Sensitivity Analysis of Electrocardiogram Features to Computational Model Input Parameters

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Abstract

Cardiac models of electrophysiology capable of generating simulated electrocardiogram (ECG) signals are an increasingly valuable tool for both personalised medicine and understanding cardiac pathologies. Sensitivity analysis (SA) can provide crucial insight into how simulation parameters affect ECG morphology.

We use two SA methods, direct numerical evaluation of integrals and polynomial chaos expansion, to calculate main and total effects for ECG features extracted from QRS complexes generated by a cardiac ventricular model. The importance of stimulation site parameters on output ECG features is evaluated.

SA methods can highlight and quantify important input parameters for different ECG morphology features, which in some cases can be linked to physiological explanations. For example R peak amplitude in lead II depends on apicobasal location of stimulation sites in the left ventricle. Furthermore, different SA methods have different strengths and weaknesses. Insight into parameter importance supports model development and allows for more nuanced and patient-specific simulation changes.

1. Introduction

Cardiac models of electrophysiology that generate simulated electrocardiogram (ECG) signals are an increasingly valuable tool for both personalised medicine and understanding cardiac pathologies [1]. Insight into how the simulation input parameters affect the morphology of the output synthetic ECG signal is crucial for tuning of model parameters.

Sensitivity analysis (SA) is a valuable tool for examining such a relationship between morphological features of the ECG and input parameters to the model [2]. Some studies have explored the sensitivity of ECG features such as the QRS complex with respect to parameter variations in myocardial cells [3]. SA of ECG features as a function of ventricular model parameters has been carried out [4].

Sobol SA quantifies the size of the effects of the model input parameters on the model outputs (i.e. ECG features) [2]. The *main effect* is the ratio of variance in the model output due to a single input parameter, to overall variance in the model output. The *total effect* for a given parameter is the main effect plus the interactions that parameter with other parameters [5].

This study examines how input parameters of one ventricular model of electrophysiology impact features of the output ECG signal, while atrial parameters remain fixed. We want to evaluate in more depth the SA process itself to understand what to bear in mind when carrying out SA of complex heart models. Here we want to (1) use SA methods to understand how synthetic ECG model parameters affect ECG morphology as measured by clinically relevant measures and (2) understand the strengths and weaknesses of SA methods for this task.

2. Method

2.1. Synthetic ECG dataset generation

To generate the synthetic QRS complexes a cohort of anatomically-specific models was used. Primary tissues of lungs, atria, blood pools, ventricles and general torso tissue were segmented. Segmentations were then meshed into volumetric finite-element meshes. All crucial aspects of cardiac electrophysiology during healthy sinus rhythm were accounted for within the models to ensure high biophysical fidelity. Given a set of model parameters, a synthetic 12-lead QRS complex could then be computed using a simulation method that combined a reaction-Eikonal method formulated without diffusion for the cardiac sources and a lead field approach for forward projec-

tion. QRS complexes were extracted at standard electrode positions [6].

Standard ECG feature extraction software typically requires a complete ECG signal, so all synthetic QRS complexes were appended to the same, generic P wave generated using a non-corresponding atrial model. To generate the synthetic P wave, a volumetric atrial model allowed regionally heterogeneous conductance properties to be assigned to spatially distinct regions of the mesh. A surface representation of the torso was used, and the boundary element method was applied to project the transmembrane voltage sources from the heart onto the body surface and the 12-lead ECG P waves were extracted at standard electrode positions [7].

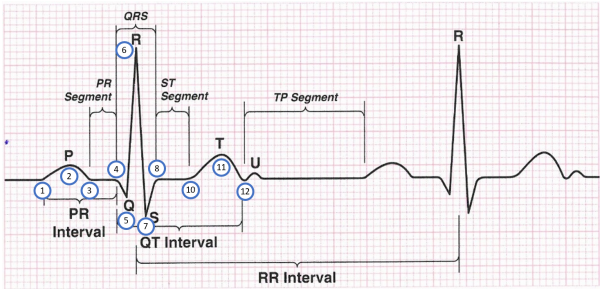

Figure 1. An ECG signal indicating the main fiducial points on the signal. Point 9 is reserved for the J point if present and is excluded here.

