

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 ($c = c_s$) 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 $a_i = a_2c = a_2c_s$ 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 τ ($=10^{-6}$ s in our simulations), which provides the probability that the transition occurs in the given time step. If $a_i\tau$ is larger than a random number drawn from a uniform distribution in $[0, 1]$ the transition is executed.