

# The Role of Extracellular Potassium Concentration and Stimulus Period on the Functional Inhomogeneity of Cardiac Tissue: A Simulation Study

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## Abstract

*The relation between extracellular potassium concentration increase and action potential duration decrease is well established. In this work, potassium concentration changes in relation with various activation patterns in an inhomogeneous tissue were in focus and effort was paid to investigate spatial patterns and draw quantitative conclusions about their effects. A series of simulations were performed with different combinations of short stimulus periods and increased extracellular potassium concentrations. The effect of these perturbations on the cellular and overall tissue activation and wave propagation characteristics was investigated.*

## 1. Introduction

The relation between extracellular potassium concentration increase and action potential duration decrease is well established. Hyperkalemia, i.e. increased extracellular potassium level, depolarizes the membrane potentials of cells, which opens some voltage-gated sodium channels, but not enough to generate an action potential. After a short while, the open sodium channels inactivate and become refractory, increasing the threshold to generate an action potential. This might lead to the impairment of cardiac conduction which can result in ventricular fibrillation or asystole. Reducing cell excitability by elevated potassium has been reported in diabetic hearts, but also as a result of physical stress such as exercise. Myocardial ischemia leads to extracellular potassium accumulation ( $\Delta[K^+]_o$ ) and, as one of its consequences, to the development of reentrant arrhythmias, a major cause of sudden cardiac death. Furthermore, hyperkalemia may be induced by medication in chronic heart failure treatment.

On the other hand, the rate at which recurrent stimuli reach an arrhythmogenic tissue may also affect activation characteristics. The most prominent effect of

decreasing the pacing period is shortening of APD, which is an important factor in arrhythmogenesis. Heterogeneity of APD and the resulting dispersion of refractoriness across the ventricular wall could provide the substrate for unidirectional block and reentrant arrhythmias. In addition, adaptation of APD can influence the degree of head-tail interaction during reentry and the stability of the reentrant circuit.

Taking into account the importance of these two conditions, the extracellular potassium level and the pacing rate, the purpose of this work is to investigate the way that different conditions of spatial heterogeneity (functional and structural) interact and formulate the tissue activation characteristics. Considering a rotating propagation wave, due to infarcted tissue, we take a closer look at the model kinetics in the area of rotation. The behavior of the action potential and ionic current features in such areas is examined, under different levels of ischemia, structural inhomogeneities and pacing rates. We show that the changes in the spatial activation properties largely depend on a combination of ischemia and fast pacing, which may effect arrhythmogenesis.

## 2. Methods

Simulated data have been used for this work, in order to test and compare different methods for a structure of known complexity and behavior. The 2D monodomain model of cardiac muscle was used. A rectangular sheet of cells was simulated with a grid of 40x200 elements, which corresponds to 40x50 cells. Each cell consists of 4 longitudinal elements (3 cytoplasmic and 1 junctional), coupled by resistances. The grid intervals were 10  $\mu\text{m}$  transversely and 25  $\mu\text{m}$  longitudinally. Luo-Rudy I model was used for ionic kinetics [1], including the following currents: "fast sodium current" component (m-h-j gates), "slow inward current" component (d-f gates, Ca), "time dependent potassium current" component (X, Xi gates), time independent potassium current (K1 gate), "plateau potassium current and background current. Simulation of propagation was implemented using Gauss Seidel

method. A variable time step size approach was applied [2], where a maximum time step  $\Delta T_{max}$  and a minimum one  $\Delta T_{min}$  are predefined, and each step size is calculated as  $\Delta t = \Delta T_{max}/k$ , where  $k = k_0 + \text{int}[dV/dt]$ , varying according to potential's time variation.

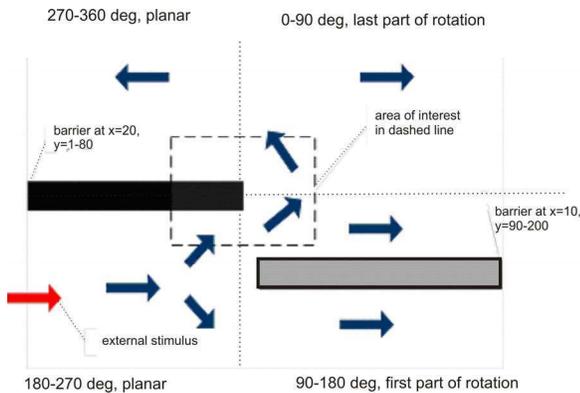


Figure 1. The experimental setup. In scheme A, both barriers were introduced, while in scheme B the barrier marked with grey color was absent.

