# Accelerating multi-scale Quantitative Systems Pharmacology models using a Bayesian surrogate modeling approach for quantitative translation from sub-cellular to whole-organ function: an example of evaluating Omecamtiv Mecarbil drug action in healthy rat hearts


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## ABSTRACT


Quantitative systems pharmacology (QSP) 3D cardiac contraction models have been developed to improve our understanding of how cell-level pathophysiology translates to organ-level cardiomyopathy phenotypes [1]. These models are complex, highly nonlinear (consisting of stiff ODEs and nonlinear PDEs) and computationally intensive to solve (each single-core simulation requiring ~4-12 hours). Previously, stiff ODE systems have been accelerated of ~10-100-fold using automatic differentiation, parallelization and GPU computing [2]. However, this level of speed up for 3D cardiac models is still too slow. The aim of our work is to enable computationally efficient evaluation of the large number of different parameter sets required for model fitting and validation, sensitivity analysis, and uncertainty quantification of biophysically detailed multi-scale mathematical models. We have applied computational techniques from engineering fields, such as aerospace and astrophysics, to pharmacological systems modeling. We employed a Bayesian probabilistic framework for replacing mechanistically detailed models with fast-evaluating surrogate models based on Gaussian processes (GPs). We incorporated the effect of omecamtiv mecarbil (OM), known cardiac myosin activator, into our virtual healthy rat heart [3]. We used Bayesian history matching (HM) in combination with GP emulation to perform model validation and global sensitivity analysis (GSA) in order to predict the underlying mechanisms of OM drug action. We compared the emulation results against the latest experimental evidence that OM indirectly alters thin filament calcium sensitivity [5]. After training, the GP emulators granted a speedup of ~14,400-fold compared to the simulation of the full model on a single core machine. This reduced time to model output prediction from an average CPU time of ~4 hours to ~1 second. As a result, we assessed in a computationally efficient manner the impact of 4 sarcomeric properties (model parameters) on 14 pressure- and volume-based indexes of left ventricular function via a GP-emulator-based GSA, requiring 140,000 GP evaluations. We performed one iteration of HM as per [4], where we evaluated predictions for 400,000 randomly and uniformly distributed input parameter points to map the specific regions in the parameter space which are compatible with the observed impact of OM in preclinical experimental in vitro and in vivo data. Using this framework we performed GSA and identified the key cross-bridge properties that determine the 3D mechanical function in healthy rat hearts. The developed framework, made available as open source [6], enables us to assess drug effects at the cell-level across multiple scales in a computationally efficient manner (i.e. a speed up of 10,000+ fold). This approach can be expanded to failing hearts and applied to other mechanistically detailed QSP or PBPK models to support novel target discovery and drug development.


## METHODS

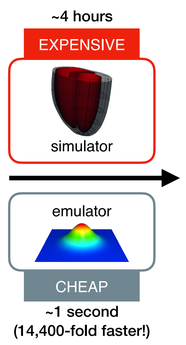
- Personalized biophysically-detailed mathematical model of 3D biventricular healthy rat heart contraction mechanics [3] (computationally expensive simulator).
- Model input: 4 parameters describing cross-bridge dynamics properties (Table 1).
- Model output: 14 features characterizing left ventricular function (Table 2).
- Bayesian surrogate model, based on Gaussian processes (computationally cheap emulator), using GPErks library [9].
- Fast and accurate emulator predictions of simulator behavior (Figure 1).
- Fast and accurate simulator output sensitivities evaluation via Sobol' indices [6] estimation with emulator-based Saltelli method [7], using SALib library [8] (Figure 2).
- OM-compatible sarcomere parameter space search using the cellular contraction sub-model [1] of the full 3D simulator (Figure 3).
- OM-compatible space mapped to LV function using emulators (Figure 4).
- OM-compatible sarcomere parameter space search using the Bayesian history matching technique [4] (Figure 5).
- OM-compatible space mapped force-calcium properties using the cellular contraction sub-model [1] of the full 3D simulator (Figure 6).

