

Modeling and designing microbial ecosystem metabolism

Daniel Segrè

Dept. of Biology, Dept. of Biomedical Engineering

Dept. of Physics, Bioinformatics Program

BU Microbiome Initiative - <http://microbu.org>

Biological Design Center

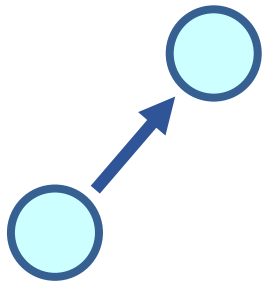
Twitter: @dsegre



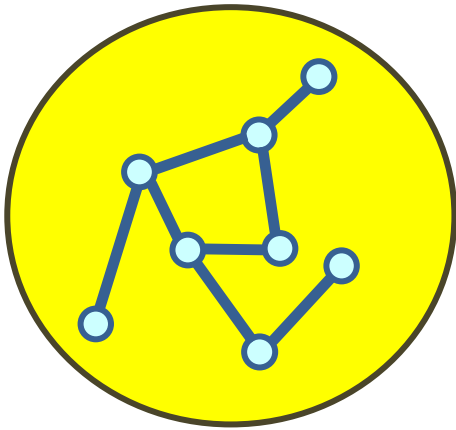
CENTER FOR
CHEMICAL CURRENCIES
OF A MICROBIAL PLANET

Metabolism is a multi-scale process

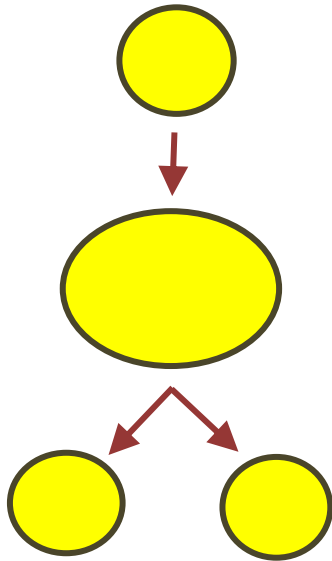
Enzymes, cells and ecosystems are all catalysts of metabolic flows



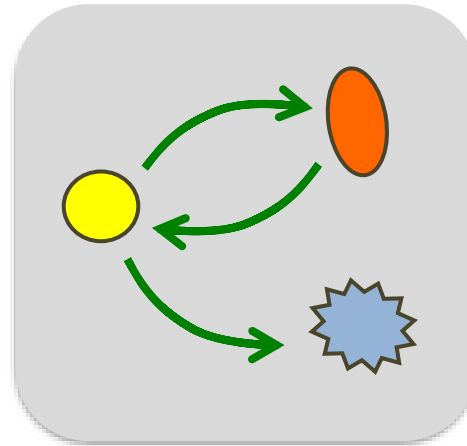
enzyme



network



cell



ecosystem



planet

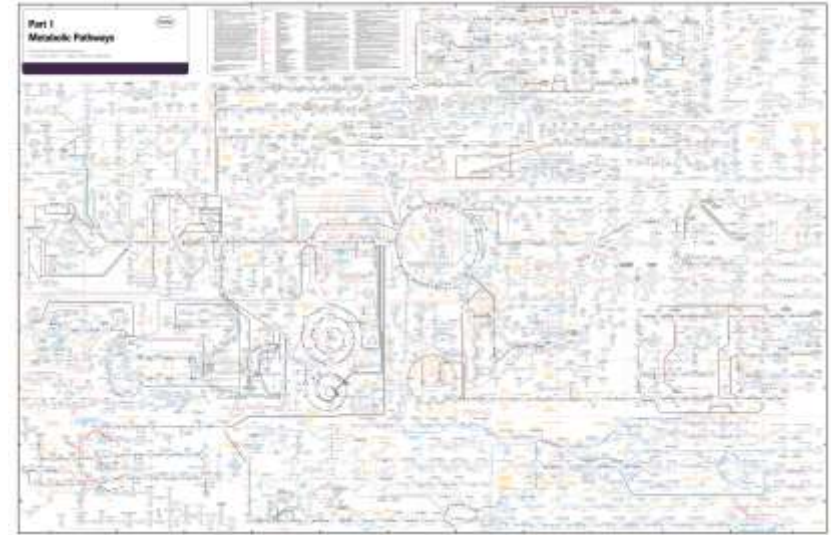
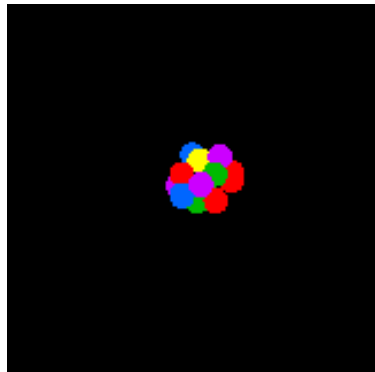
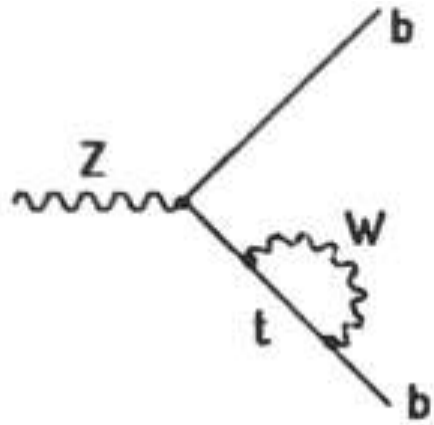
Can computational modeling help understand and control ecosystem metabolism?

1. A personal view of microbial metabolism
2. Some approaches and recent results
3. Dichotomies and outlook

Can computational modeling help understand and control ecosystem metabolism?

1. A personal view of microbial metabolism
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A personal timeline

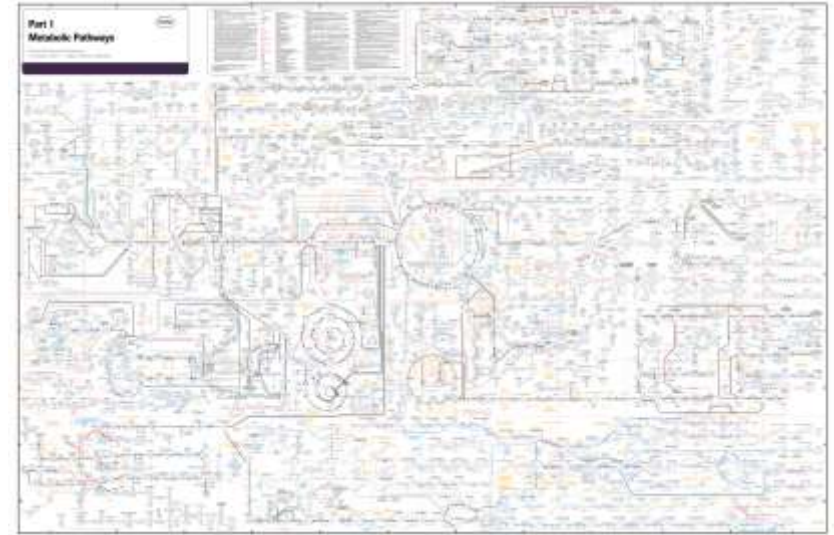
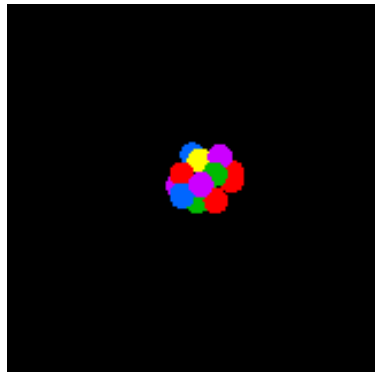
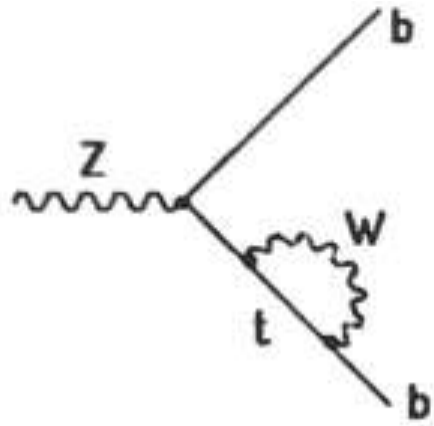


Italy, 1995

Israel, 1996-2001

Boston, 2002-present

A less-personal timeline

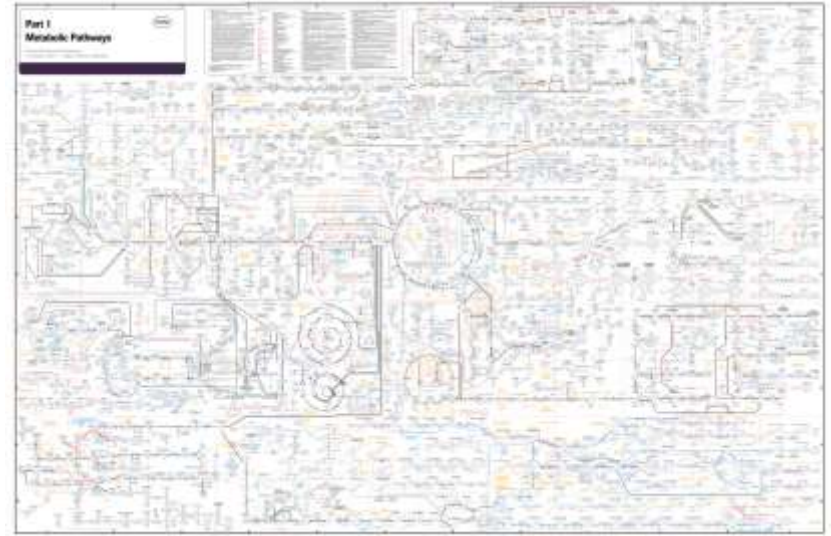
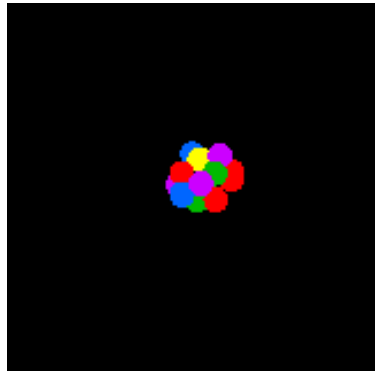
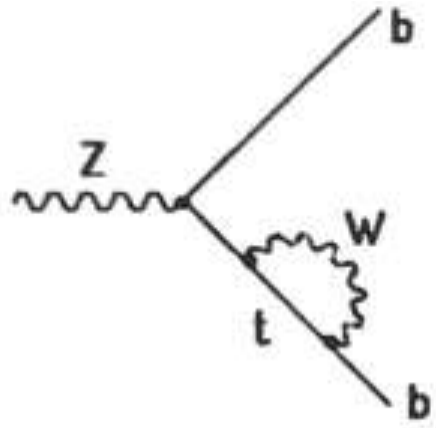


14 bya

3.8 bya

now

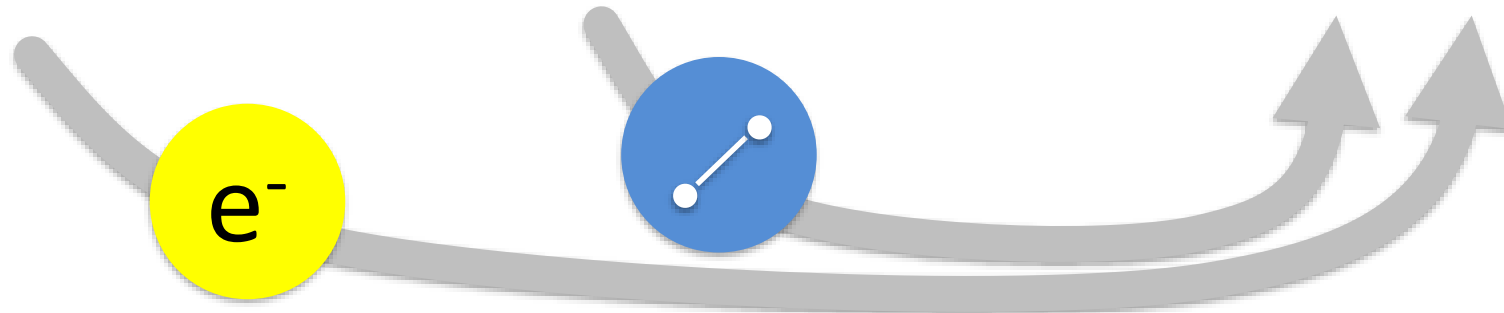
Everything is connected



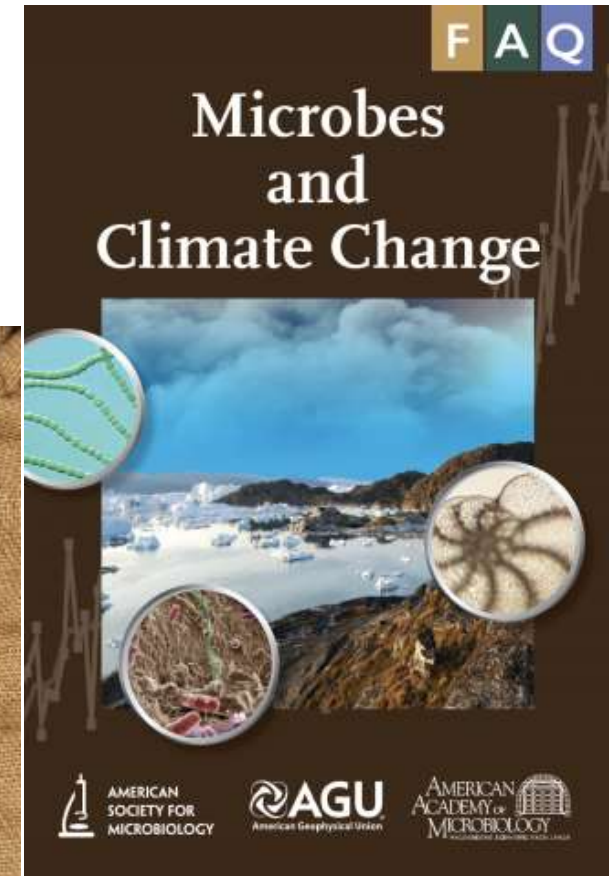
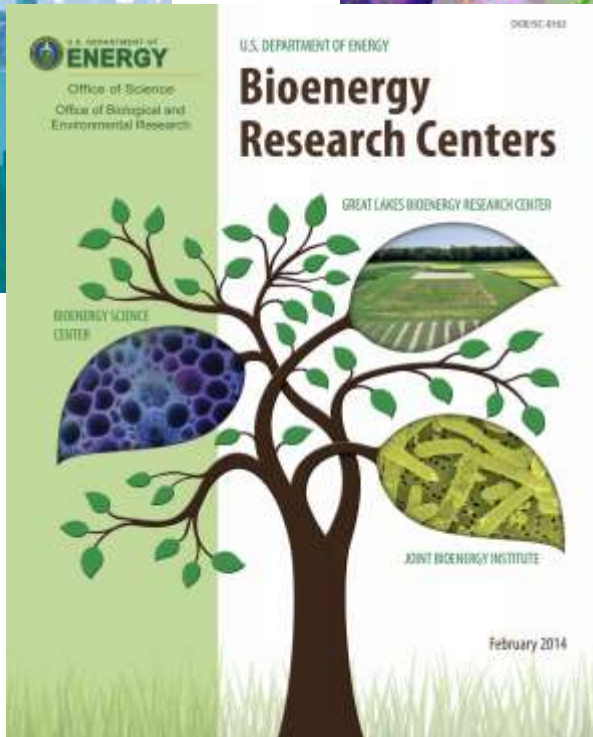
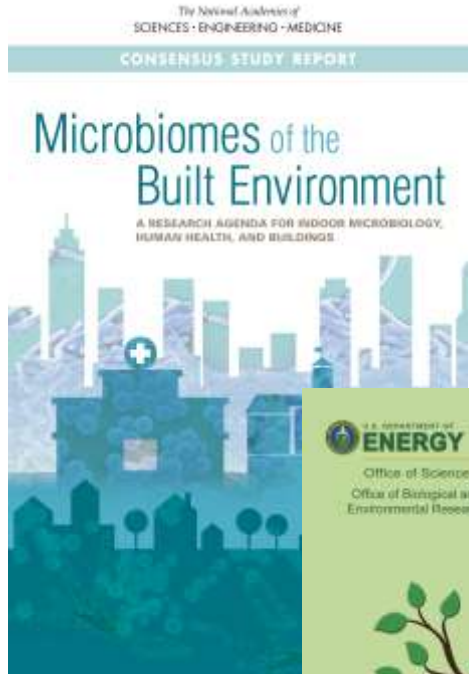
14 bya

3.8 bya

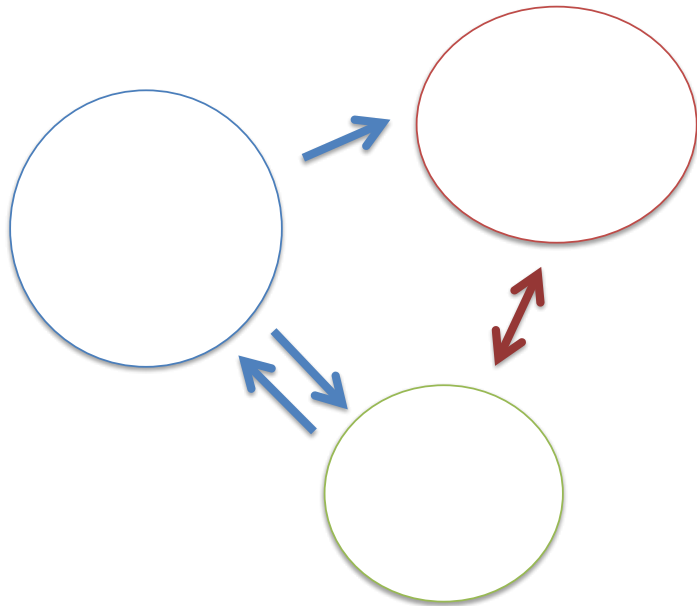
now



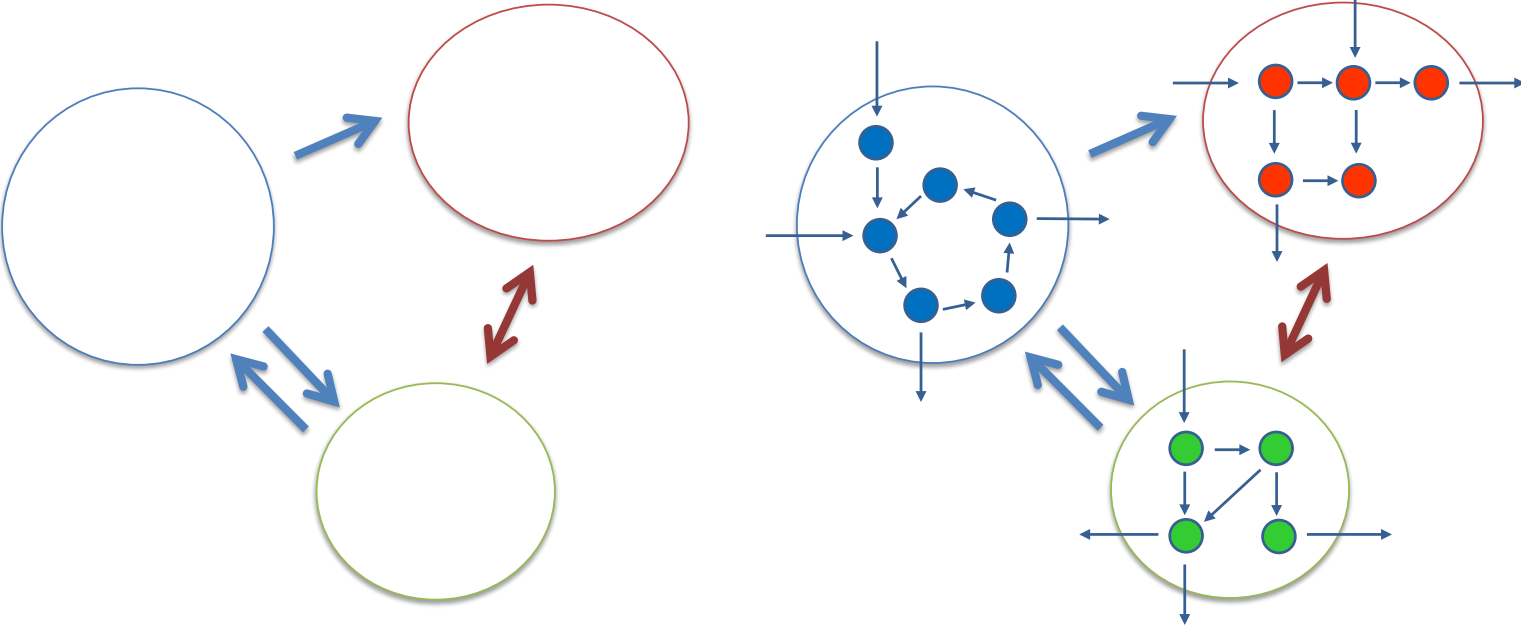
Microbial metabolism can help address global challenges



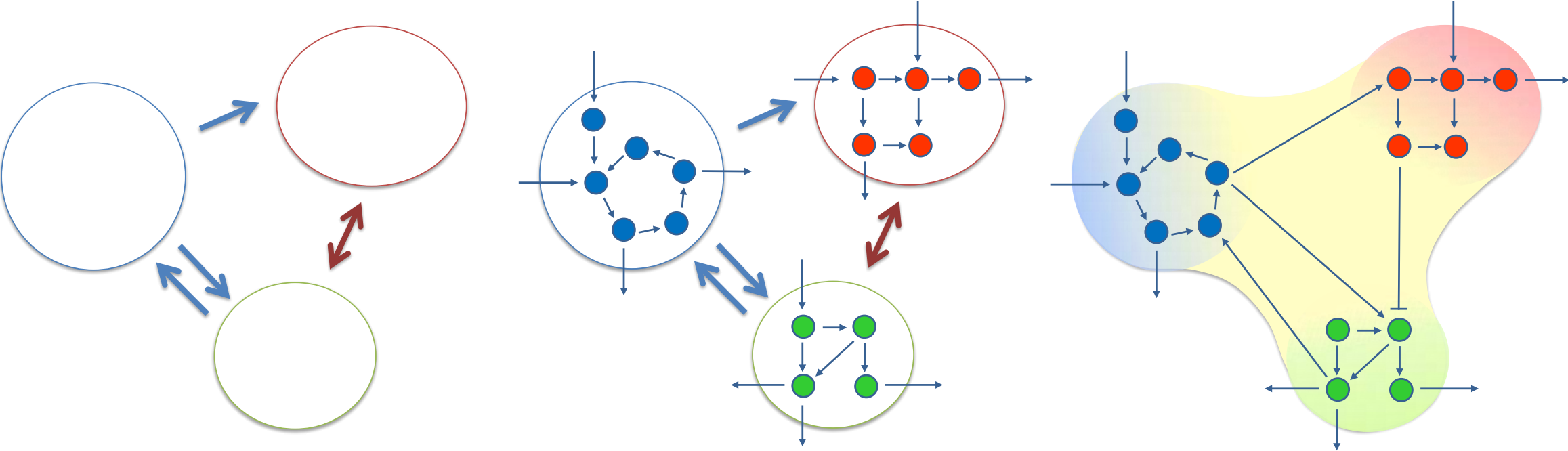
How to approach the quantitative study of microbial communities?



