1 Supplement

1.1 Equations describing propagation in cardiac tissue

Cardiac electrophysiology within the ventricular models used in this study was simulated using the set of monodomain equations:

\[ \nabla \cdot (\sigma_m \nabla V_m) = \beta (I_m - I_s) \quad (1) \]

where \( V_m \) is the transmembrane voltage, \( \sigma_m \) is the conductivity tensor, \( \beta \) is the surface-to-volume ratio, \( I_s \) is an applied stimulus current for initiating propagation and \( I_m \) is the transmembrane current given by:

\[ I_m = C_m \frac{\partial V_m}{\partial t} + I_{\text{ion}} \quad (2) \]
\[ I_{\text{ion}} = g(V_m, \eta, t) \quad (3) \]
\[ \frac{\partial \eta}{\partial t} = f(V_m, \eta, t) \quad (4) \]

where \( C_m \) is the membrane capacitance per unit area, \( I_{\text{ion}} \) is the current density flowing through the ionic channels depending on the membrane state and concentrations of ion species represented by a state vector, \( \eta \), which is described by Eq.(4) according to the chosen ionic model.

Cellular dynamics was simulated using the ten Tusscher-Panfilov model (epicardial phenotype) [2], which was modified to reproduce action potential duration values reported in the porcine heart [3]. Modifications of the default parameters of the model were implemented in both healthy and border zone (BZ) cells. In healthy cells, maximum channel conductance of both slow and rapid delayed rectifier potassium currents was increased by 230%. In BZ cells, peak sodium current was reduced by 62%, peak L-type calcium current by 69%, and peak delayed rectifier potassium currents by 31% and 54%. An initial state vector was generated by pacing each cell at a cycle length of 600 ms for 100 cycles.

The conductivity tensor \( \sigma_m \) in Eq.(1) is given by:

\[ \sigma_m = \sigma_i^\xi (\sigma_i^\xi + \sigma_e^\xi)^{-1} \sigma_e^\xi \quad (5) \]

where \( \xi = l|t \) are the eigendirections of the tissue along the cardiac fiber direction (\( \xi = l \)) and transverse (\( \xi = t \)) to it within the intracellular (\( i \)) and extracellular (\( e \)) domain. The eigenvalues of the tensors are given below in Table 1.

| Table 1: Summary of conductivity settings used in both healthy and border zone (BZ) tissue. |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Tissue | \( g_{il} \) S/m | \( g_{el} \) S/m | \( g_{it} \) S/m | \( g_{et} \) S/m | \( \beta \) \( \mu^{-1} \) |
| Healthy | 0.174 | 0.625 | 0.019 | 0.236 | 0.14 |
| BZ | 0.019 | 0.236 | 0.019 | 0.236 | 0.14 |
1.2 Numerical solution

For the spatial discretization of the monodomain equation a standard finite element method was used as detailed in the openCARP manual, Sec. 30.1). An operator splitting scheme was employed, see openCARP manual, Sec. 30.3). For the temporal discretization a Crank-Nicolson approach was used, openCARP manual, Sec. 30.3.2). The discretized system was solved using the conjugate gradient method with an incomplete LU preconditioner.

1.3 Simulations in openCARP

An idealized 2D cardiac infarct model designed with the purpose of replicating the setup used in this study (see Figure 1A) is available for download from RADAR4KIT. The data set includes:

- ilu_cg_opts
- parameters.par
- run.sh
- vm.mshz

Software for validation of our setup is available for download from the openCARP web page. Execution requires mesher for creating the test mesh, openCARP for running the simulations and meshalyzer for visualization of the simulation results.

Snapshots of $V_m$ showing reentry induction following the pacing protocol are shown in Figure 1B. Note that the set of tissue conductivities used here resulted in a propagation pattern with enhanced anisotropy ($t = 4380$ ms). Note also that conduction velocity is slower in the isthmus due to the assigned reduced tissue conductivity. In this setup, reentry was induced by a S2 beat with a coupling interval of 250 ms in respect to the last paced S1 beat ($t = 4200$ ms - 8 pulses with a pacing cycle length of 600 ms). The S2 beat blocked at the isthmus’ mouth proximal to the stimulus site at $t = 4550$ ms, traveled around the scar and reentered the isthmus from its distal mouth ($t = 4900$ ms) from where it propagated back to the myocardium.

Details of the parameter file used to simulate cardiac excitation within the idealized model are summarized below. To ascertain reproducibility of our simulation setup, all parameters are explicitly given as simulator input that can be directly used with the openCARP simulator [1]. Simulations were tested under both Linux and Mac OSX.