Regions of scar tissue were defined in order to introduce heterogeneity. The setting used in this paper is shown in Figure 1. Two barriers of scar tissue cause wavefront to follow a zigzag pathway, from a narrower area before rotation to a wider area (non-symmetric scheme), while in second (symmetric) scheme, one barrier is applied, and the areas before and after rotation are symmetric. Within an area of interest, specifically in the rectangle defined by  $15 < x < 25$  and  $67 < y < 103$ , around the rotation pivot point, thick recording take place, in a grid, with  $10 \mu\text{m}$  transverse interval and  $100 \mu\text{m}$  longitudinal interval, corresponding to one recording per cell. For this grid area, ionic/transmembrane currents and action potentials were stored for certain grid-points. Experiments were repeated with the pacing and ischemia parameters varying as described below.

Pacing rate, i.e. external stimulus period was varied as follows: assuming 380 ms as the normal APD, periodic stimulus was applied with periods 105%, 115%, 120% and 125% of this normal APD, in the sense that pacing rates are selected close to the refractory period, while shorter pacing rates would not lead to 1:1 activation. Extracellular potassium concentration was altered as 5.4, 6.5, 7.6, 8.1, 8.6, 9.4, 9.7 and 10.2 mM/l corresponding respectively to 100%, 120%, 140%, 150%, 160%, 175% 180% and 190% of normal value, i.e. spanning from normal cells to moderate and severe ischemia.

In this manner, with each set of experimental parameters, we run the model for 10 periods and then for the last activation we calculated for each point a series of

features, as described below.

## 2.1. Features and analysis

As discussed above, a grid which is near the infarcted area and the wavefront turning point was used for closer analysis. Having available the calculated data of the simulation setups within the predefined grid area, a series of features were calculated for further analysis for each grid point reflecting different characteristics of the cellular activation and tissue depolarization and repolarisation. The features were calculated after a train of ten regular stimuli were delivered.

The macroscopic features of the cells are a) Action Potential Duration (%90 APD), which is crucial for the alterations in refractory period, blockades and arrhythmias b) Action Potential Upstroke, as the maximum Action potential value, which along with c) upstroke velocity, i.e. maximum Action Potential slope, are related to the spatial properties of conduction and local impedance, and d) Minimum (negative) value of the ionic current, Ionmin, a basic morphological feature strongly affecting the membrane current and the excitability, known to be affected by heterogeneity, and specifically to decrease in the infarcted regions.

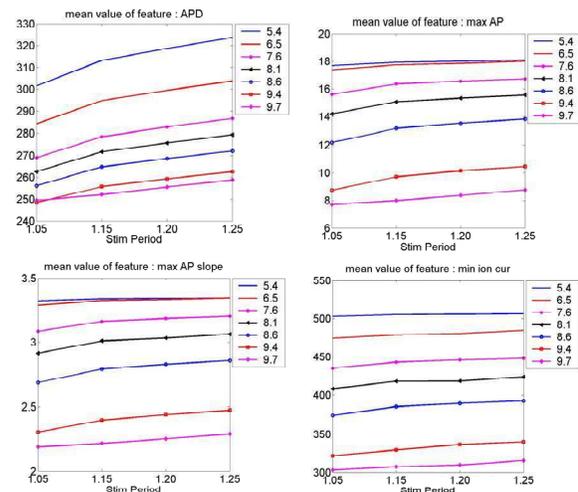


Figure 2. Mean feature values per pacing for all ischemia levels. Up (Left: APD, Right: maxAP), Down (Left: maxAPslope, Right: minIonCur).

