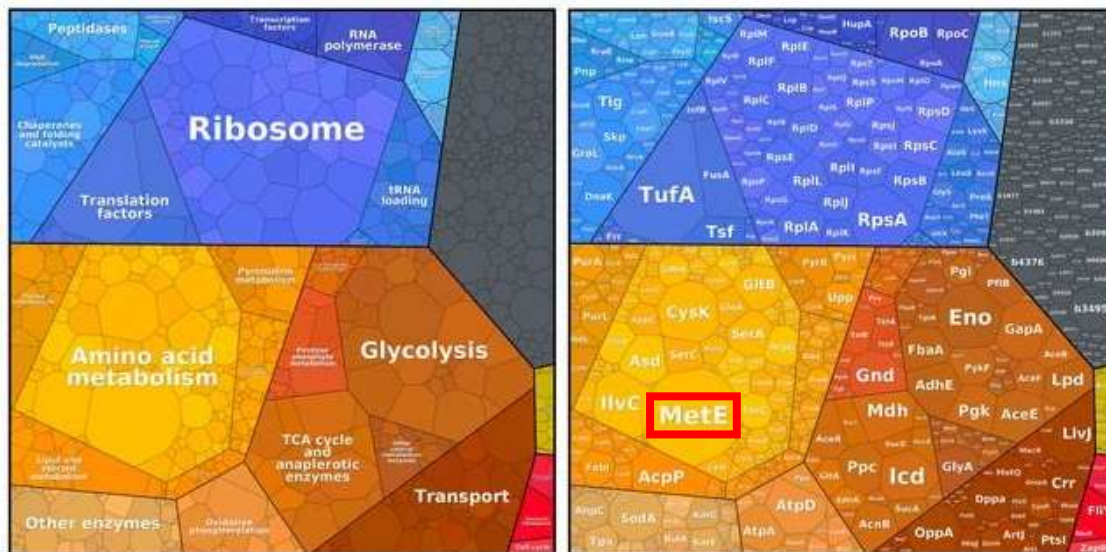


# Quantitative principles in biological systems

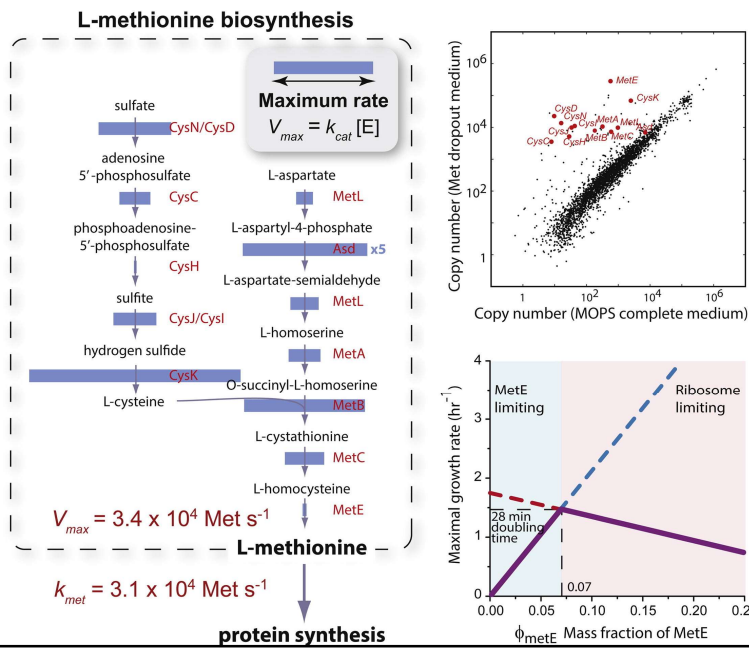
## 4<sup>3</sup>/<sub>4</sub>. Coarse-graining metabolic networks

