Statistical Metamodelling and Computer Experiments of Large-Scale Cardiac Models

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Research Background

- **Action Potential (AP):** Net changes of transmembrane potentials

![Schematic diagram of a cardiac cell](image)

Cardiac Contraction

Ventricular cell

Na+

AP
Background

- **Glycosylation:**
  - The enzymatic process that attaches glycans to proteins, lipids, or other organic molecules
Background

- Voltage-gated sodium channel (Na\textsubscript{v}) – Initiation of cellular excitation
- Altered Glycosylation $\rightarrow$ Na\textsubscript{v} channel $\rightarrow$ Cardiac function
Motivations

- Congenital Disorders of Glycosylation (CDG):
  - High infant mortality rate
  - Multi-system effects, e.g., diabetes, cardiac diseases
  - Prevalence of cardiac involvement
  - Unknown etiology of cardiomyopathy among young CDG patients

- Goals
  - Understand the pathology of cardiac disease among CDG patients
  - Develop pertinent therapeutic solutions
Gaps

- **Little is known** on how reduced glycosylation affects cardiac electrical signaling.

**Limitations**
- Study the changes at **molecular levels**
- **Connect changes** at one organizational level, e.g., ion channels, to another organizational level, cardiac cells.

**Objectives:**
- Couple in-silico studies with the wealth of data from our electrophysiological experiments to model, mechanistically, how reduced glycosylation affects Na+ activity and cardiac electrical signaling.
Challenges

- Nonlinear model characteristics
- High dimensionality of design space: 25 parameters
- Markov Model of Na⁺ channel

\[ \frac{dP(t)}{dt} = f(t, V, A, P(t)) \]

where \( P = [P_{IC3}, P_{IC2}, P_{IF}, P_{I1}, P_{I2}, P_{C3}, P_{C2}, P_{C1}, P_0]^T \), \( A \) is the 9 × 9 transition rate matrix, e.g. \( A_{1,1} = -(\alpha_{31} + \alpha_{111}) \), \( \alpha_{31} = \frac{1}{2.5 \exp\left(\frac{\theta_1 + V}{7.0}\right) + 8.0 \exp\left(\frac{\theta_2 + V}{7.0}\right)} \).
Challenges

- 3 different cardiac functional responses from pulse protocols
- High computational cost

![Diagram showing model parameter, patch clamp protocols, normalize peak currents, and modeled outputs.](image)

(a) protocol

(b) ion currents

(c) normalized peak current
Research Methodology

Simulation Model

Design variables
Machine parameters, Environmental factors, Human Factors ...

Response variables
Quality, Integrity, Performance Metrics, ...

Economical

Statistical Metamodelling
Gaussian Process, Kriging, Neural Network, ...

Space-filling Design
Sequential Design
Global Optimization

Adaptive Modeling
Research Methodology

Screening Design:

- Identify important control variables from the high-dimensional set of potential parameters

The large set of voltage-relevant parameters

Sensitive to model outputs

Curse of Dimensionality

\[ \theta_{SSA} = \{\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_{17}, \theta_{22}\} \rightarrow Z_{SSA} \]

\[ \theta_{SSI} = \{\theta_{11}, \theta_{12}, \theta_{13}, \theta_{14}, \theta_{23}, \theta_{24}\} \rightarrow Z_{SSI} \]

\[ \theta_{REC} = \{\theta_{11}, \theta_{12}, \theta_{15}, \theta_{18}, \theta_{19}, \theta_{23}, \theta_{25}\} \rightarrow Z_{REC} \]
Research Methodology

- **Space-Filling Design:**
  - Generate design points (samples) over the control variable space ($\theta$)

- **Maximin Latin Hypercube Design (LHD):**
  
  \[ d_{ij} = \|x_i - x_j\| \]

  \[ \max_{x \in [0,1]^d} \min_{i \neq j} d_{ij} \]

- [2D and 3D diagrams showing space-filling designs]

... Maximin LHD on high dimensional space
Gaussian Process

- **GP**: a collection of random variables, any finite number of which have **joint Gaussian Distribution**

\[
\begin{bmatrix}
  f \\
  f_*
\end{bmatrix}
\sim N \left( 0, \begin{bmatrix}
  K(X, X) & K(X, X_*) \\
  K(X_*, X) & K(X_*, X_*)
\end{bmatrix} \right)
\]

- \( f \) training outputs, \( f_* \) test outputs, \( K(,) \) covariance function

- **Posterior** distribution

\[
f | f_* \sim N(K(X_*, X)K^{-1}f, K(X_*, X_*) - K(X_*, X)^TK^{-1}K(X, X_*))
\]
Research Methodology

Probability of Improvement

\[
\text{ProbI} = \Phi\left( \frac{T - E\{f(x^*)\}}{s\{f(x^*)\}} \right)
\]

where \( E\{f(x^*)\} \) and \( s\{f(x^*)\} \) are mean and standard error of predictions. \( \mathcal{N}(\cdot) \) is the Normal CDF function.
Probability of Improvement

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![Diagram of Probability of Improvement](Image)
Research Methodology

- **Probability of Improvement**

\[
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\]

where \(E\{f(x^*)\}\) and \(s\{f(x^*)\}\) are mean and standard error of predictions. \(\mathcal{N}(\cdot)\) is the Normal CDF function.
Results

Refractory periods of ST3Gal4^-/- and WT cells

- **Computer** experiments: WT: 138.0 ms, ST3Gal4^-/-: 109.5 ms
- **Physical** experiments: WT: 139.8 ± 8.6 ms, ST3Gal4^-/-: 110.2 ± 10.0 ms
Results – State Transitions

Action Potential

Na+ Channel Current - $I_{Na}$

State Occupancy
Conclusions

- **Challenges**
  - Nonlinear differential equations
  - High-dimensional design space
  - Experimental protocols and functional responses

- **Methodological and Biomedical Merits**
  - Statistical metamodelling and sequential design of experiments
  - Computer experiments and calibration of large-scale cardiac models
  - Improve fundamental knowledge about the functional role of glycosylation in cardiac electrical signaling
  - New pharmaceutical designs to correct aberrant glycosylation
Acknowledges

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Publications


Thank you!
Questions?