How to approach the quantitative study of microbial communities?



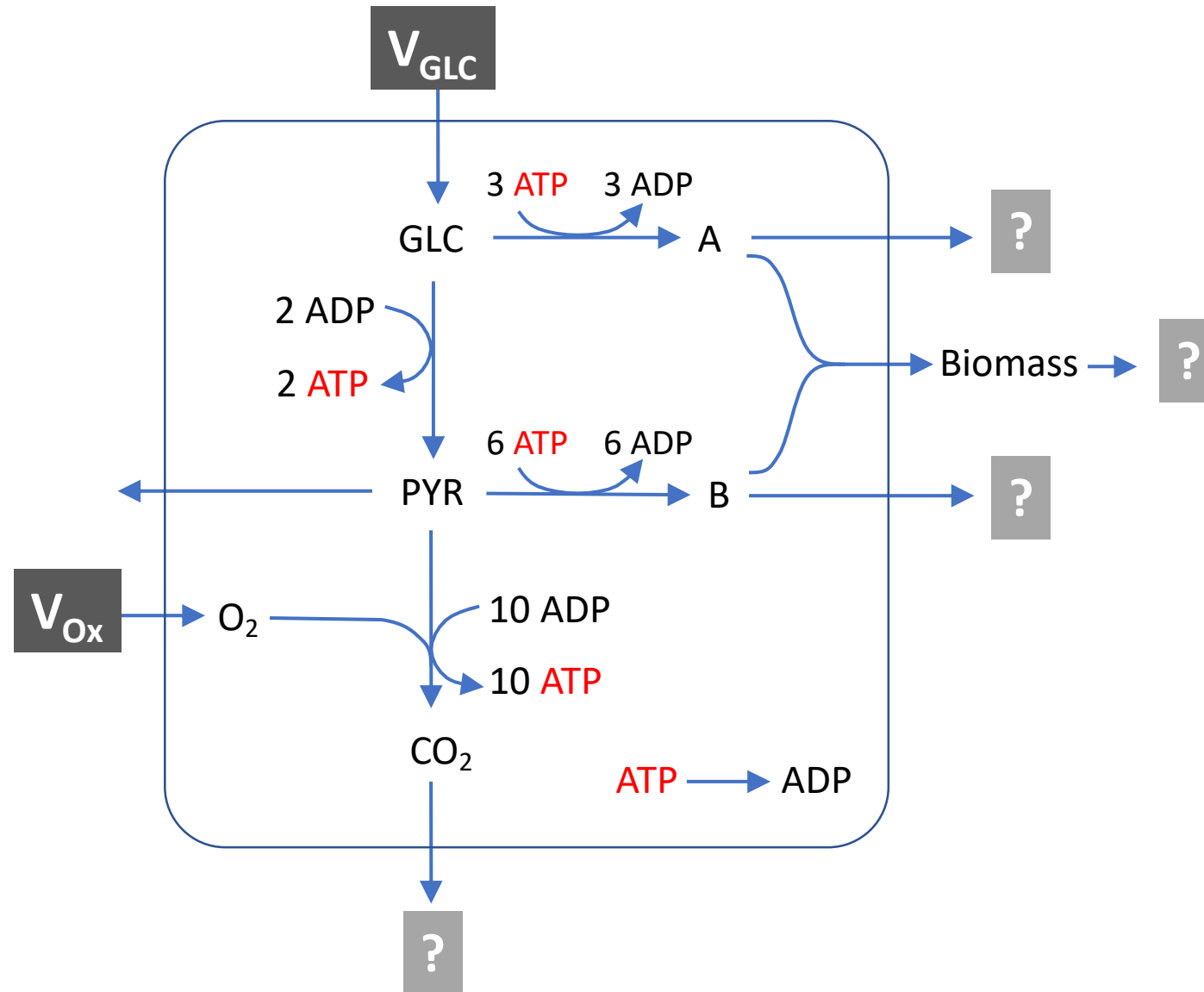
How to approach the quantitative study of microbial communities?



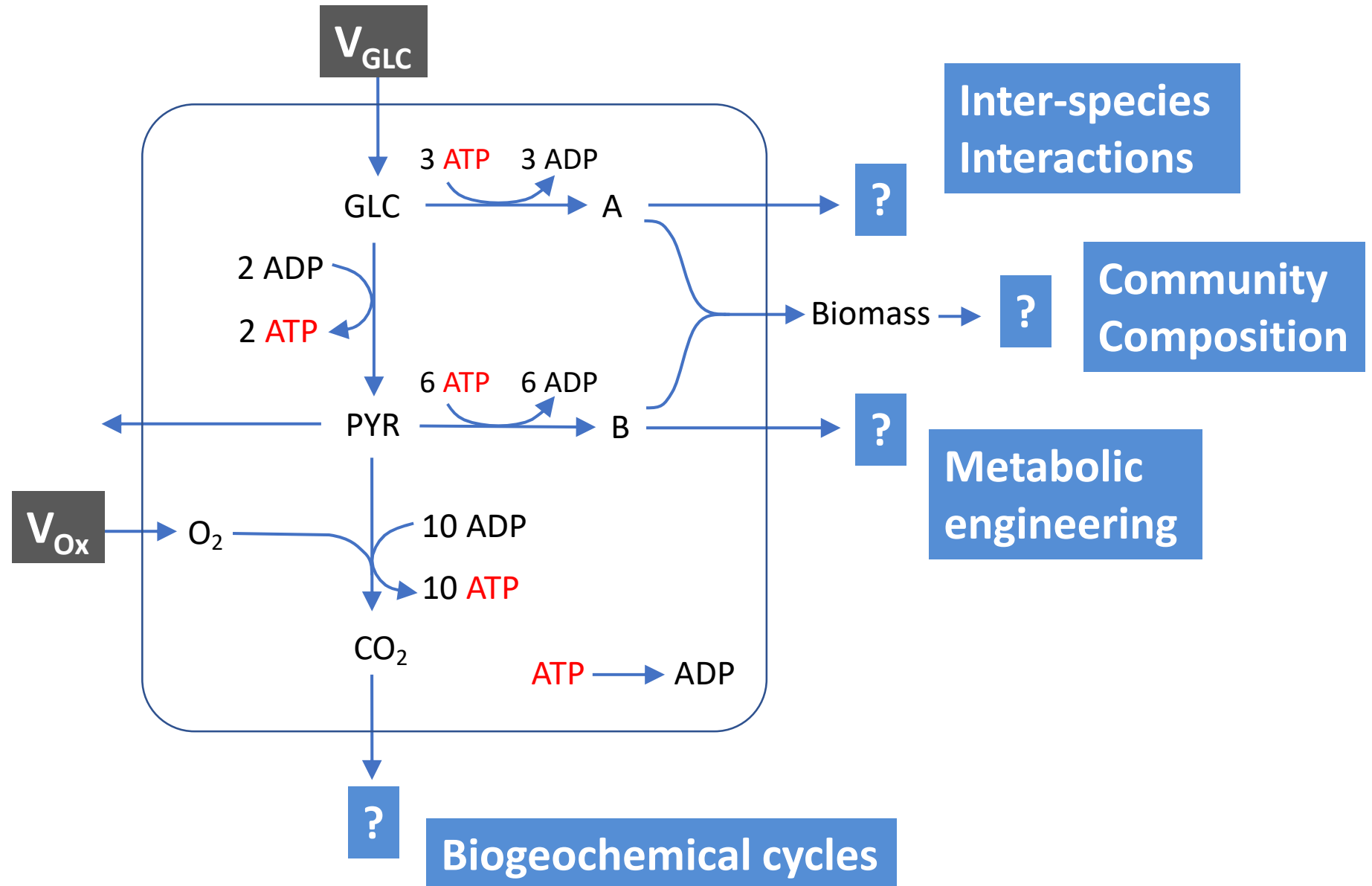
Can computational modeling help understand and control ecosystem metabolism?

1. A personal view of microbial metabolism
2. Some approaches and recent results
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Every cell solves a resource allocation problem. Can we solve it?

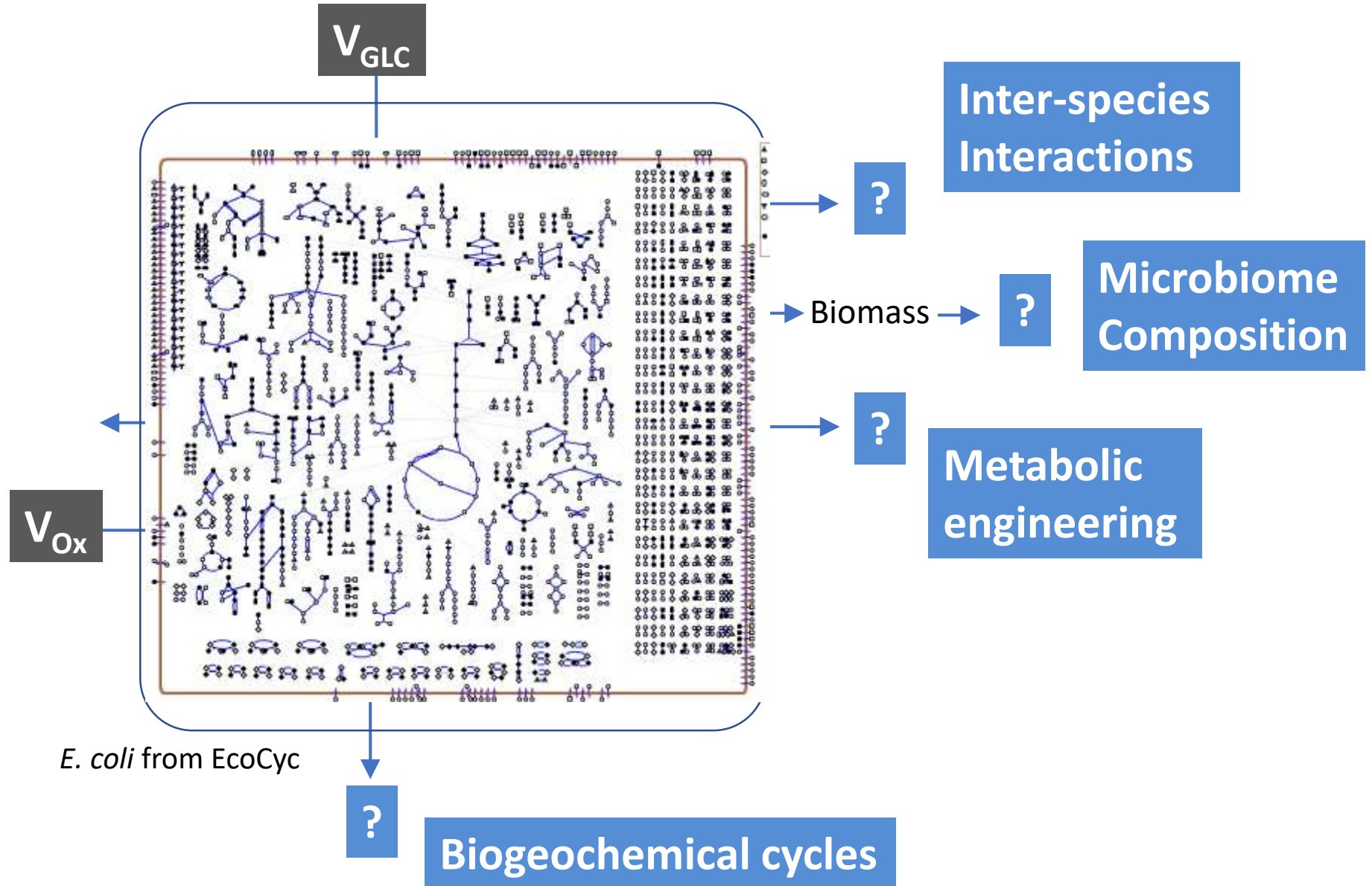


The solutions have implications for important questions



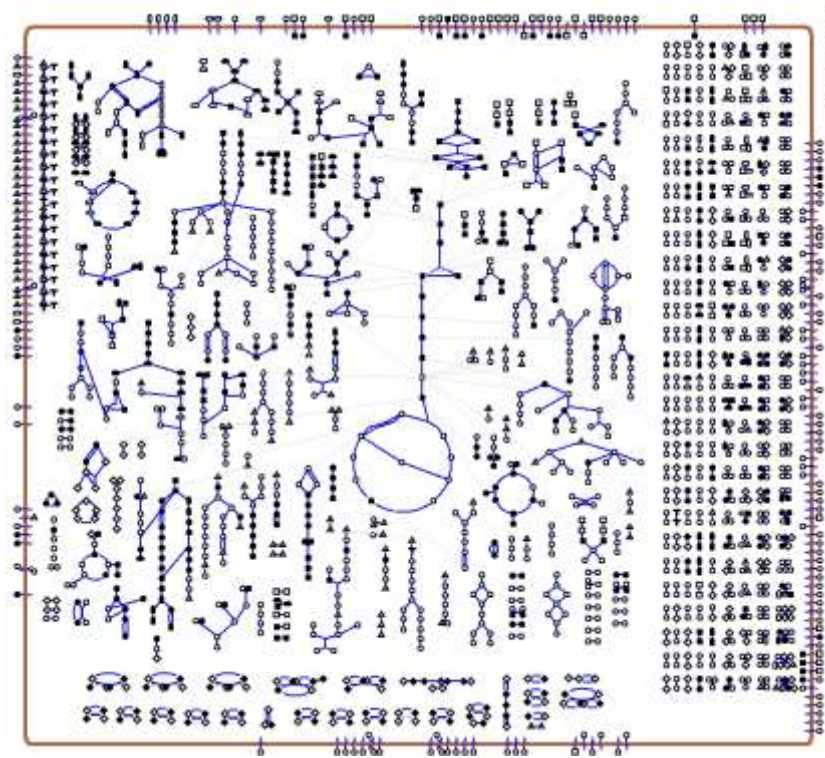
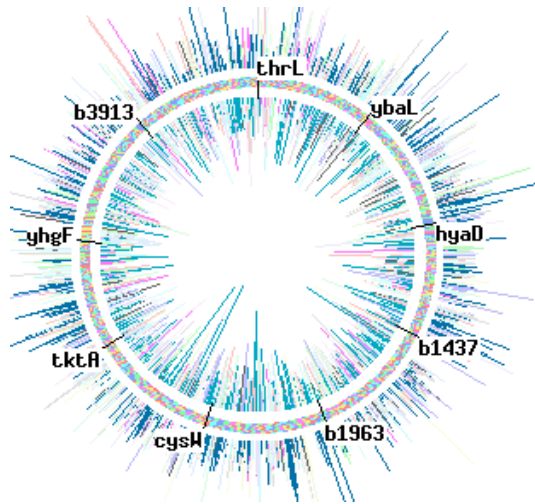
The solutions have implications for important questions

$N \sim 10^3$ reactions



From genomes to stoichiometry: constraint-based modeling

Network Reconstruction



Flux balance analysis



$$V_1, V_2, \dots, V_N$$

Reaction rates
Uptake/secretion
Growth

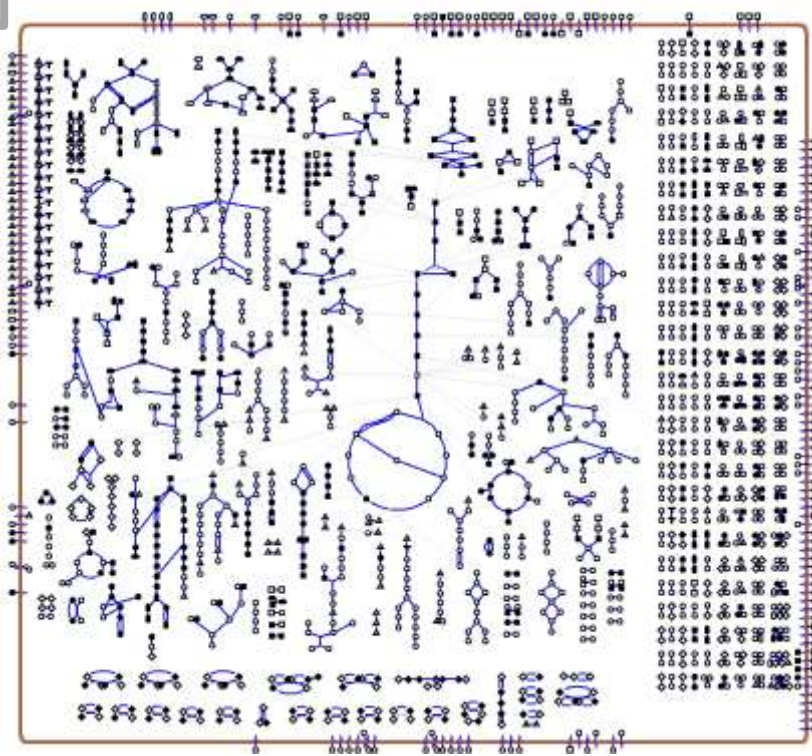
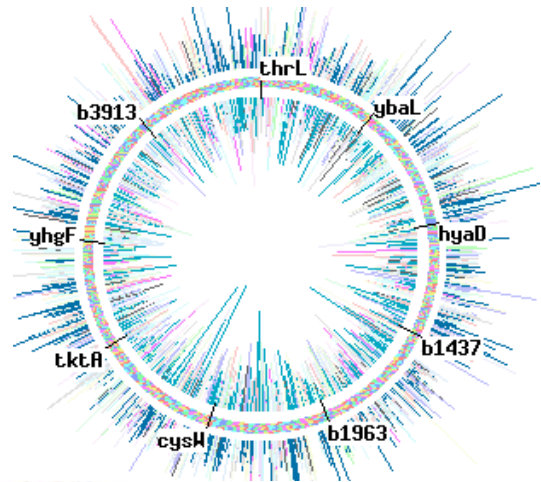
Genome
+
Environmental
Conditions

From genomes to stoichiometry: constraint-based modeling in



Model SEED Build Metabolic Model
fba_tools v.2.0.0
by cherry

FBA Run Flux Balance Analysis
fba_tools v.2.0.0
by cherry



$$V_1, V_2, \dots, V_N$$

Reaction rates
Uptake/secretion
Growth

Psimiae_RAST_Annotation
KBaseGenomes.Genome-11.0

+

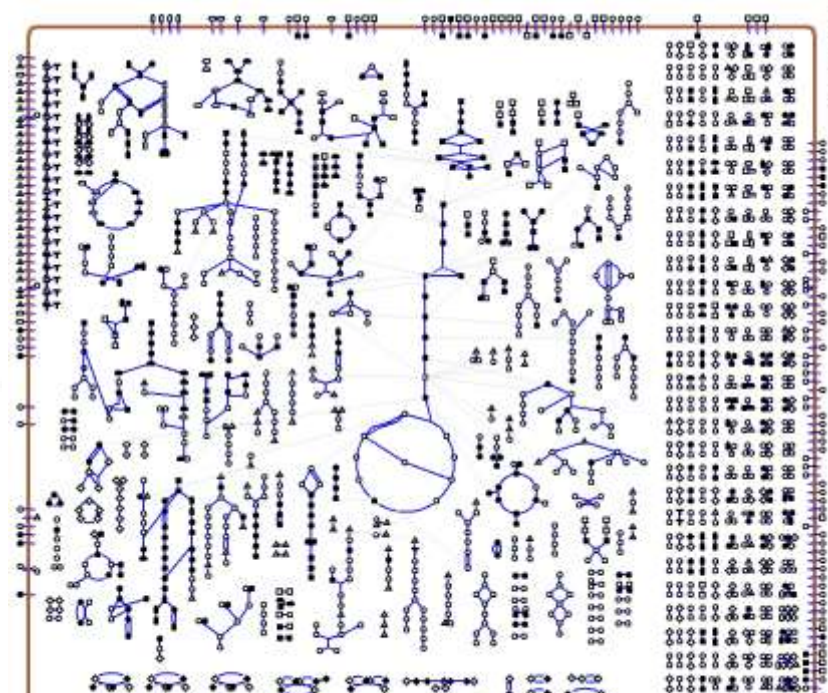
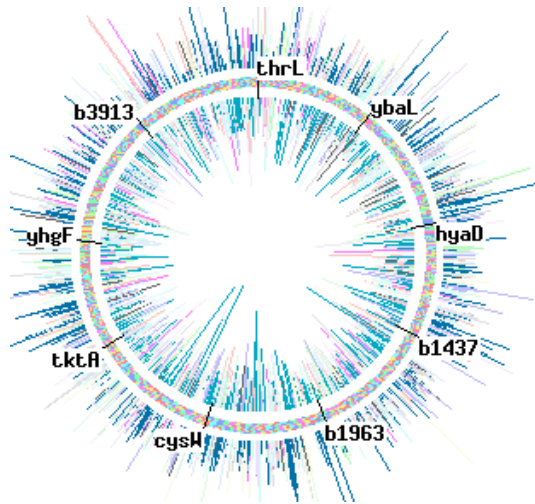
C-D-Glucose
KBaseBiochem.Media-4.0

