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Global Sensitivity Analysis for Uncertain Parameters Applied to a Cardiac Mitochondrial Model

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Abstract

Cardiac mitochondria are intracellular organelles that have several important roles. For instance, they ensure energy metabolism and calcium regulation, thus are linked to the excitation-contraction cycle of the heart cell. Mathematical models are useful to better understand the complexity of mitochondrial dynamics within a cardiac cell, and we are specifically interested in the dynamics of calcium. Literature models reflect this complexity, especially in terms of number of equations and parameters, which makes them impossible to calibrate to experimental data.

In this paper, we apply a global sensitivity analysis on our previously discussed simple mitochondria model [1], in order to quantify the uncertainty of the parameters. This analysis is done in two steps. First we eliminate non-influential parameters of the internal fluxes governing the activity of the mitochondria. Then we perform this analysis on the outputs of our ODE (ordinary differential equation) model, which are the respiratory rates.

Finally, we calibrate the remaining influential parameters using a genetic algorithm with respect to experimental respiratory data.

1. Introduction

It is widely known that cardiac contraction is triggered by calcium (Ca^{2+}), hence a perturbation in the intracellular Ca^{2+} homeostasis could lead to heart failure [2]. Cardiac mitochondria are intracellular organelles that participate in the Ca^{2+} regulation through their channels or pores: Ca^{2+} uniporter, $\text{Na}^+/\text{Ca}^{2+}$ exchanger and mitochondria permeability transition pore (mPTP). For this reason, developing cardiac models that take into account the activ-

ity of the mitochondria is important. In our previous paper [1], we introduced a mathematical model that describes key mechanisms of the cardiac mitochondria, specifically dioxygen consumption, calcium (Ca^{2+}) regulation through the uniporter and the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, and the ATP synthesis. The model consists of six state variables that describe the activity of the mitochondria through ion fluxes (Fig.1). These fluxes model the variation of the state variables in time. We recall the model's differential equations

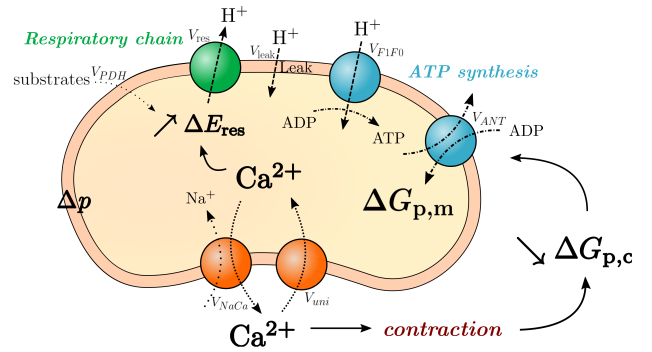


Figure 1. Reactions and fluxes described by the model. State variables are indicated by bold font.

system (S):

$$\partial_t \Delta E_{\text{resp}} = \varphi_1(\Delta E_{\text{resp}})(V_{\text{PDH}} - V_{\text{resp}}),$$

$$\partial_t \Delta G_{\text{p},\text{m}} = \varphi_2(\Delta G_{\text{p},\text{m}})(V_{\text{F1F0}} - V_{\text{ANT}}),$$

$$\partial_t \Delta G_{\text{p},\text{c}} = \varphi_3(\Delta G_{\text{p},\text{c}})(V_{\text{ANT}} + j_{\text{ext}}(t)),$$

$$\partial_t \Delta p = (12V_{\text{resp}} - 3V_{\text{F1F0}} - V_{\text{ANT}} - V_{\text{leak}} - 2V_{\text{uni}})/C_m,$$

$$\partial_t [\text{Ca}^{2+}]_{\text{m}} = f(V_{\text{uni}} - V_{\text{NaCa}}),$$

$$\partial_t [\text{Ca}^{2+}]_{\text{c}} = -\gamma \partial_t [\text{Ca}^{2+}]_{\text{m}} + \dot{c}_{\text{ext}}(t),$$

where the functions φ_i are known and the parameters f and γ account for the fraction of free Ca^{2+} in the matrix and in the cytosol, respectively. The functions $\dot{g}_{\text{ext}}(t)$ and $\dot{c}_{\text{ext}}(t)$ 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. The biological meaning of the fluxes V_j and the derivation of their expressions can be found in [1].

