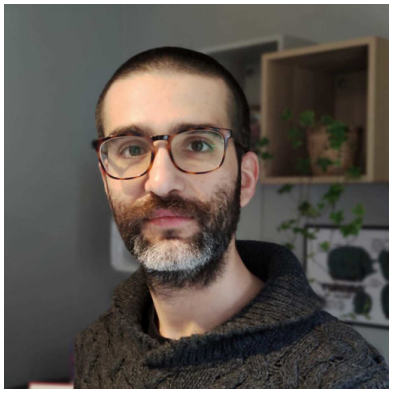
CompBioMed
A Centre of Excellence in Computational Biomedicine

e-Seminar series

e-Seminar #21

Use of Gaussian Process Emulators in Cardiovascular and Musculoskeletal Biomechanics



22 February 2022

The e-Seminar will start at 3pm CET / 2pm GMT

Presenter:
Dr Ivan Benemerito
(The University of Sheffield)

Moderator:
Tim Weaving
(University College London)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with:

VPH Institute
Building the Virtual Physiological Human

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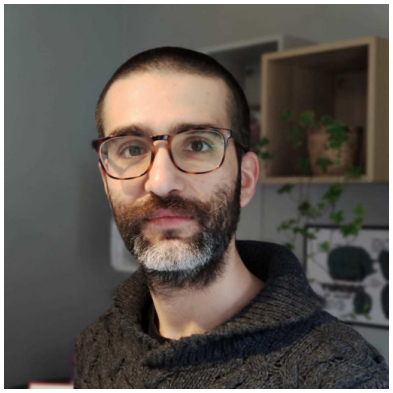

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Welcome!

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INSIGNEO

Institute for *in silico* Medicine

Use of Gaussian Process Emulators in cardiovascular and musculoskeletal biomechanics

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NHS Foundation Trust

Motivation

- Regulatory bodies require the assessment of models' credibility (VVUQ)

- Input parameters of computational models are often uncertain

HOW TO QUANTIFY THE IMPORTANCE OF THE INPUT PARAMETERS OF A COMPUTATIONAL MODEL?

Sobol's sensitivity analysis (SSA)

Decomposition of output variance into contribution from the variance of individual inputs or combinations of them

SSA quantifies the strength of the input/output dependency of a model [1]

When to use SSA?

- Biomarker identification → cardiovascular application
- Model reduction → musculoskeletal application

$$V_f = \sum_{i=1}^{d} V_i + \sum_{1 \le i < j \le d} V_{ij} + \cdots + V_{1,\ldots,d}$$

- O(1000*N) model evaluation [2]

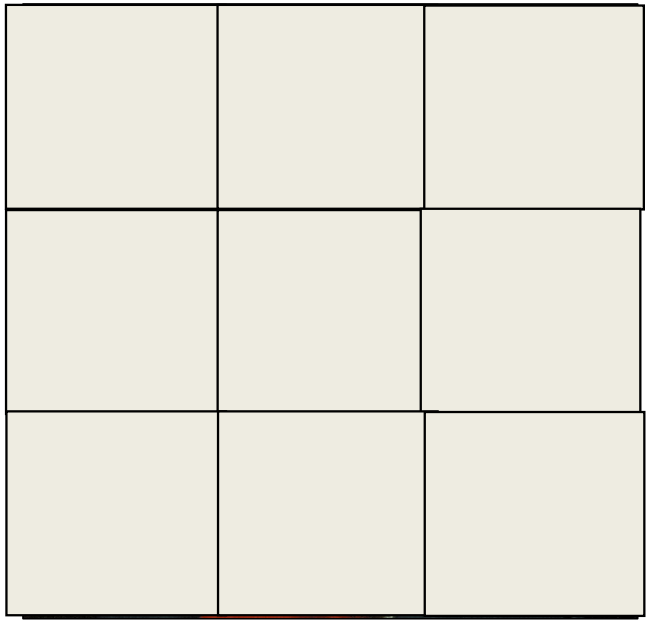
How do you explore the input space of a computational model?
What to do if the simulations are too onerous?

[1] Sobol, 2001 [2] Saltelli, 2002

Statistical emulators

An emulator is a statistical approximation of a simulator

- $\text{mean}\left(\check{f}(x)\right) = f(x)$
- Give estimates on their uncertainty: how likely is $\text{mean}\left(\check{f}(x)\right)$ to be close to $f(x)$?
- Bayes' theorem
- $\check{f}(x_i) = f(x_i)$



Rasmussen and Williams, 2005

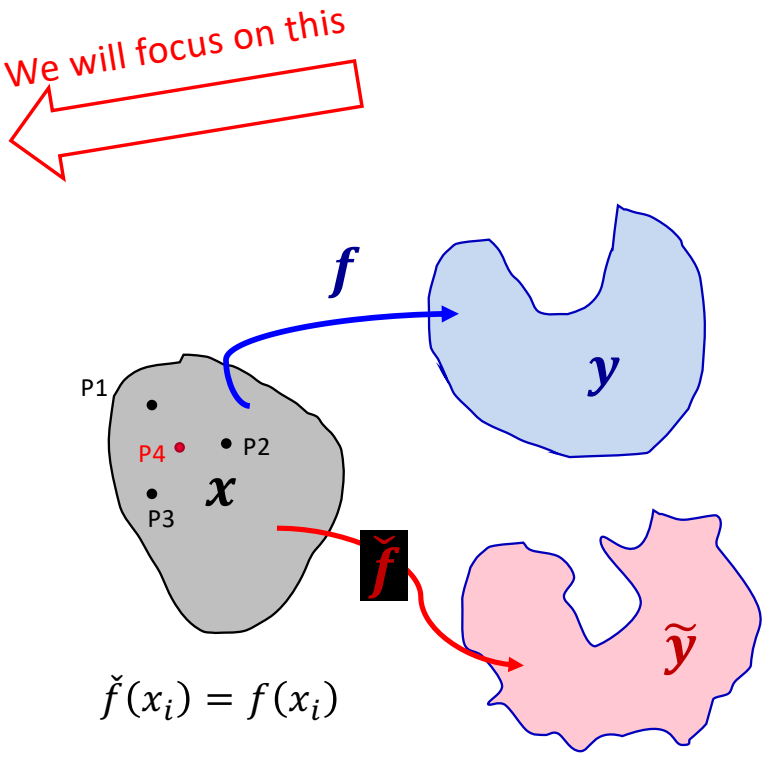
When to use an emulator?