Model SEED Gapfill Metabolic Model
fba_tools v.2.0.0
by cherry

Henry et al., Nature Biotech, 2010
Arkin et al., Nature Biotech, 2018

From genomes to stoichiometry: constraint-based modeling

Network Reconstruction



Flux balance analysis



$$V_1, V_2, \dots, V_N$$

Reaction rates
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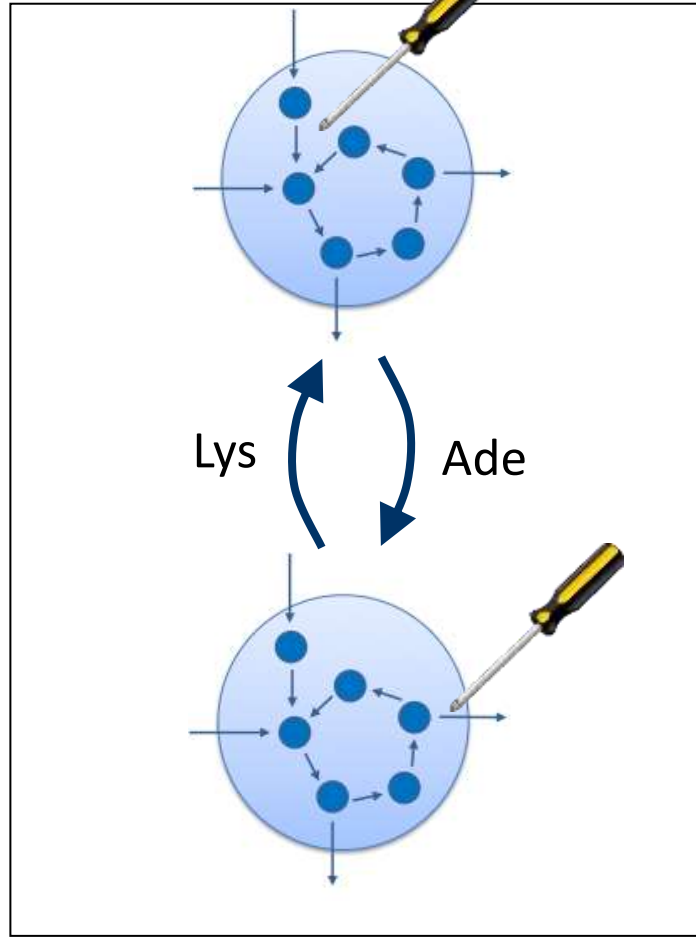
Genome
+
Environmental
Conditions

How to scale this process to
microbiomes?

1. Building many models
2. Modeling communities

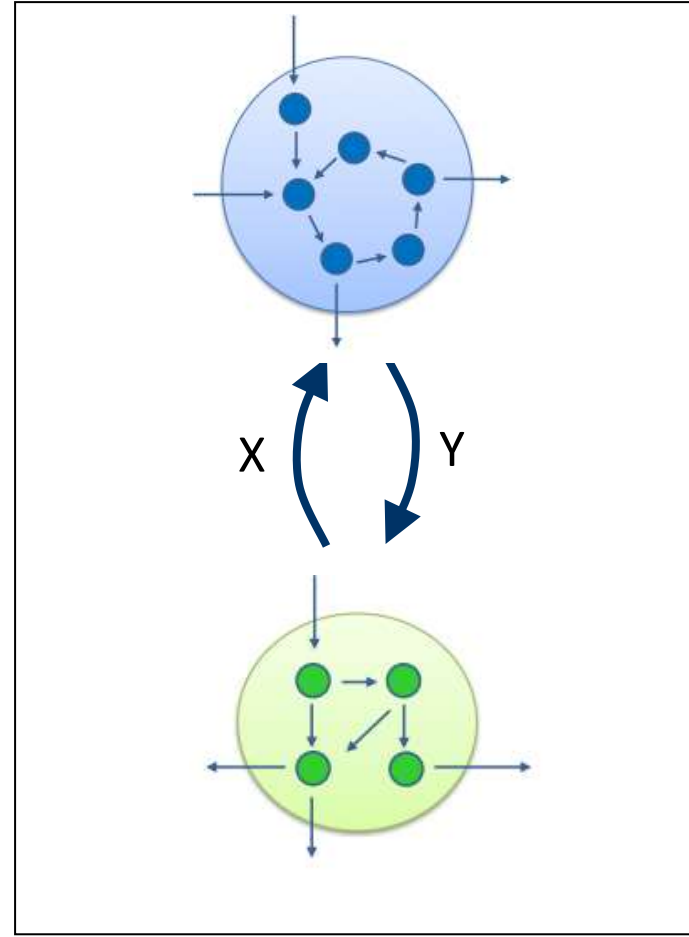
Can computational models help design synthetic microbial communities?

C,N,S,P



e.g.: Mutualistic yeasts
(Shou, Ram and Vilar, PNAS 2007)

? ? ? ? 

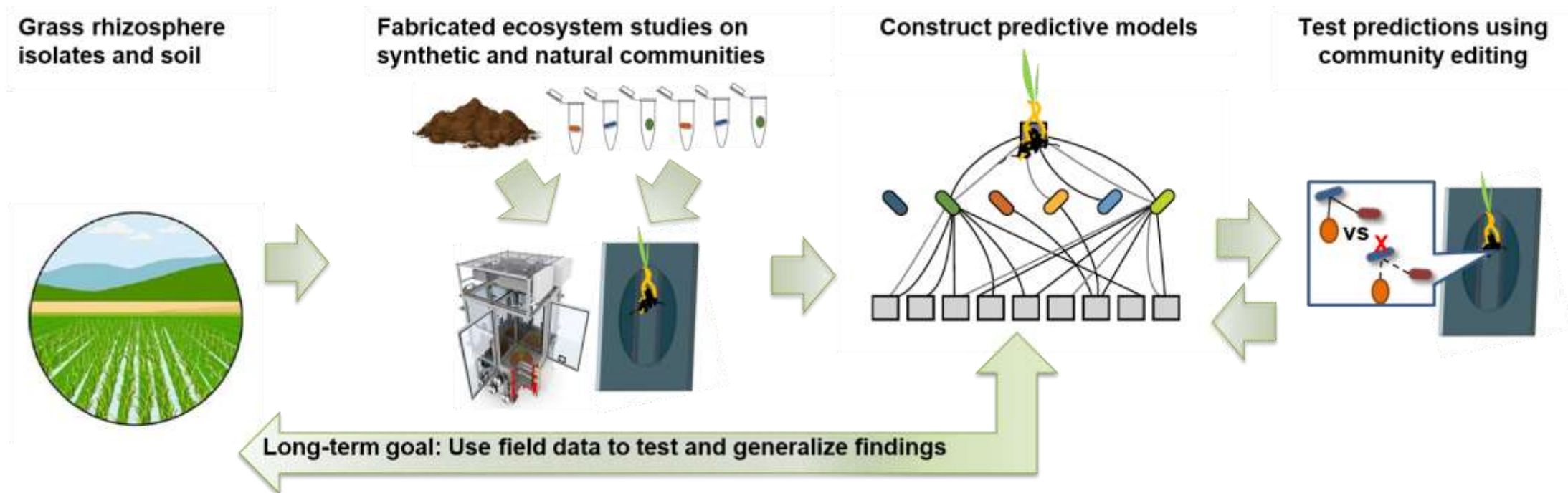


Klitgord and Segrè,
PLoS Computational Biology 2010

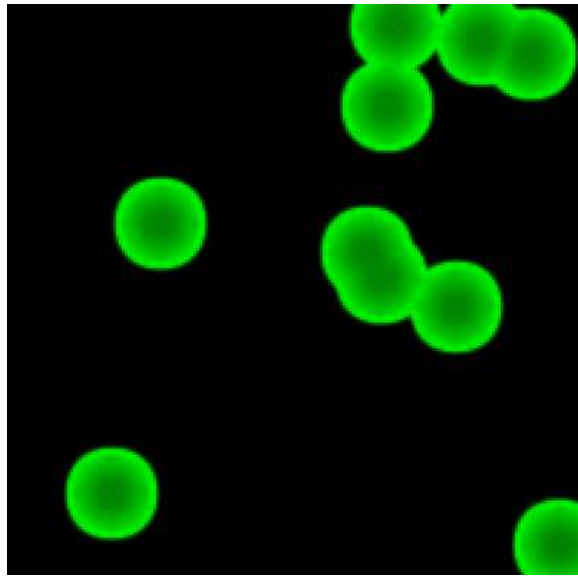
Niels Klitgord

Vision: *To develop foundational tools and understanding required to predict, alter, and design grass rhizosphere communities.* Motivation: (i) Harness plants and microbes for sustainable bioenergy; (ii) Develop predictive models of soil processes and beneficial plant microbe interactions.

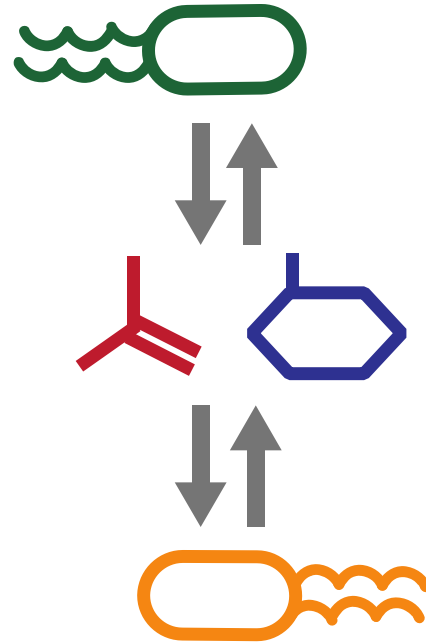
Approach:



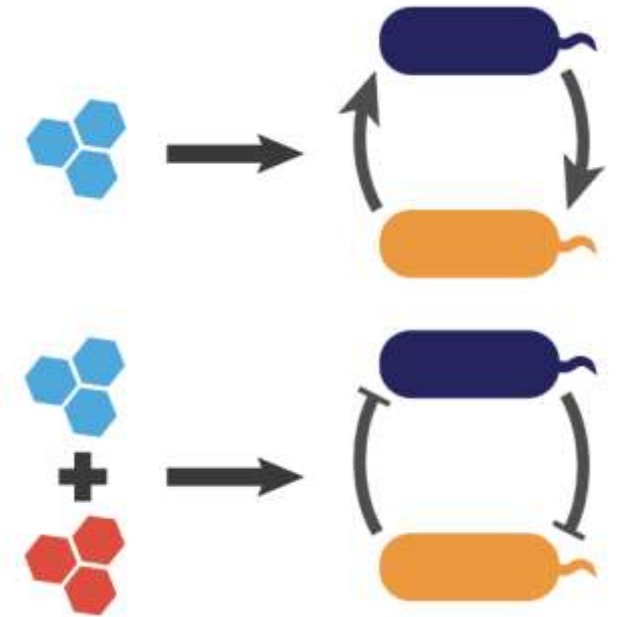
How do environmental properties affect community structure and function?



Space/Time

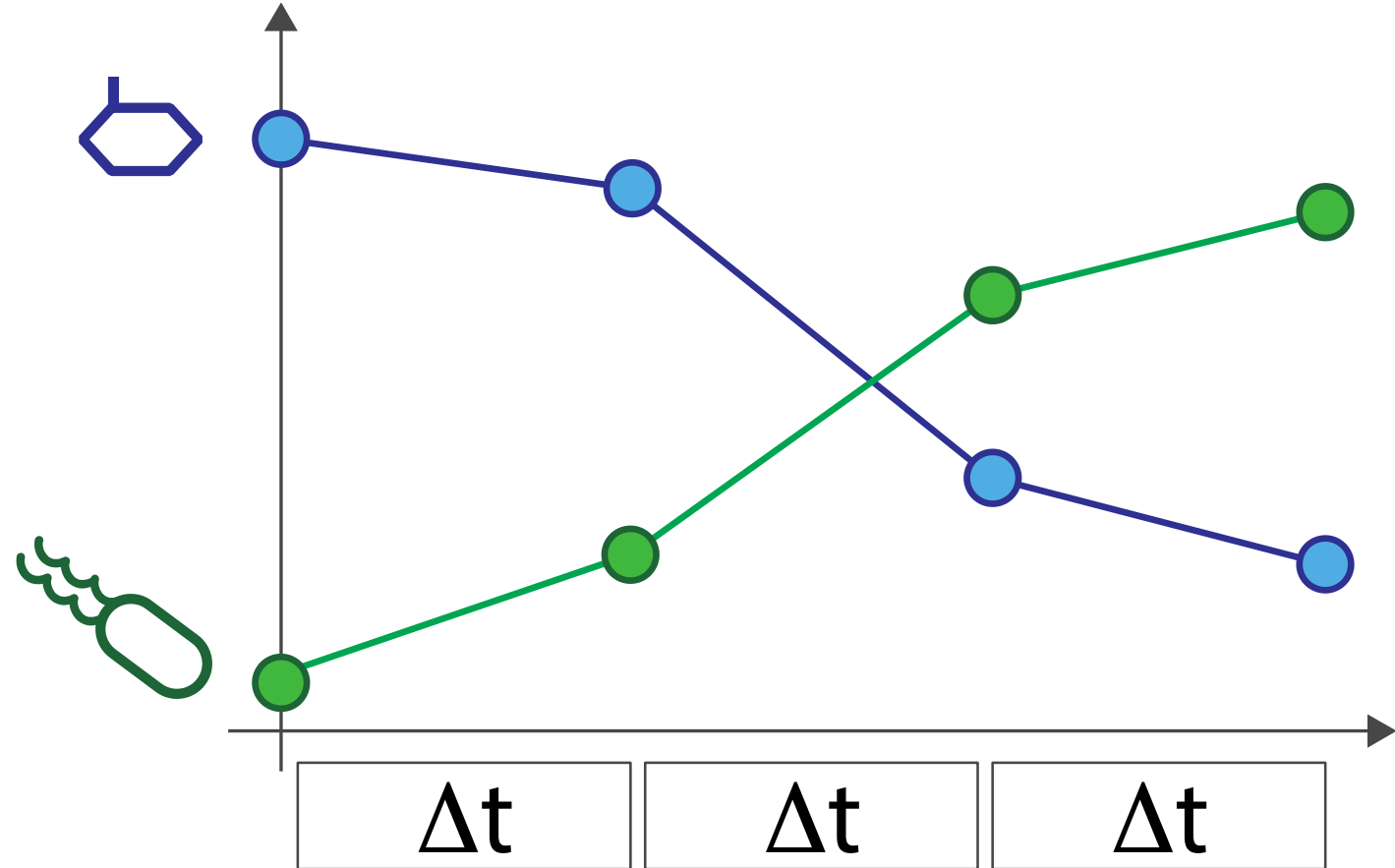
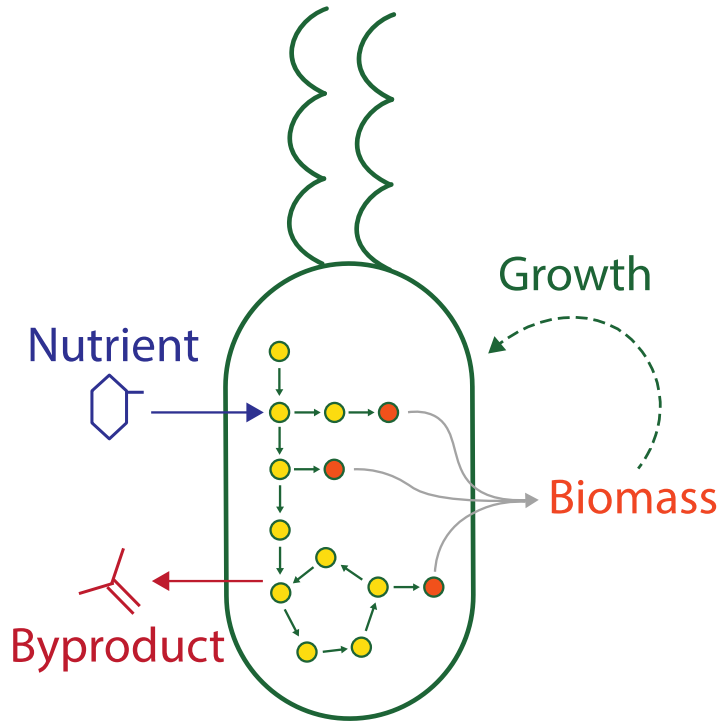


Exchange

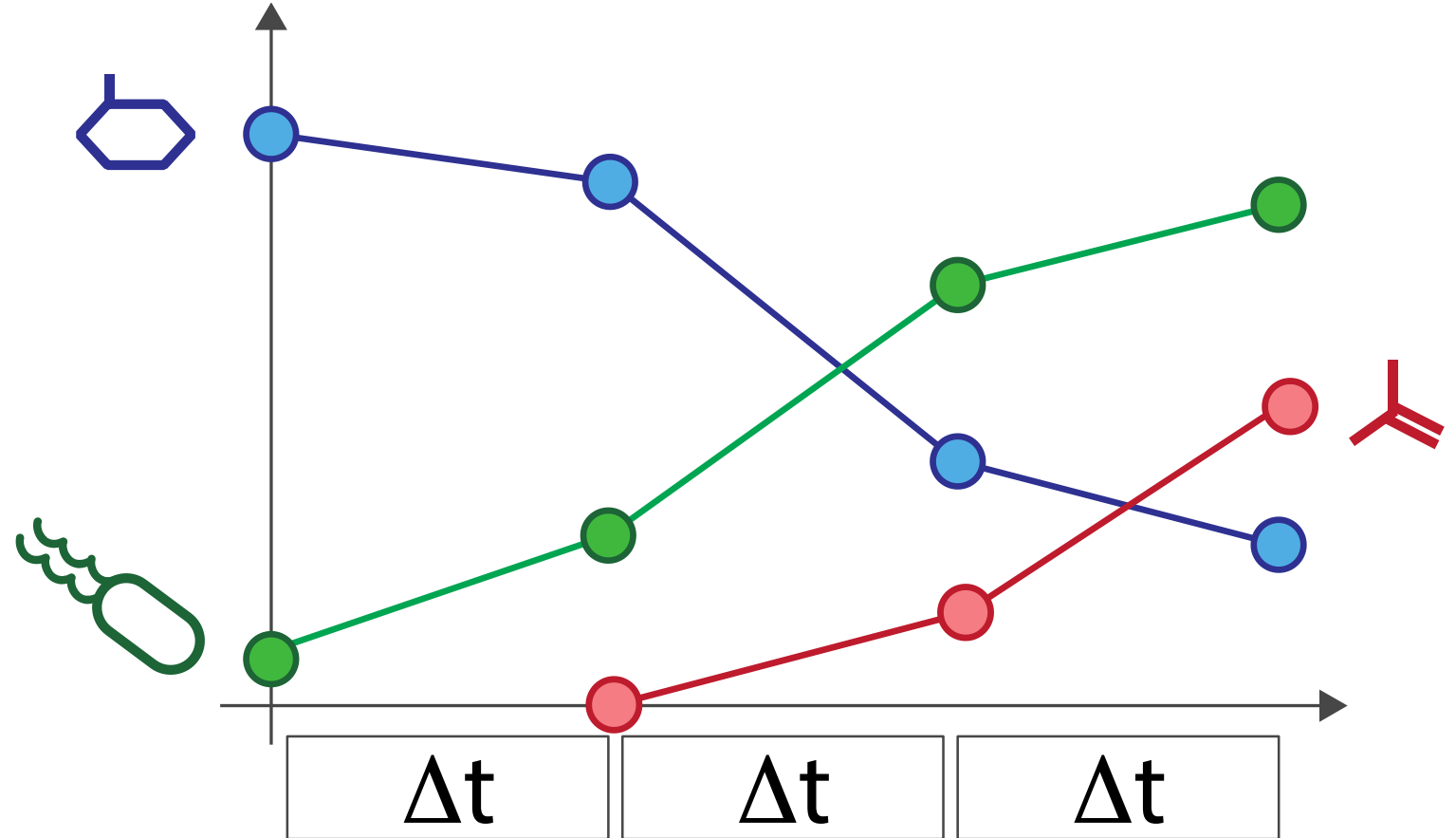
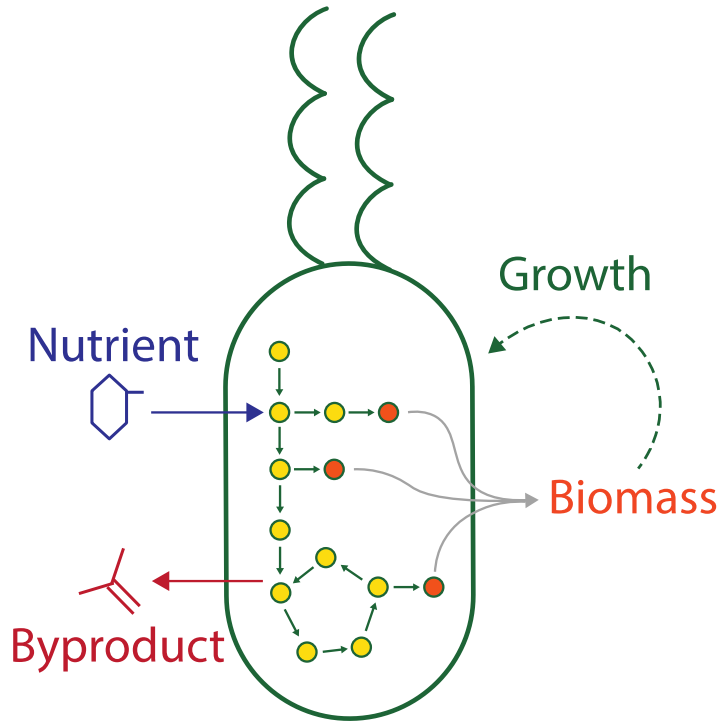


