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# Re-entry in Computational Models of Heterogenous and Abnormal Myocardium

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***Abstract.*** Regional differences in action potential duration are known to be arrhythmogenic. In this study we used biophysically accurate computational models of action potential propagation in the mammalian heart to quantify the vulnerability of one dimensional fibres with regional differences in action potential duration to re-entry. We have shown that fibres with an abrupt change in action potential duration have a wider vulnerable period than those with gradual changes. In two dimensional simulations we have shown that the re-entrant core tends to glide along an abrupt change in action potential duration, whereas a gradual change promotes the fragmentation of re-entry.

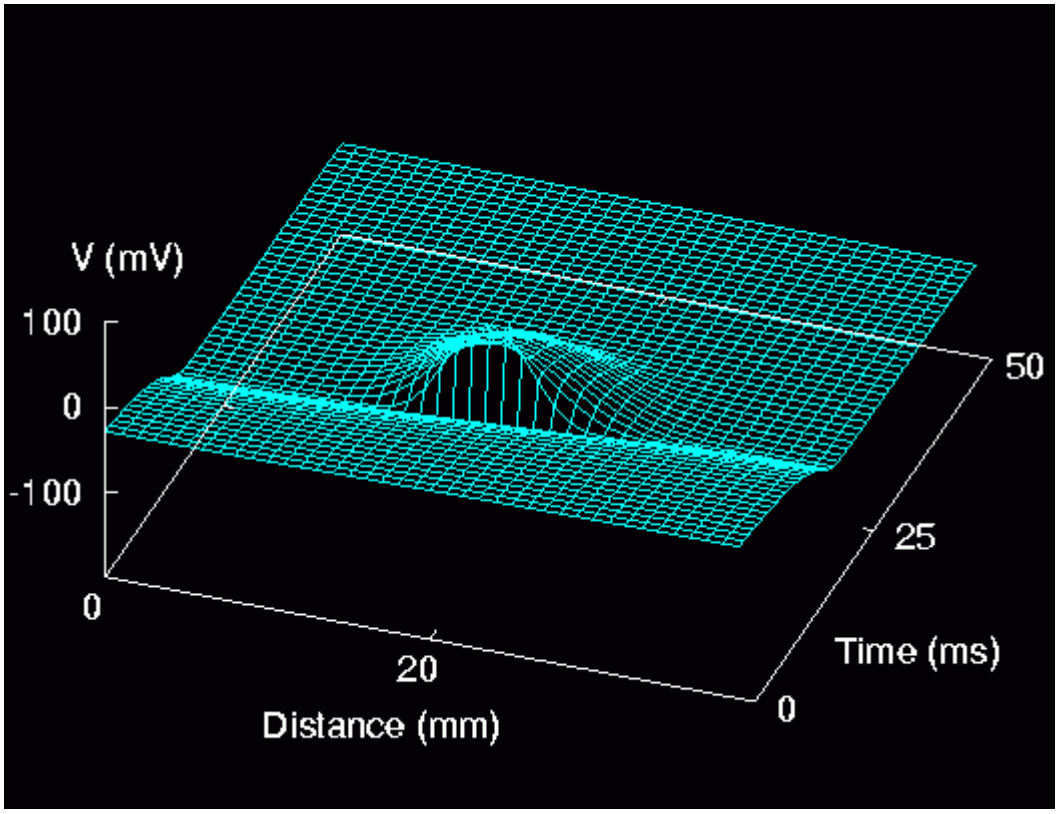
***Keywords:*** *computer model, re-entry, arrhythmia, ischaemia*

## Introduction

Cardiovascular disease is an important cause of premature sudden death in the industrialised world, and in many cases the lethal event is ventricular fibrillation (VF). Despite many decades of research, the mechanisms responsible for initiating and sustaining VF remain poorly understood and strategies for preventing VF remain largely speculative. Although VF can occur in normal and healthy hearts it is more likely in hearts which have structural or functional abnormalities, and is often associated with myocardial ischaemia and infarction.

During ischaemia and infarction myocardial cells undergo complex and poorly understood biochemical changes that result in a shortening of action potential duration (APD), a reduced excitability, and reduced cell to cell coupling [1]. If localised, these changes can result in regional differences in electrophysiology. Experiments in both animal hearts [2 ,3 ,4] and computer models [5 ,6] have shown that regional differences in just one of these properties, repolarisation, increase vulnerability to arrhythmias. Clinical studies also suggest that regional differences in myocardial APD are manifest on the surface ECG as dispersion of QT intervals and that QT dispersion is a way of assessing arrhythmia risk [7], although this observation is controversial [8].

There is evidence to suggest that re-entry is the mechanism reponsible for sustaining VF [9]. During re-entry an action potential circulates along a path whose length is given by the product of APD and conduction velocity. The re-entrant wave continually circulates, depolarising regions of tissue that have recovered from the previous depolarisation. Re-entry is initiated when a propagating beat is partially blocked, and can be initiated even in normal tissue by a premature stimulus delivered at a critical time relative to the wake of a normally propagating action potential. One dimensional simulations of action potential propagation can be used to study this process. If a premature stimulus is delivered too early (Figure 1a) then the resulting action potential is completely blocked. If it is delivered too late (Figure 1b) , then an action potential propagates in both antegrade and retrograde directions. If the timing of the premature stimulus falls within a vulnerable window however, the resulting action potential only propagates in a retrograde direction (Figure 1c).



