A Workflow for Probabilistic Calibration of Models of Left Atrial Electrophysiology

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Abstract

Atrial fibrillation is an increasingly common condition. Computational models that describe left atrial electrophysiology have the potential to be used to guide interventions such as catheter ablation. Calibration of these models to faithfully represent left atrial structure and function in a particular patient is challenging because electrophysiology observations obtained in the clinical setting are typically sparse and noisy, and can be difficult to register to a mesh obtained from imaging.

Probabilistic approaches show promise as a way to obtain personalised models while taking account of noise, sparseness, and uncertainty. We have developed a workflow in which parameter fields are represented as Gaussian processes, and the posterior distribution is inferred using MCMC. Our workflow has been tested using synthetic data, generated from simulations where the spatial variation in model parameters is known, and we have shown that both features and parameters can be recovered from simulated sparse measurements.

1. Introduction

Atrial fibrillation (AF) is an increasingly prevalent arrhythmia, and the left atrium (LA) is often the main source of fibrillatory activity [1]. Persistent AF can be treated by catheter ablation, and treatment guidance using personalised models offers promise for streamlining these procedures and improving outcomes for patients [2].

The main components of a personalised LA model are a mesh constructed from imaging data, and a calibrated model of LA electrophysiology. Model calibration is challenging because measurements available in the routine clinical setting are far from sufficient to fully calibrate biophysically detailed models. In this paper we review the different components of a workflow that has been developed to address these challenges using a probabilistic approach [3–6], with an emphasis on conduction velocity (CV).

2. Background

Our overall goal is to calibrate an electrophysiology model so that model parameters that define local CV and action potential (APD), as well as their restitution, are determined at each mesh vertex. An important constraint is that this calibration should be achieved through measurements that can be collected during routine procedures. Here we concentrate on CV alone. The starting point of the workflow is a mesh representing the left atrium (LA), and bipolar electrograms recorded at different locations within the LA and at different pacing cycle lengths. From these observations, we estimate local activation time (LAT) at the electrode locations. Bipolar electrograms are routinely used in the clinical setting because they are less susceptible to far-field effects than unipolar electrograms, but there is no generally accepted way to assign LAT to these signals [7]. We therefore developed a modified centre-of-mass method to identify LAT [3].

The second step is to interpolate LAT across the LA mesh, taking into account uncertainties arising from both identification of LAT from the bipolar signal and registration of electrode co-ordinates with the mesh. Interpolation of LAT across the LA mesh involves taking a set of uncertain measurements LAT_{mesh} obtained from clinical bipolar electrograms at a subset of mesh vertices, and using this information to interpolate LAT over the entire mesh. In this approach the noisy observations of LAT ($y_i \equiv LAT_{mesh}$) at a location x_i are modelled as

$$y_i = f(x_i) + \epsilon_i, \tag{1}$$

where ϵ_i is normally distributed noise with mean of zero

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and standard deviation σ^2. The standard deviation of the error in each observation can be different i.e. heteroscedastic noise, or the same i.e. homoscedastic. It is possible to model $f(x_i)$ using a variety of methods [8], but we chose to model it as a Gaussian process (GP).

Having obtained a probabilistic interpolation of LAT, the third step is to calculate the inverse of the gradient in LAT, to obtain an uncertain estimate of CV magnitude and direction at each mesh vertex. The fourth and final step is to use these estimates to calibrate the electrophysiology model. A key challenge at this stage is to map from model parameters to observable features such as CV. In the next section we describe the third and fourth step in more detail.

3. Uncertain CV interpolation

A GP requires a covariance function to be specified on the mesh. Standard types of covariance function, which use Euclidean distances between pairs of mesh vertices, are not suitable since Euclidean distance does not reflect distance travelled by an activation wave over the curved LA mesh. Neither is it possible to use simple geodesic distances over the mesh because the resulting covariance matrix is not positive semi-definite. We therefore initially used an approach based on Gaussian Markov random fields (GMRF), where the covariance function (more specifically the precision matrix) is approximated as a solution to a stochastic partial differential equation solved on the mesh [9].

