QUANTIFICATION OF STOCHASTIC BEHAVIOR IN CARDIAC ELECTROPHYSIOLOGICAL MODELS

by

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A proposal submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

School of Computing
The University of Utah
June 5th, 2006
THE UNIVERSITY OF UTAH GRADUATE SCHOOL

SUPERVISORY COMMITTEE APPROVAL

of a proposal submitted by

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This proposal has been read by each member of the following supervisory committee and by majority vote has been found to be satisfactory.

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I have read the proposal of Sarah Elizabeth Geneser in its final form and have found that (1) its format, citations, and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to The Graduate School.

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Intrinsically stochastic physiological phenomena are often modeled with deterministic mathematical systems to reduce complexity. In focusing on mean behaviors only, important aspects of a system's behavior may go unnoticed. We investigate the application of two computationally efficient and highly accurate methods to stochastic problems in biophysics. The stochastic Galerkin method represents stochastic functions via orthogonal polynomials and results in coupled systems of equations. In the case of systems that depend on many independent and uncorrelated random variables, this method results in large systems of coupled equations, requiring complex numerical or parallelization methods to efficiently obtain solutions. Additionally, even for systems depending on a single random variable, the implementation of the stochastic Galerkin method can be rather complex. On the other hand, the stochastic collocation method results in highly efficient solutions, even for systems with high random variable dimensionality, and are extremely simple to implement. We apply these techniques to biological models for uncertainty quantification and identification of dynamical behavior, solving stochastic systems of interest within the bioengineering, while seeking to explore and expand the mathematical and computational aspects of the stochastic Galerkin and collocation methods.
CHAPTER 1

INTRODUCTION

Though biological systems typically exhibit a distribution of responses to the same set of experimental parameters, they are often of such great complexity that modelers chose instead to treat them as deterministic, utilizing averages of populations or experiments rather than their stochastic distributions. In doing so, important information about the system’s behavior may go unobserved. By instead including the distribution of model parameters, one can gain certain insights, such as the types of behavior the system will exhibit over a range of parameter values as well as the amount of uncertainty in the forward solutions with respect to parameter uncertainty, which can aid in identification of the most important model parameters to determine with high accuracy.

A common method of understanding the effects of random or uncertain parameters impact upon the output of a mathematical model involves simulating the model multiple times, each with different values for the parameters (either varied individually or in combination). The model response to each set of parameters can then be compared to obtain an understanding of the effect of the parameters. This is similar to taking specific realizations from a randomly distributed parameter and using those values to run the deterministic model. From these discrete results, one could calculate an estimate of the response statistics, e.g., the mean and variance. As one increases the number of samples the solution statistics converge; such an approach falls under the category of Monte Carlo methods. While Monte Carlo implementation is a straightforward extension of the deterministic solver, such solutions are often computationally prohibitive even for systems of relatively low computational complexity, as they converge as $1/\sqrt{N}$ where $N$ is the number of realizations. Thus a large number of trials are necessary to obtain accurate statistics. Latin hypercube sampling [34], the quasi-Monte Carlo method [43], and the Markov chain Monte Carlo method [14] all have accelerated convergence properties compared to the Monte Carlo method. However, each method imposes certain restrictions on the process of interest which in turn limits their general applicability.

An alternative means of determining the effect of a parameter upon a particular physiological model is to assume a probability density function, and directly calculate the current as a result of the (now) stochastic physiological model. Such non-sampling methods avoid taking large
samples of repetitive deterministic solvers and include perturbation methods [31], second-moment analysis [33], and sensitivity methods [23]. Though more efficient than Monte Carlo under certain conditions, these methods have limited utility and robustness as they are only capable of resolving relatively small perturbations in both the random inputs and outputs. This is difficult to guarantee, especially for nonlinear systems where small perturbations in inputs can result in relatively large perturbations in the response.

The stochastic Galerkin and collocation methods provide highly accurate and computationally efficient solutions of stochastic systems, and have been applied with great success in the field of computational mechanics. We apply these two methods to stochastic biophysical problems.
CHAPTER 2

RELEVANT WORK

In the following chapter, we describe the biophysical problems of interest as well as the stochastic methods for generating solutions to the systems.

2.1 The Forward Problem of Electrocardiography

Currently more than 71.3 million people suffer from cardiovascular disease in United States alone, resulting in nearly 2.4 million deaths per year [57]. Computational modeling of cardiac function is one method currently providing insight to the mechanisms of fibrillation onset, re-entrant arrhythmia, and other pathological cardiac behavior. Moreover, the inverse problem of determining cardiac sources capable of producing those potentials measured on the surface of the torso is highly dependent on the forward problem of electrocardiography— that of determining the torso potentials resulting from a certain cardiac sources. We seek to quantify the uncertainty in the torso potentials of the forward problem due to uncertainty in the conductivity values of the organs as well as the model geometry. The following discussion lays out the mathematical foundations for the deterministic forward problem.

