Cell-specific action potential models for a large population of rabbit ventricular myocytes

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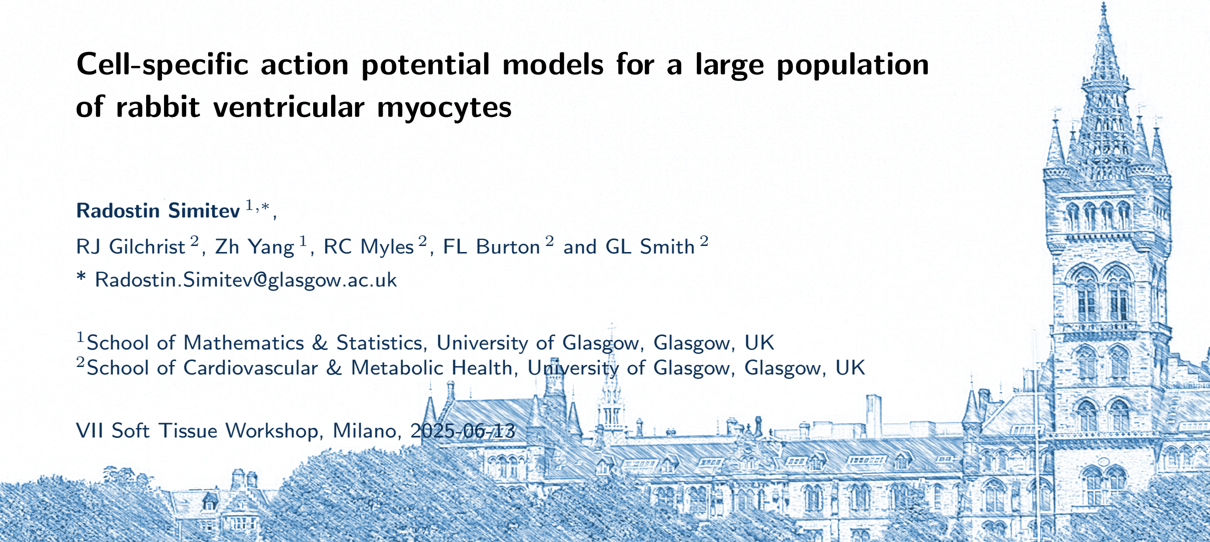
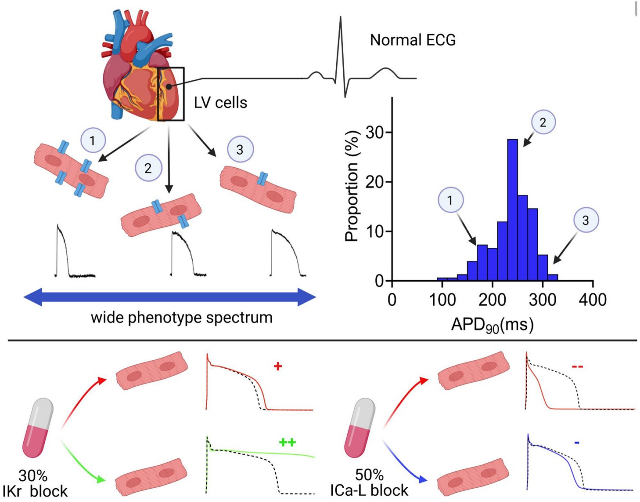


Motivation

- Healthy myocytes show substantial electrophysiological **diversity under identical conditions.**
- Inter-cell variability complicates drug response and its prediction.
- Need to **quantify and predict cell-to-cell variability**. This is best done **using mechanistic models constrained by data**.



