Ca e e [illegible] -Med a ed Me [illegible] f Ce a Ca c [illegible] T [illegible] e A e [illegible]

u a . ,[‡] a n . ı ,[†] a a ı a a n[*]

[*] [illegible]

[†] L a ı a u a a La a , a ı [illegible] L ,L , a ı a ,a [‡] a n

ı a a n ı , ı ı a , u , a

ı a u a a u n a ı a a ( ) a a ı ı a n ı , u ı ı ı ı [illegible]

Luminal control of SR Ca^{2+} release

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 equations and model parameters is given in the Appendi . In Elementar Ca^{2+} elease nit tructure we descri e the intracellular compartments and the various currents in our model. In Cell Architecture we rie descri e the geometr of ventricular m oc tes, which we use to realisticall implement our spatiall e tended model. Finall , in the su sections Luminal Gating and Luminal Buffering we present a new mathematical formulation of C N-mediated luminal gating and uffering that takes into account the transition from monomeric to dimeric forms of C N with increasing luminal free Ca^{2+} concentration.

Ele e ta Ca^{2+} e ea e ct e

E citation-contraction coupling, the process which cardiac m oc tes transform the mem rane depolari ation signal into cell contraction, is a comple process that spans multiple scales (44,45). Calcium ions (Ca^{2+}) enter the cell upon mem rane depolari ation, triggering discrete Ca^{2+} release events at the elementar C s of the , an intracellular store whose primar function is the sequestration and release of intracellular Ca^{2+}. hese Ca^{2+} sparks (46,47) are highl locali ed in space ($\sim$1 μm) and time ($\sim$20 ms). he is a saclike structure which forms a spatiall dense network of interconnected tu ules and cisternae. he tu ular network is usuall referred to as network (N), while the cisternae are referred to as junctional (J). hese cisternae are locali ed in close pro imit to the -tu ules, cell mem rane invaginations that form also a dense structure in ventricular m oc tes (48). he cisternae are usuall called d ads, and the space etween a d ad and the sarcolemma is referred to as the

num er of LCC channe s er d ad wou d resu t in a more heterogeneous I_{Ca} current am itude er C , since different num ers of channe s cou d o en 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 eventu- a the umina Ca^{2+} concentration ecomes high enough that the concentration of monomers decreases. C N un- inds 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. 8a 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 $<$

development of alternans. Inserting these expressions in Eq. 22 and linearizing, we obtain

$$\begin{pmatrix} \delta I_{n+1} \\ \delta f_{n+1} \end{pmatrix} \quad \begin{pmatrix} 1 \quad \partial R) \quad 1+\partial U) & \partial_f R \quad 1+\partial U) \\ \partial g \quad 1 \quad \partial R) \; e \quad {}^{/\tau_u} & \partial g \partial_f R e \quad {}^{/\tau_u} \end{pmatrix} \begin{pmatrix} \delta I_n \\ \delta f_n \end{pmatrix}, \tag{23}$$

where the derivatives are evaluated at the values I, f. The condition for alternating growth of the perturbations is that the eigenvalue of the matrix in Eq. 23 with the largest magnitude is $<$ 1 (for alternans, this eigenvalue is negative). This condition results in that alternans develop when

$$1+\partial U) \quad \partial R \quad 1) \; + \partial_f R \partial g e \quad {}^{/\tau_u} > 1. \tag{24}$$

This equation is the key to understanding the relative contributions of steep release-load relationship, uptake, and recovery of C N-ound channels. If we can neglect C N-mediated effects, $\partial_f R \quad 0$, $\partial g \quad 0$, or $\tau_u \ll T$

ụ ator of activit , which aụ ows us to investigate the rọ e
of C N in romoting C A. In Fig. 11 C we show the ma -

number of available channels, and vice versa. However, when the uptake is enough to reduce or eliminate the dependence of the diastolic content on the number of available channels in the previous beat, one can observe C A without significant alternations in diastolic Ca^{2+} content as in Fig. 8 c.

Another important feature of our model is that, for the first time, it simulates a realistic number ($\sim$20,000) of diffusively coupled, physiologically detailed elementary release units, where each unit has a realistic ($\sim$100) number of

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 nth 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 ef 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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