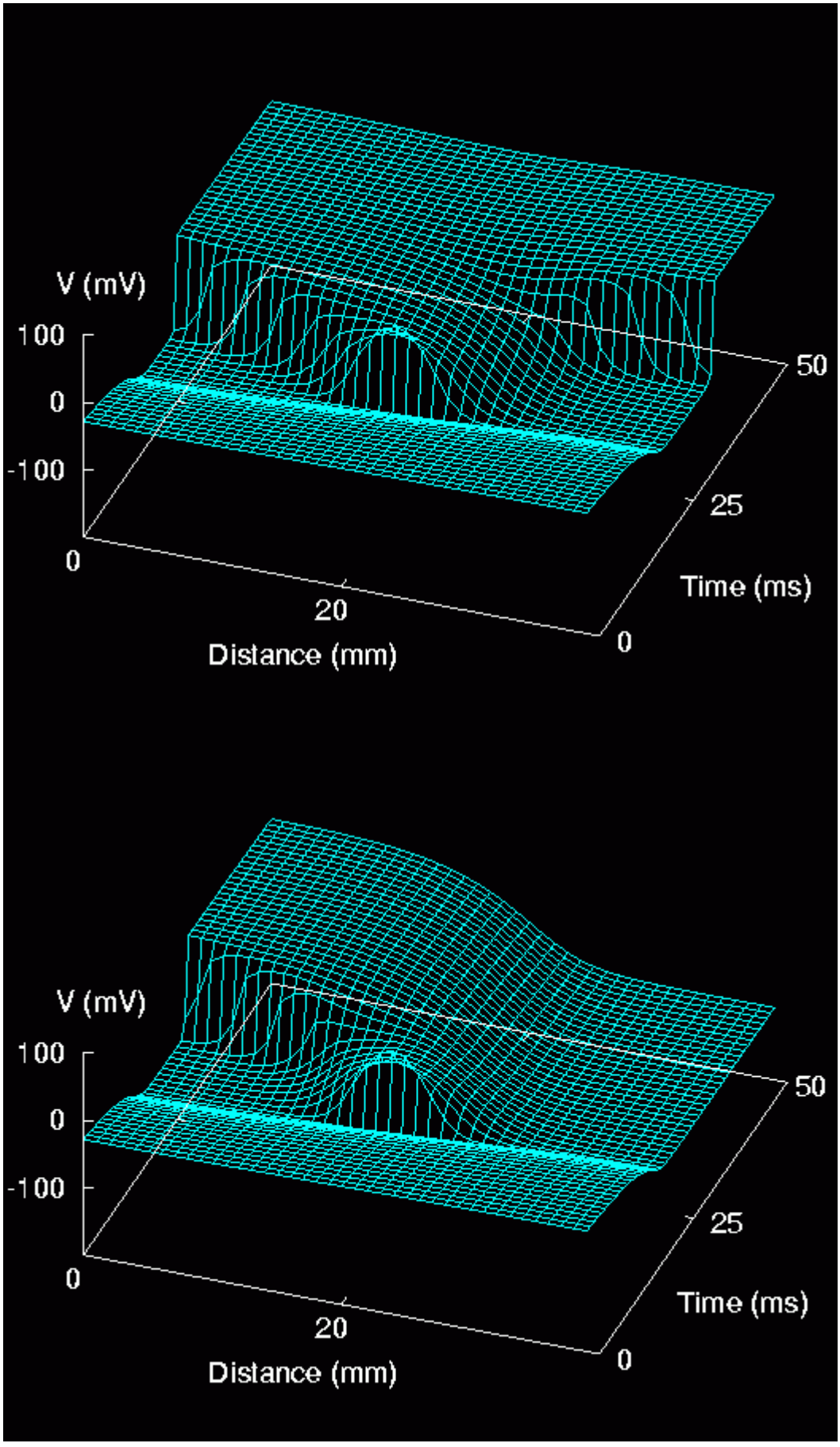



*Figure 1. Simulations in a one dimensional fibre with membrane excitability described by the Oxsoft equations as described below. Top (a) Bidirectional block. Middle (b) Bidirectional propagation. Bottom (c) Unidirectional propagation.*

If the premature (S2) stimulus is delivered at the critical time, the tissue next to the stimulating 'electrode' is partially refractory and partially excitable. By the time the refractory tissue has recovered, the action potential has begun to propagate in a retrograde direction, and has developed a refractory tail. The size of the S2 'electrode', strength of the stimulus, and the tissue conduction velocity, are all important parameters that govern the width of the vulnerable period in which unidirectional propagation can be initiated [10]. In two dimensions, unidirectional propagation results in a re-entrant wave as shown in Figure 2.

