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Parametrization strategies for matching activation sequences in models of ventricular electrophysiology

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Abstract— **Driven by recent advances in medical imaging, image segmentation and numerical techniques computer models of ventricular electrophysiology account for increasingly finer levels of anatomical and biophysical detail. However, considering the large number of model parameters involved parametrization poses a major challenge. A minimum requirement in combined experimental and modeling studies which aim at making specific predictions on a case by case basis is to achieve good agreement in activation and repolarization sequences between model and experiment or patient data. In this study we propose basic techniques which aide in determining bidomain parameters to match ventricular activation sequences. Two specific aspects will be considered. First, conduction velocity in the ventricles is orthotropic and varies in space. An iterative parametrization algorithm is implemented which determines appropriate conductivities which yield prescribed velocities. Secondly, impulse propagation in the ventricles is initiated subendocardially at Purkinje-ventricular junctions, the terminal endings of Purkinje system (PS), and, thus, the PS plays a key role in determining the shape of activation wave fronts as reflected in the QRS complex of the electro-cardiogram (ECG). While ventricular models equipped with generic PS topologies match well with experimental observation in terms of epicardial breakthrough sites, predicted ECGs match poorly with known key ECG characteristics.**

I. INTRODUCTION

In-silico models of ventricular electrophysiology are widely recognized to be an invaluable adjunct to experimental in-vitro or in-vivo models. Recent advances in medical imaging [1], image segmentation [2] and image-based finite element (FE) mesh generation [3], along with major advances in the numerical solution of model equations which lifted numerous restrictions on the level of detail that can be included in a model, have led to the generation of micro-anatomically accurate and biophysically detailed ventricular models [4].

While such models account for an increasingly finer level of anatomical and biophysical details, considering the large number of parameters in these models at the order of tens to hundreds of parameters, data assimilation and parametrization poses a major challenge. A minimum requirement in such modeling studies to be able to make case-specific predictions on ventricular electrophysiology is that activation and repolarization sequences are carefully matched.

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In this study we focus on parametrization strategies for matching of activation sequences. Two specific aspects which play a particularly important role in this regard, will be considered: i) Conduction velocity in the ventricles is orthotropic and may vary in space, thus profoundly influencing shape and location of activation isochrones; ii) Impulse propagation in the ventricles is initiated at Purkinje-ventricular junctions which are the terminal endings of a topologically complex network of fibers referred to as Purkinje system (PS). Location and timing of initiation in the ventricles define the configuration of wavefronts which depolarize the ventricles. The observed significant variation in the electrical main axis, as determined from body surface ECG recordings, suggest, a significant inter-individual variability in PS topology.

In this study an outline is given on potential parametrization strategies to better match activation sequences between in-silico models and experiments. In particular, an automatic tuning procedure is proposed which iteratively refines bidomain conductivities using observed conduction velocities in 1D cable simulations as input. Further, we propose strategies which indirectly infer characteristic features of the PS from body surface ECG recordings.

II. METHODS

A. Governing equations

The bidomain equations are considered to be among the most accurate descriptions of cardiac bioelectricity at a macroscopic size scale. In the elliptic-parabolic form they are given by

$$-\nabla \cdot (\boldsymbol{\sigma}_i + \boldsymbol{\sigma}_e) \nabla \phi_e = \nabla \cdot \boldsymbol{\sigma}_i \nabla V_m \quad (1)$$

$$\beta C_m \frac{\partial V_m}{\partial t} = \nabla \cdot \boldsymbol{\sigma}_i \nabla \phi_i - \beta I_{ion}(V_m, \boldsymbol{\eta}) \quad (2)$$

where ϕ_i and ϕ_e are intra- and extracellular potentials, respectively, $V_m = \phi_i - \phi_e$ is the transmembrane voltage, $\boldsymbol{\sigma_i}$ and $\boldsymbol{\sigma_e}$ are the intra- and extracellular conductivity tensors, respectively, β is the membrane surface-to-volume ratio, C_m is the membrane capacitance per unit area, and I_{ion} is the membrane ionic current density which depends on V_m and a set of state variables, $\boldsymbol{\eta}$. At tissue boundaries, no flux boundary conditions are imposed on ϕ_i and ϕ_e.

