

Investigating the Influence of Parameters on Electrogram Morphology Using Gaussian Process Emulators

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Abstract

Intracardiac electrograms (EGMs) are a valuable tool for assessing cardiac arrhythmias to identify tissue that serve as targets for radiofrequency catheter ablation. However, accurately interpreting EGMs is challenging due to the influence of various factors on the morphology of the signals. Computational modelling combined with global sensitivity analysis (GSA) can provide crucial insights into how these parameters affect the simulated EGM morphology. However, performing an accurate GSA necessitates a large number of simulations which are computationally expensive to perform. We propose a machine learning approach based on Gaussian process emulators (GPEs) of model simulations to enable rapid and robust inference of model parameters. We applied this framework to perform a computationally efficient GSA to quantify the total and first-order effects of input parameters across several features of the unipolar (uEGM) and bipolar (bEGM) EGMs. The trained GPEs demonstrated a high accuracy in predicting EGM features, achieving an average R^2 score and independent standard error (ISE) of 0.925 ± 0.041 and $89.7\% \pm 1.63\%$, respectively. The GSA identified fibrosis density and the electrode-wavefront angle as key parameters influencing uEGMs and bEGMs, respectively, which may lead to more informed EGM interpretation.

tors, including catheter electrode size [1, 2], myocardial thickness [3, 4], catheter orientation [4, 5], conduction velocity [3, 6] and anatomical structures such as fibrosis [6]. However, the precise influence of each factor and their combined effects on the EGMs remains poorly understood.

Computational modelling offers a valuable tool to systematically analyse the various influences on these signals, providing insights that would otherwise be challenging to obtain in clinical practice. However, running a sufficiently large number of simulations required to perform an accurate global sensitivity analysis (GSA) is unfeasible due to the high computational cost of multi-parametric and non-linear cardiac models. The development of machine learning emulator models, such as Gaussian process emulators (GPEs) [7], has facilitated low-cost statistical approximations of computationally expensive models, enabling rapid predictions of the model's output required to estimate global sensitivities. GPEs have proven valuable for conducting a GSA in several cardiac modelling applications [7, 8] to identify clinically significant model parameters.

In this study, we explored the utility of GPEs and in-silico simulations to conduct a GSA on the impact of catheter electrode size, myocardial thickness, conduction velocity, fibrosis density and electrode-wavefront angle on uEGM and bEGM features, which may inform EGM interpretation and enhance the efficacy of ablation procedures.

1. Introduction

Intracardiac electrograms (EGMs) are commonly used for electrical mapping of arrhythmogenic substrates to identify abnormal tissue as targets for catheter ablation. Nonetheless, the efficacy of ablation procedures remains low, partly due to the complexity of interpreting and analysing EGMs. The unipolar (uEGM) and bipolar EGM (bEGM) morphologies may be influenced by several fac-

2. Methods

2.1. Computational Model Generation

We generated a 3D ventricular myocardial slab model of finite tetrahedral elements with an average resolution of 0.2 mm using the Mesher program [9]. Myocardium had a size of 50 x 50 x z mm, while the surrounding bath extended 5 mm beyond the tissue along the z -axis (Figure 1).

A cylindrical region of fibrosis was defined throughout the tissue depth at the centre of the myocardium with a radius of 20 mm. Different fibrosis densities were modelled as non-conducting tissue by removing a specified percentage of finite elements from the intracellular grid at random. A single unipolar recording electrode or two bipolar recording electrodes, with a size of $e_x \times e_y \times e_z$ mm, were placed at the centre of the endocardium in contact with the tissue.

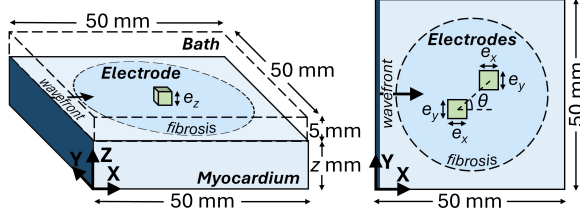


Figure 1. Computational model setup.

2.2. Electrophysiology Simulations

Cardiac electrophysiology was simulated with the ten Tusscher model of the human ventricular myocyte [10]. Bidomain simulations were performed using the Cardiac Arrhythmia Research Package (CARP) [9] to represent interactions between the intracellular and extracellular domains. The recording electrode was modelled with a high conductivity of 700 S/m [1]. The bath conductivity was set to 0.63 S/m to mimic the properties of human blood [11]. The bidomain model was initialised with isotropic intracellular (σ_i) and extracellular (σ_e) conductivities of 0.28 S/m and 1.0 S/m, respectively. A 100 mA intracellular stimulus was applied to the tissue edge for 5 ms, generating a wavefront that propagated parallel to the electrodes. In total, 8 input parameters were varied as summarised in Table 1. Table 1. Simulation input parameters (* indicates inputs varied for bipolar electrodes only.)