Interpolation (and sensitivity analysis…)

- The input space is known but only partial observations are available
- Aim: To approximate the input/output map from a limited number of simulator runs

Forward propagation of uncertainties

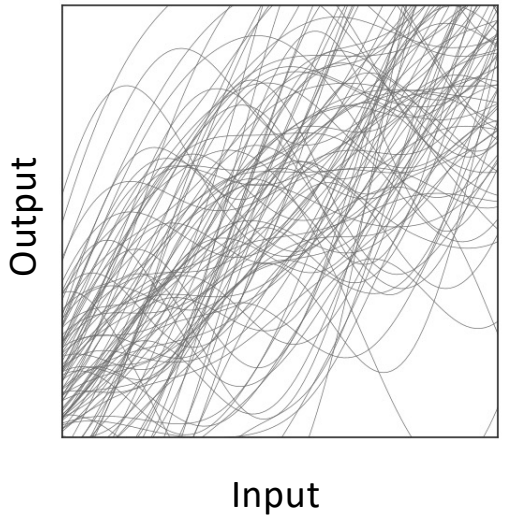
- The input parameters are uncertain
- Aim: To emulate the distribution of output under a prespecified input distribution



Rasmussen and Williams, 2005

Gaussian Process Emulators (GPE)

- Probability distribution over function space
- Kernel based methods
- Assumes smooth input/output map
- Prior and posterior distributions



Rasmussen and Williams, 2005

GPE: training

- Kernel is constructed from training points (generic hyperparameters)
- **Training**: tuning of hyperparameters in order to minimise a loss function

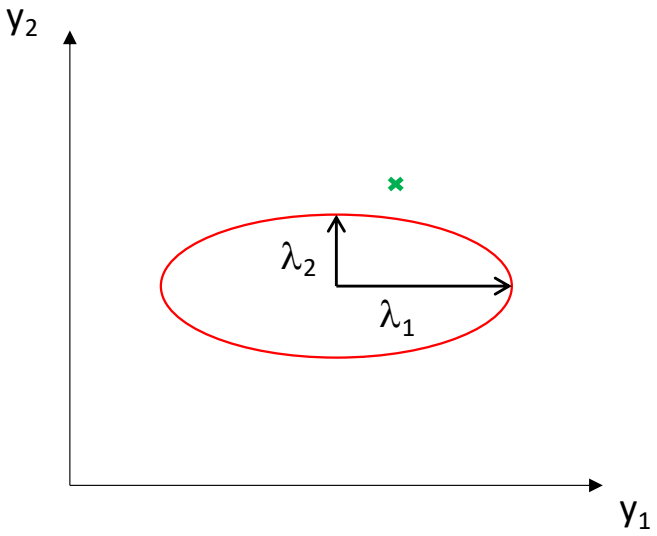
$$f(\mathbf{x}) \sim \mathcal{GP}\left(m(\mathbf{x}), k(\mathbf{x}, \tilde{\mathbf{x}})\right)$$

Mean

Covariance

Rasmussen and Williams, 2005

GPE: training



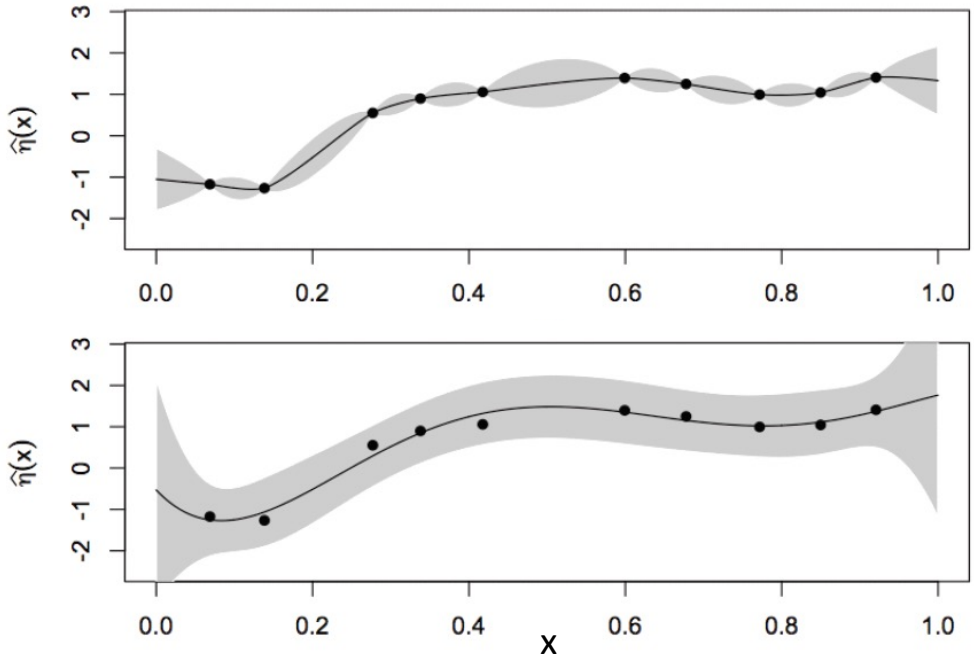
Optimisation of parameters maximises the fit to observed data points

$$\mathcal{N}(\mathbf{y}|\mathbf{0},\mathbf{K}) = \frac{1}{(2\pi)^{\frac{n}{2}}|\mathbf{K}|^{\frac{1}{2}}}\exp\left(-\frac{\mathbf{y}^{\top}\mathbf{K}^{-1}\mathbf{y}}{2}\right)$$