The Maxwell equations can be used to calculate the time-dependent potential fields due to cardiac sources. Because the tissues in the torso are assumed to have conductivities independent of field strength, the electrodynamical equations governing the behavior of heart excitation are linear [47]. Furthermore, by assuming that cardiac signals are relatively low frequency, it is possible to ignore inductive effects as well as compute the potential field, $\Phi$ on a quasi-static basis [46]. Under these assumptions, the steady-state conditions are established instantaneously so that the potentials at any time, $t$, are determined by the cardiac sources at $t$ only. Both these simplifying assumptions are quite reasonable and result in little loss of physiological fidelity. From Maxwell’s equation the electric field is $\vec{E} = -\nabla \Phi$. Taking into account the conductivity tensor, $\sigma$, the current density, $\vec{J}$ in the region of the volume conductor, $\Omega$, is $\vec{J} = \sigma \vec{E} + \vec{J}_s$ where $\vec{J}_s$ is the source current density in the heart. Because $\vec{J}$ is solenoidal, we have that $\nabla \cdot \vec{J} = \nabla \cdot (\sigma \vec{E} + \vec{J}_s) = 0$, implying the Poisson equation

$$\nabla \cdot (\sigma \nabla \Phi) = \nabla \cdot \vec{J}_s = I_{sv}$$

(2.1)

where $I_{sv}$ corresponds to the source currents which have dimension of current per unit volume.
When the region of interest includes the heart, one must represent \( I_{sv} \) in a physiologically meaningful manner. For a more detailed discussion, see [20]. This approach to solving the electrocardiographic problem excludes the heart and thus the electrical forcing function from the domain of solution, resulting in \( I_{sv} = 0 \). The electrical activity of the heart is then characterized by the potential values on the entire heart surface.

Denote the torso surface \( \Omega_t \), the heart surface \( \Omega_h \) and the closed region between and including these two surfaces, \( \Omega \). Given a description of the conductivity tensors and the potentials on the surface of the heart, \( \Phi_{\Omega_h} \), the Laplace equation governing the potential over \( \Omega \) is

\[
\nabla \cdot (\sigma(x) \nabla \Phi(x)) = 0 \quad x \in \Omega
\]

(2.2)

\[
\Phi(x) = \Phi_{\Omega_h} \quad x \in \Omega_h
\]

(2.3)

\[
\nabla \Phi(x) = 0 \quad x \in \Omega_t
\]

(2.4)

where \( \nabla \Phi(x) = 0 \) corresponds to no flux conditions across the surface of the torso. This assumption is justified, as the conductivity of air is extremely low. Because \( \sigma \) may be anisotropic the conductivity properties of the torso can be accurately represented than in other models.

This framework allows a realistic view of cardiac electrical activity and their spatial distribution, without necessitating a characterization of the anisotropic behavior of cardiac tissue. Advances in computer technology have made this once intractable problem feasible. Also, the advent of sock electrodes have enabled the measurement of potentials on the surface of the heart, making the necessary input information for this problem easier to obtain. Additionally, the body surface potentials uniquely define the cardiac surface potentials, as opposed to other models which have non-empty null spaces where sources can generate no field, making the inverse problem easier to solve. Solving equation 2.2 for any but the simplest geometries requires a numerical approximation, usually based on methods such as boundary elements or finite elements [21], which we discuss in sections 3.2.1 and 3.2.2.

### 2.2 Cardiac Ion Channel Models

Ion channels are pore-forming proteins which permit and control the flow of ions through membranes of cells and cellular compartments [22]. Such channels play an important role in numerous physiological processes, such as the transmission of neural stimulus and muscle contraction. Ion channels are the object of intensive research and have been modeled with various approaches, some developed before their existence was established. Most mathematical electrophysiological models of ion channels fall into one of two categories: Markovian and Hodgkin-Huxley type. Ion channel modeling has proven its value in addition to the traditional experimental approach, in which voltage clamping protocols are applied and electrical currents through the channels are measured. Such models are capable of reconstructing experimental data and can also provide
mechanistic insights into physiological and pathophysiological phenomena [24]. Furthermore, they allow for prediction of both channel and cellular behavior [49], and can allow computationalists to interact with experimentalists, suggesting experimental regimes that may in fact result in previously unobserved behavior. Study of cardiac ion channel function and behavior has proven useful in understanding some of the mechanisms of fibrillation and tachycardia, ultimately leading to drug prevention and intervention therapies by way of altering specific aspects of the cardiac action potential generation and transmission via chemically altered ion channel function.

Currents through single ion channels exhibit fluctuations, which result from stochastic opening and closing of the channel. These fluctuations are also visible in macroscopic currents through ensembles of ion channels. However, models of ion channel typically describe the average behavior and are formulated as having deterministic input parameters and outputs. While such restrictions result in simplified models, they do not address the stochasticity of the underlying channel behavior, e.g., the fluctuation of currents encountered experimentally by stochastic opening and closing events. These restrictions can significantly reduce the insights into systems that can be gained from simulations.

2.3 Generalized Polynomial Chaos

With increasing access to greater computing power, computational simulations are capable of solving complex mathematical systems with high numerical accuracy. Thus the confidence in computational approximations of physical systems has increased over the years. As the application of computational prediction to physical systems becomes more commonplace, one must not overlook the effect of uncertainty in input data, such as model parameters, forcing terms, boundary conditions, geometry, etc. upon the solution of such computational models.