Input Parameter	Range	Units
sodium channel conductance (g_{Na})	[40,180]	%
extracellular conductivity (σ_e)	[0.4,1.8]	S/m
tissue thickness (z)	[1.0,15.0]	mm
electrode width (e_x)	[0.2,3.8]	mm
electrode length (e_y)	[0.2,3.8]	mm
electrode height (e_z)	[0.2,3.8]	mm
fibrosis density (f_d)	[0,80]	%
electrode-wavefront angle (θ) *	[0,80]	°

2.3. Signal Feature Extraction

Simulated uEGMs were measured from the centre of the electrode and the following clinically relevant features

were computed: peak-to-peak amplitude (V_{amp}), minimum temporal derivative of the uEGM voltage downslope ($d\phi/dt_{min}$) and $d\phi/dt_{min}$ normalised by V_{amp} ($norm\ d\phi/dt_{min}$). The bEGMs were recorded as the difference in potentials recorded by the two uEGMs and the peak-to-peak amplitude (V_{amp}), EGM area (EA) and EA normalised by V_{amp} ($norm\ EA$) [12] were computed.

2.4. Gaussian Process Emulation

We used GPEs as surrogate models to accelerate the evaluation of the input parameters to obtain the simulation outputs. A Latin hypercube sampling (LHS) was performed to generate 200 input parameter samples and electrophysiology simulations were subsequently performed with this parameter space to build the training dataset. For each output of interest, a GPE was trained to maximise the model log-marginal likelihood using the GPERks emulation tool (<http://github.com/stelong/GPERks>), as previously described [7]. The trained GPE accuracy was evaluated by performing a 5-fold cross-validation, where the coefficient of determination (R^2) and independent standard error (ISE) were computed for each fold. The R^2 quantified the error between GPE predictions and expected outputs, with a value close to 1 indicating a low error. The ISE evaluated the GPE uncertainty, accounting for distance between GPE predictions and corresponding expected values. A value of closer to 100% indicated a greater proportion of data points for which the expected value fell within two standard deviations of the GPE prediction.

2.5. Global Sensitivity Analysis

A Sobol variance-based GSA [13] was performed using the Saltelli method [14] with the SALib Python library [15]. For each output, 1000 samples were drawn from the posterior distribution of the trained GPEs to compute the mean first-order effects, describing the direct contribution of an input variable on the output variance, and the total effects, which measures both the direct effects of an input variable and its interactions with other inputs on the output variance. Input parameters were subsequently ranked according to their importance by computing the maximum total effects across all outputs. This enabled identification of key inputs that explained the majority of the variation observed in the simulator outputs.

3. Results

3.1. Model Emulation

The 200 input parameter points obtained from LHS were each successfully simulated to obtain the outputs. One GPE was trained for each output, resulting in a total of 6

GPEs. The obtained average cross-validation R^2 and ISE scores used to assess the accuracy of the trained GPEs are reported in Table 2 for each output feature. For all outputs, the average R^2 and ISE were above 0.865 and 86.9, respectively, indicating that the GPEs provide an accurate estimate for all outputs. Emulator evaluations took approximately 1.0 s compared to a full simulator single-core run of approximately 80 hrs, enabling us to perform a GSA at a significantly reduced computational cost.

Table 2. GPE performance. Average R^2 and ISE over the five cross-validation splits, reported for each output.

Output Feature	R^2	ISE (%)
uEGM V_{amp}	0.992 ± 0.002	90.6 ± 4.42
uEGM $d\phi/dt_{min}$	0.947 ± 0.017	91.3 ± 3.06
uEGM $norm\ d\phi/dt_{min}$	0.895 ± 0.027	88.1 ± 4.59
bEGM V_{amp}	0.865 ± 0.066	90.6 ± 3.42
bEGM EA	0.906 ± 0.048	86.9 ± 5.00
bEGM $norm\ EA$	0.946 ± 0.009	90.9 ± 3.64

3.2. Global Sensitivity Analysis

Figure 2 shows a heatmap of total and first-order effects of all input parameters over all outputs, with darker colours corresponding to higher input-output interactions. For the uEGM, fibrosis density had the greatest impact on V_{amp} , followed by σ_e and tissue thickness. This pattern was also seen for $d\phi/dt_{min}$, though tissue thickness had a markedly reduced effect on this feature. Both $d\phi/dt_{min}$ and $norm\ d\phi/dt_{min}$ were influenced by changes in electrode width, while electrode length and height had a negligible effect on the uEGM morphology. For the bEGM, the greatest change in V_{amp} was driven by θ and fibrosis density. Notably, θ significantly contributed to explaining the variance observed in EA , followed by tissue thickness. The $norm\ EA$ was most greatly influenced by σ_e , while this parameter had little effect on V_{amp} and EA . Overall, bEGMs were largely unaffected by g_{Na} and were significantly less sensitive to electrode recording parameters compared to the uEGMs. Furthermore, total and first-order effects were comparable for each signal, therefore the effect of interactions between parameters was minimal.