Even though our model is considered simple (34 parameters overall) in comparison with models in the literature, it is still impossible to calibrate it to fit experimental data. For this reason, we first perform a global sensitivity analysis to eliminate parameters which have small influence on these fluxes (sec. 2.1). Then, using the results from this first step, we perform again the analysis, but this time on the observables of our model as output (sec. 2.2). Finally (sec. 3), we use the results of the sensitivity analysis to calibrate the few remaining parameters to experimental respiratory rates.

2. Global sensitivity analysis

The concept of global sensitivity analysis is to quantify the influence of a certain parameter on the output of a model, while spanning the whole parameter space, that can be of very high-dimension. In practice, we used the Sobol analysis method which consists in decomposing the variance of the output of a model with respect to its parameters [3]. Beside being able to explore globally the parameter space, this method can also take into account the statistical distribution of the parameters.

Typically, a model is written as $Y = f(p_1, p_2, \dots, p_k)$ where Y is the output and $p_i, i \in \{1, \dots, k\}$ are the parameters. For each parameter p_i , the total Sobol index associated to p_i is $S_{T_i} = \frac{E[V(Y/p_{\sim i})]}{V(Y)} = 1 - \frac{V(E[Y/p_{\sim i}])}{V(Y)}$, where $p_{\sim i}$ denotes all the parameters except p_i . The less influential the parameter p_i is on the output Y , the closer to zero the index S_{T_i} is, and *vice versa*. If $S_{T_i} \simeq 0$, then p_i can be fixed in its range of variability without significantly affecting $V(Y)$.

The straightforward approach for calculating the Sobol index associated to a parameter p_i is computationally expensive. To overcome this, we used the Saltelli sampling method [3] which reduces the total number of evaluations of f to $N \times (k + 2)$, where N is the size of the parameters sample. All the Sobol indices were computed using the SALib Python library [4].

2.1. Sobol's analysis on fluxes

As a first step of our sensitivity analysis, each flux V_j is considered as a separate model that depends on some parameters. Computing the Sobol indices of a parameter gives an idea of its influence on the associated flux. The

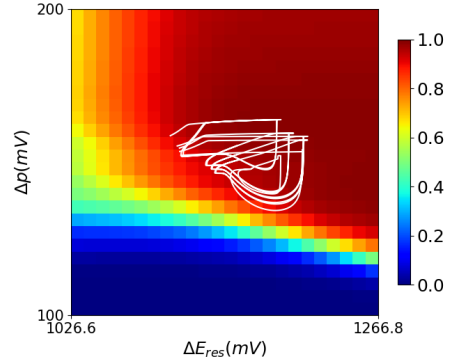


Figure 2. Total Sobol indices of parameter p_2 for the flux V_{resp} . White lines locate several trajectories in the phase space $(\Delta E_{\text{resp}}, \Delta p)$. Color depicts the magnitude of the Sobol index. Trajectories were generated using random samples of the whole set of parameters.

fluxes are not only functions of their associated parameters, but also of the state variables, and hence computing the Sobol indices for a large range of state space points is necessary.

For each flux, to be able to eliminate uninformal parameters, we checked that the trajectories of the state variables along typical mitochondrial respiratory cycles did not cross areas with high Sobol indices (Fig. 2 for an example of an influential parameter). Using this method, we were able to eliminate 7 parameters out of 27 involved in the expression of the fluxes, among the overall 34 parameters.

2.2. Sobol's analysis on the output of (S)

The ODE system (S) can be seen as an equation $y = g(p)$, where p is the set of parameters, and y is the solution over the integration time interval. To have a global idea on the influence of the remaining set of parameters \tilde{p} on the solution y , we perform the Sobol analysis on the model $y = \tilde{g}(\tilde{p})$, where \tilde{g} is the model function g with the 7 previously identified parameters fixed in their range of uncertainty.

