Master Thesis in Bioinformatics

Recon3D- and constraint-based tissue-specific metabolic model reconstruction

Nantia Leonidou

Reviewers: Jun.-Prof. Dr. Andreas Dräger

Supervisors: Dr. Reihaneh Mostolizadeh and Alina Renz

Background and Motivation

Since the sequencing and annotation of the human genome, the reconstruction of human genome-scale metabolic models (GEMs) has been of great interest. GEMs allows for an in-depth insight into the human metabolism, which involves thousands of reactions and metabolites. However, being complex organisms, humans embodied diverse cell types with different metabolic functions and phenotypes. Thus, a tissue-specific reconstruction remains a key challenge in the field of computational systems biology. In 2012, Wang et al. developed a novel computational method to build tissue-specific metabolic models, called metabolic Context-specificity Assessed by Deterministic Reaction Evaluation (mCADRE) [5]. mCADRE constructs tissue-

Figure 1: Overview of the mCADRE algorithm [5].

specific models based on human gene expression data and metabolic network topology. Similarly, to the already existing state-of-the-art method, namely the Model Building Algorithm (MBA), mCADRE initially assigns a ubiquity score (i.e, how often a gene is expressed) to each reaction establishing two sets of reactions: core and non-core. Based on a threshold, reactions with higher scores are considered as core reactions, while the remaining ones are the non-core reactions. The latter ones are then ranked based on expression data and connectivity to other reactions. One of the main goals of the algorithm is to remove all non-core reactions while keeping the model consistent and able to produce key metabolites at the same time. The elimination is done based on the rankings and in inverse order [6, 5].

Aim

So far, the mCADRE algorithm, described by Wang et al., is provided as MATLAB code and works only with the first version of the human metabolic network model, Recon 1 [3] [1]. This resulted to limited usage of the
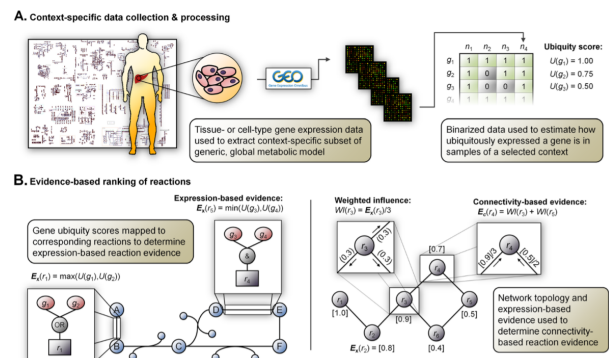
---

[1] https://github.com/jaeddy/mcadre

algorithm as two newer versions with increasing scope of this human metabolic network are now available, with Recon 3D being the newest release [2]. Hence, the aim of this project is to re-implement the algorithm in Python based on the newest Recon3D to make it widely used again. To test its functionality, the lagorithm will be applied to create multiple models of human cells relevant to the current outbreak of SARS-CoV-2. With these models the effect of viral infections of relevant human cells will be analyzed.

Requirements

- Experience in programming with Python and related libraries, such as such as COBRApy [4] and libSBML [1]

- High interest in computational systems biology, constraint-based modeling and software development

References

[1] BORNSTEIN, Benjamin J. ; KEATING, Sarah M. ; JOURAKU, Akiya ; HUCKA, Michael: LibSBML: an API library for SBML. In: *Bioinformatics* 24 (2008), Nr. 6, S. 880–881

[2] BRUNK, Elizabeth ; SAHOO, Swagatika ; ZIELINSKI, Daniel C. ; ALTUNKAYA, Ali ; DRÄGER, Andreas ; MIH, Nathan ; GATTO, Francesco ; NILSSON, Avlant ; GONZALEZ, German Andres P. ; AURICH, Maike K. u. a.: Recon3D enables a three-dimensional view of gene variation in human metabolism. In: *Nature biotechnology* 36 (2018), Nr. 3, S. 272

[3] DUARTE, Natalie C. ; BECKER, Scott A. ; JAMSHIDI, Neema ; THIELE, Ines ; MO, Monica L. ; VO, Thuy D. ; SRIVAS, Rohith ; PALSSON, Bernhard .: Global reconstruction of the human metabolic network based on genomic and bibliomic data. In: *Proceedings of the National Academy of Sciences* 104 (2007), Nr. 6, S. 1777–1782

[4] EBRAHIM, Ali ; LERMAN, Joshua A. ; PALSSON, Bernhard O. ; HYDUKE, Daniel R.: COBRApy: COnstraints-based reconstruction and analysis for python. In: *BMC systems biology* 7 (2013), Nr. 1, S. 74

[5] WANG, Yuliang ; EDDY, James A. ; PRICE, Nathan D.: Reconstruction of genome-scale metabolic models for 126 human tissues using mCADRE. In: *BMC systems biology* 6 (2012), Nr. 1, S. 153

[6] WEHRENS, Ron ; SALEK, Reza M.: *Metabolomics: practical guide to design and analysis*. Chapman and Hall/CRC, 2019