Parameter Inference in a Mathematical Model of the Pulmonary Circulation.

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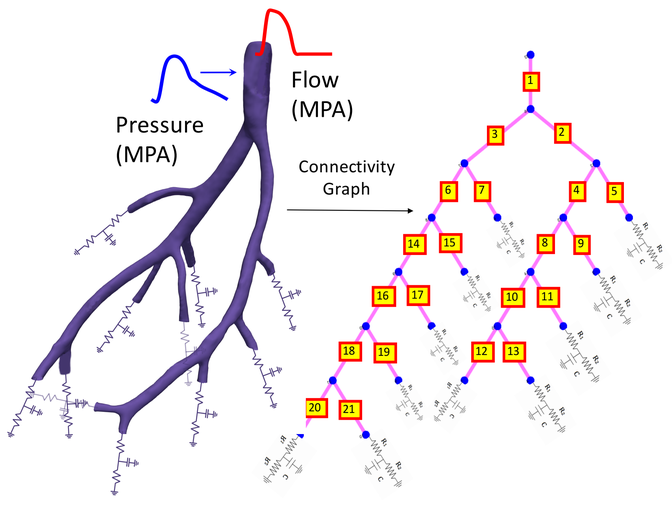
1. Introduction



Network of pulmonary vessels in a mouse lung

Pulmonary hypertension (PH) is one of the leading causes for right heart failure.
Parameter inference can be used to predict **pulmonary haemodynamics**, which helps clinicians diagnose and treat pulmonary hypertension in a systematic manner, but faces many challenges due to model complexity, high computational cost, and limited amount of data available. Often, the parameters cannot be measured in-vivo, and thus need to be learnt from the measured data.

We solve **partial differential equations (PDEs)** to find parameter estimates that minimise the Euclidean distance between measured and simulated time series of blood flow and pressure. We use **Markov Chain Monte Carlo (MCMC)** methods to **quantify uncertainty** around these estimates by approximately sampling parameters from their posterior distribution.
We significantly reduce the computational costs associated with solving the PDEs by using **Gaussian Processes (GPs)** to emulate the Euclidean distance.

2. Mathematical Model

The 1D fluids model, coupled with an Windkessel model predicts pulmonary arterial flow and pressure by solving a system of PDEs:

$$\frac{\partial q}{\partial t} + \frac{\partial}{\partial x}\frac{q^2}{A} + \frac{A}{\rho}\frac{\partial p}{\partial x} = -\frac{2\pi\mu r}{\delta}\frac{q}{A}, \quad (1)$$

$$p = p_0 + \frac{4}{3}f\left(1 - \sqrt{\frac{A_0}{A}}\right), \quad (2)$$

$$q(L,t) = \frac{1}{T}\int_0^T p(L, t-\tau)Z(\tau)d\tau, \quad (3)$$

$$\text{where } Z(\omega) = R_1 + \frac{R_2}{1 + i\omega C R_2}, \quad (4)$$

and x (cm), t (s): axial and temporal coordinates, p (mmHg): blood pressure, q (ml/s): blood flow rate, A (cm^2): cross-sectional area, f (mmHg): arterial network stiffness, R_1, R_2: Windkessel resistances enforced on the flow and C: compliance of arteries in the vascular bed.

3. Statistical Inference

Statistical model: $y_i = m_i(\boldsymbol{\theta}) + \epsilon_i$, where

- $\mathbf{y}$: noisy measured data,
- $\mathbf{m}(.)$: predicted data from (1)-(4) ,
- $\boldsymbol{\theta} = \{f, r_1, r_2, c\}$, where f: stiffness, r_1, r_2, c: resistances and capacitance adjustment factors for Windkessel parameters in (3)-(4),
- $\boldsymbol{\epsilon}$: additive Gaussian iid measurement errors.

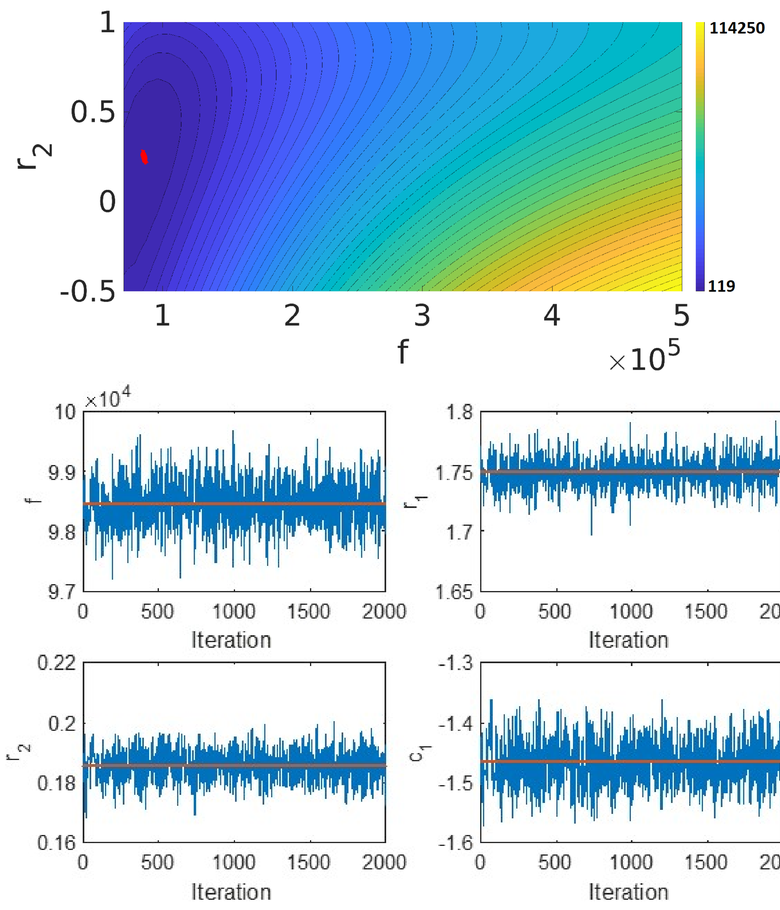
Employ **nonlinear constrained optimization** [1] to minimise the residual-sum-of-squares (S),

