Biophysical Journal, Volume *116*

Supplemental Information

Mechanisms of Calcium Leak from Cardiac Sarcoplasmic Reticulum Revealed by Statistical Mechanics

Anna V. Maltsev, Michael D. Stern, and Victor A. Maltsev

1. ISING MODEL METHODS (modified from (1))

1.1. Brief Introduction to the Ising Model. The Ising model we will work with consists of binary random variables (i.e. taking values ±1) called **spins** positioned on a 2D finite grid Λ (e.g. section 3.3.5 in (2)). A configuration of spins is a function σ that assigns 1 or -1 to each point $x \in \Lambda$. The configuration space Ω is the set of all possible assignments of spins to points in Λ, i.e. all possible functions $\sigma : \Lambda \to \{1, -1\}$. A **interaction profile** ϕ: $\mathbb{R} \rightarrow \mathbb{R}$ is a function with $\phi(x) \to 0$ rapidly as $x \to \infty$ and $\phi > 0$. We choose ϕ so that $\phi(1) = 1$. We furthermore place our finite grid Λ inside of a bigger grid Λ_b (b for boundary) and let $\sigma(x) = -1$ for any $x \in \Lambda_b \setminus \Lambda$. In this way we impose a -1 **boundary condition** on Λ. Here $\Lambda_b \backslash \Lambda$ must "frame" Λ and its thickness has to be at least as wide as the effective interaction range, which in our case will be around 5. To be precise, if Λ is a *n* by *m* grid, Λ_b will be a *n+10* by *m+10* grid with Λ situated in the middle of Λ_b. The Hamiltonian is

[1] $$H(\sigma) = -\sum_{x,y \in \Lambda_b} \phi(|x-y|)\sigma(x)\sigma(y) - h\sum_{x \in \Lambda_b} \sigma(x)$$

Here the first sum is over Λ_b instead of Λ. This is necessary to ensure the interaction with the boundary.

In physics, *h* is the magnetic field. The Hamiltonian can be interpreted as the energy of the system. The equilibrium measure (Gibbs measure) is given by

[2] $$\pi(\sigma) = Z^{-1} e^{-\beta H(\sigma)} .$$

The normalization constant *Z* is well-defined since our lattice Λ is finite, and we will not need to know it explicitly for our analysis. Here β is the inverse temperature. (For further information on the general Ising model, of which this is an instance, cf Sections 2.1 and 2.2 in (3)).

1.2. Dynamic Ising: Detailed Balance and the Transition Rates. Let Λ be a 2 dimensional integer grid of a finite size. Recall that Ω is the configuration space and let σ: $\Lambda \to \{1, -1\}$ be an element of Ω. One can introduce a dynamic on spin configurations so that the configuration space Ω becomes the state space for a Markov chain with a transition matrix P. We introduce the notation σ^x to mean

$$\sigma^x = \begin{cases} \sigma(y) & \text{for} \quad y \neq x \\ -\sigma(y) & \text{for} \quad y = x \end{cases}$$

i.e. σ^x coincides with σ everywhere except at x, where the spin is reversed. To obtain a Glauber-like dynamic for the Ising model, it suffices to choose a spin uniformly at random at each time increment and to give the probability that it flips, i.e. to give $P(\sigma \to \sigma^x)$. y

The condition on P that guarantees that π as in [2] is indeed the equilibrium measure for the Markov chain is called detailed balance, and it states that the Markov chain is reversible with respect to π (cf equation (1.30) and Proposition 1.19 in (2)). The equation for detailed balance is the following: for all $\sigma \in \Omega$ and $x \in \Lambda$ we have that

[3] $$P(\sigma \to \sigma^x)e^{-\beta H(\sigma)} = P(\sigma^x \to \sigma)e^{-\beta H(\sigma^x)}$$

This is equivalent to

[4] $$\frac{P(\sigma \to \sigma^x)}{P(\sigma^x \to \sigma)} = e^{\beta H(\sigma) - \beta H(\sigma^x)}$$

$$= e^{-2\beta(\sum_{y \in \Lambda_b} \phi(|x-y|)\sigma(x)\sigma(y) + h\sigma(x))} = e^{-2\beta\sigma(x)(\sum_{y \in \Lambda_b} \phi(|x-y|)\sigma(y) + h)}$$

The detailed balance equations will be satisfied for a wide variety of rates P, so we can choose P to be most appropriate to our CRU model. Since we know that the release channel opening rate is an exponential while the closing rate is a constant, we look for P so that the transition from -1 to 1 is exponential while the transition from 1 to -1 is a constant. This indeed can be achieved simultaneously with the detailed balance condition. If $\sigma(x) = -1$ we let

$P(\sigma \to \sigma^x) = Ce^{2\beta\left(\sum_{y\in\Lambda_b} \phi(|x-y|)\sigma(y)+h\right)}$ yielding that $P(\sigma^x \to \sigma) = C$ to satisfy detailed balance. Thus, the Markov chain is given as follows. We pick a location x uniformly at random, and define the transition matrix P to be:

$$[5] \qquad P(\sigma,\sigma^x) = \begin{cases} Ce^{2\beta(\sum_{y\in\Lambda_b}\phi(|x-y|)\sigma(y)+h)} & \text{for } \sigma(x) = -1 \\ C & \text{for } \sigma(x) = 1 \end{cases}$$

Here time is continuous and the above are transition rates. In our numerical model, time is discrete and we take Δt =0.05 ms. The transition matrix with the discretized time becomes

$$[6] \qquad P(\sigma,\sigma^x) = \begin{cases} \Delta t Ce^{2\beta(\sum_{y\in\Lambda_b}\phi(|x-y|)\sigma(y)+h)} & \text{for } \sigma(x) = -1 \\ \Delta t C & \text{for } \sigma(x) = 1 \end{cases}$$

and we ensure that Δt is small enough so that all transition probabilities are smaller than 1. Letting also $P(\sigma,\sigma) = 1 - P(\sigma,\sigma^x)$ ensures that P is indeed stochastic.

1.3. The CRU as an Ising Model. A numerical model of the CRU consists of a square grid of Ca release channels Λ and each release channel can be open or closed. We assign 1 to each open and -1 to each closed release channel, thus obtaining a configuration $\sigma : \Lambda \to \{1, -1\}$. We introduce the constant U to represent the spatial distance between nearest release channels. In our numerical model, is U = 30 nm.