The steps followed to analyse the features extracted were the following

1. Mean values for each feature were calculated for each run corresponding to a ischemia and pacing parameter set. Mean feature values show overall changes with each set of parameters.
2. Features vectors were clustered, revealing which potassium concentration and pacing combinations lead to

similar behavioural patterns.

3. Polar coordinated were calculated for the grid points, taking the tip of the barrier as polar center, around which wavefront rotation takes place [3]. Thus, consecutive areas of propagation/rotation were defined, and mean feature values were calculated in each area, allowing for more detailed spatial comparisons.

### 3. Results

Regarding the overall differences between the asymmetric and symmetric scheme (with two and one infarcted areas correspondingly), statistically significant differences were found only regarding APD, having lower mean value in the symmetric case, in all combinations of ischemia and pacing.

Overall, the simulated ischemic cells are characterized by reduced ADP, slower APD upstroke and upstroke velocity, and less negative ionic current peak. In both schemes, ADP is decreased with pacing frequency, but the relative effect of pacing is more evident in normal than in ischemic tissue. There is also a decrease of APD upstroke and velocity, and ionic current peak with pacing frequency, however, unlike APD, the relative effect is more obvious in ischemic than in normal cells. Some more detailed effects are depicted in Figure 2, indicating that relevance of the cell activation to pacing for normal cells is very different from that of ischemic cells [4].

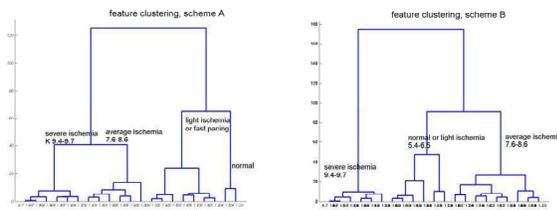


Figure 3. Feature based clustering. Left: Scheme A, Right: Scheme B.

In order to express the overall differences induced by the pacing and  $K_o$  conditions, all the  $\langle$ pacing, level of ischemia $\rangle$  cases were clustered in terms of the four-feature vector (APD, MaxAP, MaxAPslope and MinIonCur), and a dendrogram of the clusters produced was visualized, by use of manova and manovacluster Matlab methods (Fig. 3). In both schemes, three main clusters were produced; roughly corresponding to ischemia levels. For scheme A, the first cluster includes normal cells with normal pacing, the second includes light ischemia and/or high pacing, and the third severe ischemia or average ischemia. In scheme B, the three clusters include respectively: a) normal cells and light ischemia, b) average ischemia, and c) severe ischemia. It is interesting that in scheme B, which has less structural

inhomogeneity, severely ischemic clusters are more distinctly separated, so are moderate ischemic clusters, while in scheme A there is more fragmentation and interrelation of ischemia and pacing.

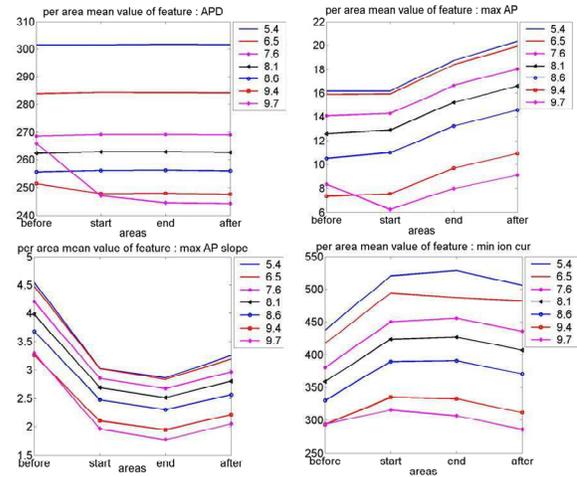


Figure 4. Mean feature values in each rotation area, for fastest pacing ( $T=105\%$ ) and various ischemia levels. Up (APD, maxAP), Down (maxAPslope, minIonCur).

The mean feature values have been calculated in four areas of the grid, as split according to their angle from the “rotation point”, and specifically in the planar area “before rotation”, in the area “starting the rotation”, “ending the rotation”, and the planar area “after the end of rotation” (see figure 4). The features values change in the area where rotation starts, this becomes more evident in the continuation of rotation, and does not get restored when wave gets planar again in the vicinity of the barrier. Spatial variation of activation features is affected by both the ischemia level and the pacing rate, especially in the severe ischemia cases.

