# Polynomial chaos uncertainty quantification of a return-map model of cardiac APD restitution

Caroline L. Ring M.S.[1] caroline.ring@duke.edu, Wanda Krassowska Neu Ph.D.[1] wanda.neu@duke.edu, Omar M. Knio Ph.D.[2] omar.knio@duke.edu

[1]Dept. of Biomedical Engineering, Duke University, Durham, NC [2]Dept. of Mechanical Engineering and Materials Science, Duke University, Durham, NC

## Introduction

- **Models of cardiac dynamics are used to study mechanisms of cardiac arrhythmia and simulate effects of drugs or diseases to see if they cause arrhythmia.**
- **Model parameters are usually derived from experimental measurements — so they have uncertainty.**
- **Uncertainty quantification (UQ) propagates uncertainty to model outputs — important for interpreting results. But UQ can be computationally intensive.**
- **We applied polynomial chaos (PC) UQ to the dynamics of a return-map model of cardiac action potential duration (APD) restitution. Results were similar to large-sample Monte Carlo (MC) UQ, in 95% less computational time.**

## Return-map model of APD restitution [1]

Cardiac cell responds to electrical stimulus by producing action potential (AP).

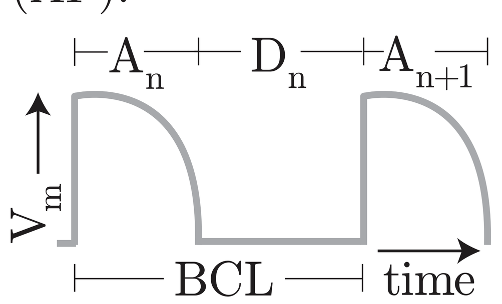


Figure 1

APD: AP duration (ms). $A_n = n^{th}$ APD.
DI: diastolic interval (ms). $D_n = n^{th}$ DI.
BCL ($B$): basic cycle length, period between stimuli (ms). For constant $B$, $B = A_n + D_n$. (Control parameter.)
APD restitution: $A_{n+1}$ depends on $A_n, D_n, \ldots$.

Model: APD restitution function as return map with 4 uncertain parameters $\boldsymbol{p}$. Discontinuity: if $D_n$ shorter than critical value $D_{min}(\boldsymbol{p})$, no APD will be elicited [1].

$$A_{n+1} = \begin{cases} \Phi(A_n, D_n, D_{n-1}; \boldsymbol{p}, B), & D_n \geq D_{min}(\boldsymbol{p}) \\ 0, & D_n < D_{min}(\boldsymbol{p}) \end{cases} \tag{1}$$

$\boldsymbol{p}$ and form of $\Phi$ derived from experimental measurements.

## APD dynamics summarized by bifurcation diagrams

Three bifurcation diagram types were observed as $\boldsymbol{p}$ was varied:

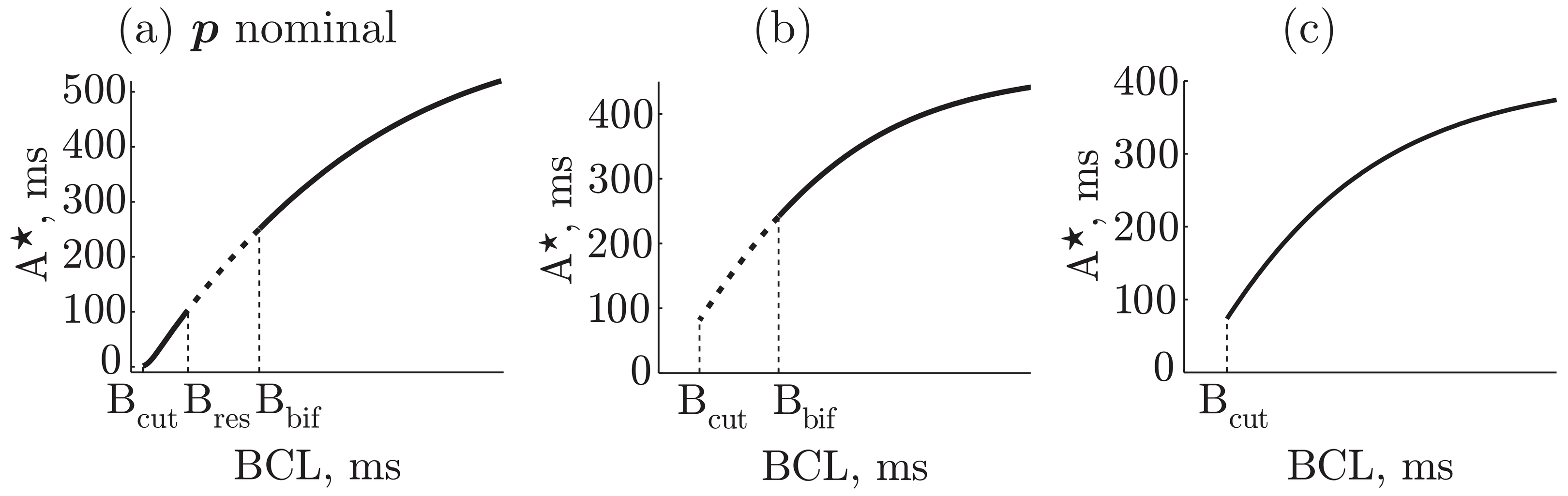


Figure 2: Bifurcation diagrams (fixed point $A^\star$ vs. $B$). Solid (dotted) line: $A^\star$ stable (unstable). No line: $A^\star$ does not exist. As $B$ decreases, (a): $A^\star$ loses stability at $B = B_{bif}$, regains stability at $B = B_{res}$, ceases to exist at $B = B_{cut}$. (b): $A^\star$ loses stability at $B = B_{bif}$, ceases to exist at $B = B_{cut}$. (c): $A^\star$ stable until it ceases to exist at $B = B_{cut}$.

Dynamics were characterized by model outputs:

- Fixed point APD: $A^\star(\boldsymbol{p}; B)$
- Existence of stable fixed point: binary response variable $z(\boldsymbol{p}; B)$. $z(\boldsymbol{p}; B) = 1$ if $A^\star(\boldsymbol{p}; B)$ exists and is stable, $z(\boldsymbol{p}; B) = 0$ otherwise
- Bifurcation BCLs: $B_{bif}(\boldsymbol{p})$, $B_{res}(\boldsymbol{p})$, $B_{cut}(\boldsymbol{p})$

## Classical PC UQ for continuous model outputs [2]

Given: model with $N_{dim}$ independent uncertain parameters $\boldsymbol{p}$ represented by random vector $\boldsymbol{\xi}$ with joint PDF $\rho(\boldsymbol{\xi})$, (optional) control parameter $B$ (no uncertainty), **output** $Y(\boldsymbol{\xi}; B)$ **varying smoothly** over support of $\rho(\boldsymbol{\xi})$:

$$Y \approx \hat{Y}(\boldsymbol{\xi}; B) \equiv \sum_{k=0}^{P} c_k(B)\Psi_k(\boldsymbol{\xi}) \tag{2}$$

$\Psi_k$: $N_{dim}$-dimensional polynomial basis orthogonal with respect to $\rho(\boldsymbol{\xi})$, formed as product of 1-d polynomials of max order $N_{ord}$.

**UQ:** By orthogonality, from (2):

$$\text{Mean}(\hat{Y}) = c_0 \tag{3a}$$

$$\text{Variance}(\hat{Y}) = \sum_{k=1}^{P} c_k^2 \langle \Psi_k^2 \rangle \tag{3b}$$

$$c_k = \frac{\langle Y \Psi_k \rangle}{\langle \Psi_k^2 \rangle} \quad \begin{matrix} \rightarrow & \text{quadrature-estimated} \\ \rightarrow & \text{analytical for most } \Psi_k \end{matrix} \tag{4}$$

To find $c_k$, evaluate $Y$ at $N_q = (2N_{ord}+1)^{N_{dim}}$ $\boldsymbol{\xi}$ quadrature nodes.

**For this model**:

$$\rho(\boldsymbol{\xi}) \approx \prod_{i=1}^{N_{dim}} \text{Normal}(\mu_i, \sigma_i); \quad \mu_i = \text{nominal parameter value}, \ \sigma_i = 0.1\mu_i$$

$$N_{dim} = 4, \ N_{ord} = 4; \quad N_q = 6561$$

## Modified PC UQ for discontinuous model outputs [3]

**Model discontinuity: Some outputs do not exist over full support of** $\rho(\boldsymbol{\xi})$.

- Transform subdomain of $\boldsymbol{\xi}$ where $Y$ is continuous to $\boldsymbol{\eta} \sim \text{Unif}[0,1]^{N_{dim}}$, using Rosenblatt transformation, numerically estimated using subset of quadrature nodes on subdomain.
- Choose $\Psi_k(\boldsymbol{\eta})$ to be Legendre, orthogonal with respect to $\text{Unif}[0,1]^{N_{dim}}$.
- Estimate $c_k(B)$ by Bayesian inference sampling, using subset of existing model evaluations on subdomain and transformed nodes.

Requires additional computational time, but no new model evaluations.