Spring 2026

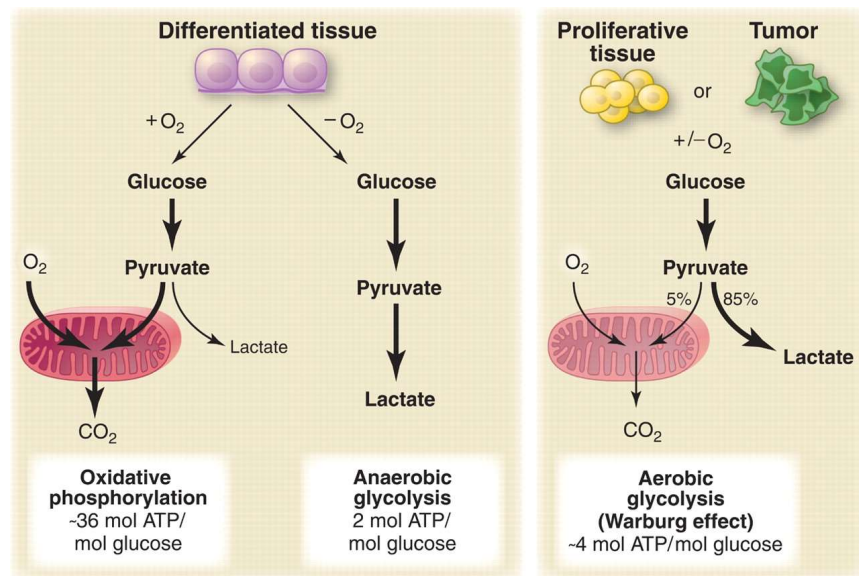
Proteome of an *E. coli* cell



The proteome fraction allocated to methionine biosynthesis is optimal.

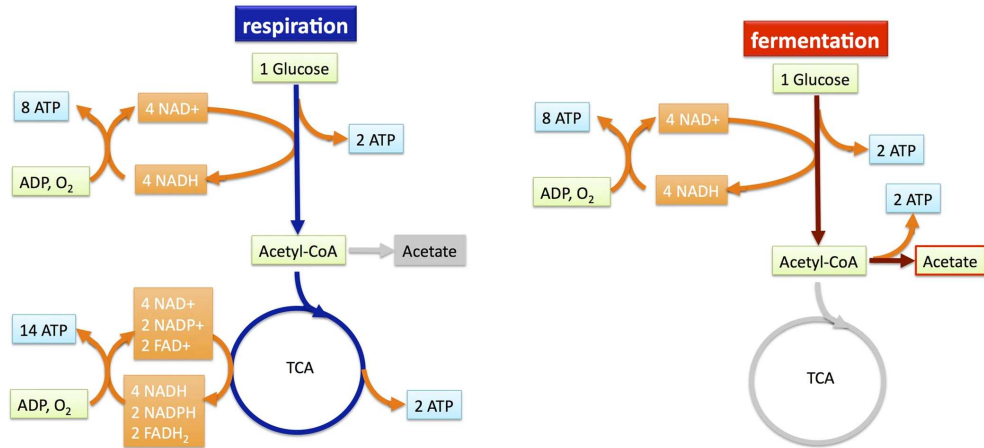


Warburg effect and metabolic efficiency



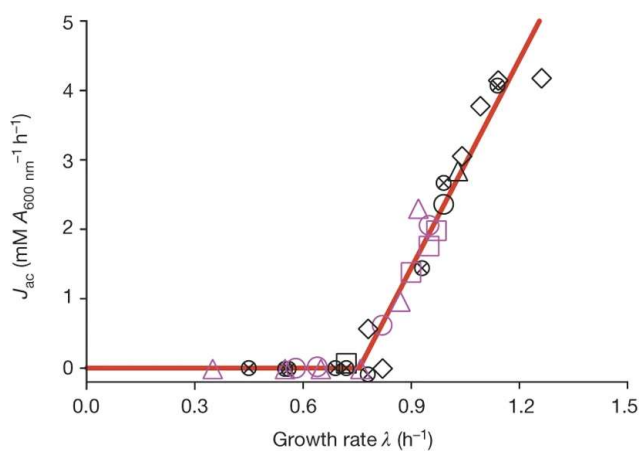
Heiden et al. *Science* (2009)

