Quantifying contributions of cellular mechanical myocardial properties on left ventricular contractile function in aortic banded rats

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ABSTRACT

Left ventricular (LV) contractile dysfunction is known to be associated with altered cellular myocardial properties. Quantitative translation from cellular mechanical properties to whole-organ cardiomyopathy phenotype, however, is an ongoing challenge. To quantitatively map cell-level pathophysiology to whole-organ contractile function in aortic banded (AB) 6-weeks post-surgery rats (Røe et al. 2017), we consider an in silico model of LV hypertrophy which combines mathematical models of cellular electrophysiology and calcium dynamics, sarcomere contraction and whole-organ mechanics solved over geometries derived from control and AB rat hearts. The resulting multi-scale computationally expensive model is regulated by >100 parameters. To assess parameters impact on the model outputs we developed a computationally effective approach for global sensitivity analysis (GSA) of rat cardiac mechanics based on Gaussian process (GP) emulation. We identified eight key parameters regulating ventricular mechanics such as myofilament calcium sensitivity (Ca_{50}) and described the LV contractile function using eleven measurements including ejection fraction (EF) and pressure-volume loop. We found Ca_{50} to be the most significant parameter in explaining the total variance in both the control and AB rat (56%, 53%, 56%, 57% of the total variance of EF, isovolumetric relaxation time, peak pressure and maximum pressure rise rate, respectively, in control, and 65%, 47%, 58%, 56%, respectively, in AB rat). Calcium unbinding rate from Troponin C and maximal cellular tension yielded, respectively, the second and the third highest impact on the above LV features' total variances. Tissue stiffness and cross-bridge cycling rate impacted EF, ejection time, diastolic time and peak and end-systolic pressure features in the AB rat only. Our GP-based GSA approach enables computationally efficient identification of key components in 3D ventricular mechanics models, a potential path towards discovering new targets for heart failure treatment.

METHODS

- *In silico* multi-scale bi-ventricular rat heart contraction model (Figure 1):

  - Ventricular anatomy: healthy (SHAM) and aortic-banded (AB) rat MRIs [1].
  - Calcium dynamics: Gattoni et al. [2] model for 6Hz paced SHAM and AB rat hearts at 37 °C.
  - Cellular contraction: Land et al. [3] model.
  - Passive material properties: Guccione constitutive equation [4].
  - Boundary conditions: three-element Windkessel model [5].

- Model input: 8 parameters describing cell, tissue and hemodynamic properties (Table 1).

- Model output: 12 features of left ventricular function (Table 2).

- Gaussian process emulator: computationally efficient surrogate of the multi-scale model.

- Global sensitivity analysis: variance based, evaluating how much of the total variance in the model output features is explained by the uncertainty in the model input parameters (Figure 2).

- Sobol sensitivity indices (first-order, second-order and total effects [6]) estimation: Saltelli method [7], SALib Python library [8]. Model evaluations (computationally expensive) substituted with the emulator's mean point-wise predictions (computationally cheap).

Sarcomere kinetics are key determinants of both **systolic and diastolic ventricular function** in sham and aortic-banded rats

METHODS (cont.)

end-diastolic pressure	p
aortic pressure	ap
aortic characteristic impedance	z
tissue stiffness	c1
reference calcium sensitivity	ca50
binding rate in crossbridge cycling	kxb
dissociation rate of Ca^{2+} from TnC	koff
maximal cellular tension	Tref

Table 1. Cell, tissue and hemodynamic parameters.

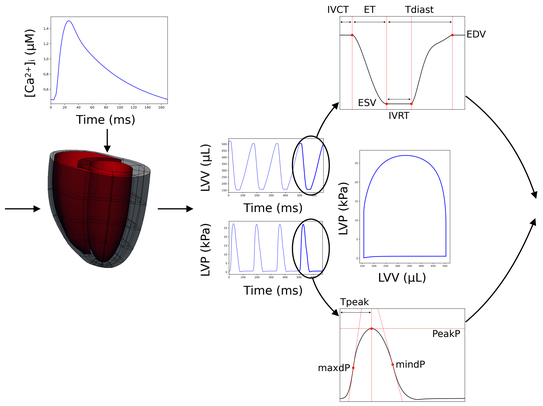


Figure 1. Multi-scale model of bi-ventricular rat heart contraction.

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

Table 2. Organ-scale left ventricular features.