Based upon the Wiener-Hermite polynomial chaos expansion [59], generalized polynomial chaos, or Stochastic Galerkin (SG), has been applied as a method for uncertainty quantification in the field of computational mechanics for a number of years and has recently seen a revival of interest [41, 4, 5, 38, 6, 36, 60, 62]. The technique is slowly being adopted by other fields as not only a means of achieving uncertainty analysis, but also obtaining the solution of mathematical systems with random inputs.

The stochastic Galerkin method represents random processes via orthogonal polynomials, utilizing specific sets of orthogonal polynomials to allow for efficient representation of random processes with arbitrary probability distribution functions. Convergence rates of the system depend on the appropriate choice of orthogonal polynomials for the underlying probability density functions of the random inputs. Thus for Gaussian random functions, Hermite polynomials provide the best convergence, whereas the Legendre polynomials should be utilized for functions of uniform distributions, etc. [61]. We denote the orthogonal polynomial set, $\phi_i(\xi)$, and any random inputs,
$a(\xi)$ can thus be represented as the weighted sum of $N+1$ orthogonal polynomials
\[ \sum_{i=0}^{N} \hat{a}_i \phi_i(\xi). \] (2.5)

Where the coefficients are projections of the random input onto the polynomials
\[ \hat{a}_i = \int a(\xi)\phi_i(\xi) d\mu \] (2.6)
in the appropriate random space, $\mu$. The random outputs are also expanded in the same manner; however, the coefficients for the outputs are obtained by projecting the entire system against test functions (as in finite elements) and solving the resulting system for the output coefficients.

Such expansions exhibit fast convergence rates when the stochastic response of the system is sufficiently smooth in the random space, e.g., bifurcation behavior is absent. When stochastic response contains discontinuity, i.e., near bifurcation point, piecewise polynomials [2, 37] can be employed to circumvent the difficulty. The stochastic Galerkin method is an efficient means of reducing the stochastic governing equations to a system of deterministic equations that can then be solved via conventional numerical techniques. In this method one conducts a Galerkin projection of the governing equations onto the polynomials basis functions defined by gPC. Such a gPC-SG approach is capable of resolving systems with relatively large perturbations in both the inputs and responses and has been successfully applied to model uncertainty in complex stochastic solid and fluid dynamic problems [18, 62, 60]. The form of the resulting equations can become very complicated if the system of differential equations has nontrivial and/or nonlinear forms. In this case, other techniques must be employed, such as the stochastic collocation method.

### 2.4 Stochastic Collocation Methods

Based on the mathematical framework of stochastic Galerkin methods, stochastic collocation (SC) methods combines the high-order accuracy and fast convergence for low dimension systems whose behavior are sufficiently smooth in the random space of SG with ease of implementation and computational efficiency for systems of high random dimension. These methods have been applied to a variety of systems and are the subject of ongoing research [1, 9, 39, 40].

Building from the stochastic Galerkin polynomial representation of stochastic processes, the SC method utilizes the existing theory of multivariate polynomial interpolations in order to compute solutions via a weighted sum of solutions at a prescribed set of interpolation points. This results in an uncoupled deterministic system even in the case where data depends non-linearly on the random input parameters. This leads to a straightforward implementation requiring only solutions of the corresponding deterministic solver similar to the Monte Carlo method. The SC method can easily handle all of the same types of random variables that SG can, e.g., Gaussian, exponential, uniform.
The complexity of the method lies in the construction of the interpolation point set, with extra care required for multidimensional random spaces. One might be tempted to use point sets based on tensor products of one-dimensional collocation points in such cases. However, these sets become too large with increasing dimensions [39, 61] and are no more efficient than Monte Carlo methods. Other choices, based on Stroud’s cubature points [54] and sparse grids from the Smolyak algorithm [52], are more efficient than brute-force Monte Carlo methods in a large range of random dimensionality. The first results in highly efficient algorithms, but provides relatively low-order accuracy, while the second offers high-order accuracy with a convergence rate depending weakly on dimensionality.

Though useful for systems of low random dimensionality, the stochastic Galerkin method results in fully coupled systems of linear equations that increasingly require efficient computational strategies or complex parallelization methods to solve as the number of stochastic dimensions in the problem increases. However, the collocation method requires only the solution of $N$ uncoupled linear systems and is embarrassingly parallelizable.
CHAPTER 3
PRELIMINARY WORK

Preliminary work on stochastic biological problems includes quantification of the effect of stochastic conductivities on the propagation of electrical potentials on the surface of the heart to the surface of the torso in a two dimensional computational model and quantification of the effect of stochastic rate constants on current responses to voltage traces in Markovian ion channel models. My work on stochastic Finite Element ECG reconstruction and ion channel modeling resulted in papers presented at the 5th Annual International Conference on Bioelectromagnetism in Minneapolis and published in the International Journal of Bioelectromagnetism [15] and the 2005 IEEE Engineering in Medicine and Biology 27th Annual International Conference in Shanghai [16, 17]. I also have a paper currently in review for the Journal of Theoretical Biology.

3.1 Stochastic Cardiac Ion Channel Models

Typical ion channel models assume a mathematical description of channel function and obtain parameters by fitting the response of the model to experimentally recorded data. In doing so, the models neglect the inherently stochastic behaviour of such systems, in which the parameters may take on a range of values over time for a single ion channel, or over a population of ion channels. We seek to utilize the stochastic Galerkin and stochastic collocation methods to obtain not only mean behaviour of such models under the assumption that the parameters vary over populations, but higher moments as well. Because the parameters are not measured, but inferred, there is no method to directly obtain the distribution of the model parameters. Thus, the SG and SC methods also provide a means of efficiently inferring the range of behaviors that the models are capable of producing.

