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# Uncertainty Quantification of the Effect of Cardiac Position Variability in the Inverse Problem of Electrocardiographic Imaging

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# 1 Abstract

**Objective:** Electrocardiographic imaging (ECGI) is a functional imaging modality that consists of two related problems, the forward problem of reconstructing body surface electrical signals given cardiac bioelectric activity, and the inverse problem of reconstructing cardiac bioelectric activity given measured body surface signals. ECGI relies on a model for how the heart generates bioelectric signals which is subject to variability in inputs. The study of how uncertainty in model inputs affects the model output is known as uncertainty quantification (UQ). This study establishes develops, and characterizes the application of UQ to ECGI.

**Approach:** We establish two formulations for applying UQ to ECGI: a polynomial chaos expansion (PCE) based parametric UQ formulation (PCE-UQ formulation), and a novel UQ-aware inverse formulation which leverages our previously established "joint-inverse" formulation (UQ joint-inverse formulation). We apply these to evaluate the effect of uncertainty in the heart position on the ECGI solutions across a range of ECGI datasets.

**Main Results:** We demonstrated the ability of our UQ-ECGI formulations to characterize the effect of parameter uncertainty on the ECGI inverse problem. We found that while the PCE-UQ inverse solution provided more complex outputs such as sensitivities and standard deviation, the UQ joint-inverse solution provided a more interpretable output in the form of a single ECGI solution. We find that between these two methods we are able to assess a wide range of effects that heart position variability has on the ECGI solution.

**Significance:** This study, for the first time, characterizes in detail the application of UQ to the ECGI inverse problem. We demonstrated how UQ can provide insight into the behavior of ECGI using variability in cardiac position as a test case. This study lays the groundwork for future development of UQ-ECGI studies, as well as future development of ECGI formulations which are robust to input parameter variability.

# 2 Introduction

Electrocardiographic Imaging (ECGI) is a functional imaging modality reconstructs cardiac bioelectric activity in detail using noninvasive body surface measurementsand a model of the torso volume conductor.<sup>1,2</sup> Most ECGI formulations consist of a forward problem and its inverse, which together form the mathematical underpinning for the process of reconstructing bioelectric sources. The forward problem captures how cardiac bioelectric activity, described by some concise model, projects through the volume conductor of the torso to produce body surface potential (BSP) signals on the torso.<sup>3</sup> Key inputs to the forward problem are the relative geometries and conductivities of the heart, torso, and any other organs of interest (a geometric model), as well as a mathematical description of the bioelectric source model. The forward problem is mathematically well-posed and considered to be a solved problem; many forward solution methods show acceptable agreement with measured body surface potentials in validation datasets.<sup>4</sup> The relationship established in the forward problem is then leveraged in the inverse problem to estimate the cardiac bioelectric activity given body surface potential measurements.<sup>2,5,6</sup> The inverse problem is physically ill-posed and leads to an ill-conditioned mathematical formulation, meaning that there may not be a unique solution and that a small perturbation in the inputs can result in large changes in the solution. Regularization is therefore needed to produce physiologically reasonable solutions.<sup>2</sup> Regularization operates by imposing additional constraints on an inverse solution based on a priori knowledge or assumptions about the cardiac bioelectric activity. Solving a regularized inverse problem is then a trade off between a solution that fits the assumptions of the regularization and a solution that matches the body surface potentials when projected back to the torso. The most commonly employed approach to regularization, called Tikhonov regularization,<sup>2</sup> enforces global constraints on the solution based on assumptions such as an assumption of a low amplitude bioelectric source (0 order Tikhonov regularization), an assumption of a low amplitude of spatial gradients of the bioelectric source (1<sup>st</sup> order Tikhonov regularization), an assumption of a spatial smoothness of the bioelectric source (2<sup>nd</sup> order Tikhonov regularization), an assumption of a sharpness of the solution (L1 Tikhonov regularization), and many more.<sup>2</sup>

Despite decades of research, ECGI is still subject to a range of common errors and inaccuracies that hinder its clinical adoption.<sup>1,7</sup> Furthermore, while studies have identified the presence of lingering errors in ECGI formulations, particularly with respect to the uncertainties of the inputs and assumptions of the geometric models, few of these studies have rigorously examined how these uncertainties affect the resulting reconstructions.<sup>8,9</sup>

Uncertainty quantification (UQ) is a field of study that seeks to determine how errors or uncertainties in model inputs affect the resulting solutions.<sup>10</sup> When the parameters of interest are well-defined and quantifiable, the resulting UQ approach is known as 'parametric uncertainty quantification'. Recently, parametric UQ has seen a range of technical improvements and novel applications to the cardiac modeling field, however much of this research has been directed at cardiac forward problems and not inverse problems.<sup>10–14</sup> Forward parametric UQ assumes the model functions as a black-box forward process, and samples this process to produce a distribution of model outputs. This formulation can be mathematically nonintrusive and computationally efficient given modern UQ tools such as polynomial chaos expansion (PCE).<sup>15</sup> The output distribution can also be readily manipulated to compute statistical moments such as the mean model output, standard deviation, and sensitivities of the solution to each of the input parameters and their combinations. However, the interpretation of the UQ results is nontrivial as the output of such an approach is a distribution of model solutions rather than a single solution.

The challenge of applying parametric UQ, which is designed to operate on forward models, to the inverse problem of ECGI has been the focus of recent research.<sup>8,9</sup> However, characterization and interpretations of the capabilities, challenges, and outputs of such UQ applications to ECGI have been limited. Recent studies have also explored a more direct application of UQ to the inverse problem of

 ECGI by incorporating the assumption of variable input parameters into a single formulation known as the 'Joint ECGI formulation'.<sup>9</sup> Such an approach does not directly yield the same statistical moments as parametric UQ (*e.g.*, standard deviation and sensitivity to parameters). However, the resulting ECGI solution includes input parameter variability in the modeling assumptions, and may present a more interpretable output than the distribution of solutions provided by convention parametric UQ. Both of these UQ applications, parametric and joint ECGI, are missing rigorous characterization, comparisons of their outputs, and applications to various sources of ECGI input error.<sup>8,9</sup>

A frequent source of poorly controlled input error for ECGI formulations is inaccuracy in the geometric model used in the forward problem.<sup>12,16,16–21</sup> Several studies have explored how errors in the geometric model, particularly those introduced by uncertainty in cardiac position, negatively impact the forward solutions.<sup>12,22–24</sup> While several studies , including our own, have sought to reduce geometric inaccuracy,<sup>17,19–21,25</sup> little attention has been given to how lingering geometric error will affect the inverse problem due to a lack of robust tools and approaches for the application of UQ to the inverse problem.

In this study, we bring to bear recent advances in both UQ and ECGI formulations to characterize the application of UQ to the ECGI inverse problem in the context of uncertainty in the cardiac position. Our goals were to demonstrate the application of UQ to the ECGI inverse problem and to compare the resulting outputs from two different UQ approaches. Using a combination of experimentally recorded and synthetic datasets, we applied both parametric UQ and a novel UQ-based inverse formulation to ECGI reconstruction of extracellular potential signals in the context of variability in cardiac position. We found that parametric UQ provided useful output statistics such as parameter sensitivity and solution standard deviation, although at times this approach produced non-physiological outlier solutions. Our novel UQ-based inverse formulation provided a straightforward solution, a single inverse solution, as well as possible novel insights into the behavior of the inverse problem itself via the selection of the regularization parameter. Overall this study presents a framework for the application of UQ to the ECGI inverse problem, and a case study of what kinds of outputs and possible complications to expect from such an application.