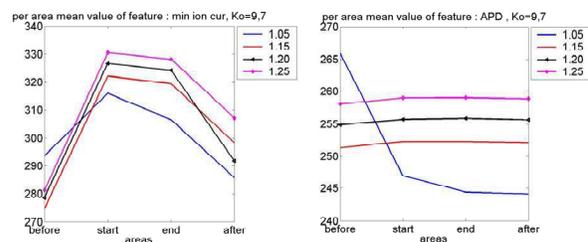


Figure 5. Mean feature values per rotation area, for severe ischemia (9.7) and various pacing rates. Left: minIoncur, Right: APD

Upstroke velocity falls in the rotation area, while Potential upstroke and MinIonCur increase. APD does

not vary significantly with rotation area, except for the case of severe ischemia and fast pacing (see figure 5).

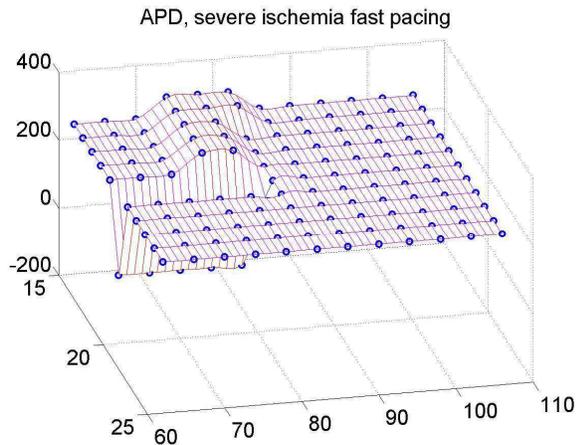


Figure 6. APD Feature values per grid-point for severe ischemia (K 9.7) and fast pacing (T 105%).

In Figure 6 and 7, it is depicted how, for severe ischemia, the dispersion of these features in the different rotation areas also varies with the stimulus period. This is especially true in the first part of the rotation area. Faster pacing leads to more evident changes. While ischemia affects the feature values overall, pacing induces spatial inhomogeneity. Increasing ischemia from 180% to 190% of normal value (i.e. to extracellular potassium 10.2), there is a high spatial dispersion of the features, and at high pacing rate, activation is not 1:1 any more.

#### 4. Discussion and conclusions

Concluding, factors of increased heterogeneity were explored in order to investigate vulnerable states. Two infarcted tissue schemes with structural differences were considered. Multiple combinations of ischemia level and pacing frequency were considered, and it was investigated how each factor (external, structural or functional), as well as their combination affects excitability and propagation characteristics, and in which areas are changes more evident.

The analysis shows that activation features are mostly affected by level of ischemia and secondarily by pacing frequency, the differences in the latter being dependent on ischemia level. In severe ischemia, fast pacing induces also a significant change of activation features in the area where the planar wavefront starts rotating. It is also important that the average feature deviations from the initial planar wavefront are not restored in the area where wave is restored to planar.

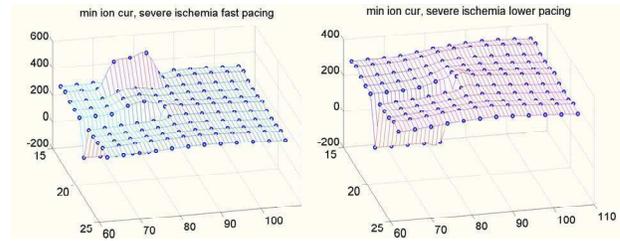


Figure 7. Minimum Ionic Current values per grid-point for severe ischemia – (left) fast pacing (105%), (right) slower pacing (125%).

Among the further steps foreseen in this analysis is the examination of the disorder of spatial patterns in different conditions by use of formal spatial or spatiotemporal complexity methods, such as recurrence plots or other nonlinear dynamics tools [5]. Furthermore, the introduction of microscopic features, directly related to gate-function is crucial, as well as the combination of the quantitative features to a qualitative vulnerability index.

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