We let ψ be the 1D slice of the time-stable spatial Ca profile resulting from the opening of one release channel. This is sufficient to contain all the information about the Ca profile since ψ is rotationally symmetric. We obtain ψ from our numerical simulation. However, ψ is an immediate result of the environment, including current, diffusion, and buffer and is not an emergent property. We interpret it as a scaled interaction profile, and let ϕ in [1] be given as

$\phi(r) = \psi(Ur)/\psi(U)$, where Ur is the distance to the open release channel. The multiplication by U accounts for the fact that the release channels are U units apart while spins are 1 unit apart. The division by $\psi(U)$ is a choice of scaling for the interaction profile function ϕ. With this scaling we have $\phi(1) = 1$. We choose this scaling for ϕ so that at the nearest neighbors its value matches the classic Ising model, where each spin interacts with 4 neighbors with a strength of 1.

The distance between CRUs is assumed to be too large for Ca from one CRU to influence another. On the other hand, Ca is diffusing out of the CRU and in this way the release channels in the CRU interact with the outside. The model would be identical if the CRU were surrounded by release channels that are always closed. In this way, the boundary condition of the CRU model is equivalent to a negative boundary condition of the Ising model.

We will compute the analogues of inverse temperature β and the magnetic field h in our CRU model as functions of initial model parameters. They play the exact same role in the mathematical description of our CRU model as they do in the Ising model even though they do not carry the same physical meaning. We will note that β is an increasing function of the concentration of Ca inside the junctional SR and we vary the SR Ca in our numerical model to test the predictions of the CRU Ising model.

1.4. Relating [Ca] and the Ising Hamiltonian. Let us introduce the set $S(x) := \left\{ s \in \mathbb{R} : s = |x - y| \neq 0 \text{ for some } y \in \mathbb{Z}^2 \right\}$. We can rewrite both the local [Ca] at x (we denote it [Ca](x)) and the exponent in the -1 to 1 transition in P in terms of a sum over $S(x)$. Given a configuration of open and closed release channels σ and a given release channel at a point x, let N_{Us} be the number of open RyRs at a distance Us from x. If the release channel at x is closed, we can approximate [Ca] at x by

[7] $$[Ca](x) = \sum_{s \in S(x)} \psi(Us) N_{Us}$$

We similarly rewrite *P*. We introduce the following notation: $T_s(x)$:= total number of spins at distance s from *x*; $L_s(x)$:= number of -1 spins at distance s from *x;* $N_s(x)$:= number of +1 spins at distance s from *x*; and we have $N_s(x) + L_s(x) = T_s(x)$.

Henceforth in this section, let us fix a site $x \in \Lambda$ and suppress the dependence on *x* in T_s, L_s, N_s, and *S* for ease of notation. Then we can rewrite the expression in the exponent of the Ising -1 to +1 transition probability in [5] in the following way:

[8] $$\sum_{y \in \Lambda_b} \phi(|x - y|)\sigma(y) = \sum_{s \in S} \phi(s)(N_s - L_s) = \sum_{s \in S} \phi(s)(2N_s - T_s)$$
$$= 2\sum_{s \in S} \phi(s) N_s - \sum_{s \in S} \phi(s) T_s \approx 2\sum_{s \in S} \phi(s) N_s - 2\pi \int_{s>.5} \phi(s)\, ds$$

In the last approximate equality, we have replaced $\sum_{s \in S} \phi(s) T_s$ by $2\pi \int_{s>.5} \phi(s) ds$ where the factor of 2π is due to the fact that $\sum_{s \in S} \phi(s) T_s$ is approximately a 2D integral of a rotationally symmetric function. We observe that the first term in the final expression in [8] is a scalar multiple of the total Ca [Ca] (*x*) as given in [7].

1.5. Crucial Parameters and the Spark Termination Criterion. We want to solve for the analogues of *h* and β in the CRU model. We again fix a site $x \in \Lambda$ and suppress the dependence on *x* in [Ca] and *S* for ease of notation. From experimental data we fit the exponential $\lambda e^{\gamma[Ca]}$ to the Ising transition rate from -1 to +1 in [5]:

$$\lambda e^{\gamma[Ca]} = Ce^{2\beta(\sum_{y \in \Lambda_b} \phi(|x - y|)\sigma(y) + h)}$$

Then we replace the LHS using [7] and the RHS using the expression derived in [8] to obtain

[9a] $$\lambda e^{\gamma \sum_{s\in S}\psi(Us)N_{Us}} = Ce^{2\beta(2\sum_{s\in S}\phi(s)N_s - 2\pi\int_{s>.5}\phi(s)\mathrm{ds}+h)}$$
$$= Ce^{-4\beta\pi\int_{s>.5}\phi(s)+2\beta h} e^{4\beta(\sum_{s\in S}\phi(s)N_s)}$$

Since we wish the above equality to hold for any configuration, we must equate the coefficients of $\sum_{s\in S}\phi(s)N_s$ to obtain

[9b] $$\beta = \gamma\psi(U)/4.$$

Next we equate the coefficients in front of $e^{4\beta(\sum_{s\in S}\phi(s)N_s)}$ to obtain

$$\lambda = Ce^{-4\beta\pi\int_{r>.5}\phi(s)dr+2\beta h}$$

yielding that

[10] $$h = \frac{1}{2\beta}\ln\left(\frac{\lambda}{C}\right) + 2\pi\int_{r>.5}\phi(r)dr$$

Rewriting h in terms of the Ca profile ψ we obtain

[11] $$h = \frac{2}{\gamma\psi(U)}\ln\left(\frac{\lambda}{C}\right) + 2\pi\int_{r>U/2}\frac{\psi(r)}{U\psi(U)}dr$$

Since h is the analogue of the magnetic field in the CRU model, the emergent behavior of release channels can be predicted based on h. During termination all the release channels begin in an open state (analogous to +1). The Ca diffusion out of CRU is equivalent to a negative boundary condition. We can hence deduce the **signal termination criterion**: If $h< 0$, then the spark will terminate and this termination is mathematically identical to reversal of polarity in ferromagnetism. Mathematically, this phase transition follows from the Lee-Yang theorem. On the other hand, if $h> 0$, the spark will not terminate.

