Feasibility of Uncertainty Quantification for Complex Physiological Models
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Introduction: The use of physiological computational models in biomedical applications is rapidly increasing. Physiological models are used in the design and evaluation of medical devices, as well as integrated into devices, or may even be the device itself [1]. Moreover, in silico clinical trials, as advanced by CDRH, require the development of reliable models of human physiology. Recent efforts to ensure the reliability of computational modeling in biomedical applications, such as the new ASME V&V40 Standard, emphasize the importance of uncertainty quantification (UQ) when assessing models. UQ involves determining the uncertainty in model inputs and then calculating the resultant uncertainty in model outputs. However, there is a disconnect between expectations in the V&V40 Standard/related documents, and what is feasible for physiological models, which typically have large numbers of parameters (often hundreds). One challenge is the experimental difficulty to characterizing uncertainty (including biological variability) in physiological parameters. Another is the high likelihood that many physiological models will fail in some way when uncertainty is integrated into the model, and the path forward if that occurs is unclear. The first aim of this work was to develop a novel model of cardiac electrophysiology and apply analytic methods not commonly used in cardiac/medical device modeling to demonstrate feasibility of comprehensive UQ for physiological models. A second aim to investigate how failure occurs in such models upon integration of uncertainty, and how can it can be handled.

Methods: A novel model of the canine action potential (AP) was developed which includes six important ionic currents yet only had 36 parameters, significantly fewer than other modern cardiac models. Uncertainty in all parameters was prescribed, via a single free parameter (σ) that controlled total uncertainty. Model robustness was evaluated by varying σ. Global sensitivity analysis was performed by computing Sobol sensitivity indices [2]. Uncertainty propagation was performed using simple Monte Carlo sampling. When model failure occurred, the parameters responsible for failure were identified using Monte Carlo filtering [2].

Results and Discussion: Under small levels of parameter uncertainty (σ = 1%), no failure was observed (Fig 1A). This is the first time any (non-phenomenological) cardiac AP model has been demonstrated to be robust to (small) interacting uncertainty in all its parameters. Outputs that were relatively robust (i.e., less variable) given the underlying uncertainty were identified; this included common outputs proposed to be used in clinical applications. Some model failure occurred upon increasing parameter uncertainty (σ = 3%; Fig 1B); significant failure occurred for larger parameter uncertainty (σ = 5%; Fig 1C). Model failures were split into three different failure modes and the parameters responsible for each were identified. Just five of the 36 parameters were responsible for all failure modes. Potentially correlated parameters were also identified. These results demonstrate general feasibility of comprehensive UQ for cardiac cellular models, and how robustness can be assessed and model failure handled.

Translational Impact: In general, a simple model with UQ may be more useful than a complex model without UQ. If simpler models can be developed that are predictive as complex models for clinically-relevant applications, they have the huge advantage that fully testing robustness to parameter uncertainty is possible. The approaches presented here could therefore be used to develop models for which important model outputs have been confirmed to be robust to the underlying uncertainty – in particular, robust to human population variability – and are therefore more reliable if used in safety-critical decision-making, such as in in silico clinical trials.