The GMRF approach could be used to obtain a posterior mean of LAT [3], and by calculating the inverse of the gradient of this field we could obtain a posterior mean for CV. However it was difficult to map uncertainty in LAT to uncertainty in CV by stochastic sampling of the posterior LAT. The posterior LAT samples were not smooth because the type of Matérn function used in the GMRF method covariance function was constrained to take a form that is not differentiable, and thus could not be used to calculate CV. An alternative, and faster, method was therefore devised to solve this problem [4] based on [10].

Key to this Gaussian process manifold interpolation (GPMI) approach is an alternative way to construct the GP covariance kernel as a basis function expansion. The basis functions are eigenfunctions corresponding to the smallest K eigenvalues of the Laplacian operator on the mesh, combined with a spectral density that takes a form based on a covariance function – see equations 2.5 and 2.6 of [4] for details. These functional forms take account of the mesh geometry and topology, can be calculated on the atrial mesh using standard approaches, and need only to be calculated once.

A further benefit of the GMPI approach is that the gradient of a GP is also a GP because gradient is a linear operator. Thus it is possible to obtain the posterior mean and the variance of *gradients* in LAT, as well as LAT itself (see equations 2.9 and 2.10 in [4]). The posterior mean of CV is then the inverse of the posterior mean of the gradient of LAT. Uncertainty in CV cannot be determined directly from the posterior variance in gradient of LAT because neither inverse nor magnitude are linear operators. Instead, the posterior CV distribution is estimated by sampling the posterior gradient in LAT 2000 times, and inverting each sample. A Python implementation of the GPMI method is available [**?**].

4. Step 4 - EP model calibration

Having obtained probabilistic interpolation of LAT and CV, the next step was to use this information for calibration of an EP model. The goal was to produce uncertain parameter fields from which samples could be drawn and simulations run that capture uncertainties in both measurements and calibration process. Identifiability of parameters remains a serious and possibly intractable problem for biophysically detailed cell models [11], and so we used a simplified and phenomenological model with 5 parameters that nevertheless reproduces key dynamic action potential features [12].

Calibration of this model to observable data required a mapping between CV and the model parameters. A key dynamic feature of cardiac electrophysiology is restitution, and understanding the relationship between tissue restitution and model parameters was an important component of calibration. To address this problem, we generated data from simulations in a tissue strip to learn the relationship between CV and a reparameterisation of the model parameters. We decomposed a set of restitution curves obtained from strip simulations using principal component analysis (PCA), finding via a sensitivity analysis that the curves could be represented either 2 or 3 principal components [5]. We then built surrogate models of these components, which provided a link between the model parameters and the restitution curves. Model parameters could then be estimated using maximum a posteriori (MAP) estimation, and the distribution of parameters estimated by Markov Chain Monte Carlo (MCMC) sampling. Here we focus on calibrating to CV recorded from constant S1 600 ms pacing (i.e. no restitution); we built a surrogate function to link model parameters and CV, which is much simpler than modeling restitution curves.

The next challenge has been to extend model calibration to the left atrial mesh [6]. This approach combines the GPMI method [4] and surrogate models. There are two important assumptions. First, we assume that uncertainty in CV at each mesh vertex is Gaussian, and this can be estimated from interquartile ranges [4]. Second, we treat the CV at each mesh vertex as independent, whereas the overall CV on the mesh is correlated.

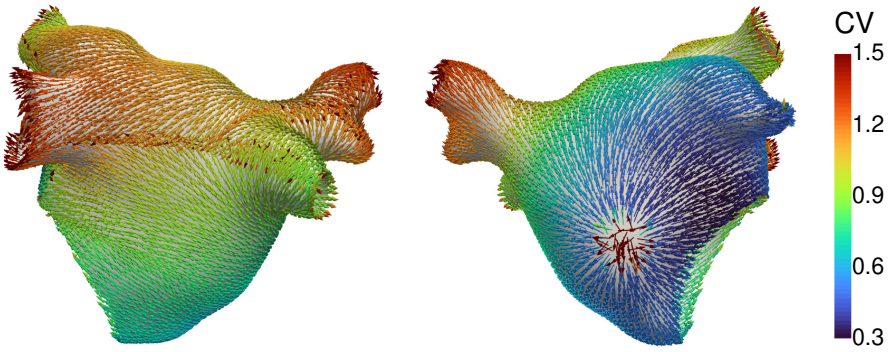

Figure 1. Ground truth CV (in m/s) from simulation with pacing at the coronary sinus. Colours show CV magnitude, and arrows show direction.