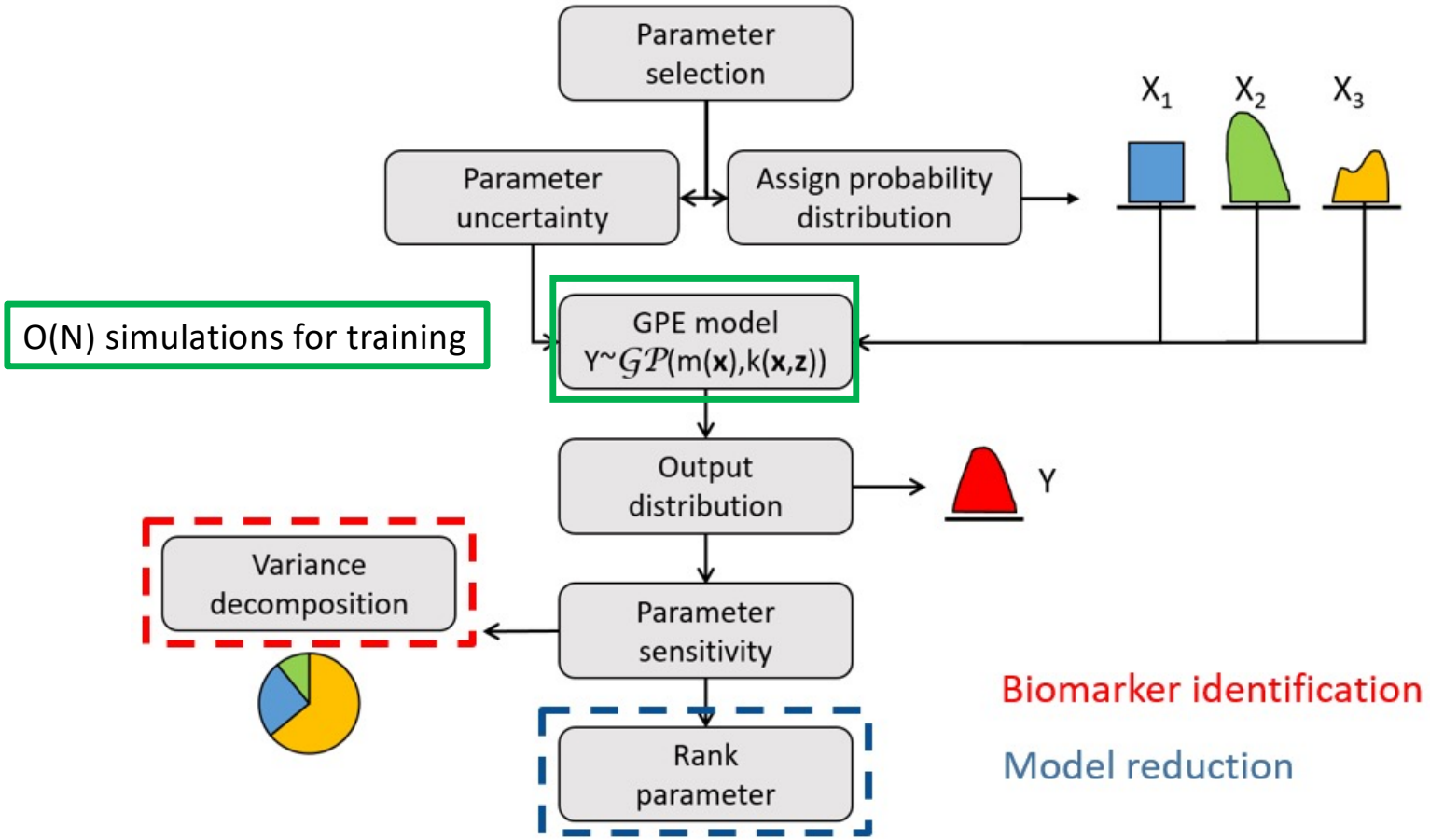
$$\mathbf{K} = \mathbf{R}\Lambda^{2}\mathbf{R}^{\top}$$

Diagonal elements of Λ: length of semi-axes
R rotation matrix

GPE vs other methods



Emulators for sensitivity analysis



Melis et al., 2017

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Use of Gaussian Process Emulators for the identification of clinically-viable biomarkers for ischaemic stroke

Ivan Benemerito[1,2], Ana Paula Narata[4], Andrew Narracott[1,3], Alberto Marzo[1,2]

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2. Department of Mechanical Engineering, The University of Sheffield, UK
3. Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, UK
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The University Of Sheffield.

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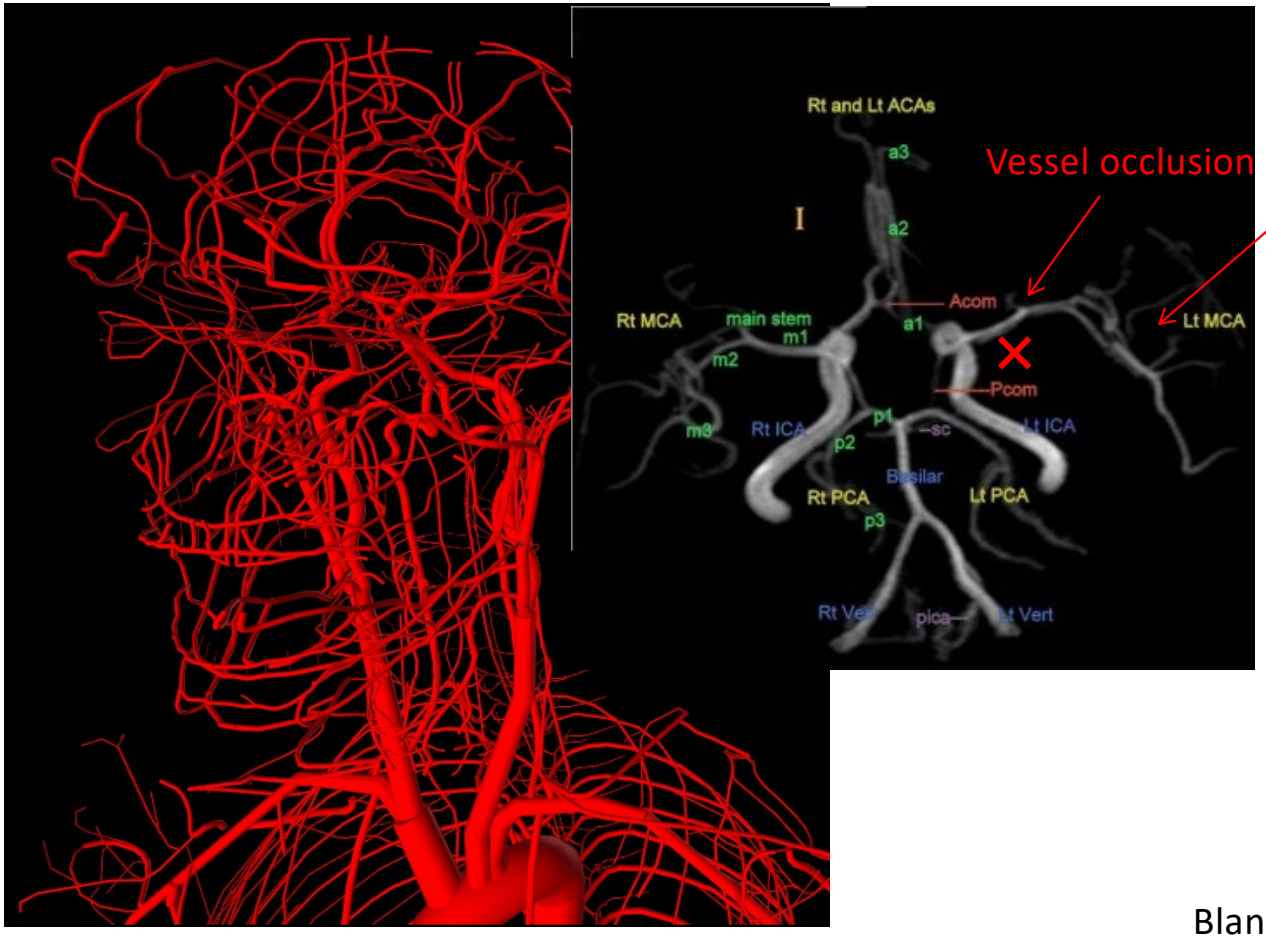
Circle of Willis (CoW) and ischaemic stroke (IS)

