MICROBIAL COMMUNITIES

Principles and Applications of Systems Biology

EPFL

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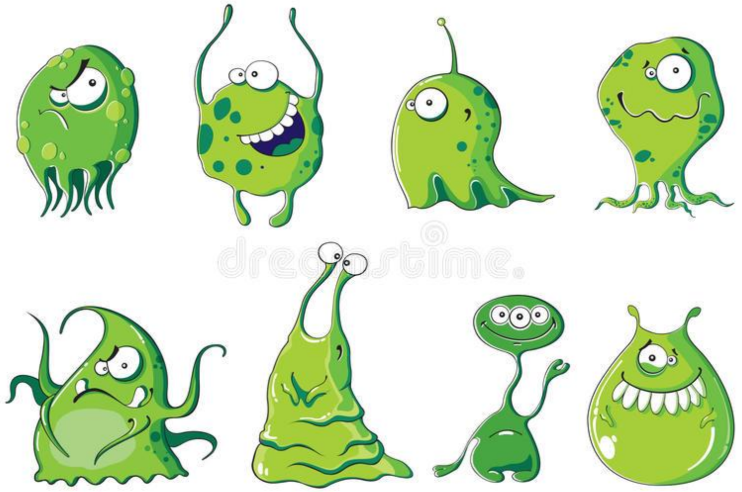
Introduction

- Microbial communities are complex, dynamic and inter-connected
- Systems engineering approaches to deal with complexity and dynamics of a system ⟶ optimization methods
- Experience of single organism modeling
- Emergent properties due to the inter-connection
- Constraint Based Optimization



Constraint-based optimization

Variables

- Continuous
- Discrete

Continuous:

- Rate of reactions
- Metabolite concentrations

Discrete:

- Gene expression (on/off)
- Knock out / Deletion (off)
- Insertions (on)

Constraint-based optimization

Variables

- Continuous
- Discrete

$v \leq Vm_{ax} \rightarrow$ limited capacity of the enzymes

Constraints

- Equalities
- Inequalities

Constraint-based optimization

Variables

- Continuous
- Discrete

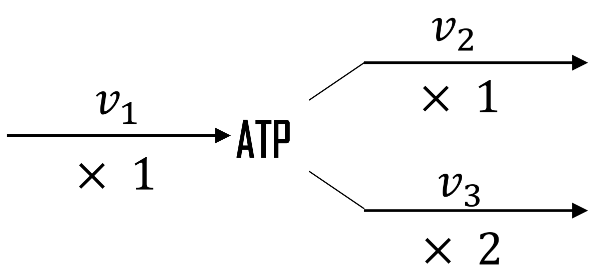
Constraints

- Equalities
- Inequalities

$v \leq Vm_{ax} \rightarrow$ limited capacity of the enzymes

$v_{consume} = v_{produce} \rightarrow$ No net accumulation of metabolites

Steady-state assumption



$$v_1 = v_2 + 2v_3$$

Constraint-based optimization

Variables

- Continuous
- Discrete

Constraints

- Equalities
- Inequalities

Objective Function

- Cost → minimize
- Reward → maximize

Glucose uptake: v_{glc}

Growth: μ

Constraint-based optimization

- If objective function and constraints are linear and variables are continuous → Linear Programming (LP) Problem

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Variables: $V_{HEX1}, V_{PGI}, V_{PFK}, V_{FBA}, V_{TPI}, V_{GAPD}, V_{PGK}, V_{PGM}, V_{ENO}, V_{PYK}$

Abbreviation	Glycolytic reactions
HEX1	[c]GLC + ATP → G6P + ADP+ H
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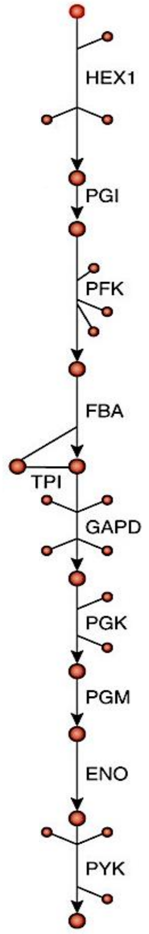

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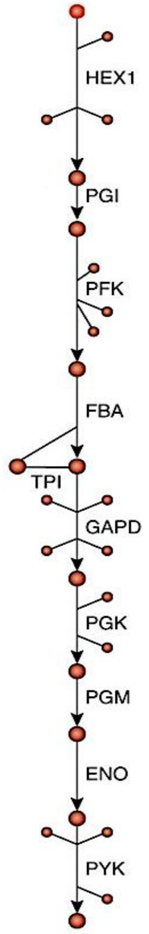

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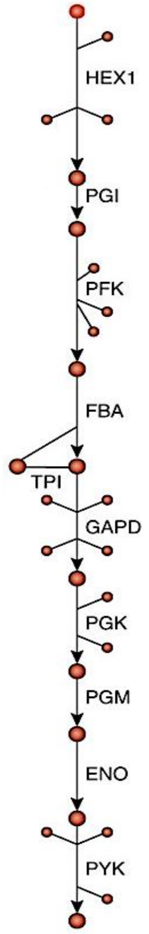

Constraint-based optimization

- If objective function and constraints are linear and variables are continuous ⟶ Linear Programming (LP) Problem

Objective: $\max V_{PYK}$

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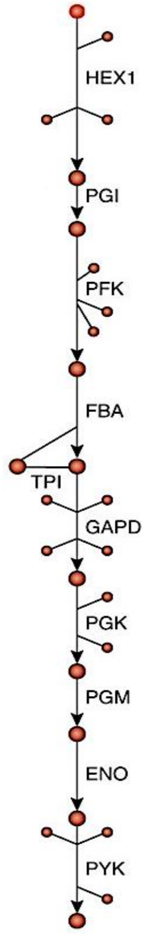

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Flux Balance Analysis (FBA)

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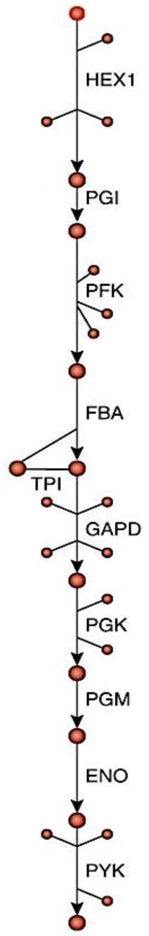

Constraint-based optimization

- If objective function is quadratic and constraints are linear and variables are continuous → Quadratic Programming (QP) Problem

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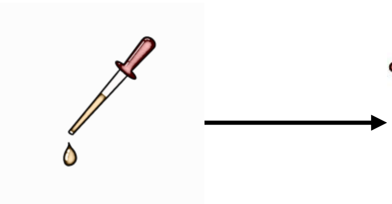

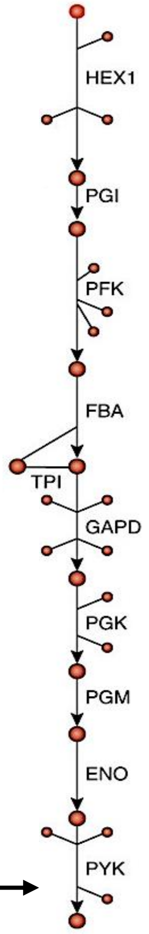

Constraint-based optimization

- If objective function is quadratic and constraints are linear and variables are continuous $\longrightarrow$ Quadratic Programming (QP) Problem

Objective: $\min(V_{PYK} - V_{measure})^2$

Variables: $V_{HEX1}, V_{PGI}, V_{PFK}, V_{FBA}, V_{TPI}, V_{GAPD}, V_{PGK}, V_{PGM}, V_{ENO}, V_{PYK}$

Constraints:

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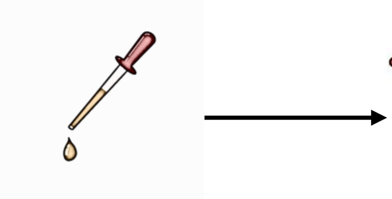

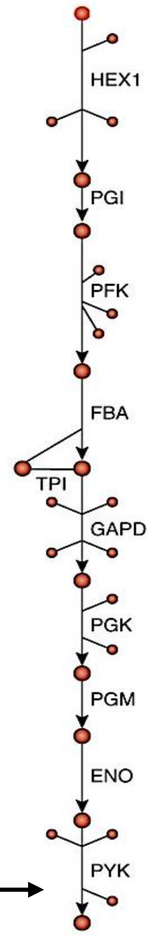

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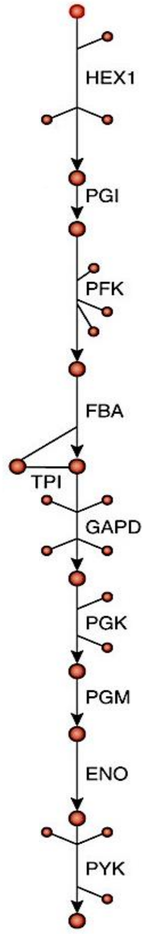

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$$V_{HEX1} \leq V_{HEX1}^{max}$$

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NADH or NADPH? □

$$ATP\colon\ V_{HEX1} + V_{PFK} = V_{PGK} + V_{PYK}$$

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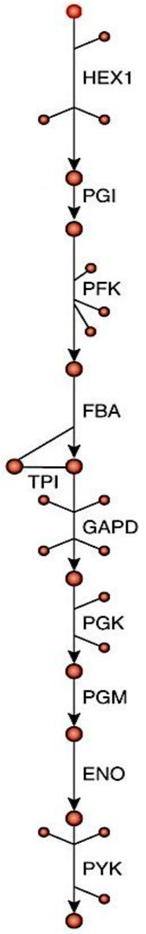

Constraint-based optimization

- If objective function and constraints are linear and variables can be either continuous or discrete $\longrightarrow$ Mixed Integer Linear Programming (MILP) Problem

Objective: $\max V_{PYK}$

Variables: $V_{HEX1}, V_{PGI}, V_{PFK}, V_{FBA}, V_{TPI}, V_{GAPD}^{NADH}, V_{GAPD}^{NADPH}, V_{PGK}, V_{PGM}, V_{ENO}, V_{PYK}$

b_{NADH}, b_{NADPH}

$b_i = 0 \; or \; 1$

Constraints:

$$V_{HEX1} \leq V_{HEX1}^{max}$$

$$V_{PGI} \leq V_{PGI}^{max}$$

$$ATP\colon\ V_{HEX1} + V_{PFK} = V_{PGK} + V_{PYK}$$

$$V_{GAPD}^{NADH} \leq b_{NADH}.V_{GAPD}^{max}$$

$$V_{GAPD}^{NADPH} \leq b_{NADPH}.V_{GAPD}^{max}$$

$$b_{NADH} + b_{NADPH} = 1$$

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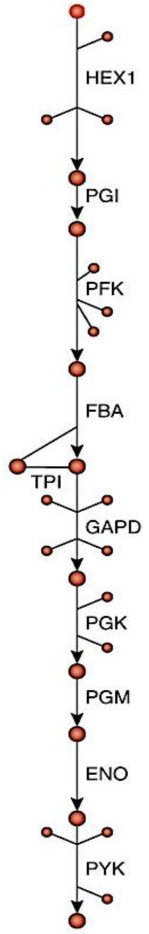
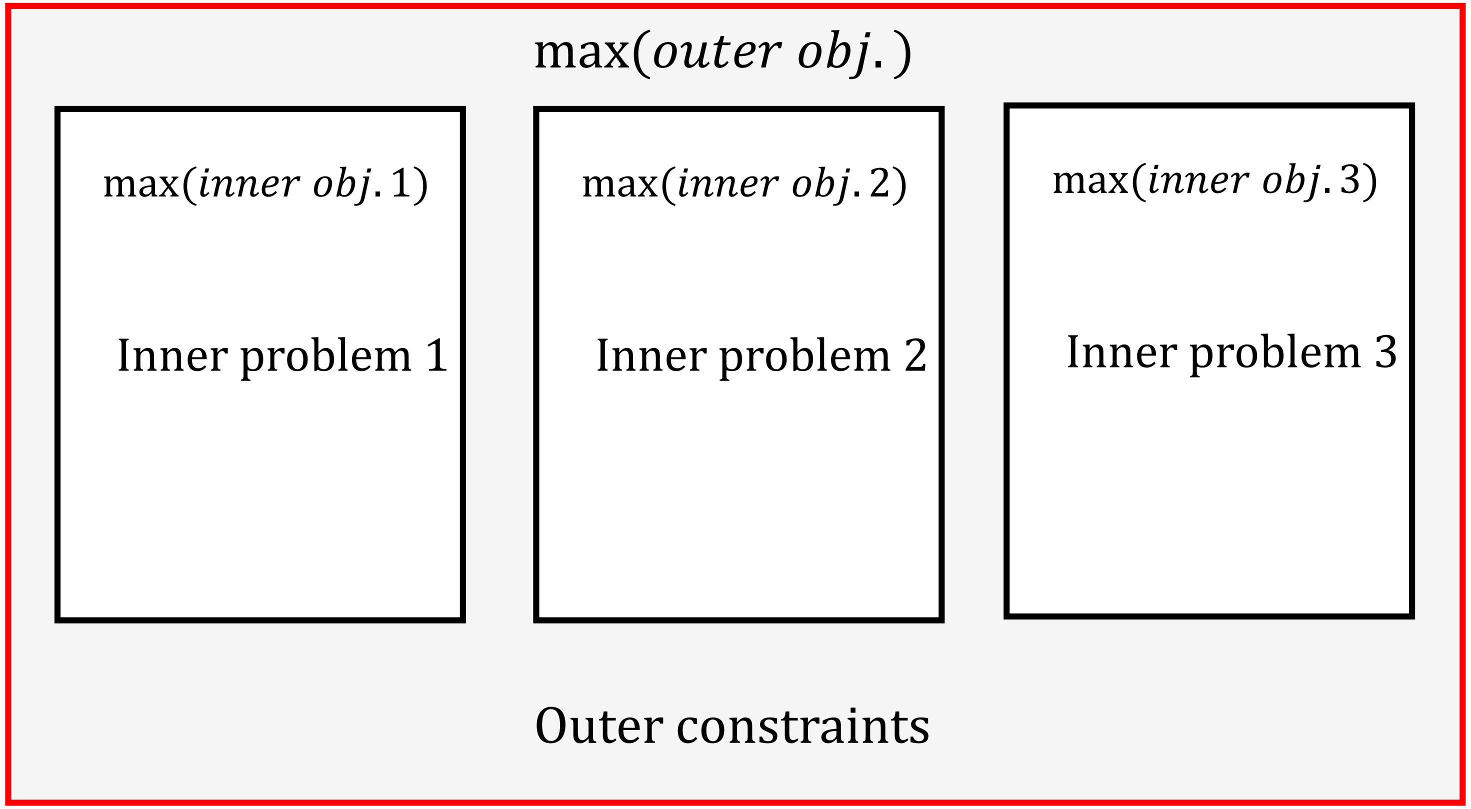


