Propagation of Parametric Uncertainty in Aliev-Panfilov Model of Cardiac Excitation*

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***Abstract*—Models of cardiac electrophysiology are useful for studying heart functions and cardiac disease mechanisms. However, cardiac models often have a great level of complexity, and it is often computationally prohibitive to simulate tissue and organ activities in a real-time fashion. To address the challenge, simplified models such as Aliev-Panfilov model are developed to reduce model complexity, while providing necessary details of cardiac functions. Simplified models may induce uncertainty, which can deteriorate the accuracy and reliability of cardiac models. In addition, model parameters are calibrated with noisy data and cannot be known with certainty. It is important to assess the effect of parametric uncertainty on model predictions. For the probabilistic, time-invariant parametric uncertainty, a generalized polynomial chaos (gPC) expansion-based method is presented in this work to quantify and propagate uncertainty onto model predictions. Using gPC, a measure of confidence in model predictions can be quickly estimated. As compared with sampling-based uncertainty propagation techniques, e.g., Monte Carlo (MC) simulations, the gPC-based method in this work shows its advantages in terms of computational efficiency and accuracy, which has the potentials for dealing with complicated cardiac models, e.g., 2D tissue and 3D organ models.**

I. Introduction

Cardiac models are widely used to study cardiac disease mechanisms. For example, mathematical models were used to study glycosylation modulation dynamics on cardiac electrical signaling among CDG patients [1]. In addition, cardiac models can also be applied in clinical setting to explore better surgical strategies [2]. Reliable models and accurate simulation results can provide useful information that cannot be obtained from in-vitro experiments, which may assist physicians for better diagnosis and treatment planning of heart diseases [3, 4].

Models of various species have been developed since the first model proposed by Hodgkin and Huxley (i.e., HH model), which provides detailed descriptions of ion channel gating and cardiac electrical signaling [5, 6, 7]. Such detailed models often include hundreds of equations. For example, the model of an adult human atrial cell includes 10 ion currents described by over a hundred equations [8]. The model complexity poses significant challenges on their clinical applications, since it is computationally demanding to study tissue and organ activity with the detailed models. To reduce the computational burden, a simplified model, i.e., FitzHugh-Nagumo model, was first developed, which uses two state variables to describe the depolarization and the repolarization of cardiac cells [9]. This model, however, cannot precisely quantify restitution property of cardiac tissue, i.e., the relationship between action potential duration (APD) and the cardiac cycle length. To overcome this issue, the Aliev-Panfilov model was developed to mimic the cardiac electrophysiology in a more realistic way.

Although the simplified cardiac models have shown great advantages in terms of computational efficiency, a main restrictive factor for using these models in clinical diagnosis and therapeutic design is model uncertainty [10]. Uncertainty, originating from model calibration or intrinsic variability of cardiac cells, may deteriorate the model accuracy. To improve the reliability and credibility of cardiac models, it is necessary to quantify and propagate uncertainty onto model predictions.

Uncertainty quantification and propagation has been well studied in engineering and science filed [11]. For example, sampling-based Monte Carlo (MC) simulation is one of the most popular methods [12]. However, MC is computationally prohibitive for multiscale cardiac modeling across disparate organizational levels, from ion channel to cell to tissue to the whole organ, since it requires a larger number of simulations.

Uncertainty propagation with the generalized polynomial chaos (gPC) expansion has been recently studied in different control, fault detection, and optimization problems [13, 14]. As compared to MC, gPC can propagate a complex probability distribution of uncertainty onto model predictions in a real-time fashion, from which the statistical moments of the model predictions can be easily and analytically estimated [14].

The work presents a gPC-based uncertainty propagation method, which can approximate parametric uncertainty with analytical expansions, and can explicitly account for nonlinear nature of cardiac models. This paper is organized as follows. Section II presents the theoretical background of gPC and the Aliev-Panfilov model. The simulation results and discussion are given in Section III followed by conclusions in Section IV.