Each evaluation of \tilde{g} requires an ODE system to be solved accurately, which can be problematic as the system includes very fast dynamics and the source term \dot{g}_{ext} has a stiff profile. A predictor-corrector numerical scheme allowed for integration of the equations in ~ 100 seconds. With $k = \text{Card}(\tilde{p}) = 34 - 7 = 27$ parameters, and using a sampling number $n = 2000$, then 58000 model evaluations were required. Computations were performed in parallel using the PlaFRIM experimental testbed. The results are presented on figure 3.

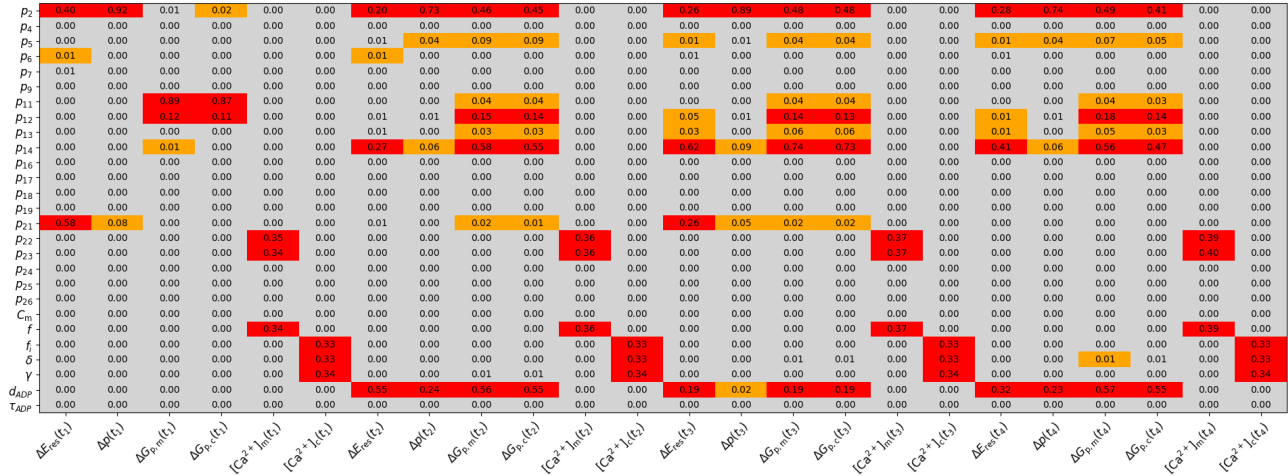


Figure 3. Total Sobol index for the set of parameters q associated to the system (S). The output of our model is considered at 4 different time points, t_1 (before first addition), t_2 (after first addition), t_3 (before second addition), t_4 (after second addition). First addition is 0.66 mM cytoplasmic ADP, second addition is 1 mM cytoplasmic ADP. The 3 colors level represent the magnitude of the total Sobol index, grey being the lowest ($S_T < 10^{-2}$), then yellow ($10^{-2} \leq S_T < 10^{-1}$), and orange being the highest ($S_T \geq 10^{-1}$).

3. Parameters calibration

3.1. Experimental data

The experimental data were obtained from heart mitochondria extracted from Wistar Male rats (from Janviers Lab, France). Isolated mitochondria were analyzed within the day following their preparation and subsequent determination of proteins concentration by the Bratford method. All effectors of the respiratory chain used herein were first prepared as concentrated mother solutions (500 mM for the substrates of the respiratory chain, glutamate and malate, and 100 mM for ADP; all compounds were purchased from Sigma-France) in the specific respiration buffer for mammal heart mitochondria. All solutions were kept on ice during the timescales of experiments.

The mitochondrial oxygen consumption rates were collected by the gold standard method in bioenergetics, that is chronoamperometry with a Clark electrode [5]. This electrochemical system determines the dissolved oxygen concentration of a liquid medium by measuring the current resulting from the 4-electron reduction of dioxygen O_2 to water H_2O on a platinum disk (at a potential of -0.8V vs the internal Ag/AgCl reference electrode). O_2 diffuses towards the platinum through a Teflon membrane protecting it from the solution. The Clark electrode was inserted in an oxygraphy chamber filled with 6 mL of respiration buffer under constant stirring, and thermostated at 28 °C with a water gasket. Substrates of the respiratory chain were injected at 5 mM final concentration, then mitochondria were injected to reach a concentration of 0.4 mgprot.mL⁻¹

in the respiration buffer. ADP was further introduced at various concentrations (0.166 to 1mM). The current at the Clark electrode was continuously measured, and the oxygen concentration determined by a simple proportionality factor (210 μ M of O_2 maximum concentration).

