Global Sensitivity Analysis of Left Atrial Electrophysiology Models

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Abstract

Personalisation of cardiac electrophysiology models remains an important challenge for development of digital twins that can be used to guide interventions in the clinic. Calibration of these models from data is a significant challenge, where establishing parameter identifiability is crucial, and global sensitivity analysis (GSA) an important first step. The study aimed to determine the sensitivity of a left atrial electrophysiology model to its parameters and how this sensitivity is influenced by left atrial size and anatomy. We used the monodomain equation with excitability described by the modified Mitchell-Schaeffer (mMS) model. An input dataset of 202 samples of model parameters was generated using Latin hypercube sampling. Each sample was used to run a simulation in each geometry, with 3×S1 beats at 800 ms cycle length followed by an S2 beat with a coupling interval of 500 ms. Local activation time (LAT) and action potential duration (APD) were determined across the mesh. These outputs were then used to build Gaussian process emulators of LAT and APD, and used to determine first order and total effect sensitivity indices. LAT and APD were most sensitive to τ_{in}, τ_{out} and conductivity. The overall sensitivity indices were similar across geometries.

1. Introduction

Atrial fibrillation (AF) is characterised by abnormal electrical activity in the heart. Typical treatment for persistent AF is radiofrequency ablation to isolate the pulmonary veins, but success rates remain low [1]. Personalised models of left atrial electrophysiology can be constructed [2], but rapid calibration of electrophysiology models from sparse and noisy clinical data remains a significant challenge.

The aims of the present study were twofold. First, we undertook a global sensitivity analysis (GSA) of a phenomenological left atrial electrophysiology (EP) model under regular pacing, in order to identify parameters that can in principle be recovered from clinical data. Second, we repeated the GSA on a set of 12 left atrial anatomies to assess how left atrial size and geometry affect the sensitivity indices.

2. Methods

The major steps involved in performing GSA were drawing a sample of EP model parameters, selecting clinically observable outputs and recording these from CARPentry simulations, training Gaussian process (GP) emulators for each output, and finally performing GSA. Each of these steps is briefly described in the sections that follow.

2.1. Electrophysiology model

For each left atrial tissue mesh, we implemented a monodomain model using CARPentry, where the reaction term was described by the modified Mitchell-Schaeffer (mMS) model [3], with isotropic diffusion and homogeneous parameter fields.

The models were paced with three S1 beats at a cycle length of 800 ms, followed by an S2 beat with a coupling interval of 500 ms. Both S1 and S2 stimuli were applied to the atrium on a patch which corresponded to a rectangular region of universal atrial co-ordinates (UACs) [4] (UAC1 $\in [0.5, 0.7]$ and UAC2 $\in [0.8, 0.9]$). Local activation time (LAT) and action potential duration (APD) were recorded at each mesh vertex.

2.2. Selection of inputs and outputs

We conducted GSA on two key outputs: the median and the 5-95 percentile range (referred as IQR) of both local activation time (LAT) and action potential duration (APD), each for the third S1 and S2 beats. This resulted in a total of 8 outputs.

Median and IQR (computed across all mesh nodes) were chosen to understand the behaviour of the typical response

and also its variability over the LA. The rationale behind choosing these outputs was that LAT can be observed in the clinical setting, and APD can be approximated from measurements of effective refractory period [5], and so in principle, these metrics can be used for calibration.

The inputs for GSA were tissue parameters for the mMS model, viz. τ_{in}, τ_{out}, τ_{open}, τ_{close}, and tissue conductivity.

2.3. Parameter sampling

As a first step, we trained a logistic regression classifier to identify parameter sets that would generate either APD alternans or an APD $> 500\ ms$. This classifier was trained on a set of ODE simulations where each of the four cell-scale parameters were sampled on a uniform $21 \times 21 \times 21 \times 21$ grid of parameters (see Table 1 for parameter ranges).

Independently, we drew 350 Latin hypercube samples of the five tissue parameters with ranges given in Table 2. 142 of these samples were discarded by the logistic regression classifier, leaving 208 samples. On performing the S1S2 simulations described in Section 2.1, it was found that 6 samples led to unphysiological responses and so these samples were discarded. A total of 202 sets of parameter samples were then used for GSA.

Table 1: Ranges of the modified parameters for cell simulations

	τ_{in}	τ_{out}	τ_{open}	τ_{close}
min	0.02	1	60	60
max	0.3	31	220	220

Table 2: Ranges of mMS paramters for Latin hypercube sampling

	τ_{in}	τ_{out}	τ_{open}	τ_{close}	conductivity (cm^2/s)
min	0.01	1	65	100	0.1
max	0.3	30	215	150	5

2.4. GP emulators and sensitivity analysis

A GP enables probabilistic modelling of datasets where an output is predicted from a set of inputs. If the GP emulates a computationally intensive model, then the emulator can be run many times cheaply. In this study we used the simulation data to fit a separate GP to each of the 8 outputs described above.

