Parameter Space Reduction for Four-chamber Electromechanics Simulations Using Gaussian Processes Emulators

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1. INTRODUCTION

Cardiac physiology results from coordinated interactions across multiple scales, from proteins through to whole heart function. Physics-based computational models can encode these multi-scale processes. Calibrating these models to clinical data measuring whole heart function potentially provides a virtual heart assay to identify the tissue and cellular scale mechanisms underpinning these clinical observations. However, these models have large numbers of parameters and are computationally intensive, making model calibration challenging. In this context, machine learning methods for parameter reduction and estimation can be of great help in reducing the number of required simulation runs and therefore make parameter fitting possible.

2. METHODS

In this paper, we applied Gaussian processes emulators (GPE), Sobol variance-based global sensitivity analysis (GSA) and Bayesian history matching (HM) to the ToR-ORd model (Tomek et al., 2019) for human ventricular action potential and the Land model for human cellular active contraction (Land et al., 2017). The code for GPE training, GSA and HM is available online and is described in detail in (Longobardi et al., 2020). All simulations were run with a basic cycle length of 1000 ms for 100 beats to reach a near limit cycle. The calcium and the active tension transients from the last beat were used to extract features of interest, that were then used to evaluate parameter importance.

We selected 29 parameters of the ToR-ORd model representing ion channel conductivity, pump and exchanger maximum flux, the maximum fluxes of the calcium pathways and buffering concentrations to study their effect on the resulting calcium transient. Four separate GPE were trained to predict the following key calcium transient features: 1) diastolic calcium, 2) transient amplitude, 3) time to peak and 4) time to reach 90% relaxation. We used 2175 latin hypercube samples and the parameter space bounds were set to $\pm 25\%$ from their default values. Using the GPE we performed a Sobol GSA to compute the total effect of each parameter on each output feature. The parameters were ranked according to their maximum effect across all outputs. These values were then normalised to sum up to 1 and the most important parameters cumulatively explaining 90% of the output variance were selected as the most important, while the others were discarded.

A HM was then run on this subset of parameters to identify areas of the parameter space that led to physiological output features. Literature experimental data for human ventricular calcium transient were used as target values. The implausibility measure of each parameter combination was computed as in (Longobardi et al., 2020), to quantify discrepancy between GPE prediction and target experimental observations, accounting for both experimental data and GPE uncertainty. We ran five HM iterations (or waves) with a cutoff on the implausibility measure of 3.5 and a sixth wave with a cutoff of 3.0.

The non-implausible areas on the ToR-ORd model parameters were then used to define calcium transients to input to the Land model. A GSA on all 17 Land model parameters and the 10 selected ToR-ORd model parameter was run to detect important parameters for the following active tension features: 1) peak tension, 2) time to peak, 3) maximum time derivative, 4) minimum time derivative, 5) twitch duration and 6) rest tension. The GSA was applied for three experiments: isometric twitch with 0 and 0.1 constant strains and isotonic twitch.

We finally applied HM on the Land model fixing the ToR-ORd parameters to their default value to identify which parameter space regions led to physiological active tension. The target values for the HM were set to be the active tension transient features obtained in the Land model original paper (Land et al., 2017) and their standard deviation was set to 10% of their value. In this case, we ran only two waves with 3.5 cutoff on the implausibility measure and one last third wave with cutoff of 3.

3. RESULTS

Ranking the ToR-ORd model parameters according to their maximum total effect on the calcium features showed that, as expected, the most important parameters were directly related to either calcium ion channel or pump conductivities or to other calcium handling regulatory processes (e.g. diffusion inside the cell, calmodulin binding or contraction proteins). The GSA allowed us to reduce the number of parameter from 29 to 10, as the 10 most important parameters were enough to explain 90% of the output variance.

These 10 parameters were then used in the HM to restrict the parameter space to areas leading to physiological calcium transients. Figure 1 shows the initial calcium transients (blue) and the ones resulting from the restricted regions until the last HM wave (red). The corresponding simulated feature values from the initial (blue) and the restricted (red) space are compared with the experimental data (black). The HM allows us to restrict the parameter space to ensure the simulations give physiological values for all features. For the last HM wave (red) all simulations result in physiologically plausible calcium transients.

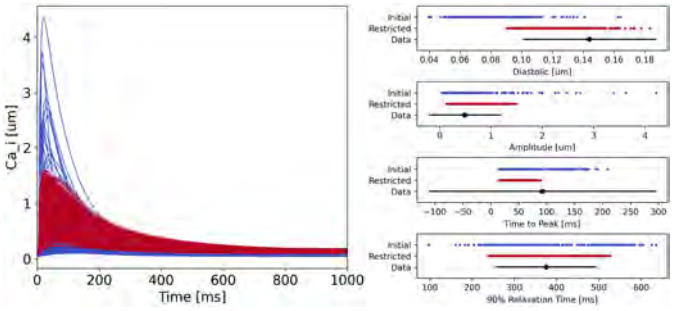

Fig. 1. **ToR-ORd HM Results.** Calcium transients (left) and extracted features (right) from the initial (blue) and from the restricted (red) parameter space. Experimental data ranges are shown in black.

The GSA on the Land model allowed us to reduce the parameters from 17 to 9. Furthermore, according to our analysis, only 4 of the original 29 ToR-ORd model parameters were necessary to explain 90% variance of the active tension transient. Therefore, the GSA allowed us to reduce the number of parameters in the ToR-ORd+Land model from 46 parameters down to 13 to explain 90% of the variance in the tension transient which drives whole heart simulations.

The HM allowed us to restrict the kinetic parameters of the Land model to values that led to physiological active tension transient when coupled with the ToR-ORd model. (Figure 2). The blue curves obtained with the initial sampling are far away from the target active tension transient from the original publication in (Land et al., 2017), while the red curves obtained by sampling the restricted regions are close to the target curve.

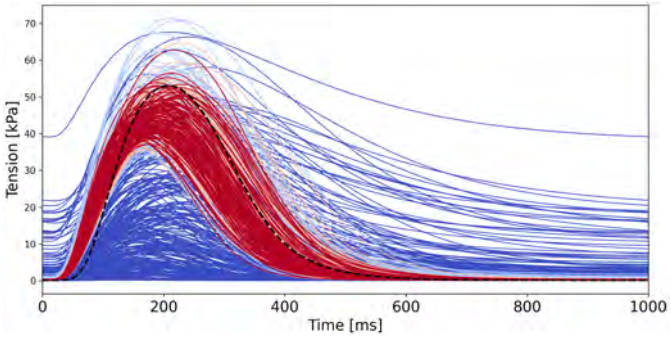

Fig. 2. **ToR-ORd+Land model HM Results.** Active tension transients from the initial (blue) and from the restricted (red) parameter space compared to the target active tension transient from (Land et al., 2017).

4. CONCLUSION

This work shows how GPE, GSA and HM can provide a systematic workflow to fit models to available experimental and clinical data while keeping the number of required simulation runs at a treatable level.

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