Multi-level optimization

- A main optimization problem with

several nested optimizations



Multi-level optimization

- A main optimization problem with

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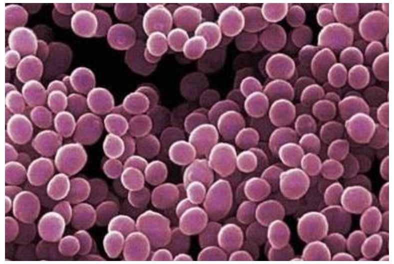
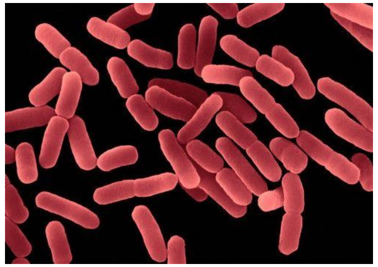
$\max(\textit{community obj.})$

$\max(\textit{species obj. }1)$

$\max(\textit{species obj. }2)$



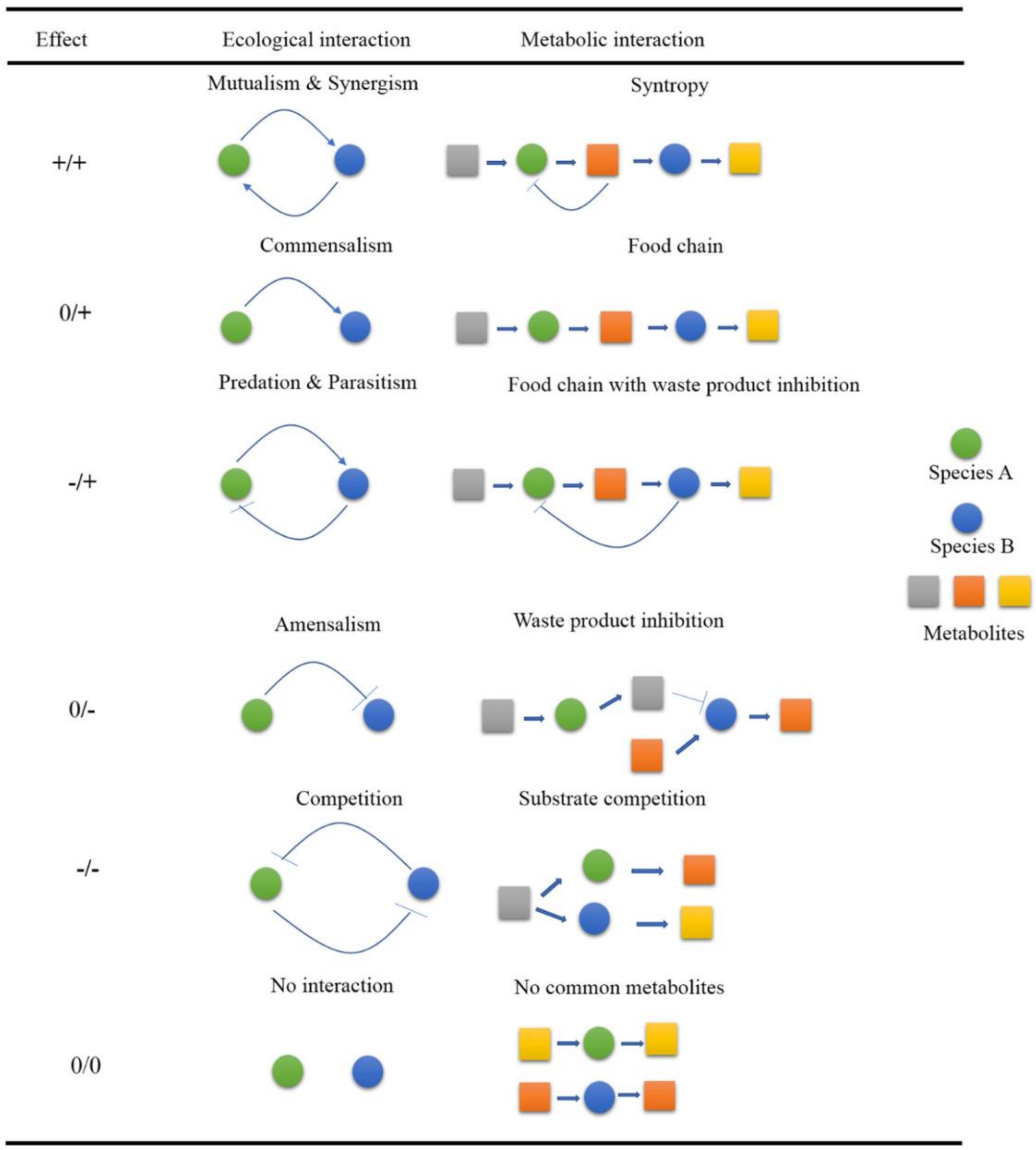
$\max(\textit{species obj. }3)$



Interactions between members

From Single Organism to Communities

- Infer from data and model complex microbial interactions
- Use experimental data to augment the model



Tshikantwa et al., Current TA, 2018

From Single Organism to Communities

- Model complex microbial interactions

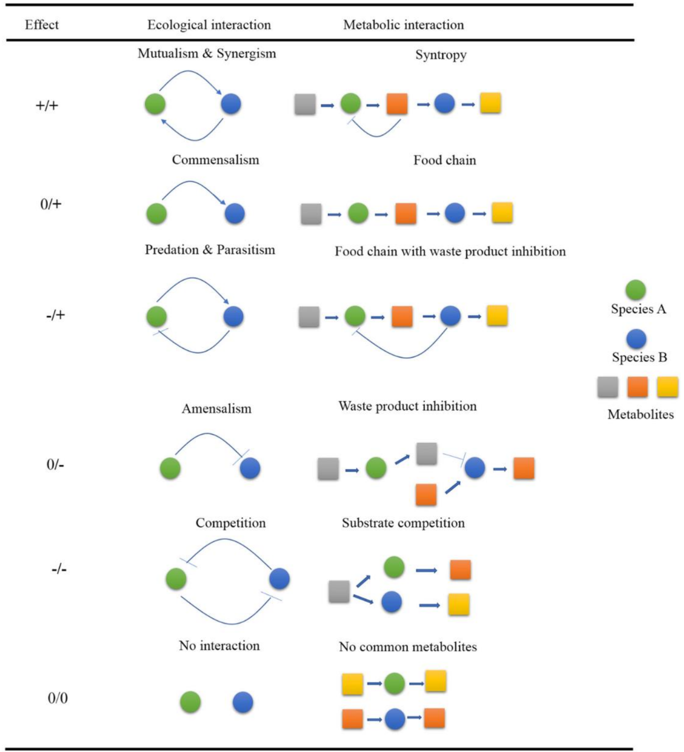
- Objective function and constraints of the community ?

  Community prosperity vs single organism prosperity

How can we translate

ecological interactions

into mathematical formulation?



From Single Organism to Communities

- Model complex microbial interactions
- Objective function and constraints?

    Community prosperity vs single organism prosperity

- Computational burden of simulating microbial communities

    Big number of variables and constraints

Can we systematically

learn from and/or

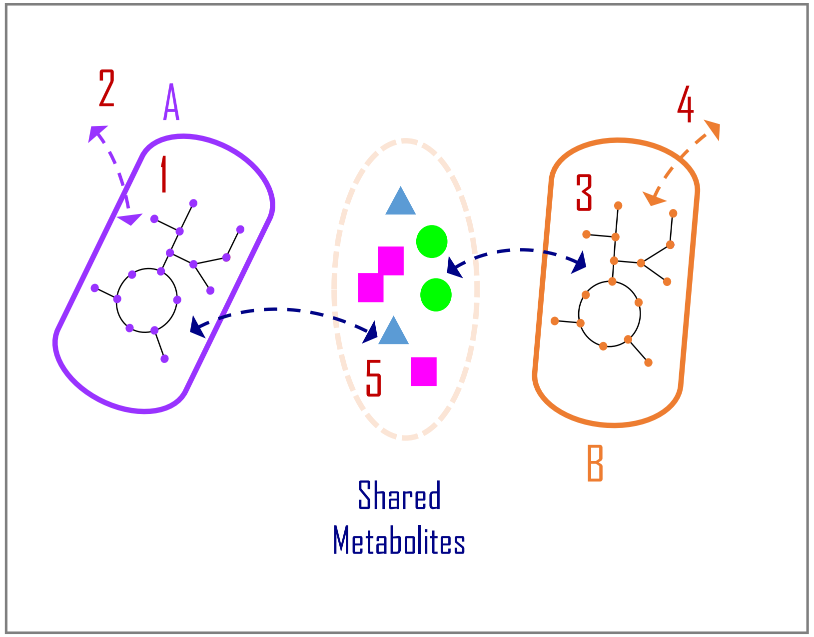
reduce complexity?

Modeling Microbial Interactions

Class I: Joint objective

- 1 problem for the whole community
- Each species is treated as different modeling compartments

A joint objective Problem



At least the following modeling compartments:

1) Intracellular A
2) Extracellular A
3) Intracellular B
4) Extracellular B
5) Shared Extracellular

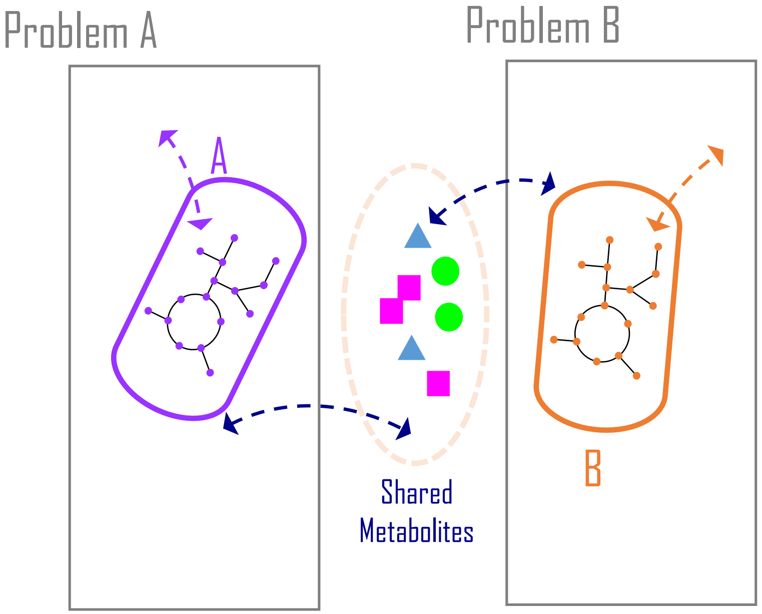
Metabolites can be transported between the compartments

Objective maximize $(w_A.\,growth_A + w_B.\,growth_B)$

Modeling Microbial Interactions

Class II: Multiple objectives

- 1 problem for each species
- After each simulation, the effect of each species on the shared metabolites is updated.