# 3 Methods

As described in Section 2, in this study, we applied UQ to the ECGI inverse problem using two separate approaches: parametric uncertainty quantification, and a novel UQ-aware formulation of the inverse problem. We first explain our ECGI and UQ formulations in a general form, then describe how we have applied these formulations to characterize UQ in the context of variability in cardiac position.

# 3.1 ECGI Framework

Our application of UQ to ECGI begins with an inverse problem formulation, in this case a Tikhonov regularized inverse problem,<sup>26</sup> selected for its common use in clinical and research ECGI systems.<sup>1,6,8,9,27</sup> Tikhonov reconstruction of cardiac bioelectric sources can be written as

$$\operatorname{argmin}_{\mathbf{H}} ||\mathbf{A}\mathbf{H} - \mathbf{B}||_{F}^{2} + \lambda ||\mathbf{R}\mathbf{H}||_{F}^{2},$$
(1)

where **H** is the  $H \times T$  matrix of cardiac bioelectric sources at H electrodes over T time instances, **B** is the  $M \times T$  matrix of body surface potentials at M electrodes at the same T time instants, and **A** is an  $M \times H$  forward transfer matrix. The forward transfer matrix is the output of the forward problem in which cardiac and torso geometry are related to each other electrically. The ill-posed inverse problem described in Equation 1 is regularized using the  $H \times H$  regularization matrix **R**. Regularization can be applied by selecting different matrices for **R**, such as the identity matrix (zero-order regularization), a surface gradient operator (first-order regularization), a surface Laplacian operator (second-order regularization), or others.<sup>2</sup> The regularization term of the equation is weighted by the regularization weight  $\lambda > 0$ . Typical Tikhonov-regularized inverse problems are formulated for vector unknowns and utilize the squared 2-norm on these vectors  $||\cdot||_2^{2.6}$  Equation 1 describes the matrix form of the Tikhonov inverse formulation where the squared 2-norm is replaced with the squared Frobenius-norm  $||\cdot||_F^2$ . This matrix form is an alternative approach to the vector form which solves and regularizes simultaneously over all T time instants rather than for a single time instant.

#### 3.2 Parametric Uncertainty Quantification

Parametric UQ creates a distribution of model solutions resulting from a distribution over input parameters given some model f. This model is parameterized according to the *j*-dimensional random parameter  $\mathbf{p}$  such that  $\mathbf{Y}_k$  is the model output for some kth value of the parameter  $(f(\mathbf{p}_k) = \mathbf{Y}_k)$ . An ensemble of model outputs can be analyzed to yield statistics of interest, and various approaches have been developed to generate the output distribution.

In this study, we employ the polynomial chaos expansion (PCE) method to approximate the output distribution due to its computational efficiency, the availability of open-source PCE tools, and the use of PCE in previous ECGI studies.<sup>8–10,12,15</sup> PCE treats the model of interest  $f(\mathbf{p})$  as a blackbox process converting parameter ( $\mathbf{p}$ ) to output ( $\mathbf{Y}$ ) and trains a *j*-dimensional, *d*-degree polynomial emulator of the model via N polynomial functions  $\psi_1 \dots \psi_N$ . This emulator can be efficiently analyzed to produce a distribution of the model outputs as well as statistical moments of interest such as means, standard deviations, and sensitivities from given input parameter distributions. The emulator is trained using a weighted least-squared fitting of K training parameter samples, weights, and the associated model outputs. These K parameter samples and sample weights can be generated using a variety of methods such as Monte Carlo, grid search, and others. Here, we used weighted approximate Fekete (WAF) sampling,<sup>28,29</sup> as this approach provides the benefit of reduced sampling (and thus reduced computational overhead), while also stabilizing the variability that can result from random sampling by optimizing the sample choices.

The primary input for the WAF sampling is the distribution defined for the parameters, which we represent as the probability density v. WAF sampling begins with an initial set of  $\tilde{G}$  randomly chosen samples which we denote as  $\tilde{\mathbf{p}}_g$ . These samples are drawn from an importance sampling density,  $v_N$ , which promotes stability and accuracy of the least squares procedure used in latter sample optimization.<sup>10</sup> For each of the  $\tilde{G}$  samples we assign a weight  $w_g$  which is the ratio of the derivative of the probability of that particular sample in the original parameter probability distribution v with respect to the derivative of the probability of that particular sample in the importance sampling density  $v_N$ . The number of samples,  $\tilde{G}$ , is selected such that given failure probability  $0 < \delta < 1$  and a relative accuracy  $0 < \epsilon < 1$ , the samples obey

$$\widetilde{\mathbf{p}}_g \sim v_N, \qquad \qquad w_g = \frac{\mathrm{d}v(\widetilde{\mathbf{p}}_g)}{\mathrm{d}v_N(\widetilde{\mathbf{p}}_g)}, \text{ and } \qquad \qquad \widetilde{G} \ge \frac{3\log(4N/\delta)}{\epsilon^2}N, \tag{2}$$

where  $w_g$  is the weight for the  $g^{\text{th}}$  parameter  $\tilde{\mathbf{p}}_g$ . These randomly selected samples are used as a first-guess initialization to solve a weighted D-optimal design problem to identify the final set of K parameters. This design problem is solved via volume maximization in the form

$$\max_{\{\mathbf{p}_k\}_{k=1}^K \subset \{\mathbf{p}_G\}_{g=1}^{\tilde{G}}} (\det(\mathbf{D}^T \mathbf{D})) \prod_{k=1}^K \frac{\mathrm{d}v(\mathbf{p}_k)}{\mathrm{d}v_N(\mathbf{p}_k)},\tag{3}$$

where **D** is a  $K \times N$  design matrix  $\mathbf{D}_{k,n} = \psi_n(\mathbf{p}_k)$ . Once the optimal K parameters  $(\mathbf{p}_1 \dots \mathbf{p}_K)$  are

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 chosen, their associated weights  $(w_1 \dots w_K)$  can be computed using Equation 2. A more complete formulation of WAF sampling as it applies to PCE can be found in Narayan *et al.*<sup>10</sup>

# 3.3 PCE-Based UQ of ECGI

In this study,  $f(\mathbf{p})$  is a solution to Equation 1 for a particular value of  $\mathbf{p}$ . More specifically, we assume that the parameters of interest only affect the forward matrix and resulting inverse estimate, and thus reformulate Equation 1 to define  $f(\mathbf{p})$  as the solution to

$$\operatorname{argmin}_{\mathbf{H}(\mathbf{p})} ||\mathbf{A}(\mathbf{p})\mathbf{B} - \mathbf{H}(\mathbf{p})||_{F}^{2} + \lambda ||\mathbf{R}\mathbf{H}(\mathbf{p})||_{F}^{2},$$
(4)

which now depicts the forward matrix and the resulting inverse estimation as a function of the input parameters  $\mathbf{p}$ . Extensions of this formulation to the case in which the parameters of interest affect more than  $\mathbf{H}$  and  $\mathbf{A}$  would be straightforward.

