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Generalized polynomial chaos-based uncertainty quantification and propagation in multi-scale modeling of cardiac electrophysiology

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ABSTRACT

Uncertainty and physiological variability are ubiquitous in cardiac electrical signaling. It is important to address the uncertainty and variability in cardiac modeling to provide reliable and realistic predictions of heart function, thus ensuring trustworthy computer-aided medical decision-making and treatment planning. Statistical techniques such as Monte Carlo (MC) simulations have been applied to uncertainty quantification and propagation in cardiac modeling. However, MC simulation-based methods are computationally prohibitive for complex cardiac models with a great number of parameters and governing equations. In this paper, we propose to use the Generalized Polynomial Chaos (gPC) expansion in combination with Galerkin projection to analytically quantify parametric uncertainty in ion channel models of mouse ventricular cell, and further propagate the uncertainty across different organizational levels of cell and tissue. To identify the most significant parametric uncertainty in cardiac ion channel and cell models, variance decomposition-based sensitivity analysis was first performed. Following this, gPC was integrated with deterministic cardiac models to propagate uncertainty through ion current, ventricular cell, 1D cable, and 2D tissue to account for the stochasticity and cell-to-cell variability. As compared to MC, the gPC in this work shows the superior performance in terms of computational efficiency. In addition, the gPC models can provide a measure of confidence in model predictions, which can improve the reliability of computer simulations of cardiac electrophysiology for clinical applications.

1. Introduction

Mathematical models of cardiac electrophysiology have been widely used to advance the fundamental understanding of etiology and pathophysiology of cardiac diseases, aid clinical diagnosis and prognosis, and assist therapeutic design and treatment development. Since Noble's first attempt to study the electrophysiology of a single cell with the Hodgkin-Huxley model [1,2], cardiac models have become more detailed due to the increased knowledge of ion channel gating and cardiac electrical signaling. Current models of cardiac electrophysiology are multiscale and highly complex, which integrate models across different organizational levels of ion channel, cell, tissue, and the organ [3]. These models have been used to examine cardiac disease mechanisms, optimize treatment and surgical planning. For example, the whole-heart model has been applied in clinical settings to localize ablation therapy [4], terminate cardiac arrhythmias [5], and design cardiac resynchronization therapy [6].

While cardiac models have shown the potentials, applications such as model-based diagnosis and therapeutic design are still limited due to the incapability of accounting for uncertainty and variability among individuals [7]. Uncertainty may originate from model assumptions, calibration of model parameters using noisy data, intrinsic time varying phenomena, and extrinsic cell-to-cell variability [8,9]. For example, physiological variability constantly presents in ion channel gating, cardiac electrical signaling, and electrical propagation in cardiac tissue, due to the stochastic nature of ion channel gating [10] and the nonlinear dynamics of alternans in cardiac action potential duration (APD) [8]. In addition, Action Potential (AP) may change from cell to cell due to quantities that genuinely vary among cells, e.g., cell size and ion channel expression [11]. However, most of the available cardiac models are deterministic with fixed model parameters, which cannot account for uncertainty. If the uncertainty in the cardiac models is not appropriately addressed, computer experiments may fail to provide reliable predictions and lead to false conclusions, thus misleading medical decisions [7].

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To improve the credibility and reliability of cardiac models, it is necessary to quantify and propagate the uncertainty to obtain confident model predictions (outputs). Uncertainty quantification and propagation techniques have been well developed in engineering and science domains [12]. Computer models are often developed and calibrated with data corrupted by various sources of uncertainty, which in turn may introduce uncertainty in model parameters. Uncertainty quantification and propagation typically assign probability distributions to model parameters to represent parametric uncertainty, which can subsequently be propagated onto model outputs to obtain a measure of confidence in model predictions. Uncertainty quantification in cardiac models has been previously studied [7,11–14]. For example, Romero et al. investigated the effect of variability in ionic current on AP in human ventricular myocytes [15]. Pathmanathan et al. [7] quantified the variability in the steady-state inactivation of fast sodium current among *canine epi* and *endocardial* cells, and further propagated the uncertainty onto higher organizational levels to study the stochasticity in upstroke velocity in AP and spiral wave dynamics in 2D tissue. Although different uncertainty quantification methods were reported, efficient algorithms that can be used to propagate parametric uncertainty onto higher organizational scales in cardiac models have not been extensively investigated [7,16].