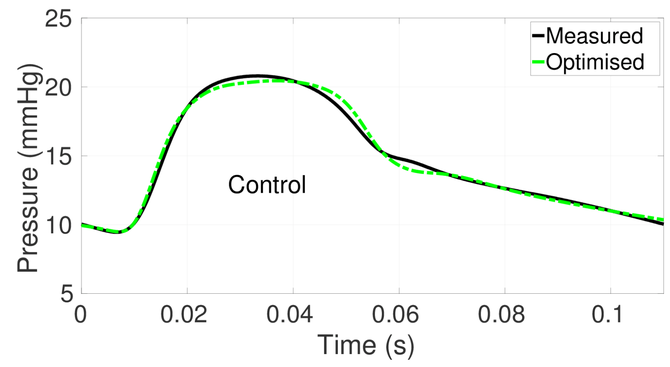
$$S = \sum_{i=1}^{n}(y_i - m_i(\boldsymbol{\theta}))^2. \quad (5)$$

Use GPs to emulate S, and quantify the uncertainty around the parameter estimates using **Adaptive Riemann Manifold Hamiltonian Monte Carlo (ARMHMC)** [2].

4. Results

Results are shown for a healthy mouse. In the left figure below, S exhibits unimodality in 2D for two of the parameters. Markov chains (superimposed in red) explore the regions of high likelihood or high posterior probability. In the right figure: the optimised pressure waveform follows closely the measured pressure.





We consider:

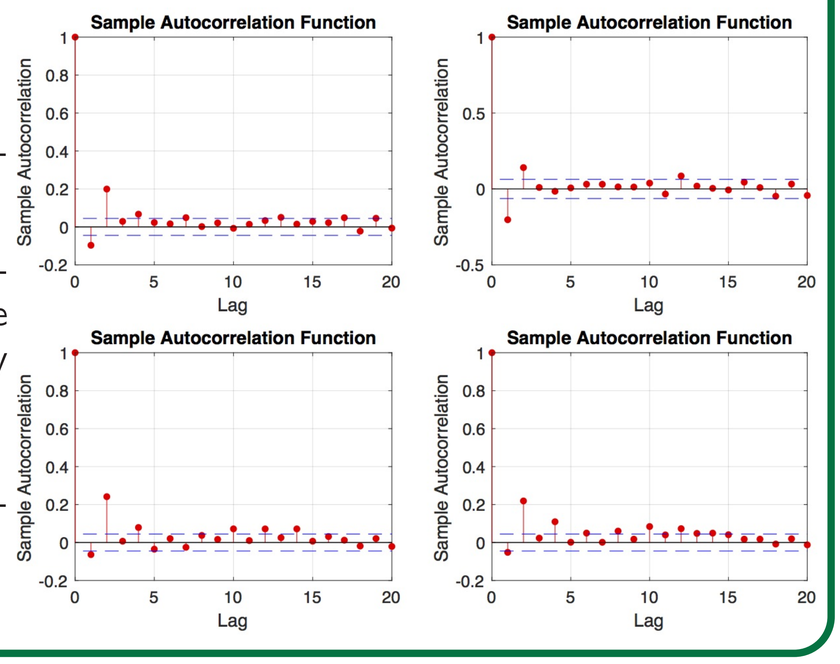
- Posterior distribution $\propto$ prior $\times$ likelihood.
- Weakly informative prior for the parameters $\boldsymbol{\theta}$.
- Inverse-Gamma prior for the noise variance.
- Normally distributed data $\mathbf{y}$.

The resulting Markov chains fluctuate around the optimised values (red vertical lines) – see left figure.

Investigate correlation between samples and report:

- Autocorrelation function (ACF) registers a decrease from lag 1.
- On average, 50% of the samples are independent, as given by the effective sample size (ESS), which corrects the total sample size by the autocorrelation.

The Markov chains, and the ACF and ESS are obtained based on MCMC combined with emulation.



5. Discussion

- Successfully predicted the pulmonary haemodynamics in a healthy mouse by inferring parameter values and quantifying uncertainty using MCMC schemes.
- Coupling MCMC with emulation leads to significant drop in computational costs compared to explicitly solving the PDEs (from several weeks or months down to a few days).
- Work can be extended to diseased mouse and human data.

6. Acknowledgements

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7. References

[1] M. Paun et al. Parameter inference in the pulmonary circulation of mice. In *Proceedings of the 32nd IWSM*, volume 1, pages 190–195, 2017.

[2] M. Girolami et al. Riemann manifold Langevin and Hamiltonian Monte Carlo methods. *J. of the Royal Statistical Society, Series B (Methodological*.

[3] M. Paun et al. MCMC methods for inference in a mathematical model of pulmonary circulation. *Statistica Neerlandica*, 2017. Accepted.

[4] M.U. Qureshi et al. A computation study of pulmonary haemodynamics in healthy and hypoxic mice. *Biomechanics and Modelling in Mechanobiology*, 2018. Submitted.