The parameter samples provided via WAF sampling are used to compute the associated model output by evaluating Equation 4 for each parameter sample. These samples, weights, and outputs are used to train the PCE emulator, which is then used to compute the following statistical moments for further analysis: mean inverse solution, standard deviation, and sensitivity to each parameter combination. Note that, in contrast to standard ECGI solutions, we treat the solutions as a stochastic ensemble; we compute optimally selected samples of this ensemble via the sampling procedure described and then evaluate the results via estimated statistics of the ensemble. We refer to this application of UQ to ECGI as the PCE-based UQ ECGI formulation, and we refer to the mean solution as the PCE-UQ mean solution. Pseudocode for the preparation of the PCE-UQ ECGI formulation is presented in the supplemental section.

#### 3.4 UQ-Aware ECGI Inverse Formulation

The UQ approach described above treats the inverse problem as a black box, noninvasively assessing the effect of parameter variability. In this section, we instead establish an invasive application of UQ to the inverse problem which produces a single inverse solution as its output.

The baseline inverse formulation established in Equation 1 assumes fixed inputs for all parameters. The PCE-UQ implementation derived in Equation 4 is one approach to the application of UQ to the inverse problem. Here we describe an alternative approach that considers an inverse problem whose solution minimizes the effects due to parameter variations. To that end, we reformulate the Tikhonov inverse problem into whatwe have previously called a Joint Inverse formulation.<sup>30</sup> The joint inverse formulation extends the standard Tikhonov inverse formulation by incorporating multiple realizations of the inverse problem into one equation that solves for a single estimate of the cardiac source. In particular, we optimize over an estimate of the *expectation* of the objective in Equation 4 via an ensemble estimator using multiple realizations of the parameter **p**. In this case, the multiple realizations come from sampled parameter values and weights.

To implement this approach, we again apply WAF sampling to generate these parameter samples and weights. We incorporate  $\mathbf{p}_1 \dots \mathbf{p}_K$  and  $w_1 \dots w_K$  by first constructing the block matrices  $\overline{\mathbf{B}}$  and  $\overline{\mathbf{A}}$  as

$$\overline{\mathbf{B}} = \begin{bmatrix} \mathbf{B} \cdot \sqrt{w_1} \\ \mathbf{B} \cdot \sqrt{w_2} \\ \mathbf{B} \cdot \sqrt{w_3} \\ \vdots \\ \mathbf{B} \cdot \sqrt{w_K} \end{bmatrix}, \overline{\mathbf{A}} = \begin{bmatrix} \mathbf{A}(\mathbf{p}_1) \cdot \sqrt{w_1} \\ \mathbf{A}(\mathbf{p}_2) \cdot \sqrt{w_2} \\ \mathbf{A}(\mathbf{p}_3) \cdot \sqrt{w_3} \\ \vdots \\ \mathbf{A}(\mathbf{p}_K) \cdot \sqrt{w_K} \end{bmatrix},$$
(5)

where each BSP matrix in  $\overline{\mathbf{B}}$  is a copy of  $\mathbf{B}$  weighted by  $\sqrt{w_1} \dots \sqrt{w_K}$ . Each forward matrix in  $\overline{\mathbf{A}}$  is a function of the heart position  $\mathbf{A}(\mathbf{p}_K)$  for  $(\mathbf{p}_1 \dots \mathbf{p}_K)$  weighted by  $\sqrt{w_1} \dots \sqrt{w_K}$ . We then combine these block matrices into a Tikhonov inverse formulation that solves for a single cardiac source given this sampling of the cardiac position parameter distribution in the form

$$\operatorname{argmin}_{\overline{\mathbf{H}}} ||\overline{\mathbf{A}}\overline{\mathbf{H}} - \overline{\mathbf{B}}||_F^2 + \lambda ||R\overline{\mathbf{H}}||_F^2$$

(6)

We call this our UQ joint-inverse formulation, and the resulting  $H \times T$  matrix  $\overline{\mathbf{H}}$  is a UQ joint-inverse solution representing an expected value of the ECGI inverse solution given our sampling of the variability in the parameter of interest,  $\mathbf{p}$ . This inverse solution,  $\overline{\mathbf{H}}$  has the same dimension as  $\mathbf{H}$  from Equation 1. Pseudocode for the preparation of the UQ joint-inverse formulation is also presented in the supplemental section.

#### 3.5 Datasets

We applied UQ ECGI techniques to data collected from large-animal experiments using a torso-tank preparation described in Bergquist et al.<sup>31</sup> All details of the study were approved by the University of Utah IACUC (Protocol #17-04016) following all institutional animal care guidelines. This experimental model consisted of isolating a canine heart in Langendorff perfusion mode supported by a second canine. The isolated heart was instrumented with a pericardiac cage, a rigid 3D-printed frame equipped with 256 Ag-AgCl electrodes.<sup>31</sup> The isolated heart was then suspended in a torso-shaped tank with 192 embedded Ag-AgCl electrodes. The torso tank was filled with electrolyte solution set to a conductivity of 500  $\Omega$  cm to mimic human torso conductivity. We recorded continuously at 1 kHz from both the pericardiac cage and torso electrodes during sinus rhythm and during stimulated ectopic beats paced at 171 bpm from both the anterior and posterior left ventricle. Signals were recorded using custom acquisition hardware described in Zenger et al.<sup>32</sup> We then baseline corrected, noise filtered, and segmented the recorded signals into individual beats using PFEIFER, an open-source software tool for processing time series data from electrocardiographic experiments.<sup>33</sup> Noise filtering was achieved using a rational transfer function as described previously.<sup>33, 34</sup> We segmented 40 heartbeats (from QRS onset to the end of the T wave) from the series of recorded beats for each of the three activation sequences (sinus, anterior ventricular paced, and posterior ventricular paced) which we refer to as sinus, aVP, and pVP, respectively. After electrical recordings, the position of the pericardiac cage within the torso tank was recorded using a mechanical digitizer. This relative position was used to register the pericardiac cage geometry into the torso tank geometry using a rigid transformation. This registered pericardiac cage geometry was then considered an adequate surrogate for the heart surface and was referred to as the nominal cardiac position. These experiments were replicated twice to produce two datasets of recorded body surface and pericardiac cage signals along with nominal heart positions relative to the torso tank geometry. Each of these datasets (Dataset 1 and Dataset 2) consisted of 120 heartbeats (40 sinus, 40 aVP, 40 pVP).

During such experiments, there will be some degree of geometric error in the registration of the pericardiac cage, which complicates our analysis of the effects of UQ in the context of heart position uncertainty. To address this limitation, we designed a third, synthetic dataset based on Dataset 2 and the nominally registered pericardiac geometry. We computed 50 different synthetic heart positions by generating random translation vectors using Monte Carlo samples of X, Y, and Z values between 0 and 40 mm. These 50 heart positions were designated as 'ground-truth' geometries from which we computed body surface potentials for each of the three activation sequences using the boundary-element-method forward problem for epicardial potentials. We then added Gaussian noise to the computed body surface signals at an SNR of 30 dB. Of these 50 positions, two produced BSP and EGM pairs that resulted in unacceptably poor ECGI solutions and were therefore excluded. The result was a dataset consisting of

 48 different ground truth heart positions, each with body surface and pericardiac cage signals for three different activation sequences (144 total), named 'Dataset 3'.

