

## [A Small Number of Cells is Sufficient to Trigger a Cardiac Arrhythmia: Stochastic Computational Studies](#)

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Cardiovascular disease is the leading cause of death world-wide and this is due in large part to arrhythmias. Here we examine the cellular and subcellular basis of  $\text{Ca}^{2+}$  dependent arrhythmias. In order to understand how calcium dynamics, plays a role in arrhythmogenesis, we have investigated normal and dysfunctional  $\text{Ca}^{2+}$  signaling in heart cells at high temporal and spatial resolution. Spontaneous calcium release occurs normally as  $\text{Ca}^{2+}$  sparks. When RyR2 open probability increases to a high level, then  $\text{Ca}^{2+}$  sparks can activate  $\text{Ca}^{2+}$  waves. These propagating elevations of  $[\text{Ca}^{2+}]_i$  can activate inward NCX current (INCX) that may contribute to early after-depolarization (EADs) and underlie delayed after-depolarization (DADs).

However, how cellular currents lead to full depolarizations of the myocardium and how they initiate extra systoles is still not fully understood. Some earlier studies that have investigated this question suggest that as many as about  $\sim 700,000$  cells must undergo such behavior to initiate a propagating action potential or an arrhythmia. Here we present the results of our study which explores how many cells must be entrained to initiate arrhythmogenic depolarizations in “realistic” computational models. The model presented here suggests that only a small number of cells must activate in order to trigger an arrhythmogenic propagating action potential. These conditions were examined in 1D, 2D, and 3D taking into account heart geometry. The finding that only a small number of cells is required to trigger an arrhythmia provides a plausible mechanism by which cardiac arrhythmias might occur.