CoW: ring of arteries that distributes blood to various brain districts

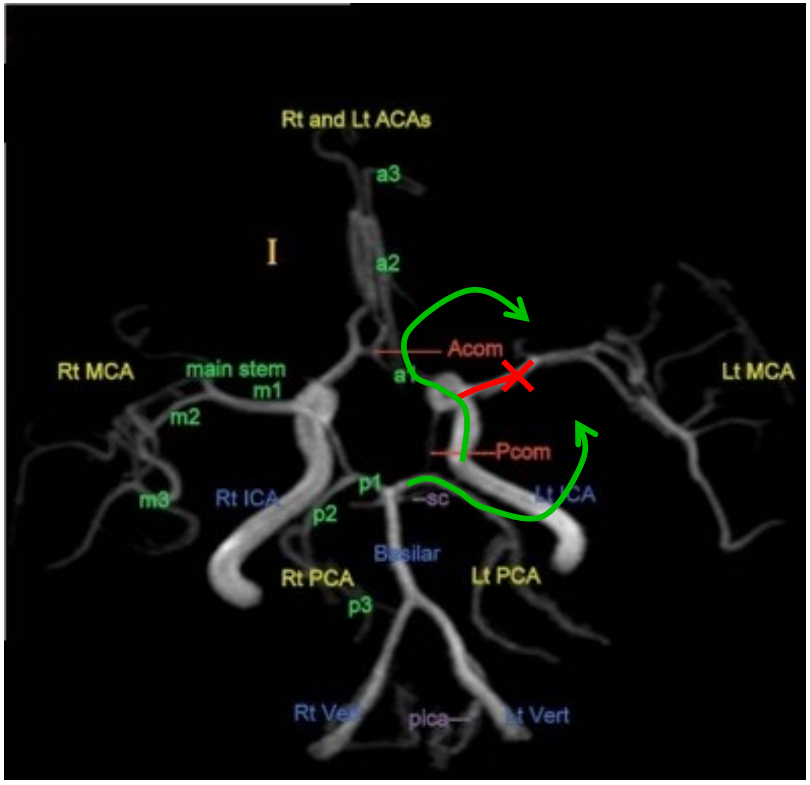
IS: occlusion of a major intracranial vessel



Blanco et al., 2014

Leptomeningeal anastomoses (LMAs)

- Small vessels that connect different districts of the brain
- Only active during stroke
- Better post-stroke outcome in patients with “good” LMAs

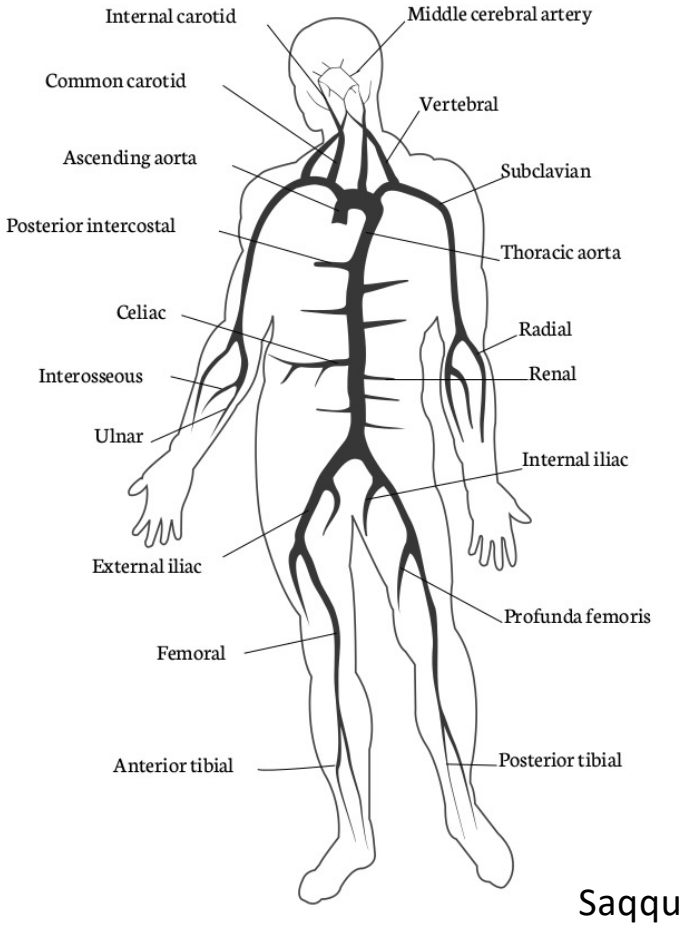


Brozici et al, 2003

Transcranial Doppler ultrasound (TCD)