#### 3.6 Implementation

In this study we parameterized heart position in terms of the UQ parameters of interest with j = 3 according to  $\mathbf{p}_k = [x_k, y_k, z_k]$ , where  $x_k$  is the scalar translation of the heart from its nominal position along the x-axis for the  $k^{\text{th}}$  parameter sample, and  $y_k$  and  $z_k$  are similiar translations along the y- and z-axes respectively. For each of these three parameters, we assumed a beta distribution with  $\alpha = 2$ ,  $\beta = 2$ . An example of such a beta distribution can be seen in Figure 1 for a parameter with a range of  $\pm 1$ . We selected  $\alpha = 2$ ,  $\beta = 2$  to produce a distribution with a shape similar to that of a normal distribution (higher probability near the mean), but also with fixed bounds (values drawn from the beta distribution will not ever be outside of the specified bounds). This was done to prevent sampling of heart positions which were translated out of the torso, which can lead to non-physiological solutions. To investigate the effect of increasing uncertainty in the position of the heart we defined six uncertainty ranges (Range 1–Range 6) for these parameter distributions as follows:  $\pm 1$  mm,  $\pm 5$  mm,  $\pm 10$  mm,  $\pm 15$  mm,  $\pm 20$  mm, and  $\pm 25$  mm, respectively. A sufficient number of WAF samples were selected for each uncertainty range to satisfy the training of a d = 5 PCE emulator. These same samples and weights were utilized in both the construction of PCE emulators as well as computation of the UQ joint-inverse solutions.

The following groups of inverse solutions were computed:

- Nominal: inverse solutions based on the nominal heart position for each heartbeat for each dataset according to Equation 1.
- **Ground truth:** inverse solutions based on the ground-truth heart position for each beat in Dataset 3 according to Equation 1.
- WAF sample solutions: inverse solutions for all the WAF parameter samples over each uncertainty range for each heartbeat for each dataset according to Equation 4.
- **UQ joint-inverse:** the UQ joint-inverse solutions over each uncertainty range for each beat in each dataset according to Equation 6.

The WAF sample solutions, along with the associated WAF weights and parameter values, were used to train a PCE emulator for each parameter range. From these emulators we extracted the statistical moments of the mean solution, standard deviation, and sensitivities to each parameter and parameter combination (7 sensitivities in total given 3 parameters in  $\mathbf{p} = [X, Y, Z]$ ). For each uncertainty range, the mean solution was considered to be the UQ inverse solution for the PCE-UQ approach.

We selected epicardial surface potentials as our bioelectric source model due to their wide use in clinical and research ECGI systems, and for ease of comparison with our measured experimental signals. We used the boundary element method to calculate all forward matrices, as it does not require remeshing of the torso geometry when moving the heart. In all cases, the regularization weight  $\lambda$  was chosen using the Frobenius L-curve criterion at the maximum curvature ( $\kappa$ ) of the L-curve over the range of  $\lambda = 10^{-10} \dots 10^{10}$ .<sup>17</sup> The regularization matrix R was selected to approximate the surface Laplacian of the epicardial potentials (2nd order regularization). The resulting Laplacian matrix was badly conditioned and required regularization which we carried out by adding  $10^{-3}$  to the singular values of the Laplacian matrix which were less than  $10^{-3}$ .<sup>30</sup> All inverse solutions were computed using the entire QRST segment of the ECGs. All PCE and UQ calculations were performed using UncertainSCI, an open



 source python package for UQ we have published previously.<sup>10, 35</sup> ECGI solutions were computed using a combination of in-house software and the open-source SCIRun Forward Inverse Toolkit.<sup>36</sup> Figures were generated using SCIRun (<sup>37</sup>), MATLAB (Mathworks, Inc), and Illustrator (Adobe, Inc).

#### 3.7 Analysis

We compared the resulting inverse solutions (nominal, ground-truth, PCE-UQ mean solution, and UQ joint-inverse) to the corresponding measured ground-truth electrical recordings using several established metrics.<sup>17, 31</sup> These metrics consisted of the root-mean-squared error (RMSE) over the QRST between inverse solutions and ground truth EGMs, the mean temporal correlation (TC) (*i.e.*, the correlation between inverse solutions and ground-truth EGMs over the QRST on an electrode by electrode basis averaged across all electrodes), and the mean spatial correlation (SC) (*i.e.*, the correlation between reconstructed and measured cardiac surface potential distributions averaged over all time instances in the QRST). For nominal, ground truth, and UQ joint-inverse solutions we also compared the curvature ( $\kappa$ ) of the L curve, the value of  $\lambda$  chosen, and the shapes of the L curves. We also visually compared the reconstructed and measured potential maps. This was done by plotting the potential maps onto a flattened projection of the cardiac geometry, as described in detail previously.<sup>17</sup> Briefly, this flattened geometry was constructed by cutting the cardiac geometry along the right side and projecting the unrolled point mesh onto a plane using an approach that preserved interelectrode spacing.

The PCE-UQ ECGI formulation also provided us with standard deviation and sensitivity values for every electrode at every time instant. We visualized both the standard deviation and each sensitivity metric (one for each parameter and combination of parameters) in the same way we visualized the potential distributions, by plotting their spatial maps on the flattened cardiac geometry.

#### 4 Results

#### 4.1 Ground-Truth Synthetic Data (Dataset 3)

The results based on forward-computing the potentials from known heart locations (Dataset 3) provided the most accessible evaluation of the behavior of the inverse problem in a setting where the level of localization error of the heart was known. Figure 2 shows the statistics summarizing the error / correlations of the inverse results for each heartbeat in Dataset 3 compared to both the ground-truth heart position and the nominal heart position as a function of shifts in heart location. For the nominal position, as geometric error increased, the inverse solution accuracy (according to RMSE, SC, and TC) decreased. As expected, the accuracy of inverse solutions in which heart shift was accounted for in generating the solution—the ground-truth heart position case—remained consistent.

The application of PCE-based parametric uncertainty quantification to the ECGI inverse problem produces a distribution of inverse solutions, and for this study, we chose to focus on the mean of this distribution as a representation of the PCE-UQ solution distribution. Figure 3 shows the accuracy of the PCE-UQ mean solution for each uncertainty range and activation sequence in Dataset 3. In uncertainty ranges 4 through 6 we observed outlier PCE-UQ solutions with RMSE well over 4.5 mV, and spatial and temporal correlations near zero.

In Supplemental Tables S.1, S.2, and S.3 we see that the median solution accuracy is stable across uncertainty ranges, which is also reflected in the distributions in Figure 3. Only nominal position and UQ mean solutions whose nominal heart geometry had low error compared to the ground truth geometry resulted in comparable accuracy to the ground truth position inverse solutions.

The inverse solutions themselves, which we visualized more directly as potential maps in Figure 4, did show subtle differences between uncertainty ranges. In Figure 4 we showed inverse solutions for the



Figure 2: Inverse solution error / correlation metrics as a function of heart location error distance for both the nominal and ground-truth positions in Dataset 3. Each point represents a single inverse solution using either the nominal heart position (diamonds) or the ground-truth heart position (circles). Colors indicate the activation sequence, where red is an anterior ventricular paced beat, green is a posterior ventricular paced beat, and blue is a sinus beat. The x-axis is the Euclidean distance (in millimeters) between the centroid of the ground-truth heart position used to generate the synthetic body-surface potentials and the nominal heart position. The scatter plot panels from top to bottom show the root mean squared error (RMSE in millivolts), the spatial correlation, and the temporal correlation.

