**Parameter estimation**

We have used experimental data, the 20 mM-caffeine induced [Ca2+]i responses, which are reported in Fig 2 of this manuscript, to estimate some of the parameters that have been used to solve the present mathematical model. While the rest of the parameters were empirically estimated by searching for those values that allow the model to best reproduce the same experimental data (Fig 2). Below, you can find a detailed description on how these parameter values were estimated.

*  Being directly related to those pumps present at the plasma membrane that remove the excess of Ca2+ from the cytoplasm, this parameter largely determines the speed of the decay phase in the caffeine-induced Ca2+ response. The value that best agrees with our experimental results is



*  This parameter is very sensitive to the time at which caffeine-induced Ca2+ response has reached maximum value. The number selected was the one that best allowed to reproduce the rate of rise vs. rise time graph shown in Fig 2B is:



*  This parameter determines the rate of SR refilling with Ca2+ after caffeine-induced Ca2+ release based on data shown in Fig 2C. The final value was obtained by fitting data shown Fig 2:



*  This is the basal concentration of free cytoplasmic Ca2+ which has been experimentally measured in the range  [1]. Here we have taken



*  The ratio of volume between SR and cytoplasm has been found to take values in the following approximated range [2]:



*  The scaling coefficient that allows the model to best reproduce the cell-variability experiments (in particular the rate of rise vs. rise time graph shown in Fig 2B) is:



*  The values for half saturation with Ca2+ and the Hill coefficient for SERCA pumps were taken from [3]:



*  This parameter represents the Ca2+buffering capacity of the cytoplasm and it has been shown that  *β* has a constant value in the physiological range of [Ca2+]i responses in smooth muscle as reported in [4]. Although the *β* value experimentally determined showed large variability among different cells, we have arbitrarily taken this value:



*  These parameters that shape the RyR open-probability function were empirically estimated so the model fits cell-variability experimental results (that is the rate or rise vs Δ[Ca2+]i response graph shown in Fig 2A):



*  This parameter, also involved in the definition of the open-probability function of RyR was computed in terms of other parameters in the model in order to comply with the idea that the resting values for both [Ca2+]i and [Ca2+]FSR should satisfy [5]:



Since in the steady state  this parameter is calculated by solving for KC in such equality, after substituting   and 

*  This parameter represents the affinity of the luminal SR Ca2+ binding proteins and the selected value allowed us to reproduce both phase 1during Ca2+ release (Fig 6) and the fast recovery of the [Ca2+]FSR (Fig 7):



*  Represents the number of Ca2+ binding sites in the absence of Ca2+. This parameter value was calculated assuming an SR luminal Ca2+ buffering capacity of approximately 10 [6]. In other words that . Thus, in the KonD situation we have that



while in the standard kinetics  is calculated as



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