Modeling variability in cardiac electrophysiology

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Electrocardiograms

Cell scale: Hodgkin-Huxley-like models

\[ V_m = u_i - u_e \]

\[ C_m \frac{dV_m}{dt} + I_{ion}(V_m, g) = 0 \]

\[ \frac{dg}{dt} + G(V_m, g) = 0 \]

Myocardium: bidomain models

\[ A_m \left( C_m \frac{\partial V_m}{\partial t} + I_{ion}(V_m, g) \right) - \text{div}(\sigma_i \nabla u_i) = A_m I_{app}, \]

\[ \text{div}(\sigma_e \nabla u_e) + \text{div}(\sigma_i \nabla u_i) = 0 \]

\[ \frac{\partial g}{\partial t} + G(V_m, g) = 0, \]

Torso: Poisson equation

\[ \text{div}(\sigma_T \nabla u_T) = 0 \]

+ transmission condition on the epicardium

\[ \text{div}(\sigma_e \nabla u_e) + \text{div}(\sigma_i \nabla u_i) = 0 \]

e.g.: Pullan et al. 05, Sundes et al. 06,...

Boulakia, Cazeau, Fernández, JFG, Zemzemi, Annals Biomed Engng 2010
First results...

In 2007...

(Sundnes et al., Springer 2006)
Standard 12-lead ECG

Transmembrane Potential $V_m$ (mV)
-80.0  20.0

Body Potential $u_T$ (mV)
-1.0   0.0

Standard 12-lead ECG

Body Potential \( u_T \) (mV)
0.0 10.0

Transmembrane Potential \( V_m \) (mV)
-80.0 20.0

ECG Simulation

N. Tarabelloni, A.M. Paganoni & F. Ieva (Politecnico di Milano)

"normal ECGs" (from Joseph Wartak)
Variability modeling

Our goal:

• Given measurements in a population of individuals
• Infer a probability density function (pdf) for some parameters

Standard approaches:

• Solve an inverse problem for each individual separately
• Population approach:
  - consider all the individuals together
  - look for average population parameters, standard deviation, …


Variability modeling

Our wishes:
- Non-intrusive: black box algorithm
- Non-parametric: no assumption on the distribution
- Moderate number of model evaluations

Our approach:
- Match the moments of the “observables” and of the measurements
Variability modeling: moments matching

• Hausdorff moment problem:
  - find a distribution given its moments
    \[ m_j = \int_{\Theta} \theta^j \rho(\theta) \, d\theta \]
  - in general, an ill-posed problem

• Regularization: **Maximum Entropy Principle** (Jaynes, 1957)
  - Maximises the Shannon entropy:
    \[ S(\rho) = -\int_{\Theta} \rho(\theta) \log(\rho(\theta)) \, d\theta \]
    Under the constraints defined by the available information
Examples

• Information:
  – $X$ a random variable with values in $[a, b]$

Maximum Entropy Principle $\implies \rho$ is a uniform pdf on $[a, b]$

• Information:
  – $X$ a random variable with values in $\mathbb{R}^*_+$
  – $\mathbb{E}(X) < +\infty$ given
  – $\mathbb{E}(\log(X)) < +\infty$ given.

Maximum Entropy Principle $\implies \rho$ is a Gamma pdf

• Information:
  – $X$ a random variable with values in $\mathbb{R}$
  – $\mathbb{E}(X) < +\infty$ given
  – $\mathbb{E}(X^2) < +\infty$ given

Maximum Entropy Principle $\implies \rho$ is a Gaussian pdf
Variability modeling: moments matching

• Moment of the parameters are not available

• But empirical moments of measurable quantities can be computed:

\[ \hat{\mu}_m(x_j) = \frac{1}{N} \sum_{i=1}^{N} y_i(x_j)^m, \quad m = 1, \ldots, n_{mom} \]

measurements at \( x_j, j = 1 \ldots N_x \)

\[ \mathbf{x} = (x, t) \in \mathcal{D} \text{ (space-time physical domain)} \]

• Assume that \( p \) parameters explain the variability: \( \boldsymbol{\theta} = (\theta_1, \ldots, \theta_p) \)

• Simulated moments:

\[ \mu_m^\rho(x_j) = \int_{\Theta} \rho(\boldsymbol{\theta}) g(x_j, \boldsymbol{\theta})^m \, d\boldsymbol{\theta} \]

unknown pdf

model outputs ("observables")
Observable Moments Matching

- **Sampling:** $\theta_i \in \Theta, \ i = 1, \ldots, N_c$

  - Pseudo-random, $N_c = 256$.
  - Sobol sequence, $N_c = 256$.
  - Sparse grid, $N_c = 257$.

