Quantitative mapping of Force-pCa curves to the whole heart contraction and relaxation

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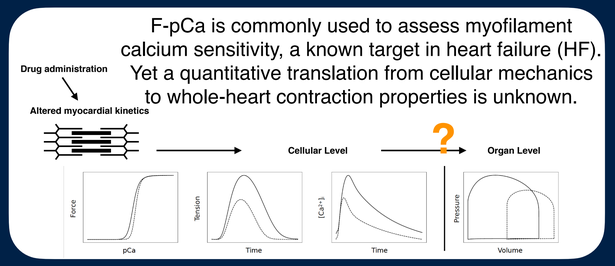
ABSTRACT

Force-pCa (F-pCa) curves and/or ATPase assays both in skinned and unskinned fibers are often used to evaluate the calcium myofilament sensitivity. Force-pCa relationship has been extensively analyzed to clarify the role of myofilament calcium sensitivity in cardiac contraction and relaxation dynamics at cellular level [1-3]. However, to date there has been no quantitative mapping of these measurements, representing the stationary state force generation, to the whole heart cardiac function. In this work we use mathematical models to quantitatively map the shifts in F-pCa curves (as a result of pharmacological and/or pathological stimuli) onto the contraction and relaxation of the whole heart. The translation of F-pCa changes onto the whole-heart pressure-volume (PV) loops is non-linear and non-monotonic, making it difficult to interpret the shifts in F-pCa onto the entire heart contraction. Using *in silico* 3D contraction rat models [4,5] that incorporate sarcomere-level description of the biophysics of cross-bridge cycling, we identify key thin and thick filament factors that result in (a) the same F-pCa curves but different left ventricular features such as ejection fraction (EF) and end diastolic volume (EDV), and (b) the same left ventricular features such as EF but different F-pCa curves. The proposed cellular to whole-heart mechanics and back computational workflow provides a quantitative understanding of the non-unique mapping in mechanics from the sarcomere to the whole-heart and back again. Our comprehensive quantitative F-pCa-to-whole-heart-mapping is critical for interpretation of F-pCa findings in the context of drug discovery and development (e.g. for target identification and selection, in vitro to in vivo translation, patient population selection).

MOTIVATION



METHODS

- Multi-scale bi-ventricular rat heart contraction model (Figure 1):
  - Ventricular anatomy: healthy rat MRIs [6]
  - Calcium dynamics: healthy rat Ca^{2+} transient
  - Cellular contraction: Land et al. [7] model, where Force-pCa is calculated as the steady state force at different intracellular Ca^{2+} concentrations
  - Passive material properties: Guccione constitutive equation [8]
  - Boundary conditions: three-element Windkessel model [9]
- Model input: 16 parameters describing cell, tissue and hemodynamic properties (Table 1).
- Model output: 14 features of left ventricular function (Table 2).
- Gaussian process emulator: computationally efficient surrogate of the multi-scale model (emulator methodology is described in [4-5]).
- Global sensitivity analysis (GSA): evaluation of how much of the total variance in the model output features is explained by the uncertainty in the model input parameters (Figure 6).
  - Sobol' sensitivity indices (first-order, second-order and total effects [10]) estimation is performed via Saltelli method [11] using SALib Python library [12].
  - For GSA, model evaluations (computationally expensive) are substituted with samples from the full emulator's posterior distribution (computationally cheap).

Myofilament calcium sensitivity assessed using **Force-pCa** *in vitro* measurements **maps non-uniquely to** *in vivo* **whole-heart function**

METHODS (cont.)

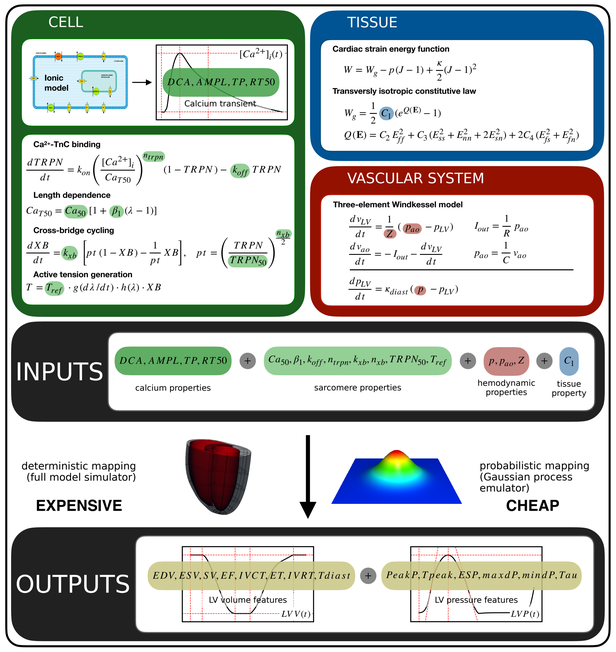


Figure 1. Multi-scale mathematical model of bi-ventricular rat heart contraction.

Ca^{2+} diastolic concentration	DCA
Ca^{2+} transient amplitude	AMPL
time to peak Ca^{2+} concentration	TP
time to Ca^{2+} half relaxation	RT50
reference Ca^{2+} thin filament sensitivity	Ca_{50}
length-dependence tension scaling factor	β_1
dissociation rate of Ca^{2+} from TnC	k_{off}
Ca^{2+}-TnC binding degree of cooperativity	n_{trpn}
cycling rate of cross-bridges	k_{xb}
degree of cooperativity of cross-bridge formation	n_{xb}
fraction of bound Ca^{2+}-TnC for half max cross-bridges activation	$TRPN_{50}$
maximal cellular reference tension	T_{ref}
end-diastolic pressure	p
systolic aortic pressure	pao
aortic characteristic impedance	Z
tissue stiffness	C_1

Table 1. Cell, tissue and hemodynamic parameters.