In a 1D case where impulse propagation occurs along a thin strand of tissue aligned with an axis ζ, or in the case of a planar wave front moving along an axis ζ, the monodomain equation

$$\beta C_m \frac{\partial V_m}{\partial t} = \nabla \cdot \sigma_{m\zeta} \nabla V_m - \beta I_{ion}(V_m, \boldsymbol{\eta}), \quad (3)$$

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is equivalent to the bidomain equation if the monodomain conductivity $\sigma_{m\zeta}$ is chosen to be the harmonic mean between intracellular and interstitial conductivities, that is,

$$\sigma_{m\zeta} = \frac{\sigma_{i\zeta}\sigma_{e\zeta}}{\sigma_{i\zeta} + \sigma_{e\zeta}}, \tag{4}$$

suggesting that conduction velocity in a full bidomain model are matched closely by an equivalent monodomain model with a harmonic mean conductivity tensor.

B. Parametrization of conduction velocities

Conduction velocity, C^v, is not a parameter in the bidomain equations and as such cannot be directly parametrized. However, assuming a continuously propagating planar wavefront along a given direction, ζ, space and time are related by $\zeta = C^v_\zeta \cdot t$ which allows to replace spatial derivatives in Eq. (3) by temporal derivatives

$$\frac{\sigma_{m\zeta}}{\beta}\frac{\partial^2 V_m}{\partial \zeta^2} = \frac{\sigma_{m\zeta}}{C^{v2}\beta}\frac{\partial^2 V_m}{\partial t^2} = C_m\frac{\partial V_m}{\partial t} + I_{ion}(V_m, \boldsymbol{\eta}). \tag{5}$$

Since membrane properties on the right hand side remain unchanged, V_m remains to be a solution of Eq. (5) as long as $\sigma_{m\zeta}/C^{v2}/\beta$ is constant. Thus C^v is governed by the proportionality relation

$$C^v_\zeta \propto \sqrt{\sigma_{m\zeta}/\beta}. \tag{6}$$

Ideally, these parameters and their spatial variation would be measured accurately *in-vivo* for a given subject, however, this is difficult, if not impossible, to achieve. Even when considering *ex-vivo* measurements, the number of reports in the literature is scarce and the variation in measured values across these studies is vast, up to a few hundred percent [5]. These uncertainties inevitably arise due to the significant degree of biological variation and the substantial errors in the measurement techniques themselves which derive the sought after quantities indirectly by making inferences based on model assumptions. Biological factors which influence $\sigma_{m\zeta}$ include inter-individual and inter-species variability, spatial heterogeneity which makes measurements depend on the exact location in the heart from where samples are taken and other factors such as age, sex or pathologies. Further differences may arise due to tissue alterations evoked by the specifics of experimental protocols, e.g. differences between *ex-vivo*, *in-vitro* and *in-vivo* conditions.

C. Iterative parametrization strategy

Considering the significant uncertainties with which bidomain parameters are afflicted, renders their choice in a modeling study a challenging exercise. In addition to biological variation and measurement errors modeling and technical uncertainties may have an impact on model predictions as well. For instance, C^v also depends on the particular model used to describe cellular dynamics, in particular, on the specific make-up of currents active during the depolarization phase. Even between models of the same species, differences in upstroke velocities in both isolated and electrotonically coupled models are observed, which may lead to noticeable differences in C^v. Uncertainties due to technical factors such as discretization errors are of lesser concern since these are, in general, small (<5%) relative to the uncertainties in model parameters. Therefore, resorting to use overly expensive numerical schemes to minimize discretization errors is not a likely candidate strategy for improving the predictive power of computer simulations. The direct use of experimentally measured conductivity values, as if these measured values reflect biophysical reality in the given experimental problem one aims to simulate, is not warranted neither when aiming to achieve good agreement with a specific experiment.