In addition, investigation of stochastic parameters can provide greater understanding of the range of behavior a model is capable of producing. This can lead to possible model reductions, or point out shortcomings to be addressed, i.e., altering the model to include behavior currently not captured. We present polynomial chaos as a computationally efficient alternative to Monte Carlo for assessing the impact of stochastically distributed parameters on the model predictions of several cardiac electrophysiological models; including the Fitzhug-Nagumo, ryanodine receptor, I_{K_\alpha} and I_{K_\gamma} models.
3.1.1 Stochastic FitzHugh-Nagumo, Ryanadine Receptor and $I_{ks}$

In the following section we analyze three representative cardiac models: the FitzHugh-Nagumo model describing cellular action potentials [11, 42], a Markovian model of sarcoplasmic ryanodine receptor calcium release, and the slowly activating delayed rectifier potassium current [27]. The behavior of each model is fully described by a set of ordinary differential equations.

The simplest of the three, the FitzHugh-Nagumo equation, is a variant of the van der Pol equation with no spatial diffusion:

\[
\begin{align*}
  u_t(t) &= \alpha u(t)(1 - u(t))(u(t) - \beta) - v(t) \\
  v_t(t) &= \epsilon (u(t) - \gamma)
\end{align*}
\] (3.1)

where $u$ is the excitation variable and $v$ is the slow recovery variable. We will consider the case where $\gamma$ is the only random input parameter. The system of equations is now stochastic

\[
\begin{align*}
  u_t(t; \xi) &= \alpha u(t; \xi)(1 - u(t; \xi))(u(t; \xi) - \beta) - v(t; \xi) \\
  v_t(t; \xi) &= \epsilon (u(t; \xi) - \gamma(\xi)).
\end{align*}
\] (3.3)

The representation of $\gamma$ via the stochastic Galerkin method is as follows

\[
\gamma(\xi) = \sum_{i=0}^{N} \hat{\gamma}_i \phi_i(\xi)
\] (3.5)

where $\hat{\gamma}_i = \int \gamma(\xi) \phi_i(\xi) d\mu$.

The orthogonal polynomial basis, $\phi_i(\xi)$ is chosen to correspond to the distribution of $\gamma$. For example, if $\gamma$ is Gaussian, we employ the Hermite polynomials as a basis. Due to the choice of polynomial basis, the representation of $\gamma$ reduces to

\[
\gamma(\xi) = \nu \phi_0(\xi) + \sigma^2 \phi_1(\xi)
\] (3.6)

where $\nu$ is the mean of $\gamma$ and $\sigma^2$ is the variance. Because $\gamma$ is stochastic, $u$ and $v$ are also stochastic and are represented via orthogonal polynomials in a similar way to $\gamma$. Because $u$ and $v$ are not guaranteed to be Gaussian, we must retain the entire representation as follows

\[
\begin{align*}
  u(\xi) &= \sum_{i=0}^{N} \hat{u}_i \phi_i(\xi) \\
  v(\xi) &= \sum_{i=0}^{N} \hat{v}_i \phi_i(\xi).
\end{align*}
\] (3.7)

These weighted sums are substituted into the original system of equations, and the result is projected against the test functions (which we take to be the same as the orthogonal polynomial basis), we obtain for each test function, $m = 0, \ldots, N$.
\[ \sum_{i=0}^{N} C_{im} \frac{d\hat{u}_i(t)}{dt} = -\alpha \beta \sum_{i=0}^{N} C_{im} \hat{u}_i(t) + (\alpha + \alpha \beta) \sum_{j=0}^{N} C_{jm} \hat{u}_i(t) \hat{u}_j(t) \]

\[ -\alpha \sum_{j=0}^{N} C_{ijkm} \hat{u}_i(t) \hat{u}_j(t) \hat{u}_k(t) \]  

(3.9)

\[ \sum_{i=0}^{N} C_{im} \frac{d\hat{v}_i(t)}{dt} = \varepsilon \left( \sum_{i=0}^{N} C_{im} \hat{u}_i(t) - \sum_{j=0}^{N} C_{jm} \hat{v}_j \right) \]  

(3.10)

where \( C_{ijkm} = \langle \phi_i(\xi)\phi_j(\xi)\phi_k(\xi)\phi_m(\xi) \rangle \). Hence our two variable system becomes an \( N \) times larger coupled system requiring only a single solve, as opposed to numerous solves as for the Monte Carlo method. Note that this inner product must be calculated with respect to the stochastic measure space. Due to the properties of the basis functions, \( C_{ijkm} \) is sparse. The remaining ion channel models were treated in a similar manner.

