PhD PROJECT PROPOSAL

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mitoXplorer 4.0 for analysing and modeling mitochondrial tissue diversity by integrating multi-omics data

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Abstract

In this project, we want to unravel mitochondrial heterogeneity on a tissue- and cell type level.
Mitochondria are the so-called powerplants of nearly all eukaryotic cells, best known for their function in producing cellular energy in the form of ATP and are additionally involved in many other cellular processes, including central cellular metabolism, Ca2+ signaling, ROS defense and signaling, apoptosis, etc. They are also extremely adaptable to the environment and change their composition and function depending on the cell type, and the cellular state during development, ageing or disease.
We have previously developed the mitoXplorer platform for analyzing and integrating -omics data from a mitochondrial perspective (1,2) which allows users to integrate -bulk- and single-cell expression and mutational data. In this new project, we want to extend mitoXplorer to allow multi-omics data integration by using multilayer networks. In addition, we want to enable modelling of mitochondrial metabolism using constraint-based modelling, directly from the mitoXplorer platform.
This new version of mitoXplorer will thus allow a deeper and more precise understanding of cell-type specific mitochondrial adaptability.

Keywords

mitoXplorer, mitochondria, mitochondrial adaptability, multi-omics data, complex networks, metabolic modelling

Scientific question and Objectives

We want to understand how mitochondria are able to adapt to their cellular environment. We have evidence that mitochondria are in fact governing cellular fate by employing part of the respiratory chain (RC), which is centrally involved in energy metabolism, and they do so via the small electron-carrier molecule Coenzyme Q (CoQ) (3). CoQ can be reduced by several oxidoreductases, which puts the RC in control of several metabolic pathways (complex I and mG3PDH: redox balance; complex II: TCA cycle; ETC: beta-oxidation; DHODH: pyrimidine synthesis). We want to unravel the mechanism that governs this CoQ crossroad using a highly interdisciplinary approach that combines computational biology, graph theory, metabolic modelling, on proprietary, systematic and multi-omics experimental data that will be collected by a co-financed collaboration partner (AM).

Proposed approach (experimental / theoretical / computational) and research plan

To reach our goal, we will extend our previously developed mitoXplorer web-tool (https://mitoxplorer3.ibdm.univ-amu.fr) to be able to integrate multi-omics data by using multilayer networks, as well as to allow modelling of mitochondrial metabolism using constraint-based modelling (4) directly from the mitoXplorer web-tool. In brief, the mitoXplorer web-tool is based on a high-quality, manually assembled and annotated mitochondrial interactome that encompasses all genes with a mitochondrial function (mito-genes). This mito-interactome is used to integrate expression and mutation data on bulk- and single-cell level and allows users with 12 highly interactive interfaces to mine -omics data from a mitochondrial perspective (1,2).

We will generate mitochondrial multilayer networks (mito-MLN) based on the mito-interactomes from mitoXplorer, as well as the mitoMammal metabolic network (4) for human and mouse, as well as extend this mito-MLNs to other model species available in mitoXplorer (fruit fly and budding yeast). We will then implement a toolbox for MLN analysis for module and pathway identification, node prioritization (5), as well as explore algorithms for temporal network analysis (6).

To link constraint-based metabolic modelling to data from mitoXplorer, we will connect the mitoXplorer web-tool to a Jupyter notebook we recently developed for constraint-based mitochondrial metabolic modelling (mitoMammal, 5) and explore further tools for interpreting and comparing results from metabolic modelling. As mitoMammal is currently limited to mouse and human, we will extend this mito-metabolic network to other species available in mitoXplorer using orthology search methods, as well as existing metabolic models for the species in question (fruit fly and budding yeast).