To find a balanced trade-off, we propose a strategy which relies on prescribing C^v directly. This is based on the consideration that C^v is a quantity which is much easier, more robustly and more accurately measurable in-vivo with mapping techniques than tissue conductivities. The proposed assumes that C^v predicted by a given computer simulation setup, $\bar{C}^v_\zeta$, can be represented as a function

$$\bar{C}^v_\zeta = \bar{C}^v_\zeta\left(\sigma_{m\zeta}, \beta, I_{ion}, \Delta\zeta, \xi\right). \tag{7}$$

which depends on the main factors conductivity along an axis ζ, $\sigma_{m\zeta}$, surface-to-volume ratio, β, the chosen model of cellular dynamics, I_{ion}, and technical factors such as spatial discretization, $\Delta\zeta$, and others such as the used spatio-temporal discretization method, convergence criteria and error tolerances in those cases where iterative solvers are employed, the influence of which shall be summarized by ξ. In most practical scenarios, ξ, I_{ion} and $\Delta\zeta$ are parameters user defined in the course of selecting a simulation software, an ionic model and a provided mesh to describe the geometry. Thus, only two free parameters, $\sigma_{m\zeta}$ and β, are left which can be tuned to achieve a close match between the pre-specified conduction velocity, C^v_ζ, and the velocity, $\bar{C}^v_\zeta$, predicted by the simulation.

In ventricular models C^v is orthotropic, thus necessitating to find parameters along each of the three eigenaxes. Among the two parameters available for fitting $\bar{C}^v_\zeta$, β as a scalar scales conduction velocity isotropically in all directions ζ. Using (6) and (3), and keeping β at a chosen default value, one can find unique monodomain conductivities which yield the prescribed conduction velocities, C^v_ζ, by iteratively refining conductivities $\sigma_{m\zeta}$ based on C^v_ζ measured in simple 1D cable simulations. The iterative update scheme we propose is given as

Algorithm 1 Iterative conductivity tuning

```
i=0
σ_mζ [i] = σ^0_mζ
repeat
  C̄^v_ζ[i] ← Simulation
  σ_mζ[i+1] = σ_mζ[i].(C̄^v_ζ[i] / C^v_ζ)^2
  i=i+1
until ‖ C̄^v_ζ[i−1] − C^v_ζ ‖ /C^v_ζ < stop_tol
```

where σ^0_m is an arbitrary initial guess which is used during the first simulation run. In each iteration

D. Validity of using an equivalent monodomain model

Bidomain and monodomain model are only exactly equivalent in 1D or in the case of planar wavefronts, but not in any other multidimensional scenario where wave front curvature is non-zero. Therefore, the validity of using an equivalent monodomain model for chosing bidomain parameters is tested in a 3D slab geometry. Slab dimensions are chosen such that wave fronts traveling with the prescribed orthotropic velocities C^v =0.6m/s, 0.4m/s,0.2m/s, arrive at the opposite faces of the slab at the same time when propagation is initiated with a point stimulus at a corner of the slab.

E. Compensation of spatial discretization effects

When using bidomain parameters as chosen based on the proposed strategy, C^v must be independent of the choice of spatial discretization, $\Delta\zeta$. In order to verify, the influence of $\Delta\zeta$ is studied in a 1D strand model of 1cm length in which $\Delta\zeta$ is varied between 1μm up to 400μm. $\sigma_{m\zeta}$ is iteratively tuned at the 1μm grid to yield a C^v of 0.6m/s, 0.4m/s and 0.2m/s, respectively. At each discretization and for each $\sigma_{m\zeta}$, propagation is initiated at the left hand side end of the cable and $\bar{C}^v$ as well as the spatial extent of the wavefront, ΔX_ζ, is measured at its center. Plots are constructed to show $\bar{C}^v$ as a function of $\Delta\zeta$. Finally, each simulation is repeated, replacing $\sigma_{m\zeta}$, as fitted for the 1μm grid, by $\bar{\sigma}_{m\zeta}$, as computed by the iterative tuning loop described in algorithm 1.

F. Integration of a Purkinje system

The PS initiates propagation in the ventricular subendocardium and as such it is key determinant of the ventricular activation sequence. A generic model of the endocardial PS [6] along with an image-based model of the free-running PS was integrated into a recent micro-anatomically accurate model of rabbit ventricles [4], [2] using an elastic registration technique [7]. Conduction delays across the Purkinje ventricular junctions were matched in both orthodromic and antidromic directions [6].

