VALIDATION OF A RABBIT VENTRICULAR BIDOMAIN COMPUTER MODEL FOR REENTRY INDUCTION

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Abstract: *In-silico* models of the cardiac excitation spread are among the most elegant methods to gain insights into the mechanisms underlying the formation of arrhythmias and their termination with electrical shocks. In recent years, models have become increasingly detailed accounting for more and more anatomical and functional features of the heart. Interestingly, although there is a wide statistical variance of parameters in biological tissue, most models rely on standard parameters which are based on a very limited number of references. Therefore it is not too surprising that simulations results often are strikingly different compared to experimental data. Consequently, to increase the predictive power of computer modelling studies it is essential to account for these statistical variations and adjust model parameters accordingly. Matching of the wavelength, λ, is considered as a minimum requirement to allow comparisons between *in-silico* and *in-vitro* data. Better agreements can be achieved by carefully adjusting model parameters to account for cardiac heterogeneities which are, although known to exist, widely ignored. In this study, a simplified validation method employing a novel technique based on measurements of the cardiac near field. Further, it is investigated to which degree the formation of arrhythmias is influenced by model parameter variations.

Introduction

Undoubtly, computer simulation of the cardiac excitation spread is among the most elegant methods to gain insights into the mechanisms underlying the formation of cardiac arrhythmias (arrhythmogenesis) and their termination with electrical shocks (defibrillation). Many parameters used in cardiac modelling, however, are uncertain due to a large variatiance in biological tissue. Most simulation studies rely on standard parameters reported in literature[1, 2, 3] which may, however, lead to strikingly different activation sequences compared to experimental observations. Consequently, to increase the predictive power of computer modelling studies it is essential to adjust model parameters to match simulation results with experimental data. A good agreement in wavelength, λ, i.e. the product conduction velocity, v, $\times$ action potential duration (APD), has to be considered as a minimum requirement to allow comparisons with experimental results, and, subsequently, to draw direct conclusions from computer simulations. However, conduction velocity and APD are not constant over the heart, but show heterogeneous variations in several ways like for instance variations in APD and AP shape in the transmural and apicobasal direction. Unfortunately, the local wavelength cannot be measured everywhere in the intact heart, but might be obtained at the epicardial surface. Multisite electrical or optical mapping techniques can be applied for this purpose, but also simpler single site techniques can be used to acquire data sequentially.

In this study, an experimental procedure using a novel cardiac near field (CNF) sensor is tested to investigate its applicability for the validation of a computer model with experimental data. Using this sensor, rabbit hearts were paced at the apex to induce action potential (AP) propagation. Subsequently, the epicardial surface was sampled with a CNF sensor to determine conduction velocity, direction of propagation and APD at each observation site. Finally, model parameters of a rabbit ventricular bidomain computer model are adjusted to reproduce the experimentally observed epciardial activation sequence. Further, the influence of model parameter variation on the outcome of standard arrhythmia pacing protocols is investigated.

Materials and Methods

Computer Model:

The bidomain description of cardiac tissue links intracellular potential, ϕ_i, and the interstitial potential, ϕ_e, through the transmembrane current, I_m.

$$-\nabla\cdot(\bar{\sigma}_i\nabla\phi_i) = -\beta I_m \quad (1)$$

$$-\nabla\cdot(\bar{\sigma}_e\nabla\phi_e) = \beta I_m \quad (2)$$

with

$$I_m = C_m\frac{\partial V_m}{\partial t} + I_{ion}(V_m,\vec{\eta}) \quad (3)$$

$$\frac{d\vec{\eta}}{dt} = g(V_m,\vec{\eta}) \quad (4)$$

$$V_m = \Phi_i - \Phi_e \quad (5)$$

where $\bar{\sigma}_i$ and $\bar{\sigma}_e$ are the intracellular and extracellular conductivity tensors, β is the surface to volume ratio of cardiac cells, C_m is the capacitance per unit area,

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$V_m = \phi_i - \phi_e$ is the transmembrane voltage, $\vec{\eta}$ is a vector describing the membrane state, and I_{ion} is the ionic current density through the membrane. The active membrane behaviour was described using the rabbit ventricular Puglisi model [4]

Further, it is assumed that the heart is immersed in a conductive fluid. Hence, the distribtution of extracellular potentials outside the heart and in the heart's cavities is governed by the Laplace equation

$$-\nabla \cdot (\bar{\sigma}_b \nabla \phi_e) = I_e. \tag{6}$$

where I_e is an extracellularly applied stimulus current. At the tissue-bath interface, continuity of the normal component of the extracellular current and continuity of extracellular potentials were enforced. The normal component of the intracellular current vanished at all tissue boundaries whereas the normal component of the extracellular current vanished at the boundaries of the bath.