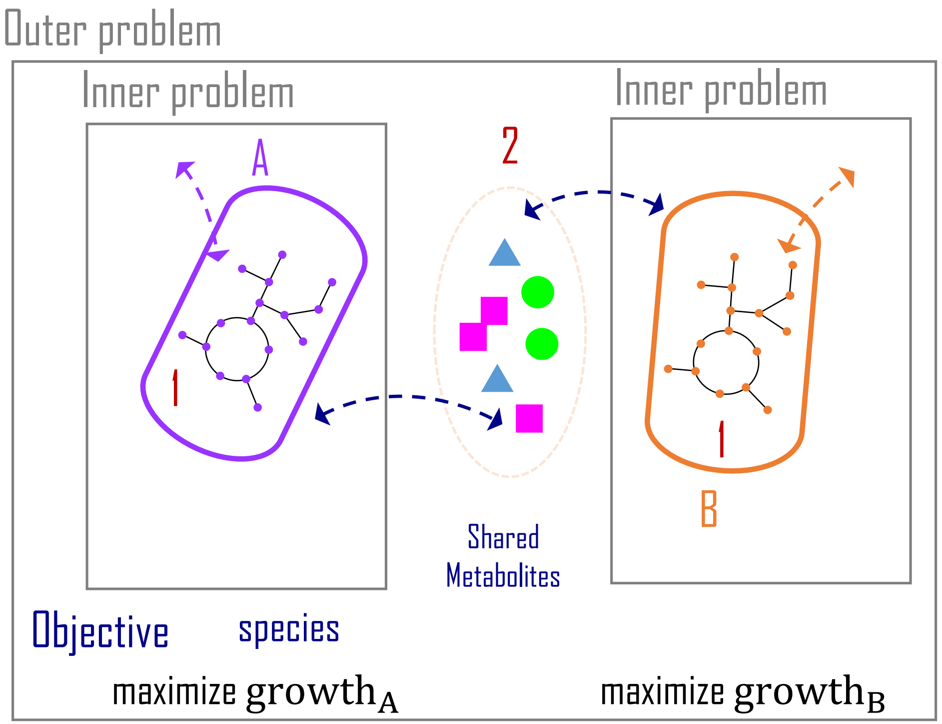
1. Solve problems with initial concentrations
2. Calculate the concentration of the cells and the shared metabolites
3. Solve problems with updated concentrations

Objective: maximize growth_A maximize growth_B

Modeling Microbial Interactions

Class III: Nested objectives

- Species-level objective for each inner problem and community-level objective for the outer problem



Structure of multi-level optimization

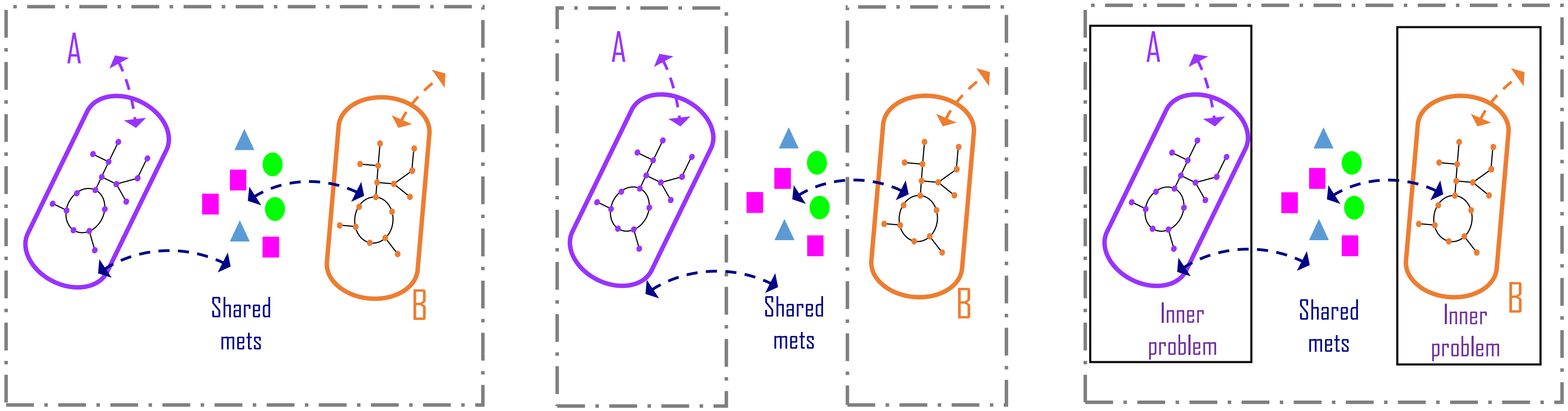
Outer constraints: shared metabolites

Inner constraints: species-specific metabolites

$\text{Objective}_{\text{community}}$ maximize $(w_A . \mathrm{growth}_A + w_B . \mathrm{growth}_B)$

Modeling Microbial Interactions

Class I: Joint objective | **Class II : Multiple objectives** | **Class III: Nested objectives**



Joint Problem | Problem A | Problem B | Outer problem

Class I: Joint objective

Objective:

$$\max\ (w_A . \text{growth}_A + w_B . \text{growth}_B)$$

1 problem for whole of the community with community objective function

Class II : Multiple objectives

Objective:

$\max\ \text{growth}_A$ $\qquad$ $\max\ \text{growth}_B$

1. Solve problems
2. Calculate the concentrations
3. Solve problems with updated concentrations

Class III: Nested objectives

Objective:

Outer Community Objective

$$\max\ (w_A . \text{growth}_A + w_B . \text{growth}_B)$$

Inner Species Objective

$\max\ \text{growth}_A$, $\max\ \text{growth}_B$

Problems per each species embedded in a large optimization problem

Modeling Microbial Interactions

Class I: Joint objective

Class II : Multiple objectives

Class III: Nested objectives

- Computationally cheap
- Sensitive to the choice of weights

Suitable for communities with prior knowledge about relative abundance or growth rates

Joint Problem

Objective:

max $(w_A.\text{growth}_A + w_B.\text{growth}_B)$

Modeling Microbial Interactions

Class I: Joint objective

- Computationally cheap
- Sensitive to the choice of weights

Suitable for communities with prior knowledge about relative abundance or growth rates

Joint Problem

Objective:

max $(w_A . growth_A + w_B . growth_B)$

Class II : Multiple objectives

- Simulate the species abundances and concentrations
- No community objective

Suitable to predict and simulate abundances and concentrations

Problem A

Problem B

Objective:

max $growth_A$

max $growth_B$

Class III: Nested objectives

Modeling Microbial Interactions

Class I: Joint objective

- Computationally cheap
- Sensitive to the choice of weights

Suitable for communities with prior knowledge about relative abundance or growth rates

Joint Problem

Objective:

max $(w_A . \text{growth}_A + w_B . \text{growth}_B)$

Class II : Multiple objectives

- Simulate the species abundances and concentrations
- No community objective

Suitable to predict and simulate abundances and concentrations

Problem A

Problem B

Objective:

max growth_A

max growth_B

Class III: Nested objectives

- Community and species objectives at the same time
- Computationally expensive

Suitable for designing new experiments and developing synthetic communities

Outer problem

Objective:

Outer Community Objective

max $(Design)$

Inner Species Objective

max growth_A , max growth_B

Translating Darwin theory into systems modeling

Assume that the metabolic network
must fulfill a cellular objective....

Cellular (evolutionary) objective:

- Grow
- Cooperate
- Outcompete

Metabolic objectives to meet cellular objective

Map evolutionary objectives to *cellular functions*

Grow

What is the maximal growth rate?

Optimize growth rate

Metabolic objectives to meet cellular objective

Map evolutionary objectives to *cellular functions*

Grow

What is the maximal growth rate?

Optimize growth rate

Cooperate

What are the biochemical production capabilities?

Optimize metabolite production

What is the tradeoff between biomass production and metabolite production?

Optimize growth rate for a given metabolite production

Metabolic objectives to meet cellular objective

Map evolutionary objectives to *cellular functions*

Grow

What is the maximal growth rate?

Optimize growth rate

Cooperate

What are the biochemical production capabilities?

Optimize metabolite production

What is the tradeoff between biomass production and metabolite production?

Optimize growth rate for a given metabolite production

Outcompete

How energetically efficient can metabolism operate?

Optimize energy consumption or nutrient uptake

Concept	Formulation	Type of problem
Community members maximize their growth rate (at the expense of or in collaboration with the other species)	$\max w_A V_A^{growth} + w_B V_B^{growth} + \cdots$	LP
Inconsistency between experimental observation and	$\min\ (V^{exp} - V^{predict})^2$	

Concept	Formulation	Type of problem
Community members maximize their growth rate (at the expense of or in collaboration with the other species)	$\max w_A V_A^{growth} + w_B V_B^{growth} + \cdots$	LP
Inconsistency between experimental observation and prediction should be minimized	$\min\ (V_{glucose}^{exp} - V_{glucose}^{predict})^2 + (V_{acetate}^{exp} - V_{acetate}^{predict})^2 + \cdots$	QP
Microbes have evolved to maintain homeostasis upon	$\min\ (V_{glucose}^{WT} - V_{glucose}^{Knockout})^2$	QP

Concept	Formulation	Type of problem
Community members maximize their growth rate (at the expense of or in collaboration with the other species)	$\max w_A V_A^{growth} + w_B V_B^{growth} + \cdots$	LP
Inconsistency between experimental observation and prediction should be minimized	$\min\ (V_{glucose}^{exp} - V_{glucose}^{predict})^2 + (V_{acetate}^{exp} - V_{acetate}^{predict})^2 + \cdots$	QP
Microbes have evolved to maintain homeostasis upon perturbation	$\min\ (V_{glucose}^{WT} - V_{glucose}^{Knockout})^2 + (V_{acetate}^{WT} - V_{acetate}^{Knockout})^2 + \cdots$	QP
Microbes have evolved to grow self-dependently → the number of exchanged metabolites is minimized	$\min b_{acetate} + b_{lactate} + \cdots$	MILP

Concept	Formulation	Type of problem
Community members maximize their growth rate (at the expense of or in collaboration with the other species)	$\max w_A V_A^{growth} + w_B V_B^{growth} + \cdots$	LP
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Developing a synthetic community by gene knockouts to maximize the production of valuable compound or the	$\max V_{phenol}^{degrade}$	MILP

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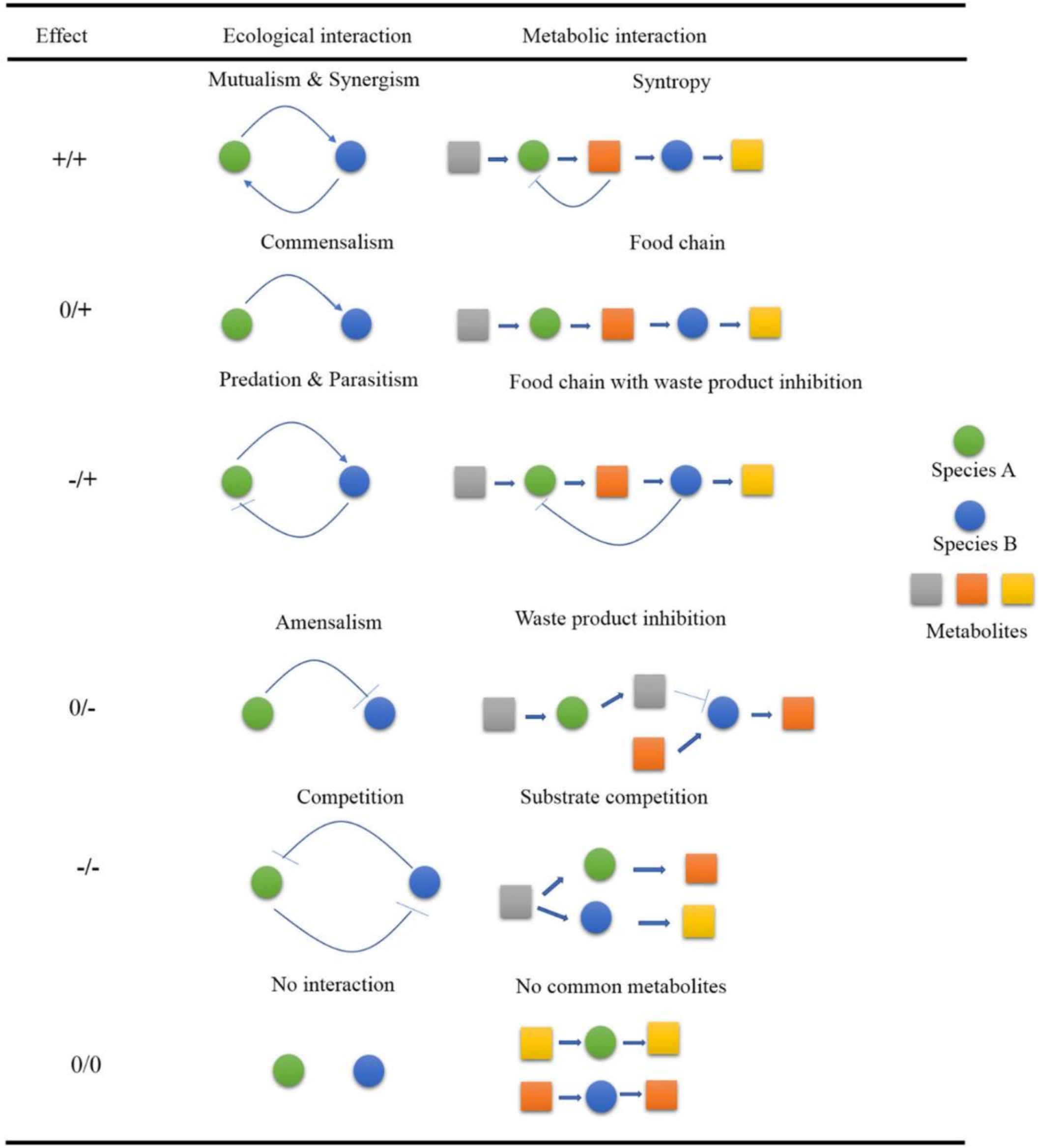
Developing a synthetic community by gene knockouts to maximize the production of valuable compound or the consumption of a toxic compound	$\max V_{phenol}^{degrade}$	MILP

From Single Organism to Communities

- The constraints that are specific to the community



Tshikantwa et al., Current TA, 2018

Microbial interactions: Competition

Negative for both species

Example: Human gut microbiata

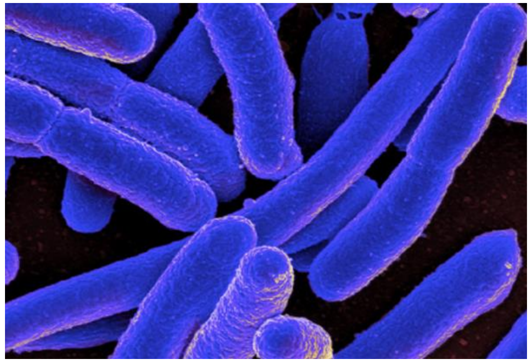
Microbial interactions: Competition

Negative for both species

Example: Human gut microbiata

Environment

NH_4^+



Escherichia coli

Salmonella enterica

Microbial interactions: Competition

NH_4+ Uptake by Community

$$Upt_{NH_4+}^{E.coli} + Upt_{NH_4+}^{S.enterica} = Upt_{NH_4+}^{env}$$

NH_4+ Uptake by *S. enterica*

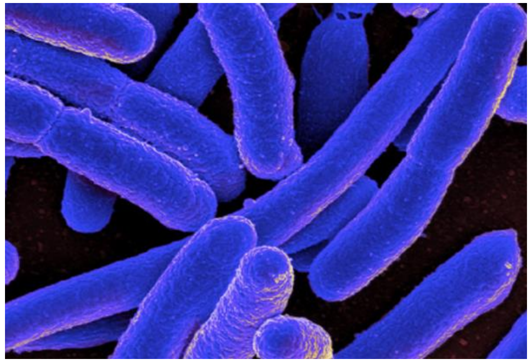
NH_4+ Uptake by *E. coli*

Negative for both species

Example: Human gut microbiata

Environment

NH_4+



Escherichia coli

Salmonella enterica

Microbial interactions: Syntrophy

Positive and obligatory for both species

Example: Rumen syntrophy

Microbial interactions: Syntrophy

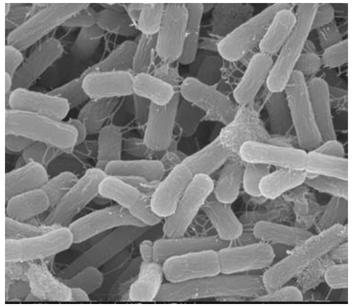
Positive and obligatory for both species

Example: Rumen syntrophy

Ruminococcus spp.

