Simulation of Microscopic Action Potential Propagation in Physiological Cell Monolayers

Charles Houston, Chris D Cantwell

Imperial College London
London, UK

Aims: The goal of this study was to develop a three-dimensional computer model of action potential (AP) propagation at sub-cellular resolution which uses realistic biophysics of cardiac cell monolayers to enable validation against analogous biological preparations.

Methods: The solver was implemented in the Nektar++ spectral/hp-element framework. Individual cells and a single interweaving extracellular space were represented as separate domains. Domains shared surfaces coupled by enforcing continuity of either active (ion channels) or passive (gap junction) current flux. The solver was first tested in two idealised cases: a cable of 10 cylindrical cells and a monolayer of 200 cuboidal cells. Next, physiological models were obtained by live-staining monolayers of the HL1-6 cardiac cell line with membrane and nuclear dyes and capturing high-resolution image slices of volumes containing ~200 cells by confocal microscopy. The volumes were segmented to produce the monolayer geometry and combined with a previously validated AP model of the HL1-6 cell in simulations across up to 24 cores.

Results: In the idealised cable, conduction velocity decreased with increasing gap junctional resistance until propagation failure. An identical stimulus applied to a boundary cell or an interior cell of the idealised monolayer would lead to wave propagation in the former case but not the latter, demonstrating source-sink mismatch. When compared to recordings of AP propagation in monolayers stained with a potentiometric dye, physiological simulations reproduced characteristic patterns of propagation including localised source-sink mismatch leading to microscopic conduction block.

Conclusion: Idealised models reproduced theoretical results supporting initial validity. Results from physiological validation further demonstrate the solver’s utility for investigations of microscopic cardiac conduction.