Text S2: Stochastic simulation method

In non-equilibrium simulations we have coupled the gating transitions to the evolution of Ca$^{2+}$ concentration $c$. At each time step we first determine the number of open channels $n$. A channel is considered open if at least three of its four subunits are in the open state. Using Eqs. 3-5 we then compute the Ca$^{2+}$ concentrations at open ($c = c_o$) and closed channels (Eqs. 4 and 5). For subunits that belong to open or closed channels, the respective $c$ values are then inserted into the transition rates to obtain the propensities $a_i$ for each subunit transition. For instance, a subunit in the state 110 that belongs to an open channel acquires the propensity $a_i = a_2 c = a_2 c_o$ for a transition to the inhibited state 111. As simple implementation of the stochastic algorithm one computes products of $a_i$ and a small time step $\tau$ (=10$^{-6}$ s in our simulations), which provides the probability that the transition occurs in the given time step. If $a_i \tau$ is larger then a random number drawn from a uniform distribution in [0, 1] the transition is executed.