

# Sensitivity analysis of a simple cardiac mitochondrial model.

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## 1. Introduction

Cardiac mitochondria play an important role in the regulation of the intracellular calcium, and thus are linked to the excitation-contraction coupling within cardiomyocytes. It is also known that arrhythmias may occur due to dysfunction in  $\text{Ca}^{2+}$  regulation [1]. For this intent, it is important to model the cardiac mitochondrial activity in order to better understand its mechanisms. Although many mathematical models can be found in the literature, they are generally complex in terms of number of equations and parameters. This complexity makes the process of calibration with experimental data almost impossible.

In this paper, we present a simplified model which has overall 33 parameters. This number can be considered low in comparison with models in the literature. However, it is still too large for calibration purposes. In order to reduce this number of parameters, we perform a global sensitivity analysis in two steps. We first eliminate parameters with little influence on fluxes governing the activity of the mitochondria, which are internal components of our model. Then we perform this analysis on the outputs of the complete model, which are respiration rates that can be compared to experimental data, as we present in the last section.

## 2. Mathematical model

This study is based on the model proposed previously [5], which focuses on few key mechanisms of the mitochondria, specifically respiration, ATP synthesis and exchange,  $\text{Ca}^{2+}$  regulation through the uniporter, and the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger.

Concentration fluxes across the mitochondrial membrane and inside the matrix were first derived taking into consideration the electrochemical force induced by chemical gradients, as done in [3]. Then the expressions were simplified by surface fitting, using as few parameters as possible.

Our model has 6 state variables: the redox potential  $\Delta E_{\text{resp}}$ , the proton motive force  $\Delta p$ , the mitochondrial

and cytoplasmic Gibbs free energy  $\Delta G_{\text{p,m}}$ ,  $\Delta G_{\text{p,c}}$ , and finally the mitochondrial and cytoplasmic  $\text{Ca}^{2+}$  concentrations. The dynamics of those variables is modeled by the following system of ordinary differential equations:

$$\begin{aligned} \partial_t \Delta E_{\text{resp}} &= \varphi_1(\Delta E_{\text{resp}})(V_{\text{PDH}} - V_{\text{resp}}) \\ \partial_t \Delta G_{\text{p,m}} &= \varphi_2(\Delta G_{\text{p,m}})(V_{\text{F1F0}} - V_{\text{ANT}}) \\ \partial_t \Delta G_{\text{p,c}} &= \varphi_3(\Delta G_{\text{p,m}}, \Delta G_{\text{p,c}})(V_{\text{ANT}} - V_{\text{hyd}} + \dot{j}_{\text{ext}}(t)) \\ \partial_t \Delta p &= (12V_{\text{resp}} - 3V_{\text{F1F0}} - V_{\text{ANT}} - V_{\text{leak}} - 2V_{\text{uni}})/C_{\text{m}} \\ \partial_t [\text{Ca}^{2+}]_{\text{m}} &= f(V_{\text{uni}} - V_{\text{NaCa}}) \\ \partial_t [\text{Ca}^{2+}]_{\text{c}} &= -\gamma \partial_t [\text{Ca}^{2+}]_{\text{m}} + \dot{c}_{\text{ext}}(t) \end{aligned}$$

where the functions  $\varphi_i$  are known, and the fluxes  $V_j$  are functions of the state variables and some other parameters that describe the correspondent reactions (see [5] for their detailed expressions). The functions  $\dot{j}_{\text{ext}}(t)$  and  $\dot{c}_{\text{ext}}(t)$  are source terms for cytoplasmic ADP and  $\text{Ca}^{2+}$  respectively. These source terms allow us to mimic an experimental condition, for instance an addition of cytoplasmic ADP.

## 3. Methods

Sobol analysis is a global sensitivity analysis method based on variance decomposition of the output of a model with respect to its parameters [4]. This method allows a global exploration of the parameter space, contrary to local methods, and it can also take into account the statistical distribution of the parameters. Typically, to study the sensitivity of the model to a certain parameter, we calculate the total Sobol index for this parameter. The closer to zero this index is, the less influential on the output of the model it is.

**Sobol's analysis on fluxes** In this paragraph, we illustrate the selection of the influential parameters concerning the respiratory flux  $V_{\text{resp}}$ , which is a function of  $\Delta E_{\text{resp}}$  and  $\Delta p$ , and includes a total of six parameters,  $p_0$  to  $p_5$ . The same procedure was applied to all fluxes.

