Induction of autorhythmicity in virtual ventricular myocytes and tissue

AP Benson[1], WC Tong[1], RH Clayton[2] and AV Holden[1]

[1] Computational Biology Laboratory, School of Biomedical Sciences, University of Leeds
[2] Department of Computing, University of Sheffield

Introduction

Pathological autorhythmicity in ventricular tissue can result in ventricular arrhythmias, and may have very different underlying causes.

It is well known that inhibition of the Na^+-K^+ pump, as seen during digoxin intoxication for example [1], can be arrhythmogenic, as it leads to elevated $[Na^+]_i$ which in turn causes $[Ca^{2+}]_i$ overload through the action of the Na^+-Ca^{2+} exchanger. The resulting $[Ca^{2+}]_i$ oscillations may interact with membrane potential [2] to cause autorhythmicity.

The time-independent K^+ current I_{K1} helps to maintain the resting membrane potential in ventricular myocytes, and suppresses autorhythmicity. Clinically, mutations in the channel subunits are implicated in LQT7, where patients may experience frequent episodes of ventricular arrhythmias [3]. Experimentally, down-regulation of I_{K1} has been shown to induce autorhythmicity in ventricular cells [4].

We modelled these two methods of inducing autorhythmicity in modified virtual ventricular cells and tissues of the Luo-Rudy (LRd00) family [5], and characterised the required conditions for the pathological tissues to initiate propagation into normal quiescent ventricular tissues.

Methods

LRd00 cell models are nonlinear, stiff, high–order ordinary differential equations that describe changes in membrane potential (V) in ventricular myocytes:

$$dV/dt = I_{ion}/C_m$$

where C_m = 1 μF/cm² is membrane capacitance and I_{ion} is the sum of trans-membrane ionic currents. Homogeneous one- (1-D) and two-dimensional (2-D) virtual ventricular tissues were constructed, with changes in V described by the partial differential equation:

$$\partial V/\partial t = D \cdot \Delta V - I_{ion}/C_m$$

where D = 0.06 mm²/ms[1] is a diffusion coefficient and Δ is a Laplacian operator. No-flux boundary conditions were used. For all simulations Δt = 0.002 ms and Δx = 0.2 mm.

$[Na^+]_i$ overload was simulated by block of the Na^+-K^+ pump in cells modified to favour $[Ca^{2+}]_i$ oscillations: two-fold increase of $I_{ns(Ca)}$ conductance, $[CSQN]_{th}$ = 7 mM, initial $[Na^+]_i$ = 20 mM and $[K^+]_i$ = 125 mM.

Down-regulation of I_{K1} was simulated by scaling the maximum conductance of the current (g_{K1}).

Results: $[Ca^{2+}]_i$ oscillations due to $[Na^+]_i$ overload

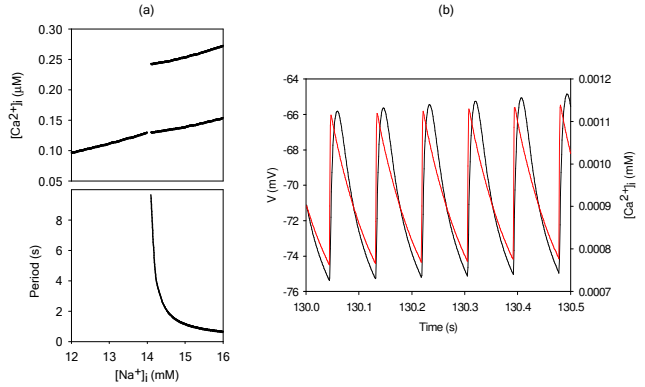

Figure 1: (a) Numerically traced bifurcation diagram (top) showing steady states and oscillation amplitudes of $[Ca^{2+}]_i$ in the voltage-clamped (dV/dt = 0 mV/ms, V = –80 mV) LRd00 calcium subsystem with $[Na^+]_i$ as the bifurcation parameter. The corresponding oscillation periods are also shown (bottom). Slow rate $[Ca^{2+}]_i$ oscillations emerge at a bifurcation when $[Na^+]_i \approx 14$ mM. As $[Na^+]_i$ is further increased to 16 mM, the oscillation period decreases to 0.65 s. **(b)** In a modified LRd00 endocardial cell these $[Ca^{2+}]_i$ oscillations (red line) drive sub-threshold voltage oscillations (black line) that lead to spontaneous action potentials.