Environmental Complexity

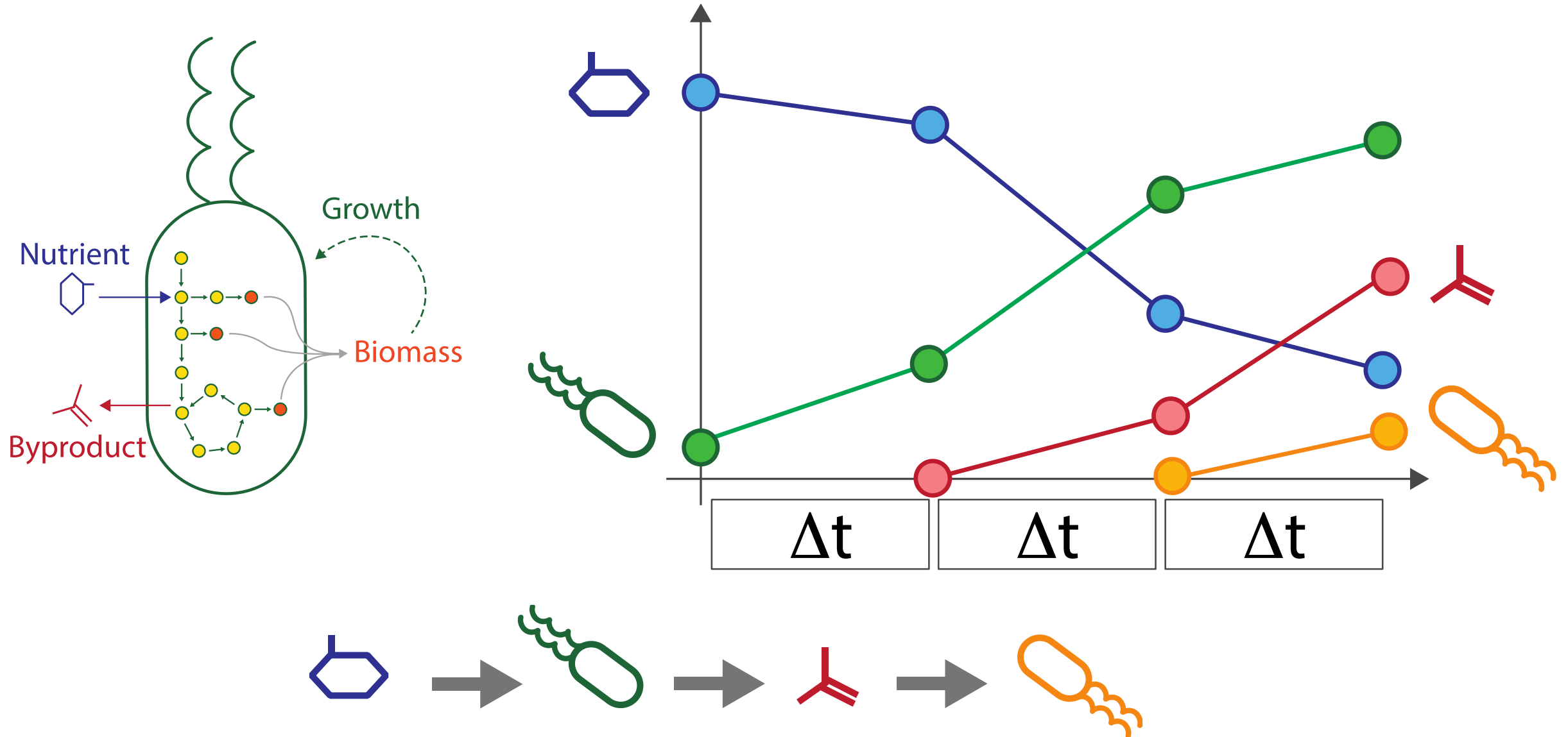
Dynamic Flux Balance Analysis (dFBA) provides a natural way for modeling microbe-microbe and microbe-environment interactions



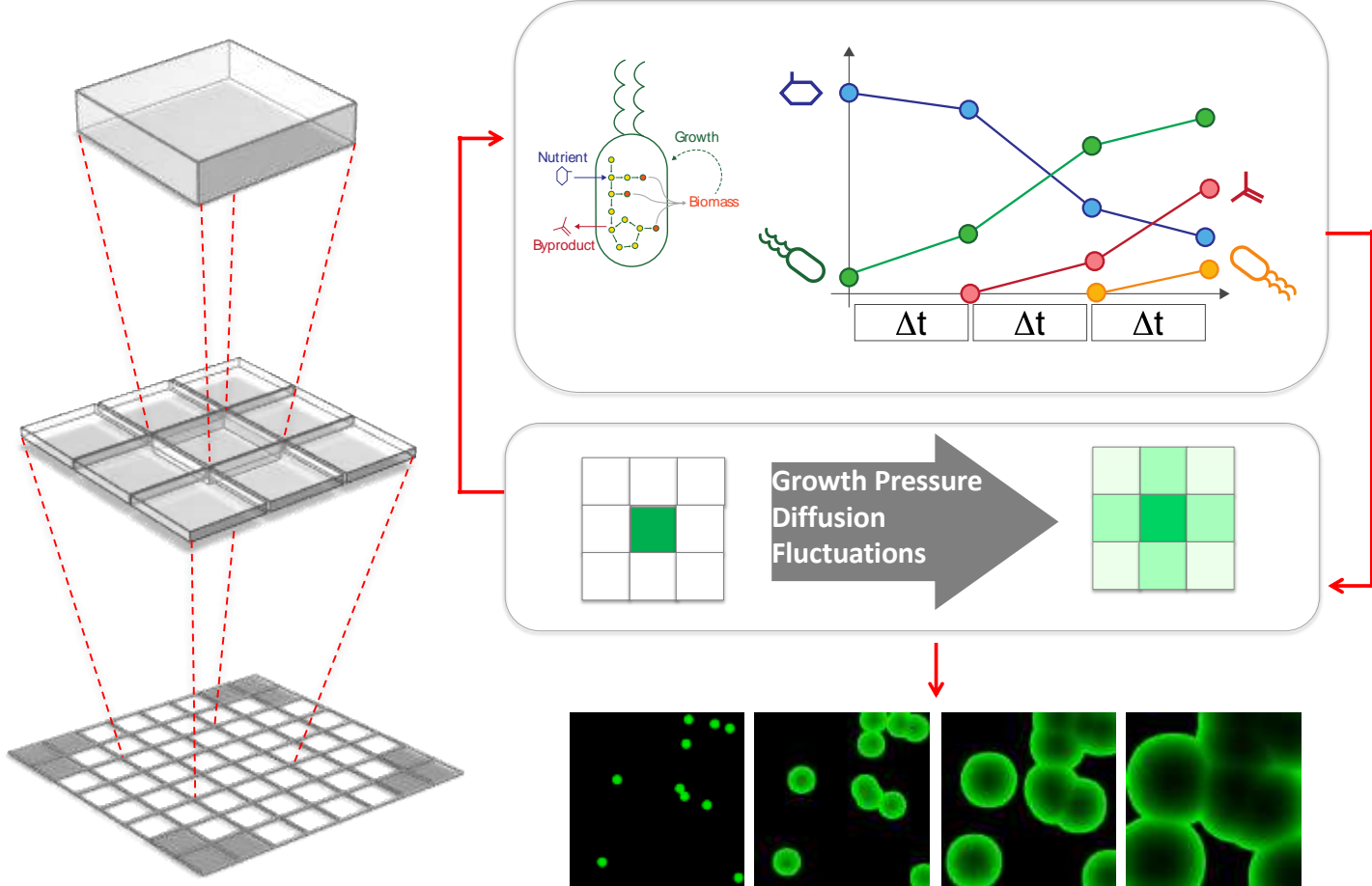
Dynamic Flux Balance Analysis (dFBA) provides a natural way for modeling microbe-microbe and microbe-environment interactions



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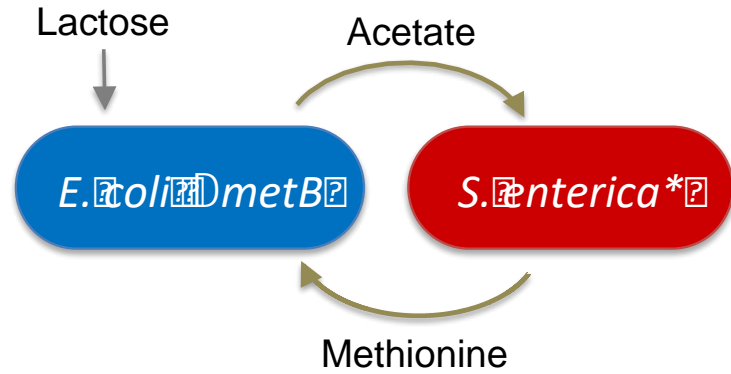
Computation Of Microbial Ecosystems in Time and Space (COMETS)



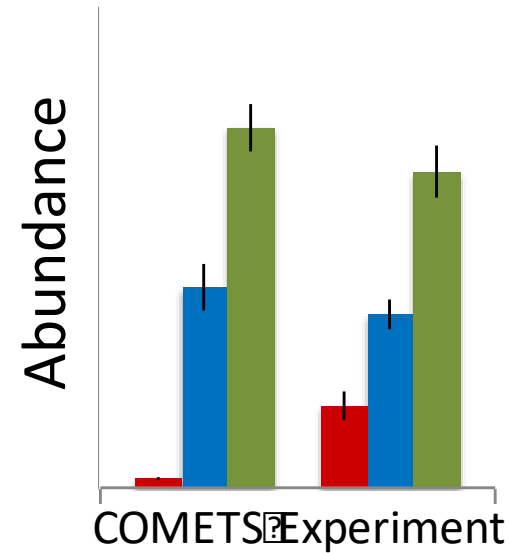
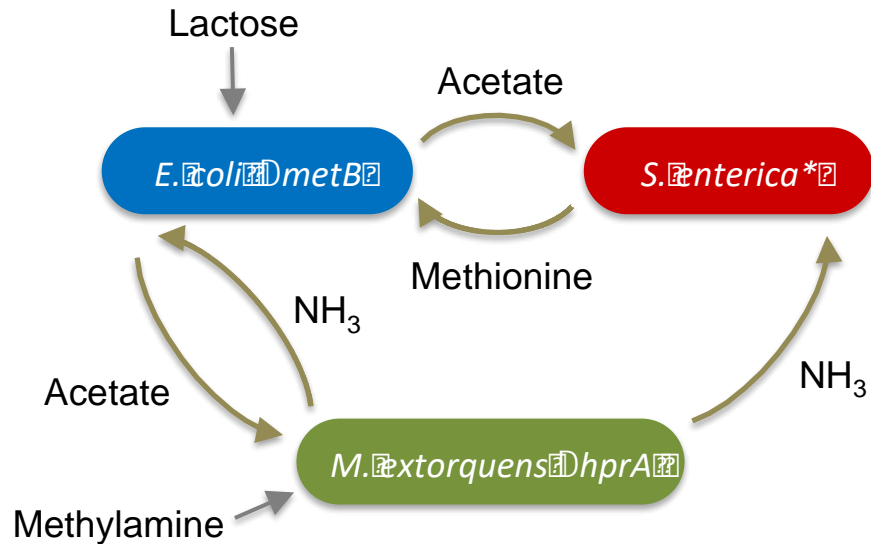
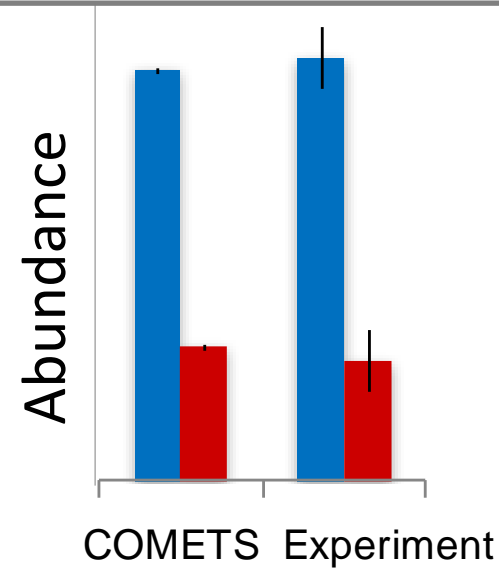
$$\frac{\partial B^\alpha}{\partial t} = \vec{\nabla} \cdot (D^\alpha \vec{\nabla} B^\alpha) - \vec{\nabla} \cdot (B^\alpha \vec{u}^\alpha) + f^\alpha(B^\alpha, Q^m)$$

$$\frac{\partial Q^m}{\partial t} = \vec{\nabla} \cdot (D^m \vec{\nabla} Q^m) - \vec{\nabla} \cdot (Q^m \vec{u}^m) + \sum_{\alpha} B^\alpha \nu^{\alpha, m}$$

Testing COMETS predictions on 2- and 3-species synthetic consortia



Harcombe, Evolution 2010

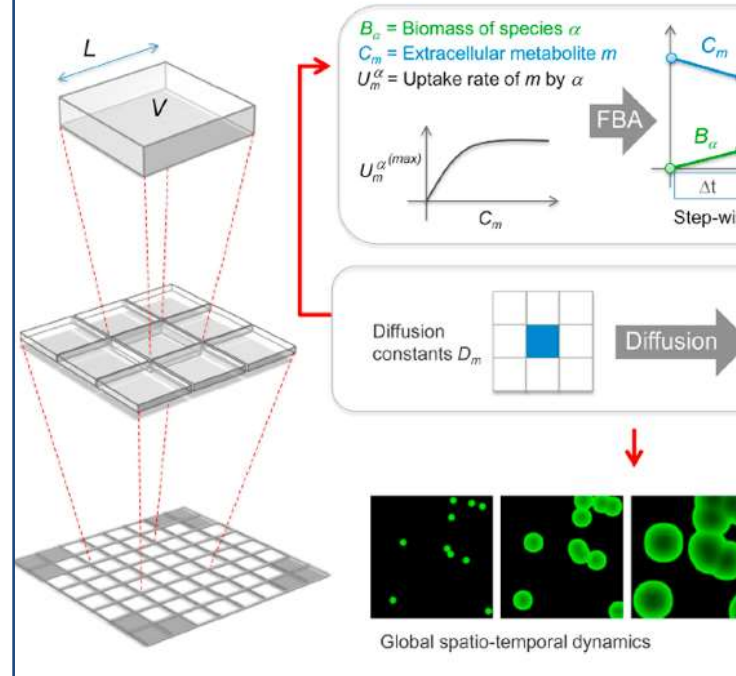


Harcombe, Riehl, et al., Cell Reports 2014

The power of collaborative software

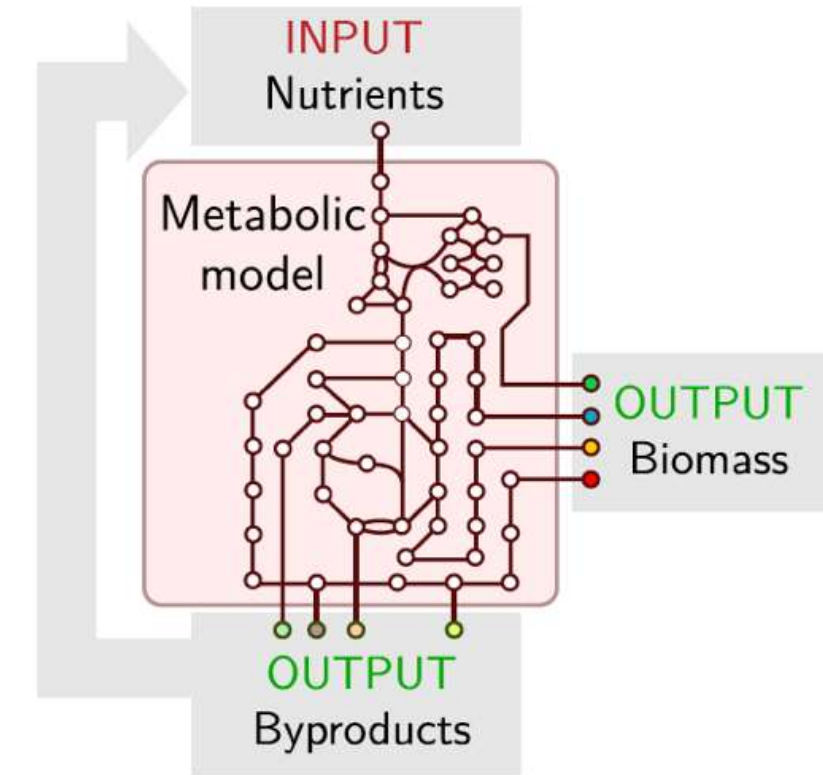
Metabolic Resource Allocation in Individual Microbes Determines Ecosystem Interactions and Spatial Dynamics

William R. Harcombe,^{1,7,8} William J. Riehl,^{2,7,9} Ilija Dukovski,² Brian R. Granger,² Alex Betts,^{1,10} Alex H. Lang,³ Gracia Bonilla,² Amrita Kar,² Nicholas Leiby,^{1,4} Pankaj Mehta,^{2,3} Christopher J. Marx,^{1,5,11,*} and Daniel Segre^{2,6}



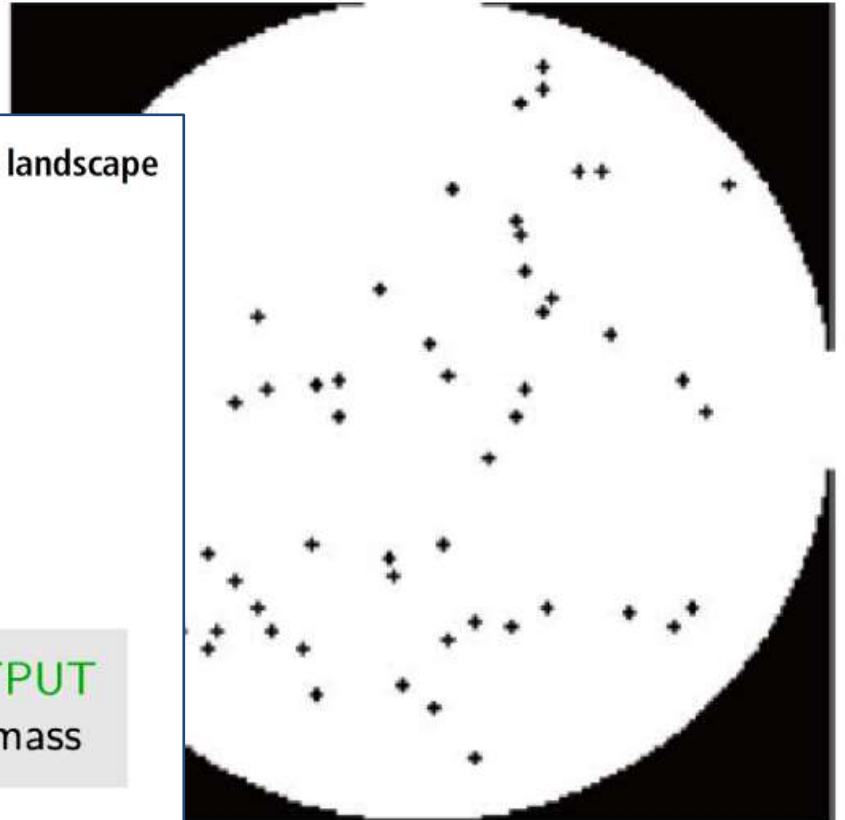
On the deformability of an empirical fitness landscape by microbial evolution