## Computational time: PC vs. Monte Carlo

**PC UQ**: Model outputs were evaluated at $N_q = 6561$ quadrature nodes for $B = 1000, 999, \ldots, 10$ ms. Computational time: 1500 s.

| Output | PC method | Additional computational time |
|---|---|---|
| $A^\star(\boldsymbol{\xi}; B)$, $B \geq 428$ ms | Classical | $\ll 1$ s |
| $A^\star(\boldsymbol{\xi}; B)$, $B \leq 427$ ms | Modified | 7930 s |
| $z(\boldsymbol{\xi}; B)$ | ** | $\ll 1$ s |
| $B_{bif}(\boldsymbol{\xi})$ | Modified | 50 s |
| $B_{res}(\boldsymbol{\xi})$ | Modified | 50 s |
| $B_{cut}(\boldsymbol{\xi})$ | Classical | $\ll 1$ s |
| Total additional computational time: | | 8030 s |

** PC inappropriate for binary variable $z(\boldsymbol{\xi}; B)$. $\langle z \rangle$ = probability that a stable fixed point exists, quadrature-estimated at each BCL.

**Monte Carlo (MC) UQ**: Model outputs evaluated at $1 \times 10^6$ $\boldsymbol{\xi}$ sample points for $B = 1000, 999, \ldots, 10$ ms.

**PC total computational time: $\approx$ 2.7 h**
**MC total computational time: $\approx$ 65 h**

## PC UQ results comparable to Monte Carlo

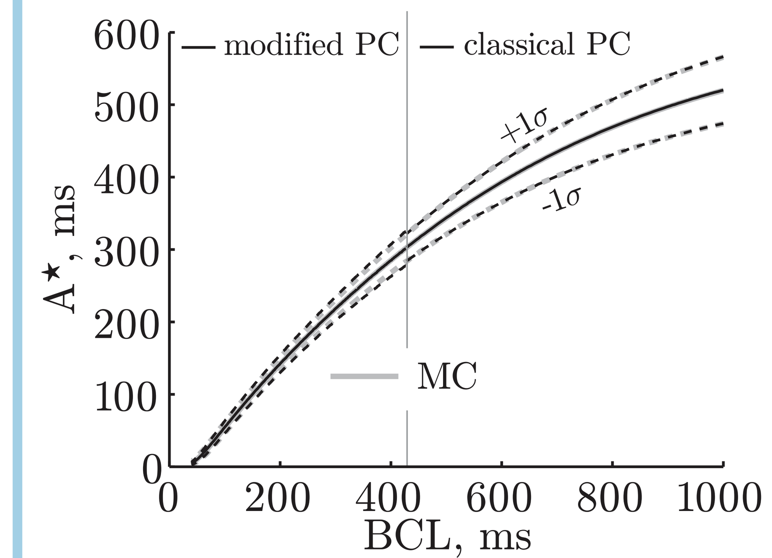


Figure 3: Fixed point APD vs. BCL, mean (solid lines) $\pm$ 1 standard deviation (dotted lines).

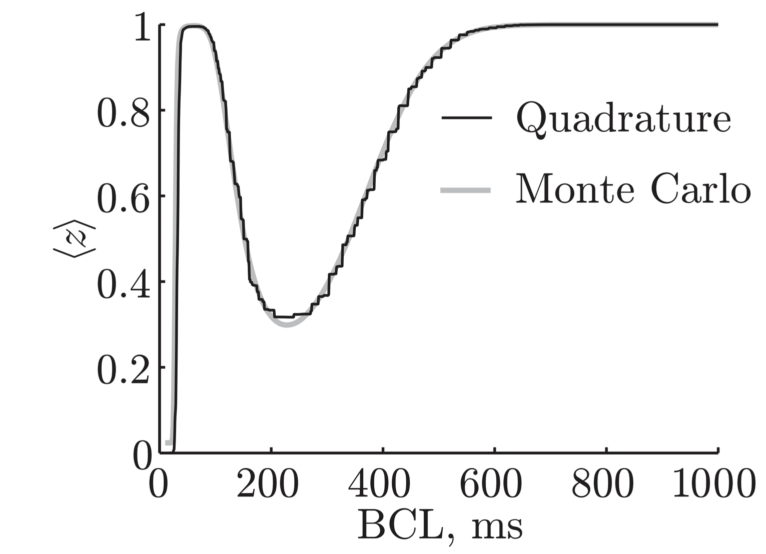


Figure 4: Probability that stable fixed point exists vs. BCL.

- Classical PC: mean and standard deviation estimates almost identical to MC.
- Modified PC: mean estimates nearly identical to MC; standard deviation estimates generally 10-30% greater than MC.