These GP emulators were then used with the GPErks package (`https://github.com/stelong/GPErks`) to obtain first and total order sensitivity indices for each combination of input and output [6]. The first order indices vary between 0 and 1, and indicate the proportion of variance on the output that may be reduced if the uncertainty on that input were removed. The total effects sensitivity index on the other hand measures the total contribution of an input variable to the output variance, including both its direct effects and its interactions with other input variables. In instances where the total effects index corresponding to an input is much larger than its first order index, it implies the presence of significant interaction effects, highlighting the complexity of the model's response to inputs.

2.5. Left atrial anatomy

To assess how LA anatomy affects sensitivity, we selected 12 LA meshes from a repository of a 100 patients where LA meshes were generated from cardiac MRI [7]. To cover a range of LA size we chose from these data four patients with the largest surface area, four with the smallest surface area, and four with the median surface area. These different meshes are shown in Figure 1.

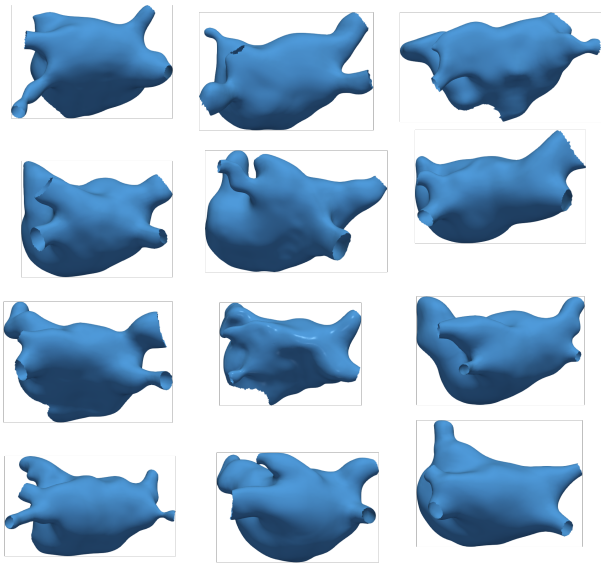
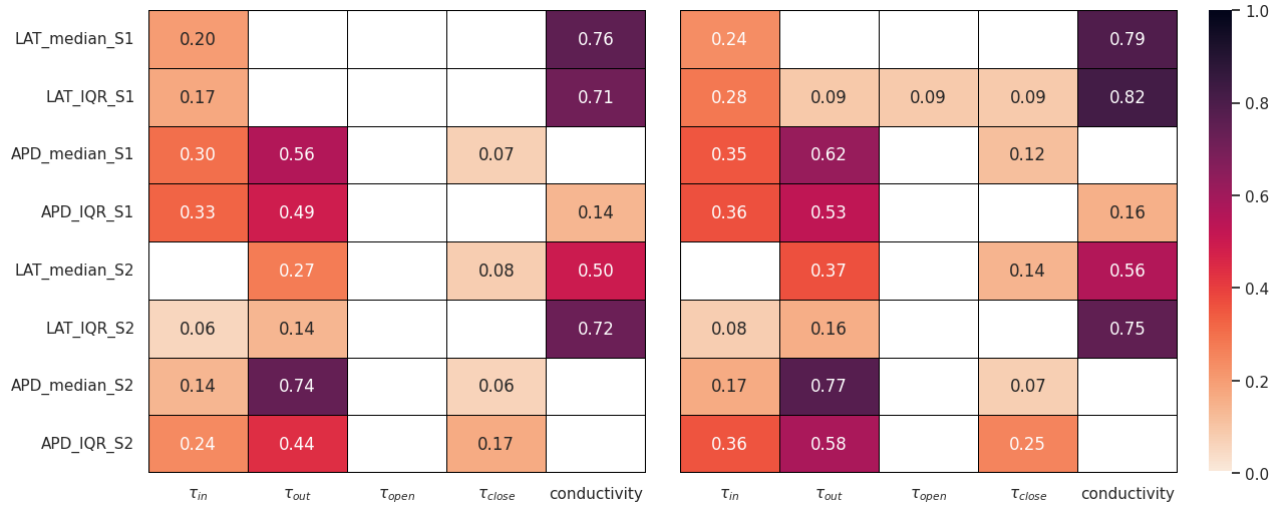