2. ESTIMATES OF CRITICAL β

2.1. Lower bound estimate using mean field approach

This calculation closely follows the lecture notes of Prof. Martin Evans from University of Edinburgh (4).

The Ising configuration energy is

$$E(\sigma) = -h\sum_{x\in\Lambda}\sigma(x) - \sum_{x,y\in\Lambda}\phi(|x-y|)\sigma(x)\sigma(y) \tag{1}$$

Let $\epsilon(\sigma(x))$ be the contributions involving spin x to this energy:

$$\epsilon(\sigma(x)) = -h\sigma(x) - \sigma(x)\sum_{y\in\Lambda}\phi(|x-y|)\sigma(y) = -\sigma(x)(h+\sum_{y\in\Lambda}\phi(|x-y|)\sigma(y))$$

We then replace the contributions from $\sigma(y)$ by their mean values:

$$\epsilon(\sigma(x)) = -\sigma(x)(h+\sum_{y\in\Lambda}\phi(|x-y|)\langle\sigma(y)\rangle) = -h_{mf}\sigma(x)$$

where

$$h_{mf} = h + 2\pi m\int_{s>0.5}\phi(s)ds \tag{2}$$

and $m = \langle\sigma(y)\rangle$. Then we replace the energy in (1) by the energy of non-interacting spins each experiencing a field with magnitude h_{mf}. In this approximation we know the single-spin Boltzmann distribution:

$$P(\sigma(x)) = \frac{e^{-\beta\epsilon_{mf}(\sigma(x))}}{\sum_{\sigma(x)=\pm1}e^{-\beta\epsilon_{mf}(\sigma(x))}} = \frac{e^{\beta h_{mf}\sigma(x)}}{e^{\beta h_{mf}}+e^{-\beta h_{mf}}} \tag{3}$$

We now must ensure that the approximation is self-consistent. The mean value of magnetization predicted by (3) should match the mean value used in (2). We obtain the equation:

$$m = \sum_{\sigma(x)=\pm1}P(\sigma(x))\sigma(x) = \frac{e^{\beta h_{mf}}-e^{-\beta h_{mf}}}{e^{\beta h_{mf}}+e^{-\beta h_{mf}}} = \tanh(\beta h_{mf}) \tag{4}$$

yielding the mean field equation for magnetization

$$m = \tanh(\beta h + 2\beta\pi m\int_{s>0.5}\phi(s)ds)$$

Setting $h=0$, we note that for low β the equation

$$m = \tanh(2\beta\pi m\int_{s>0.5}\phi(s)ds)$$

has only one solution and for high beta it has 3 solutions. The transition happens when

$$\frac{d}{dm}\tanh(2\beta\pi m\int_{s>0.5}\phi(s)ds)|_{m=0} \geq 1$$

Using a Taylor expansion of tanh near 0, we obtain that $2\beta\pi\int_{s>0.5}\phi(s)ds \geq 1$ yielding that the critical β is

$$\beta^* = \frac{1}{2\pi\int_{s>0.5}\phi(s)ds} \approx 0.0784$$

2.2. Upper bound estimate using classical 4-neighbor Ising beta critical

We can obtain an upper bound on β^* by comparing with the classical nearest neighbor Ising model with

$$J = \frac{\int_{s>0.5} \phi(s) ds}{4} = \frac{12.7586}{4} = 3.19$$

i.e. the total quantity of interactions in our model divided between for nearest neighbors. In the classical Ising model

$$\frac{J}{kT_c} = 0.441$$

for these formulae cf for example (6.2.2) and (6.2.16) of Baxter (5). Since $\beta^* = 1/(kT_c)$, dividing the (5) by J = 3.19, we obtain an upper bound for beta critical of 0.138.