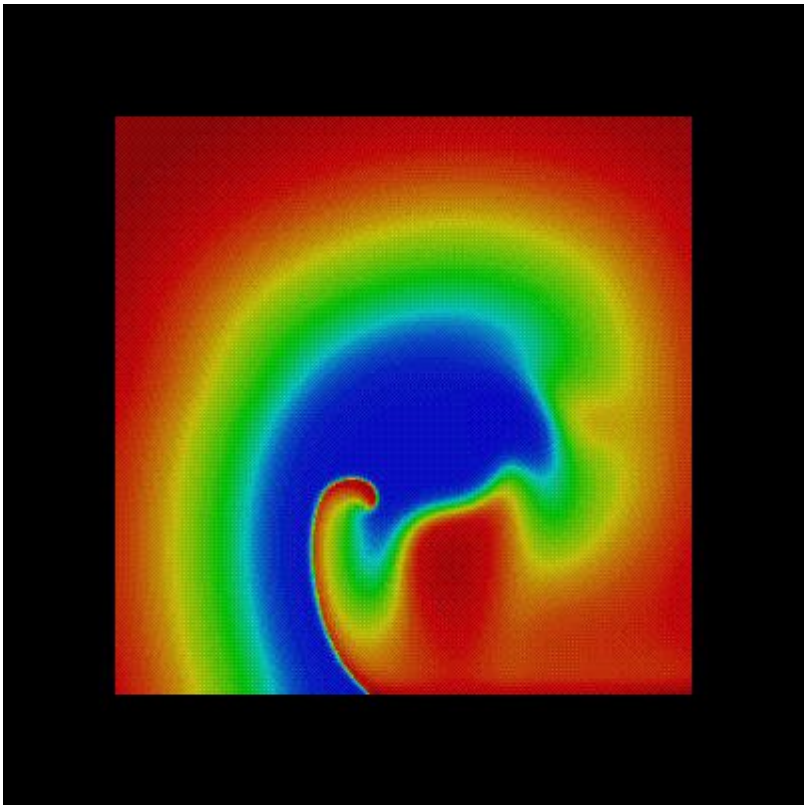


*Figure 2. Movie showing how a re-entrant wave is initiated in 2 dimensions by a critically timed stimulus in the wake of a normally propagating action potential. This simulation represents a 2 dimensional piece of tissue 10 x 10 cm, and uses the modified Beeler-Reuter equations with speeded up calcium kinetics [11].*

*(The VLC Media Player is recommended for viewing the movie.)*

In this study we investigated re-entry in computational models of mammalian ventricular myocardium with regional differences in APD. Our first aim was to quantify the size of the vulnerable window in one-dimensional simulations as the magnitude of both abrupt and graded differences in APD were increased, and our second aim was to investigate the stability of re-entry in two-dimensional simulations incorporating both abrupt and graded differences in APD.

# Methods

## Computational model

The Oxsoft equations [12] incorporate a wealth of experimental data into a model of membrane excitability in a single ventricular myocyte. We have incorporated the ordinary differential equations for a guinea pig ventricular cell into systems of partial differential equations describing propagation in one, two, and three-dimensional continuum models of ventricular tissue. This model has been described in full in an appendix to another publication [13].

For the one dimensional simulations we used simulated 10 mm fibres, and we used a simulated 30 x 30 mm sheet for the two dimensional simulations. We integrated the model using the explicit Euler method with a time step of 50 μs and a space step of 100 μm. We set the diffusion coefficient to be 31.25 $mm^2\ s^{-1}$and the membrane capacitance to 0.2 nF, these values gave a conduction velocity for a single propagating action potential as shown in Figure 1 of 0.36 $m\ s^{-1}$.

## Measurement of the vulnerable window in one dimension

Two conditioning pulses were initiated at the left hand end of a simulated 10 mm fibre with an interval of 400 ms. A second premature stimulus was delivered in the wake of the second pulse with a variable coupling interval that we denoted S2. The second stimulus was delivered by raising the membrane potential of the central 2 mm portion of the cable by 100 mV, equivalent to injecting a current of 0.4 μA into each cell. S2 was increased in steps of 1 ms. The limits of the vulnerable window were defined as the lowest and highest values of S2 for which unidirectional propagation (Figure 1c) was initiated. When S2 was smaller than the lower limit the stimulus was completely blocked (Figure 1a), and when S2 was higher than the upper limit the stimulus was not blocked at all (Figure 1b)

## Dispersion of action potential duration

In this study we sought to study the effect of APD dispersion alone, without the possible complicating effects of changes in cellular coupling. We achieved this by increasing the maximal conductance of the background $K^+$ current GbK from its default value of 0.0006 μS to 0.03 μS. Figure 3 shows the effect of increasing GbK on action potential shape and duration.