Grid Generation: Based on the San Diego rabbit ventricular model[5], a tetrahedral finite element mesh [6] was developed using an unstructured grid to allow a smooth represenation of the organ boundaries. From a macroscopic point of view, this finite element mesh is an accurate representation of a rabbit ventricle with realistic gross anatomy and anatomically realistic fiber orientations.

The heart was immersed in a tissue bath such that there was a minimum distance of at least 1 mm between bath boundary and epicardial surface. The average discretization within the myocardium was 250 μm. With increasing distance from epicardial and endocardial surface the discretization was increased to a maximum of 500 μm at the bath boundaries.

Numerical Methods: The bidomain equations were decoupled by operator splitting as described in [7] yielding an elliptic partial differential equation (PDE) with 862.515 unknowns

$$\begin{bmatrix} -\nabla \cdot (\bar{\sigma}_i + \bar{\sigma}_e) \nabla \phi_e \\ -\nabla \cdot \sigma_b \nabla \phi_e \end{bmatrix} = \begin{bmatrix} \nabla \cdot \bar{\sigma}_i \nabla V \\ I_e \end{bmatrix}, \tag{7}$$

a parabolic PDE with 547.680 unknowns

$$\frac{\partial V}{\partial t} = \frac{1}{\beta C_m} (\nabla \cdot \bar{\sigma}_i \nabla V + \nabla \cdot \bar{\sigma}_i \nabla \phi_e) - \frac{1}{C_m} i_{ion}(V, \eta), \tag{8}$$

and a set of non-linear ODE's

$$\frac{d\vec{\eta}}{dt} = g(V, \vec{\eta}). \tag{9}$$

Considering equations (7) and (8) as independent, the system can be solved sequentially by leapfrogging. The elliptic equation was solved using the conjugate gradient method with an algebraic multigrid preconditioner [8]. The parabolic equations and the ODE's of the ionic model were solved using the explicite forward Euler method. Temporal discretization was chosen to be 10 μs.

Adjusting the Conduction Velocity: Conduction velocity depends mainly on the choice of conductivty tensors, the surface-to-volume ratio β and on the sodium current of the kinetic model. It is known from core conductor theory that the velocity of AP propagation along a strand of cardiac cells is given by the porportionality relation

$$v \propto \sqrt{\frac{1}{\beta} \frac{\bar{\sigma}_i \bar{\sigma}_e}{\bar{\sigma}_i + \bar{\sigma}_e}}. \tag{10}$$

That is, varying $\bar{\sigma}_i$ and $\bar{\sigma}_e$ by a factor κ leads to an change in v by a factor $\sqrt{\kappa}$. The conductivity influences the conduction velocity in a directionally dependent manner whereas the influence of β is direction independent. Hence, $\bar{\sigma}_i$ and $\bar{\sigma}_e$ can be used to adjust both anisotropy and anisotropy ratio between intracellular and extracellular domain, and also the velocity itself by scaling the main diagonal of these tensors with the same factor. β would modify the conduction velocity independently of the direction of propagation. In this study, the conductivtiy tensors were varied to adjust the conduction velocities while preserving the anistropy ratios in both domains.

Adjusting APD: APD is influenced by many parameters. In this study, APD was adjusted by varying the peak conductivity G_{Ks} of the slow delayed rectifier current I_{Ks}.

Validation Procedure: The rabbit ventricular computer model was validated by proceeding as follows:

(1) First, an experimental protocol was duplicated to compare computed activation sequences with published experimental data [9]. Using the computer model, AP propagation was initiated in the rabbit ventricular model by apical pacing. Isochrone patterns of the initiated propagation of activation were computed. The overall shape of depolarization and repolarization isochrones, mainly determined by the fiber orientations, were computed.
(2) To bring isochrone patterns in agreement, both conductivity tensors, $\bar{\sigma}_i$ and $\bar{\sigma}_e$, where varied to obtain similar distances between isochrones using the same isochronal interval. The conductivity tensors were scaled while preserving anisotropy ratios in both domains.
(3) The influence conductivity tensor variations over the formation of arrhythmias was examined by scaling the nominal values of $\bar{\sigma}_i$ and $\bar{\sigma}_e$between 0.25 and 1. A scaling factor of 0.25 corresponds to a decrease in conduction velocity by a factor of 2. To induce an arrhythmia, the ventricles were stimulated with a pulse train of varying basic cycle length (BCL) using two plate electrodes (see fig. reffig:ReentryInduction). After the last stimulus of the pulse train, the temporal evolution of the system was simulated for another second to examine whether reentrant activity can be initiated or not.

