

Mathematical modeling of ischemia and infarction

Mostly based on Cimponeriu, Starmer and Bezerianos:

A theoretical analysis of acute ischemia and infarction using ECG reconstruction on a 2-D model of myocardium

Outline

- Definitions.
- Clinical effects.
- Cellular changes during ischemia.
- Mathematical models on cell and tissue level.
- Results.

Definitions

- A part of the heart which lacks sufficient blood supply is called ischemic. The condition is normally caused by an obstruction of one or more of the coronary arteries.
(Angina pectoris)
- If the obstruction of blood flow is sufficiently severe, the cells in the affected region start to die. This is called an infarction.

Clinical effects

- Heart failure is the number one cause of death in the western world.
- The majority of heart failures are caused by obstruction of the coronary arteries supplying blood to the heart.
- The pumping function of the heart muscle is impaired by insufficient oxygen supply, but the most dangerous effect of ischemia and infarction is that it causes arrhythmias.

Effects on cellular level

The blood flow to the heart serves two main purposes:

- To provide oxygen and energy for the hard work performed by the heart muscle.
- To remove waste products from the tissue.

When blood supply is lost, the cells stop contracting almost immediately to save energy, and waste products start piling up in the tissue.

Three important effects of acute ischemia are

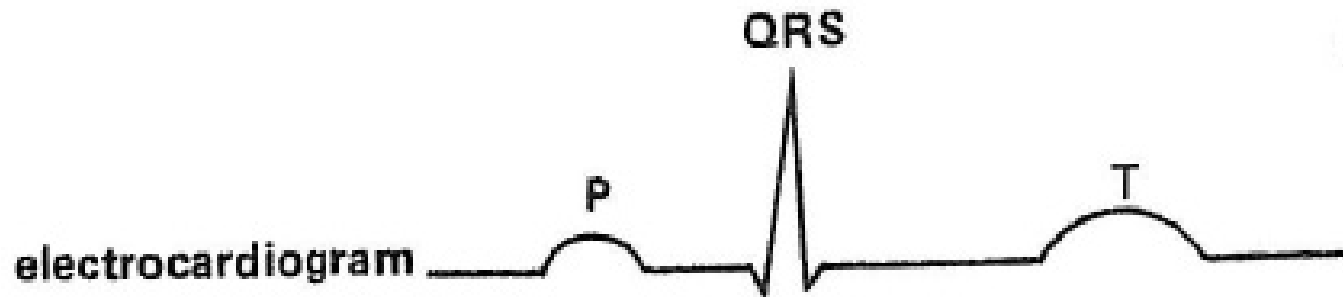
- Reduced ATP-concentration and increased ADP concentration, caused by insufficient oxygen supply.
- Reduced intracellular and increased extracellular potassium concentration. This is caused by reduced activity of potassium pumps, as well as opening of ATP-sensitive potassium channels.
- Reduced intra- and extracellular pH, caused by insufficient removal of waste products.

Effects on tissue level

- Ischemia decouples gap junctions, probably as an effect of reduced pH. This reduces the overall conductivity of the tissue.
- Necrotic tissue (infarction) has even lower conductivity, and may be regarded as non-conductive.

The electrocardiogram (ECG)

Is a recording of the heart's electrical activity from the torso surface



Components of an ECG:

- P wave: depolarization of the atria
- QRS complex: depolarization of the ventricles
- T wave: repolarization of the ventricles

Modeling ischemic cells

The remainder of the slides present results from Cimponeriu et al: Theoretical analysis of acute ischemia and infarction.