Sampling-based techniques such as Monte Carlo (MC) simulations are one of the most popular methods to propagate parametric uncertainty onto model outputs [17]. For MC, samples are randomly generated from the distribution of model parameters, simulations are then performed with each sample. Based on the simulation results, the variability in model outputs is approximated from a collection of the simulated outputs. It should be noted that MC may require a large number of simulations to ensure the convergence of the model predictions [18], which can be computationally prohibitive for complex and nonlinear cardiac models. To reduce the computational burden and improve the accuracy of uncertainty propagation, this work presents a non-sampling based uncertainty analysis technique, i.e., generalized polynomial chaos (gPC) expansion [19]. The gPC generally approximates the distribution of parametric uncertainty with orthogonal polynomial basis functions and propagates the uncertainty onto model predictions (outputs) through first-principles models. One advantage of the gPC is that it can provide analytical expressions of the statistical moments of model predictions. As compared to MC, uncertainty propagation with gPC has been proved to be more efficient in terms of computational time in different modeling, control, and optimization problems [18,20–24]. Geneser et al. [16] introduced uncertainty in rate coefficients of ion channel model, and applied gPC for uncertainty propagation in ion channel gating. However, uncertainty was randomly assigned to model parameters and the quantification of uncertainty was only studied at the ion channel level, which cannot provide the information about the effect of uncertainty on higher organizational levels such as cell and tissue. Using gPC, our previous work successfully propagated parametric uncertainty onto K^+ channel models [25]. However, the uncertainty propagation in higher organizational levels was not studied.

Uncertainty propagation in cardiac models is challenging, since models of cardiac electrophysiology are inherently multiscale and involve a great level of complexity. These models generally integrate cellular activities with tissue functions, where cellular activities are regulated by the orchestrated function of transmembrane currents and tissue functions are modeled as spatial-temporal propagation of electrical waves. The cellular models often include numerous differential equations coupled with over a hundred supporting equations. Further, the cellular models can serve as sub-models of the tissue models, which describe the electrical propagation in 2D/3D cardiac muscles using partial differential equations (PDEs) and finite elements meshes. The complexity of cardiac models poses great challenges on the gPC-based uncertainty propagation as the coupled differential equations and supporting equations can make it difficult to quantify uncertainty in model outputs resulting from parametric uncertainty. The objective in this work is to: (*i*) investigate the feasibility of the gPC-based uncertainty propagation in multiscale cardiac models across different organizational levels of ion channel, cell, and tissue, and (*ii*) quantify the effect of parametric uncertainty on model predictions in each organizational level in a computationally efficient manner.

Cardiac models are described by many equations involving hundreds of parameters. It is possible but not practical to consider uncertainty in all model parameters. To improve efficiency, we propose to identify the most sensitive parametric uncertainty. To identify the most significant uncertainty, sensitivity analysis techniques can be used. For example, Du et al. [3] used fractional factorial design to find sensitive parameters under different response functions for model calibration, and Johnstone et al. [8] used Gaussian process to find parametric uncertainty in cardiac models. However, these techniques concentrate on the sensitivity in the vicinity of the mean value of parameter and may fail to identify the most significant uncertainty. To overcome this issue, the variance decomposition-based sensitivity analysis method is used in this work to identify the parametric uncertainty that has the most significant impact on the variability in the outputs of ion channel models and the cardiac cell model. Based on the sensitivity analysis results, *a prior* known distribution will be assigned to the significant parameters to approximate uncertainty, which will be further propagated onto ion currents, cardiac cell, and tissue. Specifically, different characteristics, e.g., Steady State Activation (SSA) and Inactivation (SSI) in ion channel, APDs in cardiac cell, and spiral wave propagation in tissue, are quantified in order to visualize the effect of parametric uncertainty on model outputs. Additionally, the efficiency and accuracy of gPC are investigated and verified with MC simulations. Note that for algorithm clarification the Bondarenko's mouse ventricular model [26] is used in this work for propagating parametric uncertainty onto higher organizational levels of heart through multiscale cardiac models. We deliberately chose this model since it can provide detailed gating kinetics in ion channels, and it is considered sufficiently complicated to illustrate the computational efficiency of gPC.

The rest of this paper is organized as follows. Section 2 presents the research methodologies followed by design of computer experiments in Section 3. Simulation results and discussion are provided in Sections 4 and 5, which is followed by conclusions in Section 6.

2. Background and methodologies

2.1. Generalized polynomial chaos expansion

The generalized polynomial chaos (gPC) expansion approximates uncertainty as a function of another random variable based on a prescribed distribution from Askey-Wiener scheme [19]. Suppose a cardiac model can be defined with a nonlinear ordinary differential equation (ODE) as:

$$\frac{dy}{dt} = g(t, \boldsymbol{\sigma}, \boldsymbol{\theta}, y), \qquad 0 \le t \le T, \quad y(0) = y_0 \tag{1}$$

where g is a nonlinear function of cardiac model, e.g., the ion channel model, and y is a gating variable (i.e., output), e.g., the gating variable of activation or inactivation, with initial condition y_0 over a finite time domain $[0, T]$, $\boldsymbol{\theta}$ and $\boldsymbol{\sigma}$ are model parameters. In this current work, $\boldsymbol{\theta}$ denotes a vector of parametric uncertainties (i.e. input uncertainty) while $\boldsymbol{\sigma}$ is a vector of deterministic parameters defined with fixed values. Note that each parametric uncertainty in $\boldsymbol{\theta}$ will be described with a probability density function (PDF) around a particular mean value and specific variance in this work. The uncertainty in each parameter of $\boldsymbol{\theta}$ may originate from time-varying phenomena such as stochasticity in