1.3.1 Electrophysiology definition

Two types of viable tissues, healthy and BZ, were defined as follows:

**Healthy myocardium electrophysiology and conductivity**

| Parameter                  | Value          | Description                                  |
|----------------------------|----------------|----------------------------------------------|
| -imp_region[0].name        | Myocardium     | Name of the region                           |
| -imp_region[0].im          | tenTusscherPanfilov | ten Tusscher–Panfilov 2006 model            |
| -imp_region[0].im_param    | "GKr*2.3,GKs*2.3" | Modification of default values               |
| -imp_region[0].cellSurfVolRatio | 0.14       | Surface-to-volume ratio                      |
| -gregion[0].g_il           | 0.174          | Longitudinal intracellular conductivity      |
Figure 1: Reentry initiation in the idealized infarct model. A) Idealized infarct model. B) $V_m$ maps at different times show reentry induction following the S1-S2 pacing protocol. Arrows represent successful propagation. Lined arrows represent conduction block.

BZ tissue electrophysiology and conductivity

| Parameter                  | Value                           | Description                                      |
|----------------------------|---------------------------------|--------------------------------------------------|
| -imp_region[0].name        | BZ                              |                                                  |
| -imp_region[0].im          | tenTusscherPanfilov             |                                                  |
| -imp_region[0].im_param    | "GNa*0.38,GCaL*0.31,GKr*0.69,GKs*0.46" |                                                  |
| -imp_region[0].cellSurfVolRatio | 0.14                      |                                                  |
| -gregion[0].g_il           | 0.019                           |                                                  |
| -gregion[0].g_el           | 0.236                           |                                                  |
| -gregion[0].g_it           | 0.019                           |                                                  |
| -gregion[0].g_et           | 0.236                           |                                                  |

1.3.2 Pacing protocol

In our study, clinical S1-S2-S3 electrical stimulation protocol was applied from 17 pacing sites. Each electrode position was defined as a set of vertices according to the vertex specification file format (see [openCARP manual], Sec. 4.1.6). For each electrode the same pacing protocol was defined consisting of 8 $S1$ stimuli, one $S2$ stimulus and one $S3$ stimulus. The protocol according to was defined then as:
Parameter | Value | Description
---|---|---
-num_stim | 3 | Number of stimuli
-stimulus[0].name | S1 | Label of the pacing electrode
-stimulus[0].stimtype | 0 | Type of stimulus (transmembrane current)
-stimulus[0].strength | 100 | Stimulus strength
-stimulus[0].start | 0 | Start time
-stimulus[0].duration | 1 | Duration of stimulus
-stimulus[0].npls | 8 | Number of pulses
-stimulus[0].bcl | 600 | Basic cycle length
-stimulus[0].vtx_file | STIMxx | File name with a vertex based electrode definition
-stimulus[1].name | S2 | 
-stimulus[1].stimtype | 0 | 
-stimulus[1].strength | 100 | 
-stimulus[1].start | 4450 | 
-stimulus[1].duration | 1 | 
-stimulus[1].vtx_file | STIMxx | 
-stimulus[2].name | S3 | 
-stimulus[2].stimtype | 0 | 
-stimulus[2].strength | 100 | 
-stimulus[2].start | 4630 | 
-stimulus[2].duration | 1 | 
-stimulus[2].vtx_file | STIMxx | 

1.3.3 Solver options

Parameter | Value | Description
---|---|---
-bidomain | 0 | Solve using monodomain
-bidm_eqv_mono | 1 | Monodomain equivalent to the bidomain
-dt | 25 | Size of the time step
-parab_solve | 1 | Crank-Nicolson
-cg_tol_parab | 1e-8 | Solver tolerance
-operator_splitting | 1 | Use operator splitting
-mass_lumping | 1 | Lump mass matrix

2 References

References

[1] Plank G, Loewe A, Neic A, et al. The openCARP simulation environment for cardiac electrophysiology. Comput Methods Programs Biomed. 2021;208:106223. doi:10.1016/j.cmpb.2021.106223

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[3] Kong W, Fakhar N, Sharifov OF, Ideker RE, Smith WM, Fast VG. Optical Measurements of Intramural Action Potentials in Isolated Porcine Hearts Using Optrodes. Heart Rhythm. 2007;4(11):1430-1436. doi:10.1016/j.hrthm.2007.07.002