Sobol indices of each parameter  $p_i$  were computed using the SALib Python library [2], for a range of  $\Delta E_{\text{resp}}$  and  $\Delta p$  as shown in Fig. 1. We checked that

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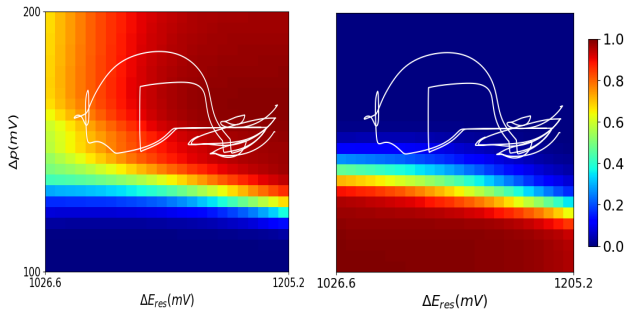


Figure 1: Total Sobol indices of parameter  $p_2$  (left) and  $p_4$  (right) for the flux  $V_{\text{resp}}$ . White lines locate several trajectories of the state variables in the  $(\Delta E_{\text{resp}}, \Delta p)$  space, whereas color depicts the magnitude of the Sobol index. Trajectories were generated using random samples of the whole set of parameters.

the trajectories of the state variables did not cross areas with high Sobol indices before excluding the considered parameter.

**Sobol's analysis on observables.** Sobol indices were also computed for the output of the whole ODE system. The latter can be seen as a function  $y = f(p)$ , where  $p$  is the set of parameters and  $y$  are the observables of the system that can be compared to experimental data.

Evaluations of  $f$  require an ODE system to be solved accurately, which can be problematic as the system includes very fast dynamics and the source term  $\dot{g}_{\text{ext}}$  has a stiff profile. We used a predictor-corrector numerical scheme, which allowed for integration of the equations in  $\sim 30$  seconds.

The observable  $y$  used below is the respiration rate.

## 4. Results and discussion

The first sensitivity analysis on fluxes only allowed us to remove 6 parameters from the starting set of 26 flux's parameters. The low number of non-influential parameters is an indication of our correct simplification procedure when writing flux expressions.

The second analysis however highlighted very few parameters as having an influence on the respiration rates. All Sobol indices were less than  $10^{-2}$  except for the parameters  $p_2$  ( $S = 0.4$ ),  $p_{14}$  ( $S = 0.7$ ) and  $p_{20}$  ( $S = 0.14$ ). The first parameter controls the maximum amplitude of the respiratory flux  $V_{\text{resp}}$ , while the parameter  $p_{20}$  controls the amplitude of the proton-leak flux across the membrane. This is expected as at that stage, without ADP, mitochondria are only respiring to compensate the proton leakage across the membrane. The parameter  $p_{14}$  is the electric potential threshold of activation of the ATP-synthase. The model's simulations matches with experimental respiration rates in both state 3 and 4 of the mitochondria (Fig. 2).

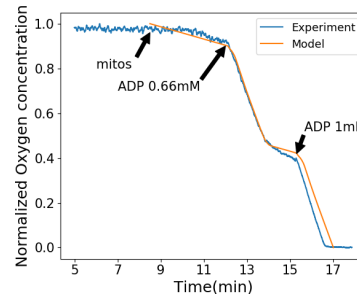


Figure 2: Comparison of the oxygen consumption between the experimental data and the model's simulation, for the respiratory states 4 (before ADP addition) and 3 (after ADP addition) of the mitochondria. Calibrated parameters:  $p_2 = 150$  mV,  $p_{14} = 1.76 \times 10^2$  mV,  $p_{20} = 0.047$  mV $^{-1}$

## 5. Conclusion

In this work, we have carried out a global sensitivity analysis on the proposed model. This analysis was completed in two steps, first on the internal fluxes of the mitochondria, and second on the respiration rate as an output of the model. Finally, using the results from the second step, we calibrated manually the three influential parameters in order to fit a given experimental respiration. We expect repeated sensitivity analysis with diverse experimental data to allow for more parameters to be calibrated.

## 6. Acknowledgements

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