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A Simple Cardiac Mitochondrial Model Validated Against Oxygen Consumption Measures Using a Global Senstivity Analysis Approach

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Cardiac mitochondria are intracellular organelles that play an important role
in energy metabolism and cellular calcium regulation.
This is done through intra mitochondrial reactions and ionic fluxes across the
inner mitochondrial membrane.
In particular, cardiac mitochondria influence the excitation-contraction cycle of the heart cell.

We proposed previously a mathematical model of cardiac mitochondria to better understand their underlying role.
With 32 parameters, our model is simple in comparison with models in the literature, yet it is still impossible to be calibrated to experimental data.

In this work, we aim to calibrate our model to experimental data that consists of measures of oxygen consumption rates of mitochondria controlled by external ADP additions.

For this reason, and to quantify the effects of uncertainties on the parameters of the model, we performed a global sensitivity analysis based on Sobol indices.
Firstly, we highlighted the parameters with little influence on fluxes governing the activity of the mitochondria, which are internal components of our model.
Secondly, with these parameters fixed in their range of uncertainty, we repeated the analysis on the oxygen consumption rate of the model, taking into consideration only the influential parameters from the first step.
The latter analysis showed that only six parameters have an important influence on the oxygen consumption rate of the mitochondria.
Finally, using a genetic optimization algorithm, we calibrated these six parameters, using five different experimental datasets, which describe oxygen concentration variation in time.

Results show that our model is able to reproduce both respiration rates of mitochondria and transitions between its different states (before and after the ADP addition), with very low variability of the parameters between each experiment (<2%).

Auteurs principaux: TARRAF, Bachar (phd student); Dr LEGUÈBE, Michael (Ph.D.); Prof. COUDIÈRE, Yves

Orateur: TARRAF, Bachar (phd student)

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