National Physical Laboratory

Sensitive Hearts: Challenges with Sensitivity Analysis of Cardiac Models

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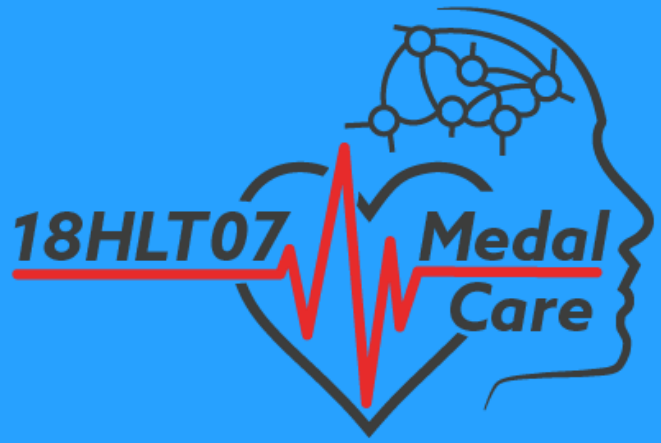
MathMet Conference, Paris, November 2022



Heart monitoring: electrocardiograms (ECGs)

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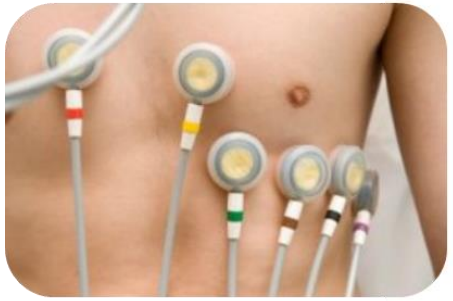
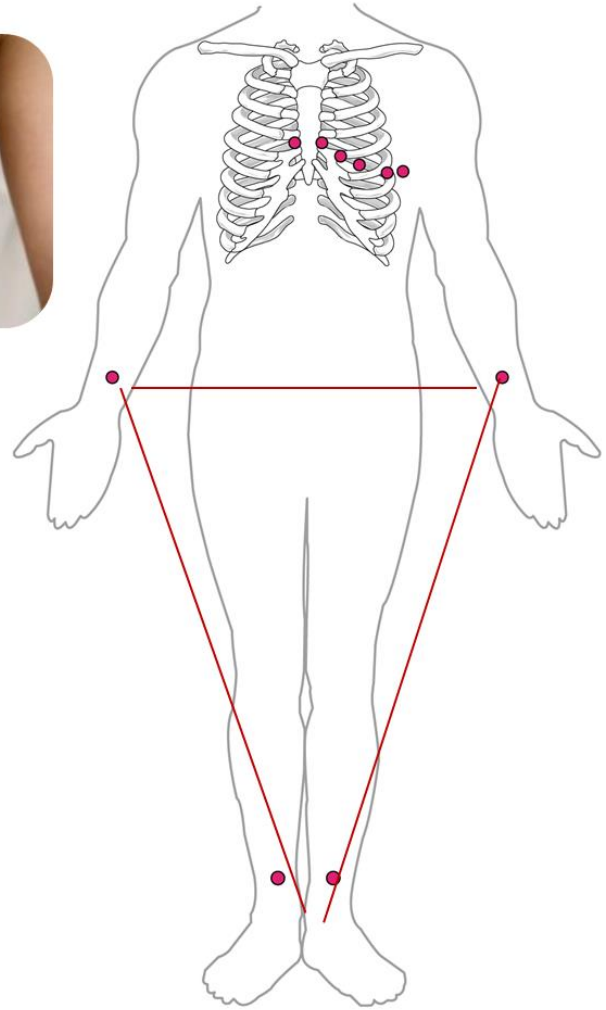
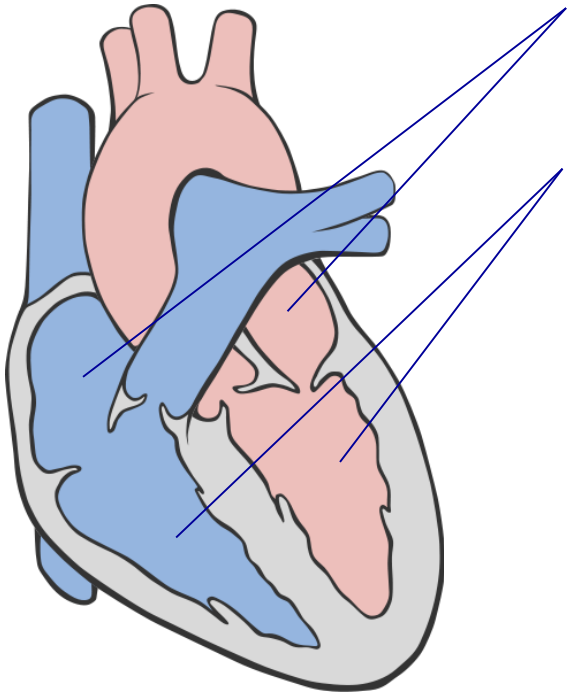
An ECG measures electrical activity from the heart



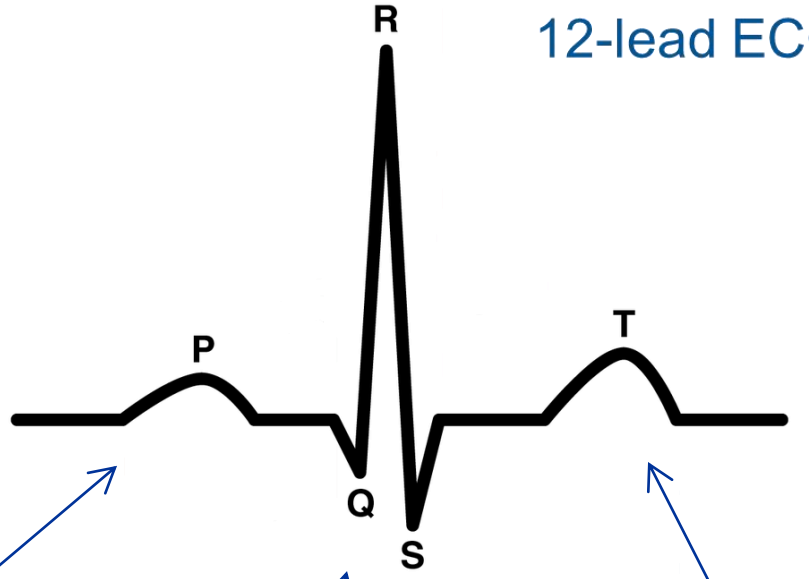
12-lead ECG





atria

ventricles



P wave
atria contract

QRS complex
ventricles contract

T wave
ventricles relax

MedalCare project

- Aimed to develop a validation strategy for cardiac arrhythmia classification algorithms based on multiparametric data analysis of electrocardiography (ECG) data.
- Used cardiac models to create a synthetic reference database.
- Applied “Turing test” via clinicians
- Analysed the synthetic data
  - Entire waveform and extracted parameters
  - Uncertainty quantification and sensitivity analysis
- Classified the results using advanced algorithms