Experimental Method: AP propagation was inititated in Langendorff perfused rabbit hearts by apical stimulation. The Langendorff setup (see fig. 2A) was modified to

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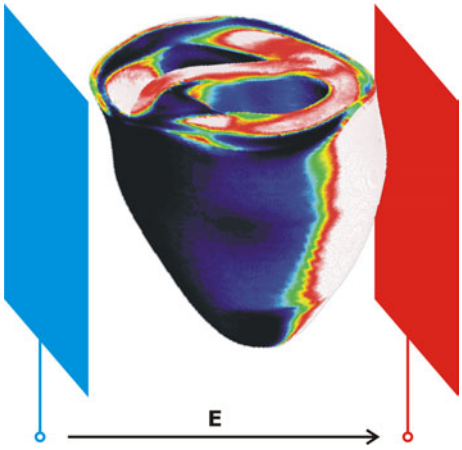

Figure 1: Setup for arrhythmia induction: A rabbit ventricular model, immersed in a tissue bath, was paced using two plate electrodes, placed at opposite boundaries of the bath. Pulse trains with a BCL of 200 ms were delivered to stimuate the heart. The electric field, **E**, established in the bath by the stimulus pulse, was ≈ 6 V/cm measured in the middle of the frontal bath boundary.

allow the rotation of the mounted heart. A angular scale at the mount point (see fig. 2B) allowed to rotate the heart to a desired angular position while keeping the sensor, mounted on a micromanipulator, at the same position. The CNF sensor, consisting of four electrodes arranged like the corners of a square (see inset in fig. 2A), measures the cardiac near field at a microscopic size scale. In a previous study, it was shown that the vector associated with the maximum field strength during depolarisation points opposite the direction of propagation. Conduction velocities were determined by computing local activation times from four unipolar extracellular signals Φ_e [10]. Further, APD was approximated by determining the activation recovery interval [11]. The underlying theoretical framework of the CNF technique has been described elsewhere [12].

Results

Comparison with published Results: The overall shape of simulated isochrones matched well with published experimental results (compare fig. 3 with fig. 1A in [9]) without any modification of model parameters, however, the distance between isochrones differed signifcantly indicating a difference in conduction velocity between model and experiment. A modest variations of up to 20 % of the conductivity tensors around the standard values allowed to obtain a good agreement. Further, to match the reported experimentally observerd average APD g_{Ks} had to be reduced by a factor of ≈0.7.

CNF Measurements: The feasibility of the CNF method to determine conduction velocity, direction of propagation and APD was examined. Both conduction velocity and direction of propagation could be determined robustly with this method whereas APD determination based on the activation recovery interval occasionally failed since no relevant repolarisation signals could be detected. The CNF measured at an epicardial observation site is shown in fig. 4

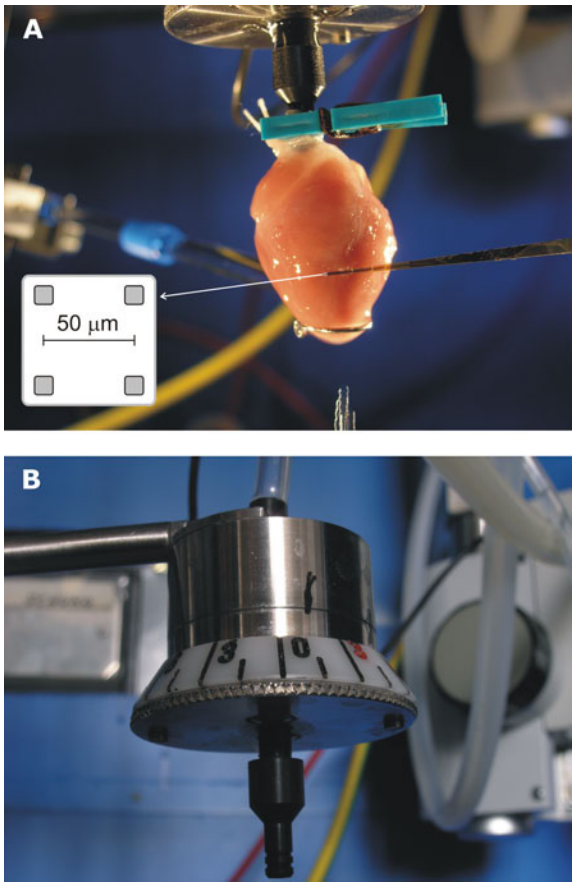

Figure 2: Experimental setup: A) Shown is a Langendorff perfused mouse heart with a CNF sensor. The sensor geometry is shown in the inset at the lower left corner. B) Shown is the mountpoint with an angular scale which allows to rotate the heart around its apicobasal axis.

