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 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, Ca^{2+} regulation through the uniporter, and the Na^+/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 ΔE_{resp}, the proton motive force Δp, the mitochondrial and cytoplasmic Gibbs free energy $\Delta G_{\mathrm{p,m}}, \Delta G_{\mathrm{p,c}}$, and finally the mitochondrial and cytoplasmic Ca^{2+} concentrations. The dynamics of those variables is modeled by the following system of ordinary differential equations:

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

where the functions φ_i are known, and the fluxes V_j are functions of the state variables and some other parameters that describe the correspondant reactions (see [5] for their detailed expressions). The functions $\dot{g}_{\mathrm{ext}}(t)$ and $\dot{c}_{\mathrm{ext}}(t)$ are source terms for cytoplasmic ADP and 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_{resp}, which is a function of ΔE_{resp} and Δp, 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 ΔE_{resp} and Δp as shown in Fig. 1. We checked that

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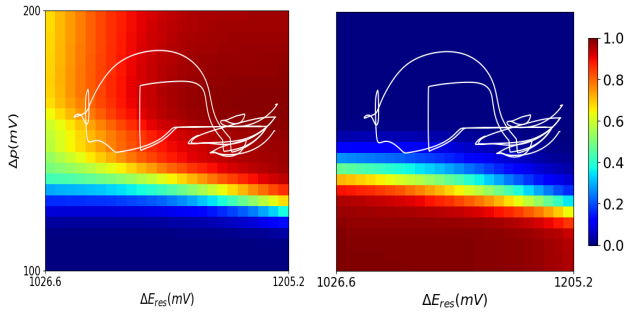

Figure 1: Total Sobol indices of parameter p_2 (left) and p_4 (right) for the flux V_{resp}. White lines locate several trajectories of the state variables in the $(\Delta E_{\text{resp}}, \Delta p)$ space, whereas color depicts the magnitude of the Sobol index. Trajectories were generated using random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

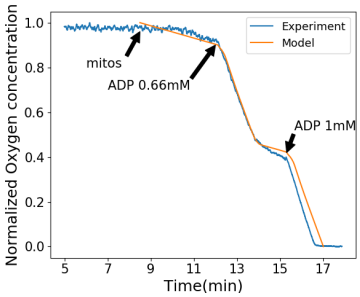

Figure 2: Comparison of the oxygen consumption between the experimental data and the model's simulation, for the respiratory states 4 (before ADP addition) and 3 (after ADP addition) of the mitochondria. Calibrated parameters: $p_2 = 150$ mV, $p_{14} = 1.76 \times 10^2$ mV, $p_{20} = 0.047$ mV^{-1}

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 influantial parameters in order to fit a given experimental respiration. We expect repeated sentivity analysis with diverse experimental data to allow for more parameters to be calibrated.

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