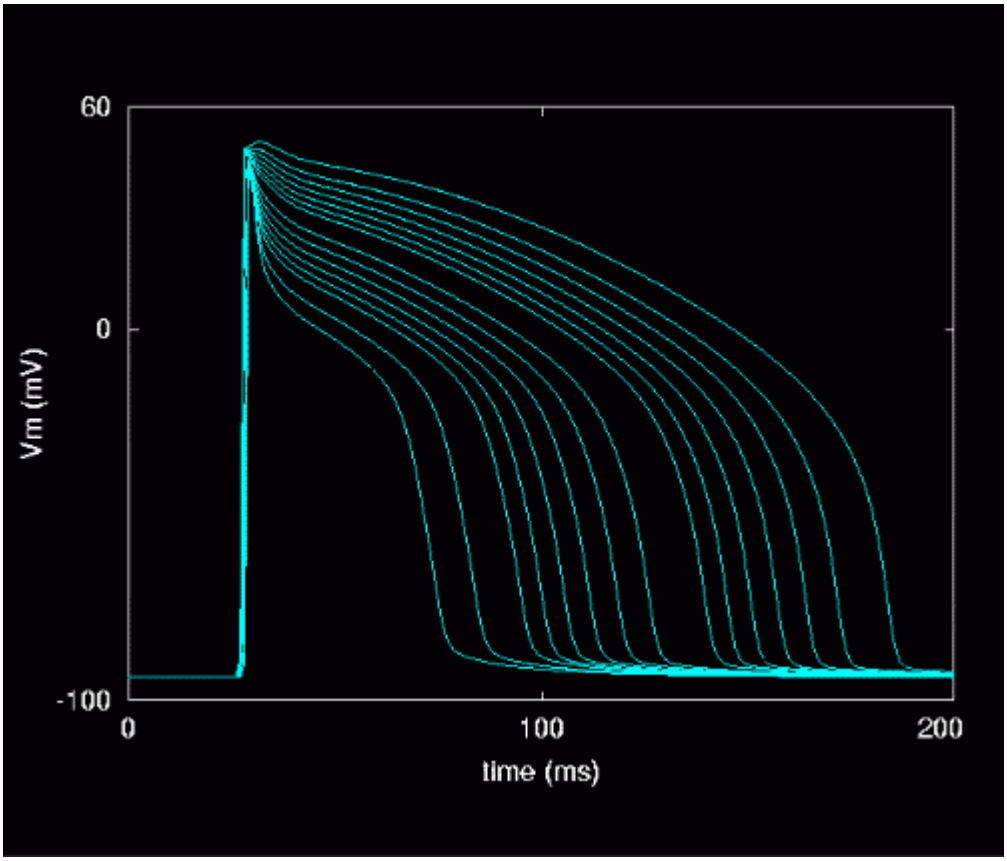



*Figure 3. Effect of increasing GbK on action potential shape and duration. Curves show action potentials for GbK of 0.0006 μS (longest APD), 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.01, 0.012, 0.014, 0.016, 0.018, 0.02, 0.025, and 0.03 μS (shortest APD).*

The effect of increasing GbK on other aspects of the model behaviour is shown in Figure 4. We measured APD from APD90, the time taken for cells to repolarise to 90 % of resting potential. Conduction velocity (CV) was calculated from the time taken for an action potential to propagate from one end of a 10 mm fibre to the other. The effective refractory period (ERP) was measured from the earliest S2 that elicited a response, minus the time taken for an action potential to propagate 4 mm to the left hand end of the S2 electrode. APD restitution was determined by delivering two consecutive S1 stimuli to the left hand end of the fibre with a coupling interval of 1000 ms and then delivering an S2 stimulus to the left hand end of the fibre. The APD90 of the S2 action potential was then measured at the right hand end of the fibre, and plotted as a function of the S2 coupling interval for each vale of GbK.