Figure 1: Snapshots of the 12 LA geometries

3. Results

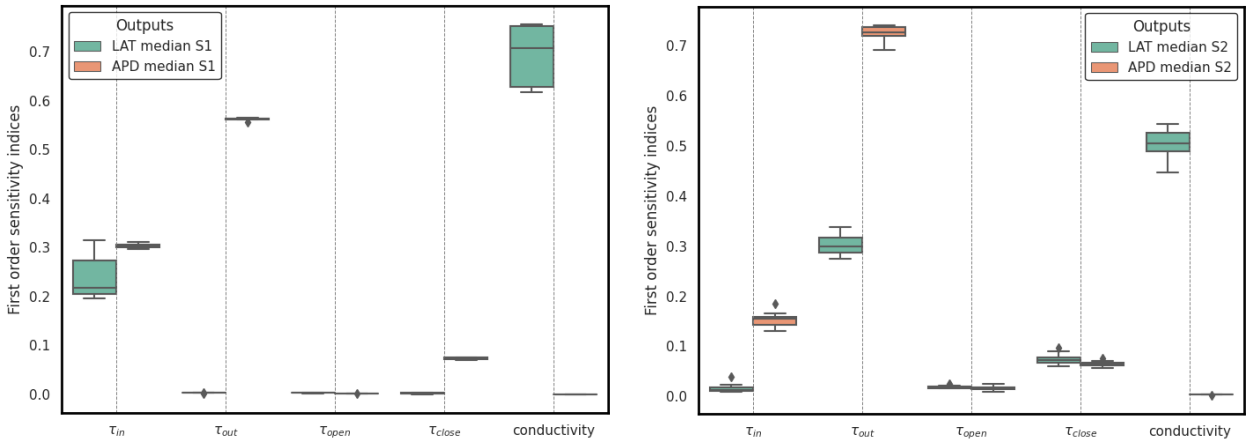
First order and total effects indices for a single LA mesh are shown in Figure 2. For the sake of clarity, any values smaller than 0.05 have been masked. Each row represents the sensitivity index of each parameter to the corresponding output.

The three parameters τ_{in}, τ_{out} and conductivity had the most important effects on the output. The only exception was for APD_IQR_S2 where tau_{close} showed a modest sensitivity. However, since tau_{close} does not contribute



(a) (b)

Figure 2: (a) First order and (b) total effects sensitivity indices for final S1 and S2 beats across each input and output for a single LA geometry



(a) (b)

Figure 3: Boxplots representing the distribution of first order sensitivity indices of the medians of LAT and APD with respect to the tissue parameters across 12 geometries for (a) final S1 beat and (b) S2 beat

to the variance of the majority of the outputs, we conclude that most of the variability in clinically observable outputs is due to that of three mMS model parameters. Furthermore, since the total effects indices are not significantly higher than the first order ones, the effect of interactions between different parameters was marginal.

We then repeated our GSA on 12 LA geometries to study the effect of shape on the EP model response. We repeated all the steps described above leading to GSA. The first order sensitivity indices are summarised for these 12 geometries in Figure 3.

Each subfigure has two sets of boxes, each set corresponding to a different output. For each output, the left hand (green) box denotes the median LAT and the right hand box (pink) median APD.

Overall, the variability in the sensitivity index was small, indicating that the effect of geometry on the sensitivity (and by implication identifiability) of each parameter was small.

The variability in LAT sensitivity indices was greater than the variability in APD. This would be expected given that the LA geometries were selected to span a wide range of LA sizes. LAT is more strongly influenced by LA size and curvature, whereas APD is mainly determined at the

cellular level. Since the trends for the IQR outputs were similar to those of the median outputs, these have not been included.

4. Discussion and conclusions

Our longer term aim is rapid calibration of left atrial EP models from routinely available clinical data. This is a challenging task because of the constraints of the clinical setting. Our previous work developed methods for probabilistic calibration based on restitution curve emulators [5]. This approach was very effective, but relies on pacing sequences that are not routinely possible.

The present study has therefore focused on the first stage of model calibration, which is to undertake GSA and determine whether model parameters are identifiable from clinical data. We have shown that in our model LAT is predominantly influenced by tissue conductivity, and APD by τ_{out}. We have also shown that the sensitivity indices are not affected greatly by left atrial size.

The next stage of this work will be to extend GSA to include heterogeneous model parameters informed by measures of LA fibrosis, establish those parameters that can be identified from data, and then to compare different approaches for rapid calibration. This future work will establish whether other features such as anisotropic tissue conductivity or preferential conduction pathways in the atria need to be included to ensure accurate calibration.

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