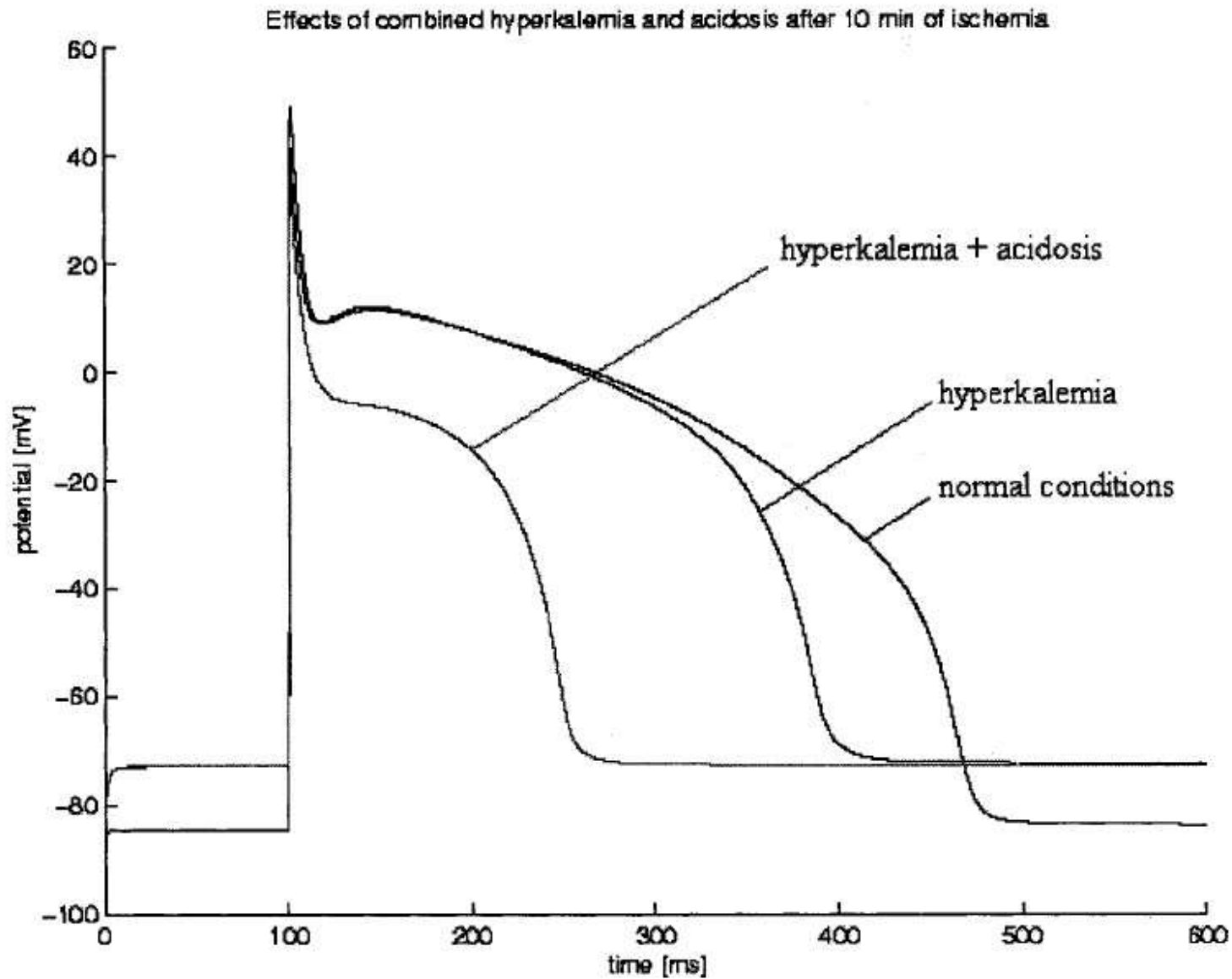
- The model for ischemic cells is based the Luo-Rudy I (LR I) cell model, which includes 5 ionic concentrations, 6 gate variables and 14 ionic currents.
- Extracellular potassium is a parameter in the model. The normal level is about 4.0 mM, and the ischemic condition is modeled by increasing this value to 9.0 mM.

- Reduced pH is known to reduce the conductance of a number of ion channels. The ischemic cell model includes this effect by reducing the conductance for sodium by 25 % and the conductance of calcium by 50 % .
- The effect of reduced ATP concentrations is not directly included in the model.