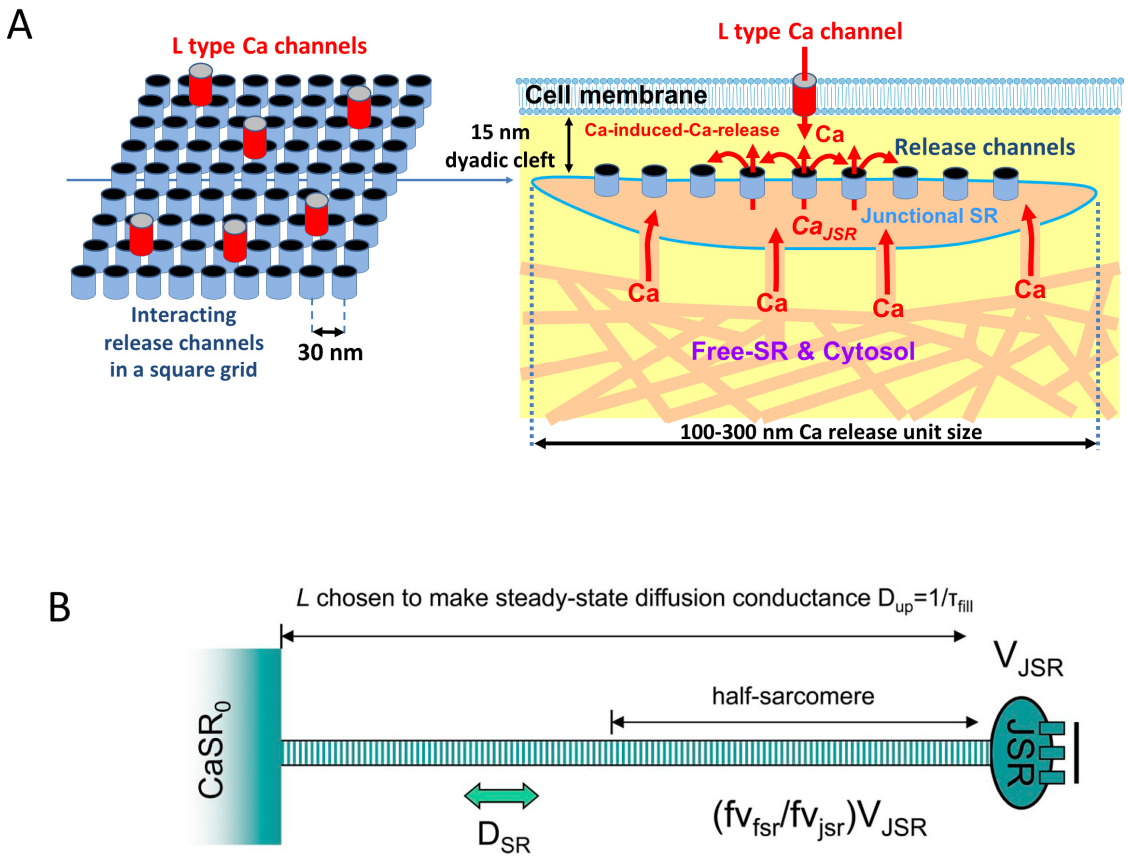

Fig. S1. A schematic representation of CRU function in cardiac cells in Stern numerical model that describes collective behavior of RyR ensemble in a CRU during spark activation and termination. **A**: Illustration of geometry and Ca fluxes in the model. Modified from Maltsev et al. (1). Each RyR operates in 2 states: open and closed, with no time-dependent inactivation, coupled gating, or allosteric interactions. A lattice of 9x9 RyRs separated from each other by U=30 nm is embedded on a JSR that features calsequestrin and a diffusive connection with a free SR (FSR) that is equipped with a Ca pump. A 15 nm dyadic space features Ca buffers and a diffusive connection to the cytoplasm. The model simulates intradyadic local Ca dynamics on a nanoscale, with a voxel size =10x10x15 nm (xyz). Individual RyRs release Ca and interact via CICR. The dyadic space includes physiological Ca buffers and the released Ca diffuses to JSR border to reach the cytoplasm that has a fixed [Ca] of 100 nM. **B**: Diffusional connection between junctional SR (JSR) to free SR (FSR) determining JSR refilling with Ca. The connection is made through a tube of local FSR, whose length and diameter are chosen to match the observed steady-state diffusion resistance (characterized by time constant τ_{fill}) and the observed volume fraction of FSR. For the standard parameters and a true half-sarcomere length of 1 μm, the effective SR tube length is 1.995 μm. From Stern et al. (6). In the numerical simulations, the boundary condition for Ca at the edge of the couplon was determined by adding, to the background cytosolic Ca (100 nM), the product of the flux of Ca leaving the couplon and an estimated diffusion resistance between the boundary and "infinity" in the cytosol. The diffusion resistance estimate was originally determined from analytical computations in cylindrical coordinates assuming a central source and numerical integration of the diffusion equation in rectangular coordinates using PDEase (Macsyma Corp, Arlington, MA).

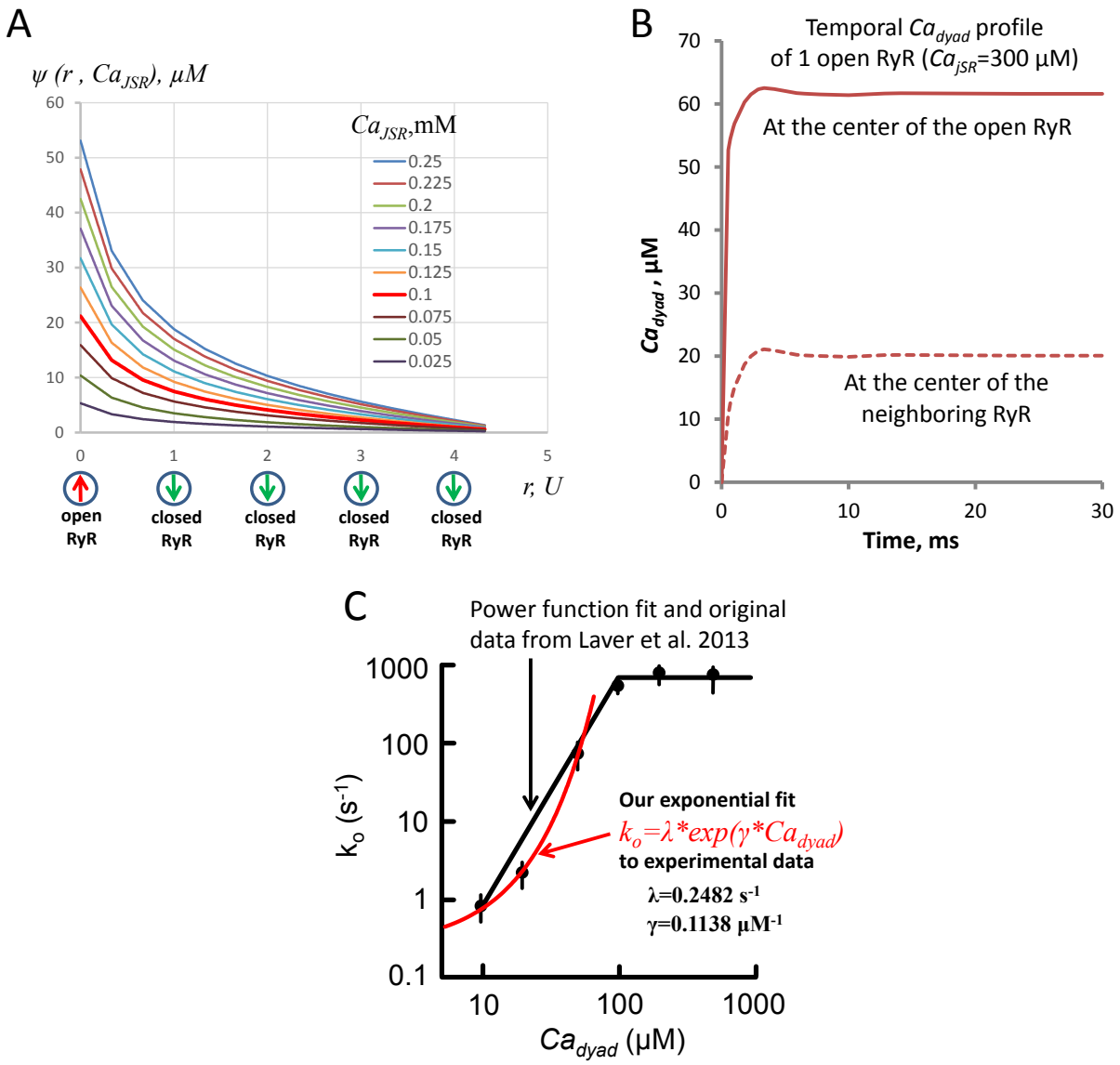

Fig. S2. Construction of an exact mapping between a CRU described by Stern model and the Ising model of interacting spins.
A, A steady-state spatial Ca_{dyad} profile at various Ca_{JSR} when one RyR is open in the center of 9x9 grid at r=0. **B**, Representative $Ca_{dyad}(t)$ when one RyR is open in the center of the grid: at the open RyR and its closest neighbor. **C**, The exponential relation of RyR opening rate vs. Ca_{dyad}. All previous models fit a power function to original data obtained in lipid bilayers. Here we fit an exponential (red line) to the same data points (original data and power fit are reproduced from Laver et al. (7). Thus, we replaced the quadratic opening rate in original Stern model with the exponential opening rate from this fit. Modified from Maltsev et al. (1).

