Efficient dynamic FBA for microbial communities.

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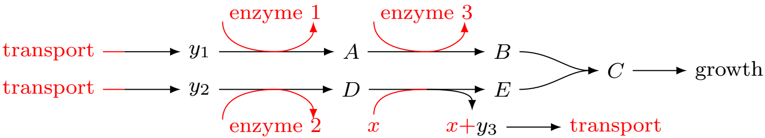
Metabolite mediated models explain growth data

To build a metabolite mediated model, we need to know:

1. What microbes are present?
2. What metabolites are present?
3. How do they interact?

Questions 1 & 2 aren't necessarily easy, but they can be answered for an individual. The practicality of metabolite mediated modeling for n-of-one situations therefore depends on question 3. We can answer it using genome-scale information about the microbes involved.



$$\Gamma = \left[\begin{array}{ccc|cccccc}
1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 \\
\hline
0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\
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0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 \\
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\end{array}\right] = \left[\begin{array}{c|c} I & -\Gamma^* \\ \hline 0 & \Gamma^\dagger \end{array}\right]$$

Metabolite mediated models explain growth data

Determine an instantaneous growth rate g of an organism by the optimization problem

$$\begin{aligned} &\max(\boldsymbol{\chi} \cdot \boldsymbol{v}) \\ &\Gamma^{\dagger} \boldsymbol{v} = 0 \\ &v_{j,min} \leq v_j \leq v_{j,max} \\ &\tilde{v}_{j,min} \leq \left(\Gamma^* \boldsymbol{v}\right)_j \leq \tilde{v}_{j,max} \end{aligned}$$

This is called *flux balance analysis* a type of *constraint based analysis* [1] .

- $\boldsymbol{\chi}$ determines a cellular objective, generally increased “biomass” (e.g. DNA or protein).
- We assume intracellular pathways are at equilibrium flux (the network is node balanced).
- There are constraints on reaction fluxes $(\boldsymbol{v}_{min}, \boldsymbol{v}_{max})$.

Notice here I’ve separated the internal and exchange reactions, that will let us also determine the rate of change in the external metabolite pools.

1

Metabolite mediated models explain growth data

The optimization of flux balance analysis (FBA) suggests a dynamical, metabolite mediated model for community growth, meaning we can define a vector field:

$$\frac{dx_i}{dt} = x_i(\boldsymbol{\chi}_i \cdot \boldsymbol{v}_i)$$
$$\frac{d\boldsymbol{y}}{dt} = -\sum_i x_i \Gamma_i^* \boldsymbol{v}_i$$

where each $\boldsymbol{v}_i$ solves the respective optimization:

$$\begin{aligned} &\max(\boldsymbol{\chi}_i \cdot \boldsymbol{v}_i) \\ &\Gamma^{\dagger} \boldsymbol{v}_i = 0 \\ &v_{ij,min} \leq v_{ij} \leq v_{ij,max} \\ &\tilde{v}_{ij,min} \leq (\Gamma^* \boldsymbol{v}_i)_j \leq \kappa_{ij} y_j \end{aligned}$$

But of course there's a few problems.

- $\boldsymbol{v}_i$ is not unique
- $\kappa_{ij}\boldsymbol{y}(t)$ is a time-dependent constraint, and we don't know κ_{ij}.
- Scalability!

An ODE Approximation

We'd like to approximate this system with a set of ODEs.

$$\frac{d}{dt}x_i = x_i(\boldsymbol{\chi}_i \cdot \boldsymbol{v}_i)$$

$$\frac{d}{dt}\boldsymbol{y} = -\sum_i x_i \Gamma_i^* \boldsymbol{v}_i$$

$$\frac{d}{dt}\boldsymbol{v}_i = \boldsymbol{h}_i(x_i, \boldsymbol{v}_i, \boldsymbol{y})$$

Smoothly evolving $\boldsymbol{v}$ should be a huge boost to computation speed, and ODE systems are easier to analyze.

Surfing on Exponentials

Consider the system

$$\frac{dx}{dt} = xv$$
$$\frac{dy}{dt} = -xv$$

where v is "maximized" with the constraints $0 \leq v \leq 1$ and $v \leq \kappa y$.

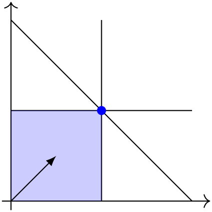
Surfing on Exponentials

Challenge:

- Decide which "waves" to ride
- Switch the set of "waves" we are riding when we need to
- Stay in $null(\Gamma^\dagger)$

Solution:

- Find the right basis



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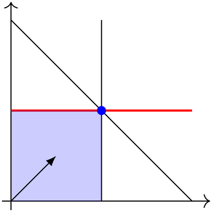

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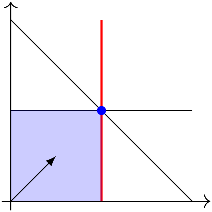

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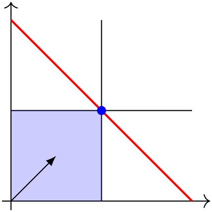

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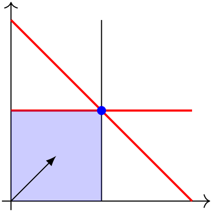

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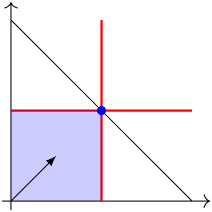

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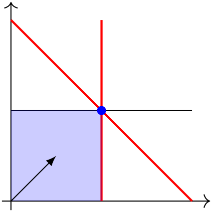


Illustrative (but not biological!) Example

Efficient dynamic FBA for microbial communities.