The deterministic FitzHugh-Nagumo equations exhibit two bifurcations points in the \( \gamma \) parameter. When \( \gamma \) assumes values between these two critical points, the system exhibits sustained oscillations. For \( \gamma \) values outside this interval, the excitation variable, \( u \), and slow recovery variable, \( v \), eventually reach a fixed steady state. When \( \gamma \) has a Gaussian distribution with both mean and standard deviation located outside the oscillatory interval, the mean solution of both \( u \) and \( v \) exhibit small oscillations. This is indicative that the stochastic solutions include some of the behavior that the system exhibits when \( \gamma \) takes on values between the critical points. The behavior of the stochastic system where \( \gamma \) has a mean located within the critical interval is markedly different. Here the solution oscillates as expected, but the standard deviations vary markedly along each period of oscillation, especially for \( u \). This is indicative of the change in period and amplitude of the oscillations for the deterministic system depending on the \( \gamma \) value. Note that from these results, we can infer that altering the \( \gamma \) parameter will not alter the phase of the solution.

While the FitzHugh-Nagumo model gives a decent generalization of cardiac behavior, it gives no insight into the function of specific ion channels. The ryanodine receptor model is a four state Markovian type model with two closed and two open states that describes the flow of calcium from the sarcoplasmic reticulum into the subspace volume. The transition dynamics between channel states are governed by rate constants. The differential equations for the model are as follows
\[
\frac{dC_1}{dt} = k_a^- O_1 - k_a^+ [Ca^{2+}]_{ss}^m C_1 \quad (3.11)
\]
\[
\frac{dC_2}{dt} = k_c^- O_1 - k_c^+ C_2 \quad (3.12)
\]
\[
\frac{dO_1}{dt} = k_a^+ [Ca^{2+}]_{ss}^m C_1 + k_b^- O_2 + k_c^- C_2 \quad (3.13)
\]
\[
-(k_b^+ [Ca^{2+}]_{ss}^m + k_a^- + k_c^+) O_1
\]
\[
\frac{dO_2}{dt} = k_b^+ [Ca^{2+}]_{ss}^m O_1 - k_b^- O_2 \quad (3.14)
\]
\[
I_R = \bar{G}_R (O_1 + O_2) ([Ca^{2+}]_{ss} - [Ca^{2+}(t)]_{ss}). \quad (3.15)
\]

Here \(I_R\) denotes the calcium outflow current of the sarcoplasmic reticulum in response to a transient elevation in subspace calcium concentration, denoted \(Ca^{2+}_{ss}\). The calcium concentration in the sarcoplasmic reticulum is denoted \(Ca^{2+}_{ss}\) and the conductivity constant is \(\bar{G}_R\).

The delayed rectifier current in human left ventricle myocytes consists of both a rapidly activating and inactivating component and a slowly inactivating component. We investigate the latter of these two components, the \(I_{Ks}\) current, to determine the effect of stochastic rate parameters on the resulting potassium current. The Markovian model for this channel type also consists of two closed and two open states. The behavior of this model is described by the following system of equations:

\[
E_K = \frac{RT}{F} \ln \left( \frac{[K^+]_o}{[K^+]_i} \right) \quad (3.16)
\]
\[
\frac{dC_1}{dt} = -\alpha C_1 + \beta C_2 \quad (3.17)
\]
\[
\frac{dC_2}{dt} = -(\beta + \gamma) C_2 + \alpha C_1 + \delta O_1 \quad (3.18)
\]
\[
\frac{dO_1}{dt} = -(\delta + \epsilon) O_1 + \gamma C_2 + \omega O_2 \quad (3.19)
\]
\[
\frac{dO_2}{dt} = -\omega O_2 + \epsilon O_1 \quad (3.20)
\]
\[
I_{Ks} = \bar{G}_{Ks} (O_1 + O_2) (V(t) - E_K). \quad (3.21)
\]

The current for this model is denoted \(I_{Ks}\), while the conductance is \(\bar{G}_{Ks}\). The equilibrium voltage is denoted \(E_K\), and the voltage clamping protocol is \(V(t)\).

We investigated the response of the two models to stochastic rate constants. In the ryanodine receptor model, we calculated the distribution of calcium outflow current across the sarcoplasmic reticulum membrane in response to a transient elevation in subspace calcium concentration while in the the \(I_{Ks}\), we found the stochastic potassium current response to voltage clamping. We utilized mean initial and parameter values given in [27]. The mean and standard deviation of the ryanodine receptor model in response to Gaussian distributed rate constant, \(k_b^-\) centred around 1.93 ms\(^{-1}\) with a standard deviation of 40% of the mean value is shown the right-most graph of figure 3.1.
Figure 3.1. Stochastic Response of Ryanodine Receptor and $I_{Ks}$ Models: The mean and standard deviation of calcium release from the sarcoplasmic reticulum where $k_b^−$ is assumed to have a Gaussian distribution centered around $1.93 \text{ ms}^{-1}$ with a standard deviation of $\sqrt{40\%}$ of the mean value is depicted in the left figure. The mean and standard deviation of the slowly-activating delayed rectifier potassium current with $\omega$ centered around $1.0748 \times 10^{-2} \text{ ms}^{-1}$ with a standard deviation of $\sqrt{40\%}$ of the mean value is depicted in the right figure.