In this study, the impact of ventricular model input parameters on ECG morphology was evaluated while atrial model parameters were fixed to reduce complexity. Twelve input parameters relating to stimulation site location were varied according to a Saltelli sampling scheme (required by one SA method, see Section 2.3), resulting in 14,000 synthetic ECG signals. The 12 input parameters were: stim0z, stim0phi, stim1phi, stim1z, stim2z, stim2phi, stim3z, stim3phi, stim4rho, stim4time, stim4z, stim4phi. These parameters control the location of the stimulation sites in a coordinate system defined relative to the heart, with the exception of stim4time which controls the timing of the stimulation in the right ventricle. A single generic 12-lead P wave was generated using mean values for the conduction velocity parameters. To create a complete 12-lead ECG, the generic P wave was appended to each of the 14,000 QRS complexes. Prior to appending, the P wave was scaled to a more physiologically realistic amplitude using P wave amplitudes from a real ECG dataset [8].

2.2. ECG feature extraction

The software ECGdeli [9] was used to identify fiducial points (FPs) on the ECG (Figure 1). Five ECG features were calculated for all 12 leads using the following FPs:

- R amplitude (value of the ECG at FP 6)
- QRS duration (difference between FP 8 and FP 4)
- QT interval (difference between FP 12 and FP 4)
- ST segment (difference between FP 10 and FP 8)
- T duration (difference between FP 12 and FP 10)

2.3. Sensitivity analysis

The main effect and total effects were calculated using two methods: direct numerical integration of integrals (Direct) and polynomial chaos expansion (PCE).

The Direct method is described in more detail elsewhere [5]. The formulae defining the main and total effects are given in terms of functions, which must be evaluated numerically. To obtain the points at which to evaluate the integrals, the input parameters were sampled according to a Saltelli sampling scheme [5].

For PCE [10, 11] the stochastic output vector $Y = (y_1, y_2, ..., y_V)$ of the model acting on a set of U random variables $X = (x_1, x_2, ..., x_U)$ is expanded in an infinite series [12] as:

$$y_j(X) = \sum_{i=0}^{\infty} \gamma_{i,j} \Psi_i(\{x_n\}_{n=0}^{U}) \quad (1)$$

Here, $\gamma_{i,j}$ are the expansion coefficients to be determined, and the polynomials Ψ_i of the multi index i represent a multivariate basis depending on the input parameter distributions. After $\gamma_{i,j}$ are determined, a mathematical surrogate model is created which allows for calculation of main and total effects. In the present case, the 12 input parameters allowed for a 4th order PCE [12], resulting in 4095 expansion terms.

Main and total effects were calculated using both the Direct method and PCE method for all ECG lead and feature combinations. Spearman's rank correlation coefficient (R) was used to compare agreement between both methods.

3. Results

3.1. Main effects

The R peak is typically the most easily identifiable feature on the ECG, and as such the detected R peak will be more reliable than harder to detect features such as the T duration [13]. Rank correlation (R) between the R amplitude main effects using the direct and PCE methods ranges from $0.45 - 0.92$. Note that these values are often dominated by one large coefficient, as typically only one or two input parameters influence the output feature (see Figure 2 for an example).

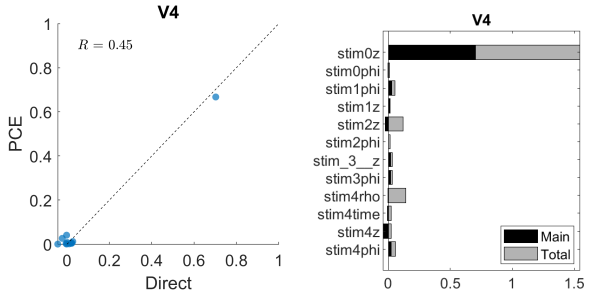

Figure 2. Rank correlation (R) between main effects calculated with PCE and Direct methods (left), and corresponding main effects for the Direct method only (right).

3.2. Convergence of main effects

Note that in Figure 2, the Direct method main effect for stim2z and stim4z is negative; these should always lie in the interval $[0, 1]$ [5]. Further examples in Figure 3 (top row) show that while the Direct main and total effects are sensible in some cases (R amplitude, lead III), in other cases they are not (QT interval, lead V5). Examining the convergence of the Direct method in these cases (by gradually increasing the sample size) showed that while the total effects converged well, the main effects did not, particularly for the interval as opposed to amplitude variables (data not shown). This is likely due to the discrete (time in ms) rather than continuous (voltage) values of these features. The same effect was not shown in the PCE main and total effects, see Figure 3 (bottom row).

