Title: Using resource allocation-based models to define advanced therapeutic strategies for stopping cancerous cell proliferation

Position: Post-doctoral position

Duration: 30 months, starting 01/06/2022.

Location: UR MaIAGE (https://maiage.inrae.fr/), Systems biology team (V. Fromion, M. Dinh, A. Goelzer), INRAE, Jouy-en-Josas, France.

External collaborations: LBBE (CNRS, Lyon, S. Peres), Cochin institute (INSERM, Paris, R. Dentin).

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Context. Cancer metabolism is one of the oldest areas of research in cancer biology, predating the discovery of oncogenes and tumor suppressors by some 50 years. The field is based on the principle that metabolic activities are altered in cancer cells relative to normal cells, and that these alterations support the acquisition and maintenance of malignant properties. Because some altered metabolic features are observed quite generally across many cancer types, reprogrammed metabolism is considered a hallmark of cancer. The key questions driving research in the field should be devoted to identifying key metabolic candidates whose inactivation might severely impair tumor cells while sparing normal cells for therapeutic benefits. Unfortunately, the high metabolic adaptability of tumor cells to find alternative pathways frequently frustrates recent therapeutic interventions.
We thus need to explore in some detail the possibilities for cancerous cells to grow, and determine if cancer cells are able to multiply using the resources available in their micro environment, in the presence or absence of specific therapeutic agents. To address this problem, an approach is to use whole-cell modeling to account not only for metabolic activities, but also for other cellular functions that can be impacted during cancer cells adaptation. Among whole-cell modeling techniques, the constraint-based modeling (CBM) framework, and especially, the resource balance analysis (RBA) framework (developed in MaIAGE, see [1-3]) is particularly promising to tackle this challenge since it offers a good trade-off between prediction accuracy of cell phenotypes and numerical tractability [1].

Research hypothesis. We propose to develop a novel and comprehensive CBM analysis using the RBA methods to predict the ability of cancer cells to grow and develop computational tools for defining therapeutic strategies. We will integrate datasets and relevant biological constraints from Cochin's lab in order to identify only the subset of application-specific, biologically relevant pathways. Thus, the scientific objectives are summarized as follows:

1. Develop genome scale models, according to biological tissues handled and to specificities of the metabolic network studied;

2. Extensively validate, test and compare the models developed above for cancer cell metabolism using available and newly generated omics datasets;

3. Extend the Resource Balance Analysis framework to eukaryotic cells to compare cancer and non-tumoral cells, predict essential processes of the cancer cell to growth

predict the alternative pathway and propose therapeutic strategies to kill the cancer cells.

Activities. The post-doctorant will be specifically in charge of:

- the development of RBA models of two types of healthy cells (hepatic and colorectal) and their associated cancerous cells;
- the calibration and validation of RBA models using publicly available and newly generated omics datasets by the Cochin institute. This part also necessitates a step of omics data analysis;
- the analysis of the model behavior to identify essential processes of the cancer cell to growth, and propose candidates for therapeutic strategies to kill the cancer cells (in collaboration with the LBBE);
- the update of the computational infrastructure allowing for the semi-automatic generation of RBA models [3] for eukaryotic (human) cells.

Moreover, he/she will interact closely with the biologists and computational scientists of the Cochin institute, and LBBE, and will benefit from the existing computational infrastructure [3] and expertise of the MaIAGE team at developing RBA models of prokaryotic and eukaryotic cells.

Skills

We are looking for candidates with a phD in bioinformatics or systems biology. Candidates having a phD in biology will be considered if they justify of a significant experience in bioinformatics/systems biology. An experience in constraint-based modeling is encouraged.
Knowledge on cellular biology/metabolism
Knowledge on logic programming would be a plus.
Capabilities of being autonomous.
Capabilities (and appetite) for interdisciplinary works.
Programming language: Python (mandatory), Matlab (optional, but recommended). The R language can sometimes be used.

References.

1. **Goelzer, A. et al.** (2015). Quantitative prediction of genome-wide resource allocation in bacteria. Metabolic engineering, *32*, 232-243. https://doi.org/10.1016/j.ymben.2015.10.003
2. **Goelzer, A., and Fromion, V.** (2019). RBA for eukaryotic cells: foundations and theoretical developments. *bioRxiv*, 750182.
3. **Bulovic, A., et al.** (2019). Automated generation of bacterial resource allocation models. Metabolic engineering, *55*, 12-22. https://doi.org/10.1016/j.ymben.2019.06.001