**APPENDIX A**

Anomalous space subdiffusion in the spatial reaction-diffusion model is defined though the relations (Metzler and Klafter, 2000)

 (A1)

 (A2)

where  denotes the Gamma function.

Ca2+ fluxes in Equation (1) can all be defined as:

 (A3)

 (A4)

 (A5)

 (A6)

where the subscript ‘n’ refers to each buffer in the cytoplasm, the superscript ‘h’ refers to the Hill constant;  and  represent the total concentrations of the indicator and buffers, respectively.  and  are the concentrations of Ca2+-bound complexes; ，， and  are the reaction kinetic parameters.  is the affinity constant, and  is the maximum rate for SR pumps. Values of the parameters are based on a previous study (Chen et al., 2013). Moreover,  and  are the Ca2+ fluxes released by the CRUs of rogue and clustered RyRs respectively, which can be written as:

  (A7)

  (A8)

where  is the Dirac delta function and  is a stochastic function for the opening of CRUs,  and are the positions of CRUs of rogue RyRs and clustered RyRs in the 2D plane respectively. The release time for rogue and clustered RyRs are defined as = 20 ms (Brochet et al., 2011) and = 10 ms (Smith et al., 1998). The equivalent source strength of rogue RyRs and clustered RyRs (Li et al., 2017), which are used to adjust the Ca2+ molar flux of the line source to a point source, are expressed by

 (A9)

**** (A10)

where the Faraday constant  is 96500 C·mol-1.  and  are the average currents through rogue and clustered RyRs. In general, currents for modeling Ca2+ waves are larger than that under normal physiological conditions (Izu et al., 2001; Chen et al., 2013). So  and  are set to be 0.15 pA/mM and 1.5 pA/mM, about twice normal physiological currents of CRUs (0.07 pA/mM and 0.7 pA/mM (Li et al., 2017)). The value 0.64 in Equations (A9) and (A10) is the conversion factor, which is used to give the identical Ca2+ distribution in 2D because Ca2+ are released from the JSR lumen into a 3D volume (Izu et al., 2001).

**APPENDIX B**

Decreased Ca2+ release flux caused by the opening of CRUs in a JSR is denoted by

 . (B1)

The Ca2+ flux due to the buffer in the JSR lumen is

  (B2)

where  represents the total concentration of calsequestrin.  is the concentration of Ca2+-bound complexes in the JSR;  and  are the reaction kinetic parameters of calsequestrin. These parameters are listed in Table 1.

The refilled Ca2+ flux  is expressed by

 **** (B3)

where free Ca2+ concentration in network sarcoplasmic reticulum (NSR) [Ca2+]NSR is 1.0 mM, time constant for Ca2+ transfer between JSR and NSR  is 10 ms, and the volume of a JSR lumen is 1×10-11 μL (Sobie et al., 2004). The beginning level of [Ca2+]lumen is 1.0 mM.

**APPENDIX C**

According to the coupled RyR gating model (Zahradnikova et al., 2010),  can be expressed as:

**** (C1)

where , a function of [Ca2+]cyto, is the firing probability per unit time of a single RyR channel.  is the RyR number in a CRU for rogue (= 3) or clustered (= 22) RyRs. Here,  is written as:

**** (C2)

where  is an empirical power function corresponded to [Ca2+]lumen and given in Walker et al.’s model (Walker et al., 2014), *m* is the regulation coefficient for rogue (*m* = 1) or clustered (*m* = 10) RyRs.

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