The mean and standard deviation of the $I_{Ks}$ model in response to Gaussian distributed rate constant, $\omega$ centered around $1.0748 \times 10^{-2} \text{ ms}^{-1}$ with a variance of $40\%$ of the mean value is depicted in the left-most graph of the same figure. For the ryanodine model, stochastic $k_b^−$ results in fairly small deviations at the maximum and equilibrium calcium current, but shows high deviations during the transition from the maximum calcium current response to the equilibrium state. This indicates that the rate constant does not greatly effect the maximum or equilibrium current, but does affect how quickly the calcium current falls off after reaching its maximum value. In the $I_{Ks}$ model, stochastic $\omega$ results in large standard deviations during the equilibrium period from 3.5 to 6 s. This indicates that $\omega$ most strongly affects the maximum current achieved by the model in response to an activation voltage clamping procedure. In these cases, the stochastic Galerkin method provides an efficient method for determining the effects of various parameters upon model solutions.

3.1.2 Stochastic $I_{Kr}$

We chose a model of the rapidly-activation delayed rectifier $K^+$ current in human ventricular subepicardial myocytes developed by Iyer et al. [27] to investigate the reaction of the rapidly activating-delayed rectifier ion channel model to stochastic parameters.

The system of ordinary differential equations describing the behavior of the $I_{Kr}$ channels is
Figure 3.2. Variability in Current Due to Distributions of Rate Constants in the $I_{Kr}$ Markovian Model: Standard deviation in the current response to an activation voltage clamping protocol due to uniform distributions in the rate constants of $\pm$ 50% of the mean values.

\[
\begin{align*}
I_{Kr} &= G O f ([K^+]_o)(V - E_K) \\
\frac{dC_1}{dt} &= -\alpha_0 C_1 + \beta_0 C_2 \\
\frac{dC_2}{dt} &= -(\beta_0 + k_f)C_2 + \alpha_0 C_1 + k_b C_3 \\
\frac{dC_3}{dt} &= -(\alpha_1 + \alpha_3 + k_b)C_3 + k_f C_2 + \beta_1 O + \Psi I \\
\frac{dI}{dt} &= -(\Psi + \alpha_i)I + \alpha_3 C_3 + \alpha_1 O \\
\frac{dO}{dt} &= -(\beta_1 + \alpha_i)O + \alpha_1 C_3 + \beta_i I \\
\Psi &= \frac{\beta_1 \beta_i \alpha_3}{\alpha_1 \alpha_i} \\
f([K^+]_o) &= \sqrt{\frac{[K^+]_o^2}{4}}.
\end{align*}
\]

with parameters and initial conditions are given in [27].

We investigated the effect of stochastic rate constants upon the mean and variance of current response of the $I_{Kr}$ model to both activation and inactivation voltage clamping protocols. We found that while the mean current responses were not greatly altered, the variance responses had a wide range of qualitative behavior. These behaviours could be grouped into categories of similar responses, with the categories being constant over varying voltage protocols (e.g., activation and inactivation). We also investigated the effect of allowing the rate constants to vary individually, or in combination. Figure 3.2 shows a comparison of the effects of varying the rate constants $\beta_1$ and $k_f$ individually and in combination as either functions of two separate random variables. The variance resulting from the combination of both as stochastic random functions appears to be an amalgam of the variance of each having independent and uncorrelated stochastic distributions.
3.2 Investigation of Stochastic Elliptic Problems: The Stochastic Forward Problem of Electrocardiography

As described in section 2.1, the forward problem of electrocardiography can be posed as the following elliptic problem

$$\nabla \cdot (\sigma(x) \nabla \Phi(x)) = 0 \quad x \in \Omega \quad (3.30)$$

$$\Phi(x) = \Phi_{\Omega_h} \quad x \in \Omega_h \quad (3.31)$$

$$\nabla \Phi(x) = 0 \quad x \in \Omega_t \quad (3.32)$$

where $\Phi(x)$ denotes the electrical potentials over $\Omega$, the torso region. The conductivities are denoted by $\sigma$, $\Phi_{\Omega_h}$ denotes the potentials on $\Omega_h$, the surface of the heart, and $\nabla \Phi(x) = 0$ corresponds to no flux conditions across $\Omega_t$, the surface of the torso.

Computational models based on realistic human physiology include many input parameters, such as the geometric discretization of the torso organs, the conductivities (isotropic or anisotropic) of the organs, and the epicardial potentials. Inherent in each parameter of the model are errors associated with approximating the physiology. Reduction and quantification of such errors are critical components of the simulation process; only then can scientists judiciously evaluate which components of the process described above are critically sensitive to perturbation, and hence may require additional attention or even more accurate measurements. In the specific case of the electrocardiographic problem, the debate continues without adequate resolution regarding the relative influence of errors in geometry and in tissue conductivity [32, 28, 29, 3, 26, 58, 48].