Nutrients

H_2 → CH_4



Methanogens

Microbial interactions: Syntrophy

Positive and obligatory for both species

Example: Rumen syntrophy

H_2 Export by *Ruminococci*

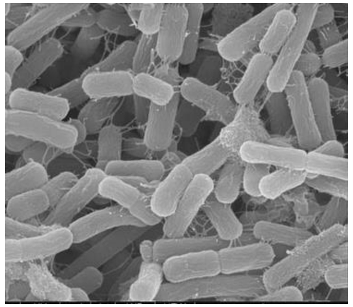
$$Upt_{H_2}^{Methanogens} = Exp_{H_2}^{Ruminococci}$$

H_2 Uptake by Methanogens

Ruminococcus spp.

Nutrients

H_2 → CH_4



Methanogens

Microbial interactions: Commensalism

Positive for one species

Example: Nitrification cycle in soil and marine environments

Microbial interactions: Commensalism

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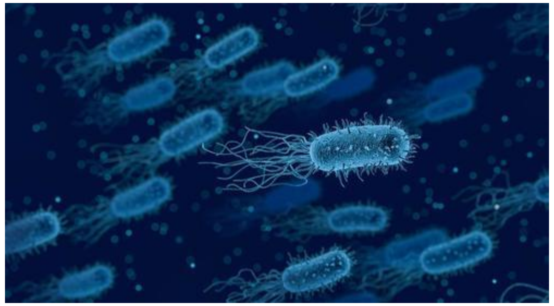
Example: Nitrification cycle in soil and marine environments

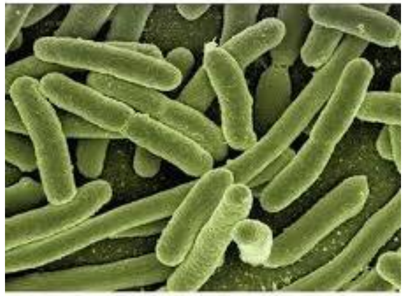


Nitrosomonas spp.

NH_4^+

NO_2^-

NO_3^-



Nitrobacter spp.

Environment

Microbial interactions: Commensalism

Positive for one species

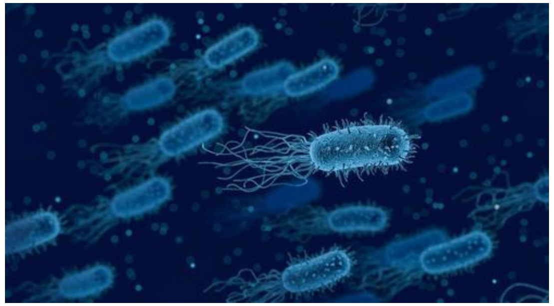
Example: Nitrification cycle in soil and marine environments

NO_2^- Export by Community

NO_2^- Uptake by *Nitrobacter*

$$Exp_{NO_2-}^{Nitrosomonas} = Upt_{NO_2-}^{Nitrobacter} + Exp_{NO_2-}^{env}$$

NO_2^- Export by *Nitrosomonas*

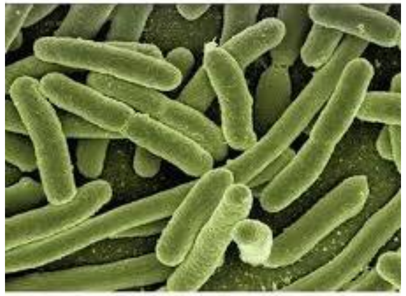


Nitrosomonas spp.

NH_4^+

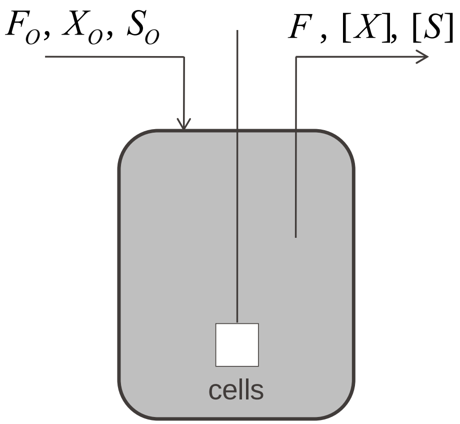
NO_2^- → NO_3^-

Environment

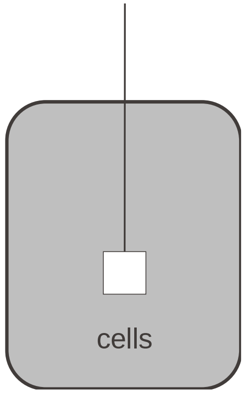


Nitrobacter spp.

Temporal dynamic



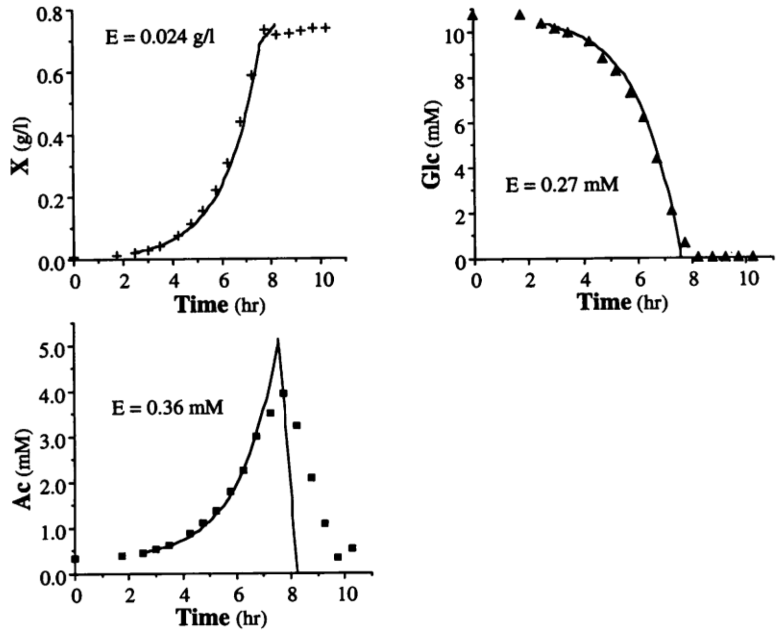
Chemostat

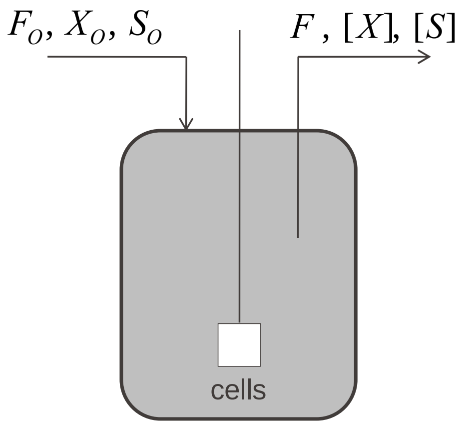


Batch

Temporal dynamic

- Single organism in batch culture
- Steady-state assumption is not valid for biomass and extracellular metabolites





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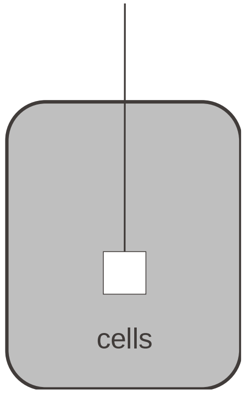

Batch

Varma, A., and Palsson, BO. "Stoichiometric flux balance models quantitatively predict growth and metabolic by-product secretion in wild-type Escherichia coli W3110." Applied and environmental microbiology, 1994

Temporal dynamic

- Single organism in batch culture
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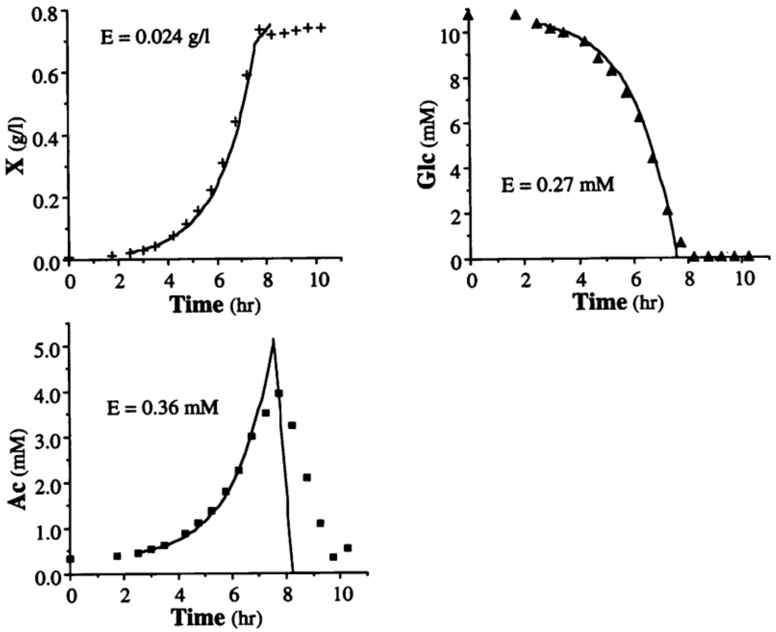
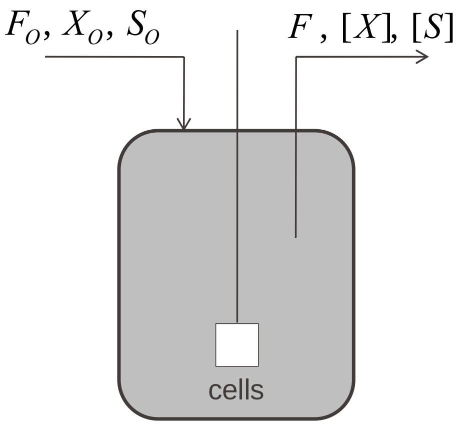
  - Taking small time-steps $\triangle t$, where the fluxes are constant





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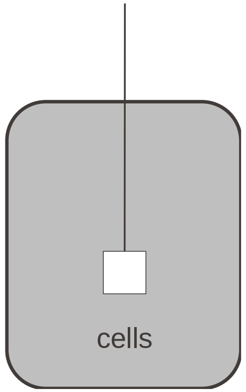

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- Steady-state assumption is not valid for biomass and extracellular metabolites
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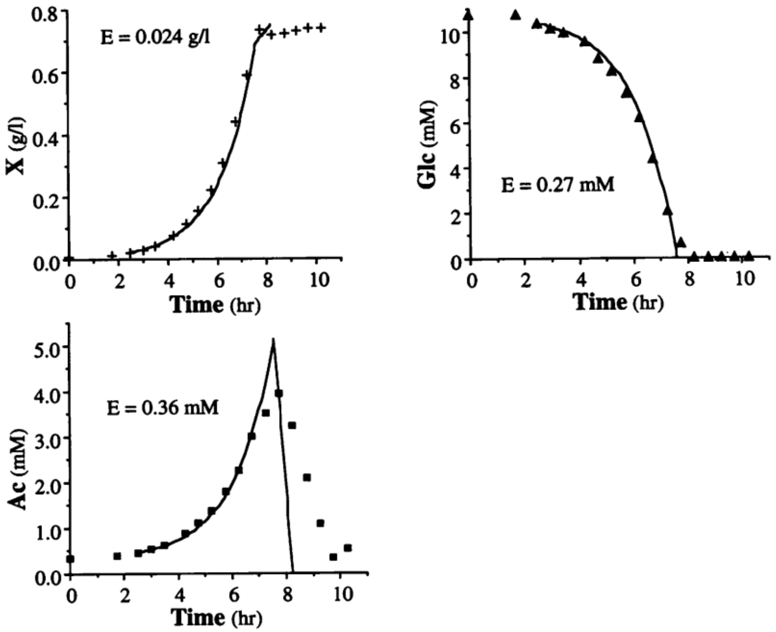