- Used in IS diagnostic
- Measures blood velocity
- Cheap and fast to use

- Does not inform on distal perfusion



Melis A. (2017) PhD Thesis, http://etheses.whiterose.ac.uk/19175/

Saqqur et al., 2019

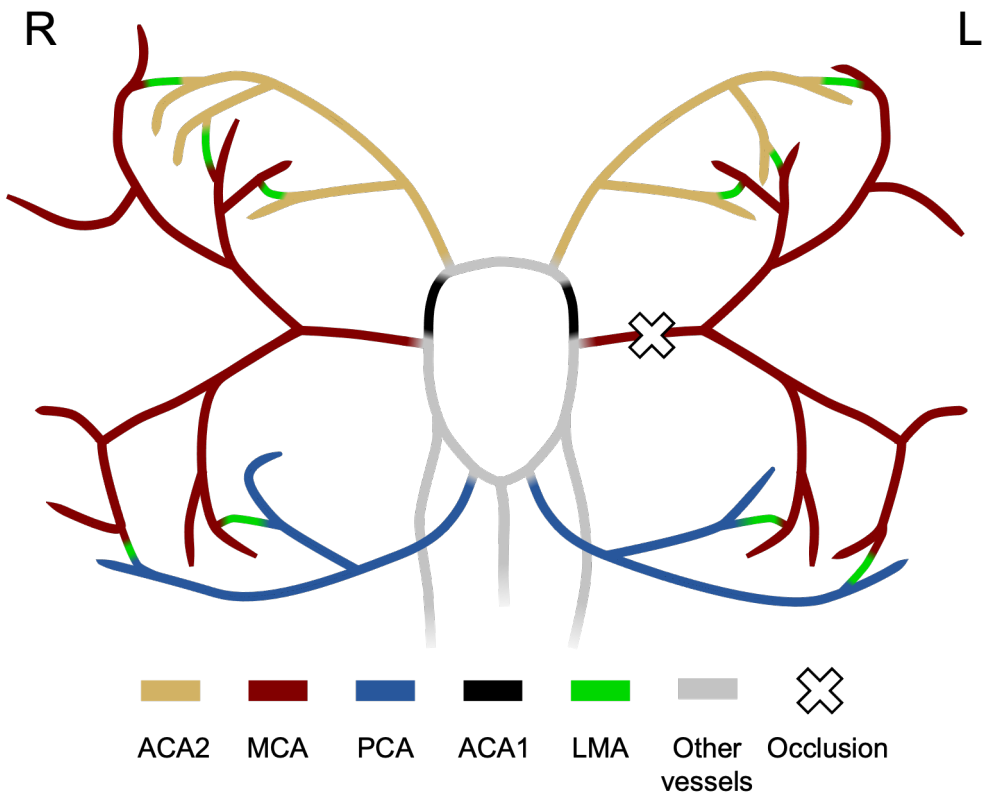
Research question

Is it possible to use TCD measurements to identify biomarker for distal perfusion following an ischaemic occlusion of the middle cerebral artery?

- Develop a mechanistic model of the LMA
- Develop a statistical emulator of the mechanistic model
- Perform sensitivity analysis to identify biomarkers
- Perform characterisation of the biomarkers

Mechanistic model

- 1D representation of the cerebral circulation
- Input: radii, Young's modulus, length
- Output:
  - Velocity
  - Flow rate
  - Perfusion



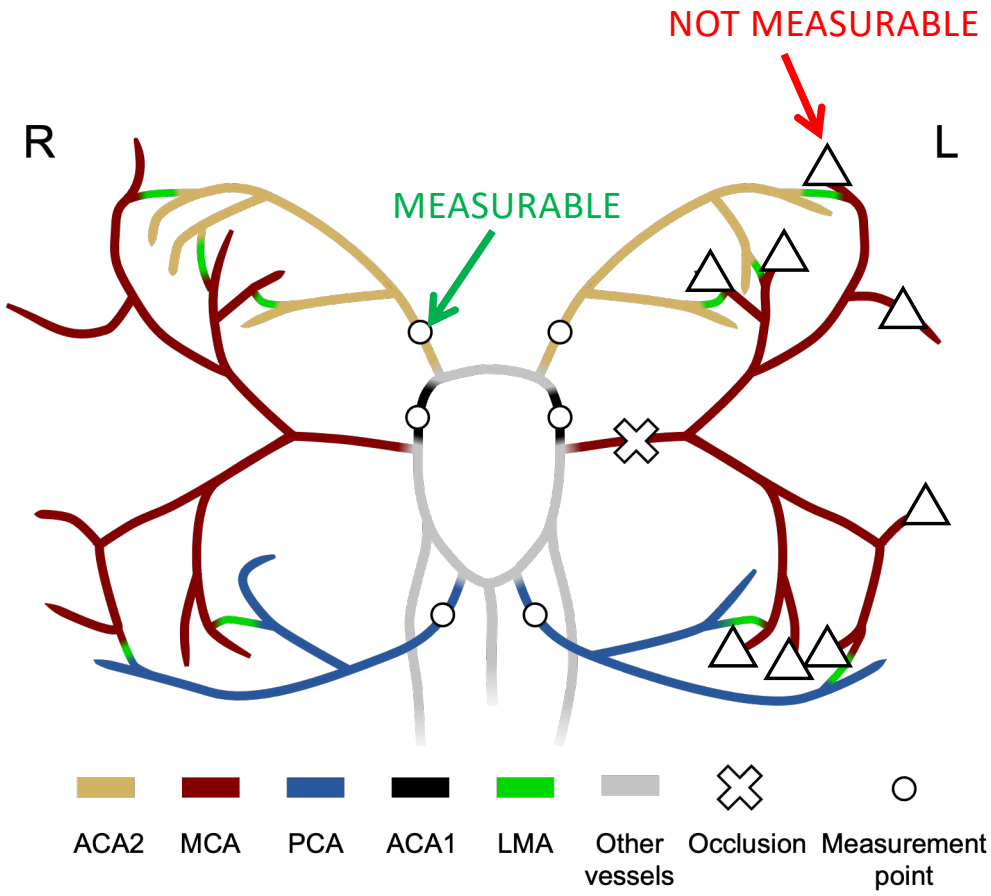
openBF: https://github.com/INSIGNEO/openBF

