Proceedings of the 4th International Conference on Statistics: Theory and Applications (ICSTA'22)
Prague, Czech Republic – July 28- 30, 2022
Paper No. 161
DOI: 10.11159/icsta22.161

Forward and Inverse Uncertainty Quantification in Cardiac Mechanics

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Extended Abstract

Ever since the publication of the seminal white paper by Mirams et al. [1], the cardio-physiological modelling community has appreciated the importance of allowing for variability and uncertainty in their computational and mathematical models. In the present study, we distinguish between forward and inverse uncertainty quantification (UQ). Forward uncertainty quantification (F-UQ) focuses on structural identifiability, i.e. whether parameters are unidentifiable as a result of the model structure per se. This is closely related to sensitivity analysis (SA), and the aim is to establish how uncertainties in model inputs (such as parameters) affect the model output. Since structural identifiability is an intrinsic feature of the model, the analysis is a priori in nature, meaning that it can be carried out based on the model alone, without need for any measurements or experimental data.

Inverse uncertainty quantification (I-UQ) focuses on practical identifiability. When parameters are unidentifiable as a result of practical restrictions related to limited availability and quality of data, they are referred to as practically unidentifiable. I-UQ is therefore a posteriori in nature, meaning conditionally dependent on experimental data.

In the present study, we have applied both paradigms to the growing field of cardiac mechanics, more specifically to the Holzapfel-Ogden model of the passive myocardium [2]. This model depends on eight constitutive parameters, which provide important pathophysiological insights for clinical applications [3], but which cannot be measured non-invasively. State-of-the-art methods therefore try to infer these parameters using magnetic resonance imaging (MRI), based on a measure of discrepancy between strains extracted from the images and those predicted by the cardiac mechanic model [4]. Since the kinematic equations of the latter have no closed-form solution, numerical simulations based on finite element discretisation have to be run repeatedly as part of an iterative optimisation algorithm, leading to computational run times of days or even weeks.

To reduce the computational complexity, statistical surrogate modelling and emulation have been proposed [5,6]. The accuracy of these approaches is known to degrade with increasing dimension of the parameter space. The objective of our present study therefore is as follows: 1) Apply F-UQ to check which parameters of the Holzapfel-Ogden model are structurally unidentifiable. 2) Apply I-UQ to quantify the degree of practical identifiability of the same parameters. 3) Compare the F-UQ and I-UQ scores and assess their consistency.

Our F-UQ study is based on the global sensitivity analysis framework proposed in [7], using Gaussian process emulation for computational feasibility [8]. Our I-UQ study is based on Markov chain Monte Carlo simulations on an emulated likelihood function, following the procedure described in [9]. Our study has found a remarkable agreement between the F-UQ and I-UQ results. The F-UQ study suggests that four of the eight constitutive parameters have very low global sensitivity scores, quantified as first-order and total-effect Sobol indices (see [7] for a definition of these scores). The I-UQ studies suggest that the same parameters have a very low degree of practical identifiability, indicated by large posterior credible intervals. These findings support a model surgery approach, whereby four of the eight constitutive parameters of the Holzapfel-Ogden model can be held fixed at nominal values and effectively be eliminated from future statistical inference applications. This model reduction has important implications for patient-specific recalibration and future clinical applications in real time.

Acknowledgement
This work was funded by EPSRC, grant reference numbers EP/T017899/1, EP/S030875/1 and EP/S020950/1.

References
[1] G.R. Mirams, P. Pathmanathan, R.A. Gray, P. Challenor and R.H. Clayton RH (2016), ``Uncertainty and variability in computational and mathematical models of cardiac physiology,'' *Journal of Physiology*, vol 594, no 23, pp 6833–6847.

[2] G.A. Holzapfel and R.W. Ogden (2009), ``Constitutive modelling of passive myocardium: a structurally based framework for material characterization,'' *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, vol 367, pp. 3445–3475.

[3] H. Gao, A. Aderhold, K. Mangion, X. Luo, D. Husmeier, C. Berry (2017), ``Changes and classification in myocardial contractile function in the left ventricle following acute myocardial infarction,'' *Journal of The Royal Society Interface* vol 14, no 132, p. 20170203.

[4] H. Gao H, W.G. Li, L. Cai, C. Berry and X. Luo (2015), ``Parameter estimation in a Holzapfel–Ogden law for healthy myocardium,'' *Journal of Engineering Mathematics*, vol 95, pp. 231–248.

[5] V. Davies, U Noe, A. Lazarus, H. Gao, B. Macdonald, C. Berry, X. Luo, D. Husmeier (2019), ``Fast parameter inference in a biomechanical model of the left ventricle by using statistical emulation,'' *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, vol 68, no 5, pp.1555–1576.

[6] U. Noe, A. Lazarus, H. Gao, V. Davies, B. Macdonald, K. Mangion, C. .Berry, X. Luo, D. Husmeier (2019), "Gaussian process emulation to accelerate parameter estimation in a mechanical model of the left ventricle: a critical step towards clinical end-user relevance," *Journal of the Royal Society Interface*, vol. 16, no 156, p. 20190114.

[7] A. Saltelli, P. Annoni, I. Azzini, F. Campolongo, M. Ratto, S. Tarantola (2010), ``Variance based sensitivity analysis of model output: Design and estimator for the total sensitivity index,'' *Computer Physics Communications* vol 181, no 2, pp. 259–270.

[8] A. Melis, R. Clayton, A, Marzo (2017), ``Bayesian sensitivity analysis of a 1D vascular model with Gaussian process emulators,'' *International Journal for Numerical Methods in Biomedical Engineering*, vol 33, no e2882.

[9] A. Lazarus, H. Gao, X. Luo, D. Husmeier (2022), ``Improving cardio-mechanic inference by combining in vivo strain data with ex vivo volume–pressure data,'' *Journal of the Royal Society Interface*, online pre-publication: doi: 10.1111/rssc.12568.