  ![Pseudo-random sampling](image)
  ![Sobol sequence sampling](image)
  ![Sparse grid sampling](image)

  $\rightarrow$ Sobol sequence in the parameter space.

- **The model is evaluated on each $\theta_i$ (off-line)**

- **Integrals over $\Theta$ approximated by quasi-Monte-Carlo**

- **We look for an approximation of $\rho(\theta_i), \ i = 1, \ldots, N_c$**
Observable Moments Matching

• Maximize the entropy $S(\rho) = -\int_{\Theta} \rho \log(\rho)$ under the constraints

$$c_\rho(x_j, m) = \mu_m^\rho(x_j, m) - \hat{\mu}_m(x_j, m) = 0,$$
for $N_k$ points $x_j \in D$

• Saddle-point problem: $\inf_\rho \sup_{\lambda, \lambda_0, \nu \geq 0} L(\rho, \lambda, \lambda_0, \nu)$

$$L(\rho, \lambda, \nu) = \phi \int_{\Theta} \rho \log(\rho) - \sum_{j=1}^{N_k} \sum_{m=1}^{n_{mom}} \lambda(x_j, m) c_\rho(x_j, m) - \lambda_0 \left( \int_{\Theta} \rho - 1 \right) - \int_{\Theta} \rho \nu.$$  

- “Inf” step done analytically. Positivity constraint automatically verified
- “Sup” step done numerically using quasi-Newton method
- Dense linear system of size $(N_k n_{mom}) \times (N_k n_{mom})$
Selection of physical points: sensitivity

Issue

• Too many points in the physical space
• Many points are redundant: big and ill-conditioned problem

Illustrative example

• Logistic equation $\frac{du}{dt} = k \cdot u(1 - u)$ for different values of $k$
Selection of physical points: sensitivity

Strategy

- Quantify how the parameters affect the variability at a given $x_j$.
- Sensitivity Gramm matrix, using the model outputs:

$$C(x_j) = \int_{\Theta} \left[ \nabla_{\theta}g(x_j, \theta) \right] \left[ \nabla_{\theta}g(x_j, \theta) \right]^T \rho(\theta) d\theta$$

- Eigenvalue decomposition of $C(x_j)$: $\lambda_{j,k}, e_{j,k}$
- $e_{j,1}$ = direction in $\Theta$ of maximum variation on average
- $\lambda_{j,1}$: mean-squared derivative of the observable along the direction $e_{j,1}$
Selection of physical points: clustering

- Points with similar dominant directions are considered as redundant
- Agglomerative hierarchical **clustering algorithm**
- The $N_x$ points of the full physical set are divided into $N_k$ clusters
- Points with maximum trace of $C(x_j)$ are chosen as cluster representative
- Subset $S$ where the moments are matched: the $N_k$ representatives
Example with an ODE

Cardiac cell Action Potential

- Two parameters $\theta_1, \theta_2$
- $N_c = 1024$ Sobol points in $[0.6, 1.8]^2$
- $N_x = 334$ time instants, $N_k = 5$ clusters

First eigenvectors of the Sensitivity Gram Matrices at each time instants
Algorithm

- Initial guess: $\rho^{(0,0)}$ uniform density over $\Theta$
- $j = 1$
- While $\|R(\rho^{(j-1,0)})\| \geq \text{tol}$
  - Clustered Sensitivities with $\rho^{(j-1,0)}$
    $\implies$ nested subsets $S^k$ of $k$ physical points
- $n = 1$
- While $\|R(\rho^{(j-1,n-1)})\| \geq \text{tol}$
  - Observable Moments Matching on $S^n$
    $\implies \rho^{(j-1,n)}$
  - $n \leftarrow n + 1$
  - $\rho^{(j,0)} \leftarrow \rho^{(j-1,n)}$
  - $j \leftarrow j + 1$
- $n_{\text{iter}} = j$

Remarks:
- Residual on all the $N_x$ physical points:
  $$R(\rho) = \sum_{j=1}^{N_x} \sum_{m=1}^{n_{\text{mom}}} c_\rho(x_j, m)^2$$
  with
  $$c_\rho(x_j, m) = \mu^\rho_m(x_j, m) - \hat{\mu}_m(x_j, m)$$
- In practice $n_{\text{iter}} \approx 3$
Example 1: Fisher-Kolmogorov

- Nonlinear parabolic equation:

\[
\frac{\partial u}{\partial t} - \alpha \Delta u = Ru(1 - u) + f(x, t)
\]

- Diffusion, reaction, stimulation

- 3 parameters responsible for variability:

\[x_0, y_0 \text{ (stimulation position)} \text{ and } R \text{ (reaction)}\]