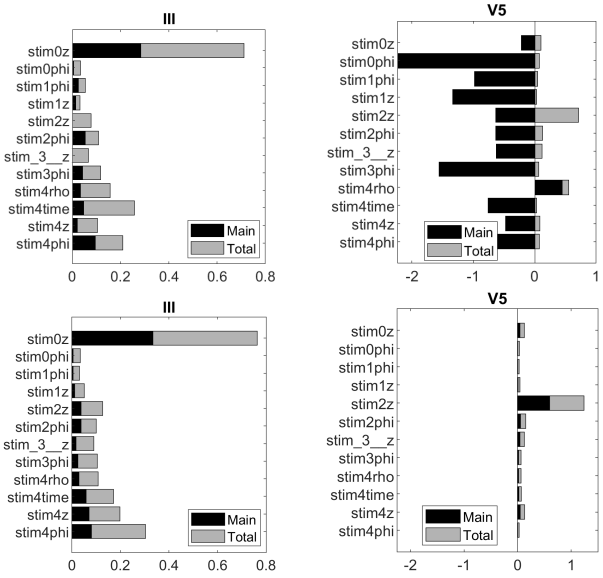

Figure 3. Example main and total effects for (top left) Direct method R amplitude, lead III, (top right) Direct method QT interval, lead V5, (bottom left) PCE R amplitude, lead III, (bottom right) PCE QT interval, lead V5.

3.3. Total effect method comparison

Rank correlation between total effects calculated with both the Direct and PCE methods showed good agreement for the features (Table 1). For a breakdown of rank correlation coefficients by lead, see Figure 4.

Table 1. Rank correlation coefficient between Direct and PCE total effects. Mean and standard deviation shown for each feature across all leads.

Feature	Rank corr. coeff.
R amplitude	0.97 (0.03)
QRS duration	0.91 (0.11)
QT interval	0.90 (0.09)
ST segment	0.93 (0.07)
T duration	0.87 (0.11)

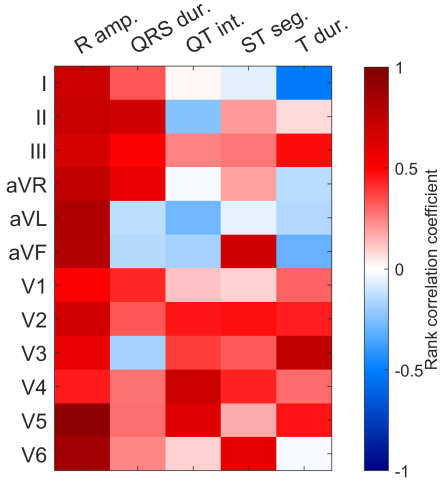

Figure 4. Rank correlation between Direct and PCE, total effects only, for each lead/feature combination.

3.4. Input parameters & ECG morphology

The largest total effect(s) for each lead/feature combination indicates which of the input parameters has most influence on that particular feature of the ECG morphology. An example of main and total effects for lead II features can be seen in Figure 5. R amplitude for lead II is very sensitive to stim0z and stim2z. These input parameters control the apico-basal location of two of the activation sites in the left ventricle. When the vector along the apex to base direction of the heart is aligned toward the same direction of lead II, more signal is detected in lead II, so this sensitivity has a physiological explanation.

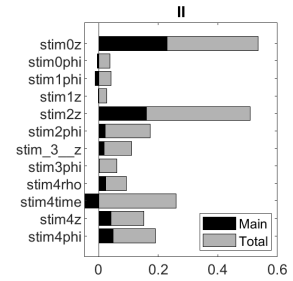

Figure 5. Direct method main and total effects for lead II R amplitude.

4. Discussion

Sensitivity analysis provides quantitative insight into how simulation input parameters can impact resulting ECG morphology. In certain cases, such as lead II R amplitude, the important input parameters can be linked to a physiological explanation. Further exploration of physiologically meaningful explanations of SA findings will be beneficial.

Here we have shown good agreement between two different methods, Direct and PCE, for calculating total effects. Convergence of the main effects using the direct methods was poor, sometimes resulting in negative main effects, and work is underway to explore this further, and to better understand the interactions between model complexity and output feature distribution to see how this impacts the final output parameters [14].

It should be noted that these results are on one dataset and conclusions regarding relationships between input parameters and ECG features should not be taken as conclusive. However, observations, such as how performance is impacted when the extracted feature is based on interval measurements, can be generalised to other studies.

The SA methods used consider the ECG simulations plus feature extraction software as one black box model, as it is concerned only with the input and output. As some ECG features are harder to detect than others [13], this will make the problem more ill posed for some features. Ongoing work is exploring the relationship between output feature distribution and main or total effect calculation [14].

5. Conclusion

We compared two widely used SA methods, Direct and PCE, for synthetic 12-lead ECG data. The methods were in good agreement, which enables a more flexible and reliable approach to SA on ECG data in practice. Sensitivity analysis provides valuable information about the relationship between simulated ECG morphology and input parameters in cardiac models, supports the model building process and can allow for more nuanced and patient-specific simulation changes.

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