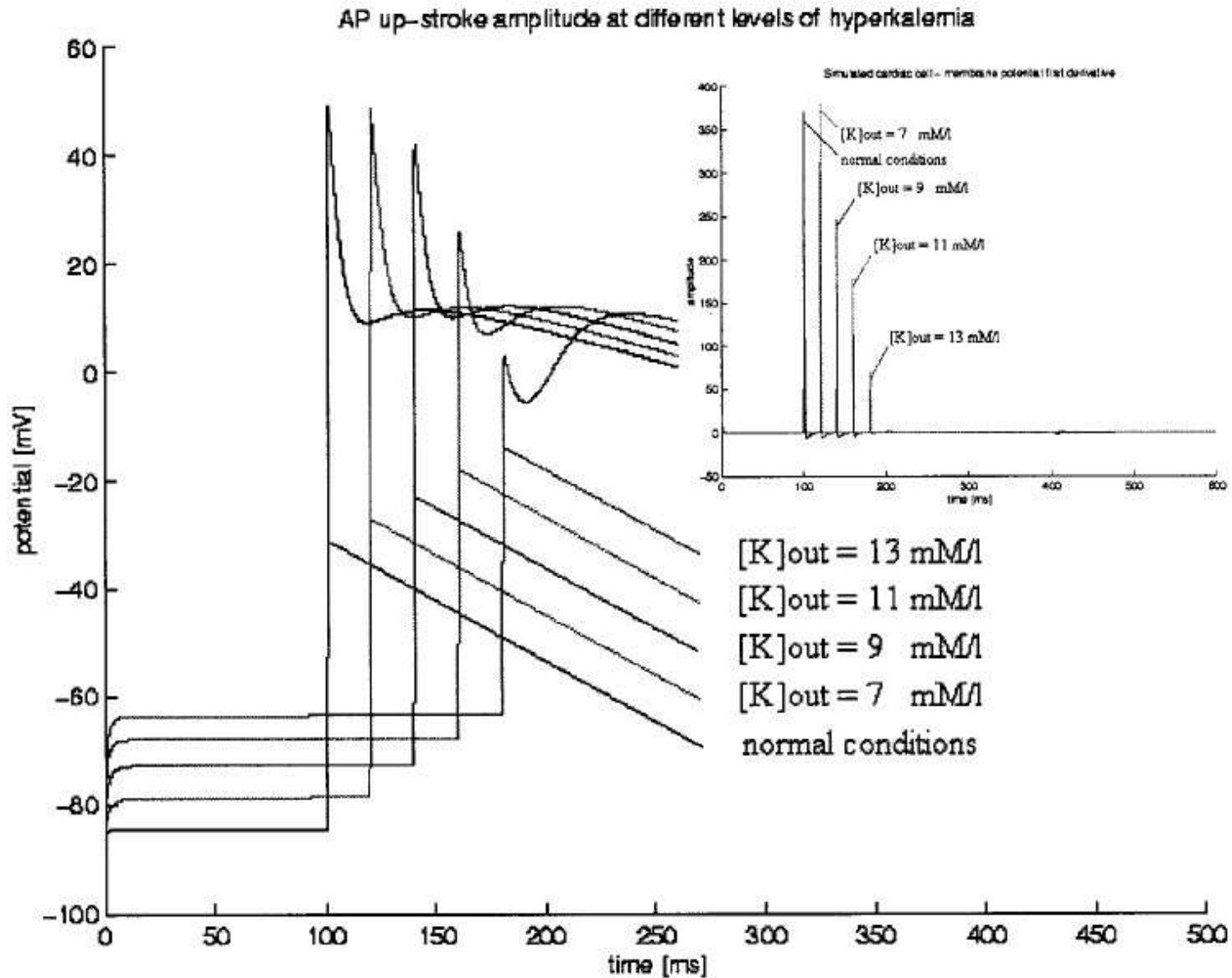
Experiments: The ischemic cell

- The cell model sketched above has been used to study the effects of ischemia on a single cell.
- Important in order to validate the mathematical model, and to be able to relate later tissue-scale observations to changes on the cellular level.

Hyperkalemia and acidosis



AP upstroke amplitude



- The previous slide shows how the upstroke amplitude is affected by hyperkalemia. The upstroke is first unaffected or slightly increasing, because the resting potential is now closer to the threshold. At later stages (higher $[K_o]$), the inactivation of sodium channels causes the upstroke amplitude to be reduced.
- Inactivation of sodium channels is not modeled explicitly, but comes as a secondary effect of the changed equilibrium potential.

A 2D model of ischemic tissue

The work in the article is based on a monodomain model of cardiac tissue.

$$C \frac{\partial V}{\partial t} = -I_{\text{ion}} + \frac{1}{R_i} \left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} \right)$$

Here, R_i is described to as the cell-to-cell resistance. (In this PDE setting, it is more correctly referred to as the spatially averaged resistance.)