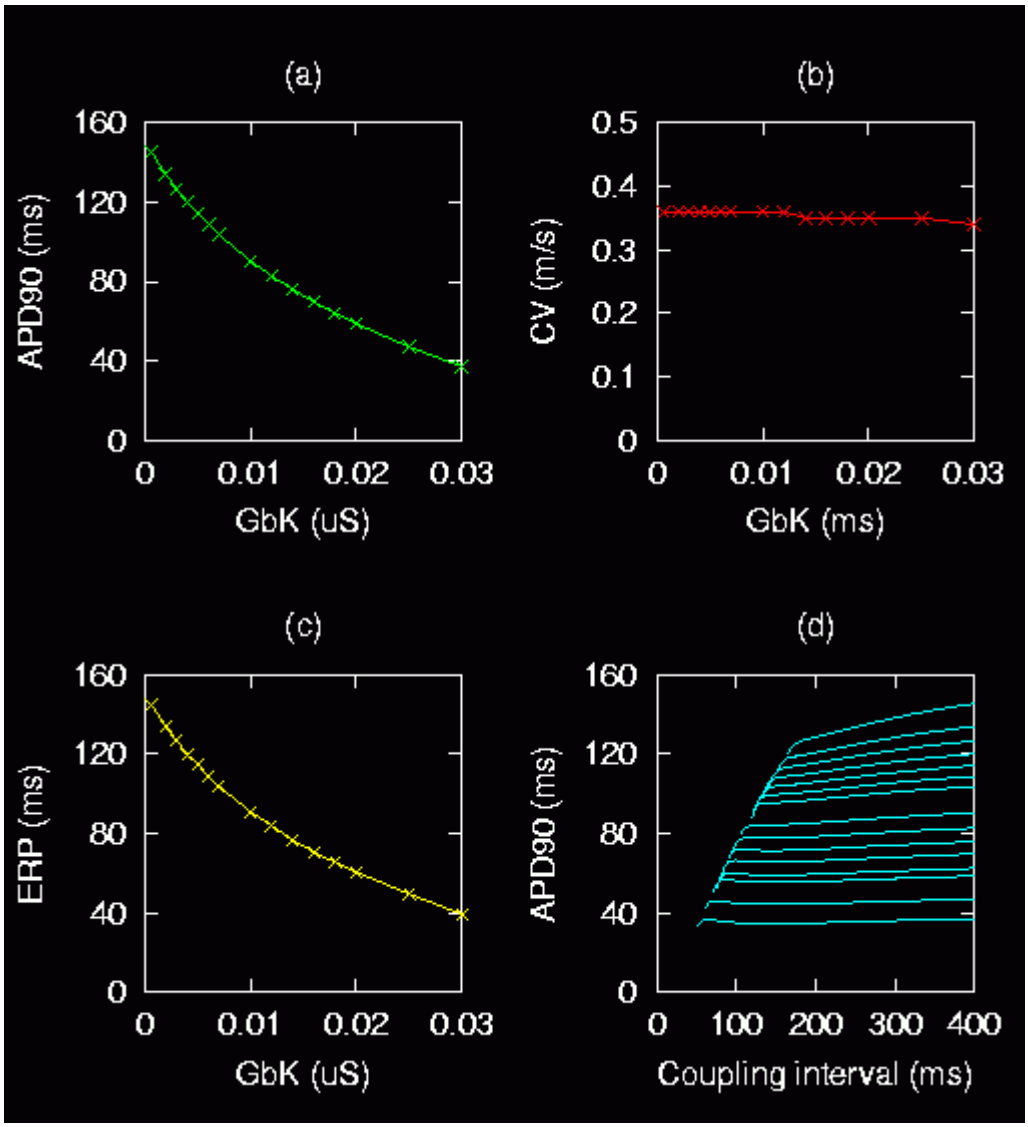
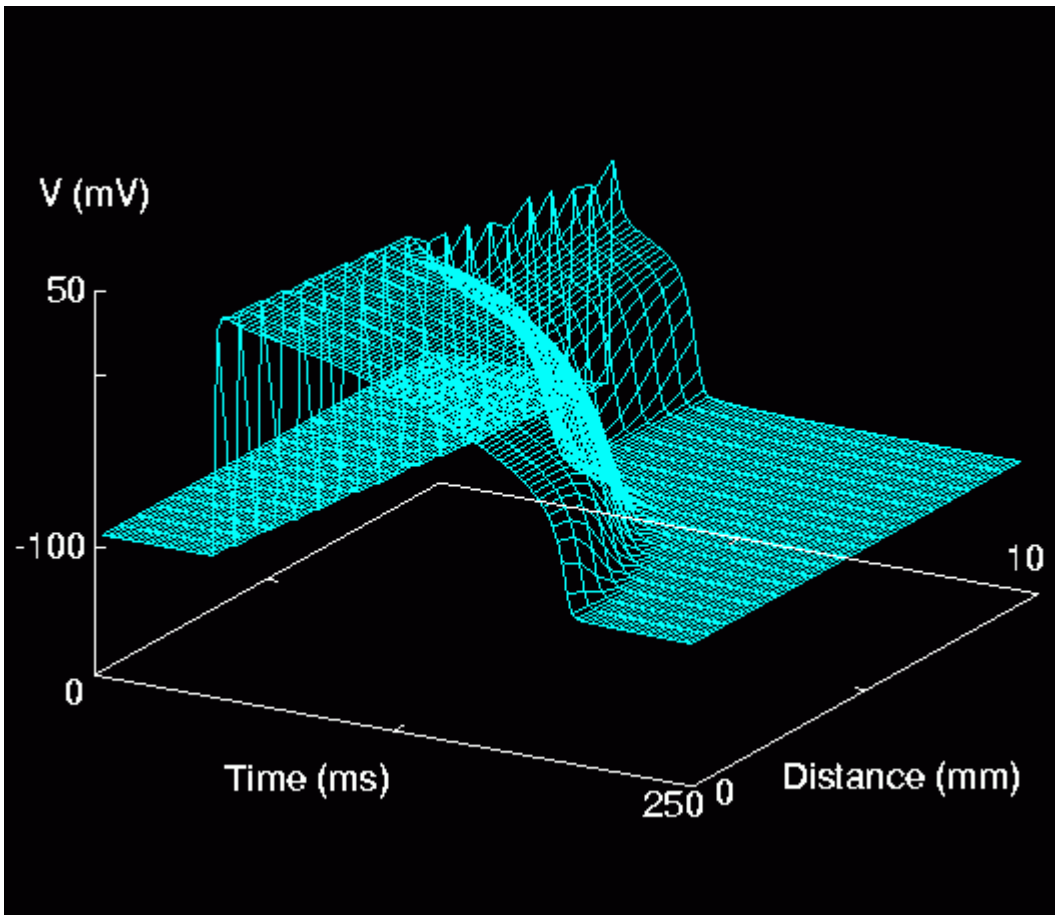