3.2. Optimization algorithm

As observed on Fig. 3, we found that 6 parameters $\{p_2, p_{11}, p_{12}, p_{14}, p_{21}, d_{ADP}\}$ are influential on the respiratory rates. The remaining parameters with a high Sobol index are not considered, since they would be rather related to Calcium fluxes. We choose to apply a genetic optimization algorithm [6] to fit these parameters to the data, because of the high dimensionality of the problem. The selection process at each iteration is based on minimizing $\|y_{sim} - y_{obs}\|_{l_2}$, where y_{obs} is the experimental normalized oxygen concentration, and y_{sim} is the simulated one. From the selected set of parameters, we apply the mutation and crossover operators to eventually obtain the next generation of parameters that is trivially better adapted to our problem. The algorithm allowed convergence to an optimum set of parameters after 25 iterations. Figure 4 shows the resulting oxygen concentration over the time compared to the experimental data.

4. Discussion

The Sobol sensitivity analysis on fluxes revealed only 7 uninfluential parameters from the starting set of 27 flux parameters. This indicate that our choices of expressions

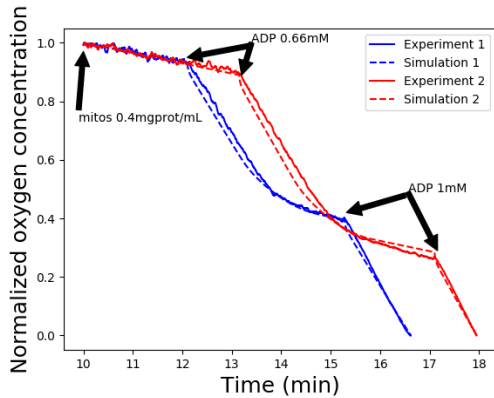


Figure 4. Comparison of the oxygen consumption between two sets of experimental data, in the presence of 5mM of glutamate and malate, and simulation, for the substrate-state (before ADP addition) and phosphorylating state 3 (after ADP addition) of the mitochondria.

for the fluxes is nearly optimal (ie minimizes the number of parameters).

However the Sobol analysis on the whole model highlighted only very few parameters as influencing the respiratory rates. We also noticed in figure 3 a block structure that discriminates parameters which influence calcium concentrations, from the ones which influence the respiratory rates. It suggests that further calibration of these subsets can be performed separately.

All Sobol indices were less than 10^{-1} except for the parameters $p_2, p_{11}, p_{12}, p_{14}, p_{21}$, and d_{ADP} , for which total Sobol indices reach 0.92, 0.89, 0.18, 0.74, 0.58, and 0.57, respectively. The first parameter controls the maximum amplitude of the respiratory rate V_{resp} . The parameters p_{11}, p_{12} , and p_{14} control the ATP/ADP and Δp dependent activation threshold of the ATP-synthase, respectively. The parameter p_{21} tunes the amplitude of the proton leak across the mitochondrial membrane. The corresponding high Sobol index before any ADP addition ($S_T = 0.58$) is thus expected, since at this stage mitochondria are only respiring to compensate the proton leakage. Finally, the parameter d_{ADP} which controls the duration of the addition of ADP has a high Sobol index which can also be expected.

The optimization algorithm converges towards an optimal set for these parameters. The relative l_2 error with respect to the data is less than 0.032 (Fig. 4). It shows the ability of our model to reproduce experimental respiratory rates in both phosphorylating state 3 and substrate-state of the mitochondria.

5. Conclusion

In this work, we firstly carried out a global sensitivity analysis on the model proposed in [1]. It was completed in two steps, the analysis on the internal mitochondrial flux functions outputs, and the analysis on the state variables of the model along a typical trajectory. It allowed to determine the main relevant parameters. Secondly, we applied an iterative optimization algorithm to successfully calibrate these six parameters to a given experimental situation. We expect repeated sensitivity analysis with diverse experimental data (e.g. calcium, reactive oxygen species) to allow for more parameters to be calibrated.

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