![](_page_11_Figure_2.jpeg)

Figure 3: Inverse solution accuracy metrics as a function of distance for the nominal, ground truth, and PCE-UQ mean solutions in Dataset 3. Each point represents a single inverse solution using either the nominal heart position (Nominal, column one), the true heart position (True Position, Column 2), or the PCE-UQ mean solution for ranges 1 through 6 (columns 3 through 8). Colors indicate the activation sequence where red is an anterior ventricular paced beat, green is a posterior ventricular paced beat, and blue is a sinus beat. The points are sorted on the x-axis for each case according to the Euclidean distance between the nominal and ground truth heart position for that beat. The scatter plots from top to bottom show the root mean squared error (RMSE in millivolts), the spatial correlation, and the temporal correlation. The RMSE y-axis is truncated to 4.5 mV maximum, which excludes outliers in ranges 4, 5, and 6.

aVP activation sequence using three different example beats from Dataset 3: one with low geometric error between nominal and true heart position (5.3 mm), one with medium geometric error (24.4 mm), and one with high geometric error (49.1 mm). We noted in particular changes in the spatial distribution of potential depressions in the low and medium geometric error cases as the uncertainty range increases from 1 to 6. The high geometric error case showed larger differences compared to the true position across all the uncertainty ranges but less pronounced changes between each range than the low-error and medium-error cases. In each case, the UQ mean inverse solutions closely resembled those from the nominal positions. The PCE-UQ also provides output statistics such as the standard deviation and parameter sensitivities, which are reported in Figure 5 and Figure 6. Standard deviations increased in amplitude with the uncertainty ranges from near 0 mV at range 1 to around 5 mV for range 6. The standard deviations also varied with the amount of underlying geometric error. The sensitivity distributions in Figure 4 revealed only marginal differences across error levels and across uncertainty ranges. The parameter interaction sensitivity (X and Y, X and Z, Y and Z, X and Y and Z) were all nearly zero, indicating minimal parameter interactions.

Figure 7 shows the accuracy of the UQ joint-inverse formulation, which produced a single ECGI solution per heartbeat, as captured by RMSE, spatial correlation, and temporal correlation. As the uncertainty range increased from Range 1 to Range 6, these metrics improved slightly and showed slightly less variability with the degree of heart position error. Similar results are visible in the Supplemental Tables in Section 6. We also note the absence of the outlier beats in Figure 3, in contrast to the results found using the UQ mean solutions.

The potential map reconstructions in Figure 8 show the joint-inverse reconstructions across the uncertainty ranges. In contrast to the UQ mean solutions in Figure 4, the joint-inverse solutions show more dependence on the uncertainty ranges. There were pronounced changes in potential distributions with ranges, including to shapes of elevated and depressed areas, and a general reduction in peak amplitude, *e.g.*, from 13 to 9 mV (elevations) and -8 to -6 mV (depressions).

The joint-inverse approach also generates values for the regularization weight  $\lambda$  selected and the curvature of the L-curve at the corner. Figure 9 shows scatter plots of the  $\lambda$  values and the curvatures ( $\kappa$ ) of the L-curve for the standard Tikhonov inverse across the uncertainty ranges using the nominal and ground truth heart positions as well as for each UQ joint-inverse solution. As the uncertainty range increased, so too did the  $\lambda$  values, starting from the ground-truth position. The  $\kappa$  values were generally slightly larger when using the ground truth heart position than for the nominal position and then increased very slightly as the uncertainty range increased. Beats with larger geometric error showed lower  $\kappa$  values both, in the nominal inverse and UQ joint-inverse cases. Figure 10 shows a comparison of L-curve morphologies among the inverse solutions using nominal, and ground-truth heart position, and UQ joint-inverse solutions across the six uncertainty ranges. In the case of the low geometric error heartbeat, the nominal and ground-truth position L-curves had similar morphologies, whereas they differed more for mid and high geometric errors. In each case, as the uncertainty range increased, the L-curves derived from the UQ joint-inverse formulation showed increasing sharpness at the corner, increasing slope of the upwards-facing feature of the curve, and a shift rightwards of the corner location.

#### 4.2 Datasets 1 and 2

 Datasets 1 and 2 explored the application of UQ to ECGI with measured body surface and heart signals and an unknown amount of geometric error. Figure 11 summarizes the mean UQ solution accuracy from PCE-UQ as compared to the standard inverse solution at the nominal position. (See Supplemental Tables in Section 6 for numerical summaries). Accuracy of the UQ mean solutions varied between datasets and across activation sequences with some showing slight increases in solution

![](_page_13_Figure_2.jpeg)

Figure 4: Example potential maps for measured data and inverse solutions in Dataset 3 using the ground truth position, nominal position, and PCE-UQ mean solution. Potential maps are shown at a time point corresponding to the peak of the root mean squared curve of the measured signals, shown in the bottom left. Inverse solutions are shown for three heart positions from Dataset 3 using the aVP activation sequence: one with low geometric error between the nominal and true position (5.3 mm, top row), one with a medium amount of geometric error (24.4 mm, middle row), and one with a high amount of geometric error (49.1 mm, bottom row). Inverse solutions using the ground truth heart position and nominal heart position are shown in the left inverse solution columns. The remaining inverse solutions are the PCE-UQ mean solutions for each uncertainty range.

![](_page_14_Figure_2.jpeg)

Figure 5: Example standard deviation maps for potentials shown in Figure 4, *i.e.*, the PCE-UQ from Dataset 3. The map in the top-left corner shows the measured potential map at the time point shown in the RMS curve below. Standard deviation maps are shown for three heart positions from Dataset 3 using the aVP activation sequence with geometric error ranges as defined in Figure 4.

![](_page_15_Figure_2.jpeg)

Figure 6: Parameter sensitivity maps for the potentials shown in Figure 4, *i.e.*, the PCE-UQ from Dataset 3. The map in the top-left corner shows the measured potential map at the time point shown in the RMS curve below. Sensitivity maps are shown for three heart positions from Dataset 3 using the aVP activation sequence with geometric error ranges as defined in Figure 4. From left to right, each column shows the parameter sensitivity for X, Y, and Z direction shifts in heart positions, respectively. No substantial sensitivity was found for any parameter combinations.

![](_page_15_Figure_4.jpeg)

![](_page_16_Figure_2.jpeg)

Figure 7: Inverse solution accuracy metrics as a function of distance for the nominal, ground truth, and UQ joint-inverse solutions in Dataset 3. The layout of the plots is similar to that in Figure 4.2, but here for the UQ joint-inverse approach. Each point represents a single inverse solution using either the nominal heart position (Nominal, column one), the ground-truth heart position (True Position, Column 2), or the UQ joint-inverse solution for uncertainty ranges 1 through 6 (columns 3 through 8).

![](_page_17_Figure_2.jpeg)

Figure 8: Example potential maps for measured data and inverse solutions in Dataset 3 using the ground truth position, nominal position, and the UQ joint-inverse formulation. As in Figure 4, the map in the top-left corner shows the measured potential map at the time point shown in the RMS curve below. Inverse solutions are shown for three heart positions from Dataset 3 using the aVP activation sequence, again as in Figure 4. Inverse solutions using the ground truth heart position and nominal heart position are shown in the left two columns and the remaining columns contain the UQ joint-inverse solutions for each uncertainty range.