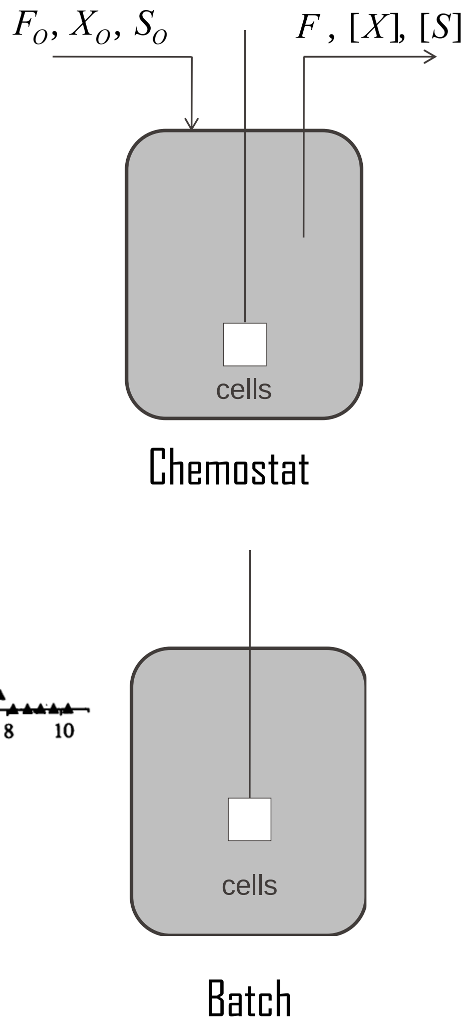

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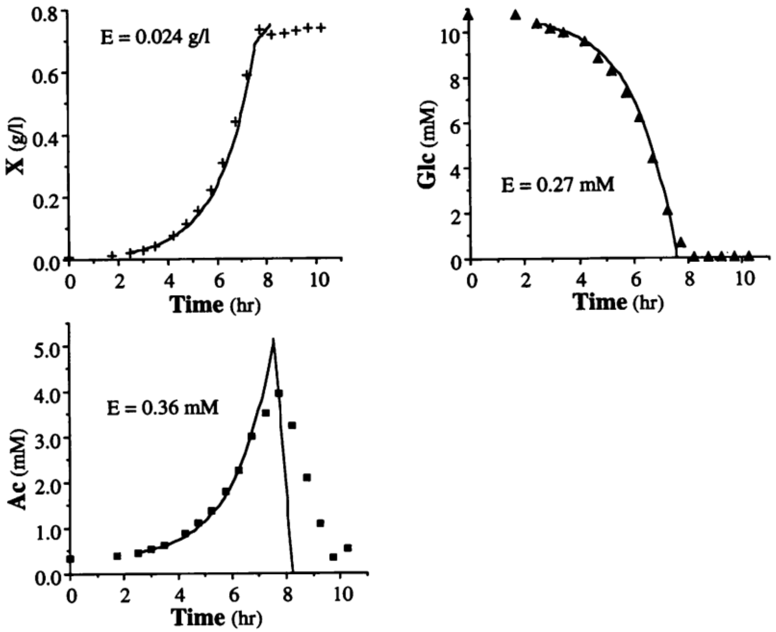
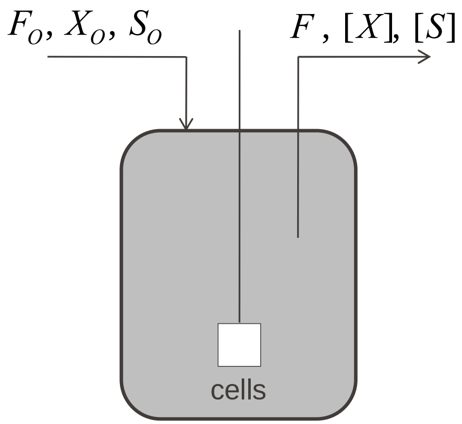
Temporal dynamic

- Single organism in batch culture
- Steady-state assumption is not valid for biomass and extracellular metabolites
  - Taking small time-steps Δt, where the fluxes are constant
  - Solving FBA in Δt to find fluxes including μ
  - The Monod equation:

$$X = X_0 e^{\mu \Delta t}$$





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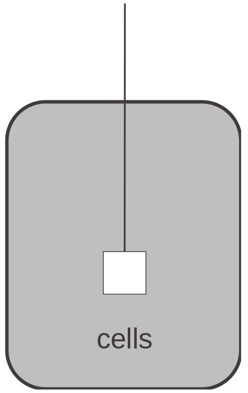

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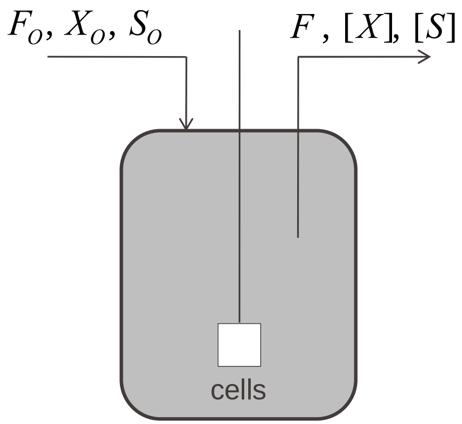
  - Similar procedure for extracellular metabolites



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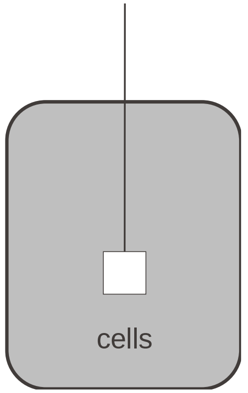

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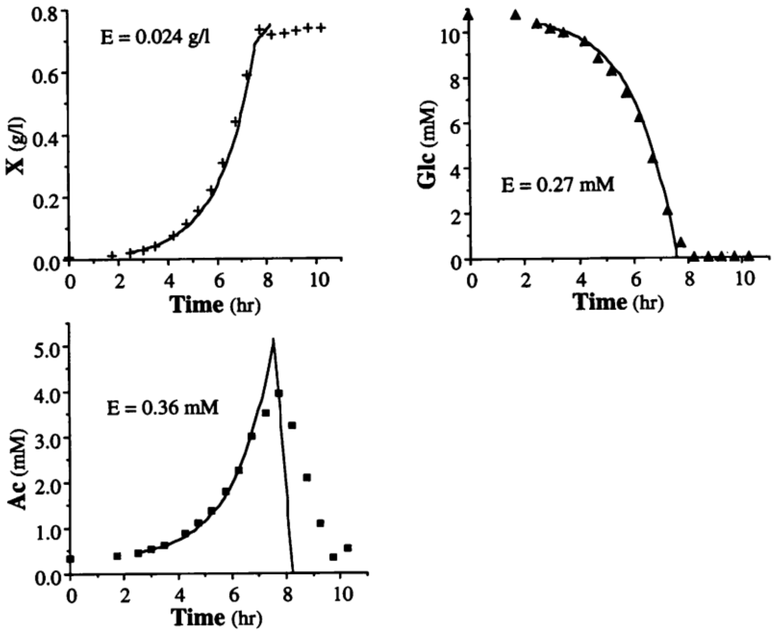

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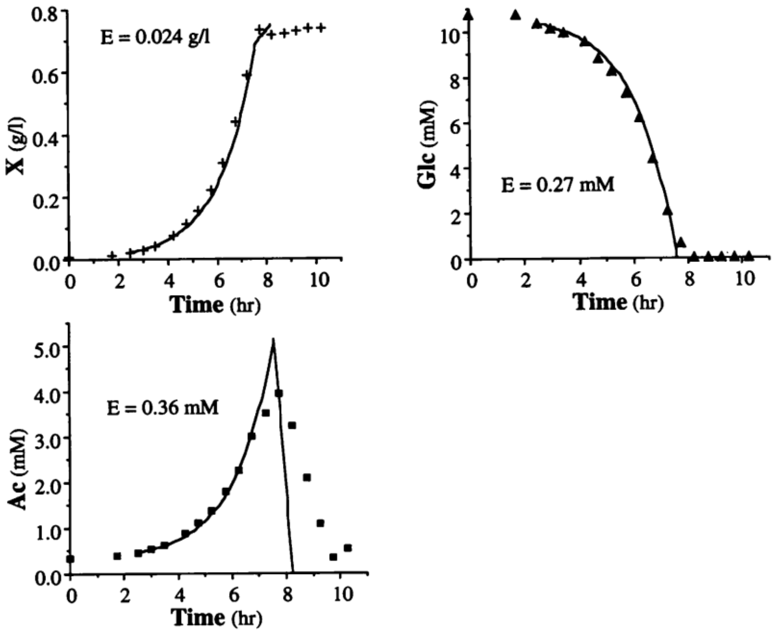
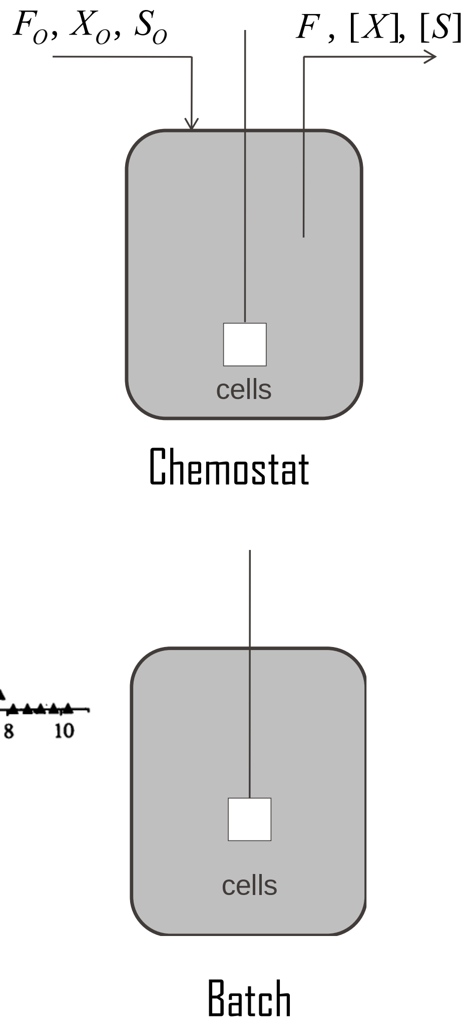
  - Similar procedure for extracellular metabolites
  - Computationally more expensive ⟶ solving an FBA for each time-step





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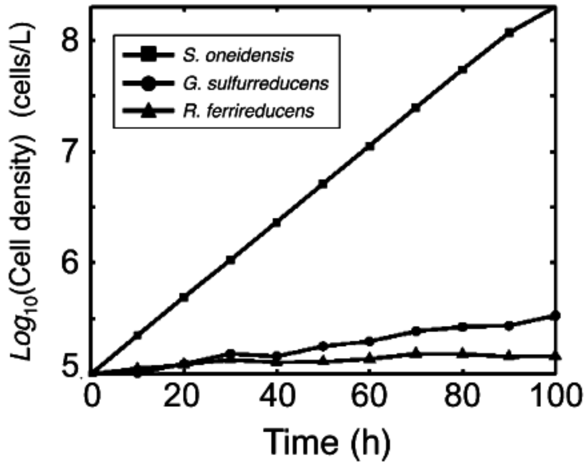

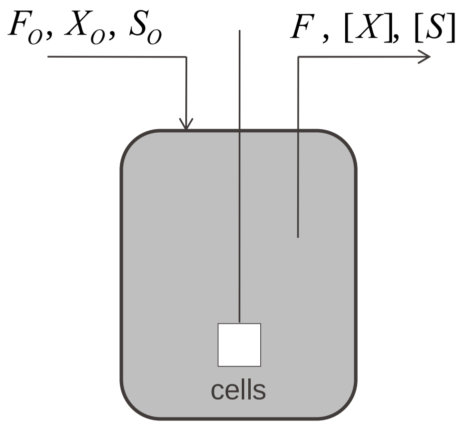

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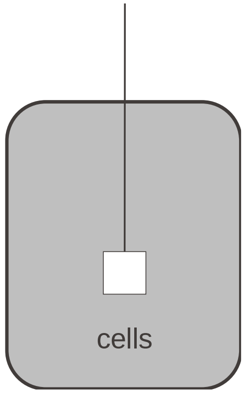

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Important computational methods

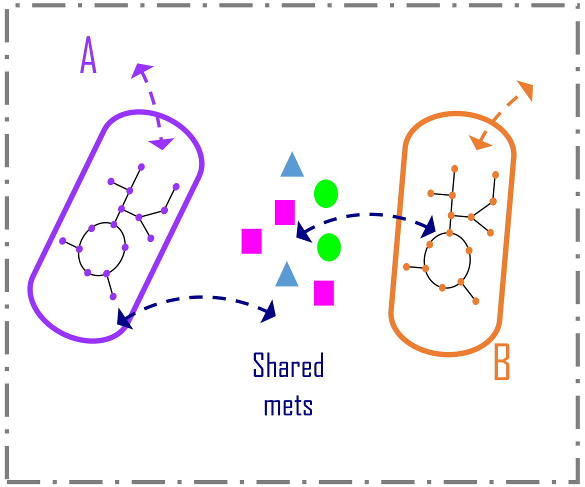
Name	Approach	Dynamic	Reference
Stoylar et al.	Joint objective	NO	Stoylar, S. *et* al., Molecular systems biology, 2007
cFBA	Joint objective	NO	Khandelwal, R. *et* al., PloS one, 2013
SteadyCom	Joint objective	NO	Chan, S. *et* al.,PLoS computational biology, 2017
DMMM	Multiple objectives	YES	Zhuang, K. *et* al., The ISME journal, 2011
OptCom	Nested objectives	NO	Zomorrodi, A. and Maranas C, PLoS computational biology, 2012
CASINO	Nested objectives	NO	Shoaie, S. *et* al., Cell metabolism, 2015
D-OptCom	Nested objectives	YES	Zomorrodi, A., *et* al., ACS synthetic biology, 2014

Case studies in literature

- Syntrophic interaction between sulfate reducer *Desulfovibrio vulgaris* and methanogen *Methanococcus maripaludis*

- Hydrogen exchange

molecular systems biology



Joint Objective

Metabolic modeling of a mutualistic microbial community

Sergey Stolyar[1,*], Steve Van Dien[1,3], Kristina Linnea Hillesland[1], Nicolas Pinel[2], Thomas J Lie[2], John A Leigh[2] and David A Stahl[1,*]

[1] Department of Civil and Environmental Engineering, University of Washington, Seattle, WA, USA and [2] Department of Microbiology, University of Washington, Seattle WA, USA

[3] Present address: Genomatica Inc., 5405 Morehouse Drive; San Diego, CA 92121, USA

* Corresponding authors. S Stolyar, Civil and Environmental Engineering, University of Washington, 478 Benjamin Hall Interdisciplinary Research Building, Box 355014, Seattle, WA 98195, USA. Tel.: +1 206 543 2094; Fax: +1 206 685 3836; E-mail: sstolyar@u.washington.edu or DA Stahl, Civil and Environmental Engineering, University of Washington, 302 More Hall, Seattle, WA, USA. Tel.: +1 206 685 3464; Fax: +1 206 685 3836; E-mail: dastahl@u.washington.edu