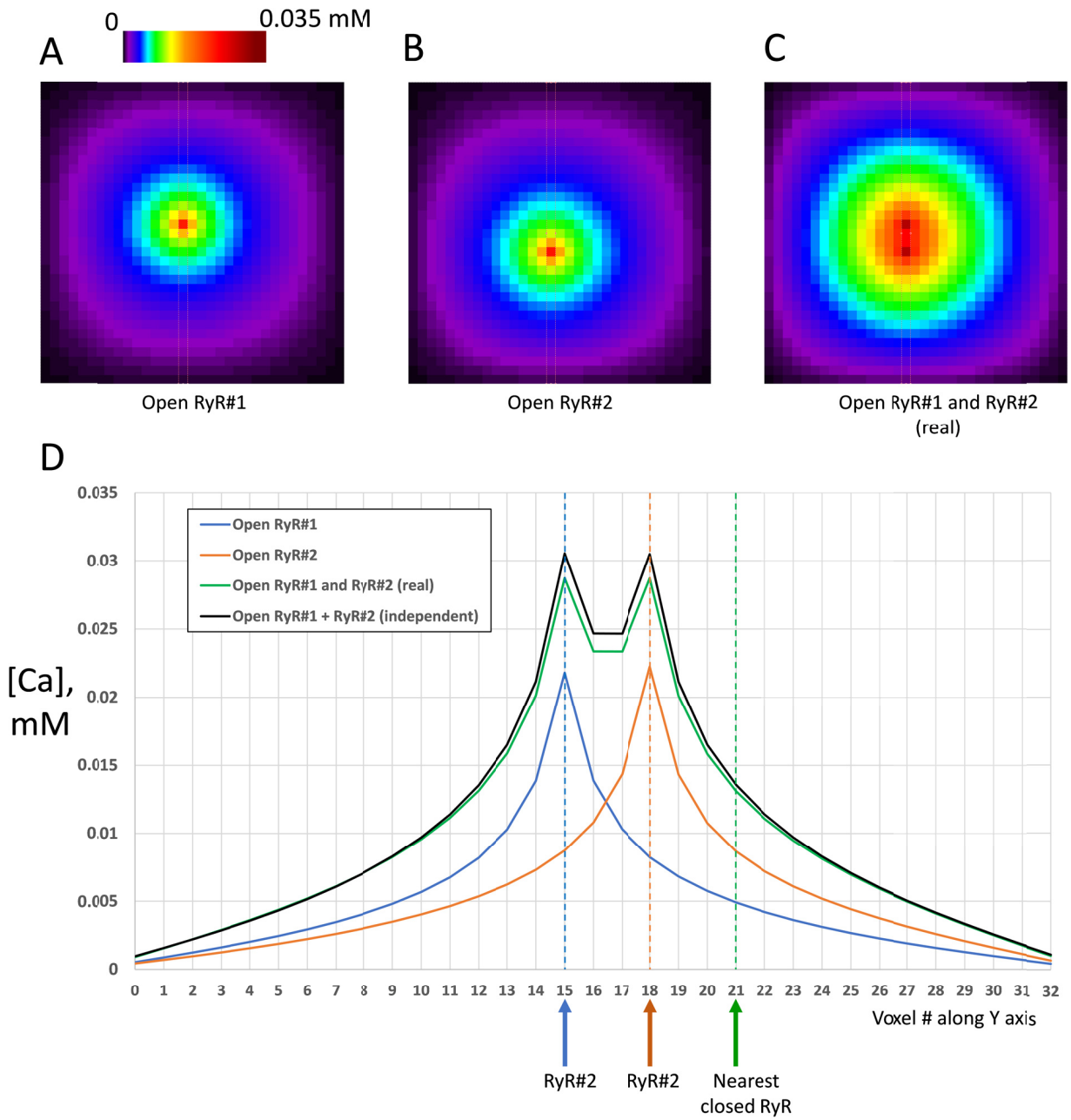

Fig. S3: Independence of Ca release flux and minor effect of driving force reduction due to open neighboring RyRs.
A-C: Simulations of steady state local Ca distributions in the dyadic space with 2 neighboring channels (RyR#1 and RyR#2) opening separately and simultaneously, respectively, at a fixed Ca SR level of 0.1 mM. **D**: Local Ca profiles through open channels along vertical (Y) axis, respectively. The local profile "RyR#1 + RyR#2 (independent)" was calculated as a formal sum of profiles "Open RyR#1" and "Open RyR#2" as if channels operate independently. The real profile "Open RyR#1 and RyR#2 (real)" generated by numerical simulation deviates negligibly from that formal sum of individual profiles. The deviation at either open channel #1 or #2 position is 5.9% and at the nearest closed neighbor is only 3.5% (arrows). See text and Table S2 for details.