![](_page_18_Figure_3.jpeg)

Figure 9: Inverse solution regularization metrics as a function of distance for the nominal, ground truth, and UQ joint-inverse solutions in Dataset 3. Each point represents a single inverse solution using either the nominal heart position (Nominal, column one), the ground-truth heart position (True Position, Column 2), or the UQ joint-inverse solution for ranges 1 through 6 (columns 3 through 8). Colors indicate the activation sequence, where red is an anterior ventricular paced beat, green is a posterior ventricular paced beat, and blue is a sinus beat. The points are sorted into groups on the x-axis for each case according to the Euclidean distance between the nominal and ground truth heart position for that beat. The scatter plots from top to bottom show the regularization weight ( $\lambda$ ) chosen for each solution and the curvature of the L-curve corner ( $\kappa$ ). Both Y axes are in log scale.

![](_page_19_Figure_2.jpeg)

Figure 10: Example L-curves for reconstructions using either the nominal position, ground-truth position, or UQ joint-inverse. L-curves are shown for the same three heart positions from Dataset 3 using the aVP activation sequence as shown in previous figures. For each curve, the corner selected by the L-curve algorithm is highlighted with a red dot. The curves for inverse solutions using the nominal heart position are shown in blue, using the true heart position in green, and using the UQ joint-inverse formulation in black. For each UQ joint-inverse solution, the L-curves corresponding to each uncertainty range are shown with a label (R1 to R6) to the right of each.

![](_page_20_Figure_3.jpeg)

Figure 11: Inverse solution accuracy metrics for the nominal and PCE-UQ mean solutions in Datasets 1 and 2. Each box plot represents all 40 solutions for a particular activation sequence using either the nominal heart position (Nominal, column one), or the PCE-UQ mean solution for ranges 1 through 6 (columns 2 through 7). Colors indicate the activation sequence where red is an anterior ventricular paced beat, green is a posterior ventricular paced beat, and blue is a sinus beat. The box plots from top to bottom show the root mean squared error (RMSE in millivolts), the spatial correlation, and the temporal correlation.

accuracy at middle uncertainty ranges, and others demonstrating minimal variation. In general, the temporal correlation of the UQ mean solutions was lowest at the highest uncertainty range, while RMSE and spatial correlation did not show consistent changes among datasets or activation sequences. The standard deviation increased as the uncertainty range increased, as Figure 12 demonstrates with uncertainty ranges 1 and 2, resulting in near zero standard deviation across the potential map. The UQ mean solution potential maps showed more pronounced changes in Datasets 1 and 2 than Dataset 3, with elevation and depression amplitudes increasing in magnitude for each uncertainty range (Figure 12). Parameter sensitivity showed minimal parameter interactions and did not substantially vary in spatial distribution across uncertainty ranges. In Figure 13 we see that the X, Y, and Z sensitivity maps at the peak of the QRS of aVP 1 for Dataset 1 resemble the sensitivity maps found for Dataset 3 (Figure 6).

Figure 14 shows the inverse metrics for the UQ joint inverse solutions at each uncertainty range in Datasets 1 and 2. Generally, the solution quality began to degrade around Range 4 in both datasets across all metrics. However, there are some exceptions such as the aVP activation sequence, which showed a consistent temporal correlation across all uncertainty ranges, and only a slight degradation in RMSE and spatial correlation. When examining the inverse problem metrics,  $\kappa$  and  $\lambda$  in Figure 15, there was a nonlinear response of the  $\kappa$  value to an increase in uncertainty range. At middle uncertainty ranges (2 through 4) in both datasets, we observed higher  $\kappa$  values than at either lower or higher uncertainty ranges. This trend was observed in both datasets and across all activation sequences with the aVP activation sequence showing the most pronounced increase in  $\kappa$ . The  $\lambda$  value on the other hand was lower in uncertainty range 1 than that found in the nominal position inverse solutions and increased steadily as the uncertainty range increased. Finally, Figure 16 shows UQ joint inverse potential map reconstructions for an aVP beat from Dataset 2 across the uncertainty ranges. We observed that as the uncertainty range increased the distribution of the potential elevation shifted from midway between the apex and base in uncertainty range 1 to more basal in uncertainty range 6.

The reconstruction at range 6 more closely resembled the nominal position inverse solution than the range-1 solution and the intermediate UQ inverse solutions showed a gradual transition. The potential elevation and depression magnitudes did not change substantially across the uncertainty ranges, unlike the mean UQ inverse solution observed in Figure 12 which showed an increased potential elevation and depression magnitude as the uncertainty range increased.

![](_page_22_Figure_2.jpeg)

Figure 12: Example maps of potential and standard deviation for measured values and inverse solutions in Dataset 2 using the nominal position and PCE-UQ mean solution. All results are for a single aVP beat at a time point corresponding to the peak of the root-mean-squared curve of the measured signals. An inverse solution using the nominal heart position is shown in the bottom left. The remaining columns contain the PCE-UQ mean solutions and their standard deviations for each uncertainty range, all in units of millivolts but with separate scaling.

![](_page_22_Figure_4.jpeg)

![](_page_23_Figure_2.jpeg)

Figure 13: Parameter sensitivity maps for the PCE-UQ in Dataset 2 using an aVP beat. The time point for all maps corresponds to the peak of the root-mean-squared curve of the measured signals, as indicated on the time plot. The leftmost map contains the measured potentials and the three sensitivity plots to the right correspond with shifts in the X, Y, and Z values, respectively.

![](_page_24_Figure_2.jpeg)

![](_page_24_Figure_3.jpeg)

Figure 14: Inverse solution accuracy metrics for the nominal, and UQ joint inverse solutions in Datasets 1 and 2. Each box plot represents all 40 solutions for a particular activation sequence using either the nominal heart position (Nominal, column one) or the UQ joint inverse solutions for ranges 1 through 6 (columns 2 through 7). Colors indicate the activation sequence where red is from an anterior ventricular paced beat, green from a posterior ventricular paced beat, and blue from a sinus beat. The box plots from top to bottom show the root mean squared error (RMSE in millivolts), the spatial correlation, and the temporal correlation.

![](_page_25_Figure_2.jpeg)

Figure 15: Inverse solution regularization metrics for the nominal, and UQ joint inverse solutions in Datasets 1 and 2. Each box plot represents all 40 solutions for a particular activation sequence using either the nominal heart position (Nominal, column one), or the UQ joint inverse solutions for ranges 1 through 6 (columns 2 through 7). Colors indicate the activation sequence where red is from an anterior ventricular paced beat, green from a posterior ventricular paced beat, and blue from a sinus beat. The box plots from top to bottom show the regularization weight ( $\lambda$ ) chosen for each solution and the curvature of the L-curve corner ( $\kappa$ ). Both Y axes are in log scale.

![](_page_26_Figure_2.jpeg)

Figure 16: Example potential maps for measured data and inverse solutions from Dataset 2 using the nominal position and the UQ joint inverse formulation. Potential maps are shown at a time point corresponding to the peak of the root mean squared curve of the measured signals for an aVP activation sequence. The RMS signal is shown on the right with a red vertical line indicating the visualized time instant. The upper left panel contains the measured potentials and the lower left panel an inverse solution using the nominal heart position. The remaining maps show inverse solutions using the UQ joint inverse approach for each uncertainty range.