The parameter ranking in Figure 3, performed according to the maximum total effects across all outputs, shows that fibrosis density, followed by electrode width, σ_e , g_{Na} , tissue thickness and electrode height are the most important parameters influencing the uEGM morphology. For the bEGM, the most significant parameters, in order of decreasing importance, were θ , σ_e , tissue thickness, fibrosis density, electrode width and electrode height. When normalising the maximum total effects to sum to 1 (i.e. 100% of explained variance), these parameters explain >90%

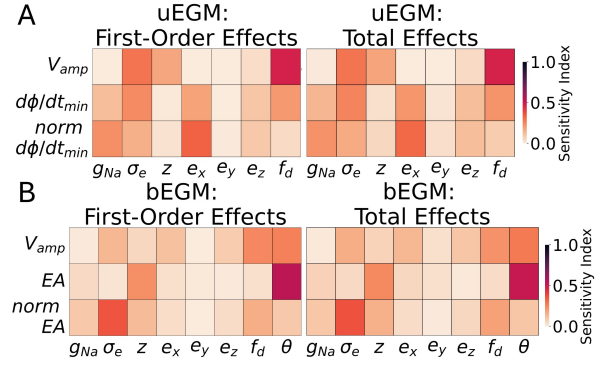


Figure 2. GSA heatmap of total and first-order effects, normalised between 0 and 1, of model inputs (x-axis) on the outputs (y-axis) for (A) uEGMs and (B) bEGMs.

of the variance observed in the EGM signals. Electrode length was an unimportant parameter as it did not significantly impact the uEGM or bEGM signals. Similarly, g_{Na} had a minimal impact on the bEGM morphology.

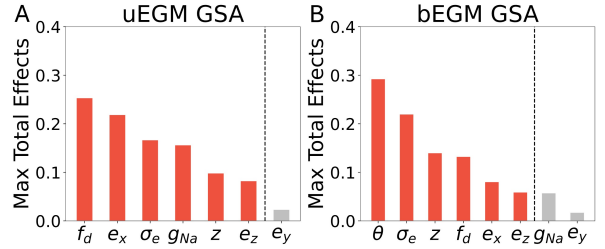


Figure 3. Barplot of the maximum total effects of each input parameter over all outputs. Parameters are ranked from most to least important. Dashed line separates important (red) and unimportant (grey) parameters.

4. Discussion

Identifying key parameters that influence morphological features of EGMs is critical to guide the selection of EGM metrics used during substrate mapping for accurate identification of tissue critical for initiating and maintaining re-entrant arrhythmias as targets for radiofrequency ablation. In this study, we demonstrated the robustness of GPEs to efficiently evaluate model inputs, enabling us to perform a high number of model evaluations required for a GSA at a fraction of the computational cost. We ranked the most influential input parameters affecting EGM signals, revealing that while electrode length had minimal impact, electrode width, tissue thickness and factors influencing conduction velocity, such as g_{Na} , σ_e and fibrosis density, played important roles. In certain cases, such as V_{amp} , key input parameters can be linked to physiological explana-

tions. For instance, fibrosis density is a significant factor as it leads to the loss of viable myocardium, resulting in slower conduction and decreased EGM amplitude. Moreover, for $d\phi/dt_{min}$, which is related to local tissue activation, and $norm EA$, which has been shown to correlate with local conduction delay [12], σ_e is expected to have a greater impact than g_{Na} as it reflects global tissue conductivity. It is well established that V_{amp} is maximum when the electrode orientation is parallel to the wavefront propagation and minimum when the electrode wavefront angle is perpendicular, emphasising its importance in governing the bEGM. Further exploration of the physiological significance underlying these GSA findings would be beneficial.

In this study, EGMs were recorded in a simple slab model with a planar wavefront. Future work should extend the GSA to include additional factors such as the catheter orientation, interelectrode spacing, realistic fibre orientations and more complex wavefront propagation. Moreover, history matching techniques to constrain the parameter space to obtain outputs consistent with clinically observed EGMs would be valuable [7]. In our GSA, we did not account for potential correlations between different outputs, but instead trained independent GPEs for each output, which allowed for independent hyperparameter tuning. Future work could explore training a multi-output GPE [7]. While we sampled the posterior distribution of the GPEs and computed average global sensitivity indices, these indices were computed without considering the emulator uncertainty. However, since the uncertainty was minimal, the sensitivity indices still accurately captured the effects of model inputs on the outputs within the parameter bounds. Future studies could explore alternative estimation methods that directly incorporate the emulator's mean and variance. Although we did not explore the precise relationship between individual factors, the GSA could be applied to eliminate less influential parameters when fitting computational models to clinical data in future work. In addition, the GSA provides a foundation for future studies to focus on exploring the specificity of the key parameters identified, thereby optimising computational effort.

5. Conclusion

We demonstrated the efficacy of GPEs to perform a computationally efficient GSA and identified key parameters influencing the EGM morphology, yielding deeper insights into the link between cell, tissue and electrode properties and simulated intracardiac EGMs.

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