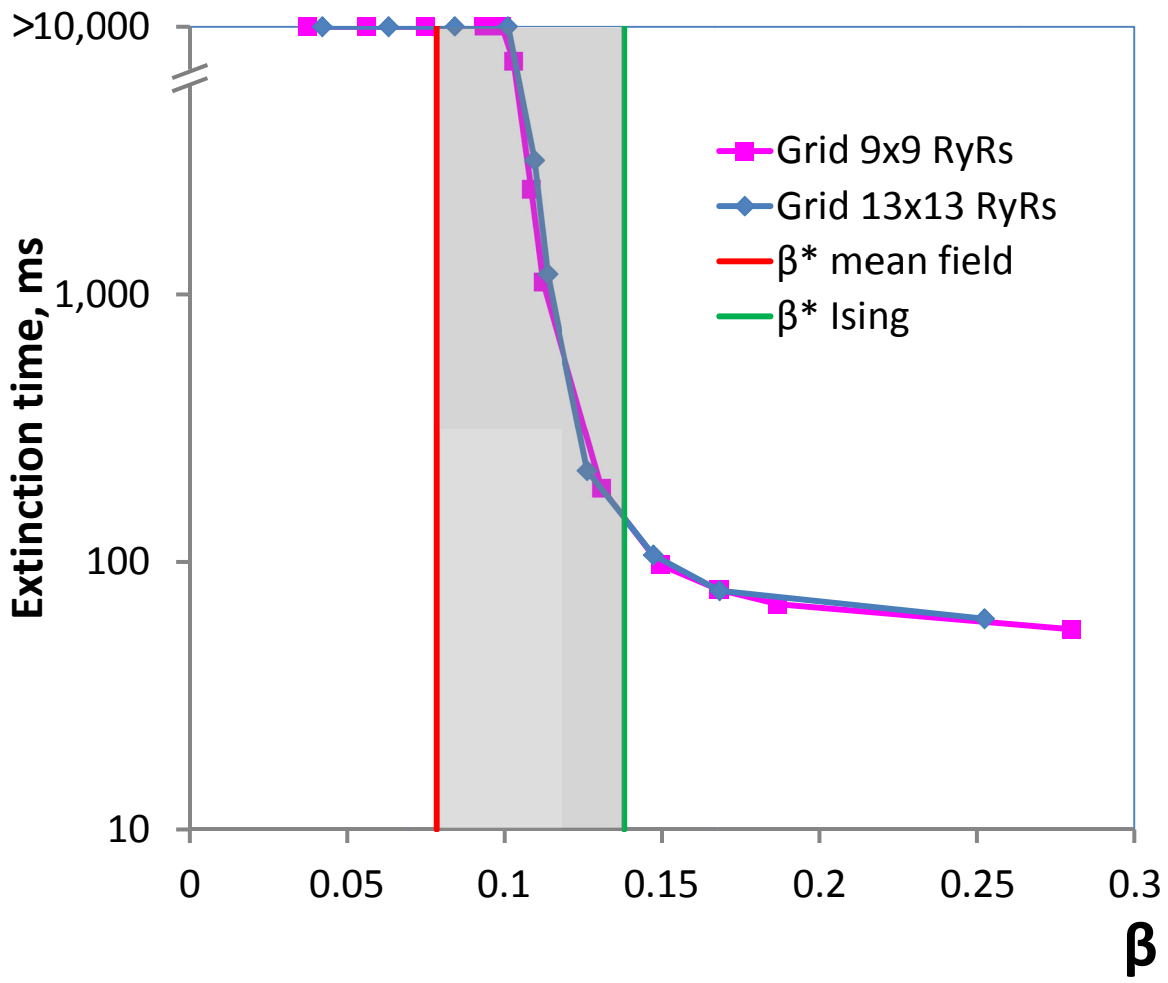

Fig. S4: "Order-disorder" phase transition occurs within the same β range for a wide range of RyR cluster sizes.
Shown are "order-disorder" phase transitions for two cluster sizes of 81 and 169 in terms of median extinction times (100 sparks for each data point) vs. β. Vertical lines show lower and upper bounds estimates for β* obtained analytically: $\beta^*_{mean\_field}$ (red line) and β^*_{Ising} (green line). The extinction times and respective phase transitions follow basically the same dependence on β within these bounds (grey area) for both cluster sizes. Note: Simulation data for 9x9 cluster size (in magenta) is the same is in Figure 2C of the main text. The magenta and blue curves overlap within the accuracy of our method evaluating 100 sparks for each data point. If we assume that phase transition happens when extinction time becomes >10,000 ms then β* = 0.09899 and 0.10097, for 81 and 169 clusters, respectively, i.e. the difference of 0.00198 is about 2%.

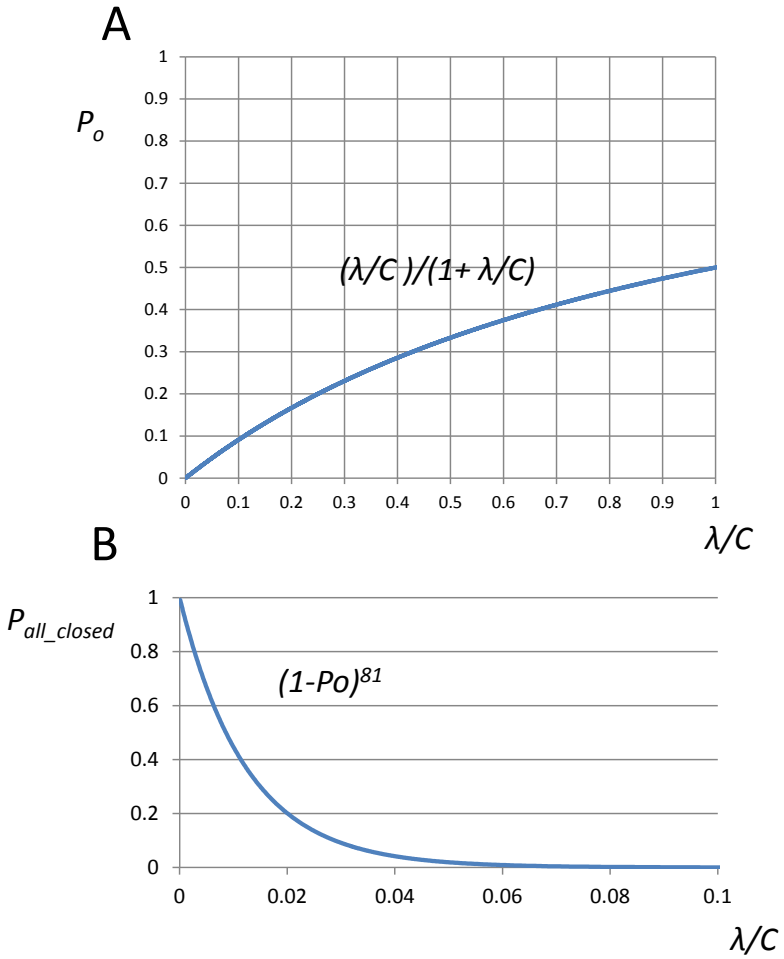

Fig. S5: Leaky operation of RyRs in subcritical regime neglecting any remaining interactions with each other.
A: Steady-state open probability (P_o) is given as balance between opening (λ) and closing (C) rates as $P_o = (\lambda/C)/(1 + \lambda/C)$. **B**: The probability that all 81 RyRs become closed.