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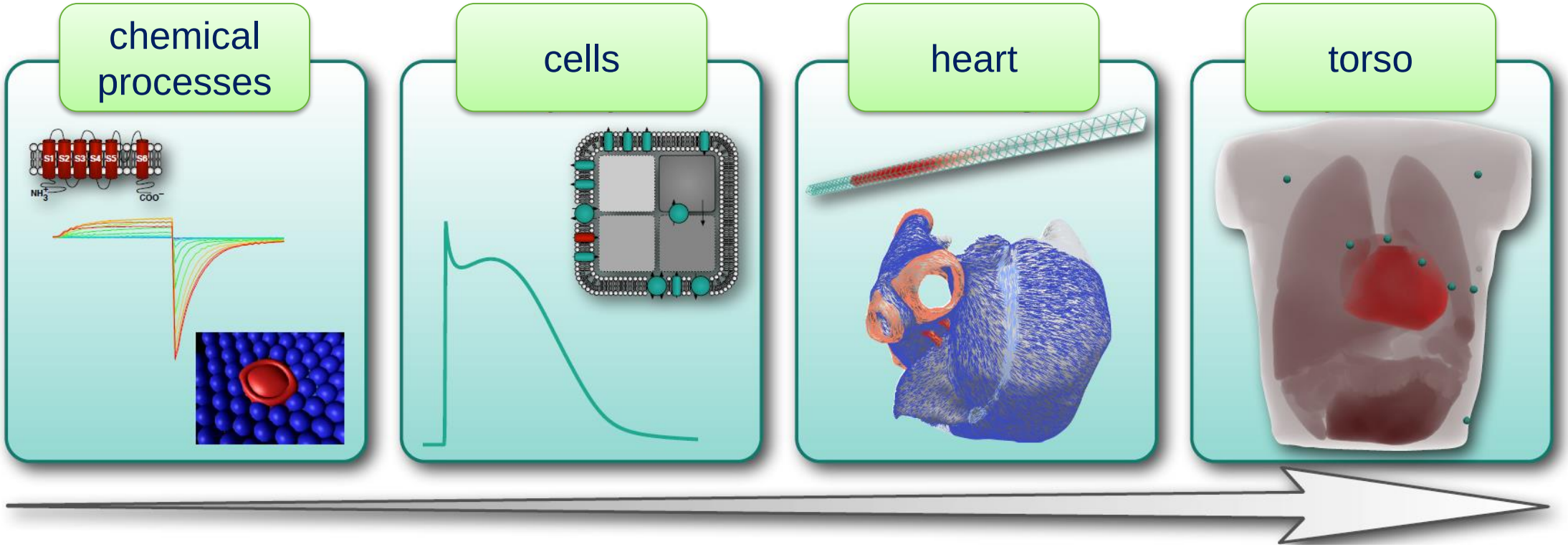
  Uncertainty quantification and sensitivity analysis
- Classified the results using advanced algorithms
- Some input parameters are difficult to measure
- Sensitivity analysis can tell us which input parameters we need to improve our knowledge of to affect particular aspects of the synthetic data

Cardiac models of electrophysiology

- Multi-scale models of electrophysiology are often used to generate synthetic ECGs



(slide from A. Loewe)

Cardiac models of electrophysiology

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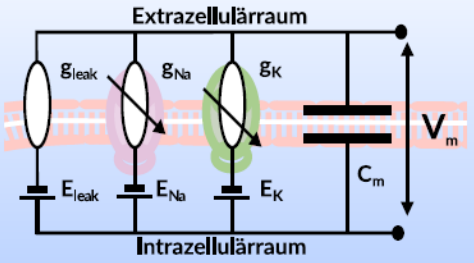
chemical processes	cells	heart	torso
ordinary differential equations (ODEs)	coupled ODEs	Reaction-diffusion model (monodomain)	Poisson's equation to compute body surface potentials

$$I_x = g_x \prod_i \gamma_i (V_m - E_x)$$

$$\frac{d\gamma_i}{dt} = \frac{\gamma_{i\infty}(V_m) - \gamma_i}{\tau_{\gamma i}(V_m)}$$



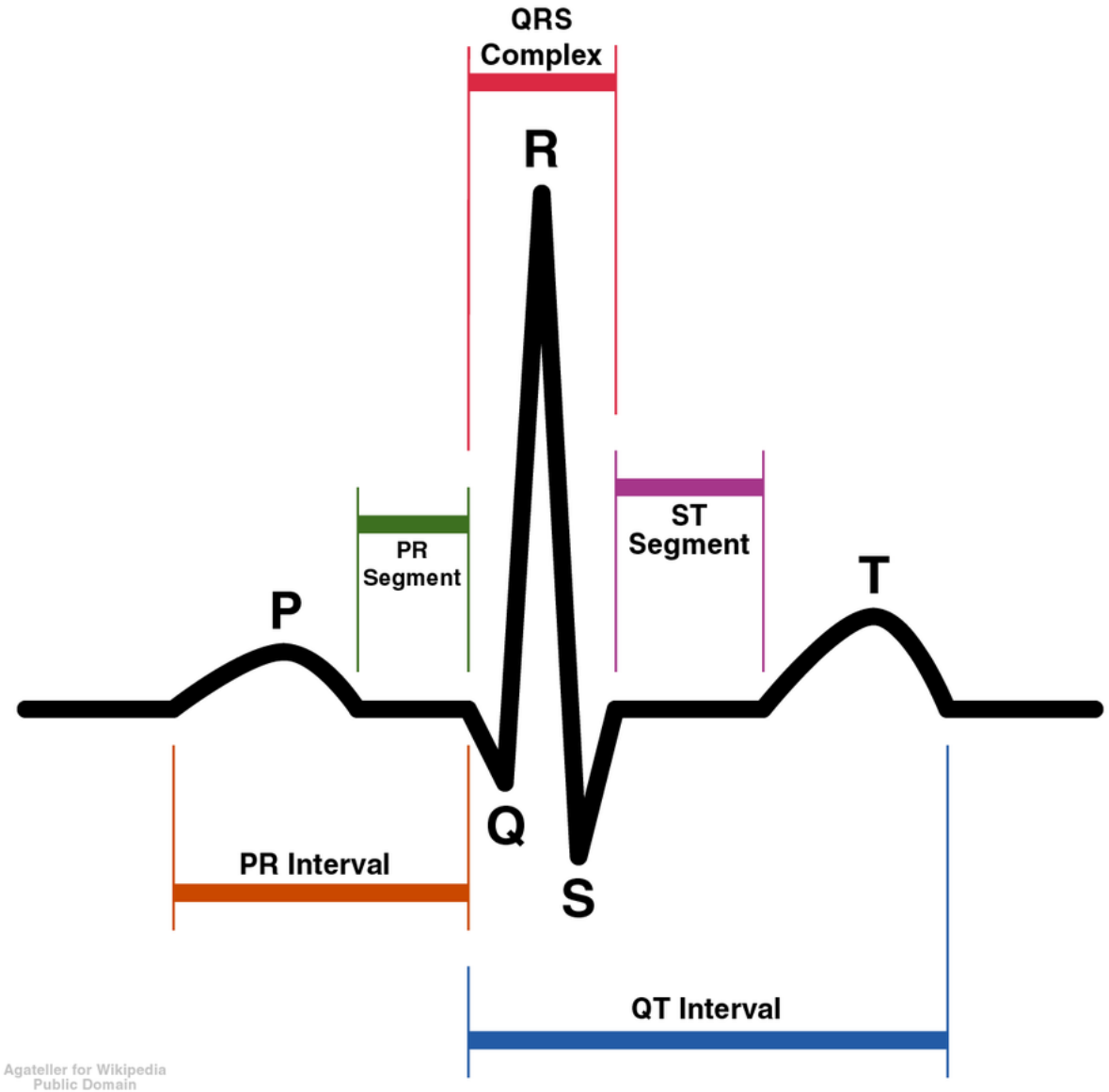
$$\frac{dV_m}{dt} = -\frac{\sum I_x + I_{stim}}{C_m}$$

$$\nabla \cdot (\sigma_i \nabla V_m) = \beta \left(C_m \frac{dV_m}{dt} + \sum I_x \right)$$

$$\nabla \cdot ((\sigma_i + \sigma_e) \nabla \Phi_e) = -\nabla \cdot (\sigma_i \nabla V_m)$$