*Figure 4. Effect of increasing GbK on (a) APD90, (b) CV, (c) ERP, and (d) APD restitution.*

Increasing GbK resulted in a nonlinear and commensurate decrease in both APD and ERP from 145 ms to 37 ms, but had only a slight effect on CV which decreased from 0.36 $ms^{-1}$ to 0.34 $ms^{-1}$. For GbK below 0.01 µS the APD restitution curve was monotonic, but for GbK above 0.01 µS the restitution curve became flatter and a small supernormal region appeared for closely coupled S2 action potentials.

We measured the upper and lower limits of the vulnerable window for fibres in which GbK varied either abruptly at the centre of the fibre or in a linear fashion from one end of the fibre to the other. The value of GbK was initially set to the normal value (0.0006 µS) at the left

hand end of the fibre, and increased steadily at the right hand end. Then the procedure was reversed, giving us estimates of the vulnerable window for beats propagating from normal to reduced APD and from reduced to normal APD. Figure 5 shows propagation of an action potential in fibres with a sudden and graded variations in GbK.



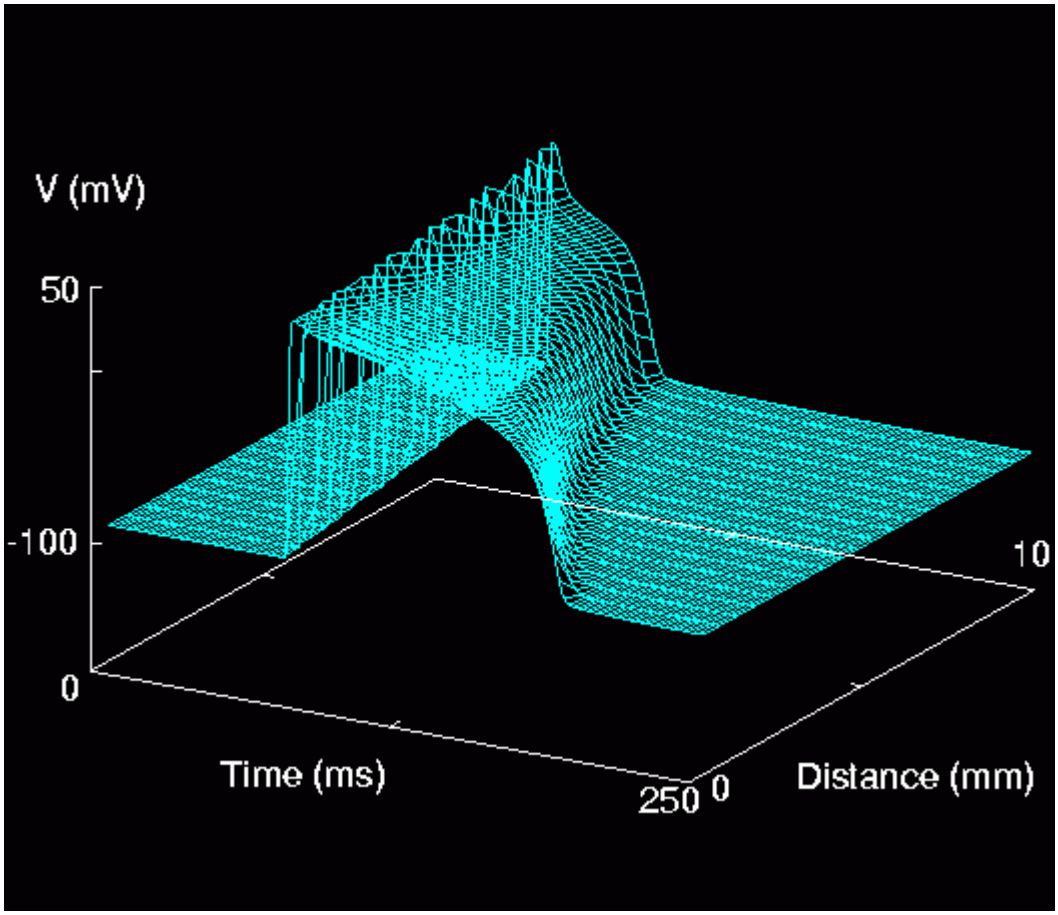



*Figure 5. Action potential propagating in fibres with sudden (top) and gradual (bottom) transitions in GbK. For the sudden transition (top) GbK varies between 0.0006 uS and 0.03 uS and the action potential propagates from region of long APD (front: GbK 0.0006 µS) to region of short APD (back: GbK 0.03 µS). For the graded transition (bottom) action potential propagates from region of short APD (back: GbK 0.03 µS to region of long APD (front: GbK 0.0006 µS).*

### Two dimensional simulations

Two simulations were run in two-dimensional media. Both simulated the behaviour of re-entry in a 30 x 30 mm slice of tissue with GbK varying between 0.03 on the left hand side and 0.0006 µS on the right hand. In the first simulation the transition between high and low GbK was abrupt, and in the second the transition was graded. An anticlockwise re-entrant wave was initiated using the phase distribution technique described elsewhere [14].