II. BACKGROUND AND METHODOLOGY

A. Aliev-Panfilov model

The Aliev-Panfilov model is used to investigate the effect of uncertainty on cardiac electrical signaling, which can be defined with two variables as:

$$\frac{du}{dt} = k_1 u(u-a)(1-u) - k_2 ur - i_{st} \tag{1}$$

$$\frac{dr}{dt} = \varepsilon(u,r)[-r - k_1 u(u-a-1)]$$

$$\varepsilon(\mathrm{u},\mathrm{r}) = \varepsilon_0 + \frac{\mu_1 r}{\mu_2 + u} \tag{2}$$

, where u is the transmembrane potential, and r is the recovery variable that initiates repolarization. Cardiac activities, such as

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the initiation and upstroke of action potential, are controlled by the first term in (1), in which parameter k_1 is an excitation rate constant and a is the threshold parameter related to the threshold potential. The term i_{st} denotes the stimulation current. The restitution properties of the action potential (AP) are determined by the term $\varepsilon(u, r)$. The Aliev-Panfilov model can not only ameliorate the description of the shape of AP, but also prevent the system from being super-repolarized [15]. Model parameters used in this work are given in Table I.

TABLE I. MODEL PARAMETERS IN ALIEV-PANFILOV MODEL

Parameter	*values*	*units*	*Parameter*	*values*	*units*
a	0.1	/	ε_0	0.0002	ms^{-1}
k_1	8	ms^{-1}	μ_1	0.0155	ms^{-1}
k_2	1	ms^{-1}	μ_2	0.3	/

B. Generalized Polynomial Chaos Expansion

In this work, the generalized polynomial chaos (gPC) is used to study the effect of parametric uncertainty on model predictions, such as action potential (AP). The gPC represents an uncertainty as a function of another random variable in the Wiener-Askey framework [14]. For brevity, let define the Aliev-Panfilov model in (1) and (2) as:

$$\dot{\boldsymbol{x}} = f\ (t, \boldsymbol{x}, \boldsymbol{v}, \boldsymbol{p}) \tag{3}$$

, where the vector $\boldsymbol{x}$ contains the two dimensionless variables u and r with initial values $\boldsymbol{x}_0$ at t=0, $\boldsymbol{v}$ is deterministic model parameters, i.e., fixed constant numbers, while $\boldsymbol{p}$ is a vector of parametric uncertainties. It is important to note that $\boldsymbol{p}$ will be defined with probability density functions (PDF) in lieu of fixed values, which can be calibrated with in-vitro data.

To evaluate the effect of parametric uncertainty on model predictions, the first step is to rewrite each parameter p_i (i = 1, 2,…, n_p) in $\boldsymbol{p}$ as a function of a set of independent random variable $\boldsymbol{\xi} = \{\xi_i\}$ as:

$$p_i\ =\ p_i\ (\xi_i) \tag{4}$$

, where ξ_i is the i^{th} random variable. It is assumed that $\{\xi_i\}$ are independent and identically distributed (*iid*). Following the definition of gPC expansion [14], the parametric uncertainty $\boldsymbol{p}$ and model predictions $\boldsymbol{x}$ can be approximated by orthogonal polynomial basis function $\{\boldsymbol{\phi}_k(\boldsymbol{\xi})\}$ as:

$$p_i(\xi_i) = \sum_{k=0}^{\infty} \hat{p}_k \phi_k(\xi_i) \approx \sum_{k=0}^{q} \hat{p}_k \phi_k(\xi_i) \tag{5}$$

$$x(t,\boldsymbol{\xi}) = \sum_{k=0}^{\infty} \hat{x}_k \phi_k(\boldsymbol{\xi}) \approx \sum_{k=0}^{Q} \hat{x}_k \phi_k(\boldsymbol{\xi}) \tag{6}$$

, where $\{\hat{x}_k\}$ and $\{\hat{p}_k\}$ are the gPC coefficients of parametric uncertainty and model predictions at each time t, and $\{\boldsymbol{\phi}_k(\boldsymbol{\xi})\}$ represent the multi-dimensional orthogonal polynomial basis functions of $\boldsymbol{\xi}$. When the PDFs of $\boldsymbol{p}$ are known, $\{\hat{p}_k\}$ can be determined such that $\boldsymbol{p}$ follows a prior distribution. Then, the gPC coefficients of model predictions, $\{\hat{x}_k\}$, can be calculated by substituting (5) and (6) into (3) and by applying a Galerkin projection onto both sides of (3) with respect to polynomial chaos basis functions $\{\boldsymbol{\phi}_k(\boldsymbol{\xi})\}$ as:

$$\langle \dot{x}(t,\xi),\ \Phi_k(\boldsymbol{\xi}) \rangle = \langle f(t, \boldsymbol{x}(t,\boldsymbol{\xi}),\ \boldsymbol{v},\ \boldsymbol{p}(\boldsymbol{\xi})), \Phi_k(\boldsymbol{\xi}) \rangle \tag{7}$$