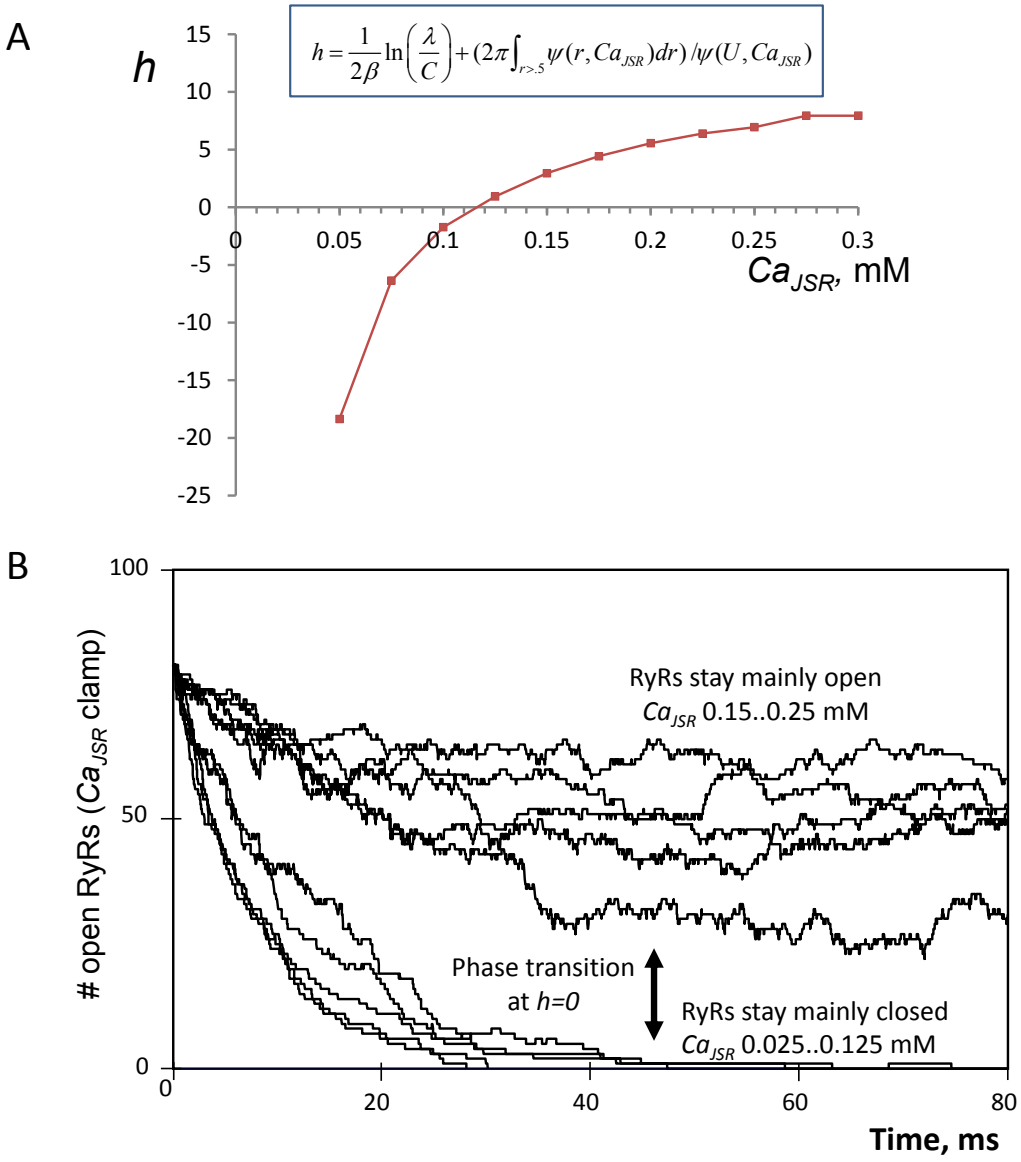

Fig. S6: Supercritical *β* regime: Phase transition in a CRU of 9x9 RyRs via *h* reversal as Ca_{JSR} is clamped at various levels in Stern model.
A: Calculation of *h* as a function of Ca_{JSR}, using modified Equation 11 in supplement (indicated in the inset). In this equation, $\psi(U, Ca_{JSR})$ is interaction profile $\psi(r, Ca_{JSR})$ taken for $r = U = 30$ nm shown by vertical arrow in Online Figure IIA. In turn, β was calculated as $\beta=\gamma\psi(U, Ca_{JSR})$. **B**: Evolution of RyR ensemble at various Ca_{JSR} levels after all RyRs are set in the open state at time 0. RyRs stay mainly closed at Ca_{JSR} below 0.12 mM, but become mainly open above 0.12 mM. The sharp transition in the numerical model behavior is in line with the Ising model prediction of the phase transition at 0.12 mM on *h* reversal. Modified from Maltsev et al.(1).

Table S1 – Relationship between the abstract Ising model and ion channels and CRU parameters

Abstract Ising model parameters	Equations	Release channel (RyR) parameters	CRU parameters
Inverse temperature β	Equation [9b] in the supplement $\beta=\gamma\psi(U)/4$	γ is opening rate exponent in $k_o=\lambda*exp(\gamma*Ca_{dyad})$ (Fig. S2C) λ is opening rate scaling factor, i.e. a virtual rate at Ca_{dyad} =0 The single channel conductance*, in Stern spark model UIC=0.35pA, i.e. i_{RyR} at resting $Ca_{JSR,rest}$=1 mM	U=30 nm is the distance between neighboring RyRs $\psi(r, Ca_{JSR},$ UIC$)$ is the interaction profile†‡, i.e. Ca_{dyad} at distance r from open channel with a given Ca_{JSR} and single channel conductance (i.e. UIC in the Stern model).
Magnetic field h	Equation [11] in the supplement $h=\frac{2}{\gamma\psi(U)}\ln\left(\frac{\lambda}{C}\right)+2\pi\int_{r>U/2}\frac{\psi(r)}{U\psi(U)}dr$		

Notes:
* The single channel conductance is present in the equations implicitly via ψ
† ψ also depends on the CRU size (it tends to decrease for very small CRUs due to boundary effects).
‡The present study does not provide an analytical formula for ψ; rather it was a read-off from numerical model simulations (Fig. S2A).