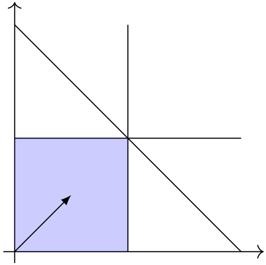
Brunner

Consider the differential algebraic system

$$\frac{dx}{dt} = x(v_1 + v_2)$$
$$\frac{dy}{dt} = -x(v_1 + v_2)$$

Where $v_1 + v_2$ is maximized subject to $0 \leq v_1 \leq 1$, $0 \leq v_2 \leq 1$, $v_1 + v_2 \leq y$.

$y = 2$



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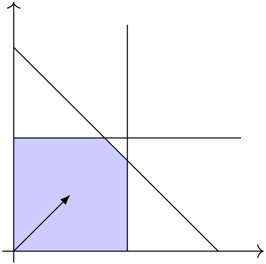

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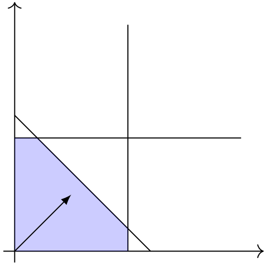

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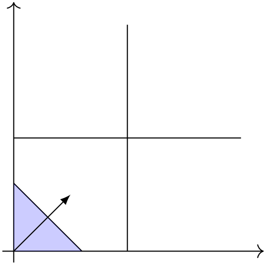

Choose a basis that lets us follow the optimal point!

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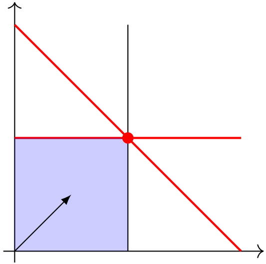

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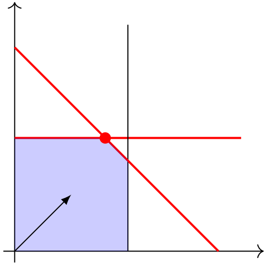

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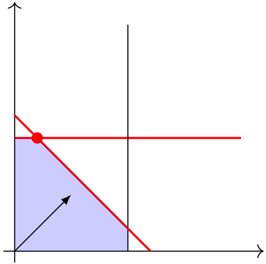

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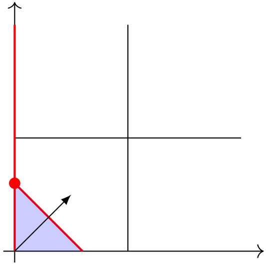
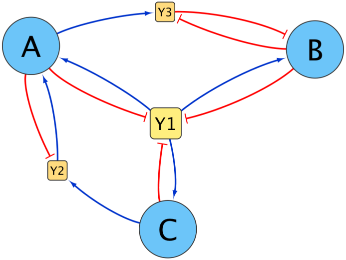


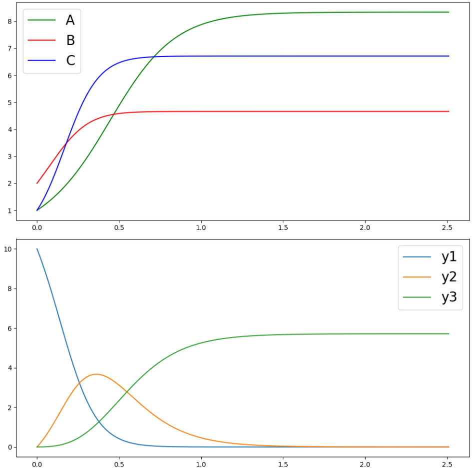
Algorithm Overview

1. Optimize growth rate
2. Compute rate of change of constraints
3. Choose constraint basis
4. While solution remains in feasible region:
   - Simulate forward
   - Check feasibility
5. Return to last feasible point and step (2)

Note that linearity of objective and convexity of feasible region insure we remain at optimal growth.

Dynamic Simulation





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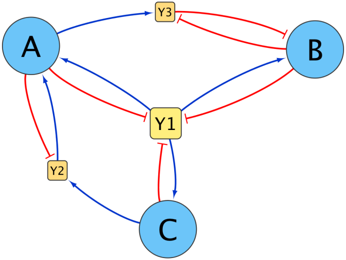
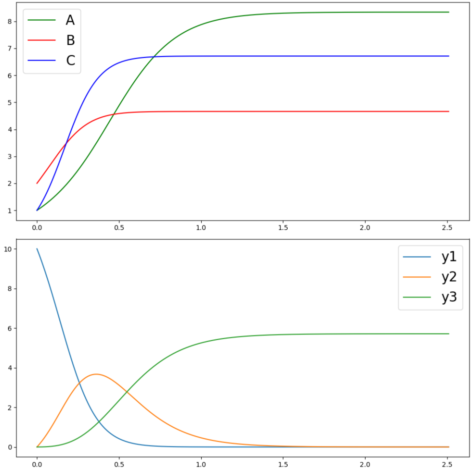


Species A has 7 reactions, B has 4, and C has 3. Execution time is ~ 0.34 seconds.



Thank You

Thank you

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