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Optimization-based analysis of metabolic networks have been used to design metabolic engineering strategies aiming at enhancing the production of a target of interest. Here, we present MeDUSA, a comprehensive tool for the calculation of a stoichiometric capacitance allowing for increasing the maximum production of a given product.

MeDUSA provides an extensive sage-based package which, given a metabolic network and an objective function, (i) computes a stoichiometric capacitance and (ii) investigates the effect of adding the calculated stoichiometric capacitance. The package MeDUSA and a tutorial are available from `https://logiciels.lina.univ-nantes.fr/medusa/`.

1 Introduction

Optimization-based analysis of metabolic networks has proved valuable in designing metabolic engineering strategies aiming at enhancing the production of a target of interest. Several approaches have been proposed, most of them are based on the seminal approach flux balance analysis (FBA) [1], which investigates reaction fluxes in a metabolic network at steady state. Recently,

[2] proposed a novel method which identifies a suitable chemically feasible transformation, called *stoichiometric capacitance*, allowing for a significant increase in the metabolic network capabilities. In extension to this, we present our tool `MeDUSA` (`MEtabolic Design Using SAge`) which, given a metabolic network and an objective function, (i) computes a stoichiometric capacitance (SC) and (ii) investigates the effect of including in the model the calculated SC. MeDUSA has been implemented using `Sage`, a free open-source python-based software that smoothly handles the use of advanced optimization packages [3].

2 Description

MeDUSA provides a comprehensive set of methods that mainly implement the algorithm proposed by [2] to compute a stoichiometric capacitance of a given metabolic network. As a first step, all the data necessary for the capacitance calculation can be loaded by simply calling the function `create_model`. The resulting object, which offers a nice interface to analyze the created metabolic model, is subsequently used to build the corresponding MILP problem and calculate the stoichiometric capacitance using the function `capacitance`. The later smoothly uses advanced optimization solvers with no need of an expertise in constraints programming. To further analyze the consequences of adding a stoichiometric capacitance to a given model, MeDUSA makes use of Flux Variability Analysis (FVA). This results in partitioning the set of reactions into four distinct types: `blocked` (unable to carry a non-zero flux in any condition); `excluded` (unable to carry a non-zero flux in all optimal metabolic pathways); `indispensable` (carrying a non-zero flux in all optimal metabolic pathways) and the remaining reactions are called `alternative`. The results obtained by performing FVA, with and without adding the calculated stoichiometric capacitance, can be exported in different graph formats, allowing data exchange with standard graph tools like `Graphviz` [4] and `Gephi` [5]. For more details, we refer to the tutorial available from https://logiciels.lina.univ-nantes.fr/medusa/.

3 Application

We apply our tool to explore the possibility of increasing the Glutamate (Glu) production in the metabolic network of amino acid synthesis [6]. The network consists of 16 metabolites and 24 reactions. In addition to the stoichiometric matrix (S) and the lower (lb) and upper (ub) bounds on the fluxes through reactions, the capacitance calculation requires the vector (T) of the standard Gibbs free energy of metabolite formation, the mass matrix (M) which contains

