

# Dynamics of induced spontaneous electrical activity of cardiomyocytes connected by gap junctions

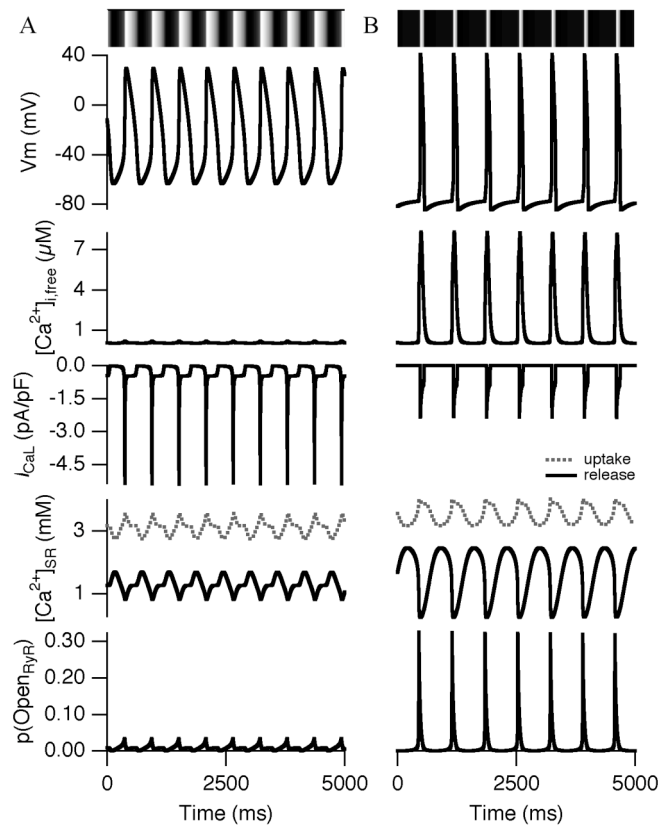
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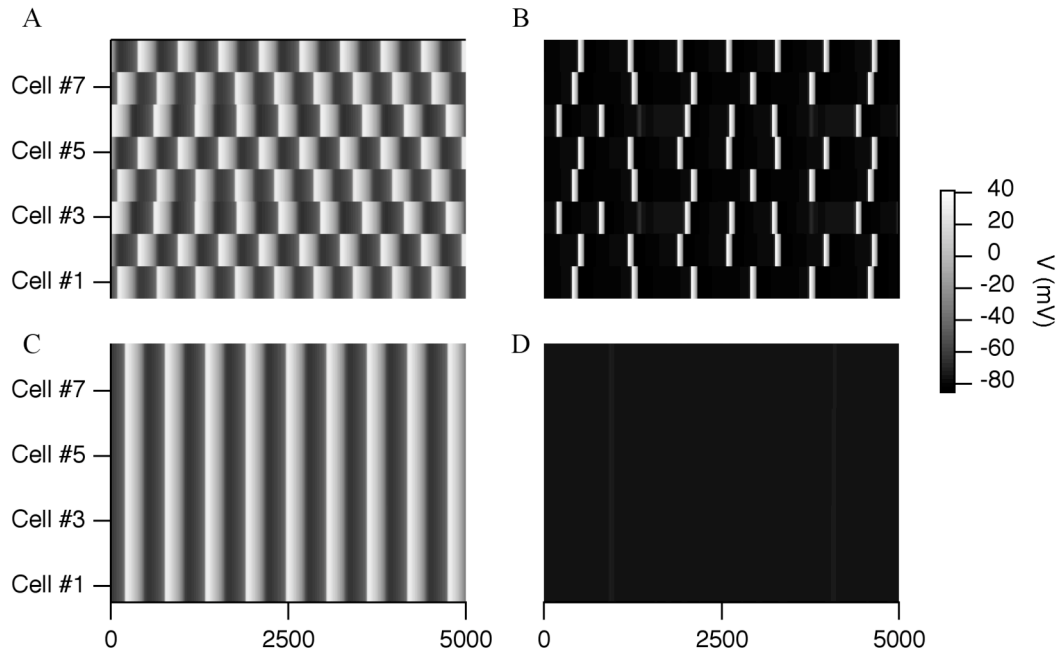
## Abstract

