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L f a af f SR Ca^{2+} e ea e

A crucial element in modeling EC coupling is the mechanism which luminal Ca^{2+} controls release. In the hiferaw model, it was assumed that the amount of Ca^{2+} release is a phenomenological nonlinear function of the Ca^{2+} load which ecomes steep for high loads (8). he origin of this nonlinear relationship, however, is not well understood. Calcium release from the is regulated the r anodine receptors (s), which open upon a rise in the local c tosolic Ca^{2+} concentration (14). here is a growing od of experimental evidence showing that luminal Ca^{2+} regulates the sensitivit of the s the interaction of auxiliar proteins (triadin-1/junctin, /J) with the luminal Ca^{2+} uffer calsequestrin (C N) (e.g., (15 17)). In particular, G orke the e uations and mode arameters is given in the A endi . In E ementar Ca^{2+} e ease nit tructure we descri e the intrace u ar com artments and the various currents in our mode . In Ce Architecture we rie descri e the geometr of ventricu ar m oc tes, which we use to rea istica im- ement our s atia e tended mode . Fina , in the su - sections Lumina Gating and Lumina Buffering we resent a new mathematica formu ation of C N-mediated umina gating and uffering that takes into account the transition from monomeric to dimeric forms of C N with increasing u- mina free Ca^{2+} concentration.

E e a Ca^{2+} e ea e c e

E citation-contraction cou ing, the rocess which cardiac m oc tes transform the mem rane de o ari ation signa into ce contraction, is a com e rocess that s ans mu ti e sca es (44,45). Ca cium ions (Ca^{2+}) enter the ce u on mem rane de o ari ation, triggering discrete Ca^{2+} re ease events at the e ementar C s of the , an intrace u ar store whose rimar function is the se uestration and re ease of intrace u ar Ca^{2+}. hese Ca^{2+} s arks (46,47) are high o- ca i ed in s ace ($\sim$1 μm) and time ($\sim$20 ms). he is a sac- ike structure which forms a s atia dense network of interconnected tu es and cisternae. he tu u ar network is usua referred to as network (N), whi e the cisternae are referred to as junctiona (J). hese cisternae are oca i ed in c ose ro imit to the -tu u es, ce mem rane invaginations that form a so a dense structure in ventricu ar m oc tes (48). he cisternae are usua ca ed d ads, and the s ace etween a d ad and the sarco emma is referred to as the number of LCC channels per dyad would result in a more heterogeneous I_{Ca} current amplitude per C , since different numbers of channels could open within some narrow time

$$k_{41} \quad \tau_u^{\ 1}. \tag{9}$$

where τ_u and τ are the characteristic un inding (s ow) and inding (fast) times, and $B^0_{C \quad N}$ 400 μM is the norma C N concentration and guarantees that $k_{14} \to \tau^{\ 1}$ for ow c_J . e wi choose these constants ased on e erimenta measured s ark restitution curves. he transition rate from the o en C N-un ound to the o en C N- ound state is taken to e the same as the one from the c osed C N-un ound to the c osed C N- ound state, k_{23} k_{14}. Fina , to satisf detai ed a ance, $k_{12}k_{23}k_{34}k_{41}$ $k_{14}k_{43}k_{32}k_{21}$, we set the transition rate from the o en C N- ound to the o en C N-un ound to e

$$k_{32} \quad k_{41}k_{12}/k_{43}. \tag{10}$$

he va ue of the arameters can e found ater in a e 10 and further detai s can e found in the A endi .

e wi mode each d ad as having 100 channe s. Each channe evo ves stochastica , inde endent of the other channe s in the d ad. However, to avoid kee ing track of the ∼20,000 × 100 channe s in the m oc te, we on kee track in each d ad of the num er of channe s that are in each of the four states. As descri ed in the A endi , these num ers can e u dated in each time-ste in a wa that is e uiva ent to individua evo ving each channe . herefore we are a e to s eed u the simu ations a factor of ∼20 (from 100 s and four L-t e channe s to the num er of channe s er state and four L-t e channe s).

A crucia feature of the mode descri ed a ove is that the transition rate from the C N-un ound to the C N- ound states de ends d namica on the umina Ca^{2+} concentration through the de endence of the monomer concentration [M] on c_J . In Fig. 2 b we ot the fraction of monomers $\hat{M}$ (

of C N- ound channe s increases. hese channe s have a ower o en ro a i it , and therefore the s ark terminates short thereafter. u se uent , the J re s, and eventua the umina Ca^{2+} concentration ecomes high enough that the concentration of monomers decreases. C N unbinds from the /J com e of the channe s, and the d ad

