CellExcite: A tool for simulating in-silico Excitable Cell

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Motivation

The rhythmic, pump-like function of the heart is driven by muscle contractions, which are in turn triggered by cell-generated electrical signals (excitations). Of special interest are cardiac arrhythmias: disruptions of the normal excitation process due to faulty processes at the cellular level, single ion-channel level, or at the level of cell-to-cell communication. The clinical manifestation is a rhythm with altered frequency (tachycardia or bradycardia) or the appearance of multiple frequencies (polymorphic Ventricular Tachycardia) with subsequent deterioration to a chaotic signal (Ventricular Fibrillation). VF is a typically fatal condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart. As a result, the heart fails to adequately pump the blood, and hypoxia may occur. In order to analyze and simulate these biological phenomena, we have developed CellExcite a sophisticated simulation environment for excitable-cell networks. As Figure 1 and Figure 2 illustrate, CellExcite allows the user to sketch a tissue of excitable cells, plan the stimuli to be applied during simulation, and customize the diffusion model.

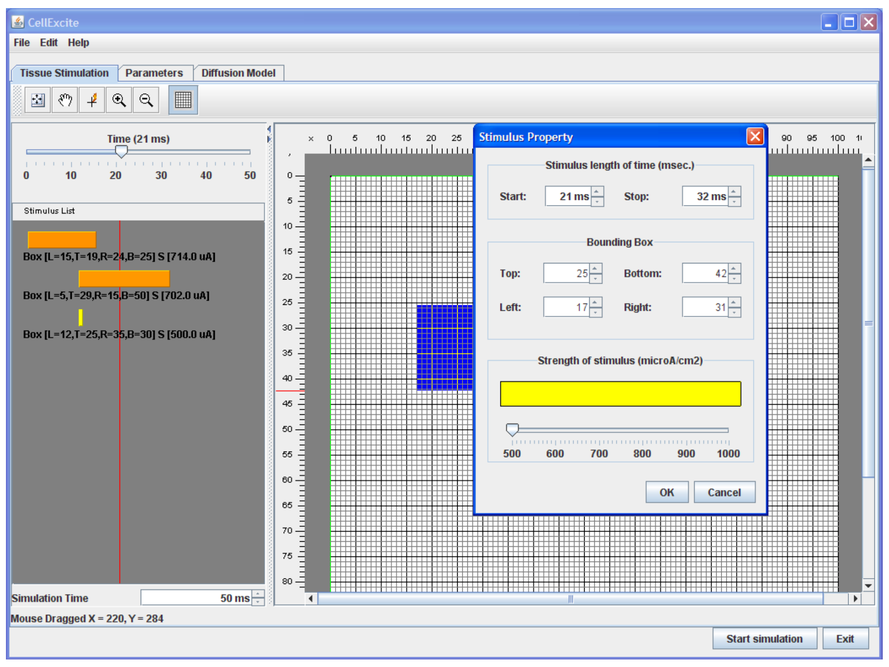

Fig. 1 - CellExcite Tissue Panel

Methods

Brain, heart and skeletal muscle share similar properties of excitable tissue, featuring both discrete behavior (all-or-nothing response to electrical activation) and continuous behavior (recovery to rest follows a temporal path, determined by multiple competing ion flows). Classical mathematical models of excitable cells involve complex systems of nonlinear differential equations. Such models not only impair formal analysis but also impose high computational demands on simulations, especially in large-scale 2-D and 3-D cell networks. CellExcite adopts Hybrid Automata (HA) as computational model to efficiently capture both discrete and continuous behavior of an excitable cell. HA, which combine discrete transition graphs with continuous dynamics, can be naturally used to obtain a piecewise, possibly linear, approximation of a nonlinear excitable-cell model. In particular a 4-state HA model, shown in Figure 3, has been developed for several representative excitable cells. These much simpler HA models are able to successfully capture the action-potential morphology of the different cells, as well as reproduce typical excitable cell characteristics, such as refractoriness (period of non-responsiveness to external stimulation) and restitution (adaptation to pacing rates). The single-cell HA models are linked in a multicellular HA array –Figure 4- and an efficient diffusion model is used to simulate the electrical wave propagation. Such simulations facilitate comprehension of the spatiotemporal behavior of electrical waves in a cardiac tissue, including complex spiralwaves underlying pathological conditions in the heart.