Received 4.7.06; accepted 21.12.06

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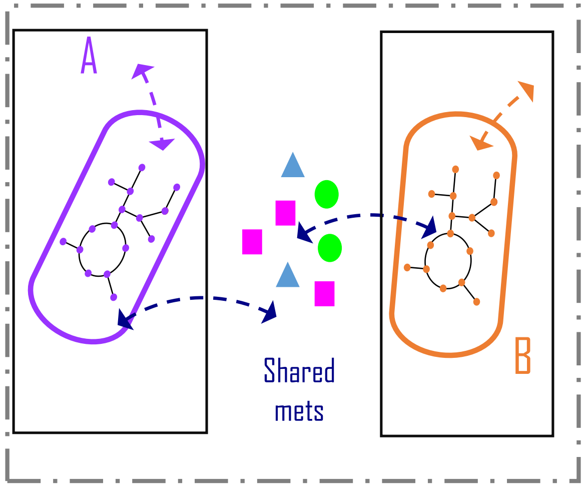

Nested Objectives

PLoS COMPUTATIONAL BIOLOGY

OptCom: A Multi-Level Optimization Framework for the Metabolic Modeling and Analysis of Microbial Communities

Ali R. Zomorrodi, Costas D. Maranas*

Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania, United States of America

Case studies in literature

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* Corresponding authors. S Stolyar, Civil and Environmental Engineering, University of Washington, 478 Benjamin Hall Interdisciplinary Research Building, Box 355014, Seattle, WA 98195, USA. Tel.: +1 206 543 2094; Fax: +1 206 685 3836; E-mail: sstolyar@u.washington.edu or DA Stahl, Civil and Environmental Engineering, University of Washington, 302 More Hall, Seattle, WA, USA. Tel.: +1 206 685 3464; Fax: +1 206 685 3836; E-mail: dastahl@u.washington.edu

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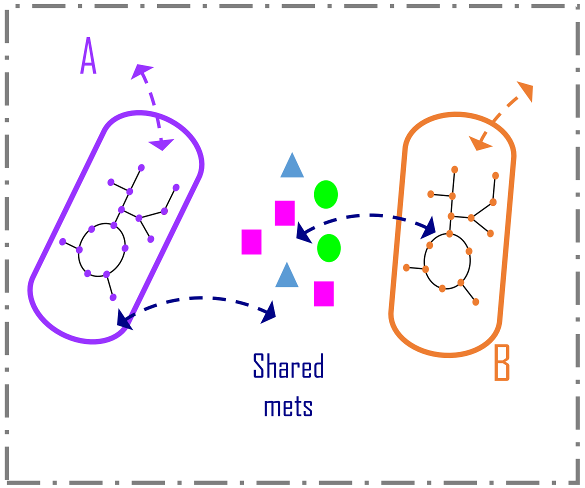
- Both methods were able to predict acetate, methane and CO_2 fluxes
- The members were inter-dependent and relative abundances were known
- Joint objective is faster and easier to be solved

Case studies in literature

- Flora of Octopus and Mushroom Springs of Yellowstone National Park (Wyoming, USA)
- Three guilds: Oxygenic photoautotrophs related to *Synechococcus* spp., filamentous anoxygenic phototrophs related to *Chloroflexus* and *Roseiflexus* spp., sulfate reducing bacteria
- Syntrophy and competition for different metabolites



Joint Objective

BMC Systems Biology

In silico approaches to study mass and energy flows in microbial consortia: a syntrophic case study

Reed Taffs[1,2], John E Aston[1,2], Kristen Brileya[1,2], Zackary Jay[1], Christian G Klatt[1], Shawn McGlynn[1], Natasha Mallette[1,2], Scott Montross[1], Robin Gerlach[1,2], William P Inskeep[1], David M Ward[1] and Ross P Carlson*[1,2]

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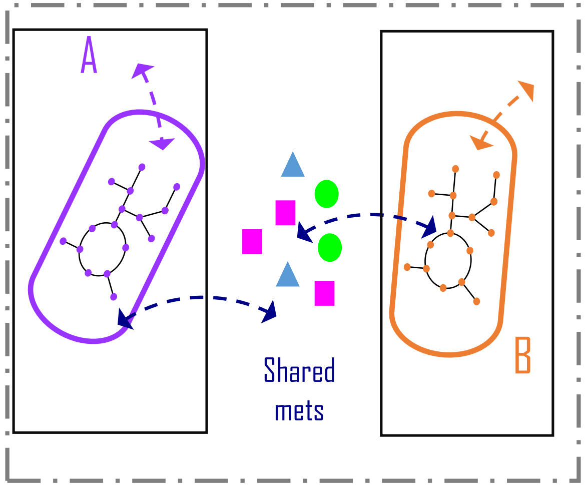

Nested Objectives

PLOS COMPUTATIONAL BIOLOGY

OptCom: A Multi-Level Optimization Framework for the Metabolic Modeling and Analysis of Microbial Communities

Ali R. Zomorrodi, Costas D. Maranas*

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OptCom: A Multi-Level Optimization Framework for the Metabolic Modeling and Analysis of Microbial Communities

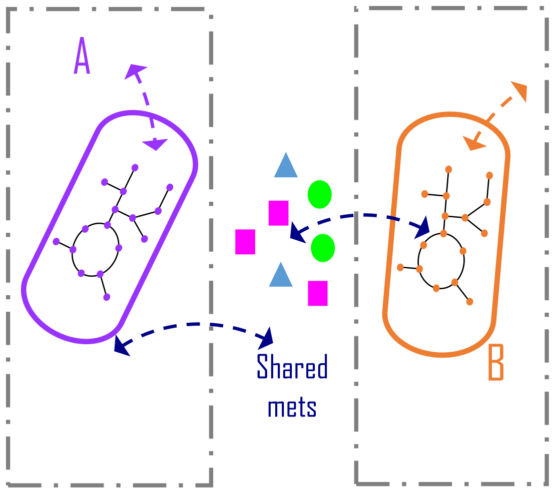
Ali R. Zomorrodi, Costas D. Maranas*

Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania, United States of America

- Over-estimation of growth rates
- Two hypotheses: selfish growth or altruistic growth
- Joint objective: selfish growth
- Nested objective: combination of both

Case studies in literature

- *Geobacter sulfurreducens* and *Rhodoferax ferrireducens* in a uranium contaminated aquifer
- Competition for Fe^{3+}, acetate and ammonium
- Dynamic modeling



Multiple Objectives

The ISME Journal (2011) 5, 305–316

www.nature.com/ismej

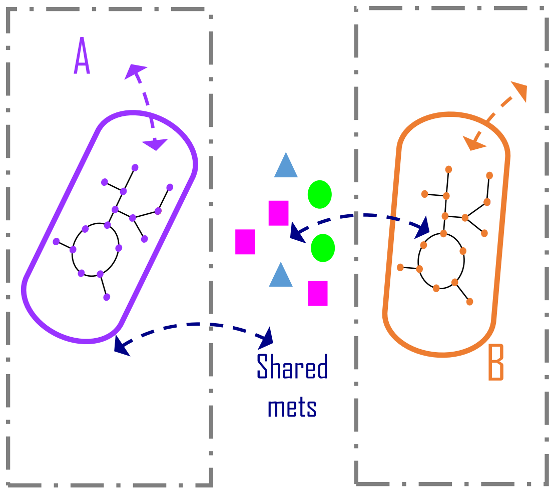
ORIGINAL ARTICLE

Genome-scale dynamic modeling of the competition between *Rhodoferax* and *Geobacter* in anoxic subsurface environments

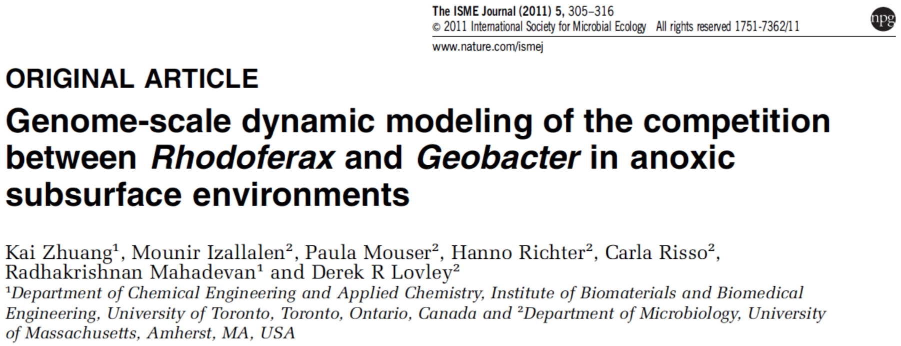
Kai Zhuang[1], Mounir Izallalen[2], Paula Mouser[2], Hanno Richter[2], Carla Risso[2], Radhakrishnan Mahadevan[1] and Derek R Lovley[2]
[1]*Department of Chemical Engineering and Applied Chemistry, Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada and* [2]*Department of Microbiology, University of Massachusetts, Amherst, MA, USA*

Case studies in literature

- *Geobacter sulfurreducens* and *Rhodoferax ferrireducens* in a uranium contaminated aquifer
- Competition for Fe^{3+}, acetate and ammonium
- Dynamic modeling



Multiple Objectives



The ISME Journal (2011) 5, 305–316

www.nature.com/ismej

ORIGINAL ARTICLE

Genome-scale dynamic modeling of the competition between *Rhodoferax* and *Geobacter* in anoxic subsurface environments

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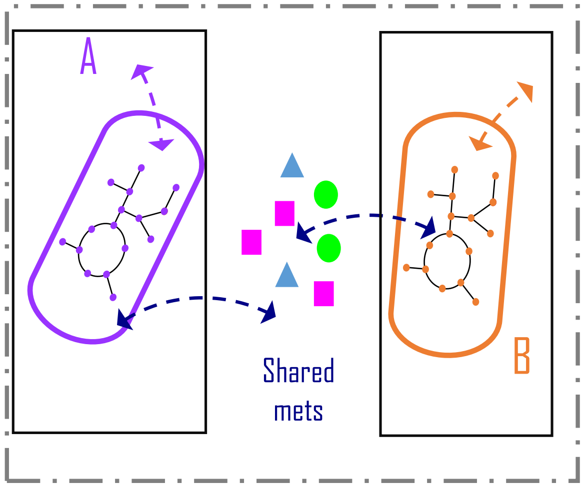
- Successful prediction of relative abundances at different time points

Case studies in literature

- *Geobacter sulfurreducens* and *Rhodoferax ferrireducens* in a uranium contaminated aquifer
- Competition and Cooperation for different metabolites
- Dynamic modeling



Nested Objectives

ACS Synthetic Biology
Research Article
pubs.acs.org/synthbio

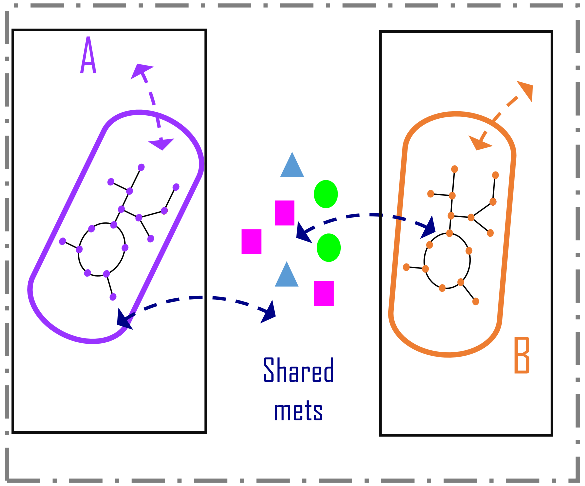
d-OptCom: Dynamic Multi-level and Multi-objective Metabolic Modeling of Microbial Communities

- Design a synthetic community for uranium bioremediation:
  - Addition of a new member
    - (Shewanella oneidensis)
  - Addition of metabolites
  - Gene knockouts

Case studies in literature

- Human gut microbiota
- 5 representative species
- Various interactions

Bacteroides thetaiotaomicron
Eubacterium rectale
Bifidobacterium adolescentis
Faecalibacterium prausnitzii
Ruminococcus bromii



Nested Objectives

Cell Metabolism

Resource

Quantifying Diet-Induced Metabolic Changes of the Human Gut Microbiome

Saeed Shoaie,[1] Pouyan Ghaffari,[1] Petia Kovatcheva-Datchary,[2] Adil Mardinoglu,[1] Partho Sen,[1] Estelle Pujos-Guillot,[3] Tomas de Wouters,[4] Catherine Juste,[4] Salwa Rizkalla,[5,6] Julien Chilloux,[7] Lesley Hoyles,[7] Jeremy K. Nicholson,[7] MICRO-Obes Consortium, Joel Dore,[4] Marc E. Dumas,[7] Karine Clement,[5,6,8] Fredrik Bäckhed,[2,9] and Jens Nielsen[1,*]

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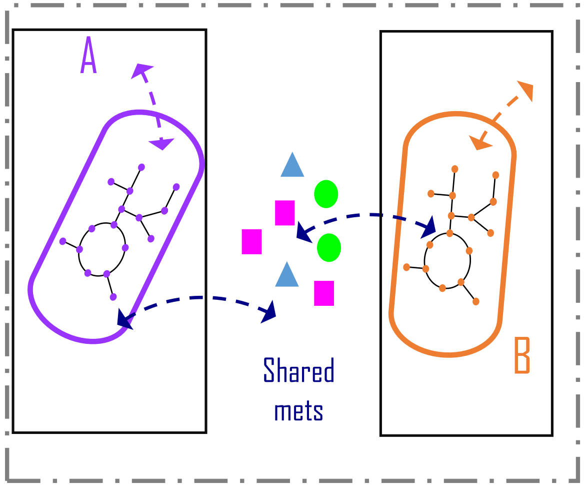

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CellPress
Cell Metabolism
Resource