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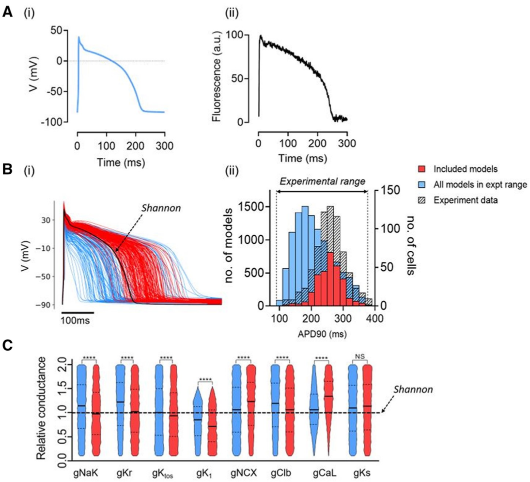
Strategies for Modelling Cardiomyocyte Variability

- Detailed mathematical **models of the myocyte action potential** (AP) are well-developed (for various species, cardiac types, health/disease) but **are generic not cell-specific**.
- **Population-based**: generate large number of random AP waveforms then calibrate biomarker distributions (e.g. APD90). No one-to-one correspondence between models and cells.
- **Sample-specific**: fit mathematical models to individual cell data. Previously restricted to small number of cells only.
- **Goal:** Construct cell-specific fits of full AP waveforms for a large population of cells.



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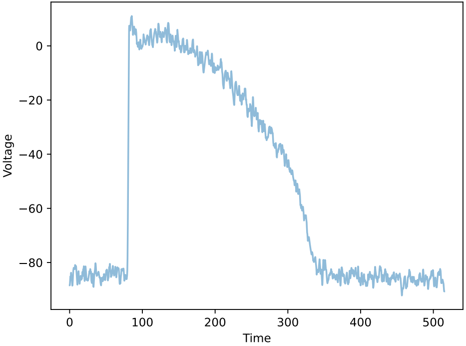
Experimental Dataset

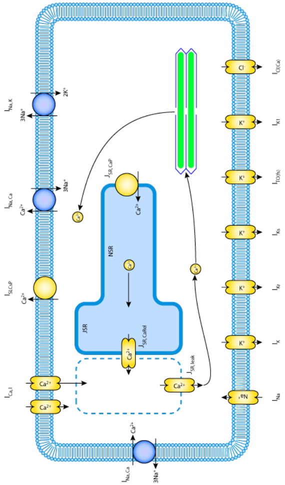
- **1300 cardiomyocytes** from different ventricular regions (apical/basal, endo/mid/epicardial) in 8 male rabbit hearts.
- Cells isolated enzymatically, **loaded with FluoVolt voltage sensitive dye**.
- Pre-paced at 2 Hz for 5 minutes.
- **Fluorescence signals recorded** at 10 kHz for 2.5 s.
- Beat-to-beat variability $< 2\%$ across APs within each cell.
- Signals averaged **into a single waveform per cell.**
- **Final dataset:**



$$\mathcal{D} = \left\{ D_i = \left\{ (t_j = j\Delta t, \mathcal{V}_{i,j}),\ \Delta t = 10^{-4}\text{s} \right\}_{j=1}^{K} \right\}_{i=1}^{N}, \qquad K = 5000,\ N = 1228.$$

Baseline Action Potential Model

- The **Shannon et al. (2004) model** is used as the baseline AP model for **single rabbit ventricular myocytes**.
- The model describes ionic dynamics across **four compartments**: Sarcoplasmic reticulum (SR), Junctional cleft, Subsarcolemmal space, Cytosolic bulk.
- Tracks 38 state variables incl. ion concentrations and gating variables.
- Involves **15 ionic currents**:
  - Major currents: I_{Na}, I_{CaL}, I_{Kr}, I_{Ks}, I_{K1}
  - Transient outward: I_{tof}, I_{tos}
  - Chloride: I_{ClCa}, I_{Clb}
  - Sodium-calcium: I_{NaCa}, I_{NaK}, I_{Cap}
  - Background and pump currents: I_{Nab}, I_{Cab}, I_{Kp}
- Total number of parameters 180 degrees of freedom.



Parameter Estimation – Problem Setup: Model and Data

- **Each myocyte is modelled by** a system of ODEs:

$$\dot{x} = f(t, x; \phi), \quad x(0) = x_0, \quad y = s\big(x(t)\big),$$

  with time $t \in \mathbb{R}$, state $x \in \mathbb{R}^d$, **model parameters** $\phi \in \mathbb{R}^k$, and **observables** y.