A 2D model of ischemic tissue

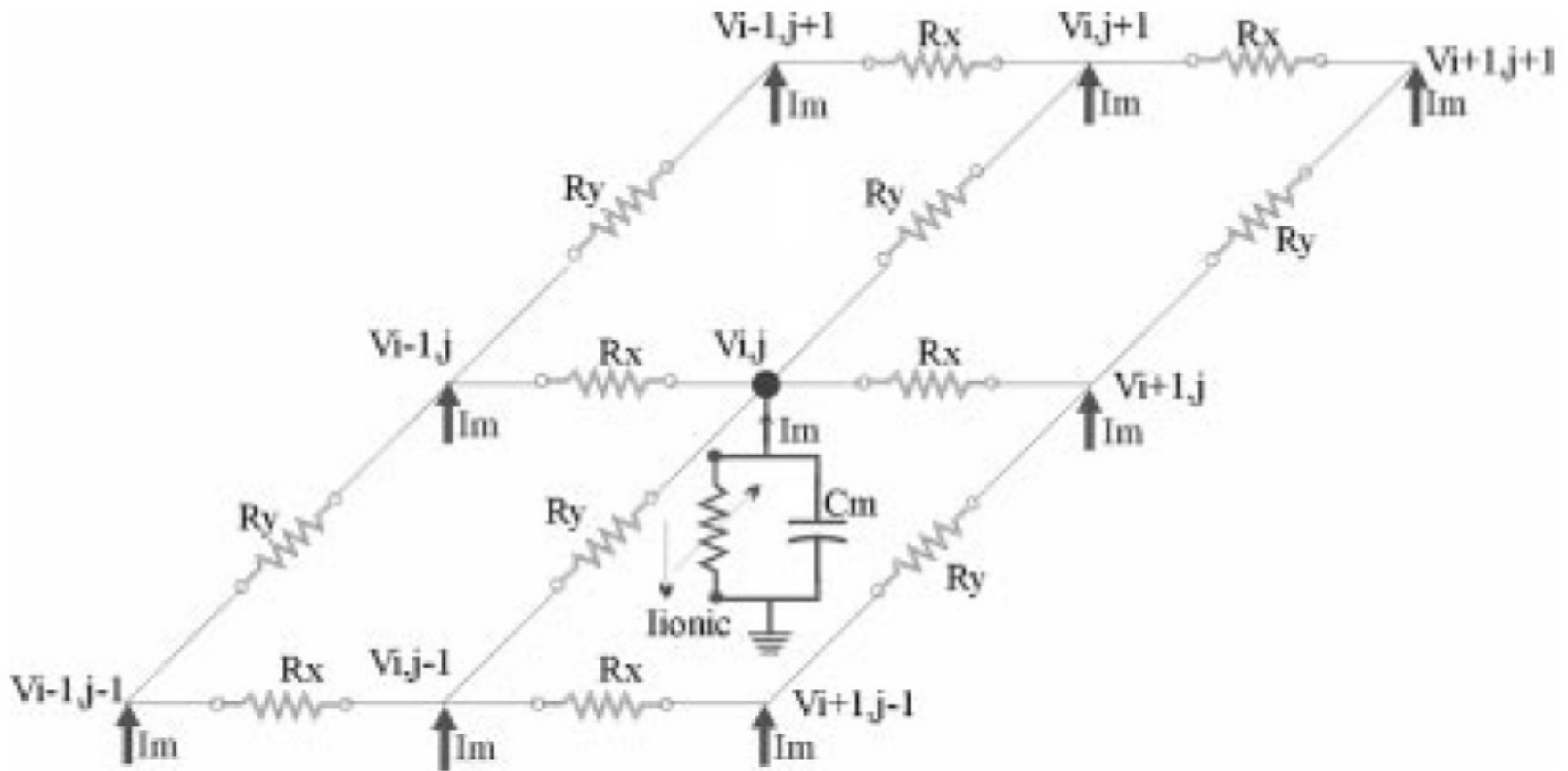


Fig. 1. Squared-grid arrangement of cells in the 2-D model of myocardium.

FD formulation

$$V_{ij}^{t+dt} = -dt I_{\text{ion}} + qV_{i-1,j}^t + qV_{i+1,j}^t + qV_{i,j-1}^t + qV_{i,j+1}^t + (1 - 4q)V_{i,j}^t$$

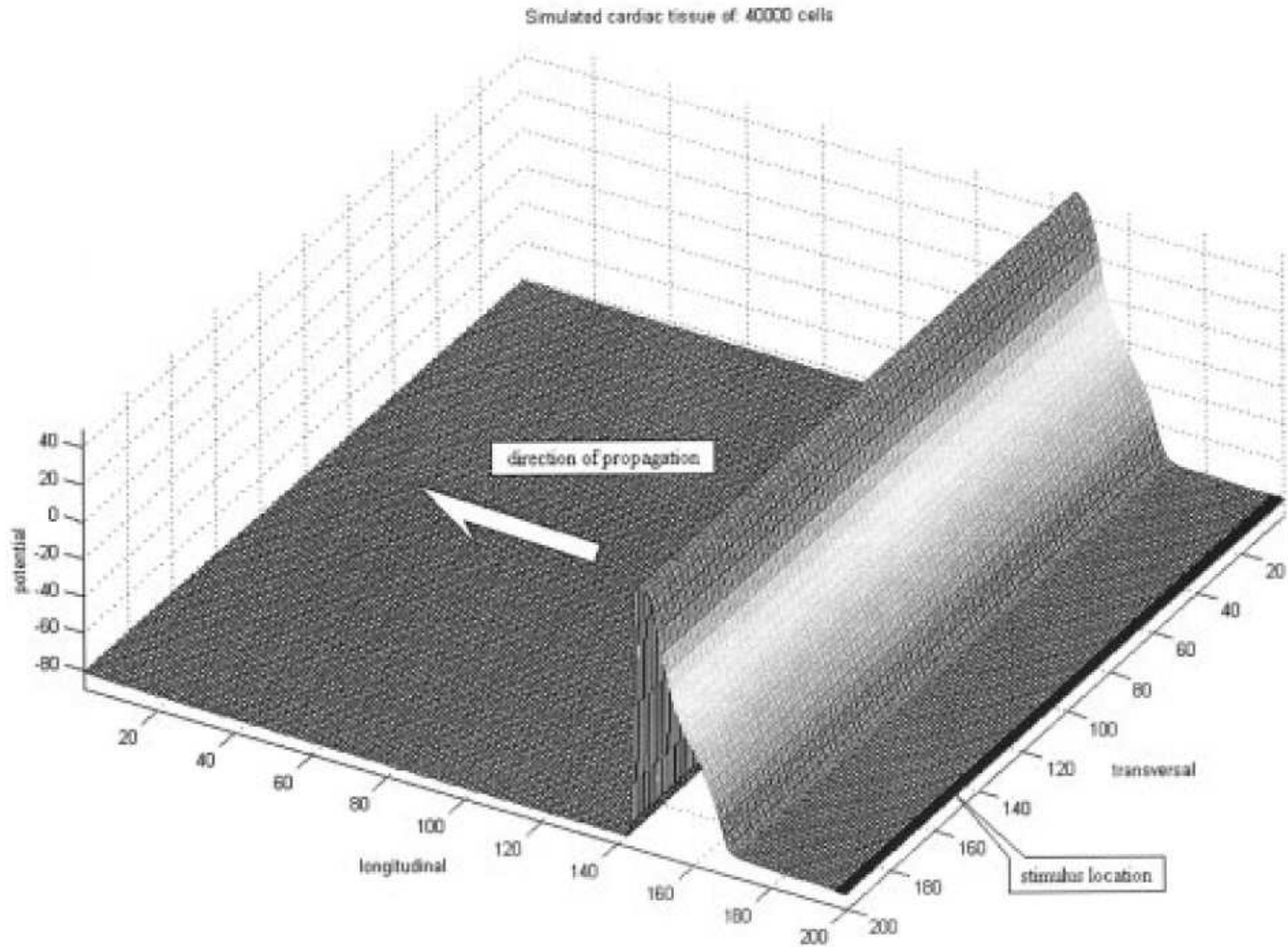
$$q = \frac{1}{R_i} \frac{dt}{dx^2}$$

- $R_i = 200\Omega\text{cm}$ in healthy tissue, $R_i = 2000\Omega\text{cm}$ in the infarcted (dead) tissue and $R_i = 1000\Omega\text{cm}$ in a borderzone of injured tissue. Hence, the tissue is modeled as isotropic.
- $dx = dy = 125\mu\text{m} = 1/8\text{mm}$.
- $dt = 0.0625\text{ms}$.