Table 1: Bifurcation BCLs, mean $\pm$ standard deviation (ms)

| | PC | MC |
|---|---|---|
| $B_{bif}$ | $389.5 \pm 98.1$ | $387.9 \pm 80.3$ |
| $B_{res}$ | $127.4 \pm 23.5$ | $137.6 \pm 31.1$ |
| $B_{cut}$ | $33.2 \pm 6.1$ | $28.5 \pm 5.6$ |

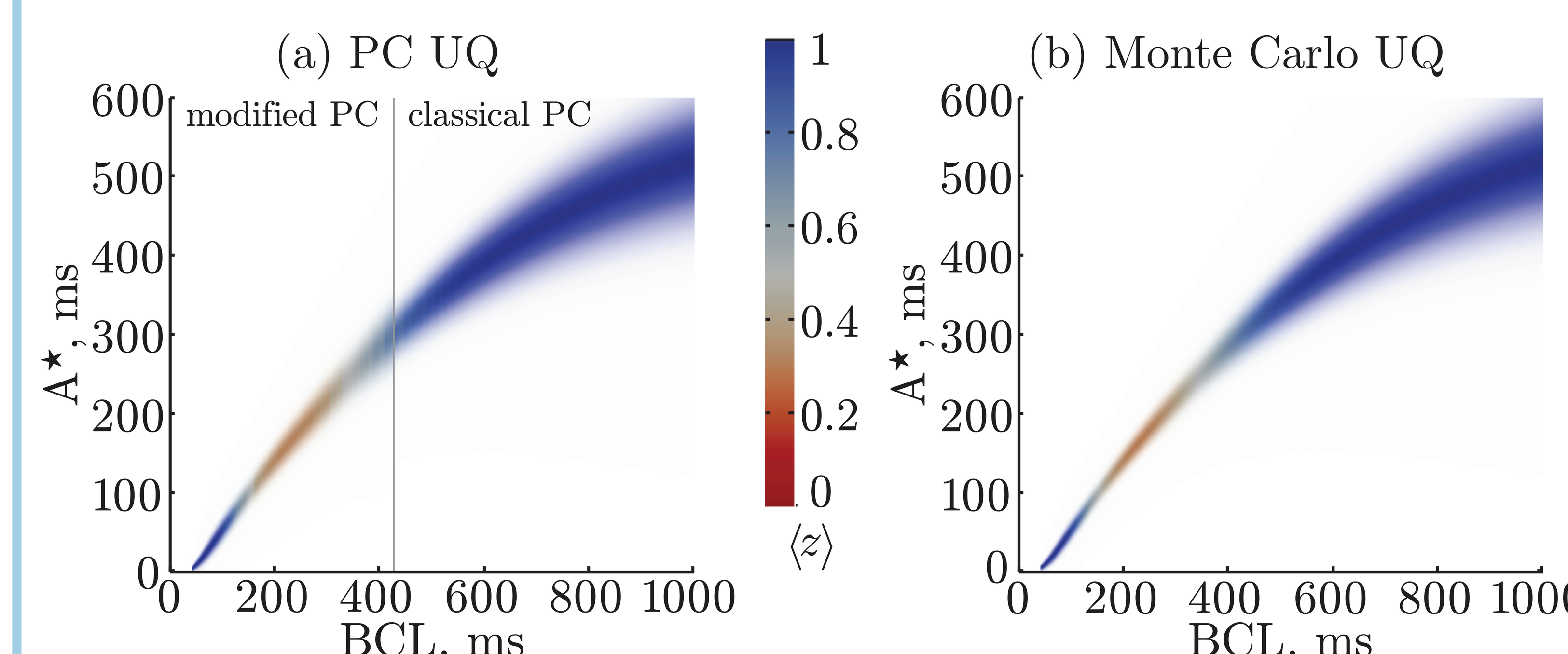


Figure 5: Probabilistic bifurcation diagrams. Probability that stable fixed point exists indicated by color at each BCL (see colorbar, center panel). Uncertainty in fixed point APD indicated by vertical width of colored area at each BCL.

## Conclusions

- **Polynomial chaos is a computationally efficient UQ method for the dynamics of a return-map model of cardiac APD response.**
- **Modified PC UQ handles discontinuous model outputs efficiently, with relatively small increase in estimated standard deviation of model output compared to large-sample Monte Carlo UQ.**
- **UQ of model dynamics provides a measure of *probability* of stability loss, which can inform the use of models to understand and predict cardiac arrhythmia.**

## References

[1] D. Schaeffer *et al.* "An ionically based mapping model with memory for cardiac restitution," *Bull Math Biol*, **69**:2, 459-482 (2007).

[2] O. P. Le Maître and O. M. Knio. *Spectral Methods for Uncertainty Quantification: With Applications to Computational Fluid Dynamics (Scientific Computation).* Springer (2010).

[3] K. Sargsyan *et al.* "Uncertainty Quantification given Discontinuous Model Response and a Limited Number of Model Runs," *SIAM J Sci Computz* **34**:1, B44 (2012).