Benemerito et al., submitted

GPE model

- Trained on USFD HPC cluster
- 110k virtual patients

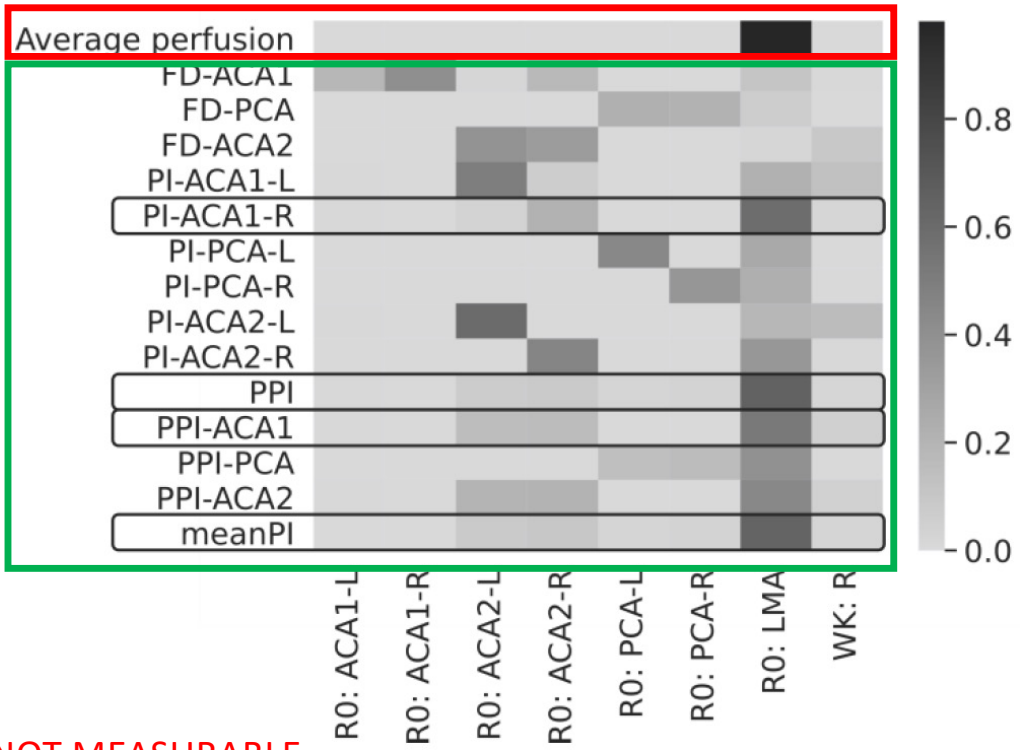
- Output:
  - Velocity in △
  - Perfusion in ○



Benemerito et al., submitted

SSA for biomarker identification

- Quantify the effect on input variation on outputs of interest (Sobol's indices)
- Outputs that match a reference signature are the biomarkers
- Four biomarkers identified

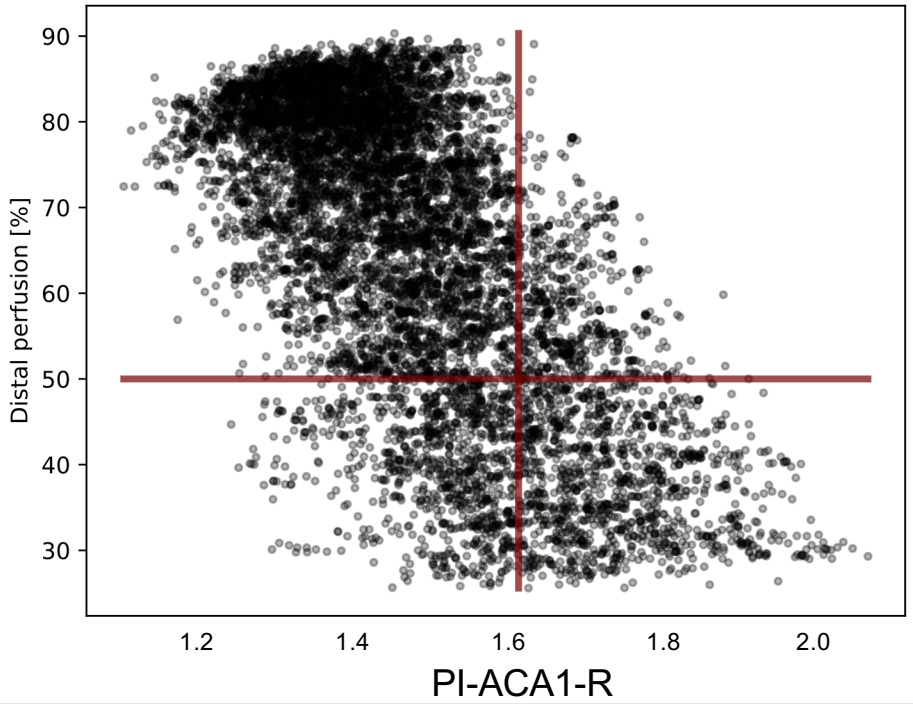


NOT MEASURABLE
MEASURABLE

Benemerito et al., submitted

Biomarker characterisation

- Evaluate correlation between biomarker and perfusion
- 90k virtual subjects (emulated)
- Knowledge of arterial radius improves predictive power



Benemerito et al., submitted

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Model reduction of musculoskeletal models: a Gaussian process-based approach

Ivan Benemerito[1,2], Erica Montefiori[1,2], Alberto Marzo[1,2], Claudia Mazzà[1,2]

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2. Department of Mechanical Engineering, The University of Sheffield, UK

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NHS Foundation Trust

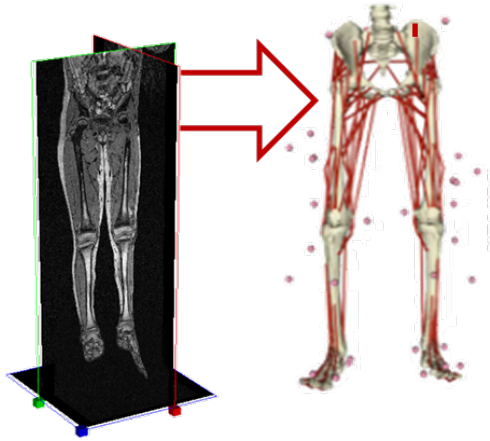
Musculoskeletal models (MSKM)

- Mathematical representation of human locomotion
- Inputs:
  - Marker trajectories
  - Ground reaction forces
  - Anatomical parameters
    - Generic
    - Subject specific
- Outputs:
  - Joint coordinates
  - Joint reaction forces