- **Experimental data** for each cell is represented as discrete sets of measurements:

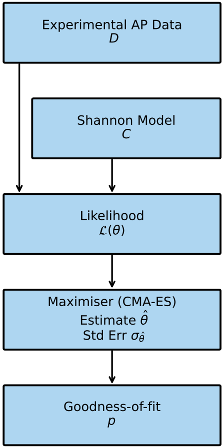
$$D = \{(t_j, Y_j)\}_{j=1}^{K}.$$

- Measurements are modeled **with Gaussian noise**:

$$Y_j \sim \mathcal{N}\big(y(t_j; \phi), \sigma^2\big).$$

- Initial conditions and noise level are **added to the parameter vector**

$$\theta = (\phi, x_0, \sigma) \in \mathbb{R}^{\ell}.$$



Experimental AP Data
D

Shannon Model
C

Likelihood
$\mathcal{L}(\theta)$

Maximiser (CMA-ES)
Estimate $\hat{\theta}$
Std Err $\sigma_{\hat{\theta}}$

Goodness-of-fit
p

Parameter Estimation – Maximum Likelihood Principle

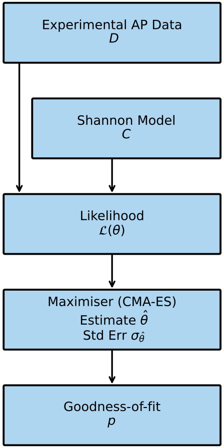
- The **likelihood** of observing a measured dataset D at given parameter values is:

$$\mathcal{L}(Y;\theta) = P(Y \mid \theta) = \prod_{j=1}^{K} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{1}{2}\frac{(Y_j - y(t_j, \boldsymbol{\theta}, x_0))^2}{\sigma^2}\right)$$

- The **maximum likelihood principle** postulates that the best point estimate $\hat{\theta}$ of the parameter values are those that maximise the likelihood

$$\hat{\theta} = \arg\max_{\theta\in\Theta} \mathcal{L}(Y;\theta) \qquad (*)$$

- This is now a **nonlinear optimization problem**.
- **CMA-ES** (Covariance Matrix Adaptation Evolution Strategy) for likelihood maximization.



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Parameter Estimation – Error and Goodness-of-Fit

- **Standard errors of estimation** can be found by a Taylor expansion of the variance about the expectation:

$$\sigma_{\hat{\theta}} = \hat{\sigma}\sqrt{\operatorname{diag}\left([J^T J]^{-1}\right)}, \quad J = \nabla_\theta y\big|_{\hat{\theta}}.$$

- **Goodness-of-fit** tests the hypothesis that deviations are due to Gaussian noise, using the chi-squared statistic

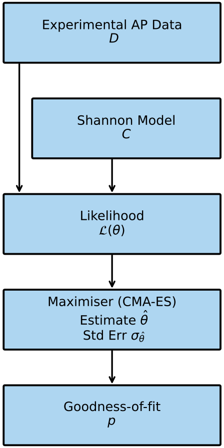
$$\hat{\chi}^2(\hat{\theta}) = \sum_{j=1}^{K} \Big(Y_j - y(t_j, \hat{\theta}, \hat{x}_0)\Big)^2 \Big/ \hat{\sigma}^2$$

and computing the p-value

$$p = \Pr(\chi_\nu^2 \geq \hat{\chi}^2(\hat{\theta}) \mid H_0) = \int_{\hat{\chi}^2}^{\infty} P(\chi_\nu^2)\, d\chi_\nu^2$$

to assess fit.

- **Fits are accepted if** $p > 0.3$ used.