## Results

Figure 6 shows the limits of the vulnerable window and the vulnerable window width for different values of APD and ERP dispersion achieved by varying GbK. An abrupt change in APD resulted in a wider vulnerable window than a gradual change. For each abrupt change in APD, the vulnerable window was wider if the conditioning beat propagated from a region with shortened APD (ie increased GbK) to a normal region, and narrower if the conditioning beat propagated from a normal region to a region with shortened APD and ERP (figure 6b). Suprisingly, the width of the vulnerable window decreased below 1 ms when the conditioning beat propagated from a normal region (GbK 0.0006 µS, APD 145 ms) to a region with a modest reduction in APD (GbK 0.002 µS, APD 134 ms). The effect of gradual changes on the vulnerable period mirrored the effect of abrupt changes, although for equal differences in APD the vulnerable window was narrower. For a given gradual change in APD, the vulnerable window was wider if the conditioning beat propagated from a normal

region to a region with shortened APD and ERP (ie increased GbK), and narrower if the conditioning beat propagated from a region with shortened APD and ERP to a normal region (figure 6d). The width of the vulnerable window decreased below 1 ms when the conditioning beat propagated from region with shorted APD (GbK 0.004 µS, APD 120 ms) to a normal region (GbK 0.0006 µS, APD 145 ms).