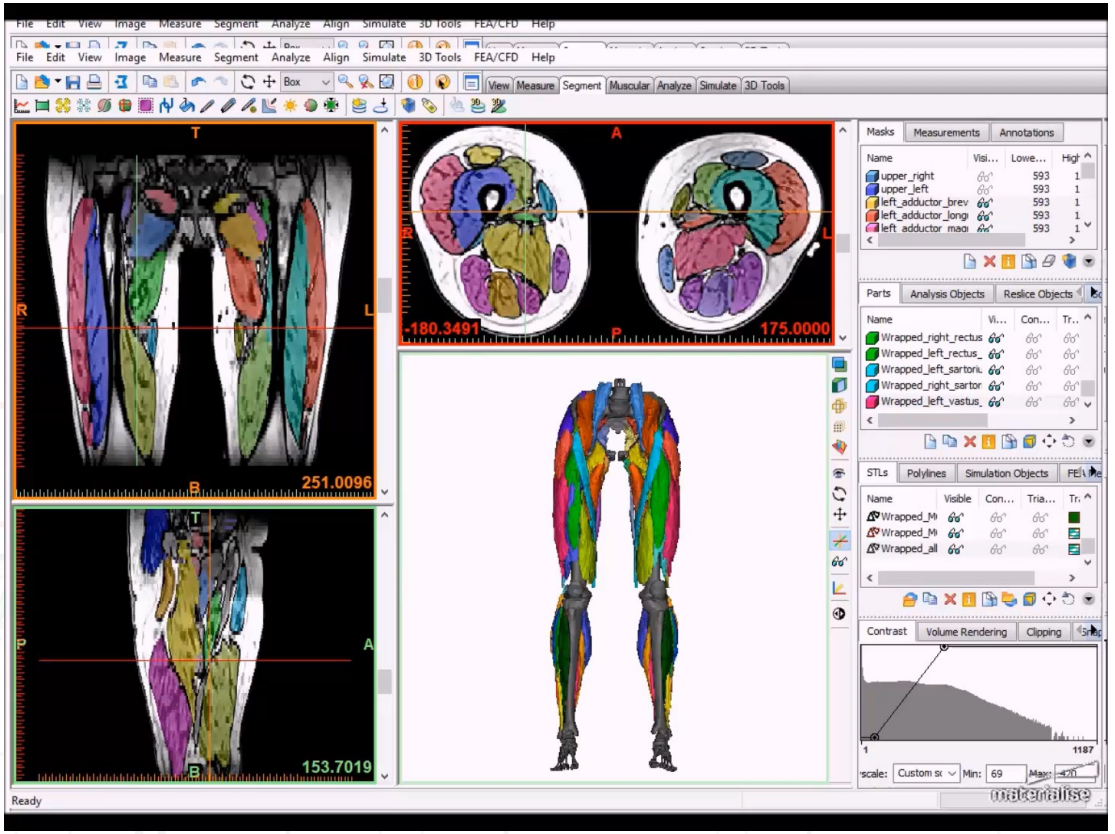
Montefiori et al., 2019

MSKM: pipeline

- Bone segmentation
- Muscle segmentation
- Personalised muscle path



MRI



Montefiori et al., 2019

Subject specific MSKM

- Typical model:
  - 23 muscles per leg (29 muscle lines)→ ~ 60 parameters
  - Segmentation time: 20 hours
  - Simulation time: 5 minutes

Could we segment just the most important muscles?

How do you rank muscles?

Altai et al., 2021

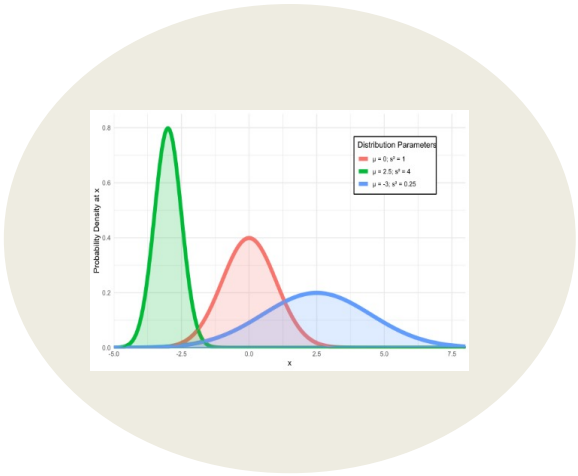
Research question

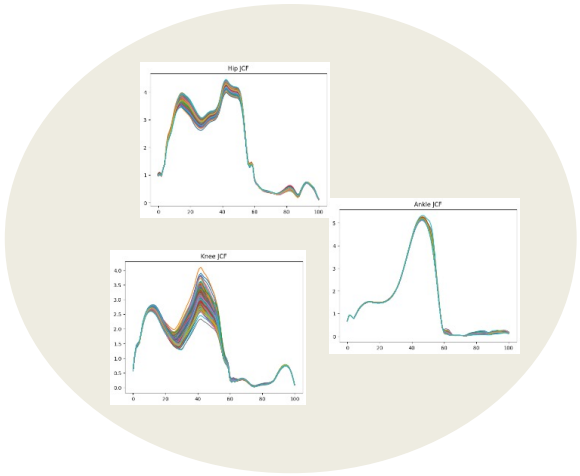
Is it possible to develop a reduced model, where only a limited set of muscles is personalised, that is as accurate as the original one?

- Generate virtual subjects and run mechanistic MSK simulations
- Train emulator
- Perform sensitivity analysis to identify the smallest set of required muscles

Benemerito et al, in preparation

Musculoskeletal simulations





- 11 subjects
- Statistical distribution of each muscle

Sample 200 virtual subjects from muscles distribution

Compute hip, knee, ankle joint contact forces (JCFs)

Benemerito et al, in preparation

Why GPE?

For 60 parameters:

- O(60000) simulations for SSA
- 5 minutes per simulation → **200 days**

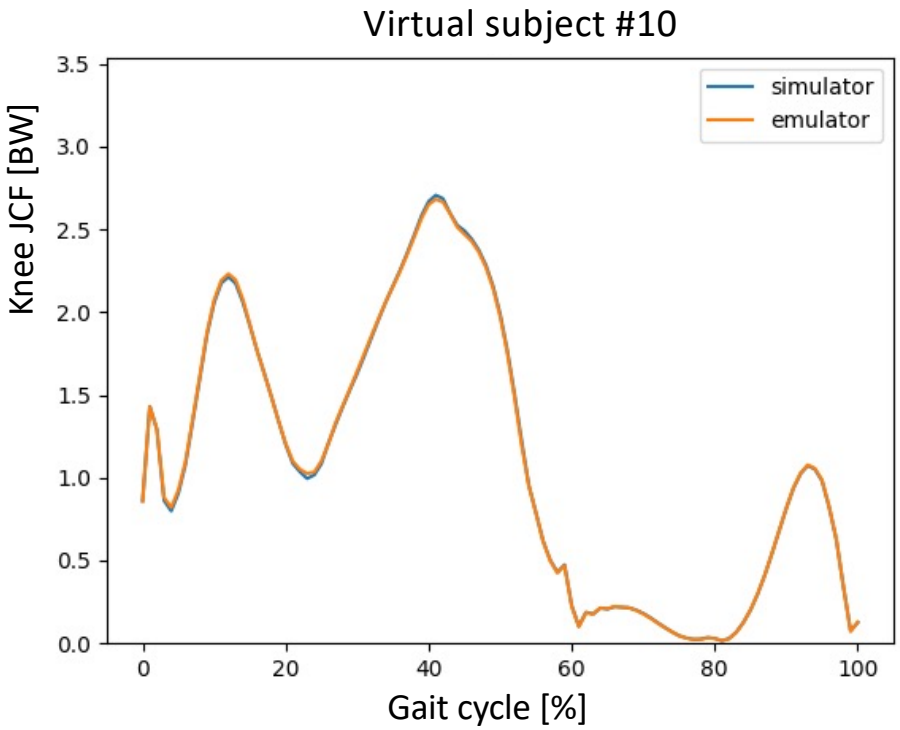
If using a GPE:

- O(N) simulations for training → **5 hours**
- Computation of Sobol's indices: **1 hour**

GP emulation of JCFs

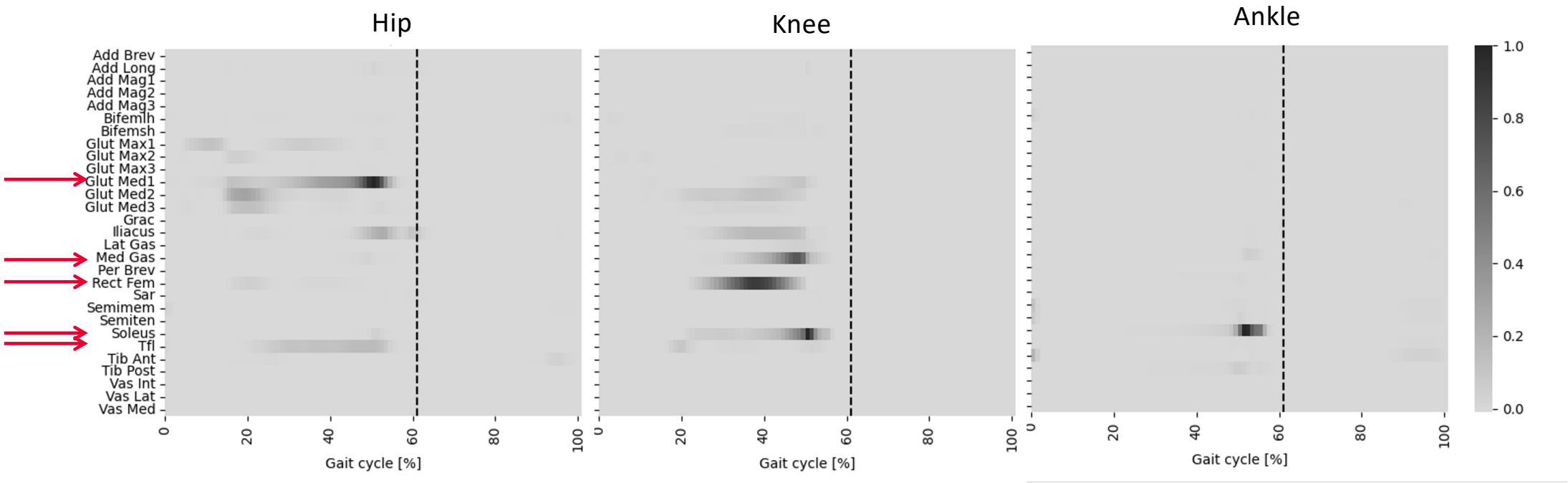
- GPE's input: muscle parameters
- GPE's output: JCFs

- Training: 50 simulations
- Validation: 150 simulations



Benemerito et al, in preparation

SSA



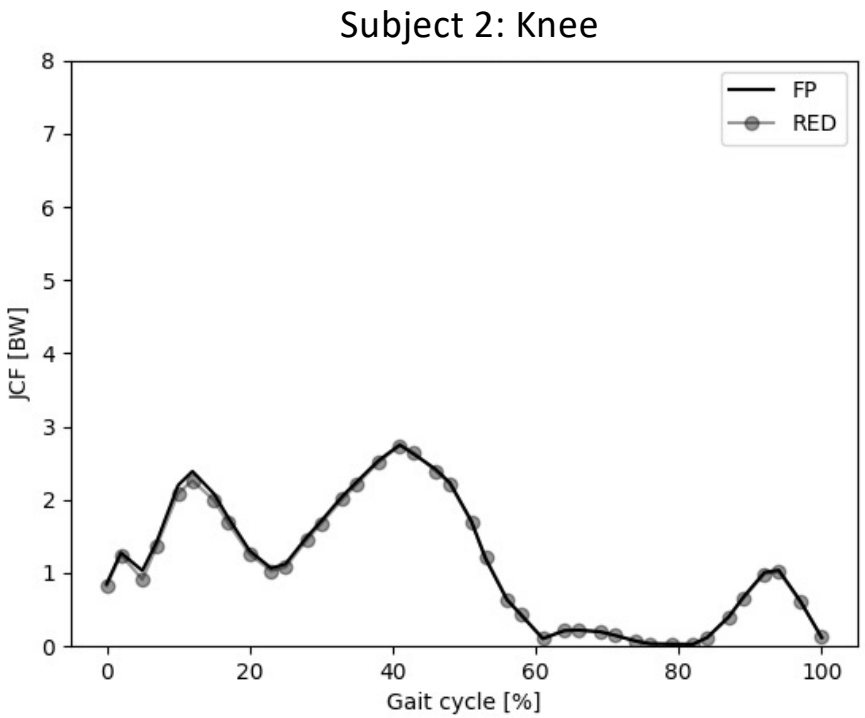
For each time point, quantify the influence of each muscles on JCF

5 muscles are identified as more influential

Benemerito et al, in preparation

Reduced models

- Emulation of model with only 5 of 29 muscles personalised
- Minimum discrepancy between full and reduced models



Benemerito et al, in preparation

Take home message

Gaussian process emulators are effective tools for performing sensitivity analysis of complex computational models

Acknowledgements

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EPSRC
Engineering and Physical Sciences
Research Council

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Q&A

To pose a question, you can write your question in the “Questions” tab

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