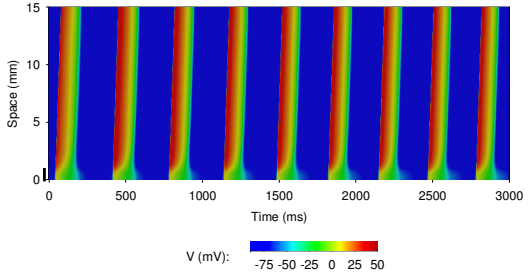

Figure 2: Space-time plot showing that, in a 1-D 15 mm endocardial virtual tissue strand, at least 0.8 mm of $[Na^+]_i$ overloaded tissue located on one border (indicated by the black bar on the ordinate) is required to produce repetitive propagation of spontaneous depolarisations into quiescent tissue. As no-flux boundary conditions are used, the liminal length is 1.6 mm. The same liminal length was found in strands composed of midmyocardial and epicardial tissue.

Results: Down-regulation of I_{K1}

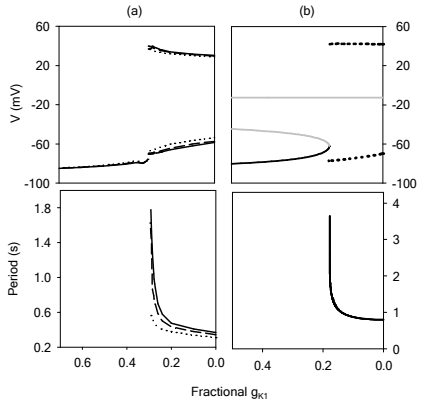

Figure 3: (a) Numerically traced bifurcation diagram (top) and the corresponding periods (bottom) for V in LRd00 cells with fractional g_{K1} as the bifurcation parameter: epicardial (solid line), M (dotted line) and endocardial (dashed line). For all cell types, as fractional g_{K1} reduces to ~ 0.3, large period oscillations emerge, which quickly decrease to 0.3 s (M cells) and 0.36 s (epicardial and endocardial cells). **(b)** The human ventricular cell model of ten Tusscher *et al.* [6] with constant ion concentrations shows qualitatively similar results. Top: bifurcation diagram showing stable (black) and unstable (grey) solutions generated with XPPAUT [7]. Bottom: the corresponding periods. Oscillations emerge at fractional $g_{K1} \approx 0.178$, much higher than the numerically computed value (~ 0.078) when dynamic ion concentrations are included. A period of 0.8 s with fractional g_{K1} = 0 is found in both cases.

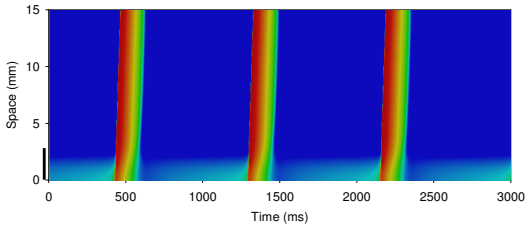

Figure 4: A minimum of 2.6 mm of I_{K1} down-regulated tissue (g_{K1} = 0, black bar) at one end of a 15 mm LRd00 epicardial strand is required to induce repetitive propagation into normal ventricular tissue. For voltage key see Figure 2. Due to no-flux conditions, the liminal length is 5.2 mm.

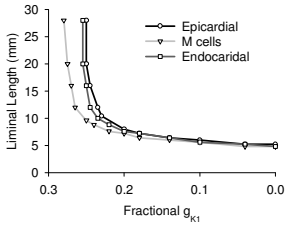

Figure 5: The liminal length for 1-D homogeneous tissues of all LRd00 cell types were very similar with > 80 % reduction of g_{K1}, but differences emerged when the fractional g_{K1} moved towards the bifurcation values of the single cells. For a 2-D homogeneous epicardial tissue with a circular area of I_{K1} down-regulated tissue (g_{K1} = 0), the liminal radius was 3.8 mm.

References

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Conclusions

- The large decrease in the period of the $[Ca^{2+}]_i$ and voltage oscillations close to their emergence at a bifurcation suggests homoclinic rather than Hopf bifurcations.
- A critical mass of abnormal ventricular tissue with autorhythmic activity, expressed as the liminal length in a 1-D tissue strand and the liminal radius in a 2-D tissue, is capable of initiating ectopic propagation into normal quiescent ventricular tissue.