(slide from A. Loewe)

Extracting features from the ECG



We extracted the same things from the synthetic ECG that a clinician would use for diagnosis

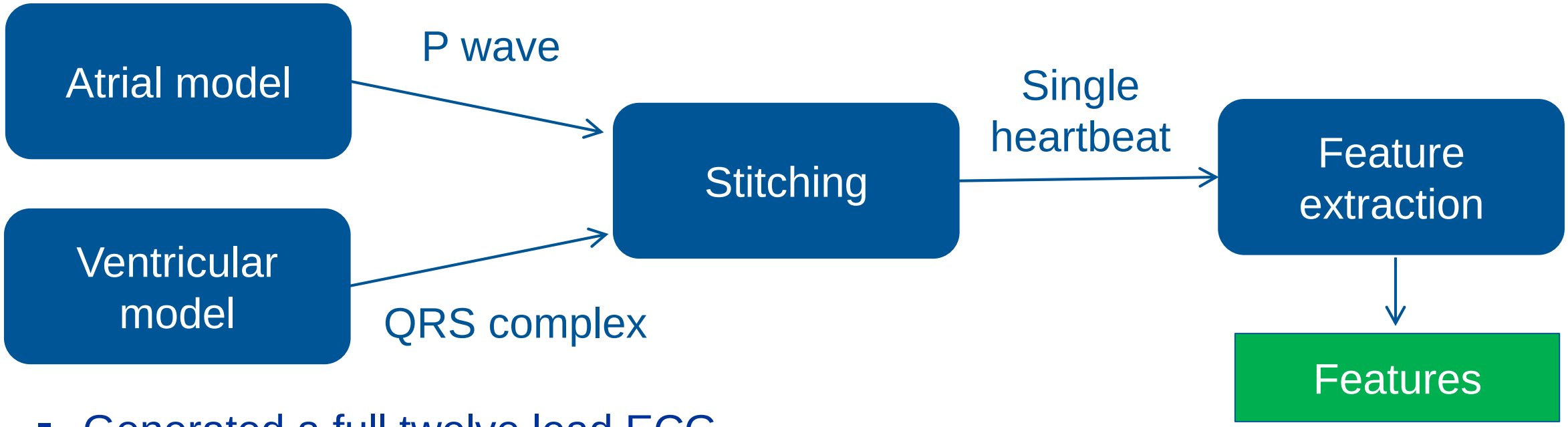
Generated ECGs are sets of (time, voltage) pairs at fixed time intervals.

Features can therefore be continuous or discrete:

- R, P, T peaks are continuous
- QT, QRS durations are discrete

Used an automated toolbox to detect so got some outliers

Model that generates ECG features



- Generated a full twelve lead ECG
- Effectively a single black box with multiple input parameters
- Used Sobol indices to look at sensitivity

  We used direct calculation; PTB project partners calculated via a polynomial chaos expansion

Sobol sensitivity coefficients

(Sobol, 1993)

- Apportion variance of the model outputs to different inputs through conditional expectation and conditional variance

$$Y = f(X_1, X_2, \ldots, X_N) = f(\mathbf{X})$$

$$S_i = \frac{\mathrm{Var}_{X_i}[E(Y|X_i = x_i)]}{\mathrm{Var}(Y)}$$

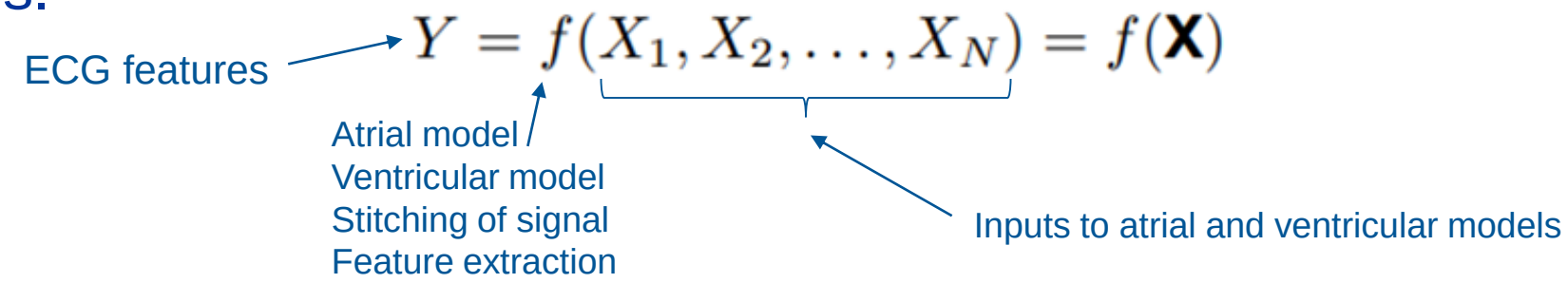
Main effect: variance of (the expected value of Y conditional on a fixed value of X_i), relative to total variance.
"Variability due to X_i acting alone"

$$S_i^T = \frac{E_{\mathbf{X}_{\sim i}}[\mathrm{Var}_{X_i}(Y|X_j = x_j \forall j \neq i)]}{\mathrm{Var}(Y)}$$

Total effect: expected value of (the variance of Y conditional on a fixed value of everything *apart from* X_i), relative to total variance.
"Variability due to X_i and all its interactions with the other inputs"

Direct calculation of indices

- Conditional expectation and variance require evaluation of multidimensional integrals.



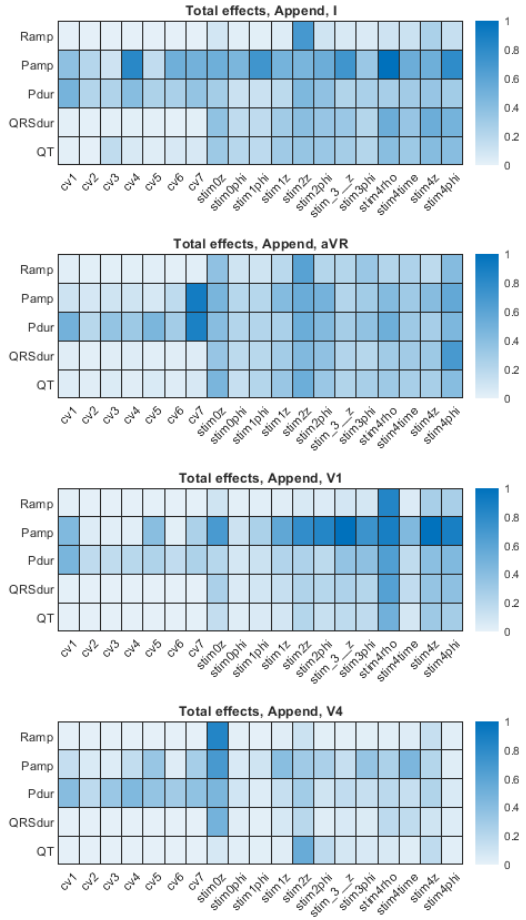
- Our model is a multi-stage black box, so we need a numerical approach to evaluate those integrals.