Experiments: Propagation

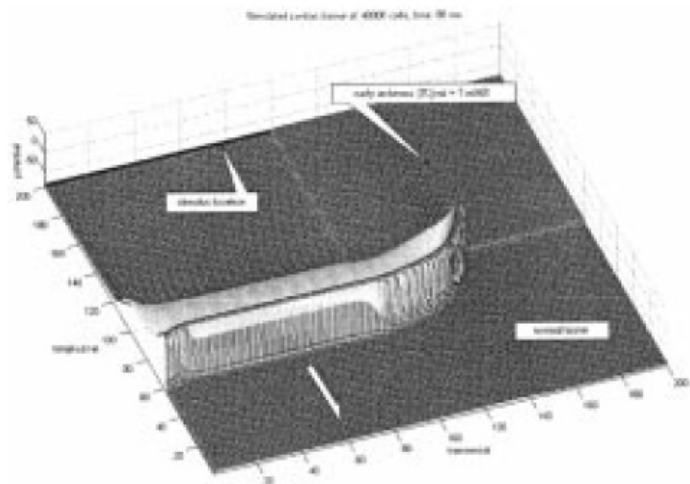
- What are the effects of ischemia and infarction on action potential propagation ?
- 2D simulations on a layer of 200×200 “cells”.
- Propagation in normal conditions: A straight line depolarization wave (Figure 6).

Normal propagation

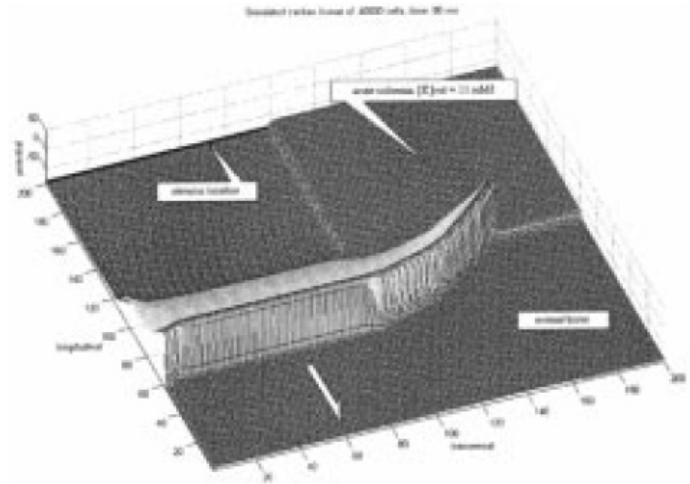


Propagation with ischemia

- An ischemic region, with hyperkalemia and acidosis, is defined as one quarter of the simulation domain.
- Demonstrates a visible tendency of re-entry, in particular in the early stages of ischemia.
- The re-entry tendency is linked to increased excitability and faster recovery of the ischemic cells.
- The phenomenon is still visible at later stages (higher $[K_o]$), but much less severe.
- Preliminary conclusion: The risk of arrhythmias is largest in the early stages of ischemia. It is hence important to identify this condition in a clinical setting (ECG), and this motivates further experiments.



(a)