Djordje Bajić^{a,h,1,2}, Jean C. C. Vila^{a,h,1}, Zachary D. Blount^{c,d,e}, and Alvaro Sánchez^{a,h,2}



The spatial and metabolic basis of colony size variation

Jeremy M. Chacón^{1,2} · Wolfram Möbius^{3,4} · William R. Harcombe^{1,2}



Sanchez Lab, Yale
Harcombe Lab, U. Minnesota



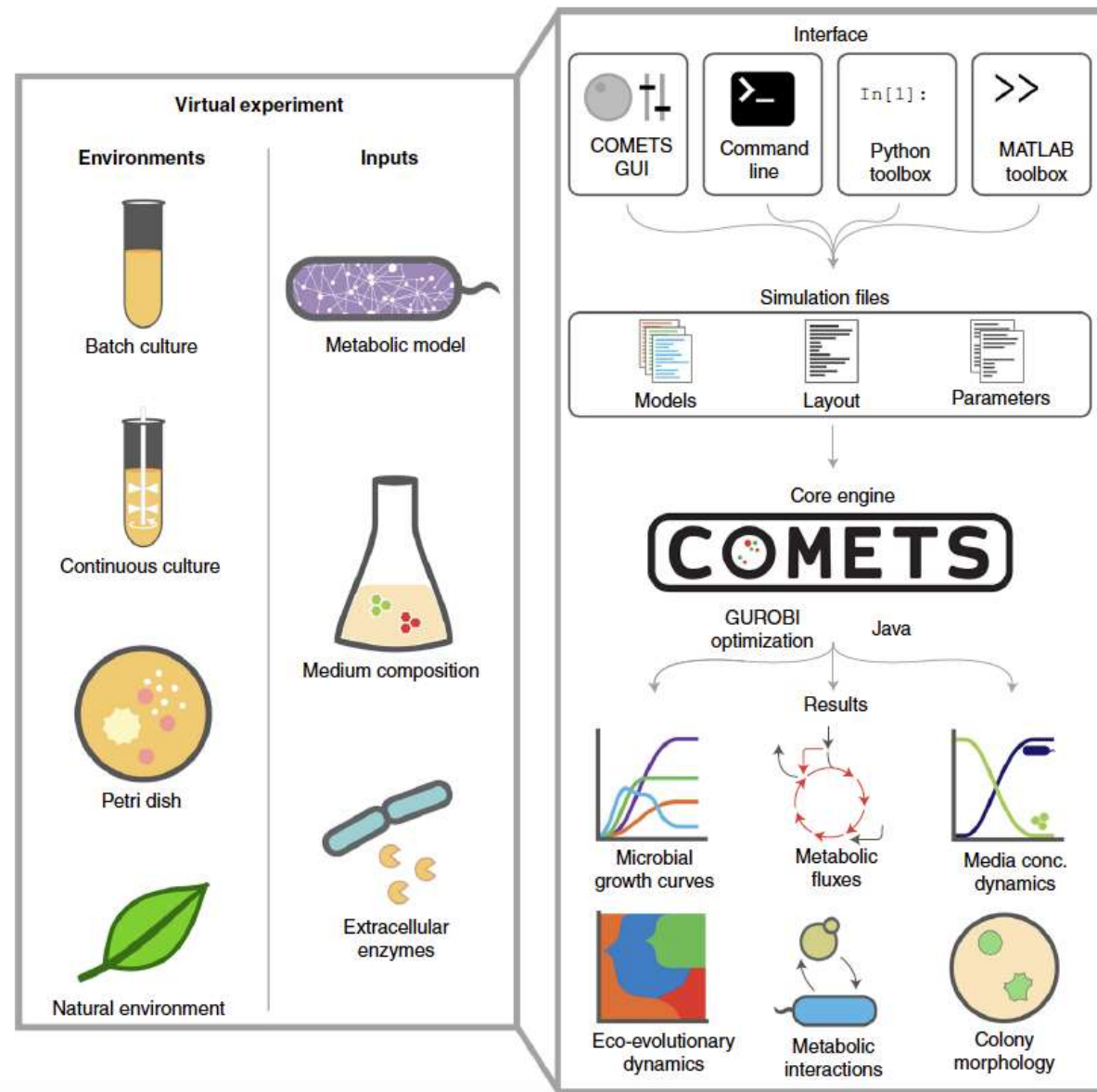
New capabilities and user interfaces in COMETS 2.0

<http://runcomets.org>

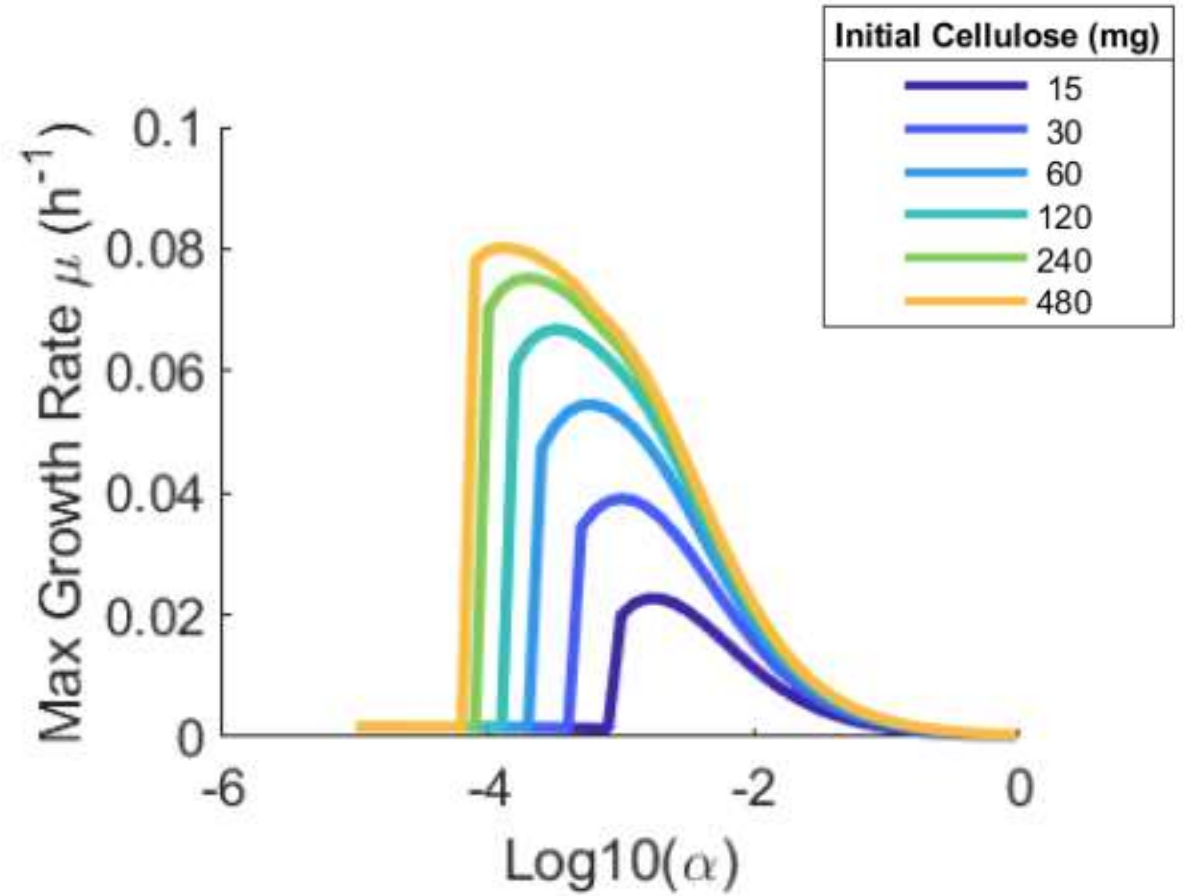
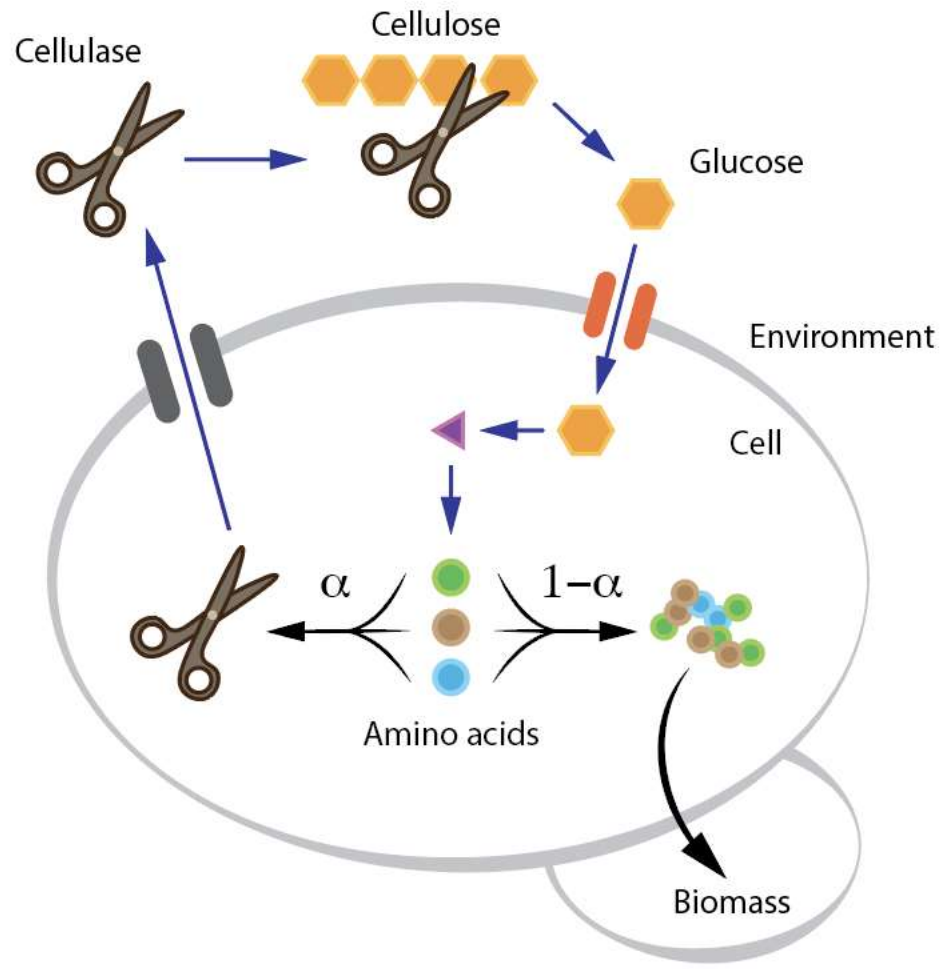


A metabolic modeling platform for the computation of microbial ecosystems in time and space (COMETS)

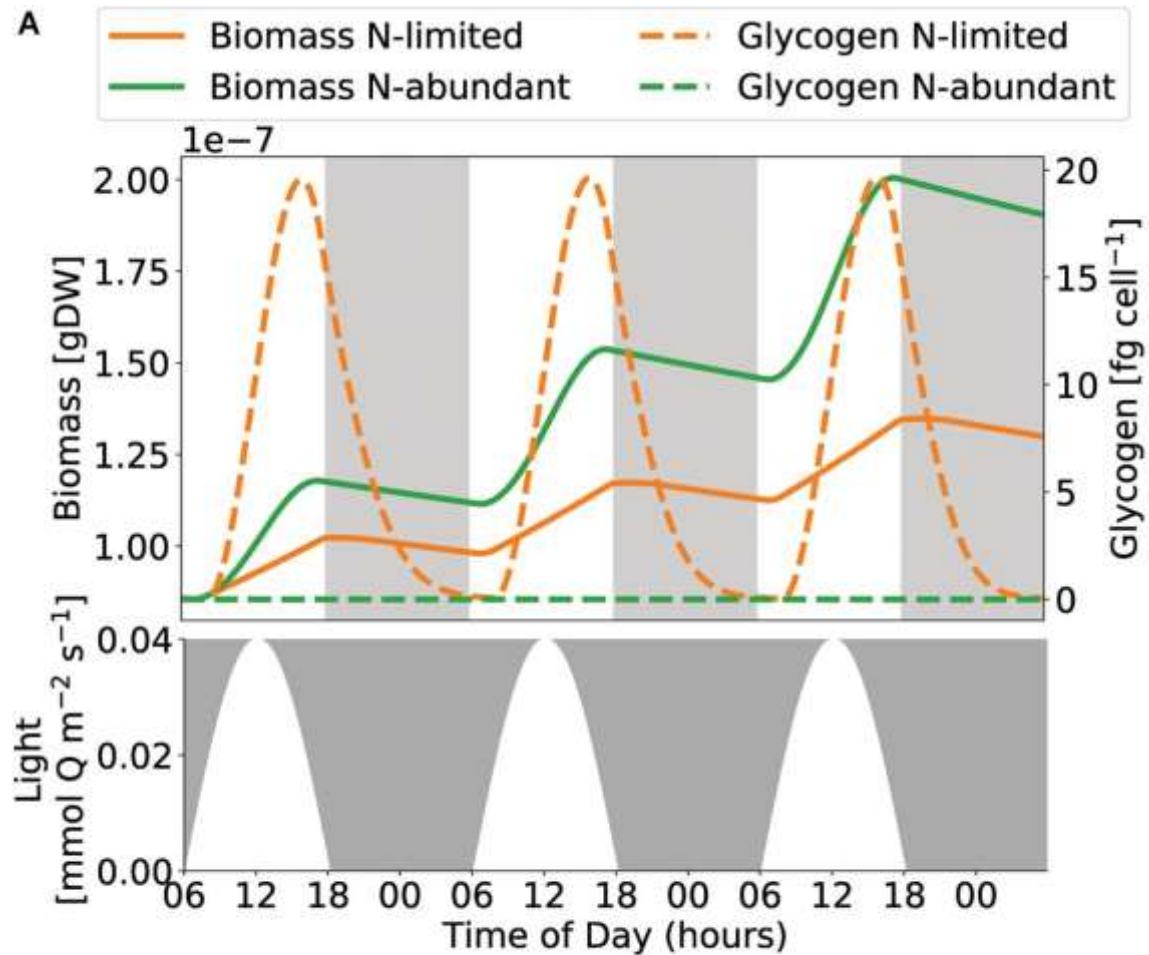
Ilija Dukovski^{1,2,13}, Djordje Bajić^{3,4,13}, Jeremy M. Chacón^{5,6,13}, Michael Quintin^{1,2,13}, Jean C. C. Vila^{3,4}, Snorre Sulheim^{1,7,8}, Alan R. Pacheco^{1,2}, David B. Bernstein^{1,2,9}, William J. Riehl¹⁰, Kirill S. Korolev^{1,2,11}, Alvaro Sanchez^{3,4}, William R. Harcombe^{1,5,6} and Daniel Segrè^{1,2,9,11,12}✉



Extracellular enzyme secretion in COMETS paves the way for more realistic simulations of plant biomass degradation



Photosynthesis and day/night cycles in COMETS simulations of Prochlorococcus



Ofaim, Sulheim, et al., *Frontiers in Genetics*, 2021 (collab with Daniel Sher, Eivind Almaas)

HFSP, NSF

+ Just started NSF center:



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**CHEMICAL CURRENCIES
OF A MICROBIAL PLANET**

B

Legend for B:

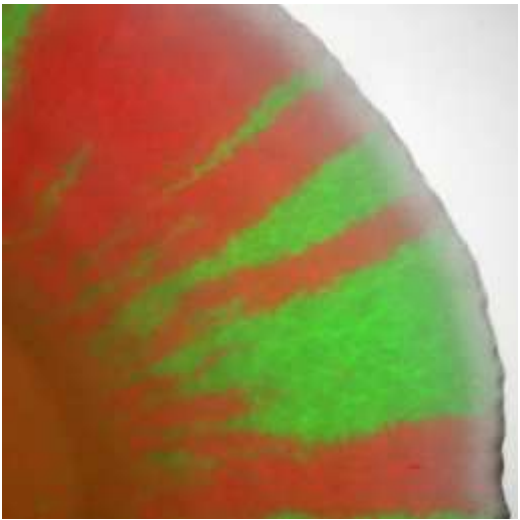
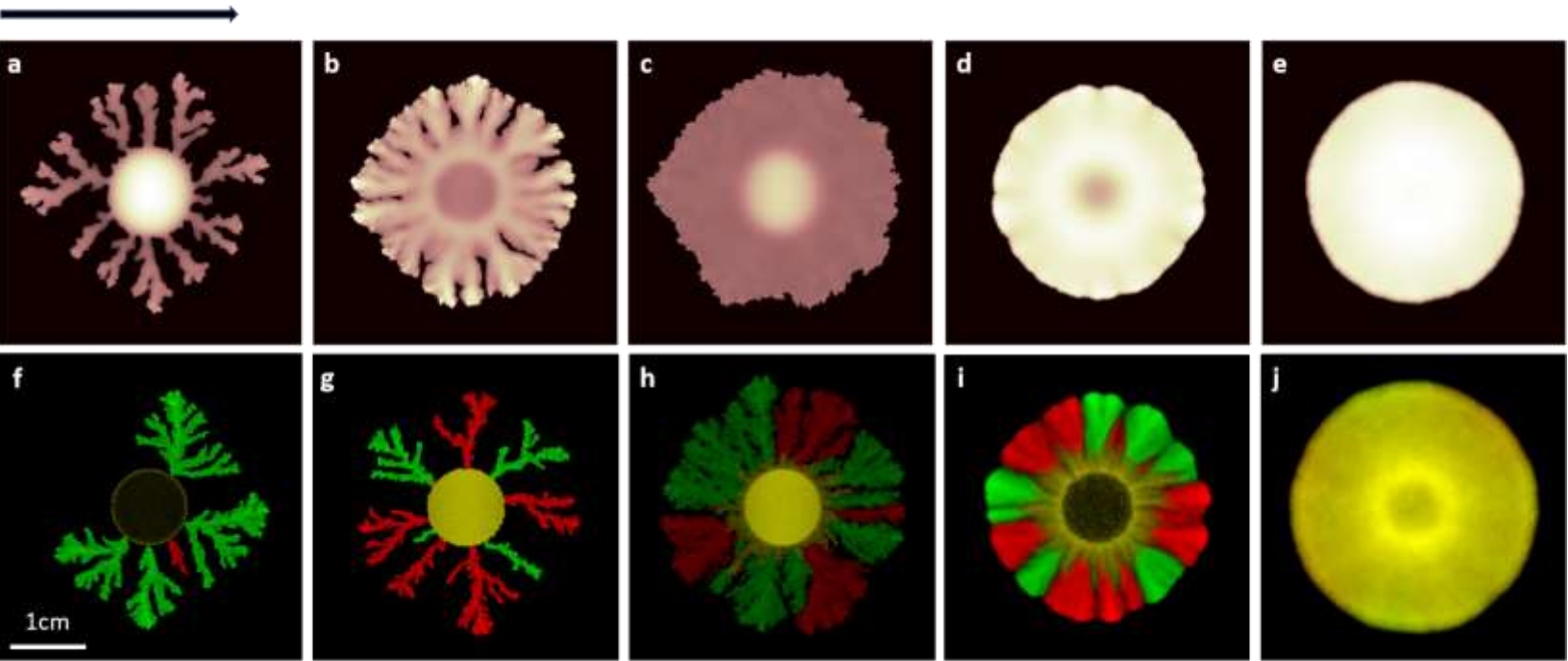
- Nitrogen limited (solid orange line)
- Nitrogen abundant (dashed green line)

(PI: Liz Kujawinsky)

Enhanced COMETS predictions of colony morphology

With Ilija Dukovski, Kirill Korolev, Melisa Osborne (in prep)

Furcated to flat

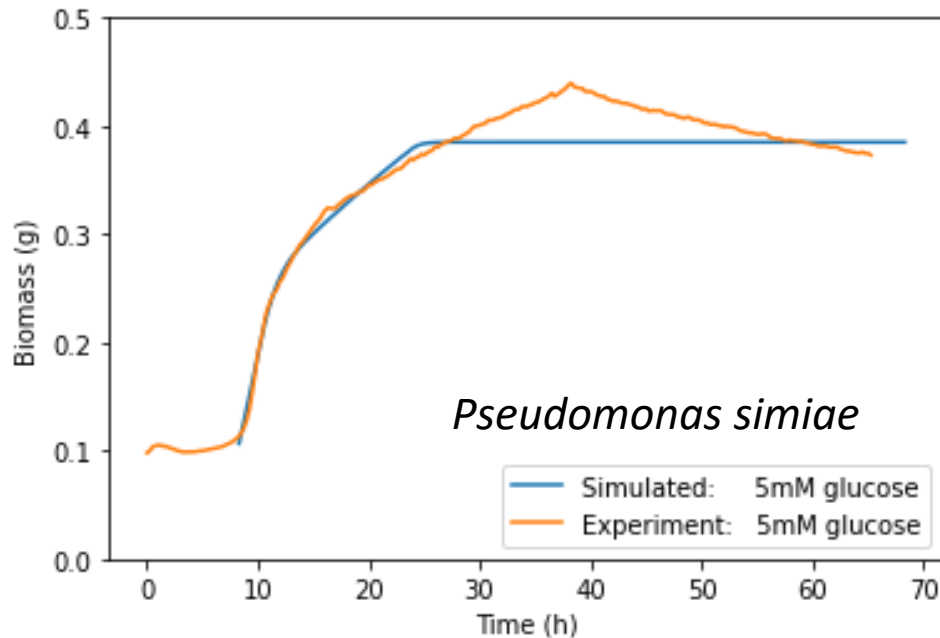


E. coli on LB media
DH5a+E0040m (GFP) and
DH5a+E1010m (RFP)

Towards integration of experimental data and COMETS simulations for rhizosphere community modeling

