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How to optimize metabolites concentrations and fluxes in a metabolic pathway?

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Introduction

The modelling of metabolic pathways is developed here for application to sugar metabolism of tomatoes during fruit expansion. In the now classic calculation of network fluxes, we add concentrations. Under assumptions of steady state and of "minimal effort" as proposed in [1], fluxes and concentrations, respecting constraints of experimental measurements and of thermodynamics, are searched. In order to obtain a well-posed problem, a preliminary mathematical study is in progress.

Backgrounds and Basics

The development time of tomato fruit is about 50 days. This period is subdivided in 50 daily phases numbered by l . At the scale of a phase (day), we suppose that the flux vector is at steady state and follows some fixed constraints. But at the scale of the development, these constraints will change. So we formulate a general problem at a phase scale l and solve it for $l = 1 \dots 50$.

Notations

1. $X = (X_1, \dots, X_m)$ the vector of internal metabolites,
2. $V = (v_1, \dots, v_n)$ the flux vector composed by the rate v_j of each reaction j in the network.
3. $S = (s_{ij})_{i=1 \dots m, j=1 \dots n}$ the stoichiometry matrix (only refers to the internal metabolites) where s_{ij} is the stoichiometric coefficient of metabolite X_i in reaction j .
4. $\tilde{S} = (\tilde{s}_{ij})_{i=1 \dots m, j=1 \dots n_i}$ a submatrix extracted from the stoichiometry matrix containing only the stoichiometric coefficients of internal reactions (reactions between internal metabolites).

Previous approach and results: problem n°1

Constraints Steady-state (for all internal metabolites) assumption

$$dX/dt = SV = 0$$

Bounds on the fluxes (the values $v_{l,j,min}$ and $v_{l,j,max}$ are constants)

$$v_{l,j,min} \leq v_j \leq v_{l,j,max} \quad \text{for } j = 1 \dots n$$

Proposition. $\min_{V \in A_l} \|V\|^2$ admits a unique solution where A_l is the non empty following feasible set

$$A_l = \{V \in \mathbb{R}^n, SV = 0, v_{l,j,min} \leq v_j \leq v_{l,j,max} \text{ for } j = 1 \dots n\}$$

Thermodynamics Basics

Let us recall that the **Gibbs free energy change** for a reaction r_i



is defined by

$$\Delta G_{r_i}^0 = \Delta G_{r_i}^0 + RT \ln \frac{X_3^{n_3} X_4^{n_4}}{X_1^{n_1} X_2^{n_2}}$$

where $\Delta G_{r_i}^0 = n_3 \Delta G_{f_{X_3}}^0 + n_4 \Delta G_{f_{X_4}}^0 - n_1 \Delta G_{f_{X_1}}^0 - n_2 \Delta G_{f_{X_2}}^0$ is a constant, R the gas constant, and T the absolute temperature in Kelvin.

Generalisation: With m metabolites et n_i internal reactions, let us set

$$\Delta G_r(X) = \begin{pmatrix} \Delta G_{r_1}(X) \\ \dots \\ \Delta G_{r_{n_i}}(X) \end{pmatrix} \quad Y(X) = \begin{pmatrix} \Delta G_{f_{X_1}}^0 + RT \ln(X_1) \\ \dots \\ \Delta G_{f_{X_m}}^0 + RT \ln(X_m) \end{pmatrix}$$

Proposition.

$$\Delta G_r(X) = {}^t \tilde{S} Y(X)$$

Simple Example: problem n°1

$$S = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & -1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}$$

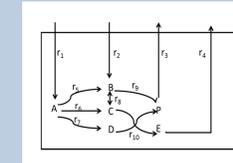
if $v_{l,j,min} = 0 \forall j \neq 1, 2, 8$ and

$v_{l,j,min} = v_{l,j,max} = 1$ for $j = 1, 2$

then the unique solution is

$$V \approx (1, 1, 1.31, 0.69, 0, 0.31, 0.69, 0.38, 0.61, 0.69)$$

$$\tilde{S} = \begin{pmatrix} -1 & -1 & -1 & 0 & 0 & 0 \\ 1 & 0 & 0 & -1 & -1 & 0 \\ 0 & 1 & 0 & 1 & 0 & -1 \\ 0 & 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}$$



New Approach

In this new modelling, in addition to the fluxes, we introduce metabolite concentrations (as in [2]), which are also supposed to be at steady state. In order to ensure thermodynamic reliability, we add the Gibbs free energy change of each reaction. Still assuming some "minimal effort", we simultaneously minimize $\|V\|^2$ and $\|\Delta G_r(X)\|^2$. We add an other set of constraints B_l for the metabolites to take into account some experimental measurements.

Mathematical Formulation

$$\min_{(V,X) \in K_l} (\|V\|^2, \|\Delta G_r(X)\|^2)$$

with

$$K_l = \{(V, X) \in A_l \times B_l, \Delta G_{r_i}(X) v_i < 0 \text{ for } i = 1 \dots n_i\}$$

and

$$B_l = \{X \in \mathbb{R}_+^m, M_l X = T_l\}.$$

This problem is a multi-objective optimization with uncoupled functions but with constraints (respect the second law of thermodynamics $\Delta G_{r_i}(X) v_i < 0$) that may be conflicting. So a rigorous answer to this problem comes from understanding the separated problems.

Study of problem n°2

Proposition. $\min_{X \in \mathbb{R}_+^m} \|\Delta G_r(X)\|^2$ admits a space of solutions of dimension equals to $\dim(\ker({}^t \tilde{S}))$.

The problem **without constraints** is solved...

Simple example: problem n°2

$\dim(\ker({}^t \tilde{S})) = 1$, so $X = (X_1, \dots, X_6)$

with $X_i = \exp\left(\frac{\alpha - \Delta G_{f_{X_i}}^0}{RT}\right)$, $\alpha \in \mathbb{R}$ are the only solutions.

References

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Conclusion

Why a mathematical study ?

With only numerical computations, the set of optimal solutions may not be exhaustively described. To find all the solutions (if they exist) of the multi-objective problem, understand each separated problem is a pre-requisite. Moreover this formal outcome will fit to any other network.