## Cell to Whole Organ Global Sensitivity Analysis and Parameter Inference on a Four-chamber Heart Electromechanics Model Using Gaussian Processes Emulators

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**Abstract:** Cardiac pump function arises from a series of highly orchestrated events across multiple scales. Computational electromechanics can encode these events in physics-constrained models. However, the large number of parameters in these models has made the systematic study of the link between cellular, tissue, and organ scale parameters to whole heart physiology challenging. A patient-specific anatomical heart model, or digital twin, was created. Cellular ionic dynamics and contraction were simulated with the Courtemanche-Land and the ToR-ORd-Land models for the atria and the ventricles, respectively. Whole heart contraction was coupled with the circulatory system, simulated with CircAdapt, while accounting for the effect of the pericardium on cardiac motion. The four-chamber electromechanics framework resulted in 117 parameters of interest. The model was broken into five hierarchical sub-models: tissue electrophysiology, ToR-ORd-Land model, Courtemanche-Land model, passive mechanics and CircAdapt. For each sub-model, we trained Gaussian processes emulators (GPEs) that were then used to perform a global sensitivity analysis (GSA) to retain parameters explaining 90% of the total sensitivity for subsequent analysis. We identified 45 out of 117 parameters that were important for whole heart function. We performed a GSA over these 45 parameters and identified the systemic and pulmonary peripheral resistance as being critical parameters for a wide range of volumetric and hemodynamic cardiac indexes across all four chambers. Finally, we used Bayesian history matching in combination with GPEs to restrict the parameter ranges to where the model behaved in agreement with the available clinical data for the patient. We have shown that GPEs provide a robust method for mapping between cellular properties and clinical measurements. This framework can be applied to identify parameters that can be calibrated in patient-specific models or digital twins, and to link cellular function to clinical indexes.