# **Emulators speed up** input to output mapping for **QSP models**, enabling efficient analysis, fitting and uncertainty quantification

## Input to output mapping can be performed using either full model (expensive) or surrogate model (cheap)

| | |
|---|---|
| cross-bridge cycling rate | kXB |
| cross-bridge formation degree of cooperativity | nXB |
| fraction of bound $Ca^{2+}$-TnC complexes for half-maximal cross-bridges activation | TRPN50 |
| maximal reference tension | Tref |

**Table 1**. Model input parameters.




| | |
|---|---|
| EDV | end-diastolic volume |
| ESV | end-systolic volume |
| EF | ejection fraction |
| IVCT | isovolumetric contraction time |
| ET | ejection time |
| IVRT | isovolumetric relaxation time |
| Tdiast | diastolic time |
| PeakP | peak pressure |
| Tpeak | time to peak pressure |
| ESP | end-systolic pressure |
| maxdP | max. pressure rise rate |
| mindP | max. pressure decay rate |
| SV | stroke volume |
| ET/Tdiast | ejection time over diastolic time |

**Table 2**. Model output left ventricular features.

## Emulators accurately predict the simulator output

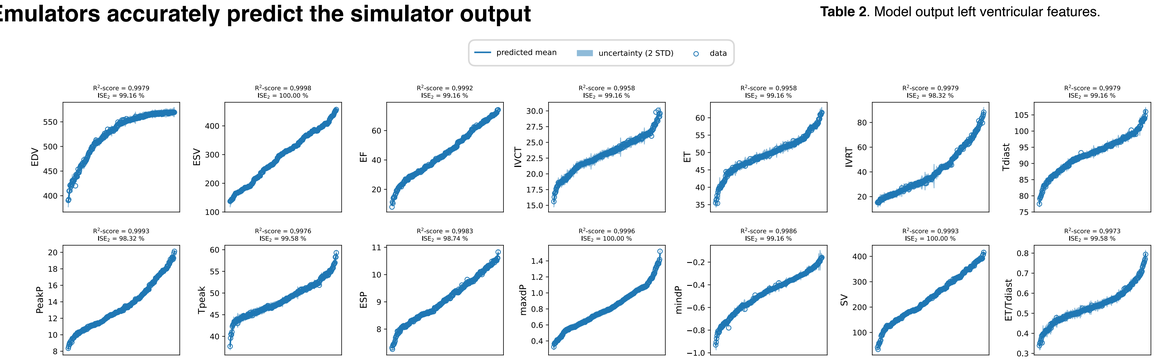



**Figure 1**. Emulators predicting each of the output LV features at a given set of test input parameter points. The resulting values (predicted mean) are compared with the true values (data), and the match is almost perfect within 2 standard deviations (uncertainty) predicted confidence intervals. R2-score and ISE2 regression metrics' values are also provided.