It is challenging to carry out comprehensive analysis of the effects of parameter variation on simulation accuracy, especially in complex problems with many, potentially interacting parameters. Rigorous sensitivity studies are often very computationally expensive and time consuming to accomplish, because they require repeated executions with slightly varied parameter values, as with the approach known as Monte Carlo analysis. Although in theory easy to implement, Monte Carlo statistical sensitivity analysis is often impractical due to the large number of samples needed to infer statistically valid results. The time required to compute these samples often forces researchers to revert to highly under-sampled Monte Carlo—running a few simulations with perturbed conductivity values to gain some understanding of the qualitative behavior of the system. We sought to quantify the uncertainty in the resulting torso potentials of the forward problem due to various stochastically distributed input parameters utilizing the computationally efficient SG and SC methods. These efforts are described in the following sections.
3.2.1 The Effect of Stochastic Conductivity upon Variances in Torso Potentials in a Two Dimensional Finite Element Model

Sensitivity to conductivity is of particular interest because accurate tissue conductance measurements are difficult to obtain experimentally and vary experimentally and physiologically with factors such as temperature, hydration level, signal frequency, etc, [58, 45, 53]. Indeed, textbook values of conductivity for certain in-vivo tissues can differ by more than 50% [12, 8, 13, 10]. Clearly it is critical to quantitatively evaluate the effects of such uncertainty on the accuracy of the entire forward problem.

We utilized the stochastic Galerkin method to investigate the effects of stochastic conductivity upon torso potentials in a two-dimensional computational model of the torso. The geometry and conductivity values utilized for the study are presented in [28]. Solving the elliptic problem for any but the simplest geometries requires a numerical approximation, usually based on methods such as boundary elements or finite elements [21]. In order to facilitate the subsequent application of polynomial chaos, we employed a high-order finite element method [25, 56, 30]. High-order elements refer to the polynomial order of the basis functions used to describe spatial variation of the variable(s) of interest. Basis functions with greater than first/linear order provide a means of capturing more rapid variation of the variable—and potentially higher accuracy—without the need for refining the geometric mesh.

Applying polynomial chaos to study the effects of stochastic conductivity tensor, $\sigma(x; \xi)$, on the torso potentials, we must first express $\sigma(x; \xi)$ in terms of an (n+1)-dimensional random variable vector $\xi = (\xi_0, \xi_2, \ldots, \xi_n)^T$, where the distributions of the random vector components are known. We chose a single uniform distribution to describe the stochastic conductivities in order to prevent these parameters from attaining negative values. The resulting stochastic version of equation 3.30 is then

\[
(\nabla \cdot \sigma(x; \xi) \nabla) u(x; \xi) = 0, \quad x \in \Omega \tag{3.33}
\]

\[
u(x; \xi) = u_0(x; \xi), \quad x \in \Gamma_D \tag{3.34}
\]

\[
\mathbf{n} \cdot \sigma(x; \xi) \nabla u(x; \xi) = 0, \quad x \in \Gamma_N \tag{3.35}
\]

where the solution $u(x; \xi)$ is now also a function of the stochastic variable vector $\xi$. The conductivity tensor and solution field, as random processes, can be represented via the generalized polynomial chaos expansions as

\[
u(x; \xi) = \sum_{i=0}^{P} \tilde{\nu}_i(x) \phi_i(\xi) \tag{3.36}
\]

\[
\sigma(x; \xi) = \sum_{i=0}^{P} \tilde{\sigma}_i(x) \phi_i(\xi), \tag{3.37}
\]
where the functions \( \phi(\xi) \) are polynomials ranging up to \( P^{th} \) order. The form of the polynomials used is chosen based upon the PDF of the stochastic processes to improve the convergence properties of the method [61]. Since the PDF of the “input” random process (in this case, the conductivity) is known, it is possible to select polynomials appropriate for that process e.g., for a Gaussian process, Hermite polynomials and for a uniform process, Legendre polynomials.

Substituting the above expressions into the stochastic elliptic system given by equation 3.33 and projecting (in the Galerkin sense) the resulting system into the random space spanned by the basis polynomials, \( \phi_k \), leads to the following linear system:

For \( k = 0, \ldots, P \)

\[
\sum_{i=0}^{P} \sum_{j=0}^{P} C_{ijk} \nabla \cdot (\bar{\sigma}_i(x) \nabla \bar{u}_j(x)) = 0 \quad x \in \Omega \tag{3.38}
\]

\[
u(x; \xi) = u_0(x; \xi) \quad x \in \Gamma_D \tag{3.39}
\]

\[
\bar{n} \cdot \sigma(x; \xi) \nabla u(x; \xi) = 0 \quad x \in \Gamma_N \tag{3.40}
\]

where \( C_{ijk} = \langle \phi_i(\xi) \phi_j(\xi) \phi_k(\xi) \rangle \) denotes the inner product over the appropriate probability measure space. The probability measure within the integration is determined by the PDF of the random variables used. By using numerical quadrature to evaluate the inner product given above [18, 61, 62, 60], equation 3.38 reduces to a large linear combination of elliptic systems for the coefficients \( \bar{u}_j(x) \). Since the unknowns are now only functions of space, standard finite element techniques can be employed to transform this into a large linear system of deterministic stiffness equations and right-hand-side vectors.

Our results showed that for uniform distributions of \( \pm 50\% \) of the mean values, stochastic lung conductivity resulted in the largest maximum variation in torso potentials, and stochastic fat conductivity resulted in the smallest maximum variation regardless of the epicardial potentials (see figure 3.3. This indicates that for the two-dimensional model under consideration, the conductivity of the lungs are most important to measure accurately, as they have the greatest effect upon the torso potentials.