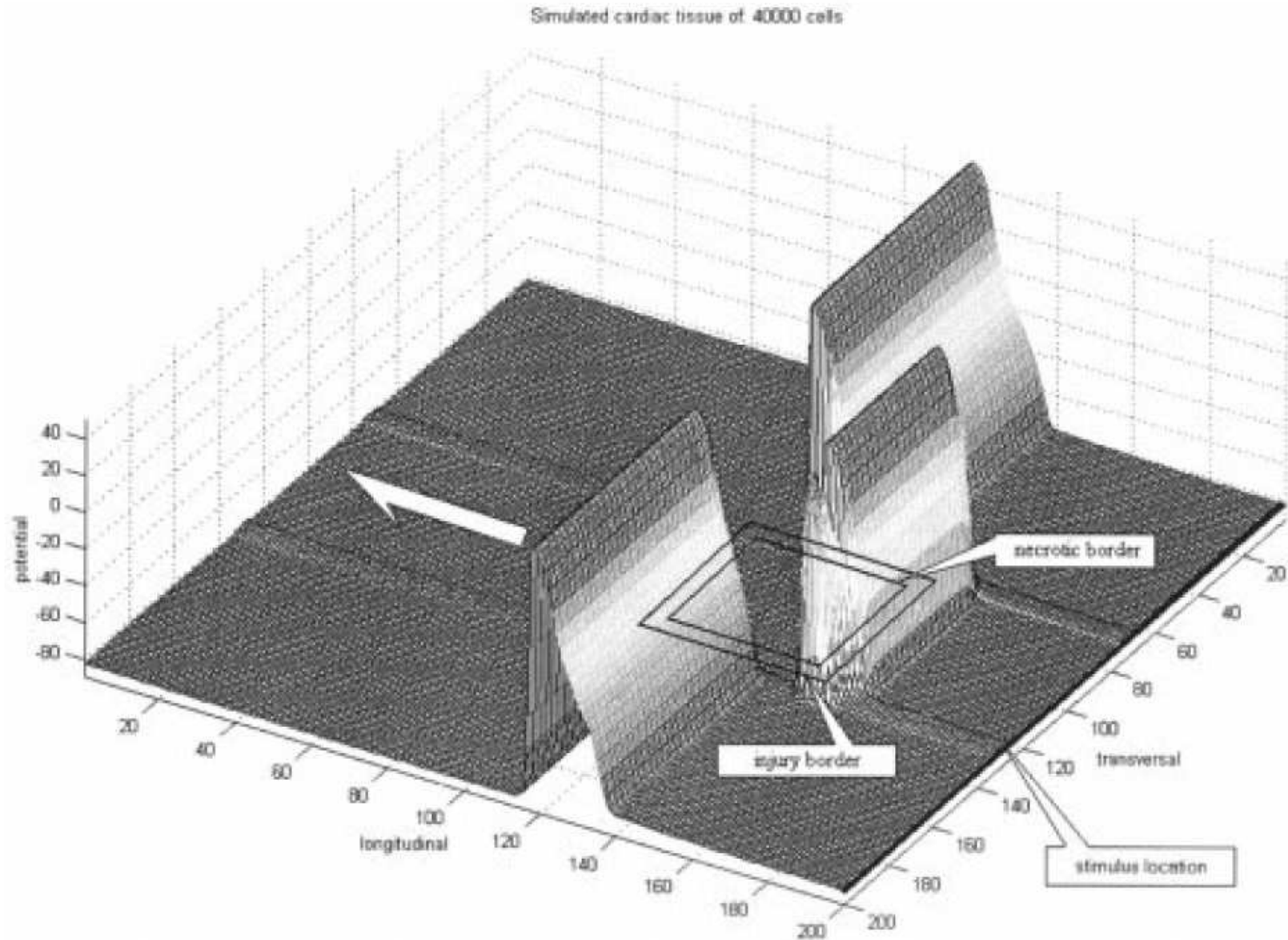
(b)

Fig. 8. Wave propagation in the simulated myocardium partially affected by ischemia.

Propagation with an infarction

- An infarcted region (low conductivity, and hyperkalemia?) is defined as a square in the middle of the simulation domain.
- The infarct is surrounded by a transitional zone of injured tissue.
- Figure 7 shows the propagation obtained with this set-up. The depolarization wave breaks up because of the lower conductivity. This break-up of the signal may cause re-entry and arrhythmias.

Propagation with infarcted region



Experiments: Reconstructed ECGs

- The findings of the previous experiments motivates further studies, more related to a clinical setting.
- In particular, it is of interest to study the changes on the ECG signal during the early phases of ischemia, when the risk of dangerous arrhythmias was found to be particularly high.
- Computation of the ECG signal is difficult, because the model does not include neither the extracellular potential or a body surrounding the heart.

The ECG signal is reconstructed based on volume-conductor theory. Given the membrane current

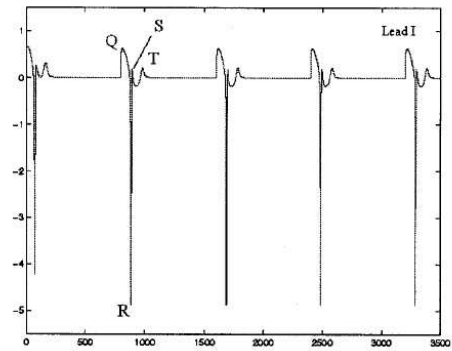
$$I_{\text{membrane}} = I_{\text{ion}} + C \frac{\partial V}{\partial t},$$

the potential at a distant point (x_p, y_p, z_p) is given by

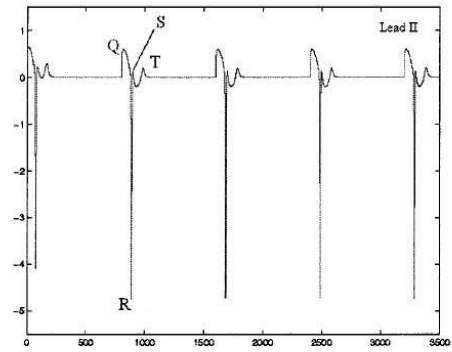
$$e_p = \int \int_{\text{surface}} \frac{I_{\text{membrane}}}{\sqrt{(x - x_p)^2 + (y - y_p)^2 + z_p^2}} dx dy$$

- Based on the described formula, the electrical potential is computed in 3 different points P_1 , P_2 and P_3 .
- Three ECG leads are defined as the potential difference between these points.

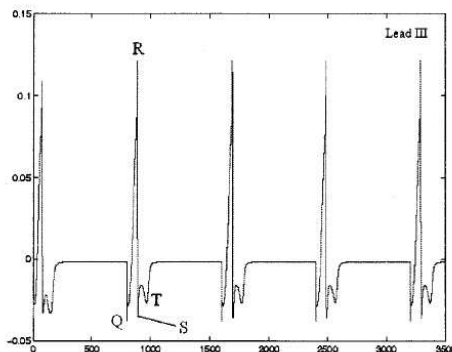
Results: Normal ECG



(a)



(b)



(c)

Fig. 9. Reconstructed three-lead ECG from the normal myocardium.