Note that infinite terms are used to estimate the PDFs of parametric uncertainty and model predictions in (5) and (6). For practical application, however, truncation is required. The total number of terms of $\boldsymbol{x}$ in (6), i.e., Q, can be calculated as function of an arbitrary order q in Eq. 5 and the number of parametric uncertainty (n_p) in $\boldsymbol{p}$ as:

$$Q\ =\ ((n_p\ +\ p)!\ /(\mathrm{n}_p!\,p!))\ -\ 1 \tag{8}$$

As seen in (8), the number of terms for the model predictions in (6) increases as the polynomial order q in (5) and/or the total number of uncertainty n_p in (9) increases. To improve the computational efficiency, sensitivity analysis will be used to identify significant parametric uncertainty before applying the gPC expansions, which will be discussed later.

The inner product in (7) between two vectors is defined as:

$$\langle \psi(\boldsymbol{\xi}), \psi'(\boldsymbol{\xi}) \rangle = \int \psi(\boldsymbol{\xi})\psi'(\boldsymbol{\xi}) W(\boldsymbol{\xi}) d\boldsymbol{\xi} \tag{9}$$

, where the integration is calculated over the domain defined by random variables $\boldsymbol{\xi}$, and $W(\boldsymbol{\xi})$ is the weighting function, i.e., the PDF of $\boldsymbol{\xi}$, which is selected according to polynomial basis functions. For example, Hermite polynomial basis functions are the choice of normal distributed $\boldsymbol{\xi}$.

Once the gPC coefficients in (6) are available, it is possible to quickly compute the statistical moments of $\boldsymbol{x}$ at any given time instant t as a function of the coefficients $\{\hat{x}_k\}$ in (6) as:

$$\begin{aligned} \mathrm{E}(x(\mathrm{t})) &= \mathrm{E}\left(\sum_{i=0}^{Q} \hat{x}_i(t)\phi_i\right) \\ &= \hat{x}_i(t)E(\phi_i) + \sum_{i=1}^{Q} E(\phi_i) = \hat{x}_0(t) \end{aligned} \tag{10}$$

$$\begin{aligned} \mathrm{Var}(x(\mathrm{t})) &= E\left(\hat{x}(t) - E(\hat{x}(t))^2\right) \\ &= \mathrm{E}\left(\left(\sum_{i=0}^{Q} \hat{x}_i(t)\phi_i - \hat{x}_{(i=0)}(t)\right)^2\right) \\ &= E\left(\left(\sum_{I=0}^{Q} \hat{x}_i(t)\phi_i\right)^2\right) = \sum_{i=0}^{Q} \hat{x}_i(t)^2 E(\phi_i^2) \end{aligned} \tag{11}$$

The first and second statistical moments calculated from (10) and (11) are the mean and variance of $\boldsymbol{x}$, respectively. It is important to note that the variance in $\boldsymbol{x}$ originates from the parametric uncertainty. In addition, the gPC enables the rapid calculation of the PDF profiles of model predictions $\boldsymbol{x}$ with analytical formulas above. Thus, the computational burden can be significantly reduced for uncertainty propagation, which will be further discussed in the results section below.

III. RESULTS AND DISCUSSION

A. Sensitivity Analysis

Cardiac models may involve many model parameters, and uncertainty in model parameters may have different effect on the model predictions. The appropriate selection of the most

sensitive uncertainty is essential for uncertainty propagation. Thus, the effect of parametric uncertainty on model prediction is studied in this section.

As shown in Section II A, there are six model parameters, i.e., a, k_1, k_2, ε_0, μ_1, μ_2, in the Aliev-Panfilov model, which can possibly affect the shape and duration of action potential (AP). For this reason, the effect of each parameter on the AP duration was studied by measuring the 90% of the AP amplitude, which corresponds to the 90% repolarization, e.g., APD_{90}.

