

Bridging the gap between secondary pharmacology and hemodynamics findings via Quantitative Systems modelling

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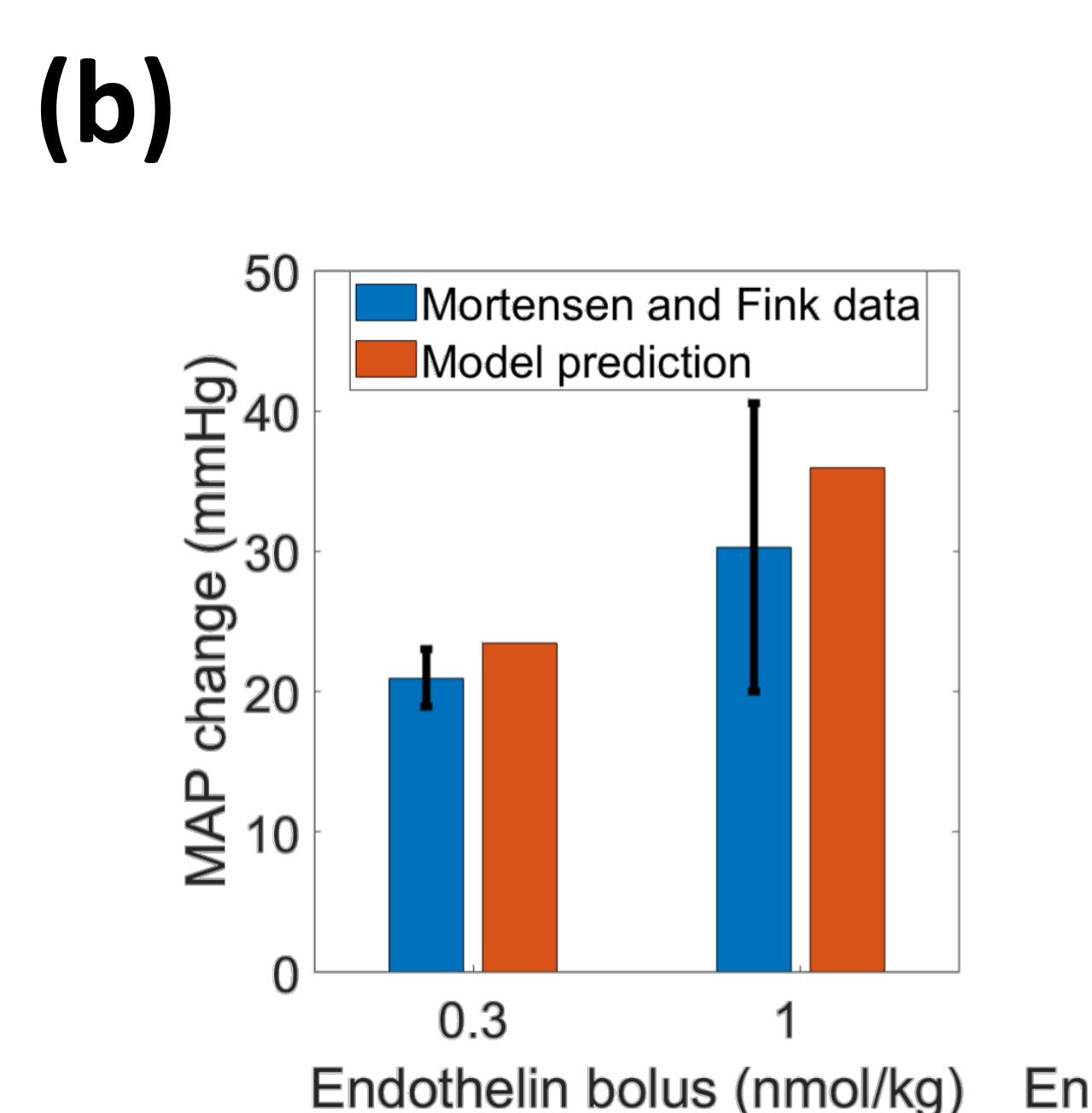
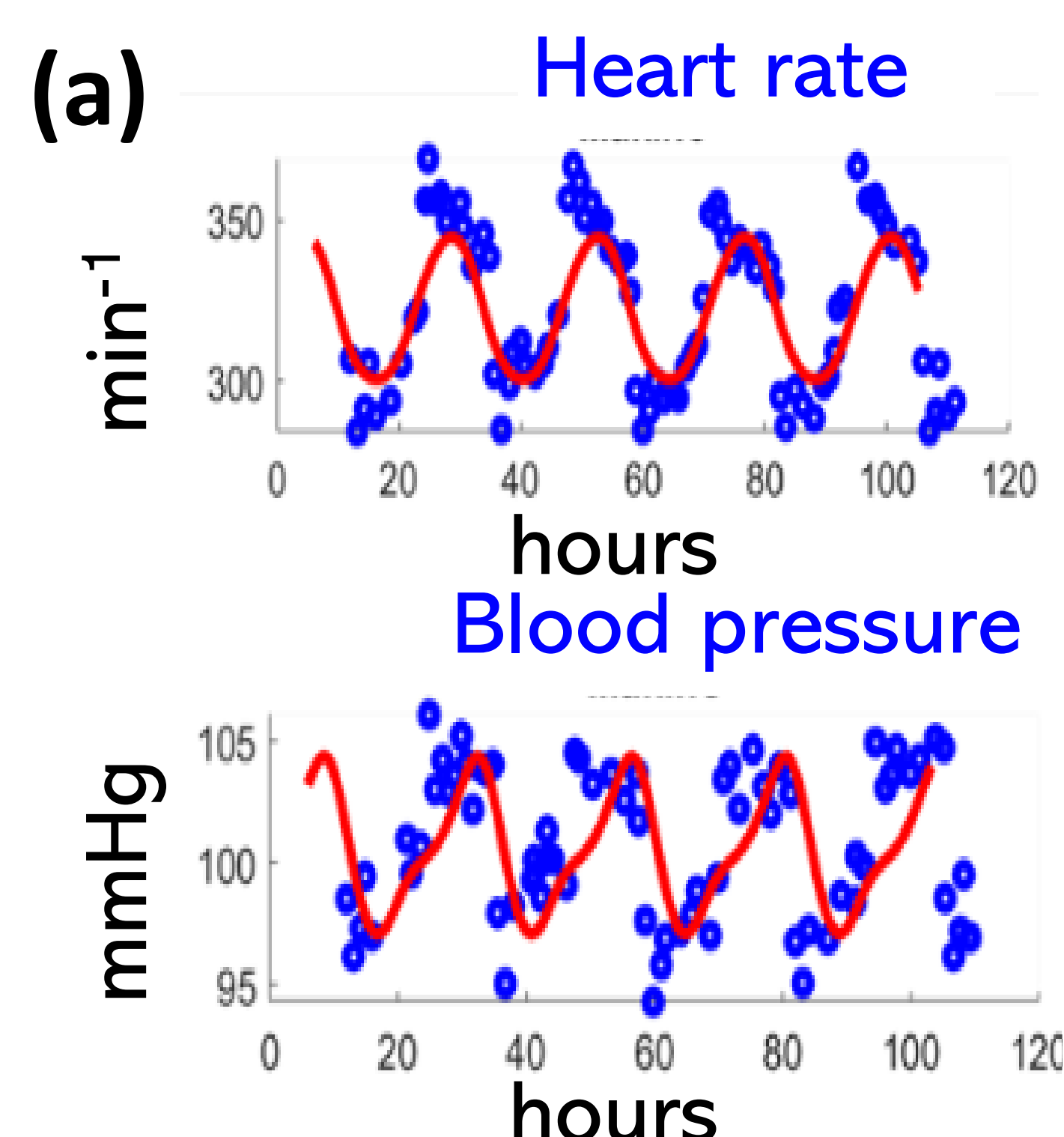
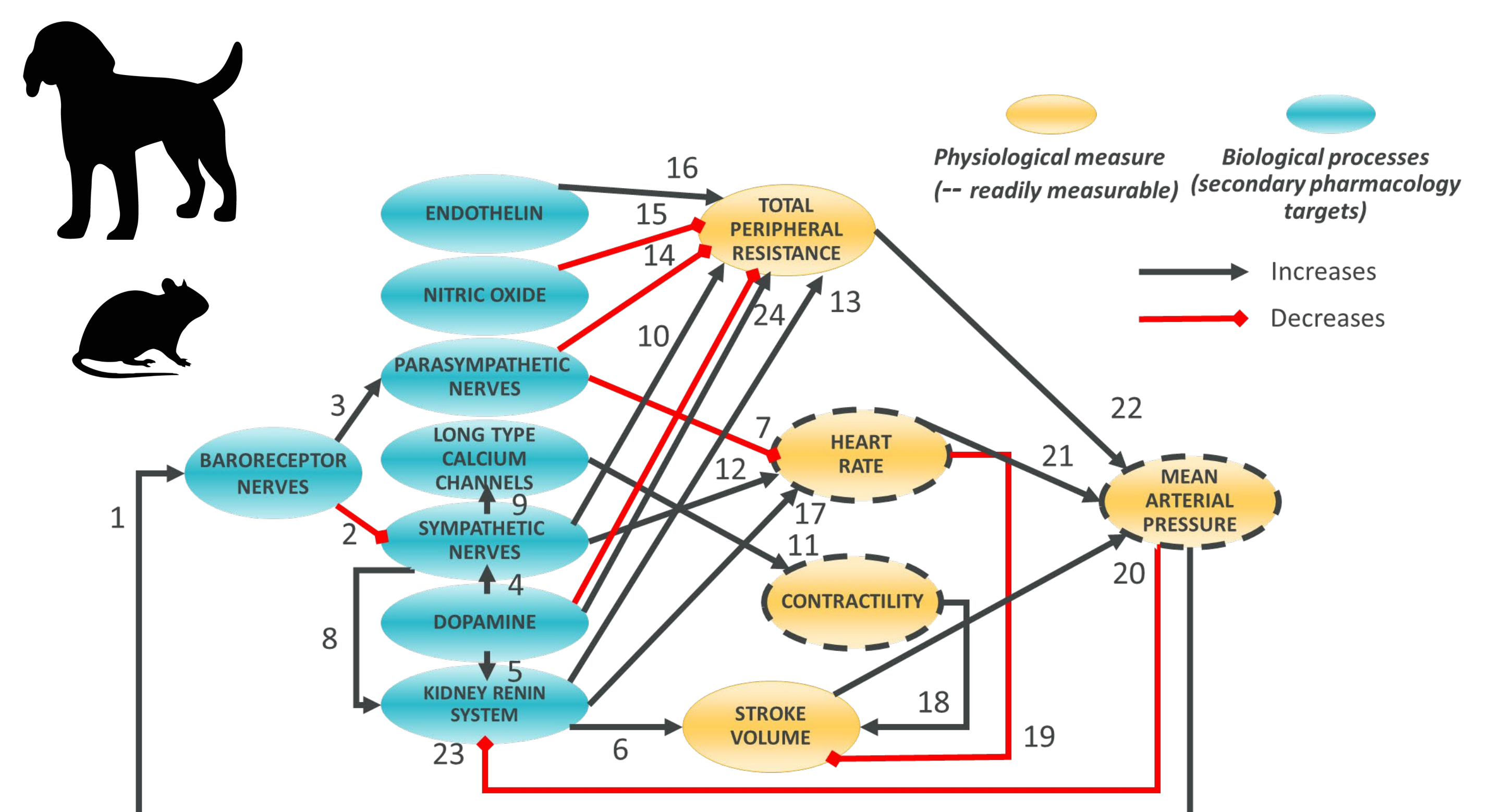
Introduction: Pharmaceutical companies routinely screen compounds for hemodynamics related safety risk, but translation of preclinical findings remains a significant challenge.