Table S2 – Independence of Ca release flux via neighboring RyRs, i.e. minor effect of driving force reduction due to open neighboring RyRs. See Figure S3.

Condition	[Ca] at the nearest closed RyR, μM	[Ca] at RyR#2, μM
Open RyR#1	4.904	8.234
Open RyR#2	8.66	22.256
Open RyR#1 and RyR#2 (independent)	13.564	30.49
Open RyR#1 and RyR#2 (real)	13.094	28.701
Difference of independent and real	0.47	1.789
relative change in %	3.465	5.867

Table S3 - Supplemental calculations & results (median extinction times) for the main text Figure 2.

Pairs of γ and λ values (highlighted) were constructed to have h=0 in a CRU with 9x9 RyRs. This is a copy of Excel spreadsheet; each column is explained below:
C: closing rate C=0.117 ms^{-1}= const.
CaJSR: Ca_{JSR}=100 μM=const.
ψ(U): the value of interaction profile at the distance of the nearest RyR neighbor; *ψ(r)* is given in Figure S2A, i.e. we take here the ψ value at r=1 for the 0.1 mM Ca_{JSR} curve (red line).
Int0.5toInf $= \int_{r>.5} \psi(r)dr$. The integral is calculated for interaction profile *ψ(r),* that is the red line in Figure S2A. The integral is taken from r=0.5 to infinity (to the end of the grid, that is 4.33 in our case).

SpaceInt=*2*π*int0.5toInf/ψ(U)*. This is the normalized 2d integral in Equation [10] of the supplement.
γ: independent variable here, it varies from 0.02 to 0.15 1/μM.
β=*ψ(U)* **γ*/4, i.e. Equation 9b in the supplement.
λ=*C*exp*(-2**β**SpaceInt). This is the solution of the Equation [10] in the supplement for h=0. Each λ value was calculated for each γ (independent variable).

$$h = \frac{1}{2\beta}\ln\left(\frac{\lambda}{C}\right) + 2\pi\int_{r>.5}\phi(r, Ca_{JSR})dr = \frac{1}{2\beta}\ln\left(\frac{\lambda}{C}\right) + SpaceInt = 0$$

extin time: Median extinction time for 100 sparks simulated with parameters in each row.
*h=ln(λ/C)/(2*β)+SpaceInt*: analog of magnetic field that must be 0. We calculated h just to make sure that it is indeed 0.

C	*CaJSR*	*ψ(U)*	*int0.5toInf*	*SpaceInt*	*γ*	*β*	*λ*	*extin time*	*h*
1/ms	mkM	mkM	mkM	NoDim	1/mkM	NoDim	ms-1	ms	NoDim
0.117	100	7.47087	15.1703	12.7586	0.02	0.0373544	4.51E-02	>10000	0
0.117	100	7.47087	15.1703	12.7586	0.03	0.0560315	2.80E-02	>10000	0
0.117	100	7.47087	15.1703	12.7586	0.04	0.0747087	1.74E-02	>10000	0
0.117	100	7.47087	15.1703	12.7586	0.05	0.0933859	1.08E-02	>10000	0
0.117	100	7.47087	15.1703	12.7586	0.053	0.098989	9.36E-03	>10000	0
0.117	100	7.47087	15.1703	12.7586	0.055	0.1027245	8.51E-03	7397.46	0
0.117	100	7.47087	15.1703	12.7586	0.058	0.1083276	7.37E-03	2473.98	0
0.117	100	7.47087	15.1703	12.7586	0.06	0.1120631	6.70E-03	1110.41	0
0.117	100	7.47087	15.1703	12.7586	0.07	0.1307402	4.16E-03	188.308	0
0.117	100	7.47087	15.1703	12.7586	0.08	0.1494174	2.58E-03	97.4777	0
0.117	100	7.47087	15.1703	12.7586	0.09	0.1680946	1.60E-03	78.6526	0
0.117	100	7.47087	15.1703	12.7586	0.1	0.1867718	9.96E-04	69.4714	0
0.117	100	7.47087	15.1703	12.7586	0.11	0.2054489	6.19E-04	no data	0
0.117	100	7.47087	15.1703	12.7586	0.12	0.2241261	3.84E-04	no data	0
0.117	100	7.47087	15.1703	12.7586	0.13	0.2428033	2.38E-04	no data	0
0.117	100	7.47087	15.1703	12.7586	0.14	0.2614805	1.48E-04	no data	0
0.117	100	7.47087	15.1703	12.7586	0.15	0.2801576	9.19E-05	56.0243	0

Table S4 – Values of *h* for the results in Figure 3 (main text).

JSR [Ca], mM	*h*
0.0125	-100
0.025	-44
0.0375	-25
0.044	-20
0.05	-16
0.0625	-10
0.075	-7
0.1	-2

Supporting Material Reference List

1. Maltsev, A.V., V.A. Maltsev, and M.D. Stern. 2017. Clusters of Ca release channels harness the Ising phase transition to confine their elementary intracellular signals. Proc Natl Acad Sci U S A 114:7525–7530.
2. Levin, D.A., Y. Peres, and E.L. Wilmer. 2008. Markov Chains and Mixing Times. American Mathematical Society.
3. Martinelli, F. 1999. Lectures on Glauber Dynamics for Discrete Spin Models. *In* Lectures on Probability Theory and Statistics. Bernard P, editor. Springer-Verlag, Berlin Heidelberg.
4. Evans, M. Lecture Notes. Section 11: Exact results for the Ising Model https://www2.ph.ed.ac.uk/~mevans/sp/sp10.pdf.
5. Baxter, R.J. 1989. Exactly Solved Models in Statistical Mechanics. Academic Press.
6. Stern, M.D., E. Rios, and V.A. Maltsev. 2013. Life and death of a cardiac Ca spark. J Gen Physiol 142:257-274.
7. Laver, D.R., C.H. Kong, M.S. Imtiaz, and M.B. Cannell. 2013. Termination of Ca-induced Ca release by induction decay: an emergent property of stochastic channel gating and molecular scale architecture. J Mol Cell Cardiol 54:98-100.