  Saltelli (2010) identified an efficient calculation approach: to get main and total effects for a model with k inputs using an N-term sum, need N(k+2) model runs.

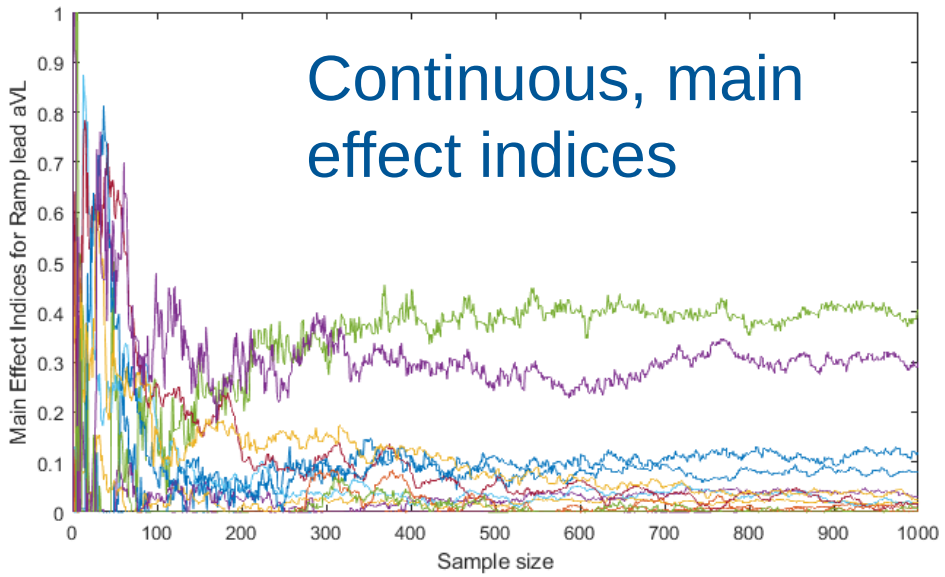
- 12 input parameters being varied, sample size N = 1000: 14000 model runs
- Sampled values based on quasi-random Sobol sequences.
- Look at convergence by keeping running totals and plotting against N.

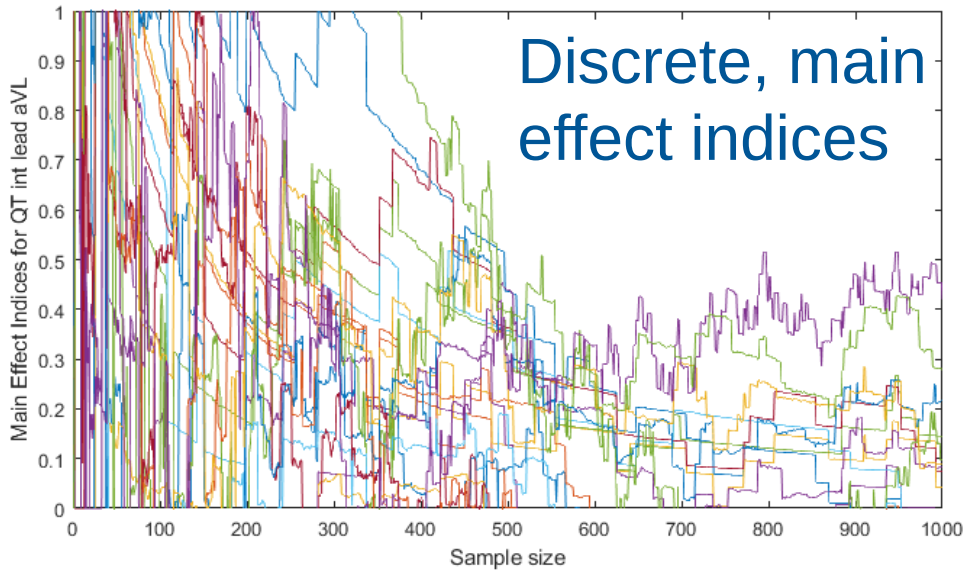
Physiological explanations

- Discussed results with the model owners.
- Provided physiological explanations for the input parameters that most strongly affected many of the features.