The heartbeat is initiated from a specialized region known as the sinoatrial (SA) node, where an electric impulse is spontaneously generated. The failure of impulse generation often results in cardiac rhythm disorders, so a variety of approaches, including gene therapy strategies, to create an artificial biological pacemaker from quiescent myocardium have been proposed. The growing interest in the details of the mechanism underlying the regeneration of the impulse has inspired the simulation of the electrical activity of an artificial biological pacemaker, to give a quantitative description of the pulse generation at the single cell level. In light of a recent report that tissue heterogeneity of the SA node is an important aspect in the stable generation of the impulse, assessment of the spontaneous pulse generation at the myocardium level is a prerequisite. This study demonstrates the dynamics underlying the spontaneous electrical activities of cardiomyocytes, as induced via two different gene therapy strategies: suppression of inward rectifying  $K^+$  current ( $I_{K1}$ ) and introduction of hyperpolarization-activated cation current ( $I_{ha}$ ). Simulation with a single ventricular cell model showed that both strategies are able to induce spontaneous electrical activity from an electrically quiescent cell. The single-cell model was expanded to a heterologous, one-dimensional (1D) cable model consisting of eight cells electrically connected by gap junction channels, in which the heterology of the fiber was represented by varying the  $I_{K1}$  or  $I_{ha}$  properties of individual cells. Simulation with the 1D cable model demonstrated that desynchronized spontaneous electrical activity was synchronized in the  $I_{K1}$ -suppressed heterologous cardiac fiber. On the other hand, the  $I_{ha}$ -introduced heterologous cardiac fiber lost its automaticity owing to closure of  $Ca^{2+}$ -dependent gates

in gap junction channels by the accumulation of intracellular  $\text{Ca}^{2+}$  and differences between the membrane potentials of two adjacent cells, which canceled out the rapid depolarization of the membrane via the forward mode of  $\text{Na}^+/\text{Ca}^{2+}$  exchange. The 1D cable model will enable more in-depth assessment of different gene therapy strategies, especially in terms of tissue heterogeneity, and thus will provide a conceptual framework for designing stable, artificial, biological pacemakers.



**Figure 1. Spontaneous electrical activities induced by suppression of  $I_{K1}$  (A) and introduction of  $I_{ha}$  (B) to the single ventricular cell model.** Dynamic changes in membrane potential ( $V_m$ ) are indicated by the gray scale on top.  $[\text{Ca}^{2+}]_{i,\text{free}}$ , changes in intracellular  $\text{Ca}^{2+}$  concentration;  $I_{\text{CaL}}$ , L-type  $\text{Ca}^{2+}$  current;  $[\text{Ca}^{2+}]_{\text{SR}}$ ,  $\text{Ca}^{2+}$  concentration in sarcoplasmic reticulum (SR);  $p(\text{Open}_{\text{RyR}})$ , fraction of ryanodine receptor (RyR) channels open. The spontaneous action potential is fired via activation of  $I_{\text{CaL}}$  in the  $I_{K1}$ -suppressed ventricular cell and of  $I_{\text{Na}}$  in the  $I_{ha}$ -introduced ventricular cell. Introduction of  $I_{ha}$  to a single ventricular cell causes accumulation of  $[\text{Na}^+]_i$  during diastolic slow depolarization phase, which eventually leads to a gradual increase in  $[\text{Ca}^{2+}]_{i,\text{free}}$  due to reversal of  $\text{Na}^+/\text{Ca}^{2+}$  exchange. The gradual increase in  $[\text{Ca}^{2+}]_{i,\text{free}}$  causes accumulation of  $\text{Ca}^{2+}$  on the SR, leading to opening of the RyR channel, which also increases  $[\text{Ca}^{2+}]_{i,\text{free}}$ . The  $\text{Na}^+/\text{Ca}^{2+}$  exchange flips back to forward mode when  $[\text{Ca}^{2+}]_{i,\text{free}}$  reaches a certain level, contributing to depolarization of the membrane in addition to  $I_{ha}$ .



**Figure 2. Assessment of synchronized automaticity in heterologous cardiac tissue**

The  $I_{K1}$ -suppressed and  $I_{ha}$ -introduced models were expanded to the 1D cable model. To represent heterologous cardiac tissue, conductance amplitudes of  $I_{K1}$  or  $I_{ha}$  in cells 1, 4, and 7 were decreased by 10%, and in cells 3 and 6 were increased by 10%. The heterologous fiber models consisting of (A)  $I_{K1}$ -suppressed cells and (B)  $I_{ha}$ -introduced cells were first simulated without electrical connection between cells, as shown as gray-scale tracings of spontaneous electrical activities of each cell in the fiber. The models were then electrically connected via gap junctions. Results demonstrate (C) successful synchronization of spontaneous electrical activity in the heterologous fiber model comprising  $I_{K1}$ -suppressed heterologous cells and (D) disappearance of the spontaneous firing of action potential from the model comprising  $I_{ha}$ -introduced cells.