3.2.2 The Effect of Stochastic Geometry upon Variances in Torso Potentials in a Three Dimensional Boundary Element Model

Though studied extensively [51, 44, 7, 50, 55, 19], the effect of heart and body position on the body-surface electrocardiogram is still not fully understood. While most recent studies take advantage of the information provided by large scale body surface potential mapping of human subjects [55, 19], they are limited in that the underlying mechanisms of variation are inaccessible to direct observation.

In their study, MacLeod et al. [35] utilized the CVRTI torso tank to measure the potentials resulting from paced hearts located at various positions along three orthogonal directions within
Figure 3.3. Uncertainty Due to Stochastic Distributions of Conductivity Values in the Forward Problem of Electrocardiography: Standard deviation over the entire two-dimensional torso surface resulting from uniform distributions of ± 50% of the mean conductivity values for lung, muscle, and fat organs.

the tank. They employed the boundary element model to obtain computational solutions as it only requires a mesh on the surfaces of the model, unlike finite elements, which calculates solutions at points interior to the model as well as the surfaces. Because the conductivity values in this study are isotropic and homogeneous throughout the interior of the tank, the only surfaces of import are the cardiac and torso surfaces. Thus boundary elements provides an extremely efficient solution for this model as compared with the finite element method. They concluded that the geometry, position and other physiologic factors can also be varied in a reproducible manner to investigate their affect upon the body surface potentials.

Computational modeling via the boundary element method provides an accurate reproduction of the torso tank recordings as shown in figure 3.4 and also allows greater flexibility than the torso tank laboratory model. For example, in the torso tank experiments, the tank itself has a fixed geometry, while computational models are not constrained in this manner. Additionally, the torso tank model is restricted to fairly rudimentary torso conductivities. Currently, air sacks can be inserted to mimic lung conductivity, while the remaining volume of the tank is filled with a homogeneous and isotropic conductive fluid. While the additional complexity of physiological organ geometries and conductivities may not be necessary to draw valid conclusions concerning the effects of such variations upon torso potentials, more complex models may provide additional insights that simpler ones cannot. As the model complexity increases, i.e., incorporation of additional organ categories, or non-homogeneous or even anisotropic conductivities to the model, the boundary element method is no longer a viable option and the finite element method should be employed to efficiently obtain solutions to the stochastic model.

Forward solutions of the computational model can be obtained in less time and preclude the need for animal sacrifice. Combing a finite element or boundary element forward solution within the stochastic collocation framework, we can obtain the mean and variance in the torso
Figure 3.4. Comparison of Calculated and Experimentally Recorded Torso Potentials: The torso potentials calculated via the BEM method, using recorded epicardial potentials and the corresponding experimentally recorded torso potentials are rather close under visual comparison. Note that the experimental potentials are recorded on a subset of the model points.

potentials resulting from stochastically distributed geometries or positions. Thus the effects of changes in geometry or heart position can be investigated with greater flexibility and efficiency than obtaining experimental measurements.

We have begun a preliminary investigation of the effect of cardiac position upon the torso potentials while mimicking the study of MacLeod et al. [35] in which the conductivity within the torso is a single isotropic value. This allows us to employ the boundary element method for the set of forward solutions required by the collocation method. A subset of these results are depicted in figure 3.5, which shows the variation in electrical potentials over the three-dimensional torso surface due to uniformly distributed translation of the heart position in all three dimensions over a 10 centimeter range, as well as the result of rotation of the heart position about the z-axis uniformly distributed over a 180 degree range.
Figure 3.5. Uncertainty Due to Changes in Heart Position in the Three-Dimensional Forward Problem of Electrocardiography: Variation in electrical potentials over the entire three-dimensional torso surface resulting from uniform distributions of heart geometry translation in the x, y, and z directions, and rotation of the heart about the z axis. In the translation experiment, each translation is a function of a separate independent and uncorrelated random variable and is uniformly distributed $+/-\ 5$ mm from the mean position, while the rotation varies uniformly $+/-\ 90$ degrees from the mean heart position.
CHAPTER 4

PROPOSED WORK

Aims

- **Aim 1.** Determine the effects of stochastic rate constants upon current response to activation and inactivation voltage clamping procedures in Markovian ion channel models.

- **Aim 2.** Further explore the underlying features of variability in ion channel models via a simplified two state Markovian model and step voltage clamping procedures.

- **Aim 2.** Investigate the effect of stochastic conductivity on the two-dimensional forward problem of electrocardiography.

- **Aim 3.** Calculate variability in the body surface potentials due to changes in geometry and heart position in the three-dimensional torso tank experiment.

- **Aim 4.** Investigate the underlying mechanisms of current response to stochastic rate constants in a simplified two state ion channel model.

Planned Paper Submissions


- Influence of Cardiac Position on Computed Body Surface ECG *IEEE Transactions on Biomedical Engineering* 2006

Time line

**Summer 06:**

- Submit two-dimensional high-order finite element cardiac uncertainty paper
• Work on mechanisms of stochasticity in the simplified ion channel model

• Work on three-dimensional boundary element study of cardiac variability due to changes in geometry and heart position

**Fall 06:**

• Start writing dissertation

• Continue work on three-dimensional boundary element study of cardiac variability due to changes in geometry and heart position

**Spring 07:**

• Submit three-dimensional boundary element study of cardiac variability due to changes in geometry and heart position

• Finish writing dissertation

• Defend
REFERENCES