Continuous vs. discrete valued features

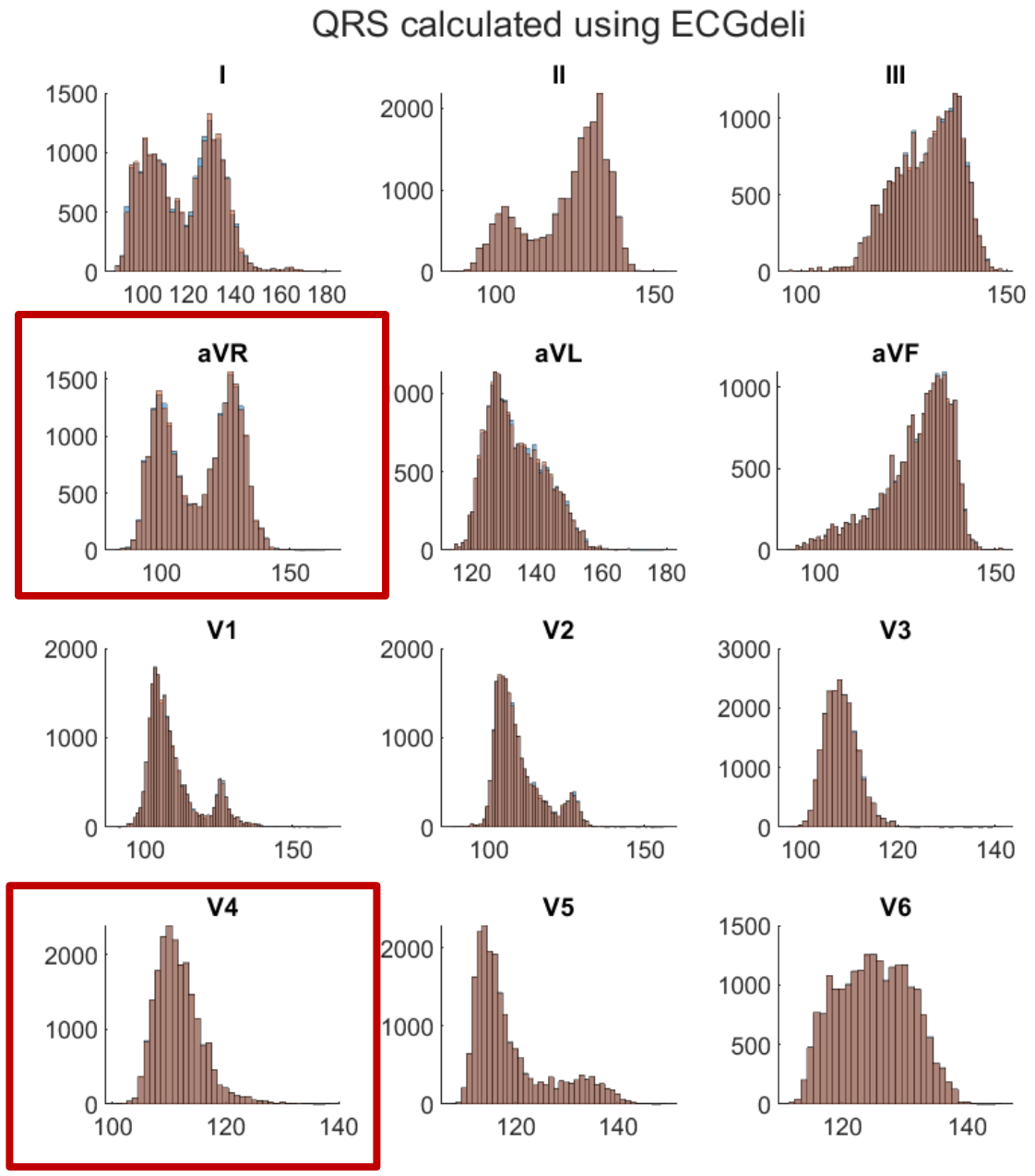




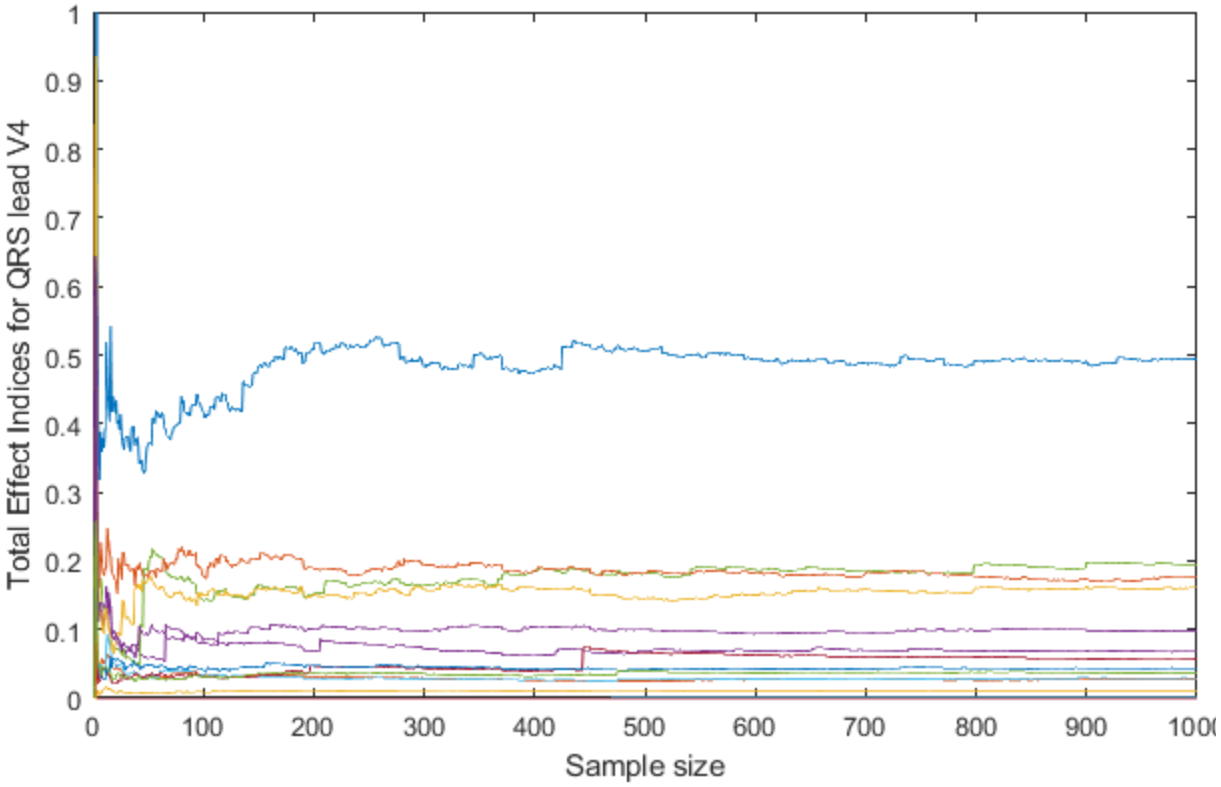
- PTB fitted a polynomial chaos expansion (PCE) to features data and extracted Sobol main effect coefficients.
- Comparison showed agreement, particularly for continuous-valued features.
- PCE not designed for discrete data: struggled to get good results for intervals and durations.
- Convergence generally worse for discrete data, but tried adding U[-0.5, 0.5] to make values continuous and it made no difference.

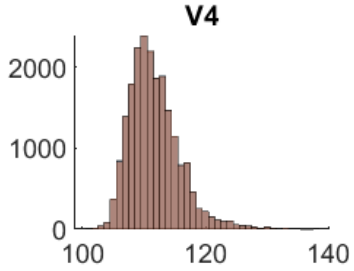
Compare QRS on two leads

- Distributions of calculated QRS durations for all leads show variation.
- Several have multi-modal distributions.
- Some have outliers.
- Focus on V4 and aVR from here on.