Fig. 2 - CellExcite Diffusion Model: Square Grid (left) and Triangular Grid (right)

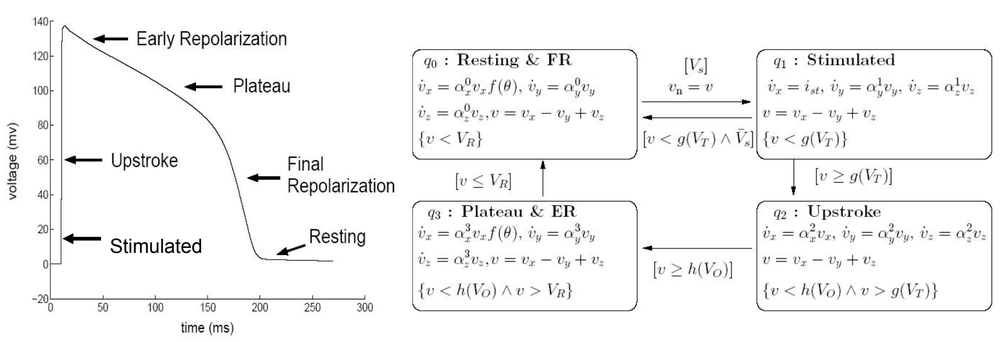

Fig. 3 – The behaviour of a single cell (left) is described by a 4-state Hybrid Automata (right)

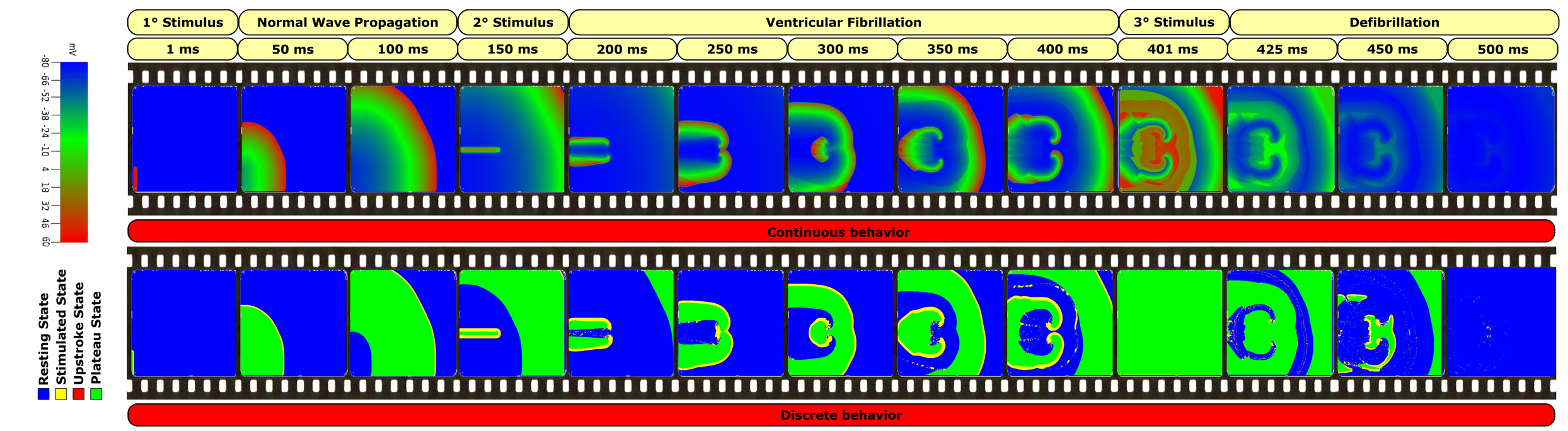

Fig. 4 – In-silico experiment using CellExcite. On the top is shown the continuous behaviour of the multicellular HA representing the tissue while on the bottom is shown its discrete behaviour

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