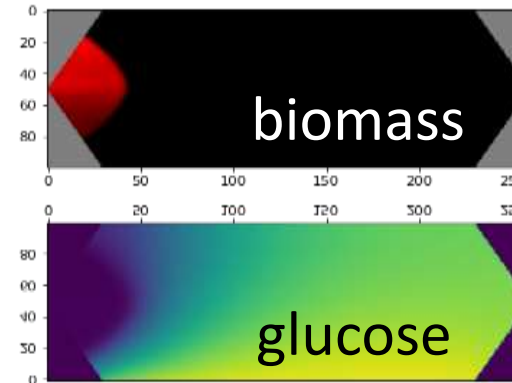
Ilija Dukovski, Jing Zhang
m-CAFES

Calibrating COMETS growth curves



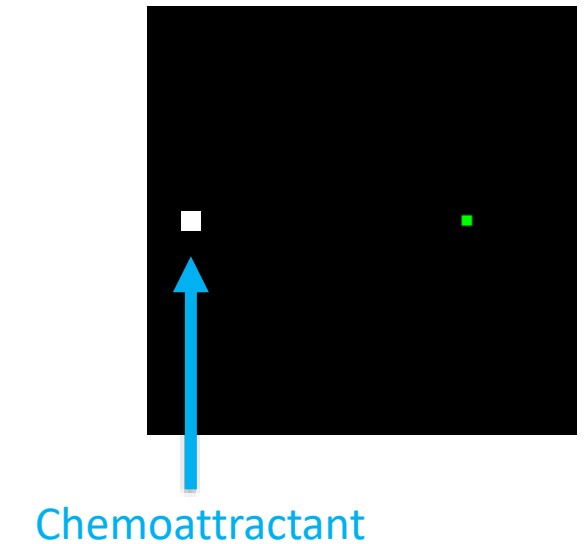
with Adam Deutschbauer, LBNL

COMETS simulations of EcoFab devices



with Peter Kim

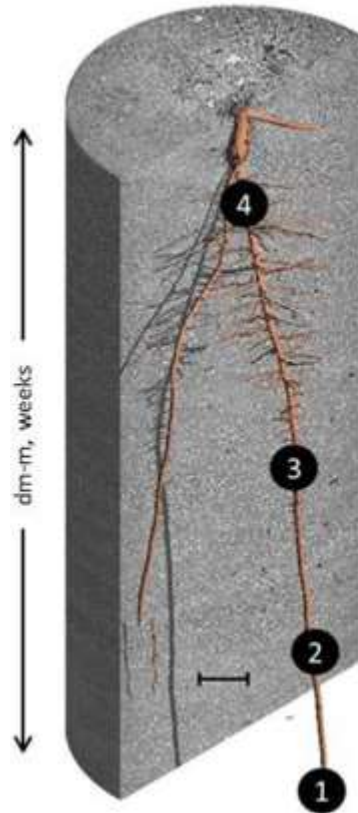
Adding Chemotaxis in COMETS



with Hui Shi

A complementary EMSL project to advance high resolution COMETS simulations of rhizosphere community dynamics

With Ilija Dukovski, Melisa Osborne, Jing Zhang
(just started)



Vetterlein et al., *Frontiers in Agronomy* (2020)

1

Exometabolomics to parametrize uptake rates and test secretions

2

Proteomics of monoculture and co-culture to validate fluxes

3

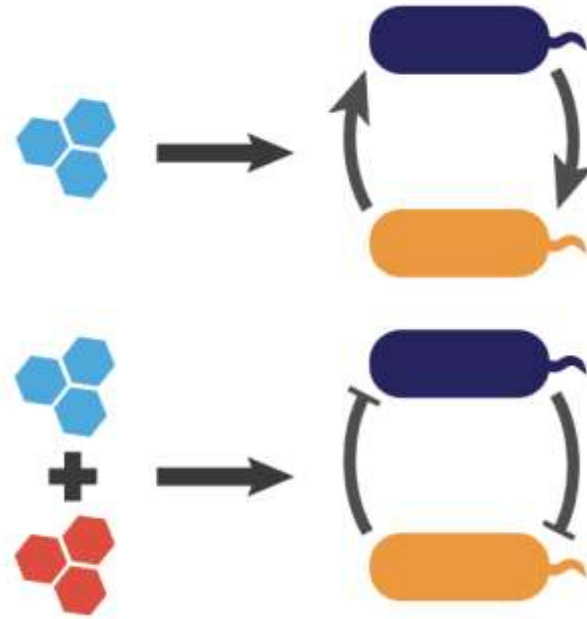
High-performance computing to implement 3D spatio-temporal simulations of communities around roots

4

Imaging mass-spec to test COMETS predictions of metabolites in time and space

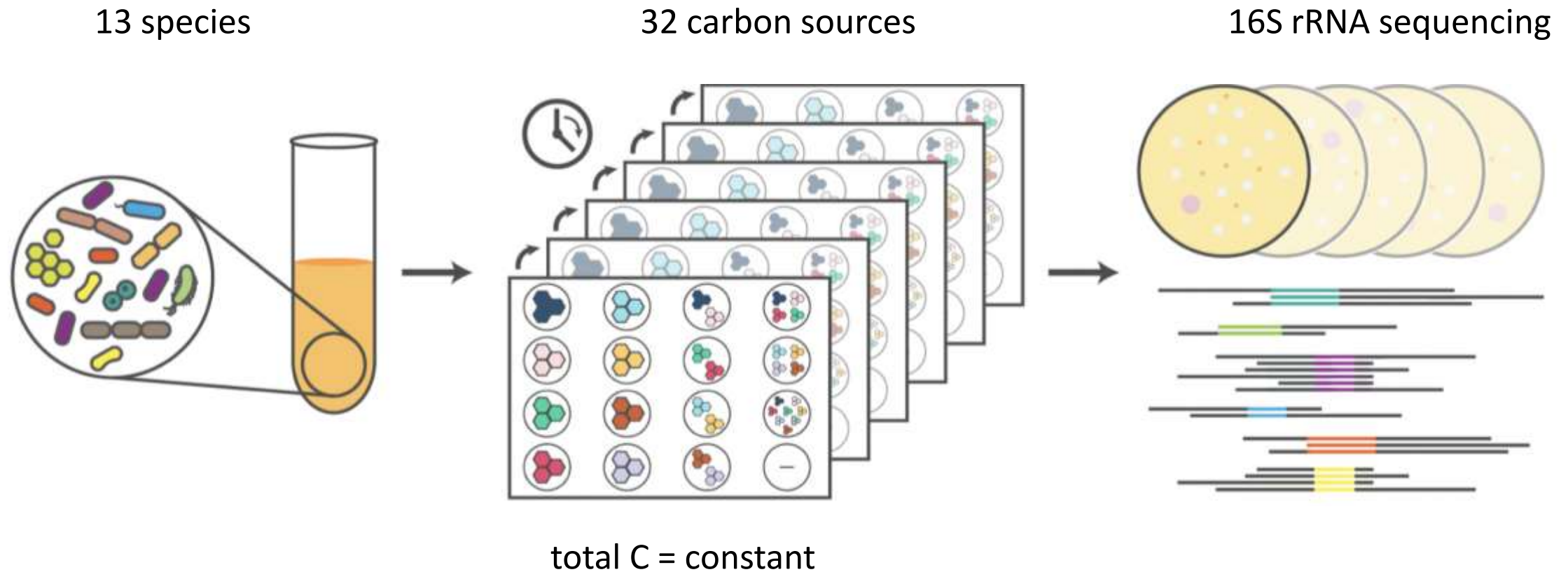
A lot of testing/calibration is done under single carbon sources.

How do microbial communities behave as environmental complexity increases?

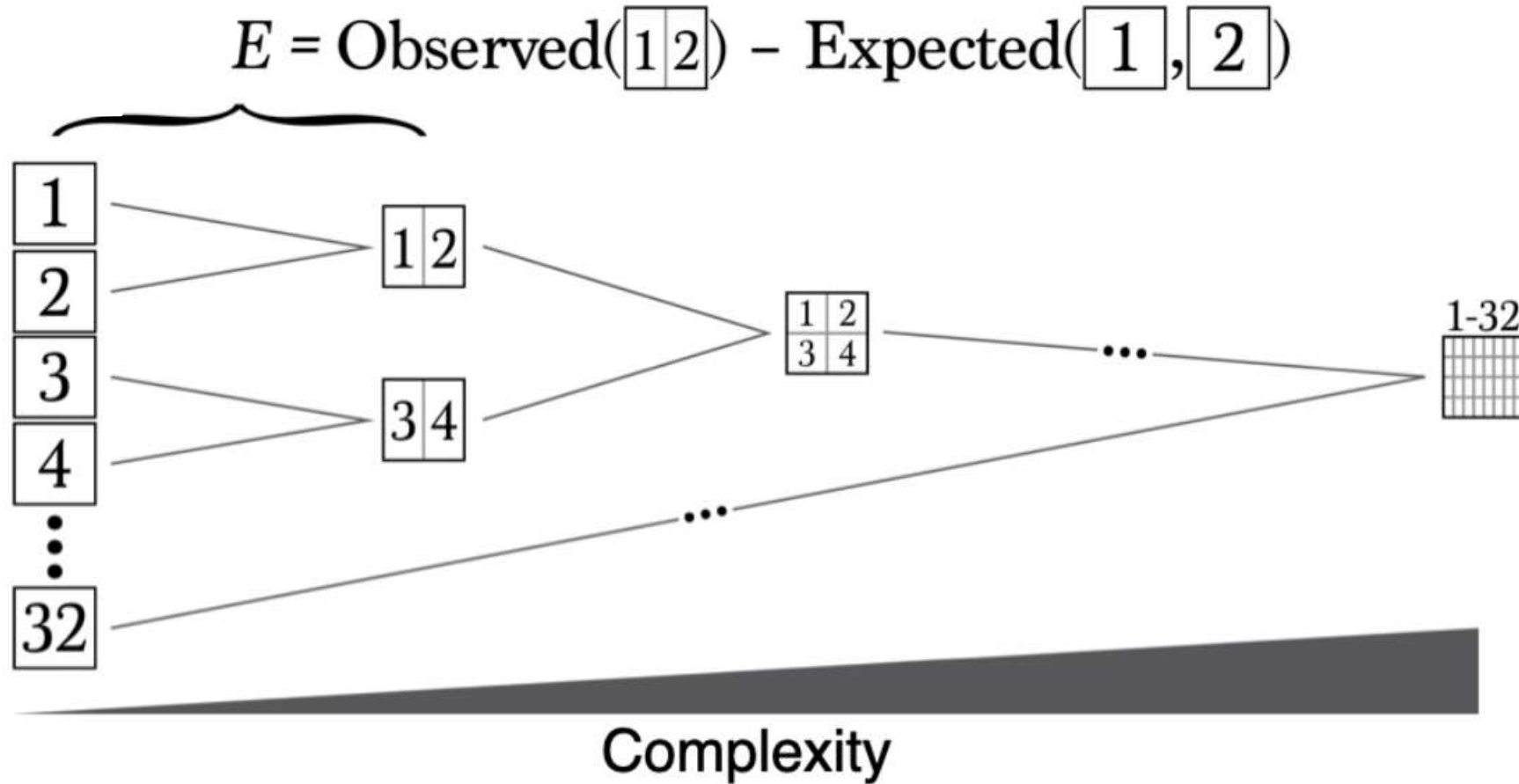


A combinatorial synthetic ecology approach to study the effects of environmental complexity

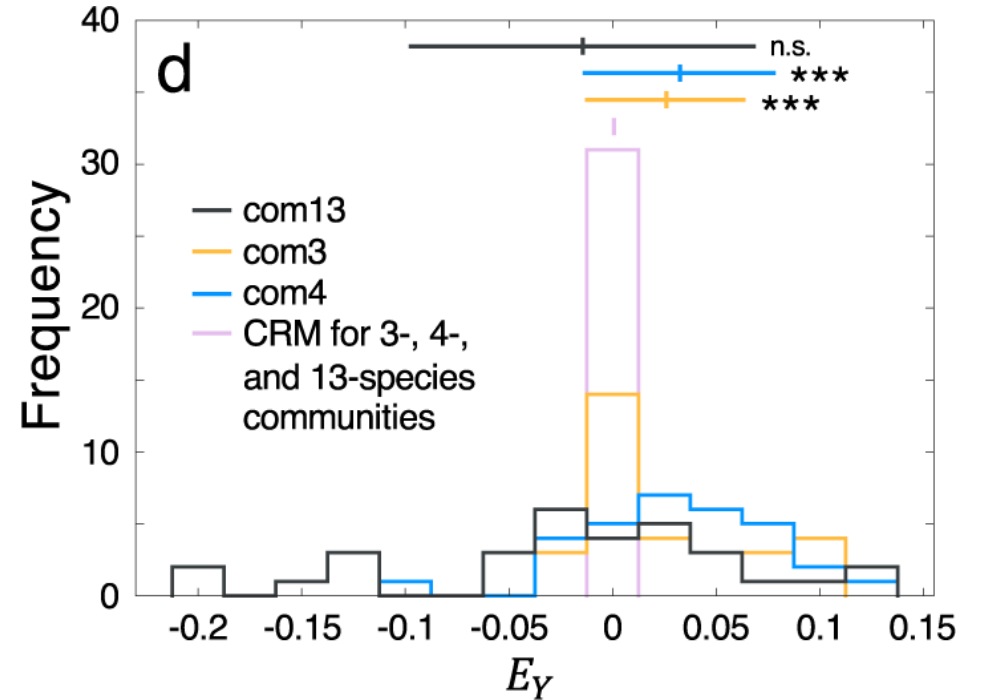
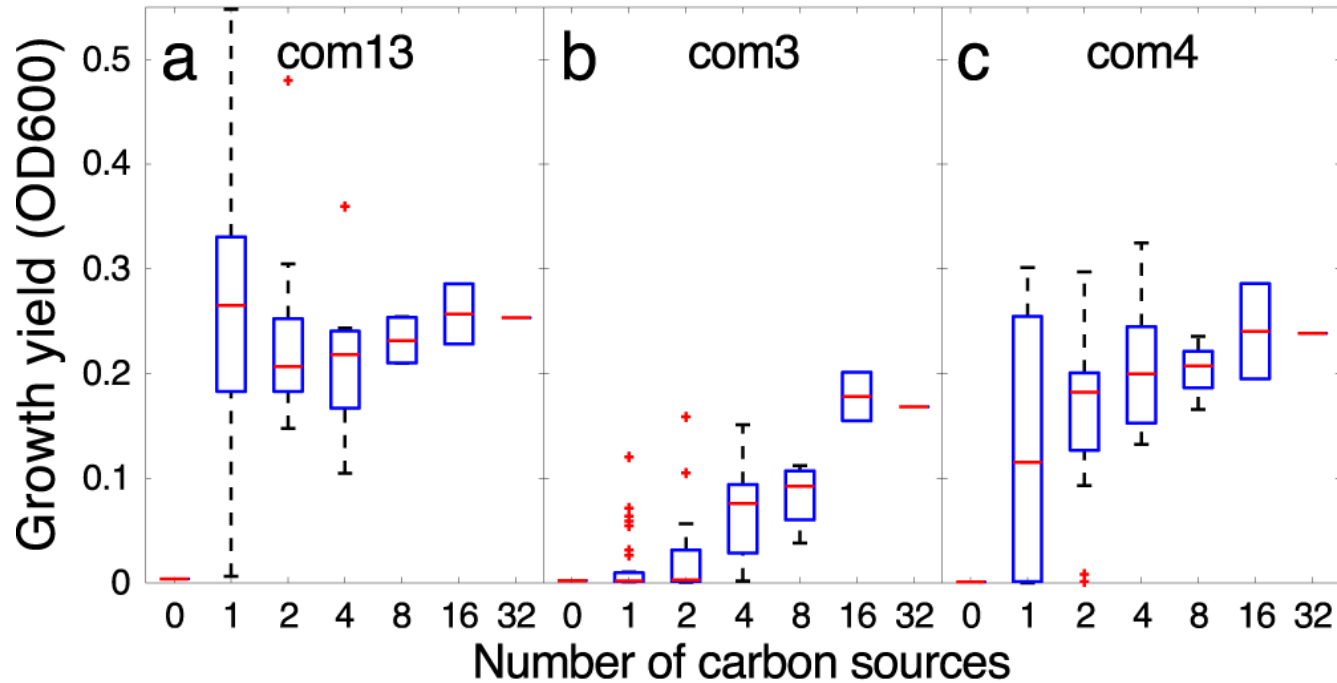
Alan Pacheco
Melisa Osborne (experimental)



A combinatorial synthetic ecology approach to study the effects of environmental complexity

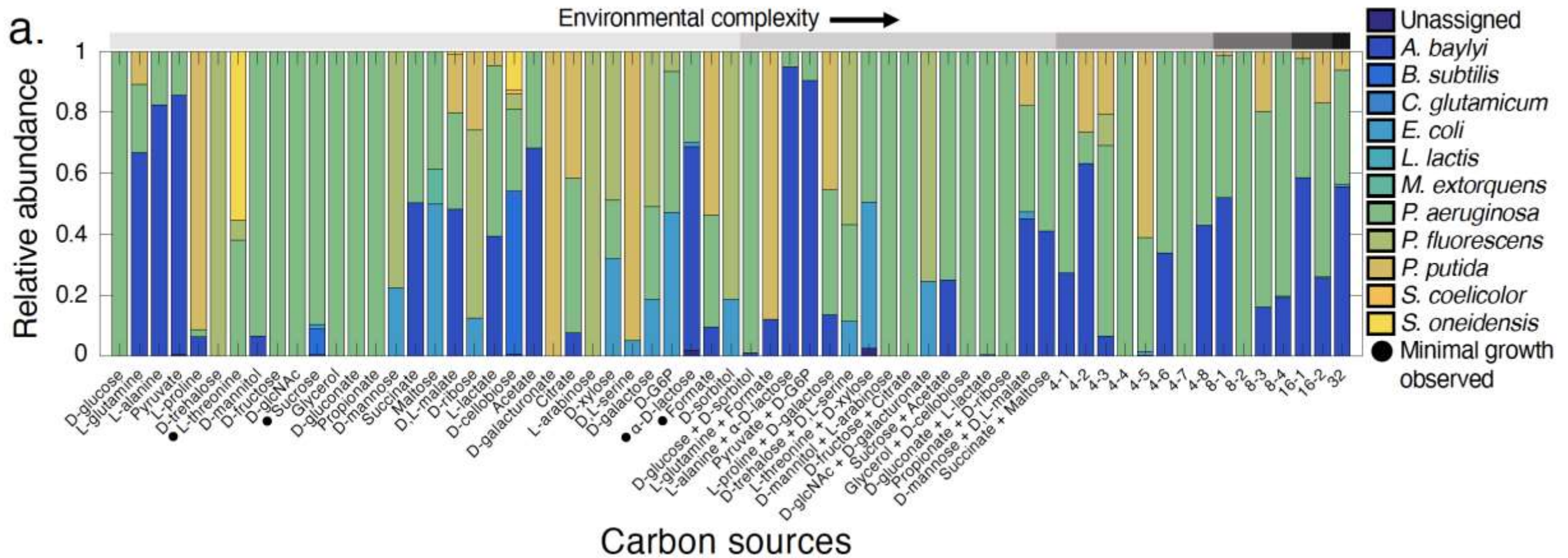


On average, for the 13 species community, overall yield does not change significantly with environmental complexity