We developed a mathematical modelling platform to assist in conciliating *in vitro* and pre-clinical species *in vivo* findings and to improve translation.



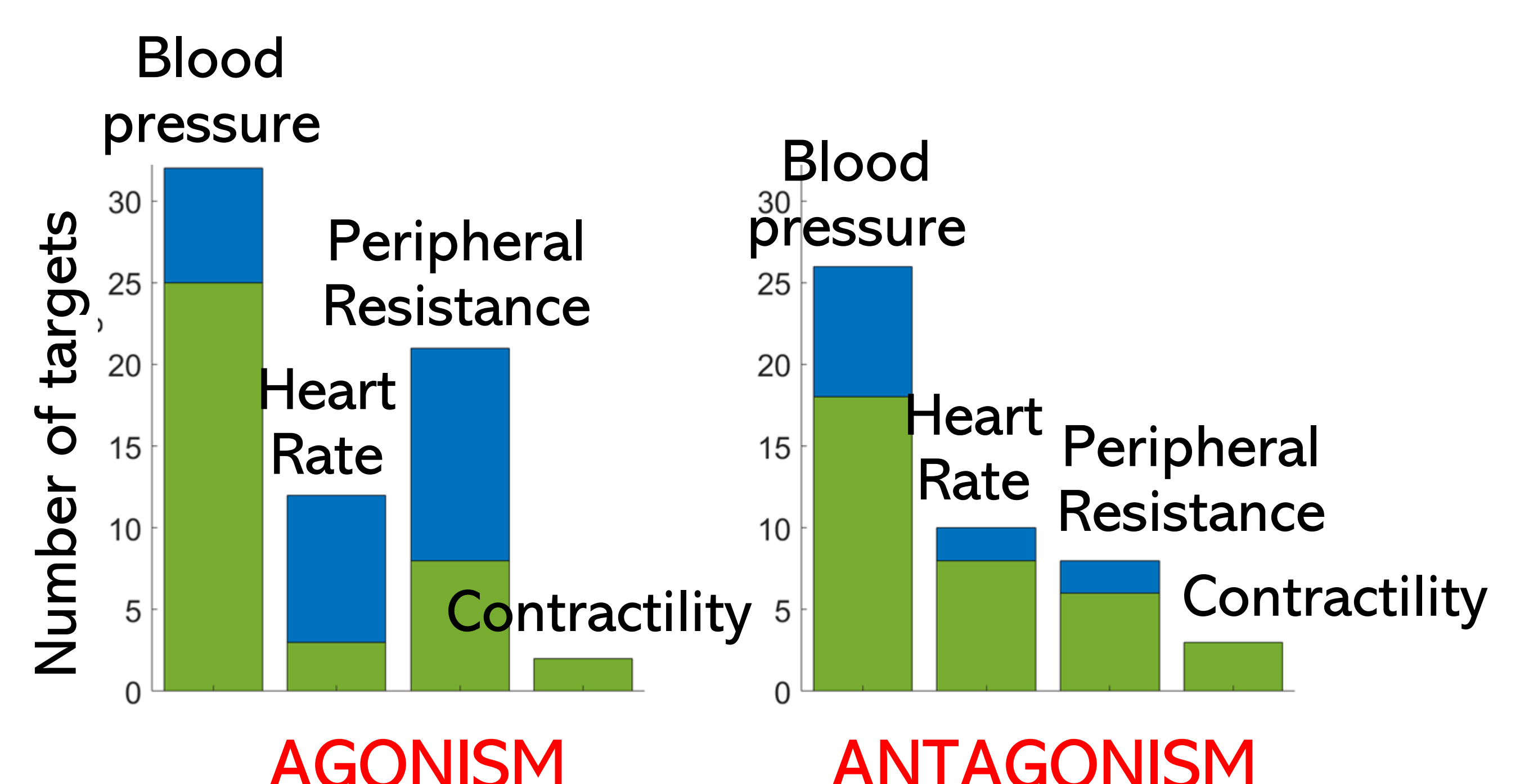
A number of pathways are known to interact with normal hemodynamic functions such as heart rate or blood pressure. *In vitro* assays give controlled results on molecular targets but not on their interactions. *In vivo* studies give overall changes but cannot provide explanation of underlying mechanisms. While many targets are tested for secondary pharmacology, we lack quantitative understanding about its integration into overall functions.

A Quantitative Systems Pharmacology (QSP) or Toxicology (QST) approach was proposed to bridge the gap between molecular and animal findings. Following extensive literature review, we explicitly incorporated various Physiological processes which were decomposed and individually parametrized by leveraging on a wealth of *in vitro*, *in vivo* and *ex-vivo* research in pre-clinical species. The model was developed for both rat and dog species.



We explored simulations of undisrupted daily changes as well as predictions for various interventions and found good agreement overall (more than 50 simulations). Examples of (a) daily changes in heart rate and blood pressure or (b) effect of administering endothelin in rats.

Agonism and antagonism of secondary pharmacology sites of action was benchmarked against literature reports. All predictions were found to be aligned with the reported directions of change. **Green:** can elicit large changes. **Blue:** elicits small changes.



Summary: We developed rat and dog models that integrate many regulatory pathways and their interactions which give rise to hemodynamics changes. The models have similar structure but different parametrization (one set per species). They can incorporate the site of actions of at least 50 known secondary pharmacology targets. We demonstrated that they could reproduce various interventions in intact animals in a series of *in silico* experiments. A publication will provide full details of the literature search modelling details and main findings (currently under review).