III. RESULTS

A. Monodomain-bidomain equivalence in 3D

While the exact equivalence between bidomain and monodomain model using harmonic mean conductivities does not hold in 3D, along the principal eigenaxes the agreement between the models is quite good (Fig. 1). This close agreement suggests that the computationally much cheaper equivalent monodomain model can be used within the iterative tuning loop 1, yielding a set of conductivities which enforce the prescribed C^v also when using a full bidomain formulation.

B. Parametrization of conduction velocities

Using the iterative algorithm 1, conductivities were chosen to arrive at the prescribed velocities of C^v_ζ =0.6, 0.4 and 0.2m/s for planar wave fronts traveling along the axes $\zeta = f, s, n$, respectively. Fig. 2A shows how simulated

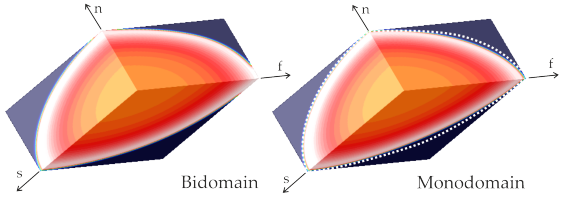

Fig. 1. Comparison between bidomain and an equivalent monodomain model in a 3D slab model. White dashed lines in the Monodomain panel indicate position of the wavefront in a bidomain setting for the same instant in time. f, s and n are orthotropic main axes.

velocities $\bar{C}^v_\zeta$ are affected when increasing grid resolution $\Delta\zeta$ stepwise from 1μm to 400μm. For the used discretization schemes numerical errors of 5% incurred at different spatial resolutions of $\Delta\zeta$ =275μm, 180μm and 90μm for C^v_f, C^v_s and C^v_n, respectively. As expected, scaling of simulated velocities with the prescribed velocity, i.e. $\epsilon_v = \bar{C}^v_\zeta / C^v_\zeta$, reveals that spatial discretization errors are mainly governed by the ratio $\Delta\zeta/\Delta X_\zeta$ (Fig. 2B). Convergence experiments were repeated for C^v_f =0.6m/s and all discretizations $\Delta\zeta$, but equations were re-parametrized using the automatic parametrization strategy (APS) as described in algorithm 1. While conductivities varied in the range between -6 to +24%, wave fronts propagated with the exact prescribed C^v, independently of $\Delta\zeta$.

C. Purkinje system and ECG

Integrating detailed models of the PS is a key determinant of the ventricular activation sequences and thus should be included in ventricular models. Although alternative methods based on programmed endocardial stimulation exist [8] which can be used to model sinus sequences, in pathological situations such as bundle branch blocks or during early phases of arrhythmia formation these method are not suitable. The PS used in this study was carefully matched with experimental findings and produced epicardial activations patters which are in good agreement with experimental observations. Nonetheless, prediction of ECG traces were rather poor, suggesting that more elaborate parametrization strategies for the PS have to be conceived in future studies.

IV. DISCUSSION

Minimum requirements for matching activation sequences in models of ventricular electrophysiology is a parametrization of the bidomain equation which correctly predicts orthotropic conduction velocities. When using unstructured meshes, as it is standard in concurrent finite element modeling studies [4], the average spatial discretization governs C^v. In this study an iterative parametrization strategy is proposed that allows to find appropriate tissue conductivities which result then in the prescribed C^v_ζ along the orthotropic eigenaxes f, s and n of the tissue. Computationally cheap 1D equivalent monodomain models can be used in the parametrization loop to determine conductivities