- Figure 9 shows the resulting three-lead ECG signals in normal conditions.
- Most of the important parts of a real ECG recording are present. One exception is the P-wave which results from the depolarization of the atria.
- The T-wave is inverted, because all the cells in the tissue model are of the same type.

Results: Early and acute ischemia

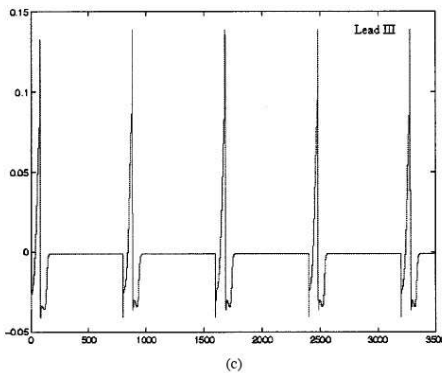
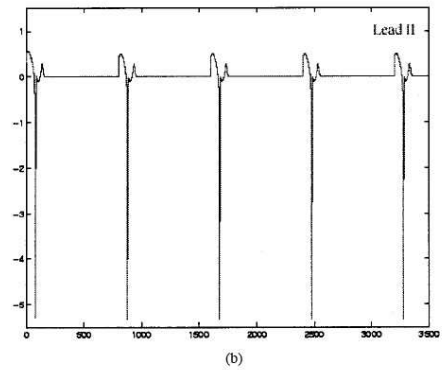
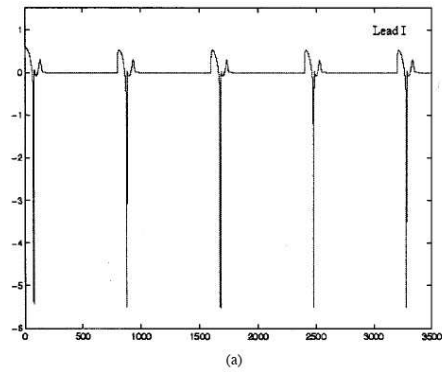


Fig. 10. Reconstructed ECG during early ischemia ($[K]_{out} = 7 \text{ mM/l}$).

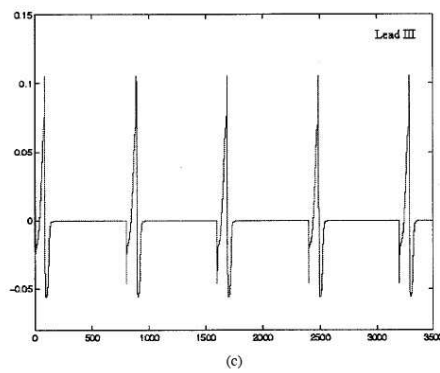
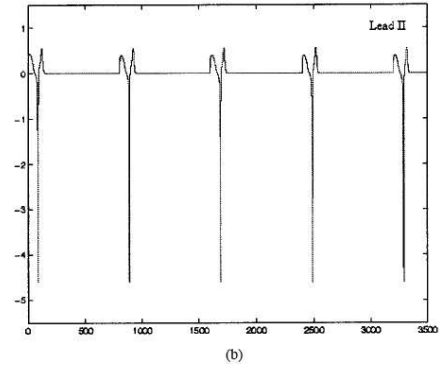
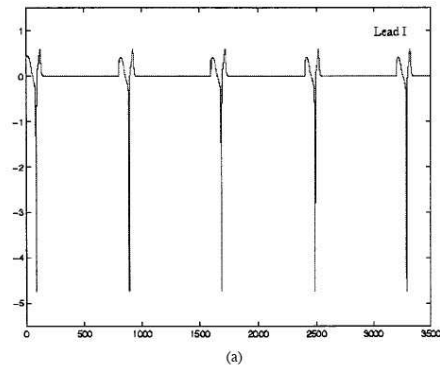


Fig. 11. Reconstructed ECG during acute ischemia ($[K]_{out} = 9 \text{ mM/l}$).

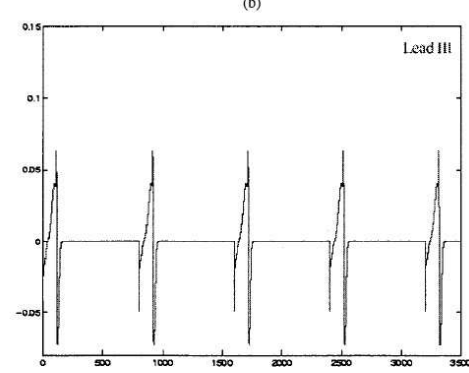
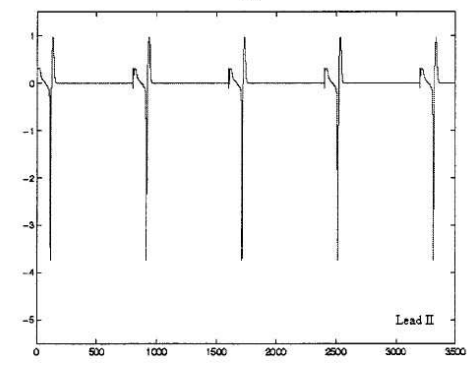
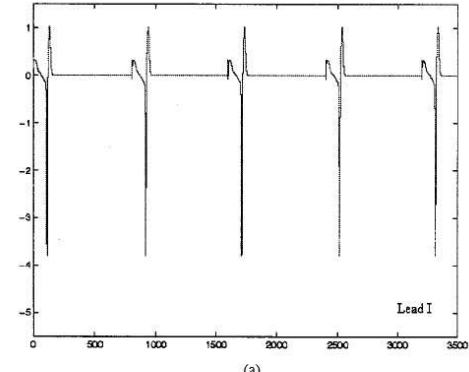