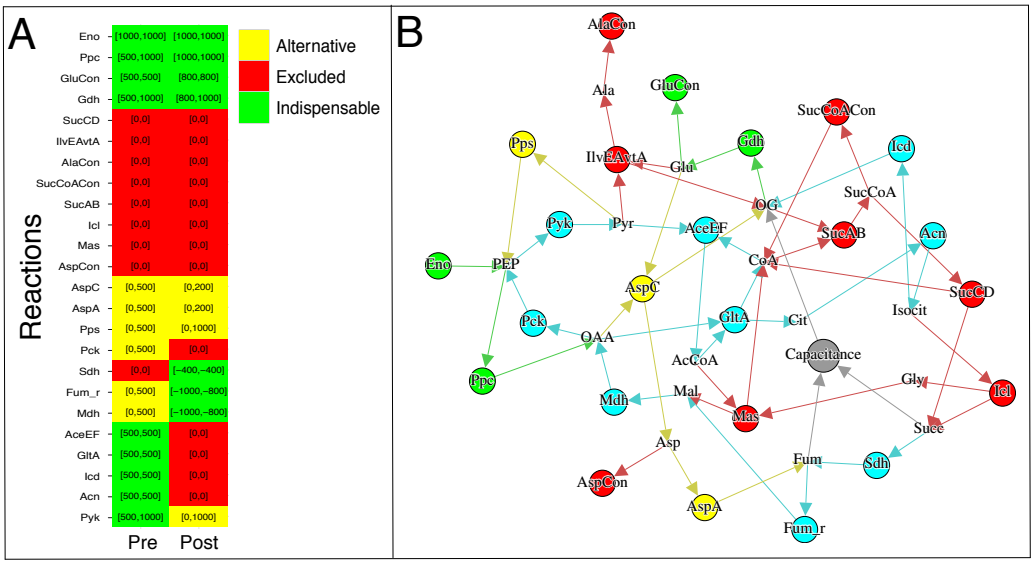

Figure 1: *Visualization of the results obtained from the analysis of the metabolic model of amino acid synthesis in E. coli from [6]. (A) Changes in the types of reactions (blocked, excluded, indispensable and alternative) before (Pre) and after (Pos) the inclusion of the calculated stoichiometric capacitance (SC). The FVA flux ranges before and after adding the SC are indicated as well. (B) The metabolic network including the calculated SC. Metabolites are shown by their names and reactions are depicted as colored nodes: gray for the SC, cyan for reactions whose type changes due to the inclusion of the SC, and yellow (resp. red or green) for reactions which are alternative (resp. excluded or indispensable) before and after adding the SC.*

the molecular sum formulas of the metabolites, the reversibility of reactions (*rev*) and the index (*obj*) stating the objective function to be optimized (ex. biomass production). Vectors indicating the names of reactions (*rxn_names*) and metabolites (*met_names*) and the indices (*exc_indices*) of metabolites that must not occur in the capacitance can be used as well. All data is available in the MeDUSA package.

We first construct an object *my_model* using the loaded data. Then, we use *my_model* to build the corresponding MILP problem in order to perform the capacitance calculation. The resulting MILP problem can be solved using the state-of-the-art MILP solvers (ex. `Cplex` and `Gurobi`):

sage: *my_model = MetabolicModel.create_model(S,M,ub,lb,T, met_names,rxn_names,obj,rev,exc_indices,'Gurobi')*

Next, we compute a stoichiometric capacitance by fixing an upper bound on its flux (ex. 1000) and a maximum number of metabolites to be used (ex. 4).

sage: *(sol,cap) = my_model.capacitance(1000,4)*

Finally, we use FVA to investigate the changes in the importance of metabolic reactions for performing the network objective. To achieve this, we call the function `fva` while setting fluxes through the reactions `indices` to `values`.

sage: *(min_values,max_values) = my_model.fva(indices,values)*

Based on the above calculations, we obtain the stoichiometric capacitance *3 Fum + 2 Suc* $\longrightarrow$ 4 OG , whose inclusion in the metabolic model results in an increase of the Glutamate (Glu) production by 60%. Figure 1 shows how this capacitance is connected to the reactions defining the considered metabolic network. More importantly, the figure emphasizes the changes in the types of reactions due to the inclusion of this capacitance. All the obtained results can be exported by MeDUSA in different formats.

The calculated capacitance is a bypass of Oxoglutarate (OG) synthesis, which is the only substrate of Glu. Analyzing capacitance's consequences emphasizes that reallocations of flux from Pyruvate (Pyr), Co-enzyme A (CoA) and Isocitrate (Isocit) synthesis leads to modify Succinate (Succ) and Fumarate (Fum) synthesis pathways from Oxalacetate (OAA).

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