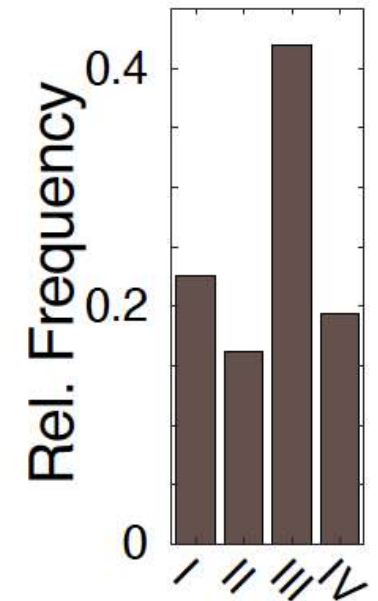
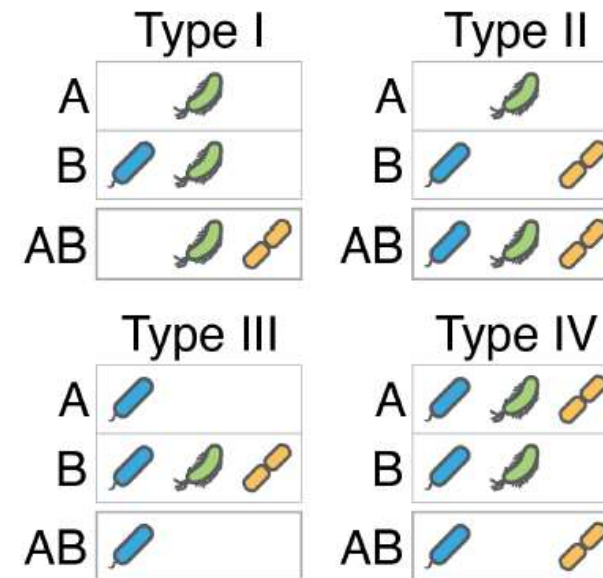
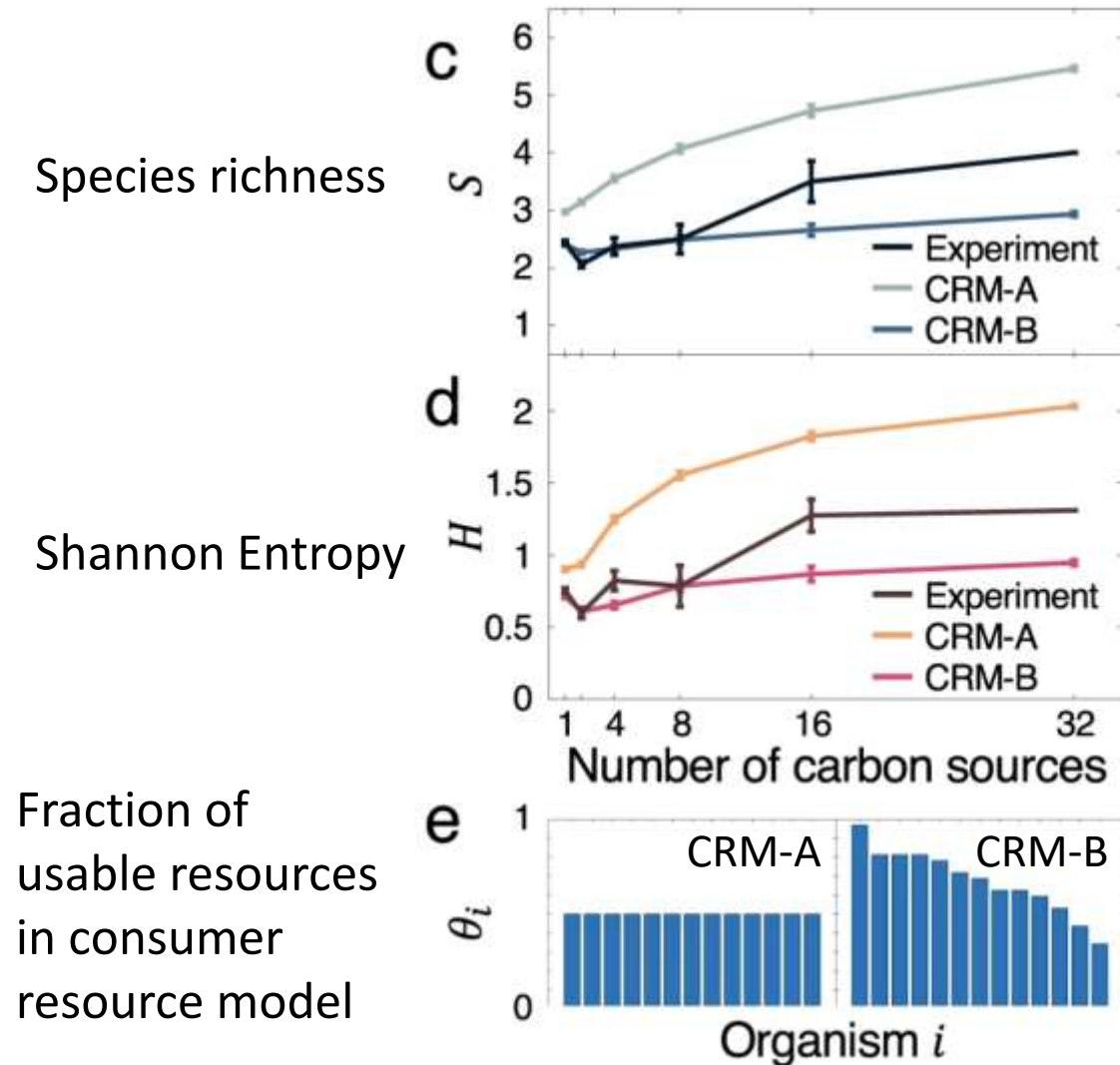


$$E_Y = Y(AB) - (Y(A) + Y(B))/2$$

Ecosystem diversity grows slowly at increasing molecular complexity

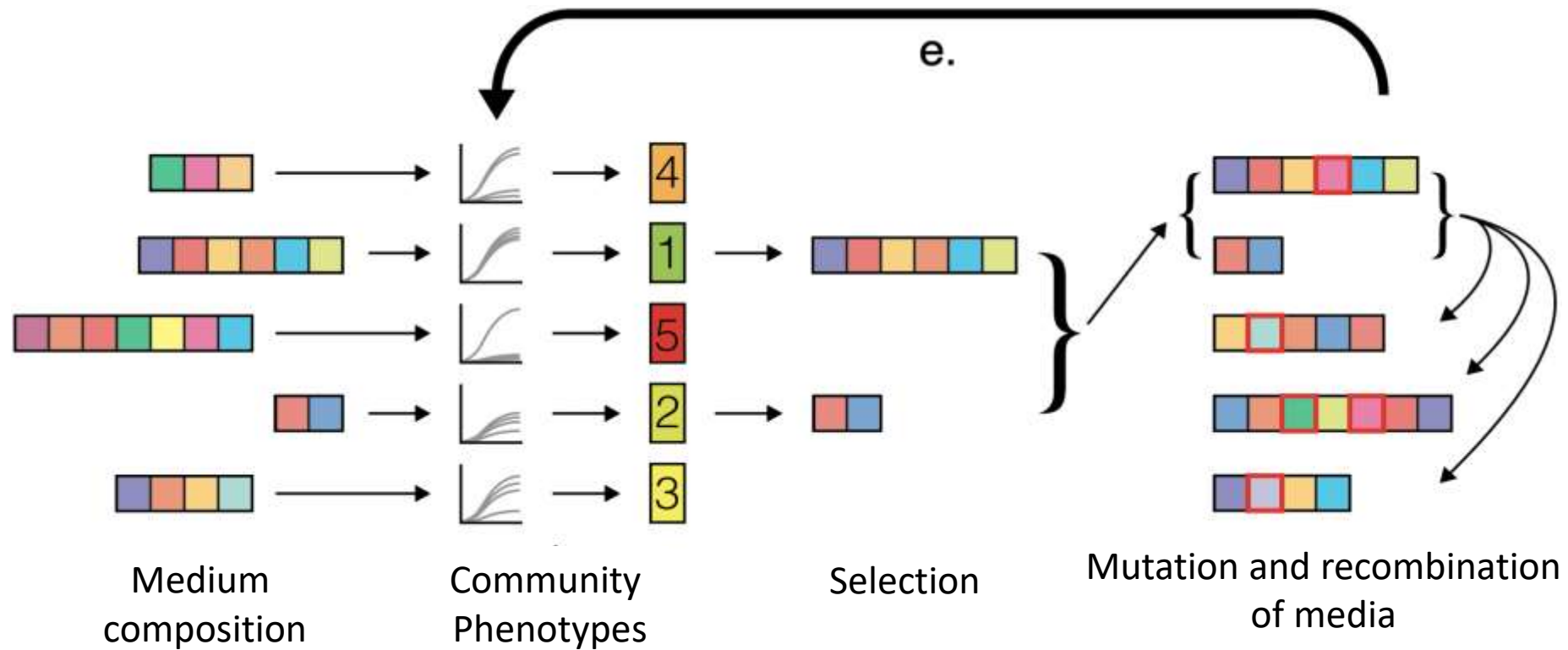


Antagonistic epistasis between environments limits microbial diversity



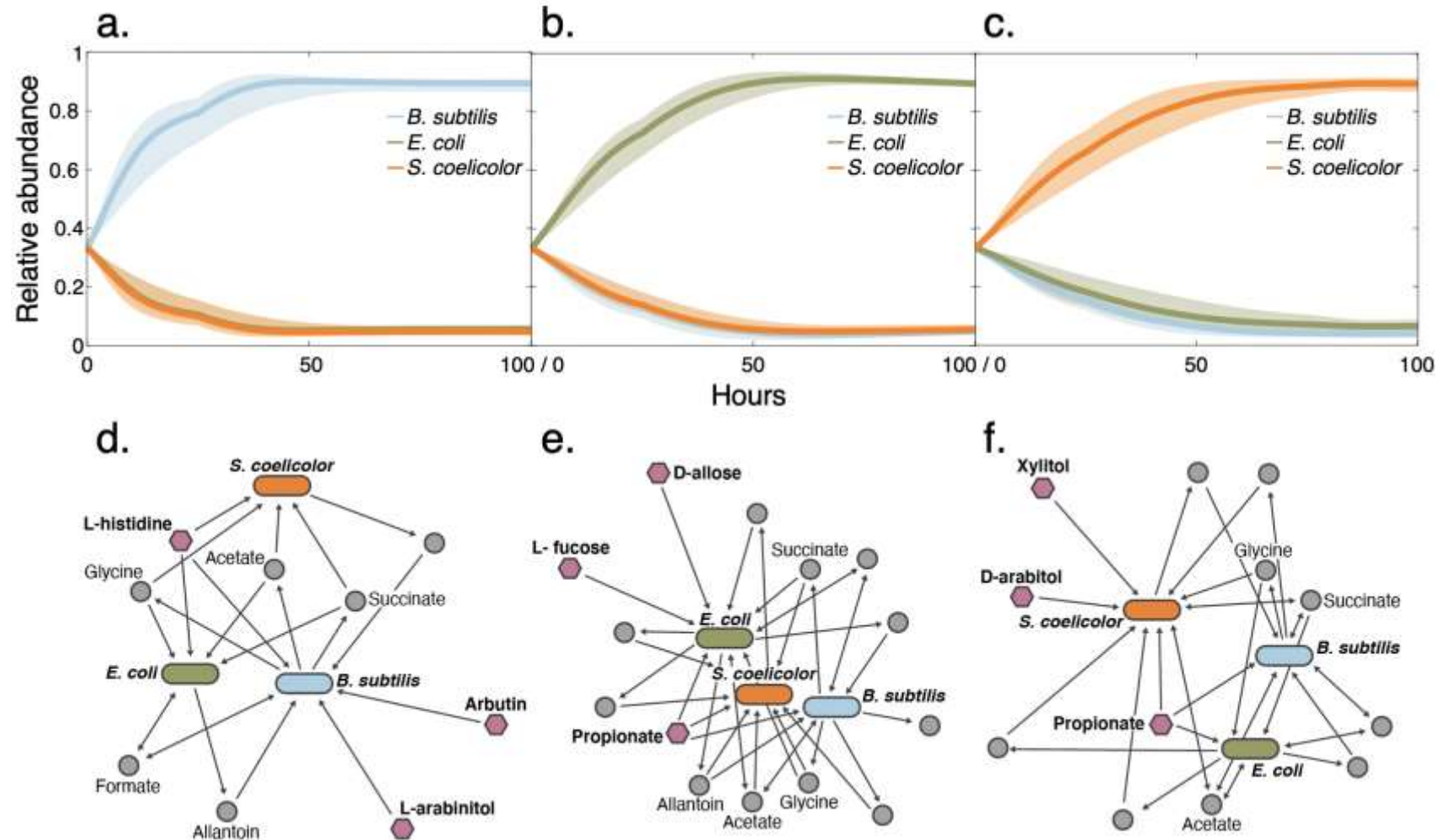
The next step: can we tweak environmental metabolites to reach a desired community structure?

An algorithm that combines machine learning and community phenotyping



The next step: can we tweak environmental metabolites to reach a desired community structure?

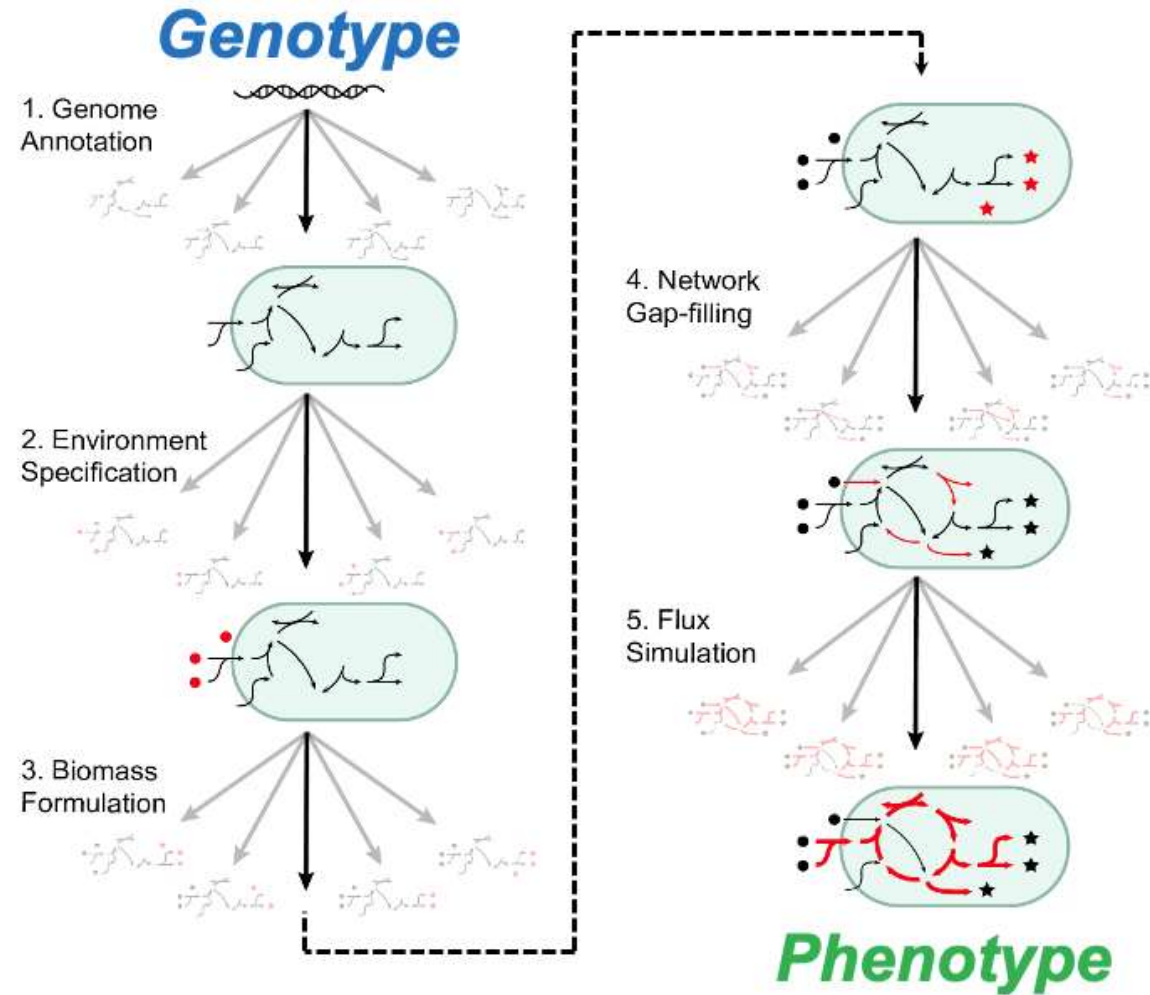
A computational implementation using a Genetic Algorithm and COMETS



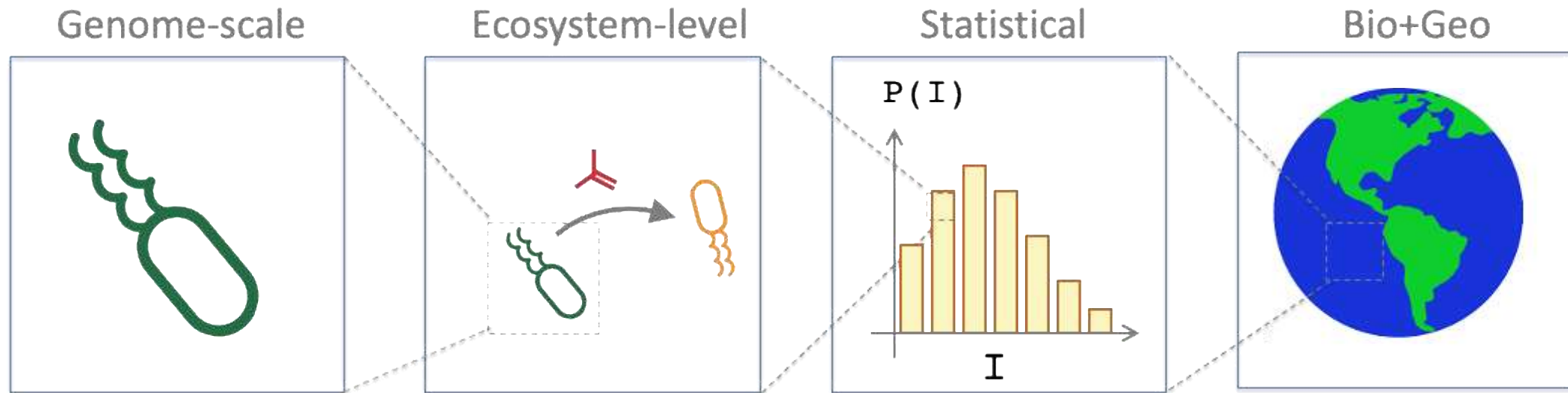
Can computational modeling help understand and control ecosystem metabolism?

1. A personal view of microbial metabolism
2. Some approaches recent results
3. Dichotomies and outlook

Documenting and embracing uncertainty



Dichotomy 1: Detailed vs. Coarse-grained / statistical models

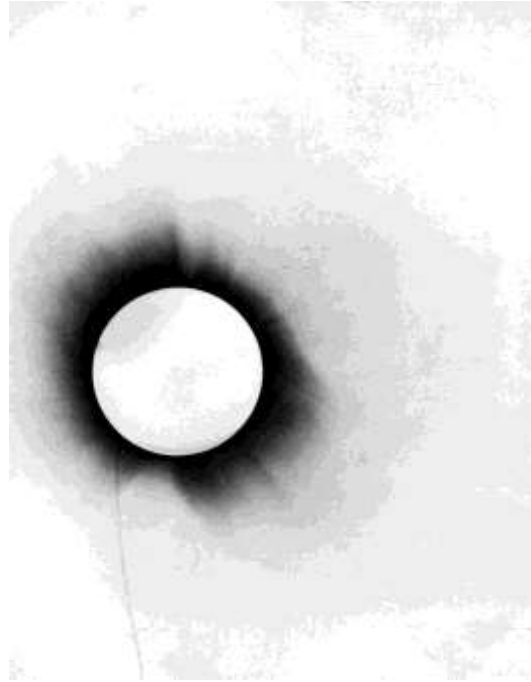


Detailed models can be used to parametrize global models (e.g. CUE)

Saifuddin et al., Nature Comm 2019

Both needed, new theory to be developed

Dichotomy 2: Immediately testable vs. “out there”



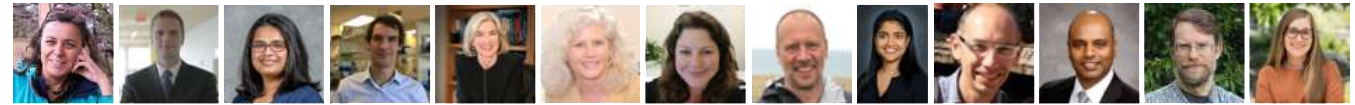
Arthur Eddington, 1919

Both needed!

Dichotomy 3: Mechanistic models or machine learning?



