

# Sensitivity Analysis of Electrocardiogram Features to Computational Model Input Parameters

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## Abstract

*Cardiac models of electrophysiology generating simulated electrocardiogram 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.*

*Here we use two SA methods, direct numerical evaluation of integrals and polynomial chaos expansion to calculate Sobol coefficients for QRS complexes generated by a ventricular model. The importance of stimulation site parameters on output ECG features is evaluated.*

*SA methods can indicate parameter importance for different ECG morphology features, with physiologically sensible explanations, and different SA methods have strengths and weaknesses. Insight into parameter importance supports model development and can allow 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. Insight into how the simulation input parameters affects the morphology of the output synthetic ECG signal is a crucial area, and allows more useful signals to be generated. Sensitivity analysis (SA) is the study of how variation in the output of a model can be attributed to the model input [1] and SA methods are a valuable tool for examining how cardiac models impact ECG morphology.

Other studies have explored the sensitivity of ECG features such as the QRS complex with respect to parameter variations in myocardial cells [2]. SA of ECG features as a function of ventricular model parameters have been carried

out [3].

This study examines how input parameters of one ventricular model impact features of the output ECG signal, and evaluates 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

The synthetic ECG signals were generated in two parts, the P wave and the QRS complex. To generate the 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**. To generate the QRS complex 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 ECG 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 projection.

In this study, the impact of ventricular model input pa-

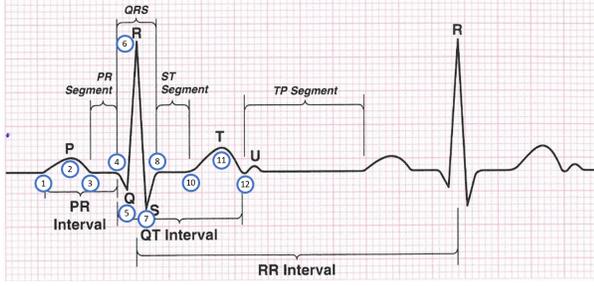


Figure 1. An ECG signal indicating the main fiducial points on the signal.

Parameters on ECG morphology were 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 14000 synthetic ECG signals. A single generic 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 14000 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.

## 2.2. ECG feature extraction

The ECG software ECGdeli [4] 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. Sobol coefficient calculation

Sobol coefficients (SCs) quantify the size of the effects of the model input parameters on the model outputs (ECG features here). They 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]. In summary, the main SC is the ratio of variance in the model output due to a given parameter alone, to variance in the overall model output. The total SC for a given parameter is the sum of all SCs that involve that parameter. 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].

The polynomial chaos expansion (PCE) was developed in 1938 as a means to approximate Gaussian random variables in terms of Hermite polynomials [6] and has been generalized in recent years to non-Gaussian distributed parametric uncertainty [7]. In the PCE, the stochastic output vector  $Y = (y_1, y_2 \dots y_M)$  of the model  $M$  acting on a set of  $N$  random variables  $X = (x_1, x_2 \dots x_N)$  is expanded in an infinite series [8] as:

$$Y(x, t) = \sum_{i=0}^{\infty} \gamma_i(x, t) \Psi_i(\{x_n\}_{n=0}^N) \quad (1)$$

with  $\gamma_i(x, t)$ , the expansion coefficients to be determined, e.g. from model evaluations, and the polynomials  $\Psi_i$  represent a multivariate basis depending to the input parameter distributions.

After determining the expansion coefficients via linear regression from a set of model evaluations, a mathematical surrogate model of the underlying dataset is created, which allows for the calculation of Sobol indices by rearranging and summing up the appropriate model terms.

The main and total effect SCs were calculated using both the Direct method and PCE method for all ECG lead and feature combinations.

## 3. Results

### 3.1. Main effect Sobol coefficients

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 [9]. Rank correlation ( $R$ ) between main SCs using the direct and PCE methods range 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).

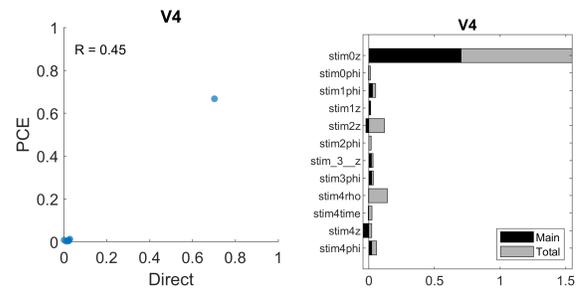


Figure 2. Rank correlation between main SCs calculated with PCE and Direct methods (left), and corresponding SCs for the Direct method only.

### 3.2. Convergence of main Sobol coefficients

Note that in Figure 2, the Direct method main SC for **stim2z** and **stim4z** is negative; SCs should always lie in the interval  $[0, 1]$  [5]. Further examples in Figure 3 show that while the 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 (Figure 3).

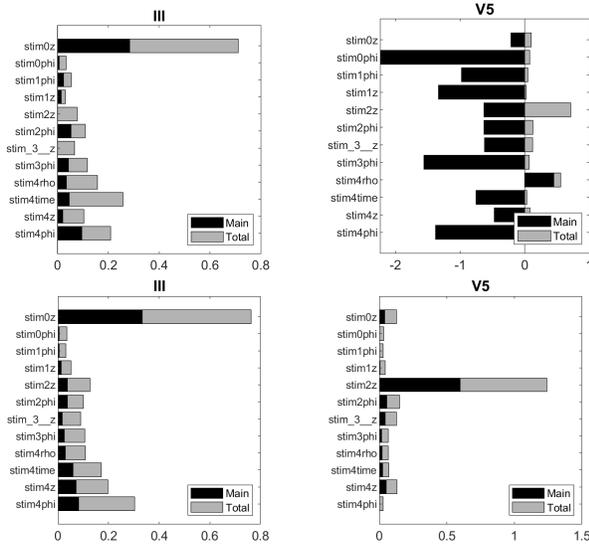


Figure 3. Example SCs for different lead and feature combinations

### 3.3. Total effect SC method comparison

Rank correlation between total SCs calculated with both the Direct and PCE methods showed good agreement for the features (Table 1).

Table 1. Rank correlation coefficient between Direct and PCE total SCs. Mean and standard deviation shown.

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)

### 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 ECG morphology. **Three examples** of SCs for lead II features can be seen in Figure 4. 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.

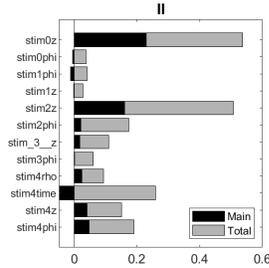


Figure 4. SCs for lead II R amplitude.

## 4. Discussion

Sensitivity analysis such as the calculation of Sobol coefficients (SCs) provides insight into how input parameters of ECG simulations can impact resulting ECG morphology. In certain cases, such as the 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 SCs. Convergence of the main SCs using the direct methods was poor 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 [10].

While interesting 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 treat the ECG simulations and ECGdeli feature extraction software as one black box model. As some ECG features are harder to detect than others [9] this will make the problem more ill posed for some features than others. Ongoing work is exploring

the relationship between output feature distribution and SC calculation [10].

## 5. Conclusion

With the Direct and PCE SA methods, we compared two widely used methods to calculate Sobol coefficients for variance-based sensitivity analysis on synthetic, single beat, 12-lead ECG data. We found good agreement between the methods, which enables a more flexible and reliable approach to SA on ECG data in practice as both methods exhibit individual strengths and limitations. 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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