- Measurements: \(N_x = 81\) points in space \(\times\) 200 time instants

- Synthetic data: \(10^3\) parameters sampled from a normal distribution

\[
\mu = [0.55, 0.55, 0.50], \Sigma = \sigma^2 \times I_3, \text{ with } \sigma = 0.1
\]

- Model evaluated for each sample + noise addition + different mesh
\( N_c = 2048 \) Sobol points over \( \Theta = [0.1, 1.0]^3 \),

\( n_{mom} = 3 \)

\( N_k = 48 \) selected space-time points

\( n_{iter} = 3 \) iterations
Example 2: Darcy equation

- **Darcy equation:**
  \[
  \begin{align*}
  \mathbf{u} + K \nabla p &= 0 \\
  \text{div } \mathbf{u} &= 0,
  \end{align*}
  \]

- **Measurements:** \( p \) and \( u_x \) on domain boundaries

- **Variability:** 5 coefficients \( \theta_k \) defining the permeability
  \[
  K(x, y) = 1 + \sum_{k=1}^{5} \theta_k \Psi_k(x, y)
  \]
• Synthetic data:

Evaluation of the model for $N = 10^4$ samples of $\theta = (\theta_1, \ldots, \theta_5)$ drawn from an uncorrelated multivariate normal distribution $\mu = 2.5 \times 10^{-2} \times [1, 1, 1, 1, 1], \Sigma = \sigma^2 \times I_5, \sigma = 3.3 \times 10^{-2}$.

• Moment matching algorithm:

$N_c = 16384$ Sobol points over $\Theta = [-0.2, 0.2]^5$

$n_{mom} = 3$

25 points selected by the Clustered Sensitivities algorithm (out of 400 sensors)
Cardiac cell model

Action potential: $V_m = u_i - u_e$

Biomarkers:

\[
\begin{cases}
C_m \frac{dV_m}{dt} + I_{ion}(V_m, g) = 0 \\
\frac{dg}{dt} + G(V_m, g) = 0
\end{cases}
\]

(Hodgkin-Huxley 52, Cronin 81, Pullan et al. 05, Sundes et al. 06, ...)

Extra-cellular potential: $u_i$
Extra-cellular potential: $u_e$

Circuit analogy

APD

Intracellular medium
Membrane
Extracellular medium

Biomarkers:

\begin{itemize}
  \item APD90
  \item APD50
  \item APD20
  \item APD00
  \item RMP
  \item $V_20$
  \item $dV/dt_{\text{max}}$
\end{itemize}
Example 3: atrial fibrillation

- Measurements from 2 populations: healthy (SR), atrial fibrillation (AF)
- Observable: set of AP features (4 biomarkers) for 469 subjects
- Strong inter-subject variability

• Model: Courtemanche-Ramirez

• # samples: $N_c = 16384$; # moments: $n_{mom} = 2$; # clusters: $N_k = 6$
Example 4: Canine Action Potential

- Measurements (100 APs) from canine heart cells
- Observable: set of AP features (biomarkers)
- Beat-to-beat variability

Marginal distributions of 3 parameters estimated from experimental data.

- Model: Davies
- Hypothesis: only 3 parameters responsible for the variability
- Validation with individual parameter identification (evolutionary algo: CMA-ES)
- # samples: $N_c = 8192$; # moments: $n_{mom} = 2$; # clusters: $N_k = 3$
Conclusions & Perspectives

Summary

- Approximate parameters distribution from observed variability in a population
- Non-parametric and black-box approach
- Tested with synthetic & experimental data

Perspectives

- How to determine which parameters are responsible for variability?
- What to do with the remaining parameters?
- How to choose relevant biomarkers? [Eliott Tixier’s talk]
- Use the obtained distribution as a prior for more sophisticated inverse problem algorithms
J-F. Gerbeau, D. Lombardi, E. Tixier, “A moment-matching method to study the variability of phenomena described by partial differential equations”, available on HAL: https://hal.archives-ouvertes.fr/hal-01391254/


• You can test it: https://github.com/eltix/omm_jrsi.git
■ Bi-variate **log-normal** distribution

■ Strongly skewed

■ Numerical settings: $N_c = 2048$, $n_{mom} = 4$ and $N_x = 10$

Observables moment matching applied to synthetic data. Log-normal distribution
- Gaussian mixture **bimodal** distribution
- $\theta_1$ and $\theta_2$ are strongly correlated
- Numerical settings: $N_c = 2048$, $n_{mom} = 4$, $N_x = 16$

Observable moment matching applied to synthetic data. Bimodal distribution