To identify the most significant parametric uncertainty, the factional factorial design and the half-normal probability were used. It is assumed that each parameter can be varied between two levels, i.e., +1 and -1. For example, parameters can be randomized with a +10% change and a -10% change in their nominal values as given in Table I. For each parameter, two model predictions with respect to APD_{90}, e.g., $w_{p_i}^{+}$. and $w_{p_i}^{-}$., can be calculated with respect to each level. To evaluate the effect of parameter on model prediction, the model output is also calculated when parameters are maintained at nominal values, e.g., $w_{p_i}^{0}$. The effect of uncertainty in parameter p_i (i = 1, 2,…, n_p) on the model prediction is then evaluated as:

$$\delta w_{p_i} = \frac{\left|w_{p_i}^{+} - w_{p_i}^{0}\right|}{w_{p_i}^{0}} + \frac{\left|w_{p_i}^{-} - w_{p_i}^{0}\right|}{w_{p_i}^{0}} \qquad (12)$$

, where p_i is the i^{th} parameter in $\boldsymbol{p}$. The effect δw_{p_i} in (12) is evaluated for each parameter for two case scenarios to identify significant parametric uncertainty. For the first case scenario, each parameter is randomized with a +10% change and a -10% change, while each parameter is assumed to be vary between +20% and -20% in the second case scenario.

To illustrate the effect of parametric uncertainty on the AP duration, the half-normal probability diagram is used. The key is to use a normal curve as the reference distribution against which the significance of effect is tested [16]. This can be calculated as:

$$\left[\Phi^{-1}\left(0.5 + \frac{0.5[i-0.5]}{k}\right), \delta w_{p_i}\right] \qquad (13)$$

, where i=1,⋯,k represents the i^{th} parameter in $\boldsymbol{p}$, Φ^{-1} is the cumulative distribution function of a standard normal distribution. The effect calculated in (12) for each parameter can be organized in an increasing order and can be shown against the coordinates based on the half-normal diagram. Fig. 1 shows the sensitivity analysis result of half-normal diagram.

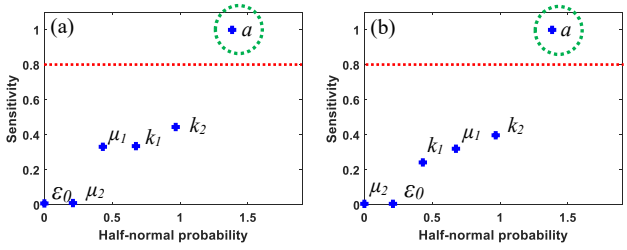

Figure 1. Half-normal probability plots for sensitivity analysis: (a) Results for ±10% change; (b) Results for ±20% change

As seen in Fig. 1, most of the parameters have relatively lower effect on model predictions as compared to the threshold parameter a in both case scenarios. Therefore, parameter a was identified as the most sensitive parametric uncertainty, which will be approximated with gPC as explained in Section II B.

B. Uncertainty propagation and model predictions

Using the sensitivity analysis results above, the effect of parametric uncertainty in a on model predictions of the Aliev-Panfilov model was further investigated. For clarification, it is assumed that parameter a follows a normal distribution. The value of a given in Table I was used as the mean values, and a standard deviation is assumed to be 1% of its mean value. To obtain orthogonality Hermite polynomial was selected as the basis functions, which is suitable for normal distribution [14]. The simulation results of AP are shown in Fig. 2.

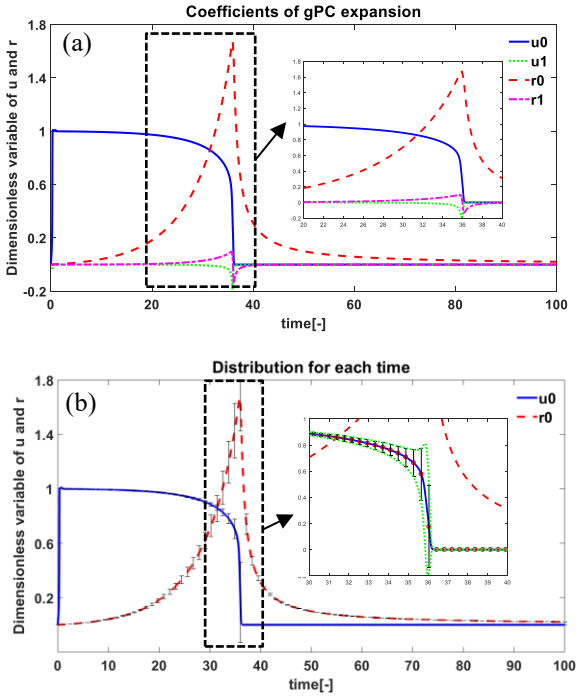

Figure 2. Parametric uncertainty propagation in Aliev Panfilov model using the gPC expansion

In the presence of parametric uncertainty in a, Fig. 2 (a) shows the gPC coefficients the transmembrane potential u and the recovery variable r. Since one uncertainty was considered (n_p=1), and two terms can be used to estimate a, i.e., p=2, thus two terms (i.e., Q=2) are used in the gPC models of each model prediction. As seen in Fig. 2 (a), u_0 and r_0 represent the mean values of the model predictions, while u_1 and r_1 are the gPC coefficients that can be used to estimate the variance resulting from uncertainty in a. As seen, due to the uncertainty, there is noticeable variations in repolarization region in Fig. 2 (a).