RESULTS — Impact of model parameters on cardiac features

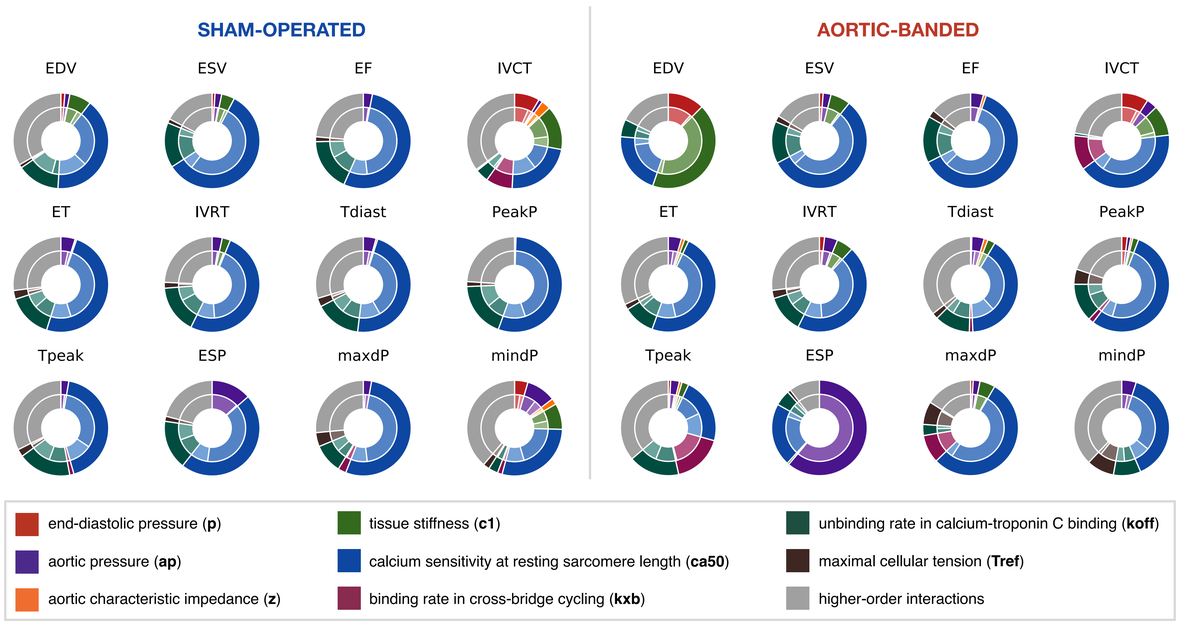
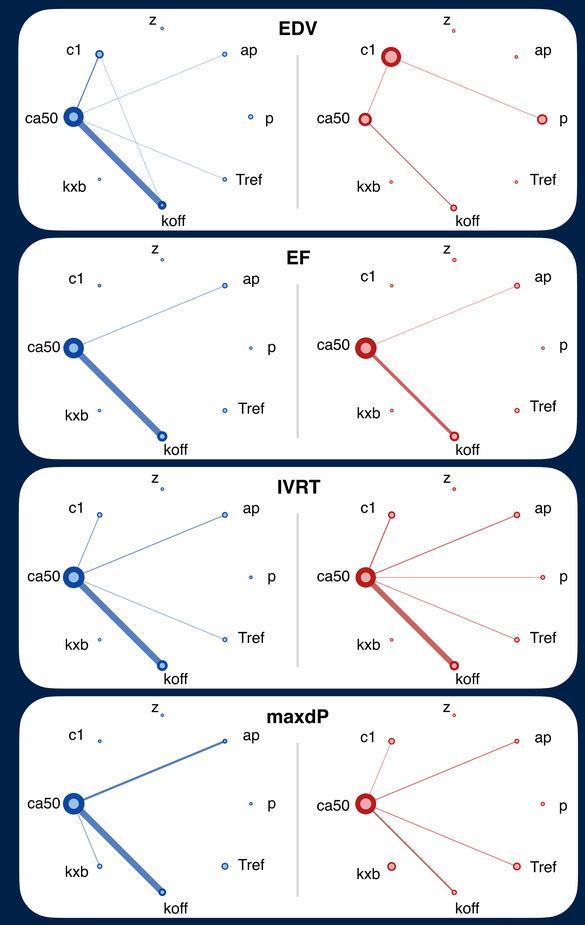


Figure 2. The impact of cell, tissue and hemodynamic properties on organ-scale features in **SHAM** and **AB** models. Inner wedges show how the contribution of one parameter alone is sometimes split into first- and second order effects, colored with the darker and lighter color variants respectively. Outer wedges (colored in the darkest color variant) represent the sum of first- and (when present) second-order effects. For each LV feature, higher-order interactions (colored in grey) were represented by the sum of total effects minus the sum of all first- and second-order effects.

RESULTS — Parameters interactions

SHAM-OPERATED Vs AORTIC-BANDED



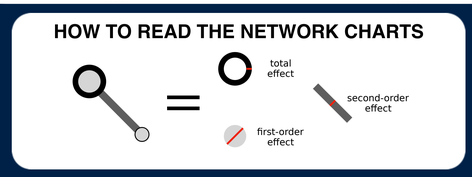


Figure 3. First- and second-order parameter interactions.

- Calcium sensitivity (ca50) and dissociation rate of Ca^{2+} from TnC (koff) are the most important parameters in explaining the total variance of all the above illustrated left ventricular features. Their joint contribution (second-order effect) is a recurrent pattern as well, and it is always bigger in SHAM than in AB (thicker parameters linking line).

- Ejection fraction is characterized by similar patterns of parameters interactions in both SHAM and AB.

- Tissue (c1) and hemodynamic parameters (p, ap, z) contribute more in AB than in SHAM.

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