A VIRTUAL DRUG DEVELOPMENT FOR THE RECOVERY OF A HEART FAILING RAT WITH PRESERVED EJECTION FRACTION CONDITION INDUCED VIA TRANSVERSE AORTIC CONSTRICTION

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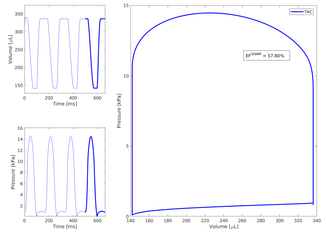
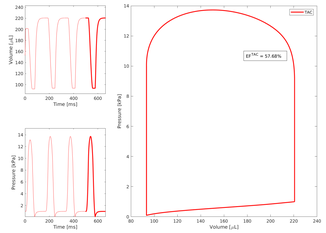
TWO RAT PHENOTYPES UNDER STUDY

We developed a mathematical model of *transverse aortic constricted* (TAC) rats, as an animal model of pressure overload-induced cardiac hypertrophy.



SHAM-operated rat



TAC rat

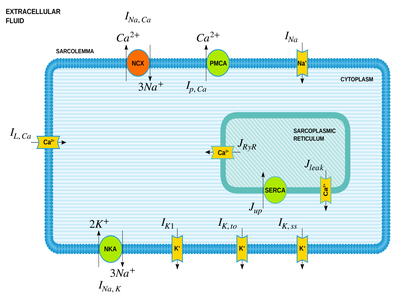
Model was run for three beats (light curves) and then a pressure-volume curve was generated (dark curves).

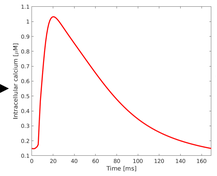
GOAL

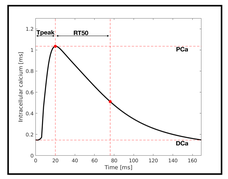
Predicting **drug targets** at cellular level in order to recover TAC rat heart left ventricular function. In particular, we aim to revert 9 key TAC rat heart's LV contraction features to the values recorded in the SHAM rat heart.

WORKFLOW - CELLULAR LEVEL

$$\mathbf{p} = \begin{bmatrix} N \\ g_f \\ g_{to} \\ g_{K1} \\ g_{MPCa} \\ g_{NCX} \\ g_{Na} \\ g_{SERCA} \\ g_{SRL} \\ g_{ss} \\ i_{NaK} \end{bmatrix}$$







$$\mathbf{c} = \begin{bmatrix} DCa \\ PCa \\ RT50 \\ Tpeak \end{bmatrix}$$

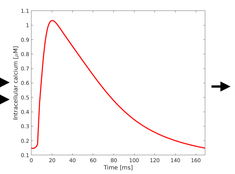
WORKFLOW - ORGAN LEVEL

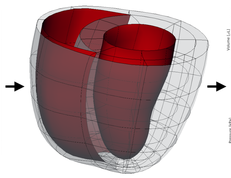
$$f(\mathbf{q}, t) = (q_1 - q_2)\left[q_3 \frac{1}{t} + e^{\frac{t - q_3}{q_4}}\right]^{-1} + q_2$$

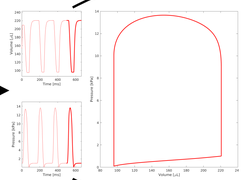
phenomenological Ca²⁺ transient

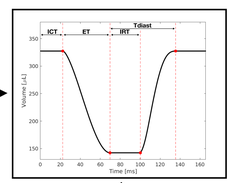
or

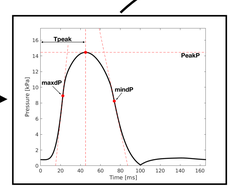
electrophysiological model









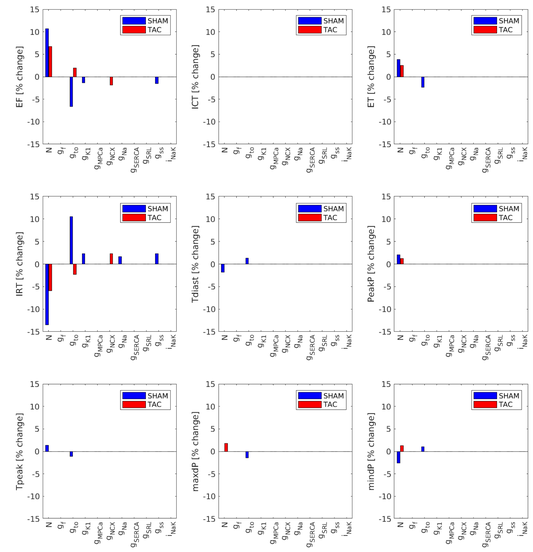


$$\mathbf{d} = \begin{bmatrix} EF \\ ICT \\ ET \\ IRT \\ Tdiast \\ PeakP \\ Tpeak \\ maxdP \\ mindP \end{bmatrix}$$

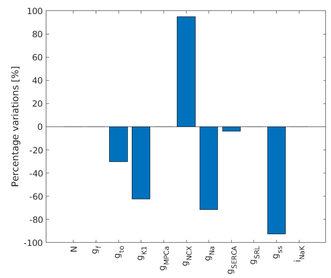
METHODS

- Performing a **local sensitivity analysis** to study how changes in protein scale function affect the 9 organ scale features under study.
- Using the obtained sensitivity matrix to identify the proteins which, if inhibited or enhanced, could lead to recovery performances (requires solving an **inverse problem**).

CONTRACTION FEATURES LOCAL SENSITIVITY TO PROTEINS DENSITIES VARIATIONS



- **SHAM** and **TAC** 1% sensitivities are shown.
- Variations below a fixed threshold (1e-2 %) where considered negligible and set to zero.
- **SHAM** and **TAC** models are characterized by different protein densities:



Initial proteins parameters' percentage variations between **TAC** and **SHAM**

CONCLUSIONS

The five most relevant identified proteins, namely L-type calcium channel, transient outward and inwardly rectifying potassium channels, sarcolemmal and sarcoplasmic calcium pumps, had the largest effect on ejection fraction, ejection time, isovolumetric relaxation time and peak pressure values. Some organ scale phenotypes were insensitive to the small perturbations in cellular parameters applied. However, we would expect larger cellular parameter changes to impact all organ scale phenotypes.

We have developed a novel framework for quantitatively linking changes in protein function through the whole organ phenotypes providing a system for identifying drug targets to manipulate LV contractile function.

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