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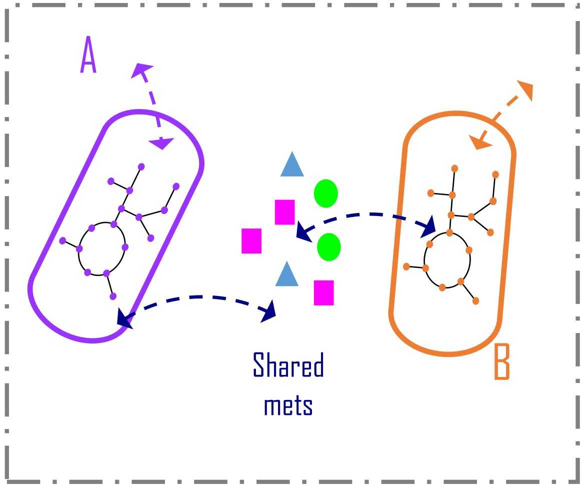
- Altered fecal and serum amino acid levels in response to diet intervention
- The interactions were inferred from the experimental data

Case studies in literature

- Human gut microbiota
- 9 representative species
- Various interactions



Joint Objective

Species	Phylum
Bacteroides thetaiotaomicron (*B. thetaiotaomicron*)	Bacteroidetes
Eubacterium rectale (*E. rectale*)	Firmicutes
Faecalibacterium prausnitzii (*F. prausnitzii*)	Firmicutes
Enterococcus faecalis (*E. faecalis*)	Firmicutes
Lactobacillus casei (*L. casei*)	Firmicutes
Streptococcus thermophilus (*S. thermophilus*)	Firmicutes
Bifidobacterium adolescentis (*B. adolescentis*)	Actinobacteria
Escherichia coli (*E. coli*)	Proteobacteria
Klebsiella pneumoniae (*K. pneumoniae*)	Proteobacteria

PLOS | COMPUTATIONAL BIOLOGY

SteadyCom: Predicting microbial abundances while ensuring community stability

Siu Hung Joshua Chan, Margaret N. Simons, Costas D. Maranas*

Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania, United States of America

Case studies in literature

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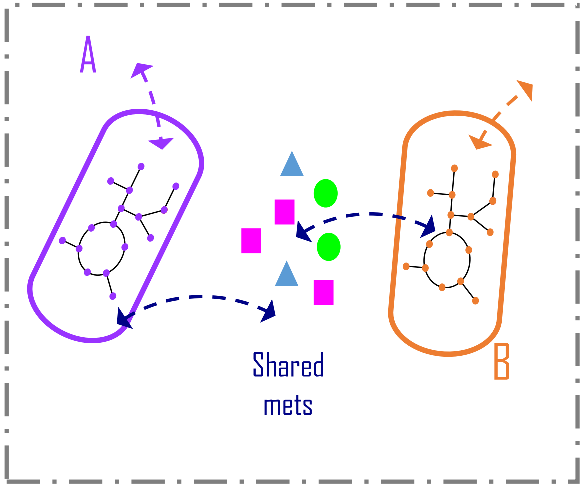

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PLOS | COMPUTATIONAL BIOLOGY

SteadyCom: Predicting microbial abundances while ensuring community stability

Siu Hung Joshua Chan, Margaret N. Simons, Costas D. Maranas*

Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania, United States of America

Predicted the changes in species abundance
in response to changes in diet

Data integration

- Experimental data can be used to enhance model predictions:

Data integration

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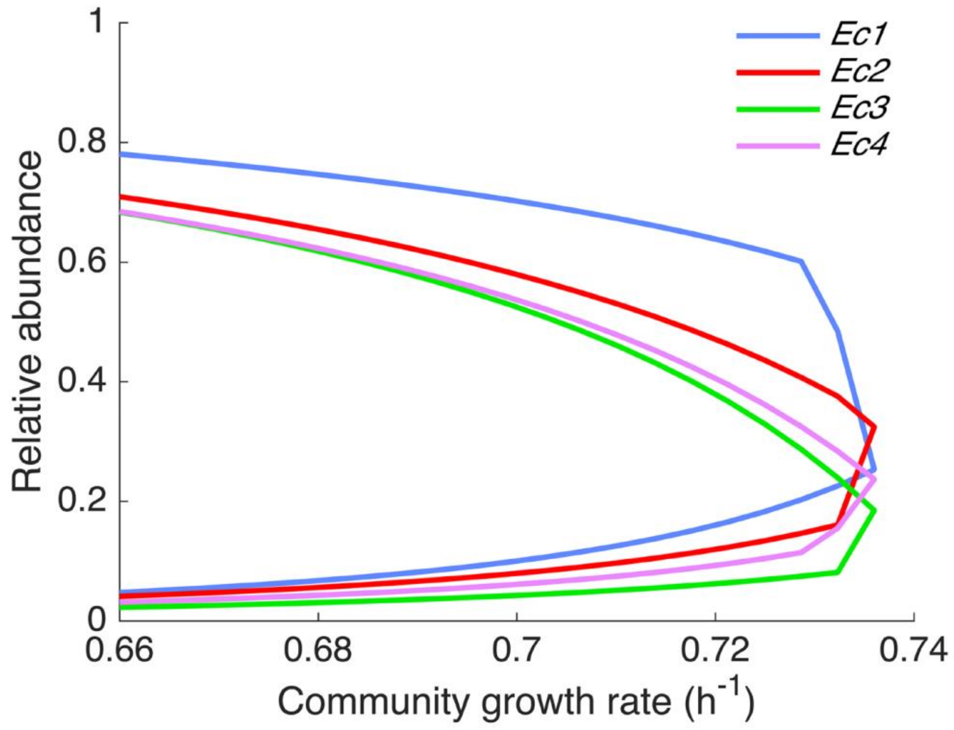
  - Relative or absolute abundances → weight of objectives, etc.



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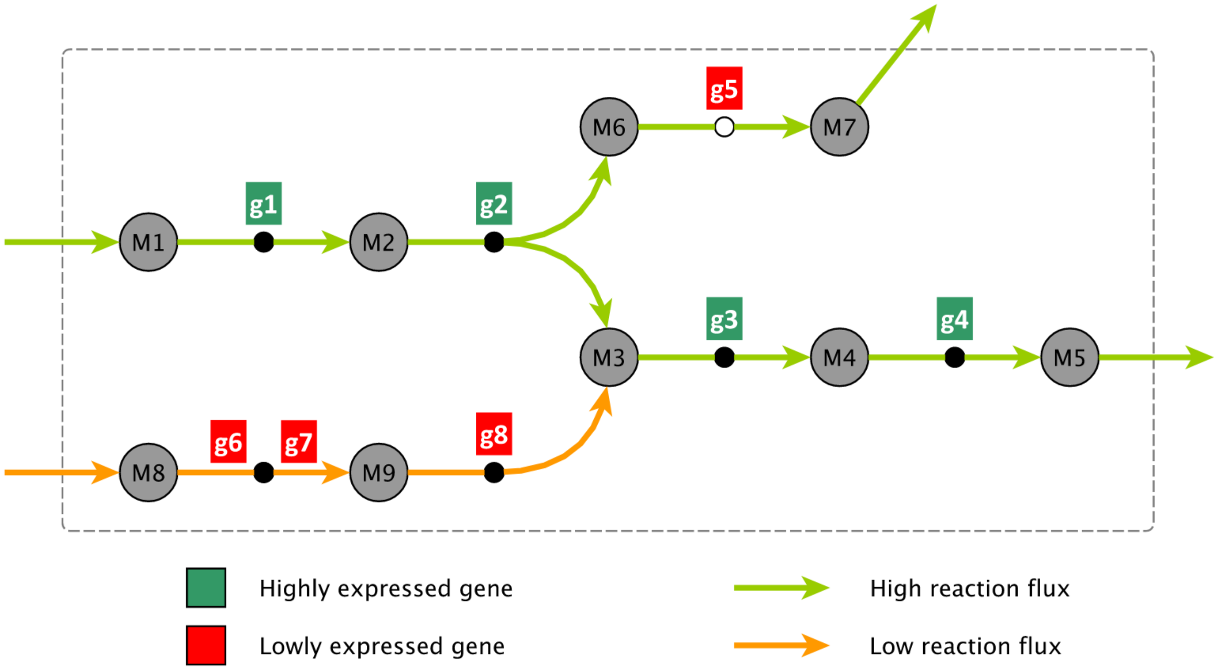

Pandey V, Gardiol DH, Chiappino-Pepe A, Hatzimanikatis V. TEX-FBA: A constraint-based method for integrating gene expression, thermodynamics, and metabolomics data into genome-scale metabolic models. bioRxiv. 2019 Jan 1:536235.

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Thermodynamic constraints:

- Net flux is toward either forward or backward direction

$$\Delta_r G_i' < 0$$

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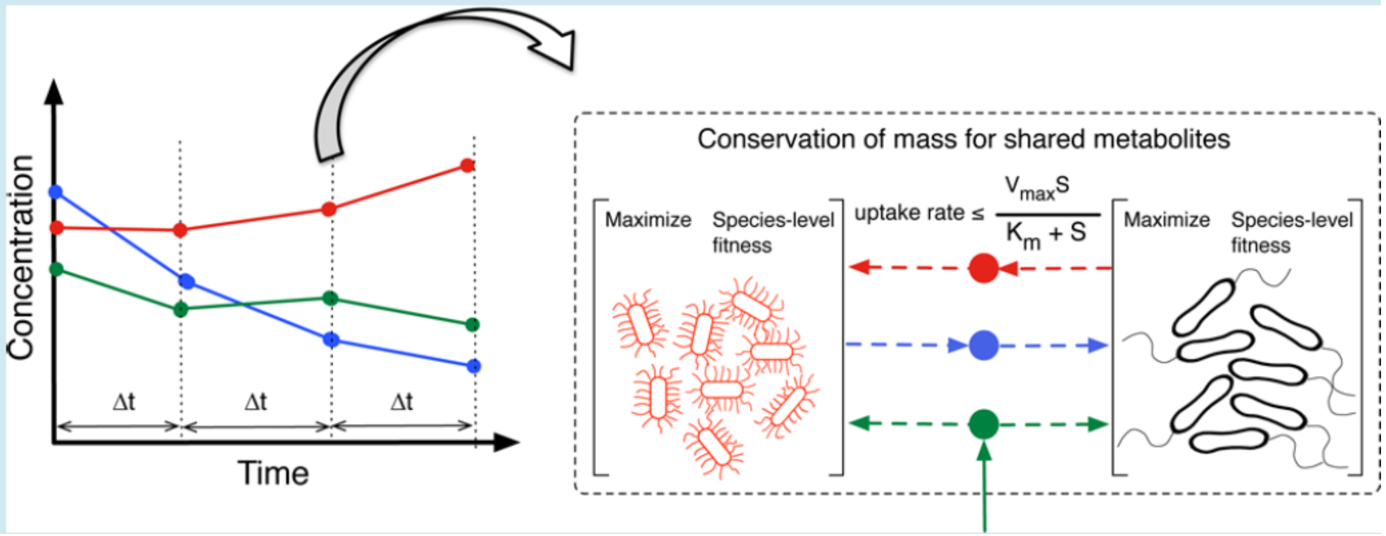
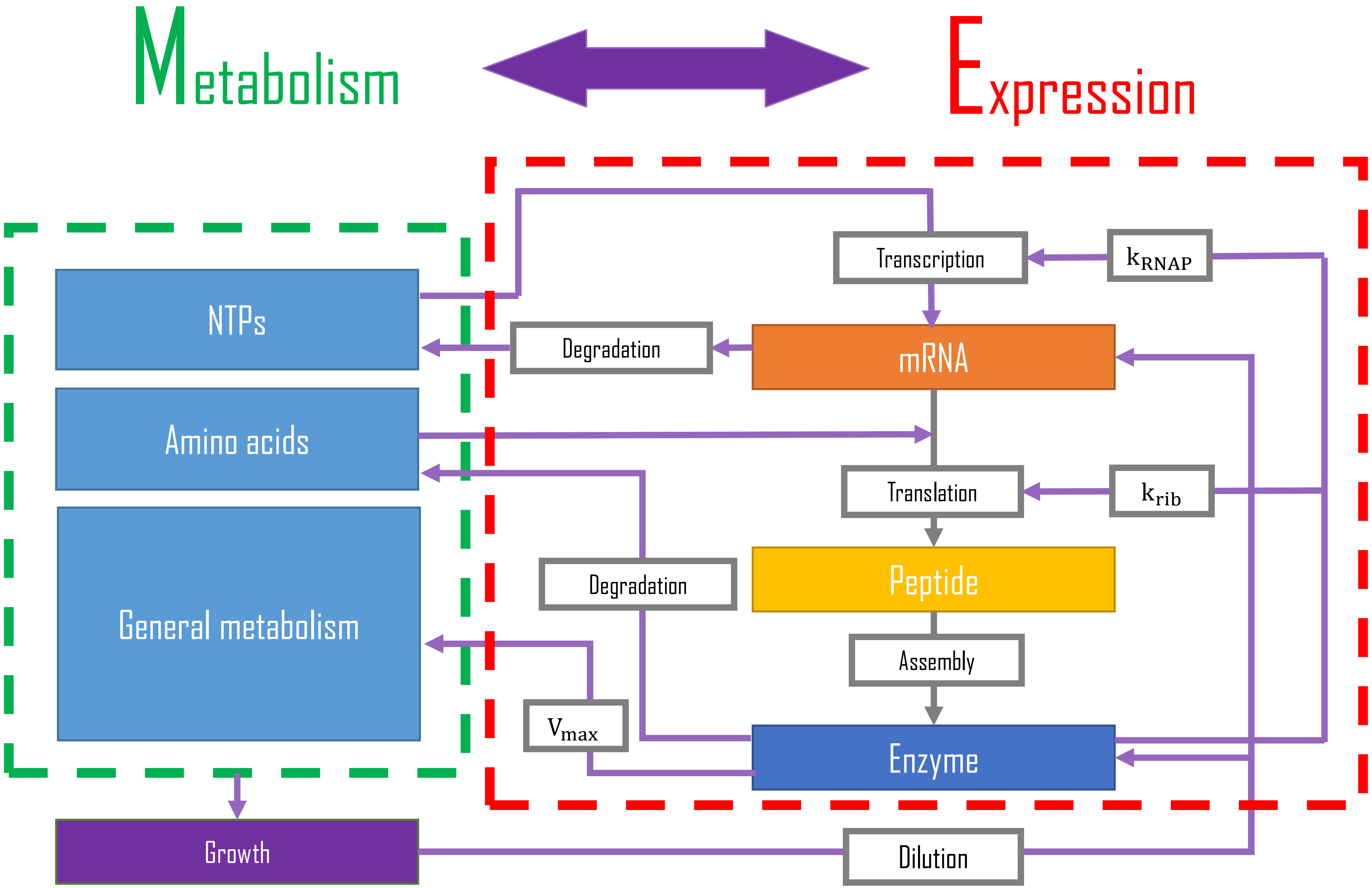
  - Kinetic parameters of uptake and secretion → dynamic models
  - Extracellular metabolite concentration → dynamic models