## Emulators enable computationally efficient global sensitivity analysis studies

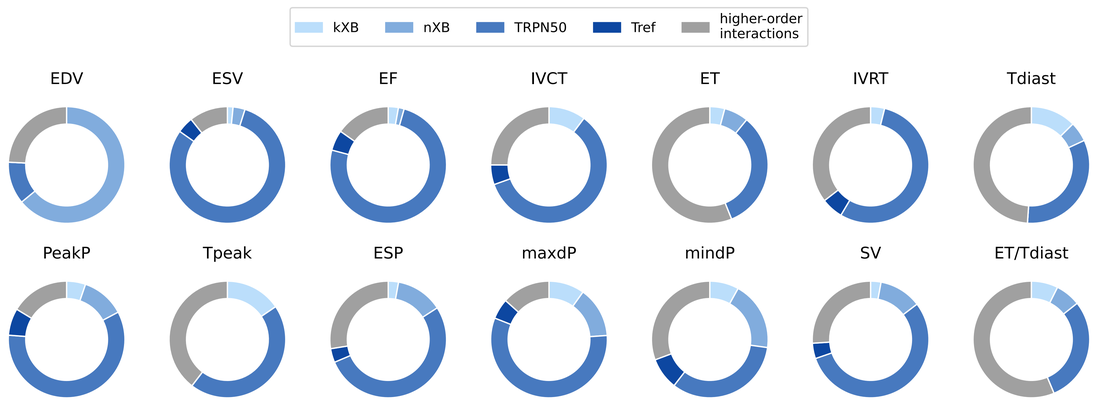



**Figure 2**. The impact of cross-bridge dynamics properties on LV features in a personalized healthy rat heart contraction model. First-order effects (blue color variants) represent the contribution of each parameter alone into explaining the features' total variance. Higher-order interactions (grey), given by the sum of all the total effects minus the sum of all the first-order effects, represent the contribution of each combination of any two or more parameters.

## Inferring OM effects on LV function from *in vitro* rat force-calcium measurements

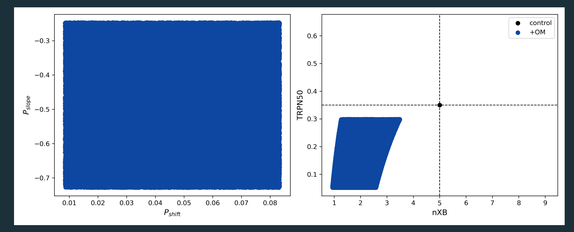



**Figure 3**. OM-compatible sarcomere space as encoded by 2 parameters (nXB, TRPN50), inferred from in *vitro rat* force-calcium data.

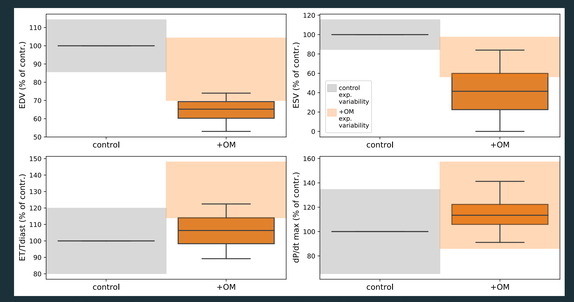



**Figure 4**. The median values of emulated LV features' distributions with OM administration (dark orange boxes) are in qualitative agreement (same direction of change) with exp. data [10] (shaded areas).

## Inferring OM effects on the sarcomere from *in vivo* pig LV hemodynamics measurements

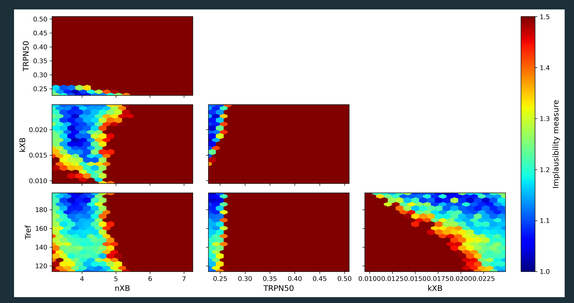



**Figure 5**. OM-compatible sarcomere space as encoded by 4 parameters (kXB, nXB, TRPN50, Tref), inferred from *in vivo* pig LV hemodynamics data.

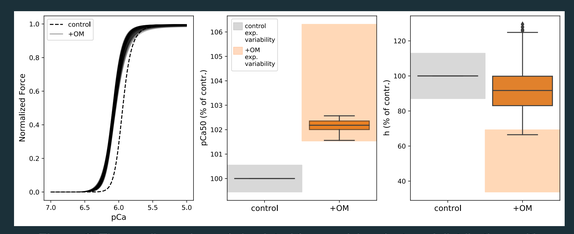



**Figure 6**. The median values of simulated force-calcium features' distributions with OM exposure (dark orange boxes) are in qualitative agreement (same direction of change) with exp. data [11,12,13] (shaded areas).

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