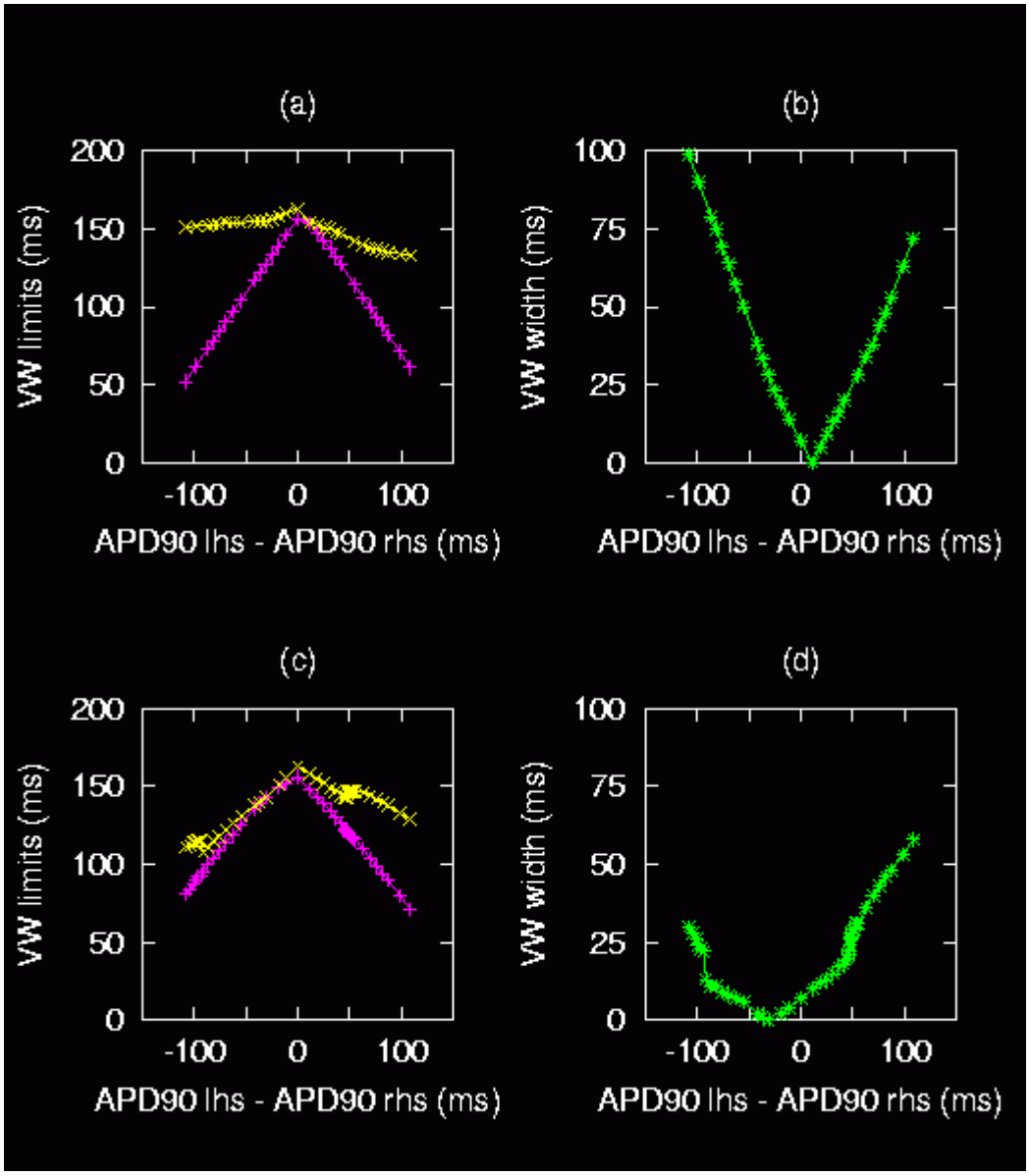



*Figure 6. Size of the vulnerable window measured in one dimensional simulations. (a) Upper (x) and lower (+) limits of the vulnerable window and (b) width of vulnerable window for fibres with an abrupt change of APD. (c) Upper (x) and lower (+) limits of the vulnerable window and (d) width of vulnerable window for fibres with a graded change of APD.*

Movies of the two-dimensional simulations are given in Figure 7. For the simulation with an abrupt change in APD, the core of the re-entrant wave moves down along the boundary until it moves into the inexcitable region and the re-entrant wave is extinguished. For the simulation with a gradual change in APD, the re-entrant wave breaks up into multiple wavelets before it too is extinguished.

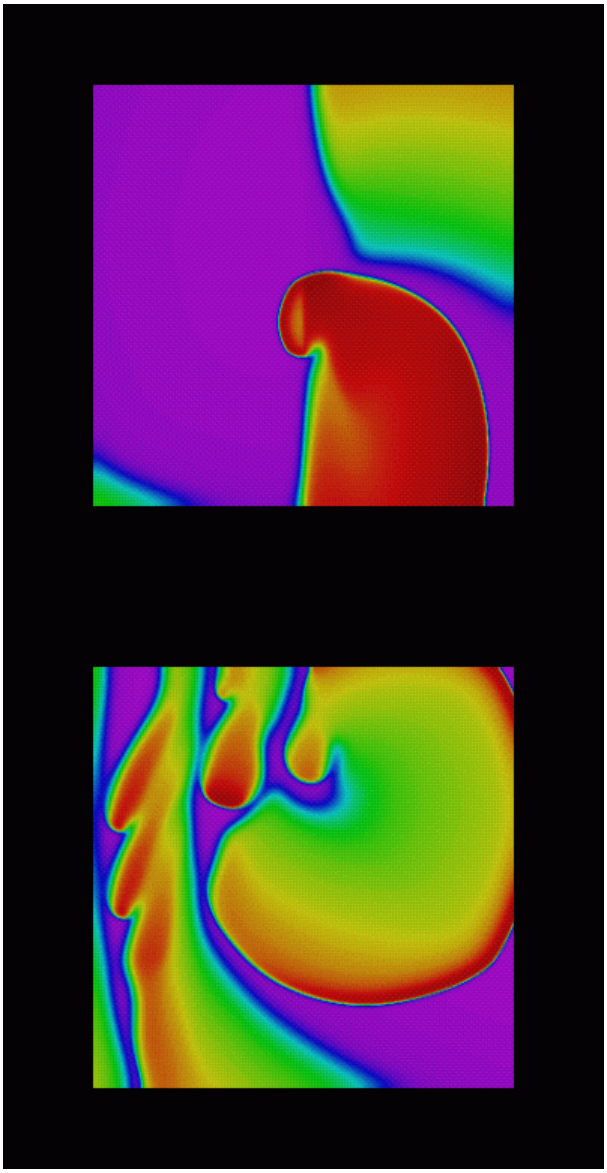


*Figure 7. Movies showing behaviour of re-entrant waves in two dimensional simulations with region of reduced APD (GbK 0.03 µS) on the left hand side and normal APD (GbK 0.0006 µS) on the right hand side. Top movie shows medium with an abrupt change in APD, and bottom movie shows medium with a gradual change in APD.*
*(The VLC Media Player is recommended for viewing the movies.)*

# Conclusions

There is already experimental and clinical evidence that regional dispersion of APD associated with myocardial ischaemia favours the initiation of arrhythmias. In this study we have shown that in a computational simulation of mammalian tissue

- Abrupt differences in APD result in greater vulnerability to re-entry than gradual changes in APD, and vulnerability increases with increasing APD difference.
- For small differences in APD vulnerability is actually lower than for homogenous tissue, but the pattern is different for abrupt and gradual changes in APD. Larger (>50 ms) differences in APD always result in increased vulnerability.
- Abrupt differences in APD encourage the drift of re-entrant waves along the boundary, whereas graded differences in APD result in spiral wave breakup.

This study has focussed on the effect of regional differences in one component of cellular electrophysiology. Re-entry in the ischaemic human heart is a much more complex process.

Even under normal conditions conduction of action potentials in the human ventricles depends on the three dimensional geometry as well as the orientation of sheets and fibres of myocardial tissue, and is affected by both the geometrical and electrophysiological consequences of contraction. Although this study has stripped away these layers of complexity to focus on just one aspect of possible arrhythmia initiation, our findings are in broad agreement with other experimental and clinical observations.

## Acknowledgements

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