Fig. 12. Reconstructed ECG during acute ischemia ($[K]_{out} = 11 \text{ mM/l}$).

- Figure 10 shows that the amplitude of the QRS complex increases in the early stage of ischemia, following the increased excitability of the cells.
- Figures 11 and 12 shows that the amplitude is reduced with increased hyperkalemia, following the reduced excitability caused by inactivation of sodium channels.
- Figure 12 shows that the QRS-complex becomes wider when $[K_o]$ is increased. This is caused by a reduced conduction velocity caused by the reduced excitability.

Results: Infarction

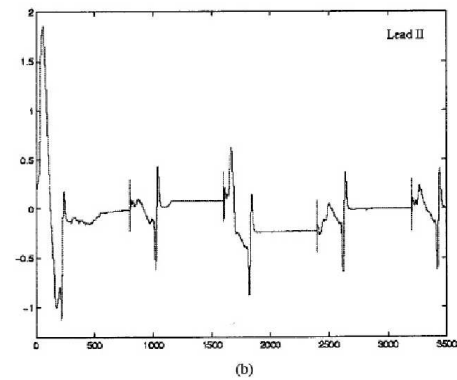
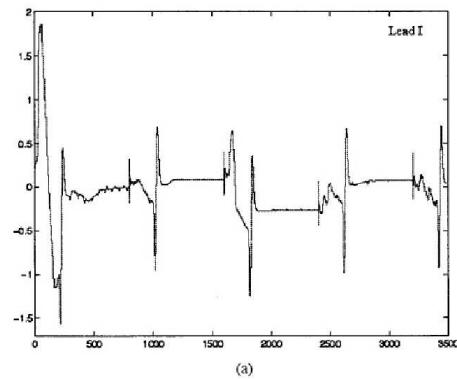


Fig. 13. Theoretical ECG reconstructed during simulated myocardial infarction.

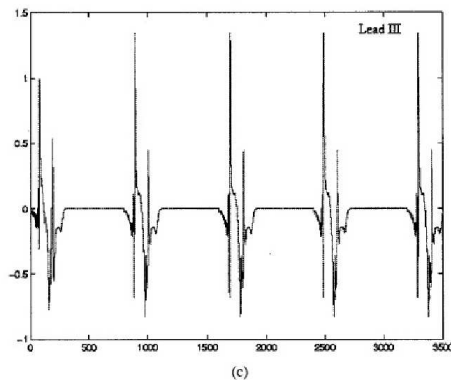
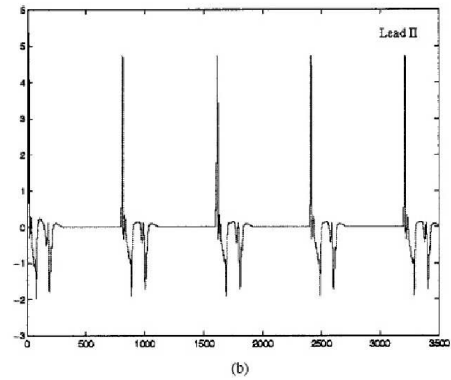
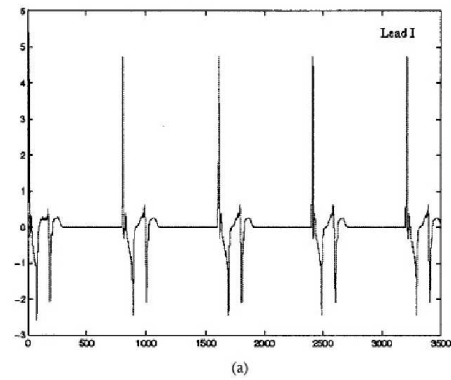


Fig. 14. Theoretical ECG reconstructed from the simulated infarcted myocardium after resolving.

- The nonuniform conductance and ionic concentrations ($[K_o]$) cause differences in the resting potential between the infarcted region and its surroundings. This leads to “injury currents”.
- Comparing figures 13 and 14, we see that the most severe changes in the ECG signal are reversible, they are caused by the altered chemical concentrations. However, even after the chemical values have returned to normal, the ECG recordings are severely affected by the changed conductivity properties of the tissue.

Conclusions

- A fairly “simple” cardiac cell model was used to simulate normal and ischemic cells.
- An arrangement of 200×200 cells was used to study the effects of ischemia and infarction on signal propagation and ECG recordings.
- This simple experimental set-up was able to reproduce the qualitative characteristics of ECG signals.
- The ECG signal changed significantly during ischemia and infarction.
- Most important result: A simple mathematical model was sufficient to produce clinically interesting results.