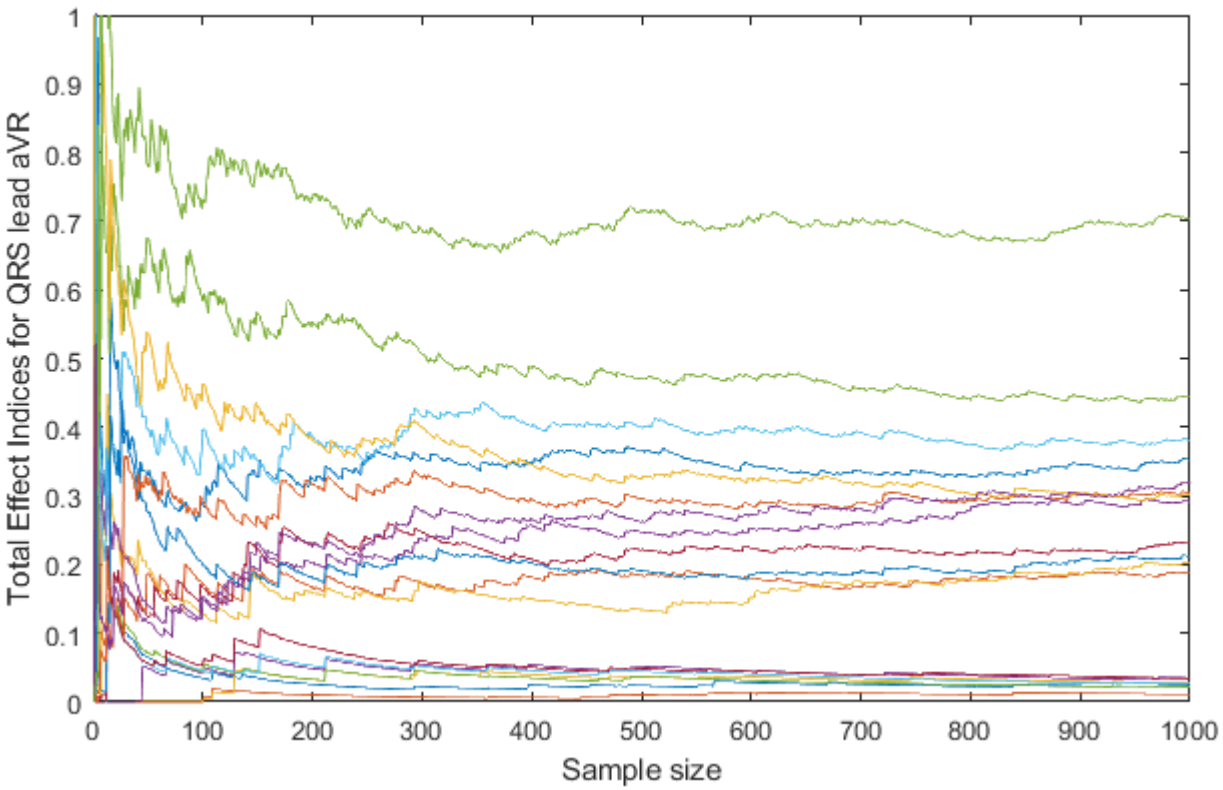


Convergence of total effect calculations

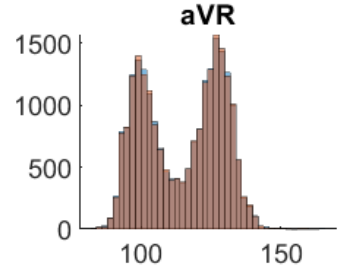




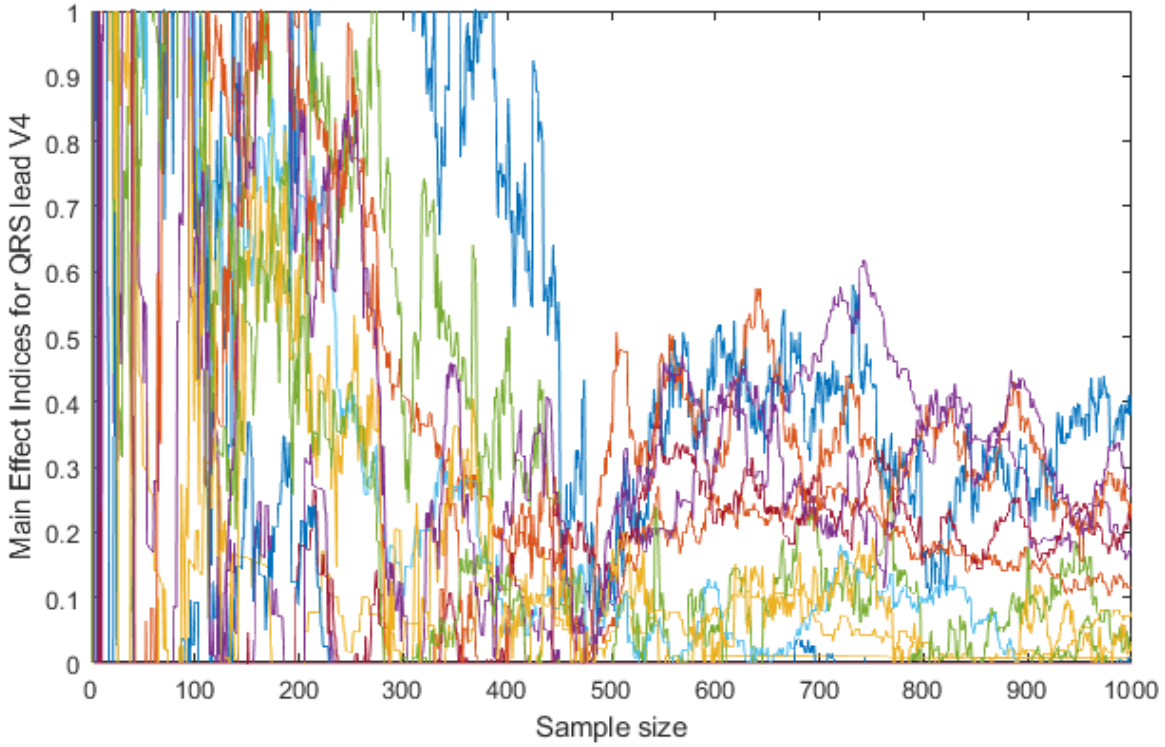
Convergence measure: 0.0027

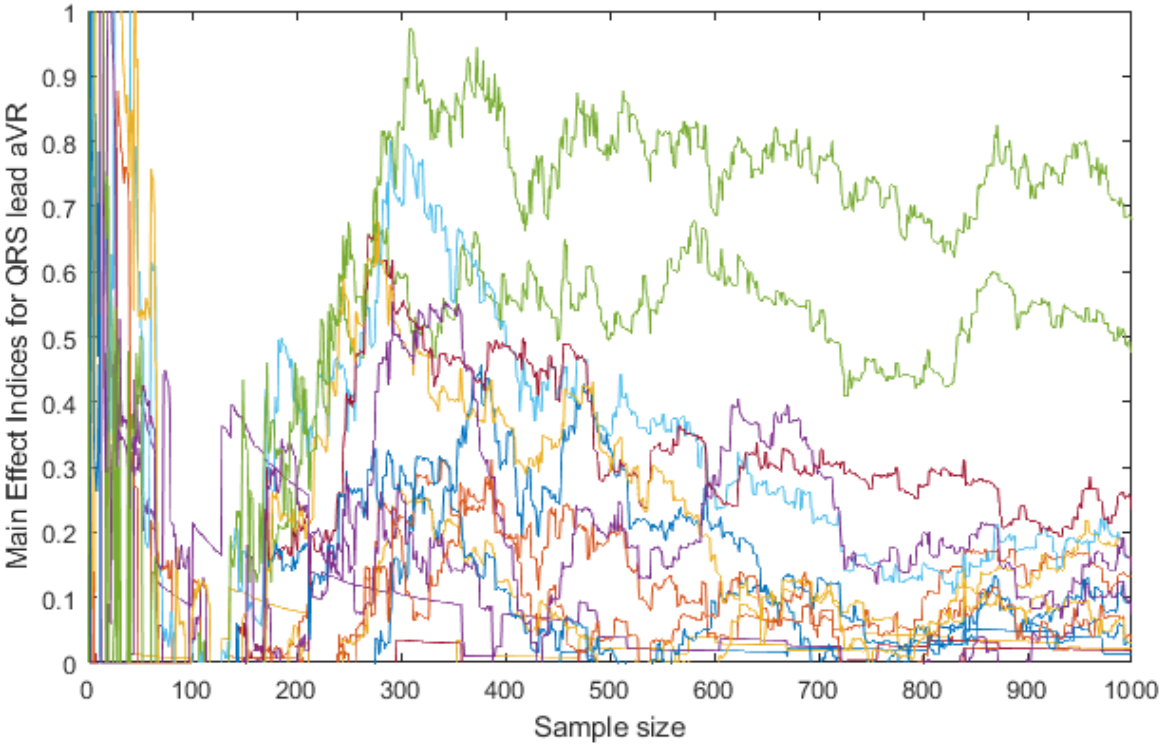


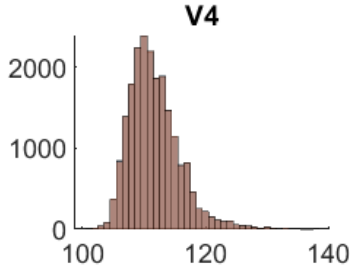
