Delayed afterdepolarizations generate both triggers and a vulnerable substrate promoting reentry in cardiac tissue

Michael B Liu; Enno de Lange; Alan Garfinkel; James N Weiss; Zhilin Qu

Supplemental Materials

Supplemental Methods

Simulations were carried out in 1D cable and 2D tissue models. The partial differential equation governing voltage for the 1D cable is

$$\frac{\partial V}{\partial t} = -I_{ion}/C_m + D\frac{\partial^2 V}{\partial x^2} \qquad (1)$$

Where V is the membrane voltage, C_m=1 μF/cm^2 is the membrane capacitance, D is the diffusion constant (proportional to gap junction conductance) with its control value set as 0.0005 cm^2/ms. For 2D tissue, the equation for voltage is

$$\frac{\partial V}{\partial t} = -I_{ion}/C_m + D(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}) \qquad (2)$$

The AP model and generation of DADs were described previously by Xie et al [24]. A spontaneous Ca release flux was formulated as $J_{spon}=g_{spon}g_1g_2(\beta c_j-c_s)$, where g_{spon} is the maximum conductance, β is the sub-membrane space/SR volume ratio, c_j and c_s are the Ca concentrations in the junctional SR and sub-membrane space, respectively. g_1 and g_2 are sigmoidal functions of time formulated as $g_1=1/(1+\exp(-(t-t_0)/\tau_1))$ and $g_2=1/(1+\exp((t-t_0)/\tau_2))$, where τ_1=10 ms and τ_2=30 ms, and t_0 determines the timing (latency) of the DAD. For suprathreshold DADs, J_{spon} was turned off at the onset of the TA upstroke and the L-type Ca current caused the SR Ca release during the TA as in a normal AP. For random latency, we used a Gaussian distribution as:

$$p(t_0) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(t_0-\bar{t}_0)^2/2\sigma^2} \qquad (3)$$

In the simulations, unless specified the maximum Na channel conductance (g_{Na}) was 12 pA/pF and the Na channel steady-state inactivation curve (h_∞) was left-shifted 5 mV, i.e., the $V_{1/2}$ was changed from -66 mV to -71 mV. Fig.1A shows example traces of DADs and TA for different g_{spon} values and Fig.1B shows the maximum voltage versus g_{spon}. The threshold for suprathreshold DADs or TA in a single cell is g_{spon}=0.066 ms^{-1} (arrow in Fig.1B) without the shift of h_∞ but with a 5 mV left-shift, it becomes 0.0695 ms^{-1}(dashed line in Fig.2C).

Numerical simulations were carried out in workstations using computing graphics processing units (Tesla K20c, NVIDIA Corporation). $\Delta x=\Delta y$=0.015 cm, and an operator splitting and time adaptive algorithm [25] was used with time step (Δt) varying between 0.01 ms and 0.1 ms.

Supplemental Results

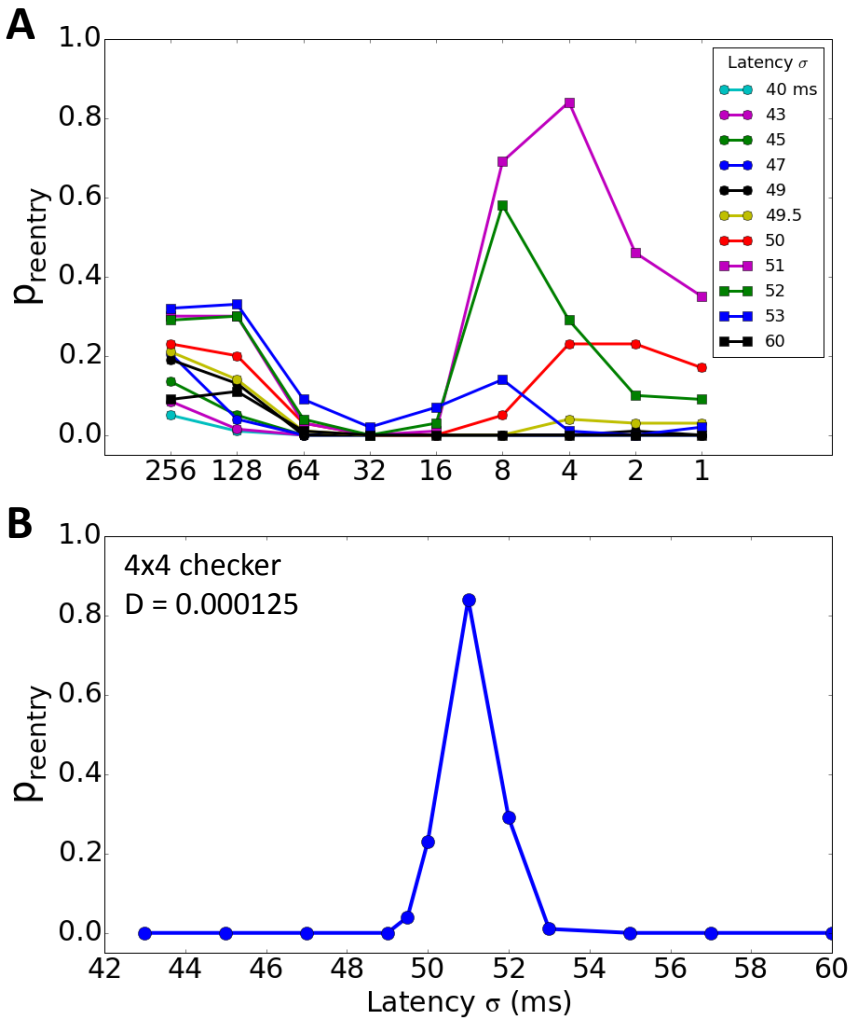

Figure S1. Reentry dependence on DAD latency distribution.
A. Probability of reentry versus checker size for different DAD latency standard deviations (σ). There is a different optimal σ for reentry at each checker size, which is related to TA propagation and subthreshold DAD formation. When TA propagation is too difficult, there will be no suprathreshold DADs to trigger reentry; when TA propagation is too easy, there will be no subthreshold DADs to provide a substrate for reentry. A mixture is required for reentry, resulting in an optimal value.
B. Probability of reentry versus latency standard deviation (σ) for a single checker size of 4x4 cells. There is a narrow optimal range at this checker size for reentry.