EDV	end-diastolic volume
ESV	end-systolic volume
SV	stroke 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
Tau	isovolumetric pressure relaxation time constant

Table 2. Organ-scale left ventricular features.

RESULTS

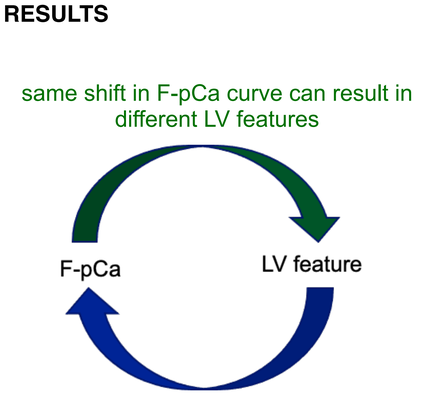


Figure 2. Illustration of the overall conclusion of our work that shifts in F-pCa map non-uniquely to LV features and vice versa.

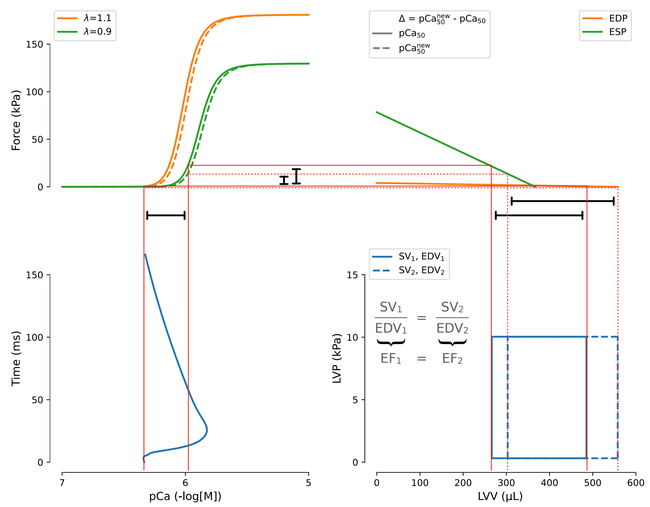


Figure 3. Illustration of F-pCa curves translation to Force-volume relationships at the end-diastolic and end-systolic pressures (orange EDP and green ESP lines) and to PV loops. Myofilament calcium desensitization in the sarcomere resulting in a shift to the right in F-pCa (orange and green dashed lines) may preserve EF yet not improve the LV contractile function.

RESULTS (cont.)

Fig. 4. Alterations of different parameters can result in the same pCa shift

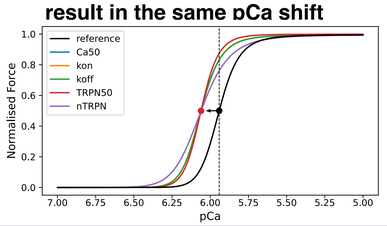
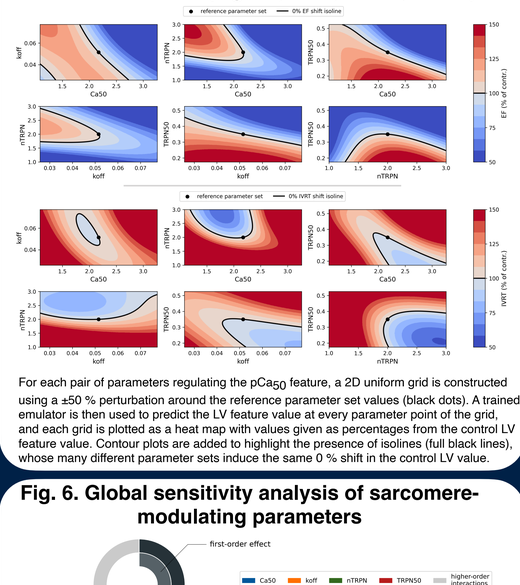
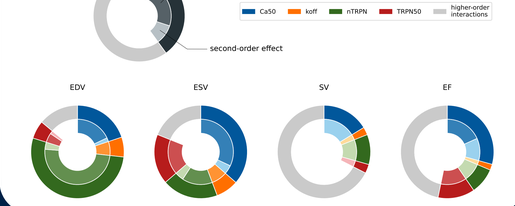


Fig. 5. Different parameter sets can generate the same LV features (e.g. EF, IVRT, PeakP, mindP)



For each pair of parameters regulating the pCa_{50} feature, a 2D uniform grid is constructed using a ±50 % perturbation around the reference parameter set values (black dots). A trained emulator is then used to predict the LV feature value at every parameter point of the grid, and each grid is plotted as a heat map with values given as percentages from the control LV feature value. Contour plots are added to highlight the presence of isolines (full black lines), whose many different parameter sets induce the same 0 % shift in the control LV value.

Fig. 6. Global sensitivity analysis of sarcomere-modulating parameters



CONCLUSIONS

- To the best of our knowledge, this is the first time that a multi-scale *in silico* framework is developed for quantitative translation from F-pCa measurements to whole-heart behavior in healthy rats.
- Due to non-unique mapping between F-pCa curves and LV features as well as the inability of F-pCa to account for changes in Ca^{2+} transient, the shift in F-pCa on its own cannot predict the whole-heart behavior. Importantly, the developed framework can be used to investigate the pathophysiology underlying HF with preserved EF (e.g. the case of the same EF).
- Our simulation studies suggest that additional experimental data such as Ca^{2+} transient dynamics, tension changes in time or sarcomere length changes in time are needed for predicting the PV loop behavior.

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