Not mutually exclusive, but synergistic



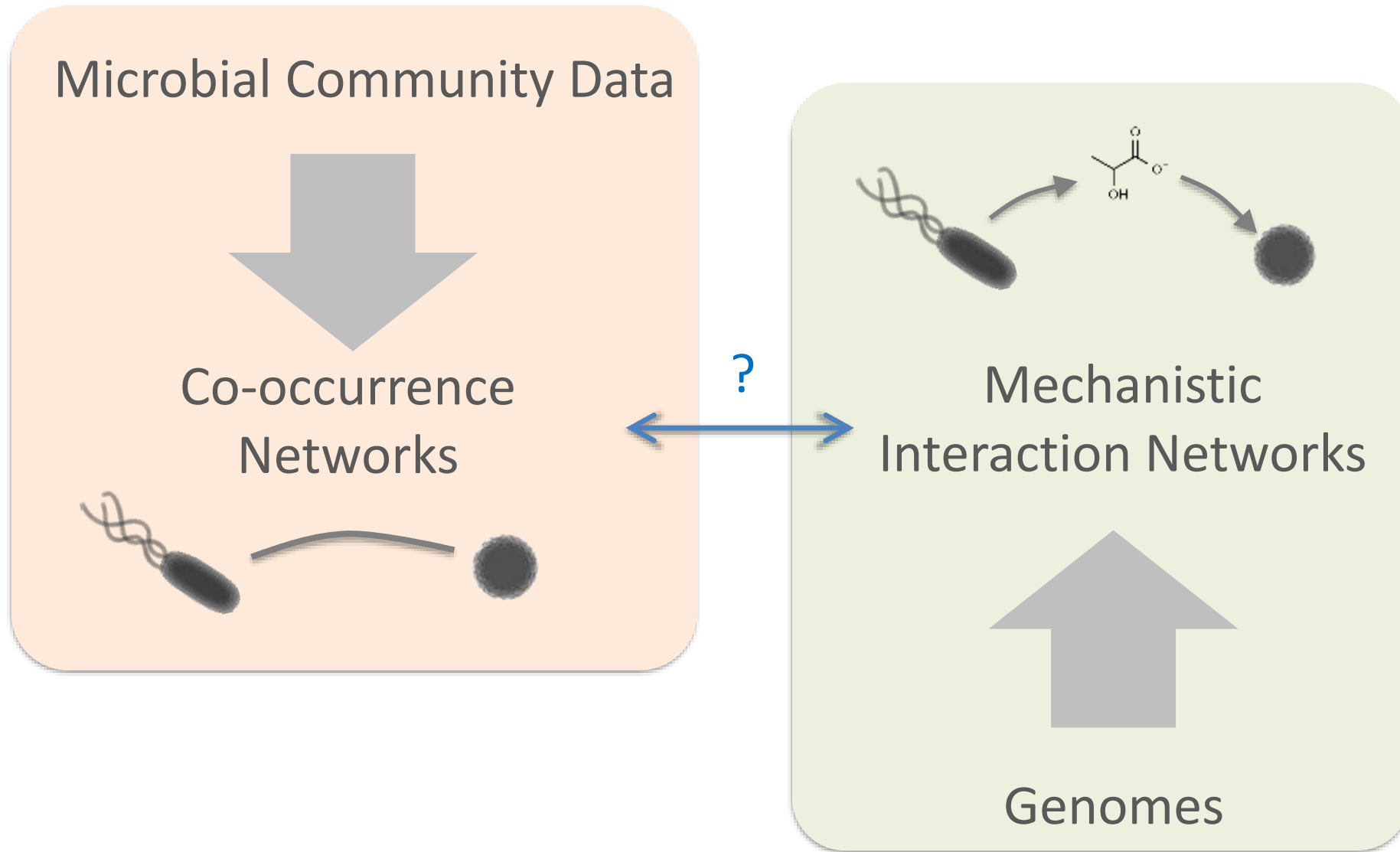
Ilija Dukovski, Melisa Osborne, Dileep Kishore, Elena Forchielli, Michael Silverstein, Devlin Moyer, Jing Zhang, Ziwei Huang, Michael Silverstein, Helen Scott, Mike Quintin, Alan Pacheco

Collaborators: Trent Northen, Adam Deutschbauer & m-CAFEs team, Jenny Bhatnagar (BU), Kirill Korolev (BU), Daniel Sher (Haifa)

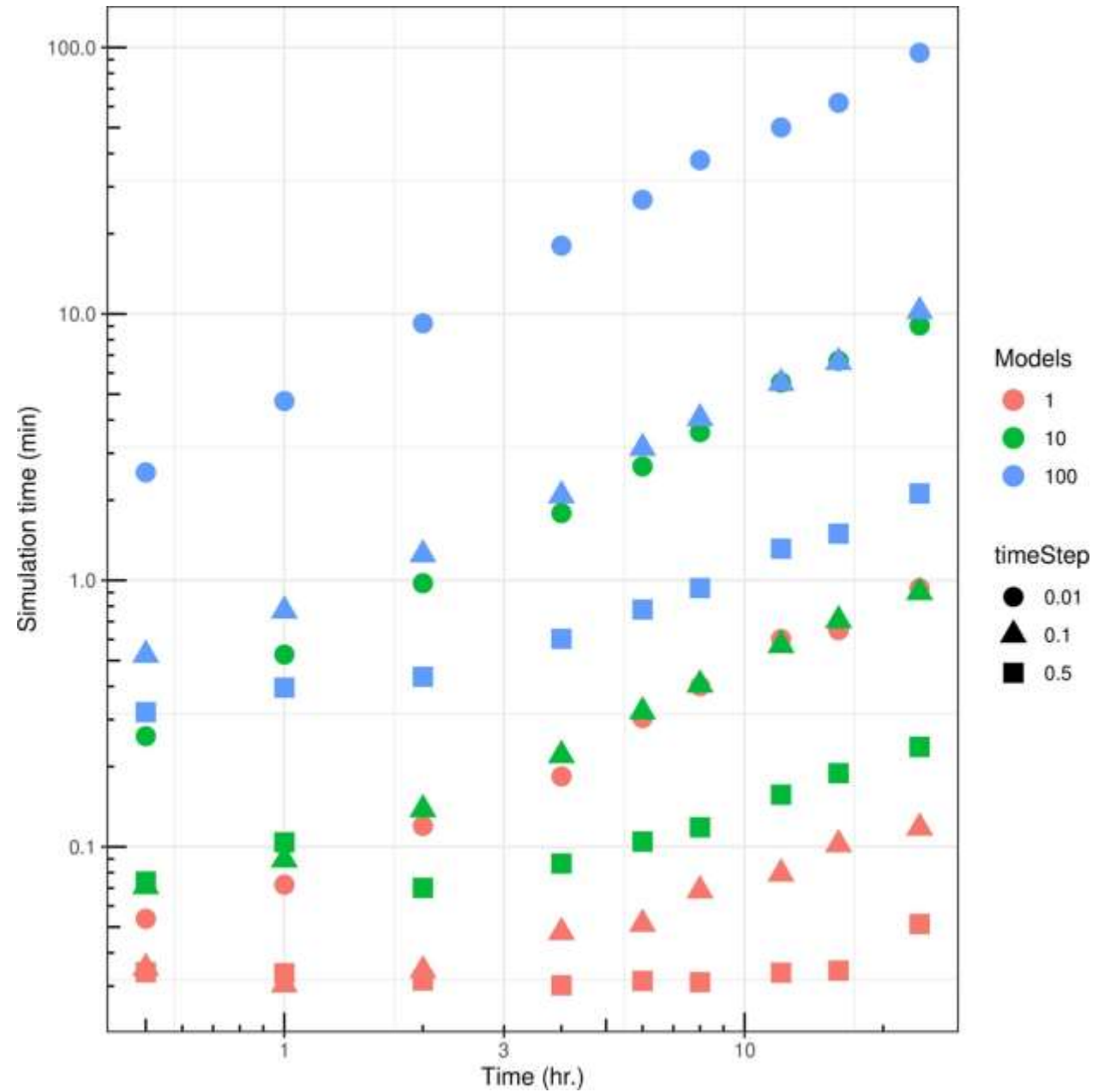


EXTRA

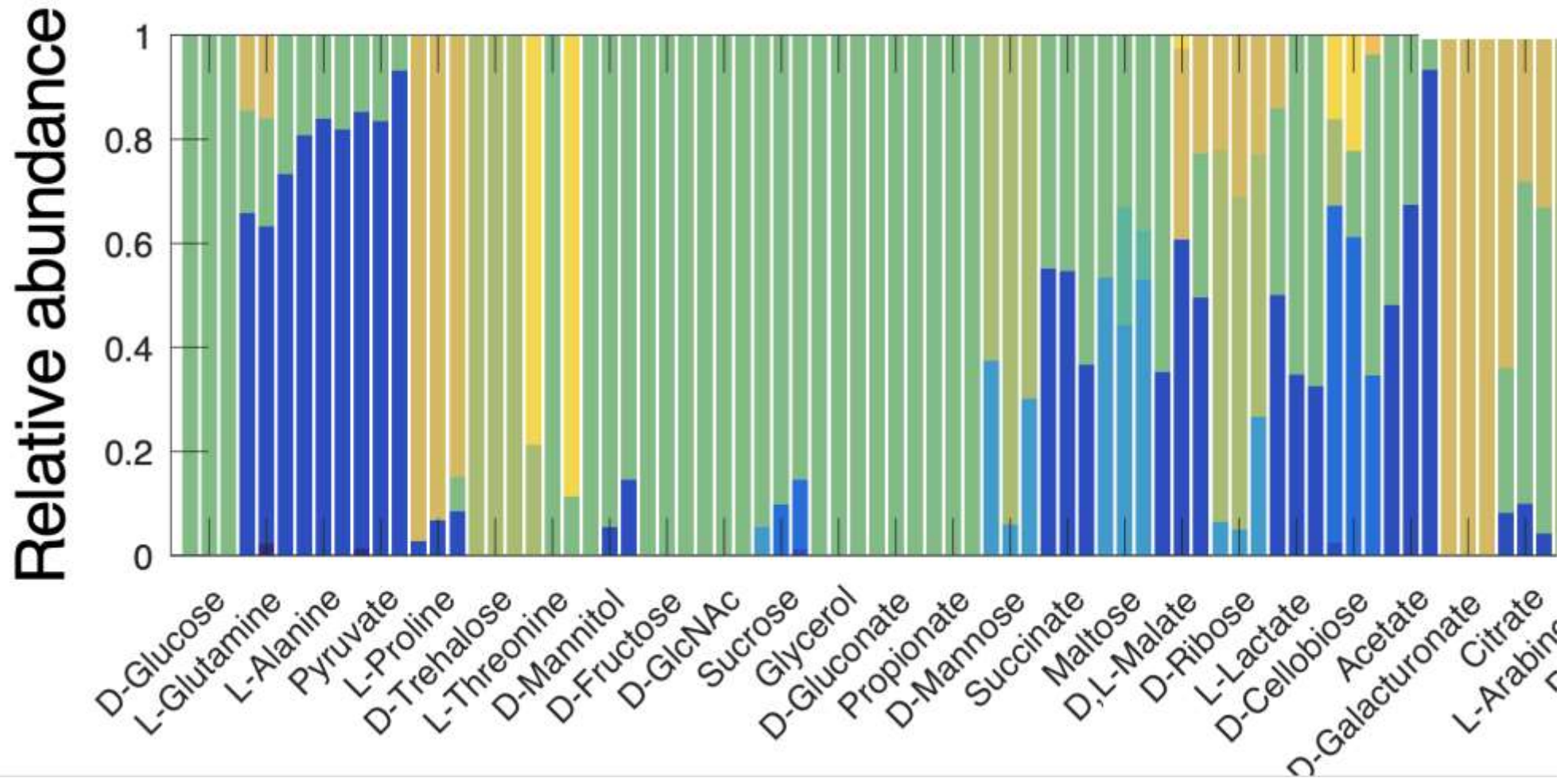
Integrating top-down and bottom-up approaches



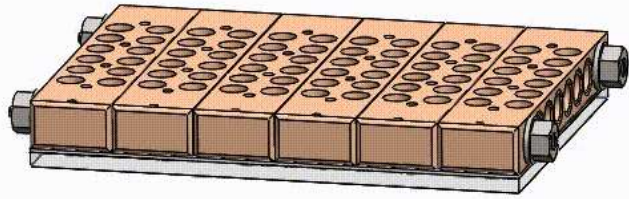
COMETS CPU time



Community composition is largely consistent across replicates

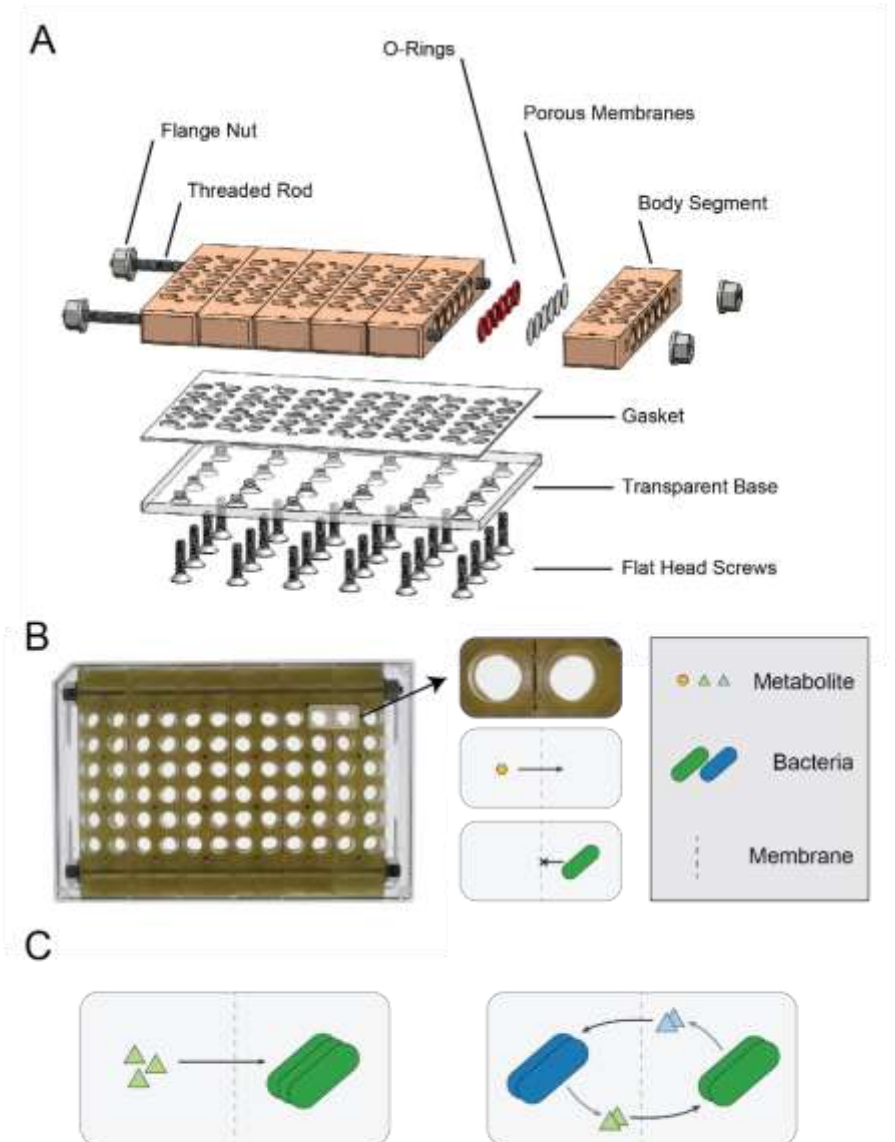


How to directly measure metabolic exchange?

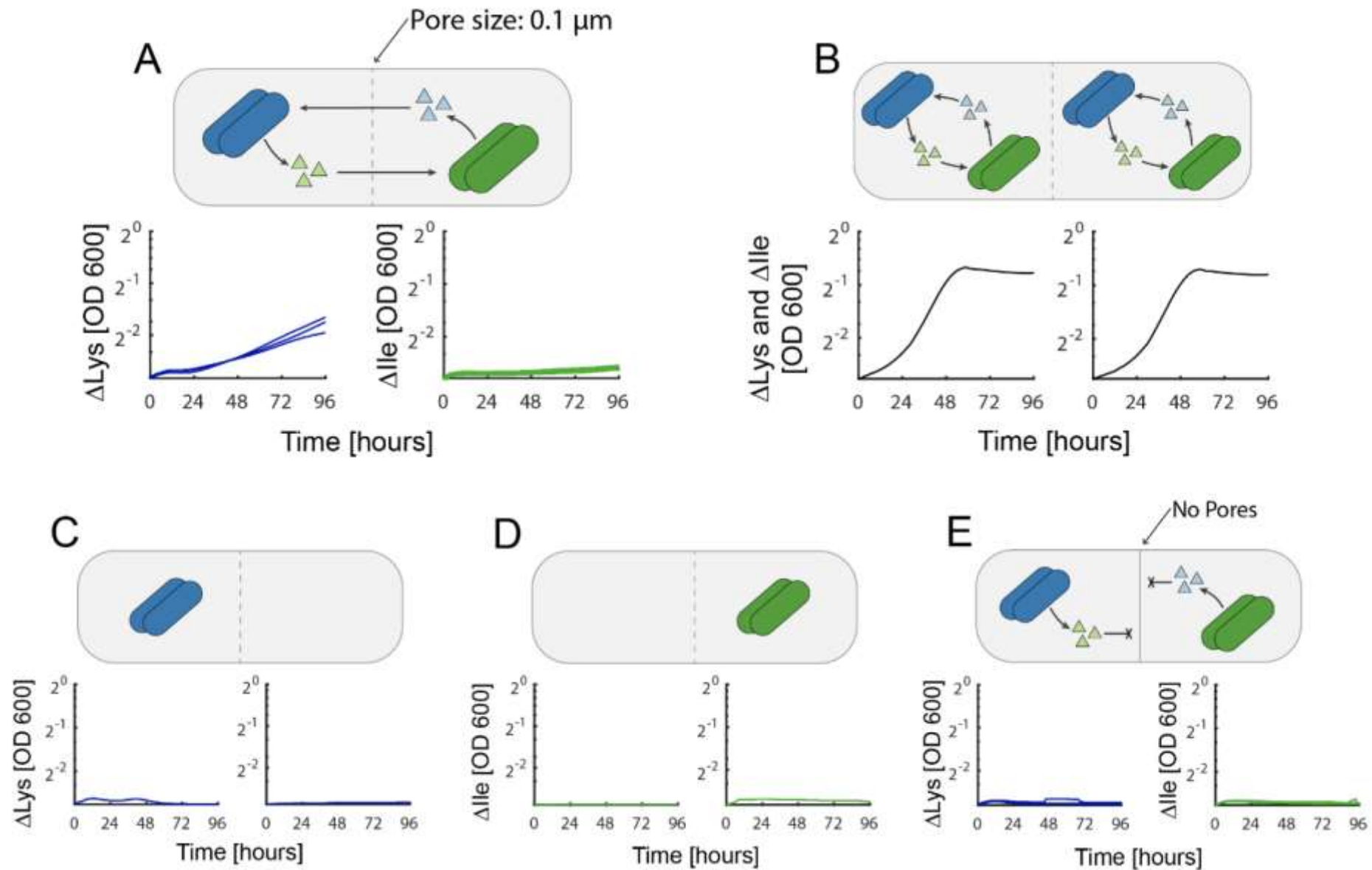


Standard 96-well microplate architecture
Real-time growth dynamics
Accommodate genetically intractable bacteria

Charles Jo*, David B Bernstein*, Natalie Vaisman, Horacio M Frydman, Daniel Segrè: A co-culture microplate for real-time measurement of microbial interactions, BioRxiv (2021),



How to directly measure metabolic exchange?



Metabolic capabilities of a large compendium of bacteria



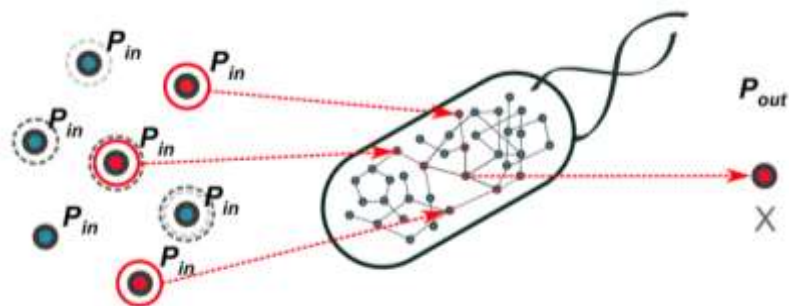
David Bernstein



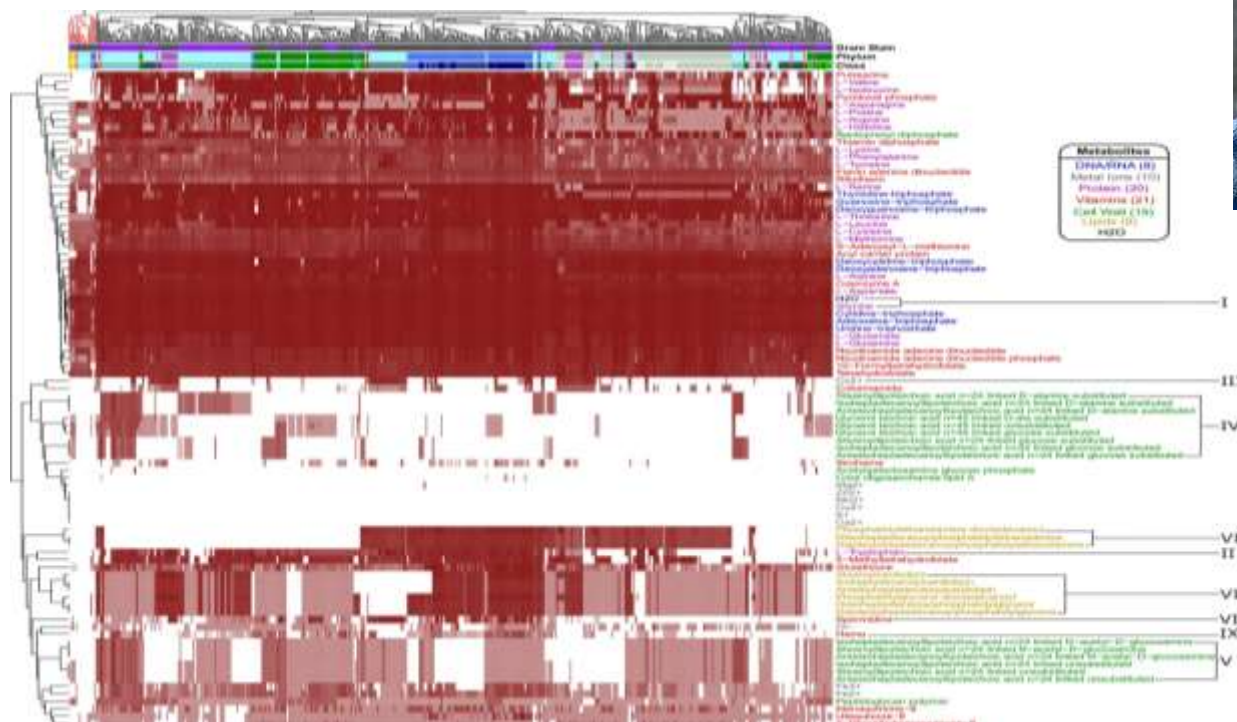
456 strains



“Producibility”



88 Metabolites



456 Strains

