VIRTUAL MITOCHONDRION : A Modular and Multi Level Whole-Mitochondrion Model

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Abstract

Introduction: Virtual Mitochondrion is a project of a multilevel modelling of mitochondrial bioenergy metabolism.

It involves:
- A molecular/atomic level with stochastic modelling (Gillespie) of electrons and protons transfers in respiratory chain complexes and super complexes of respiratory chain. It allowed us to predict a natural bifurcation of electrons in complex III (proof of Q-cycle hypothesis of Mitchell) to clarify the antimycin inhibition constraints and to simulate the ROS production in complex I and III. It also permits to jump to the upper level of enzyme kinetics.
- A mitochondrial level with the global modelling of the respiratory chain. The aim is to understand how local changes (pathological mutations for instance, drug effect, competition between respiratory substrates) in respiratory complexes influence the global behavior of the oxidative phosphorylation.
- A cell level with the description of simple(s) model(s) of central energy metabolism easy to manipulate and to understand. The aim is to coherently integrate various types of data, metabolomics, fluxomics, transcriptomics and to follow the rerouting of metabolism, their regulations and controlling steps/targets (Metabolic Control Analysis).

Conclusion: We would like to emphasize the connection between lower and upper levels: how the functioning at a given level explains (or does not explain) the functioning at the upper/integrated level? Thus, in this work, the purpose of a model is not only to fit the experimental results accurately but rather to evidence inconsistencies that will lead to unveil mechanisms/properties which were hitherto not taken into account or even unknown.

Keywords: Mitochondria, metabolism modeling, Stochastic modeling

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