Zomorrodi, A.., Islam M., and Maranas CD, "d-OptCom: dynamic multi-level and multi-objective metabolic modeling of microbial communities." ACS synthetic biology, 2014



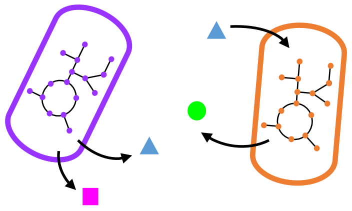
Salvy, Pierre, and Vassily Hatzimanikatis. "The ETFL formulation allows multi-omics integration in thermodynamics-compliant metabolism and expression models." *Nature Communications* 11.1 (2020)

Closing remarks

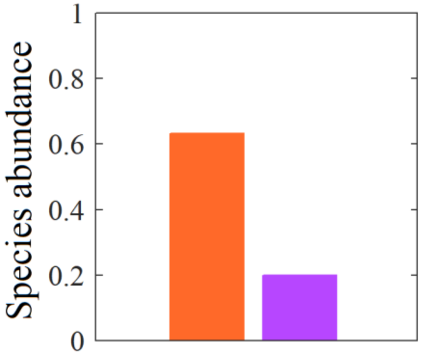
- Size and complexity of the problem
- Importance of a suitable objective for the community
- Prospecpective and retrospective study
- Enumeration of sorting the alternative solution
- Integration of experimental data

Microbial Communities Models

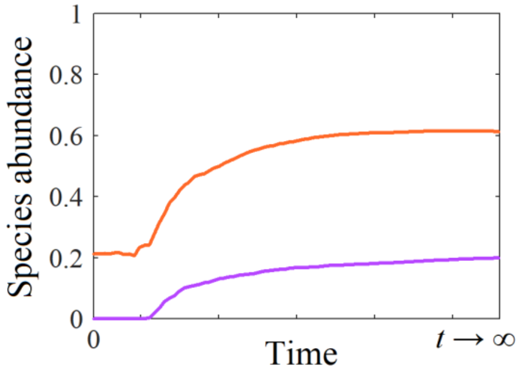
Constrained-based models



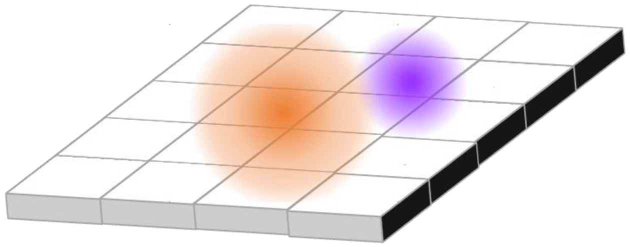
Steady state



Dynamic



Spatio-temporal



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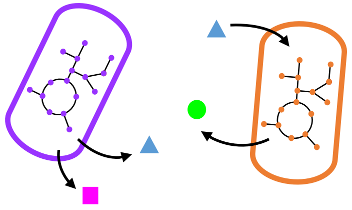

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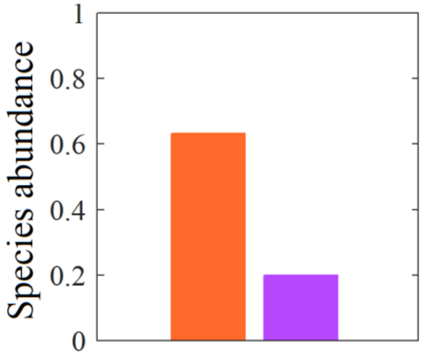

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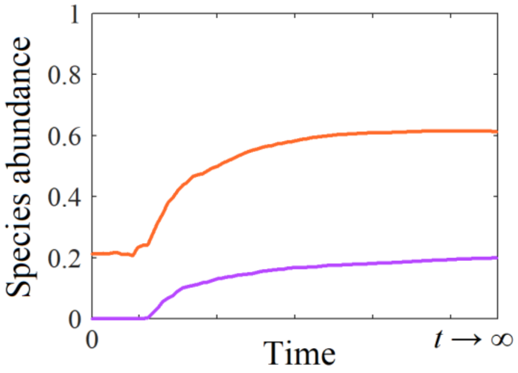
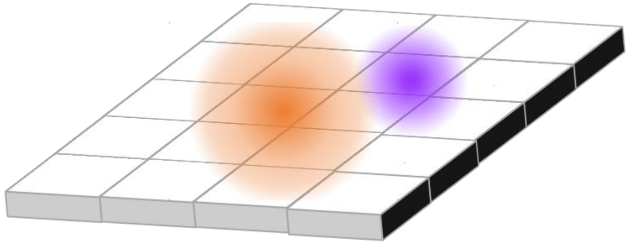


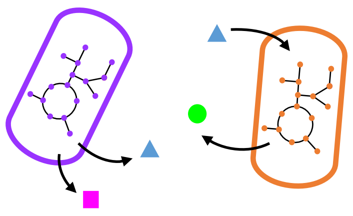
Spatio-temporal



- Well-mixed system.
- No accumulation of metabolites or biomass.

Microbial Communities Models

Constrained-based models



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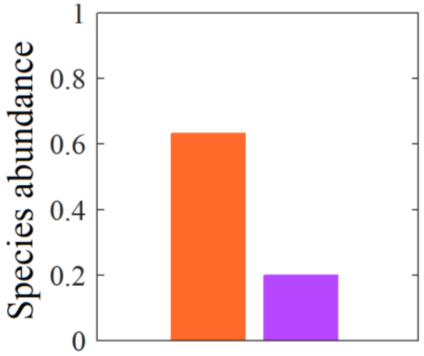

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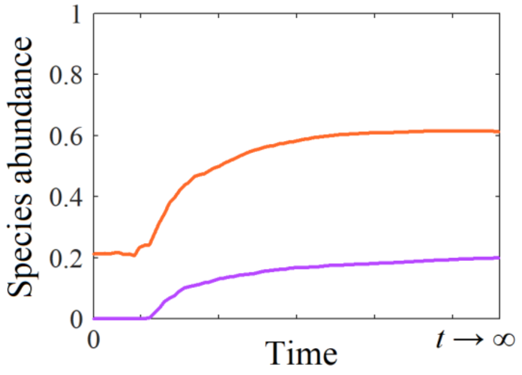
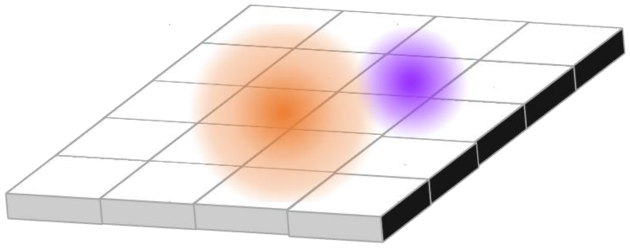


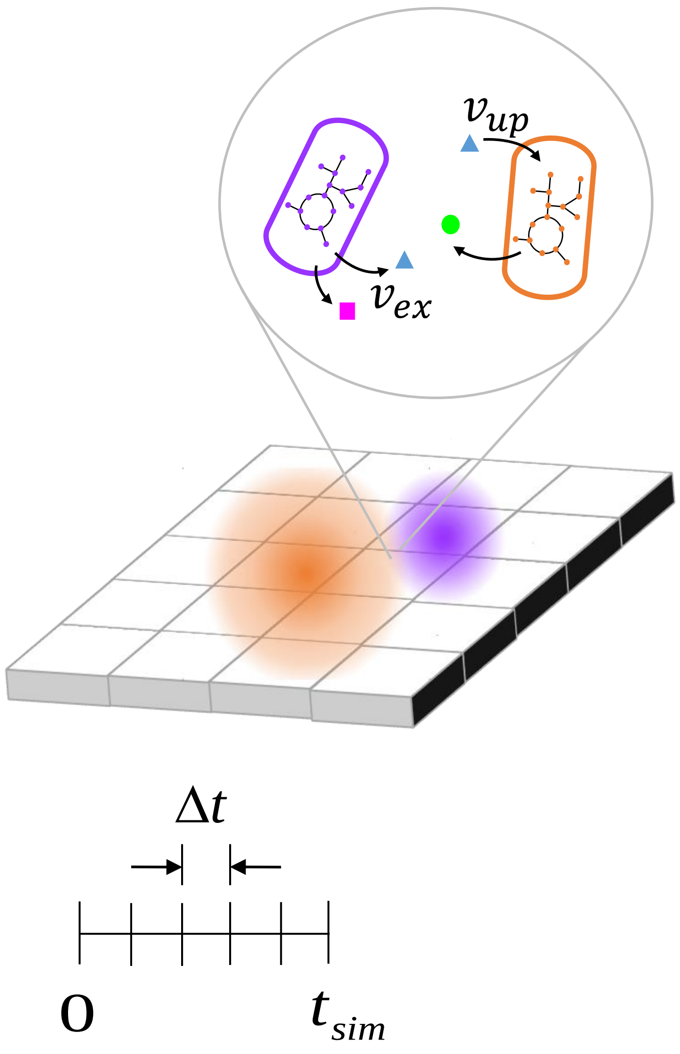
Spatio-temporal



- ❖ Well-mixed system.
- ❖ No accumulation of metabolites or biomass.

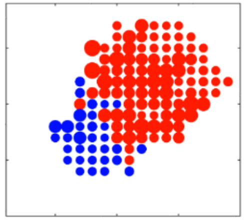
- ❖ Well-mixed system.
- ❖ Changes in metabolites and microbial abundance.

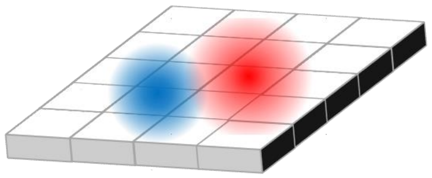
Spatio-temporal modeling

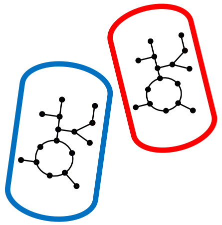


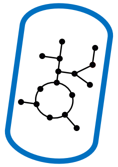
- Heterogeneous system.
- Space and time components.
- Changes in extracellular metabolites and microbial abundance.
- Compartmentalized model.

Spatio-temporal modeling









Individual-based approach	Population approach
Karimian and Motamedian. 2020. *Sci Rep* **10**:8695. Borer et al. 2019. PLOS Comput Biol 15:e1007127. Bauer et al. 2017. PLOS Comput Biol 13: e1005544. Angeles-Martinez and Hatzimanikatis. 2020. Submitted.	Harcombe et al. 2014. Cell Rep 7:1104-1115. Chan, et al. 2019. *Processes* 7:394. Phalak et al. 2016. *BMC Syst Biol* **10:90**.
Cole et al. 2015. BMC Syst. Biol. 9:15. Biggs and Papin. 2013. PLOS One. 8:e78011.	Chen et al. 2016. *BMC Syst Biol* **10:21**. Fang et al. 2011. J Contam Hydrol. 122:96–103.

Spatio-temporal modeling

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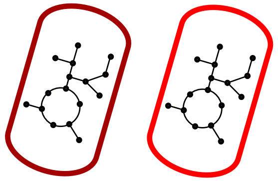
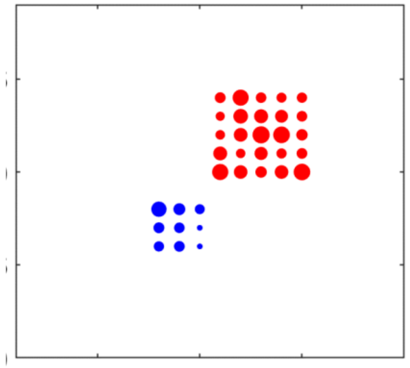
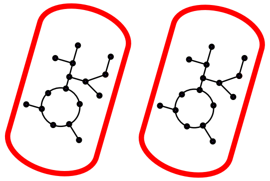


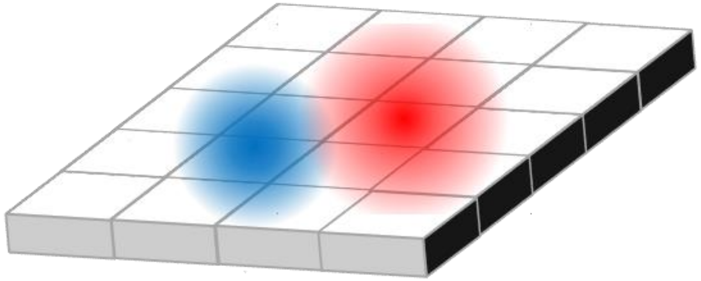


Cells increase in size too!

Population approach



$$\frac{\partial \rho_{sp}}{\delta t} = \nabla \cdot \left(D_{sp} \nabla \rho_{sp}\right)$$



Spatio-temporal modeling