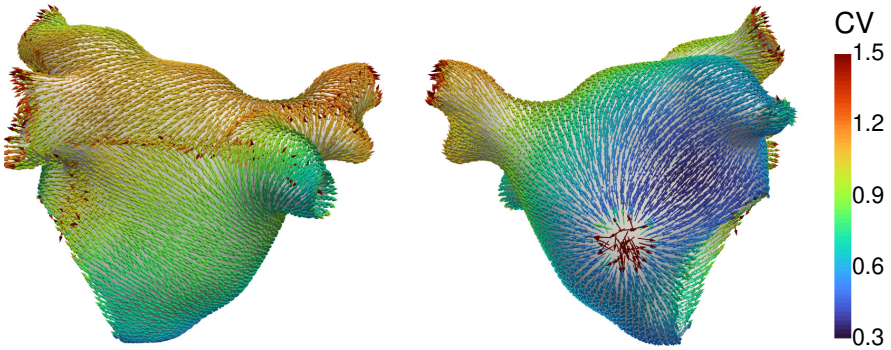

Figure 2. Predicted CV (in m/s) obtained by running a simulation using parameters inferred via "observations" of CV.

GPMI is used to represent each model parameter θ as a spatially correlated random field extending over the LA mesh at locations $\mathbf{x}$

$$\theta(\boldsymbol{x}) = m + \alpha \sum_{k=1}^{K} \eta_k \sqrt{S\left(\sqrt{\lambda_k}, \rho\right)} \phi_k(\boldsymbol{x}), \qquad (2)$$

$$\eta_k \sim \mathcal{N}(0, 1). \qquad (3)$$

Here the mean m, amplitude α and lengthscale ρ are hyperparameters that are learned, conditional on CV obtained at locations where LAT was observed, through Bayesian inference; S is a spectral density determined from the covariance kernel; λ_k and ϕ_k are the K eigenvalues and eigenfunctions obtained from solving the Laplacian on the mesh [4]. The distributions of parameters are then obtained conditional on observations by MCMC, using 64 eigenfunctions. This model is very similar to that used for interpolation of LAT (in which GPMI is used via regression rather than MCMC), but is more flexible in that m, α, and ρ can all be given priors, and the likelihood on the observations can be anything we choose. Model parameters on the mesh, determined by (2)-(3), are then mapped to CV via a surrogate function. Given hyperparameter priors and a likelihood function, MCMC can be performed.

Figure 1 shows CV obtained from a simulation with pacing at the coronary sinus, with heterogeneity in model parameter producing heterogeneity in CV. A separate simulation was then performed, using the same model parameters and with pacing at the right pulmonary vein. Observations of LAT, with added Gaussian noise with standard deviation 1 ms and at a set of simulated electrode locations were then used to infer CV across the mesh, and this information was used to estimate the recovered model parameters. This was done with MCMC, using a Gaussian likelihood for CV 'observations' and the prior of equations (2)-(3). Figure 2 shows the CV obtained from a simulation with the recovered parameters and pacing at the coronary sinus.

5. Discussion and outlook

This work has addressed the problem of probabilistic interpolation and model calibration on a manifold. We have shown that it is possible to interpolate clinical observations and to recover model parameters used to produce synthetic observations. We demonstrate this for CV here. In [6] we

concentrate on inference for the parameters that determine ERP, using a similar methodology.

Other approaches have been developed [13] that model the diffusion tensor field directly and link this field directly to LAT observations. However, uncertainty quantification is difficult to include in such approaches, which are computationally expensive.

The identification and uniqueness of model parameters is a serious and fundamental difficulty, especially for biophysically detailed models. However, with the goal of guiding catheter ablation it is important to probe whether calibration of simplified models is possible with routinely available data.

A related question is whether spatial heterogeneity in model parameters is actually important. A key factor in this discussion is the extent to which spatial heterogeneity in parameters affects the behaviour of re-entry and prediction of ablation targets. It is well known that structure, and especially fibrosis, has an important impact on both of these features. Integration of structural data such as fibrosis maps obtained from imaging, will be an exciting next step in the development of the ideas discussed in this paper.

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