Convergence measure: 0.0126

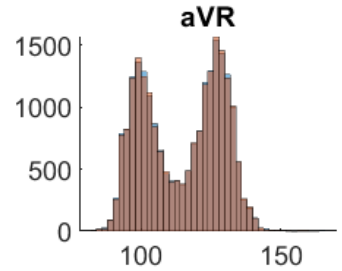


Convergence of main effect calculations

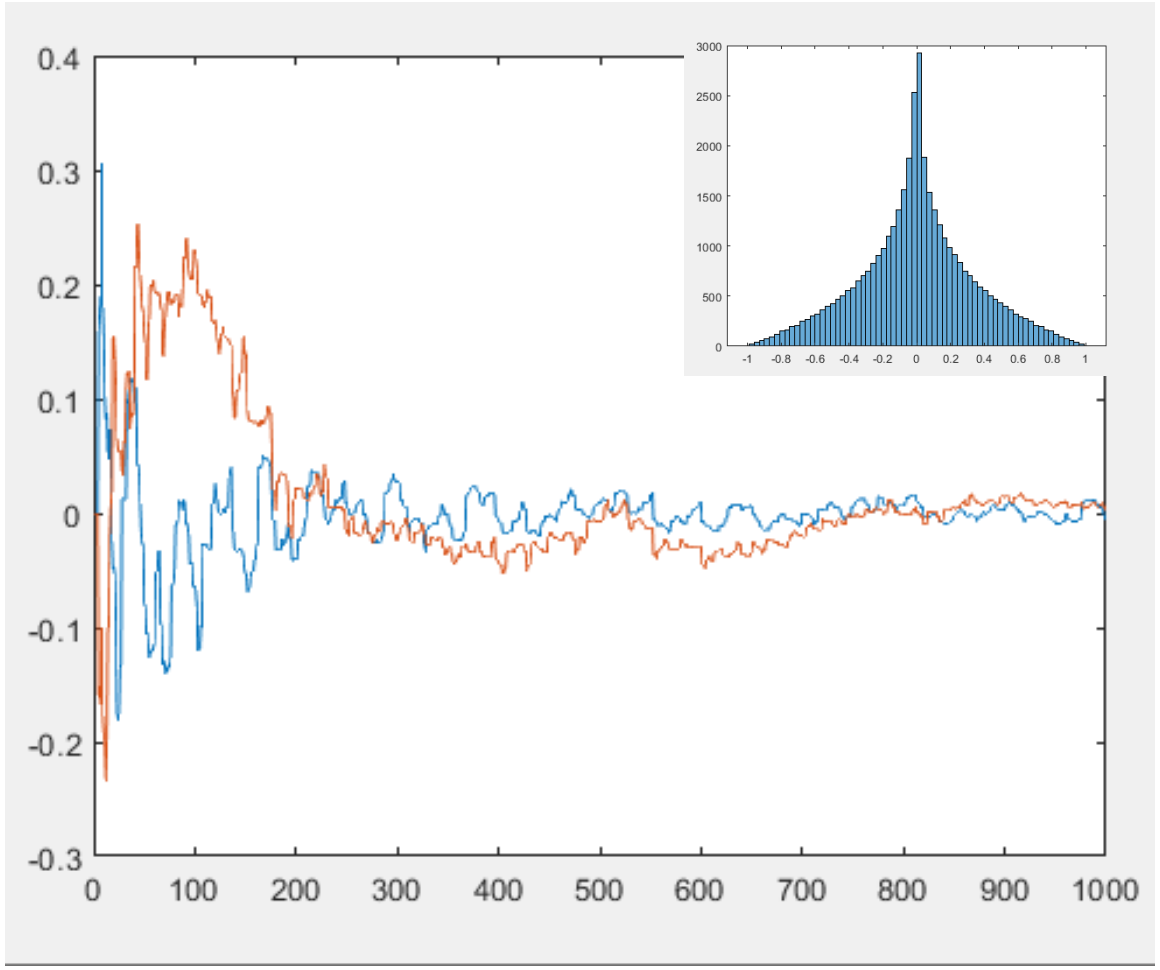


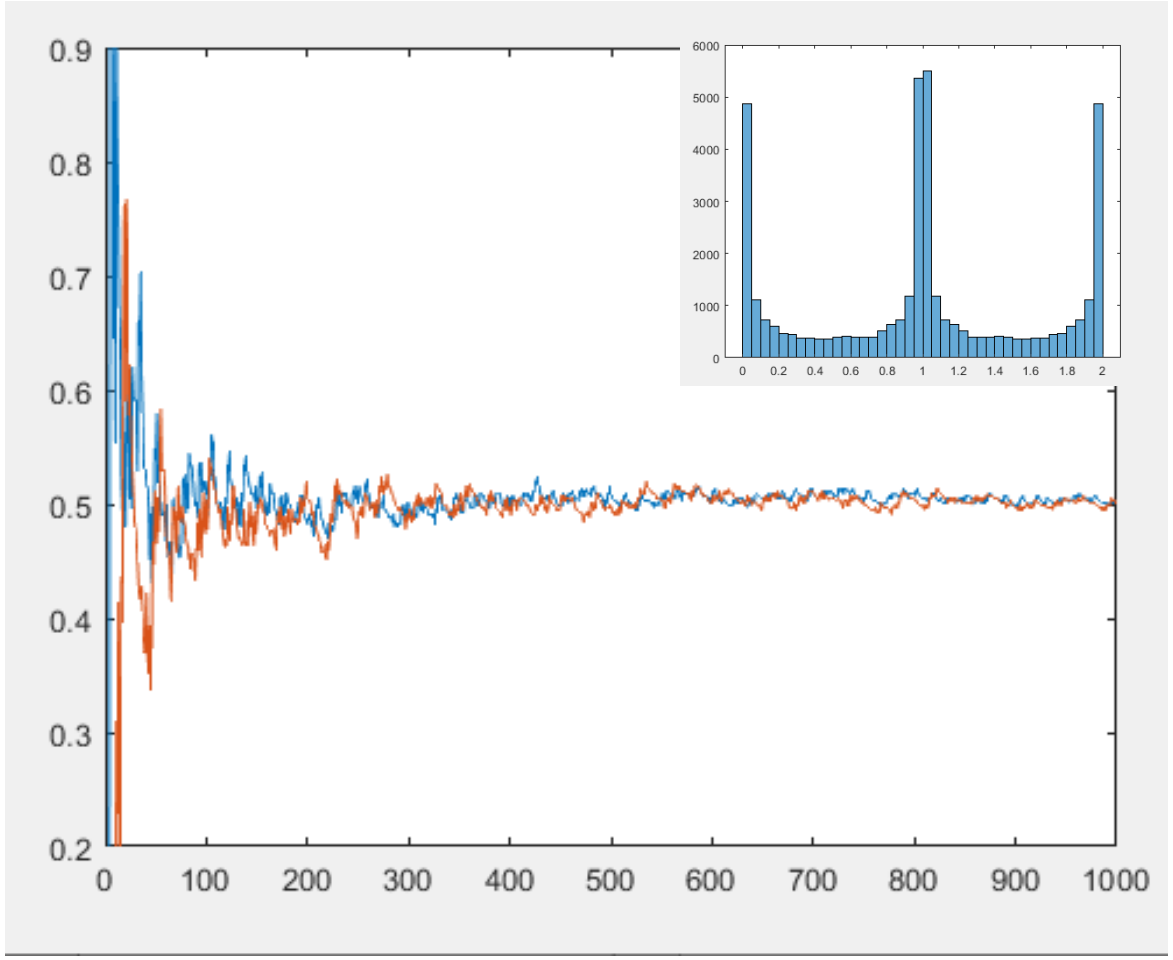






Toy problem





Perhaps counterintuitive: literature suggests multimodal functions are more difficult.