To quantitatively evaluate the uncertainty in the model predictions resulting from parametric uncertainty a, Fig. 2 (b) shows the variance calculated with gPC coefficients. It was found that the transmembrane potential u appears relatively larger variability in repolarization (34~36 *ms*). Further, the effect of uncertainty on recovery variable r is more significant in the range of 20 to 40 *ms*. It should be noted that gPC enables implicit mapping between uncertain parameters and the model perditions with explicit functions. The model predictions can be expressed with a series of orthogonal polynomials, from

which statistical moments can be quickly calculated from the gPC expansion coefficients given in (10) and (11).

Given the stochastic models of the cardaic cell, we further investigated the APD restitution in the presence of uncertainty. The simulation protocol used to generate APD restituion is designed as follows. Cardiac cell was stimulated every 100 *ms* for 10 cycles to reach a steady state, then another stimulation was triggered after 100 *ms*, 80 *ms*, 50 *ms*, 40 *ms*, and 32 *ms*, respectively. The APDs and their variances in the last cycle were measured in each experiment, and the results are shown in Fig. 3. As seen in Fig. 3 (a), the mean of the APD_{50} decrease as the *Cycle Length* (CL) decreases, i.e., the APD_{50} for the five aforementioned CL are 8.36 *ms*, 17.53 *ms*, 21.84 *ms*, 27.22 *ms*, and 28.91 *ms*, respectively. In addition, the variance of APD_{10}, APD_{50}, and APD_{90} were estimated to illustrate the effect of uncertainty on different APDs, which are shown in Fig. 3 (b). It was found that larger CL leads to bigger variability, and the variance of APD_{10} is most sensitive to the change of CL.

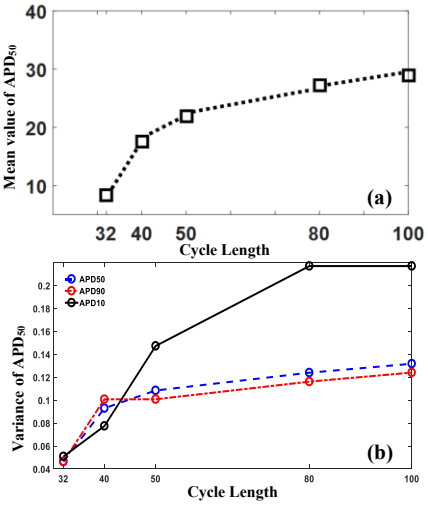

Figure 3. APD restitution in the presence of uncertainty. (a) mean value of APDs vs. Cycle Length, (b) Variance of APDs vs. Cycle Length

C. *Computational efficiency*

Further, experiments were conducted to compare the efficiency between the proposed gPC method and Monte Carlo (MC) simulations in terms of computational time. For the gPC method, ~60*s* were needed to calculate the gPC coefficients, whereas ~250*s* were required for 100 samples with the MC. It is important to note that the gPC coefficients can be used to rapidly estimate the mean and variance in model predictions with (10) and (11). In addtion, it was found that 100 samples in MC may fail to provide accurate results, as compared to the gPC, e.g., the upper and lower limits of action potential (AP) at each time instant, which can further affect the estimation of the effect of uncertainty on the AP duration. Thus, an even larger number of samples are required in MC, which could further increase the computational cost.

IV. CONCLUSION

This work presents an approach to propagate parametric uncertainty in the Aliev-Panfilov model onto the model predictions of membrane potential. The influence of each parameter on model predictions was evaluated via a sensitivity analysis. Parametric uncertainty with the highest sensitivity index was quantified with a gPC model, and its effect on model prediction was approximated with a Galerkin projection. The gPC shows its advantage in terms of computational efficiency, which enables efficient uncertainty analysis across different organizational levels such as cells, tissues, and the heart.

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