Induction of Reentry Starting with standard settings for $\bar{\sigma}_i$ and $\bar{\sigma}_e$ (scaling factor κ=1.0), the application of a train of 4 stimuli with a BCL of 200 ms did not induce reentrant activation. Decreasing κ stepwise down to 0.25, the wavelength λ became increasingly smaller until λ became short enough to provide the substrate for the induction of reentrant activation. Consistent with experimental results, with κ=0.25, this shock protocol led to sustained reentrant activation. A stable figure of eight reentrant circuit formed in the apical region. This activation sequence was sustained for at least 2 seconds.

Discussion

In this study, implications of the choice of parameters in todays cardiac in-silico models were examined and a simplified method of improving the agreement between computer model and experimental data was presented. It could be shown that the outcome of computer sim-

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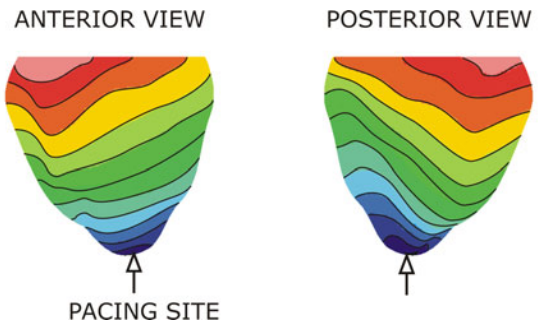

Figure 3: The overall shape of isochrones matched well with published experimental data (compare fig. 3 with fig. 1A in [9]). Intra- and extracellular conductivity tensors were adjusted to obtain matching conduction delays between apex and base.

ulations depends strongly on the choice of parameters. Consequently, when immediate comparsions between *in-vitro* experimental data and simulated *in-silico* data are required, it is essential to match at least the wavelength λ. Otherwise comparisons are impossible and conclusions drawn from computer simulations might be misleading.

Computational Aspects: A decade ago, when simulations of AP propagation along a one-dimensional fiber strand were considered as state of the art, validation of simulation results was an almost trivial task. Today, complex computer models incorporating detailed descriptions of the cardiac anatomy are employed to gain insights, the validation process, however, has become a painful procedure. Computed cardiac activation sequences depend on a number of parameters among which the following play an important role: 1) the conductivity tensors $\bar{\sigma}_i$ and $\bar{\sigma}_e$ which influence conduction velocity, anisotropy and anisotropy ratios between intracellular and interstitial domain. 2) the surface-to-volume ratio β which is approximately inversely related to the radius of an assumed cardiac fiber, and 3) the ionic models which, in recent state-of-the-art descriptions, comprise tens of parameters influencing both conduction velocity and APD.

Assuming that the inter-individual variation in cardiac fiber orientation is negligible, and that the principal fiber directions in todays models are a reasonably accurate approximation of the fibrous organization in real hearts, the overall activation sequence between model and experiment should be similar. Under these circumstance, model parameter tuning reduces to the task of adjusting conduction velocity and APD. A systematic approach for this validation process would be invaluable to allow the quick adjustment of computer models to a particular experimental situation. For the future development of cardiac computer models, it is desireable to increase the number of available computational grids for a particular species, since almost all studies rely on the same mesh. Hence, systematical errors or peculiarities of a single heart which was chosen for the model generation, may bias the results of all studies based on a particular computational grid.