of Fig. 7 we plot the averaged cytosolic Ca^{2+} concentration c_i (Eq. 1) as a function of time for a pacing period of $T = 220$ ms. In the bottom panel we show the proximal space Ca^{2+} concentration c_p as a function of time for a transversal line of dyads across the myocyte, indexed in the vertical axis. This panel shows that, even though there is well-defined whole cell CA, individual dyads do not necessarily reflect this, since, in the time interval shown, there are some dyads firing only in the beats with large c_i, some firing every beat, and some firing irregularly, examples of which are indicated with the horizontal arrows and marked as a, b, and c, respectively. The vertical arrows in the top panel indicate the time of pacing. In Fig. 8 a we show the maximum values of the averaged Ca^{2+} cytosolic concentration during steady state pacing for different pacing periods. A bifurcation to CA appears when the pacing period is decreased at $<$

deve o ment of a ternans. Inserting these e ressions in E . 22 and ineari ing, we o tain

$$\begin{pmatrix} \delta \mathsf{I}_{n+1} \\ \delta \mathsf{f}_{n+1} \end{pmatrix} \quad \begin{pmatrix} 1 \quad \partial \mathsf{R}) \ 1+\partial \mathsf{U}) & \partial_{\mathrm{f}}\mathsf{R} \ 1+\partial \mathsf{U}) \\ \partial \mathsf{g} \ 1 \quad \partial \mathsf{R}) \ \mathsf{e}^{\quad /\tau_{\mathrm{u}}} & \partial \mathsf{g} \partial_{\mathrm{f}} \mathsf{R} \mathsf{e}^{\quad /\tau_{\mathrm{u}}} \end{pmatrix} \begin{pmatrix} \delta \mathsf{I}_{n} \\ \delta \mathsf{f}_{n} \end{pmatrix}, \tag{23}$$

where the derivatives are eva uated at the va ues I, f. he condition for a ternating growth of the ertur ations is that the eigenva ue of the matri in E . 23 with the argest magnitude is $<\ 1$ (for a ternans, this eigenva ue is negative). his condition resu ts in that a ternans deve o when

$$1 + \partial \mathsf{U}) \quad \partial \mathsf{R} \quad 1) \ + \partial_{\mathrm{f}} \mathsf{R} \partial \mathsf{g} \mathsf{e}^{\quad /\tau_{\mathrm{u}}} > 1. \tag{24}$$

his E uation is the ke to understanding the re ative contri- utions of stee re ease- oad re ationshi , u take, and recover of C N- ound channe s. If we can neg ect C N-mediated effects, $\partial_{\mathrm{f}} \mathsf{R} \quad 0$, $\partial \mathsf{g} \quad 0$, or $\tau_{\mathrm{u}} \ll \mathsf{T}$

u ator of activit , which a ows us to investigate the ro e
of C N in romoting C A. In Fig. 11 c we show the ma -

num er of avai a e channe s, and vice versa. However, when the u take is enough to reduce or e iminate the de en-dence of the diasto ic content on the num er of avai a e channe s in the revious eat, one can o serve C A without signi cant a ternations in diasto ic Ca^{2+} content as in Fig. 8 c.

Another im ortant feature of our mode is that, for the rst time, it simu ates a rea istic num er (~20,000) of diffusive cou ed, h sio ogica detai ed e ementar re ease units, where each unit has a rea istic (~100) num er of

Dff f a ace be b a e

rohi itive, since diffusive cou ing etween adjacent C s re uires the simu taneous rocessing of gating d namics. o reduce the com utation time to reasona e eve s, we do not simu ate each individua channe in a given C , ut rather kee track of the num er of channe s in a given C that are in each state. he num er of states in the n^{th} d ad in the o en C N- ound (3), o en C N-un ound (2), and c osed C N-un ound (1) are denoted $x_3^{n)}$, $x_2^{n)}$, and $x_1^{n)}$, res ective (the num er of s in the c osed C N- ound state is $x_4^{n)}$ 100 $x_1^{n)}$ $x_2^{n)}$ $x_3^{n)}$.) Henceforth we wi omit the su erscri t (n). he re ease current I_r de ends on on the fraction of states in the o en states P_o $(x_2 + x_3)/100$, rather than on which articu ar channe s are in each state. herefore, at each time ste we on need to com ute the num er of channe s that make transitions from one state to another. ince we have the ro a i ities for the transition of an individua channe , the distri ution of the num er of channe s making a transition from state j can e o tained from a mu tinomia distri ution with the num er of tria s eing the num er of s in state j and the ro a i ities of success eing the ro a i ities of transition to another state given the e ressions in E . 55. e remark that, so far, this is an e uiva ent mathematica formu ation of the rocess that re uires, for the arge num er of channe s we consider, ess com utationa effort. Further a ro imations a ow us to increase the e cienc of the simu ation. In ractice, the ro a i ities of transition er unit time are sma and we can treat transitions to different states as inde endent. For e am e, if at time t there are x_1 channe s in the c osed un ound state, the ro a i it that x_{12} of these channe s makes a transition to the o en un ound state and x_{14} channe s make a transition to the c osed ound state in the time interva $[t, t + \Delta t)$ is

$$p\ x_1, x_{12}, x_{14}) \quad M\ x_1, k_{12}\Delta t, k_{14}\Delta t) , \qquad (56)$$

$$\approx B\ x_1, k$$

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