, D. Laver, H. Hwang, S. Davies, D. Roach, H. Duff, D. Roden, A. Wilde, and B. Knollmann. 2009. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nature Medicine*. 15:380-383.