Interdisciplinarity and Implication of the three labs

The success of this project depends on an interdisciplinary effort.
BH is expert in mitochondrial computational biology, her team has developed the mitoXplorer web-tool, as well as the mitoMammal network for metabolic modelling. She has also experience in temporal network analysis and together with LT, her team developed the TimeNexus (6) and Phasik (7) tools for complex network analysis. She is the coordinator of this ANR-financed project and the student will be affiliated primarily with her group.
LT is an expert in complex graph theory. He is an associate professor and part of the MABioS team (Mathematics and Algorithms for Systems Biology) located in the Institute of Mathematics of Marseille (I2M). The MABios team is widely recognized for its expertise in logical modelling of biological processes, large-scale mining of biological interaction networks and in the development of network-based predictive methods.
AM has 15 years of experience in mitochondrial bioenergetics and genetics. His team hosts experts with complementary expertise in biochemistry (mitochondrial bioenergetics, enzymology and energy metabolism), cell biology (mitochondrial dynamics and ultrastructure), physiology (mouse physiology and mitochondrial diseases). The Mourier Team is affiliated with NG Larsson team at Karolinska Institute (Sweden). His team will perform all the experimental work that feed into this project.
This consortium combines the experimental expertise of the AM team in mitochondrial bioenergetics and metabolism, with the data mining expertise of the BH team and the complex network and modelling expertise of the LT team. BH has already published with AM and LT on related topics.

Specify with whom the person recruited will collaborate and on what aspects

The student will be affiliated with the team of Bianca Habermann and work under her supervision and in close collaboration and under the co-supervision of Laurent Tichit. She/he will regularly interact with the team of Arnaud Mourier and work with the data generated by the AM team.

PhD student's expected profile

The candidate should have solid programming experience and be familiar with Python, which will be the primary programming language. As mitoXplorer is written in Python, Javascript and PHP and involves also MySQL, additional

experience in these programming languages would be a plus. At least the student should be willing to invest in learning these languages. Training in -omics data analysis would be a plus, but are not strictly required, especially in bulk and single-cell RNA-seq and/or proteomics and metabolomics. We seek a dedicated, curious and open-minded individual who is able and willing to work in a team.

References related to the project

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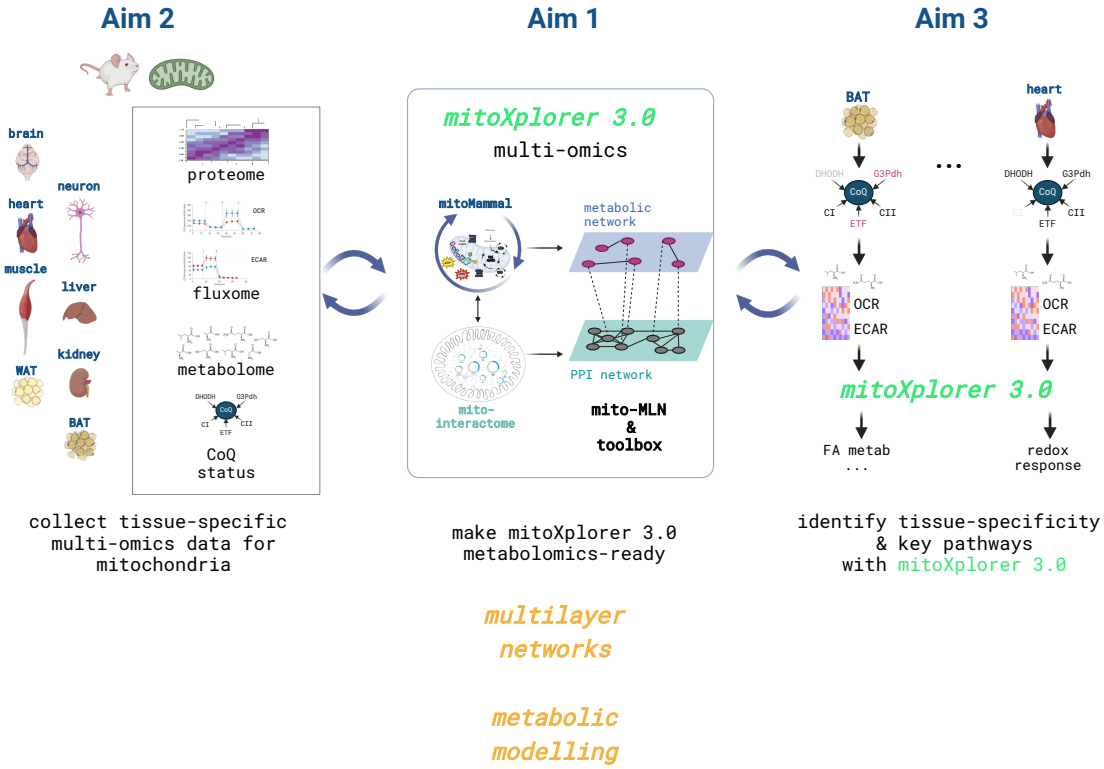
Project's illustrating image



In case you are interested, please contact: bianca.habermann@univ-amu.fr!