# 5 Discussion

In this study, we implemented two extensive applications of uncertainty quantification to the inverse problem of ECGI in the context of variability in the cardiac position. We sought to address two main goals: 1) demonstrate the feasibility of applying UQ to geometric uncertainty of the ECGI inverse problem and 2) compare the resulting outputs from different UQ approaches. To manage the scope of this multidimensional analysis, we selected a small subset of activation sequences, and a simplified parameterization of heart position. Even with these constraints, analysis and interpretation of the results were challenging. Adding to the challenges was the fact that few have addressed the topic of UQ in the context of the ECGI inverse problem and there is a paucity of standard modes of analysis. We sought to develop and evaluate such modes of analysis, a summary of which we present in this study.

Our first approach was parametric uncertainty quantification (PCE-UQ), which produces a distribution of solutions to the model of interest (in this case the inverse problem of ECGI), given parameterized estimates of input variability, in this case the position of the heart, in the form of probability distribution. The second approach produces a single inverse solution that incorporates assumptions of input parameter variability. This approach is derived from the joint-inverse formulation, a novel ECGI formulation that we have developed previously.<sup>9,30</sup> To date, very few studies have explored applications of parametric UQ to the ECGI inverse problem,<sup>8</sup> even fewer have applied our UQ joint-inverse formulation,<sup>9,30</sup> and none have compared the two. A final product of the study was a general framework to compare the results from such approaches.

#### 5.1 PCE-UQ ECGI Formulation

The PCE-UQ provides a complex and rich output when applied to ECGI, however, it is not immediately clear how to interpret the results in terms of the effects of parameter variability on model accuracy. Here, we focused on the mean of this output distribution, which provides a single set of cardiac potential for each case, a result that represents in some overall sense, the impact of parameter uncertainty. Further studies should develop more elaborate techniques to leverage and assess the entire output distribution. Within these mean potentials maps, we observed subtle changes in Datasets 1 and 2 as the uncertainty range increased. For example there was an increase in the size and amplitude of the potential elevation during the peak of the QRS as seen in Figure 12. However, this effect did not carry over to Dataset 3, which was created under synthetic but controlled conditions. There were only minimal differences between potential maps across the uncertainty ranges. Furthermore, results from Dataset 3 were fairly similar between the case of the nominal position solution and the mean solution with UQ applied. This finding indicates that the nominal solution would be a substantially similar surrogate for the UQ mean, a conclusion only accessible through the use of UQ.

While the mean values of the PCE-UQ distributions provide general insight into the behavior of the ECGI inverse problem, the statistical moments of this approach provide additional insight into the effects of uncertainties of the input parameters. In particular, we focused on the standard deviation and parameter sensitivities. We found that the magnitude of standard deviation depended largely on dataset and uncertainty range. For example, in Dataset 1, the maximum standard deviation was below 1 mV up to uncertainty range 4 ( $\pm$  15 mm), whereas for Dataset 2 the maximum was slightly higher in each uncertainty range, but still remained low (below 1.5 mV) through uncertainty range 2 ( $\pm$  5 mm). These results corroborate a common rule of thumb that geometric errors should be kept below 5 mm, and represents a target applied in some geometric registration studies.<sup>31, 38</sup> Dataset 3 produced outlier solutions for some beats in the higher uncertainty ranges, which is apparent in the high max RMSE (> 50 mV), high max standard deviation (>  $\pm$ 200 mV), low min spatial correlation (< 0.1), and low min temporal correlations (< 0.1) (See supplemental Tables in Section 6)The presence of these outliers

is likely due to instability in the individual inverse solutions used to train the PCE emulator during the parameter sampling process, which we observed in some cases where the regularization weight  $\lambda$  was poorly chosen by the L-curve method. We hypothesize that this instability may be ameliorated by developing a more robust method for the selection of  $\lambda$  in the context of these UQ samples. Despite this limitation, we observed that the majority of the beats in Dataset 3 produced errors well within the limits typical for this ECGI formulation.

The parameter sensitivity analysis provides insight into the relative contribution of each parameter to the observed solution variability. In addition to individual parameter contributions, UQ provides an assessment of the interactions between parameters. Perhaps surprisingly, we found no appreciable parameter interaction between variations of the X, Y, and or Z parameters in any of our test scenarios. These results may reflect the orthogonal nature of these parameters but also provide reassuring evidence of independence of the effects of translation uncertainties in heart location. UQ analysis is uniquely able to provide such insights and guidance when solving inverse problems.

#### 5.2 UQ Joint-Inverse

The UQ joint-inverse solution we have developed avoids the the challenges of interpreting the results of the PCE-UQ analysis by providing a readily interpretable output in the form of a single inverse solution, given a parameterization of the input variability. By providing a single output solution, the UQ joint-inverse formulation eliminates the ambiguity of interpreting a distribution of solutions, while at the same time removing potential insights gained from the distribution detailed above. A further benefit of UQ joint-inverse formulation was enhanced stability, producing no outlier solutions across any of our datasets. This increased stability may be due to the fact that the joint-inverse formulation considers the collection of heart positions simultaneously, as opposed to the PCE-UQ approach, which computes an inverse solution for each heart position sample individually. Another reassuring finding was that the UQ joint-inverse solutions became increasingly smoothed as the uncertainty range increased, likely a direct result of the correspoding increase in regularization weight ( $\lambda$ ). This smoothing can be seen in the potential maps in Figures 8 and 16.

In the face of increasing ranges of heart-position uncertainty, the UQ joint-inverse solutions showed variable changes in accuracy. For Dataset 3, for example, the spread of the solution accuracy improved (decreased) with increasing range of uncertainty, but only for the lower-accuracy reconstructions. Solution accuracy from higher-accuracy reconstructions, in contrast, worsened slightly as the range of uncertainly in the location increased. The main surprise in this finding was that output accuracy would ever improve in the face of increasing ranges of uncertainty in heart position. It must be noted, however, that these differences in the output accuracy were very small and we suspect the decrease in spread was a symptom of the increased regularization weight chosen for larger uncertainty ranges (see Figure 9), resulting in overly smooth solutions.

In contrast, for Datasets 1 and 2, the reconstruction accuracy generally performed as expected, degrading as the uncertainty range increased. The UQ joint-inverse solution operates as an expected value over the range of input parameter variability, thus as the range increases, it would be expected that the solution accuracy would degrade. The degree of this degradation may provide insight into the effect of position uncertainty on the inverse solutions. Furthermore, the UQ-joint inverse formulation explicitly includes the possible presence of heart position variability, as described by our parameterization, in contrast to traditional inverse formulations which fail to account for heart position variation.