An open question

- What is the best method for quantifying sensitivity?

  Really depends on what question will be answered using the quantified value.
- Sobol indices are widely reported, but assume that variance is the most important measure of sensitivity.

  Can lead to contradictory results for highly skewed functions.
- Recent work has developed alternative metrics that consider the whole distribution.
- PAWN metric is obtained from the difference between CDFs generated using fixed values of one variable

  May offer an alternative with broader scope?

Concluding remarks

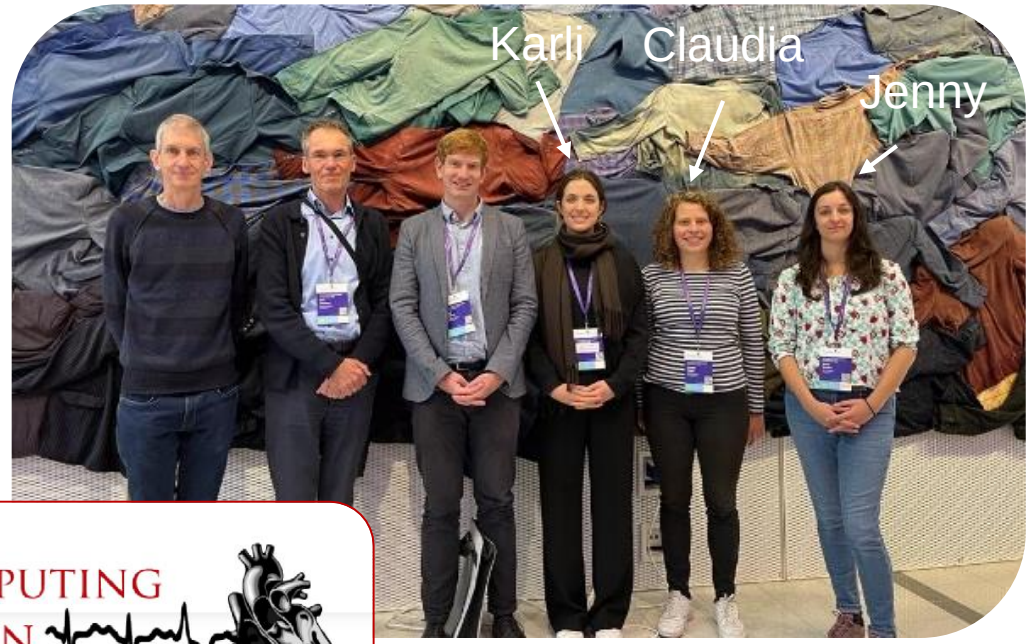
- Sensitivity analysis can help to identify which input parameters to a model would most affect the model results and so should be determined with lower uncertainty.
- Sobol indices are a common method of quantifying uncertainty.

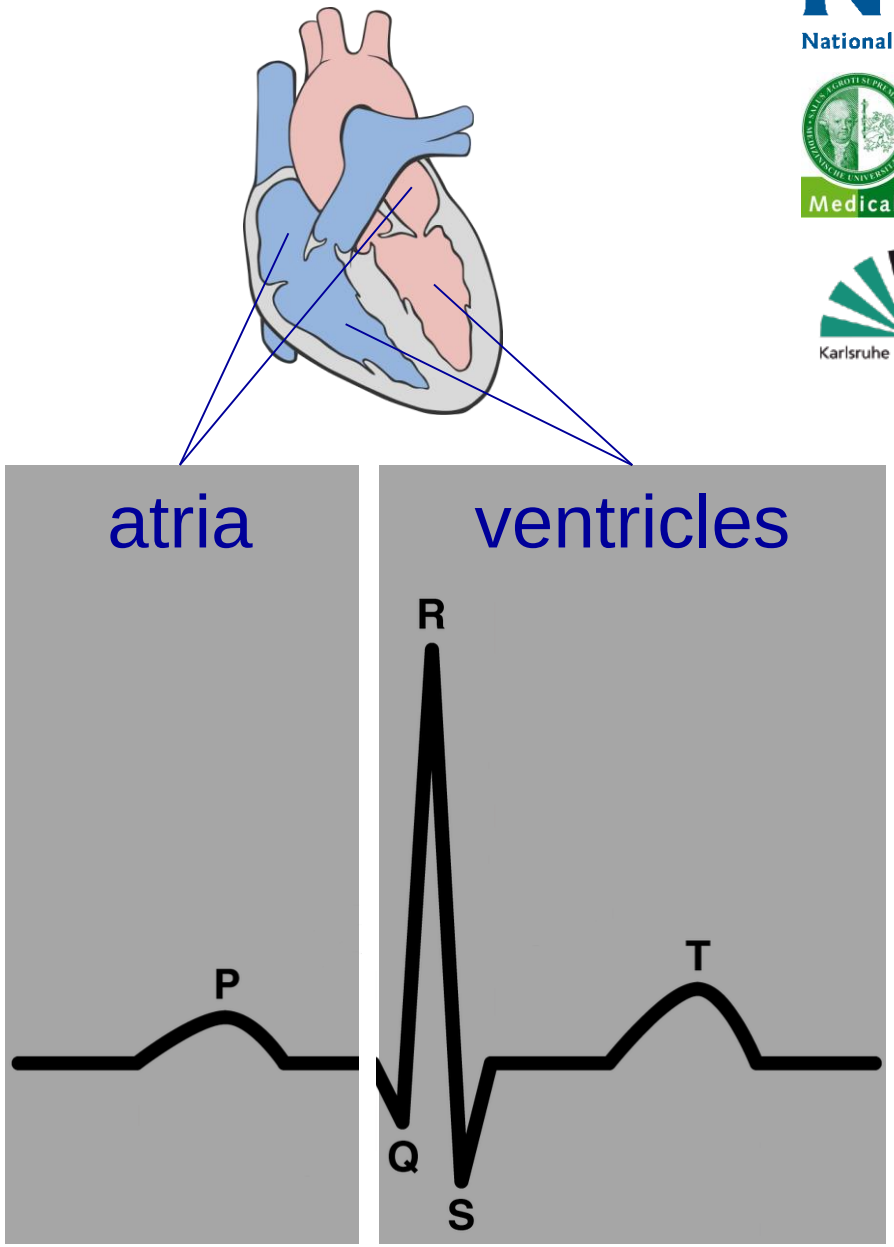
  But aren't the only candidate method.
- Checking convergence for Sobol index calculations is important.
- Total effects indices seem to converge more rapidly than main effects indices.
- The link between the distribution of the model result and its convergence behaviour is not clear.

  Particularly for high dimensional input spaces.

Thanks go to the wider team

- Claudia Nagel, Atrial modelling
- Karli Gillette, Ventricular modelling
- NPL, Sensitivity analysis





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