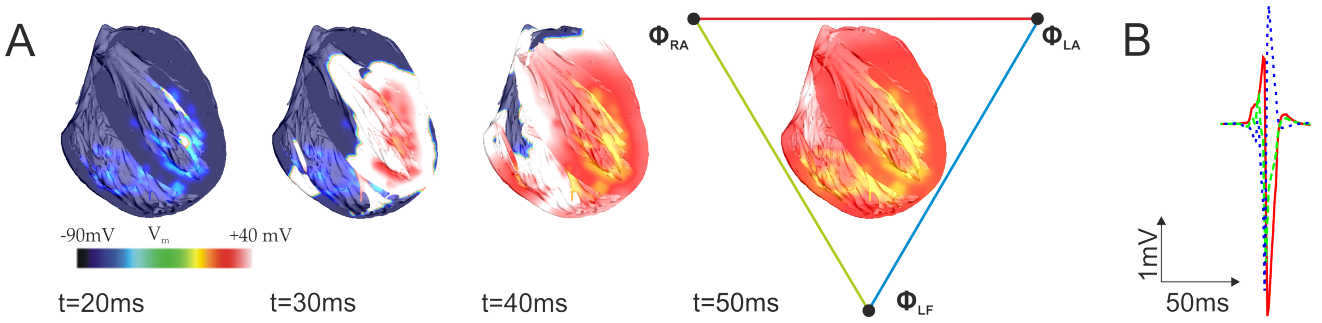

Fig. 3. A) Recordings of complex V_m distribution patterns following His-bundle stimulation on a rabbit ventricular model, where the free-running and sub-endocardial specialized conduction system were present, are shown at $t = 20ms$, $t = 30ms$ and $t = 40ms$. B) Φ_e traces were recovered to compute clinical 3-lead ECG's. Red, green and blue traces represent Einthoven leads I-III.

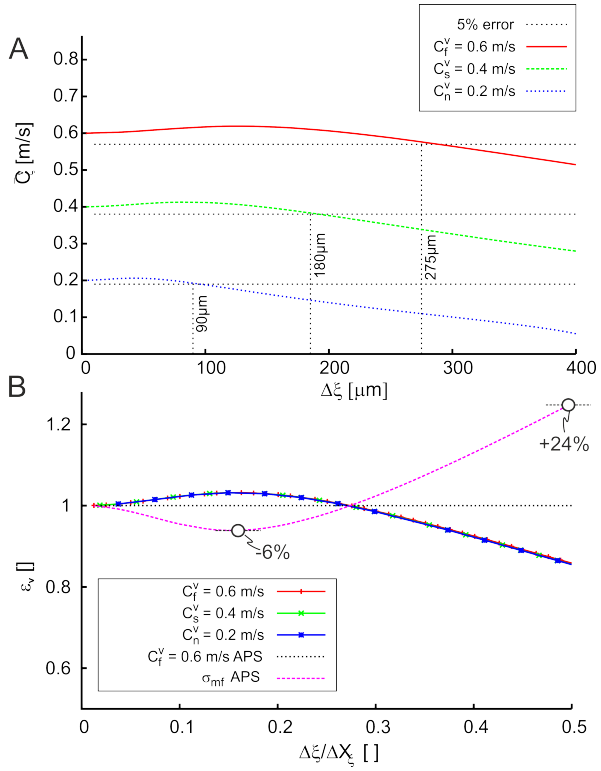

Fig. 2. A) Influence of spatial discretization $\Delta\zeta$ upon predicted conduction velocities for propagation along the axes f, s and n. B) Deviations in relative velocity, $\epsilon_v = \bar{C}_\zeta^v / C_\zeta^v$ depend on the ratio $\Delta\zeta$ to spatial extent of wave front, ΔX_ζ. Using APS, predicted C^v (black dotted trace) is independent of $\Delta\zeta$, at the cost of minor variations of the chosen conductivity value, σ_{mf} (pink trace)

which are also suited for bidomain simulations. While these conductivities lead to a virtually perfect match along the tissue's eigenaxes, when propagation proceeds in any other direction discrepancies between monodomain and bidomain arise. However, as illustrated in Fig. 1, these differences are negligible when compared to overall model uncertainties. Further, it is worth noting that parameter variations due to the automatic parametrization strategy, between -6% up to +24% around the nominal values, are well below the experimentally measured variability. The effectiveness of the methods is demonstrated for spatial discretizations of up to $400\mu m$, however, for even coarser discretizations this may not be the case anymore. However, in line with the current trend towards anatomically detailed ventricular models, finer spatial resolution down to average discretizations of around $\approx 100\mu m$ are becoming standard to resolve geometric details. With such finer spatial steps $\Delta\zeta$, relative discretization of wave fronts $\Delta\zeta/\Delta X_\zeta$ is less than 0.3 and necessary modifications of conductivity values are below 6%.

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