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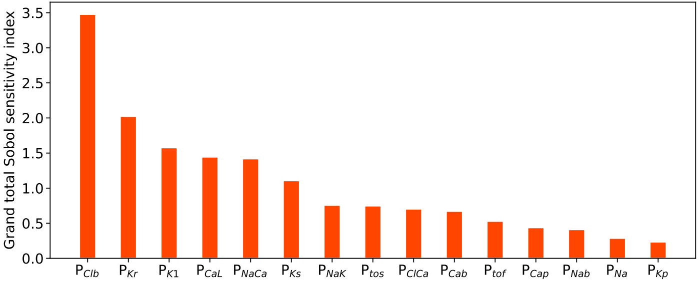
Sensitivity Analysis and Estimands

- **Parameters fitted**: The **maximal conductances** of 8 selected ion currents in the Shannon model.

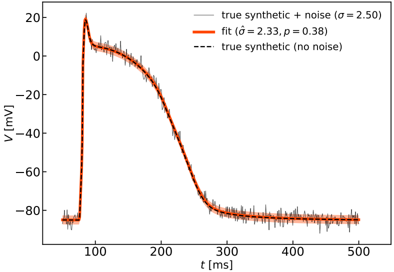
$$\theta = [G_{\mathsf{Kr}}, G_{\mathsf{Ks}}, G_{\mathsf{K1}}, G_{\mathsf{tos}}, G_{\mathsf{CaL}}, G_{\mathsf{Clb}}, I_{\mathsf{NaK}}, I_{\mathsf{NaCa}}, \sigma]^T$$

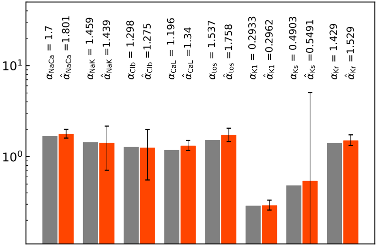
- Estimands **selected based on a Sobol global sensitivity analysis** of the Shannon model.



Ranking of the grand total Sobol sensitivity index of 6 selected biomarkers to variation of parameters.

Validation Against Synthetic Ground-Truth Parameters



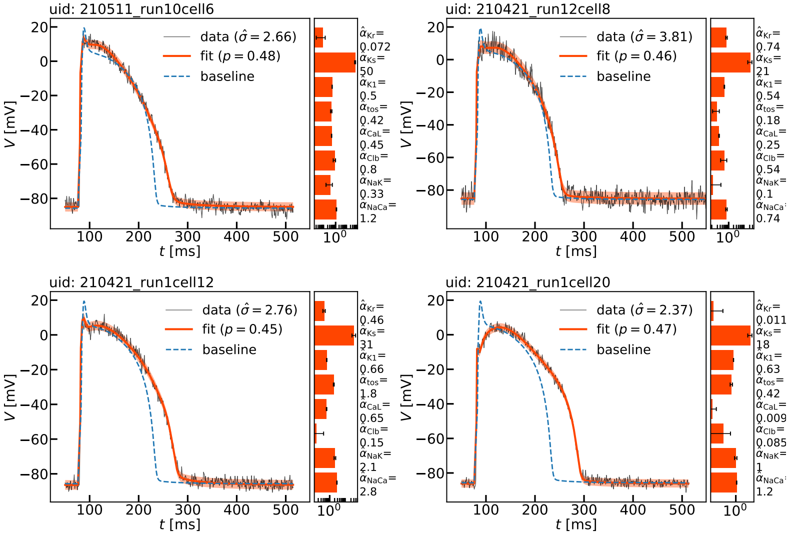


- **Synthetic AP trace** generated using randomly selected parameter values.
- Gaussian noise added with std dev $\sigma = 2.5$ for close resemblance to actual data.
- **Parameters recovered accurately** with absolute errors $\mathcal{O}(10^{-2})$ – much smaller than the std err of estimation.
- **Nearly exact match** between synthetic and refitted AP traces, e.g. root-mean-square deviation in V:

$$RMSD(\hat{V})/V_{\mathrm{amp}} = 10^{-4}$$

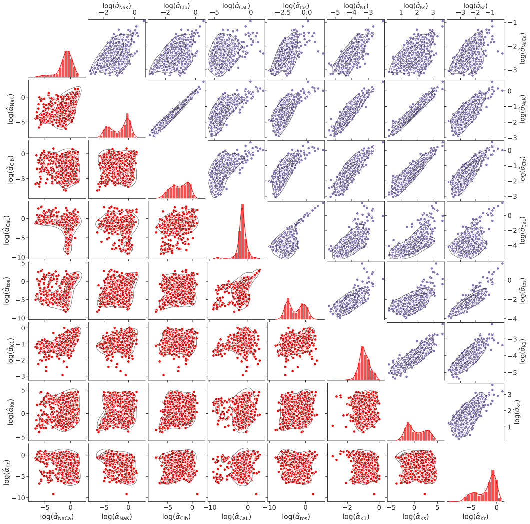
- Conclusion: the fitting procedure is **robust and accurate** under known conditions.

Illustrative Demonstration for a Subset of Cells



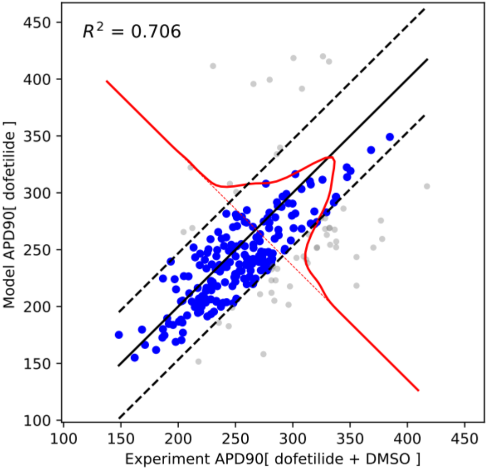
- Four representative actual myocytes.
- Parameter estimates $\hat{\boldsymbol{\theta}}$ shown as bar charts.
- Experimental AP waveform (t_j, V_j) compared to fitted model output $\hat{V}(t)$.
- Goodness-of-fit $p \approx 0.5$.
- Noise level $\hat{\sigma}$ visualized – shaded band.

The cell-specific model population



- 1200 cell-specific Shannon models accepted with $p > 0.3$.
- Interpret as a random sample from the phenotype distribution of healthy myocytes.
- Many estimands exhibit bimodal or skewed distributions.
- Most parameter pairs exhibit weak or no mutual correlation.
- Std errs appear more strongly correlated.
- Indicates high physiological variability and weak identifiability of individual conductances.

Application: Prediction of Dofetilide Response



- **Dofetilide administered in solution with DMSO** (Dimethyl Sulfoxide) which has non-spec EP effects.
- **DMSO effects** are measured only on population level: Distribution is $f\left[\Delta A^{\textbf{expr}}_{\textbf{veh}}(q)\right]$.
- **Solution effects** measured on paired (before-after drug) cells: $\Delta A_{\textbf{sol}}(j)$.
- **Action of drug** (30 nM dofetilide) is modelled as 30% reduction in G_{Kr}. **Effect is** $\Delta A^{\textbf{comp}}_{\textbf{drug}}(j)$.
- We assume total effect is additive and compare distributions:

$$f\left[\Delta A^{\text{expr}}_{\text{sol}}(j) - \Delta A^{\text{comp}}_{\text{drug}}(j)\right] \approx f\left[\Delta A^{\text{expr}}_{\text{veh}}(q)\right]$$

- **A good agreement found.**

Conclusion

Conclusions

- Demonstrated that cell-specific fitting of full APs at scale is feasible for large populations of cells.
- Provides tools for mechanistic prediction of drug effects.
- Open questions remain: the uniqueness of fit. Needs to be assessed further.

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References & Code and Data

- Simitev et al. (2025). Roy Soc Open Sci. 12(3): 241539
- Yang et al. (2025), PLOS One, PONE-D-25-13282 (under review)
- Lachaud et al. (2022). Cardiovasc Res, 118(15), 3112-3125.

Code and data: `https://doi.org/10.5281/zenodo.11191649`