Because the joint UQ approach was based on a Tikhonov regularization formulation, it made sense to evaluate the effects of uncertainty on the regularization parameter,  $\lambda$ . We examined both the selected regularization weight and the sharpness of the L-curve corner for each uncertainty range. In Datasets 1 and 2, there was an increase in  $\lambda$  at each uncertainty range, and an increased curvature within the

middle uncertainty ranges. These findings lend another angle of inquiry to research by Rodrigo et al. and others who have suggested that the sharpness of the corner of the L-curve is related to the geometric accuracy of the forward model.<sup>21</sup> Further corroborating this suggestion were the results from Dataset 3, in which higher geometric error generally produced lower L-curve curvature and higher  $\lambda$  values as seen in Figure 9. This trend, however, lacked consistency in our study. For example, when using the true cardiac position in inverse solutions for Dataset 3, particularly for sinus beats, the cardiac positions which were more distant from the nominal position produced lower curvatures in the L curves. By contrast, there was higher L-curve curvature using the nominal position rather than the true cardiac position (Figure 9) This nominal cardiac position was approximately in the center of torso geometry, which may suggest that not only the error in the heart position but also the relative heart position with respect to the torso may contribute to the sharpness of the L-curve. The L-curve shape also varied with range of position variability, becoming sharper as the range of position uncertainty increased. A unique feature of applying UQ analysis directly to inverse problems, rather than indirectly via the associated forward problem, is the range of analyses that become possible. For example, regularization is so integral to almost all inverse problems, yet its role in evaluations of UQ can only really be revealed with this type of combined approach.

The regularization parameter selection by the L-curve is clearly affected by variability in cardiac position, yet because these features of the L-curve are not considered a part of the model output but rather an intermediate feature of the inverse solver, the relationship between cardiac position and the L-curve is more difficult to interpret. However, this relationship could perhaps be leveraged to produce more sophisticated regularization methods which are informed by, agnostic to, and/or robust to input uncertainty. As most regularization techniques are derived from applying *a priori* assumptions about the solution as constraints in the inverse solver, there may be a way to include an assumption of input parameter variability into such regularization operations. Such potential relationships between input parameter uncertainty and regularization in the inverse problem warrants further investigation.

#### 5.3 Limitations

This study approached the application of UQ to the inverse problem of ECGI from a broad perspective and the subsequent observations are therefore only general. These observations are also based on general, but incomplete error metrics, *e.g.*, RMSE, spatial correlation, and temporal correlation. More specific applications of ECGI, *e.g.*, to localize sites of early and breakthrough activation, warrant more specific metrics and realistic, application specific types and ranges of uncertainties.

We selected cardiac position as the sole source of uncertainty due to its applicability across ECGI applications (all ECGI applications require a geometric model), as well as the interpretability of variability in cardiac position (several known sources of error are well characterized). While the results presented here can only be explicitly interpreted in the context of error in X, Y, and Z translation, the general approach and types of outputs can be translated to other input variables of interest. Other areas of possible input variability may include inputs such as the position of the torso electrodes, the shape of the torso, or various other parameters of the ECGI bioelectric source, forward formulation, or solution method. For such inputs, we suggest that a key problem facing an ECGI UQ application is development and implementation of parameterization. For example, while torso shape may be parameterized by statistical shape models in a similar fashion to what others have done for the heart,<sup>39</sup> such a study would require a repository of torso shapes and associated body surface map recordings. Additionally, the tuning and integration of such a torso shape parameterization into an ECGI formulation would be nontrivial. Inputs such as the position of the electrodes on the torso may also prove difficult to implement. For example, parameterizing each electrode position as a 2D coordinate on the torso surface would result in a large parameter space for the upwards of 200 torso electrodes used in many ECGI implementations.

Such a large parameter space would not only greatly increase the computational burden of any UQ study, but also the complexity of the analysis in the face of so many parameters and parameter interactions. Succinct and robust parameterization of ECGI inputs is an outstanding challenge facing future ECGI UQ studies.

The need to select the regularization weight  $\lambda$  in both the PCE-UQ and the UQ joint-inverse formulation was an added complication that deserves future development and attention. For this study we allowed  $\lambda$  to vary for each individual inverse solution used to train our PCE emulator. Doing so introduced a source of variability which, while related to the variability of our parameters of interest, was less direct and interpretable. Indeed the value of  $\lambda$  chosen in these cases was a function of the cardiac position, however, this additional output was not considered by the UQ formulation when constructing the distribution of ECGI solutions. Furthermore, we observed that the PCE-UQ approach produced outlier solutions at higher uncertainty ranges, a finding we attribute to poor selection of regularization weight by the L-curve. In the case of the UQ joint-inverse formulation, regularization also presents a confounding factor. We selected a single  $\lambda$  value for each heartbeat in the UQ joint-inverse formulation, despite the range of heart positions. The joint formulation could be adjusted to allow for a variable  $\lambda$ values computed using each individual position first, then incorporated as a diagonal matrix inside the regularization term of Equation 6. Such a complex approach may, however, result in similar instabilities as those seen in the PCE-UQ formulation. Finally, we chose the Frobenius L-curve criterion to select a single value of  $\lambda$  over the entire signal. Other approaches such as a time-varying regularization or a median regularization weight from individual time instances, as well as other regularization selection methods altogether (CRESO, U curve) have been proposed by others and these different regularization approaches may affect the UQ results.<sup>6</sup>

The datasets used for this study consisted of experimentally recorded electrocardiographic signals (BSP's and EGM's) which are subject to their own levels of unknown error. We addressed this limitation by supplementing the analysis with synthetic data (measured EGM and simulated BSP using numerically sampled cardiac positions), however, these approaches are limited and future studies should seek to apply these UQ techniques to a wider collection of datasets. Furthermore, cardiac source signals in this study were recorded from a pericardiac cage, which we have presented previously.<sup>31</sup> The signals on the pericardiac cage are smoother and attenuated when compared to true cardiac surface electrograms. The benefits of using the pericardiac cage over an epicardial array include its more complete and even sampling and superior geometric accuracy when registering the pericardiac geometry, however, the UQ results might be different with true epicardial potentials. This study is also limited by the experimental setup based on the electrolytic torso tank, which represents a simplified scenario of a homogeneous volume conductor and a static heart position. Such an arrangement offers profound advantages, including fine control over geometric parameters and reduction of measurement errors, however, an inhomogeneous, moving torso would provide more rigorous testing of ECGI, provided there were some way to capture the geometry. The mostly feasible approach will likely be based on synthetic geometry and signals based on a highly resolved, time-varying, inhomogeneous geometric model.

# 5.4 Prospective View

 Throughout this study, we presented a broad characterization of the result of UQ analyses in the context of cardiac position uncertainty. However, meaningful levels of output variability, accuracy thresholds, and error metrics are often determined by the specific physiological or pathophysiological features of interest, which would require more narrowly focused, but limited, study designs. Instead, we sought to present an overall framework for the application of UQ to the inverse problem as a starting point for future research into specific ECGI use cases such as arrhythmia detection and localization. This proof-of-concept study should enable such future research.

 The solutions provided by UQ are not strictly superior to standard approaches, but rather they provide a window into how the solutions respond to unavoidable uncertainties in their inputs. In the specific case of ECGI, understanding how input uncertainties affect the diagnosis of patients and guide subsequent therapy is paramount for developing robust clinical implementations. The approaches presented here will hopefully provide a starting point for further investigation. We envision that further development of UQ applications to ECGI may yield both technical improvements to ECGI as well as more sophisticated clinical tools. Such clinical tools we envision will provide not only an ECGI solution but also clinically useful information about the possible variability of that solution and the sources of this variability. This information would possibly provide clinicians using ECGI with a more precise view of the variability of the ECGI solution, enabling more effective and reliable use of ECGI in a clinical setting.

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