Experimental Aspects: Typically, due to technical

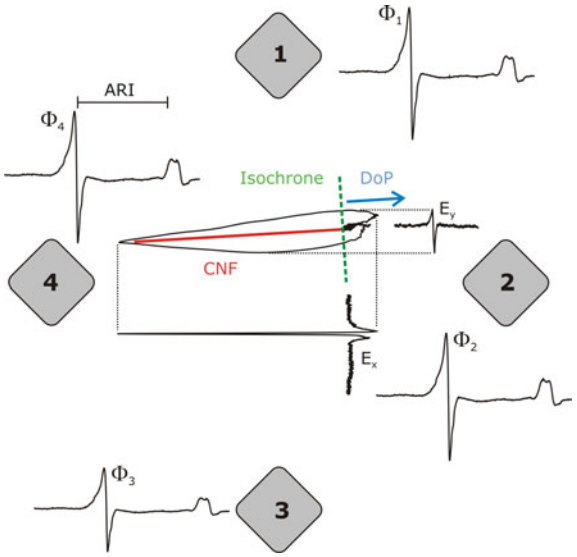

Figure 4: The CNF measured at an epciardial observation site: The CNF depolarisation signals forms a vector loop which points opposite the direction of propagation (DoP, blue vector), i.e. the maximum CNF vector (red solid line) is perpendicular to the local isochrone (green dashed line) at the time of local activation. Further, unipolar signals Φ_e are shown for each electrode of the four-element electrode array (position indicated by gray squares). Conduction velocities can be determined using the derivatives $\dot{\Phi}_e$ of Φ_e signals. The components of the gradient signals, $E_x = (\Phi_{e2} - \Phi_{e4})/\mathrm{DD}$ and $E_y = (\Phi_{e1} - \Phi_{e3})/\mathrm{DD}$, are plotted next to the CNF vector loop. The dipole diameter DD (distance between the centers of pad 1 and 4) was 50 μm.

limiations only epicardial or endocardial potentials can be measured in intact hearts, the intramural activation sequence remains unknown. However, it is reasonable to assume that a computer model which correctly reproduces both epicardial and endocardial activation sequence, will also predict a correct intramural activation sequence. Multi-electrode mapping setups are suited to obtain activation times for the construction of isochrones at cardiac surfaces which can be used for model validation. However, this approach suffers from several disadvantages. The spatial resolution of multisite mapping systems is very limited, trade-offs between the number of electrodes, sampling rate and spatial resolution have to be made. Hence, complex propagation patterns at the microscopic size scale cannot be detected with such systems. Further, the exact mapping between recording site and computer model is a non-trivial problem. Since landmarks like arteries are missing in todays computer models, it is difficult to determine the correct correpsondence. Further, regions which are anatomically complex like, for instance, the endocardial regions around the terminal crest and the pectinate muscles cannot be easily mapped with multisite recording devices.

The CNF approach suggested in this study does not suffer from these limitations. The determination of the local direction of propagation does not depend on lo-

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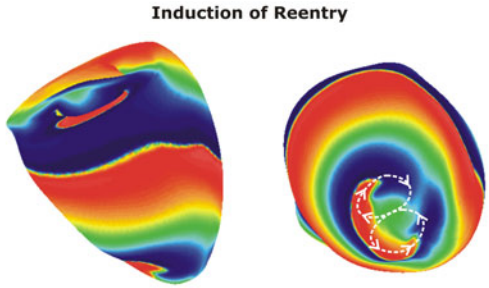

Figure 5: Setting the conductivity scaling factor κ=2 led to a stable Figure-of-Eight reentry in the apical region. The movement of the phase singularities is indicated with white dashed lines. The arrhythmia was sustained over the entire observation period of 2 seconds.

cal activation times giving robust and reliable answers even in the case of complex activation patterns which are often associated with fractionated electrograms. The CNF sensor is mounted on a flexible tongue which follows the excursions of a cardiac surface during contraction and allows access of regions, like e.g. under the appendages, which are not accessible otherwise. The mapping between experiment and computer model is straightforward. The location of a recording site is easily determined with two parameters, azimuth angle and distance to the apex. Only the ”zero meridian” has to be matched between model and experiment which is usually readily accomplished by setting the angular scale to zero at the intraventricular sulcus which can be easily identified in both models.

The disadvantage of the CNF method is its sequential nature. The construction of global activation patterns rely on the assumption that activation sequences are stable which is not always the case. However, for the sake of model validation this is not essential. Knowing conduction times between apex and observation site, direction and velocity of conduction at the observation site for a limited number of recording sites should be good enough to determine appropriate parameters in order to obtain a reasonably good match between in-silico model and experiment.

Conclusions

To increase the predicitive power of todays cardiac computer models, methods allowing a fast adjustment of model parameters to match in-silico and in-vitro models of the heart are sought after. Matching the wavelength between computer model and experiment can be considered as a minimum requirement, however, this procedure does not account for cardiac heterogeneities. Since the outcome of AP propagation in todays computer models, particularly when studying the formation of arrhythmias and their termination with defibrillation shocks, depends heavily on the choice of parameters, a fast and robust validation method is almost indispensable to complement theoretical studies. .

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