## Overflow metabolism and metabolic efficiency



Basan et al. *Nature* (2015)

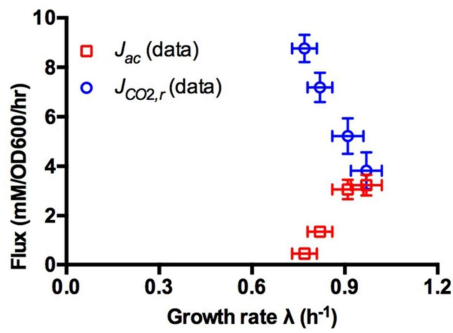
Growth rate is a **unifying variable** that describes overflow metabolism.



Strain	Description	Carbon	Symbol
NCM3722	WT	Glucose	○
NCM3722	WT	Lactose	△
NCM3722	WT	Glycerol	□
NCM3722	WT	Other	⊗
NQ1243	Uptake titration	Glucose	○
NQ381	Uptake titration	Lactose	△
NQ636			
NQ638	<i>glpK</i> mutant	Glycerol	□
NQ640			
NQ3722	+ 7 AA	Various	◇

Basan et al. *Nature* (2015)

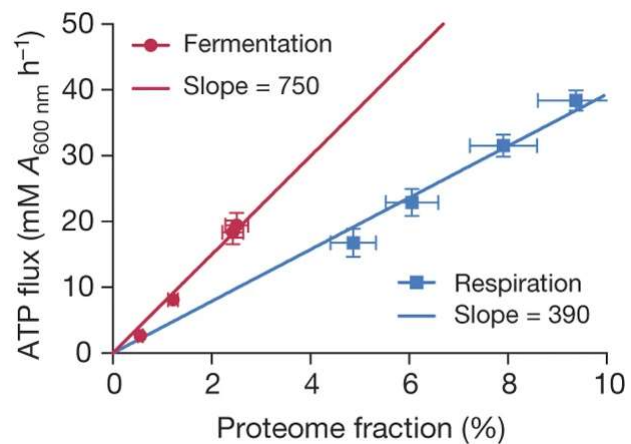
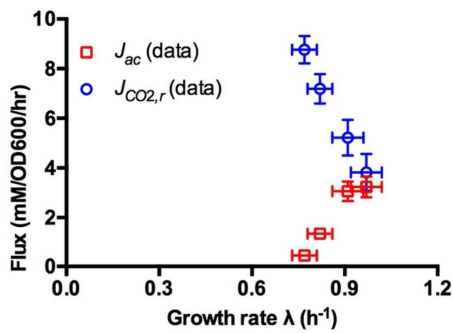
Fermentation is >50% more proteome-efficient at generating ATP than respiration.



Quantity	Symbol	Unit	NQ381	NQ381	NQ381	NCM3722	Note
3MBA		$\mu\text{M}$	400	500	800	0	
Growth rate	$\lambda$	1/h	0.77	0.82	0.91	0.97	Measured
Acetate excretion rate	$J_{ac}$	mM/OD <sub>600</sub> /h	0.44	1.35	3.06	3.24	Measured
CO <sub>2</sub> evolution rate	$J_{CO_2}$	mM/OD <sub>600</sub> /h	11.96	11.50	11.56	10.57	Measured
Lactose uptake flux	$J_{lac}$	mM/OD <sub>600</sub> /h	2.38	3.06	3.27	3.46	Measured
CO <sub>2</sub> flux by respiration	$J_{CO_2,r}$	mM/OD <sub>600</sub> /h	8.49	6.90	4.90	3.47	Supp. Note 2

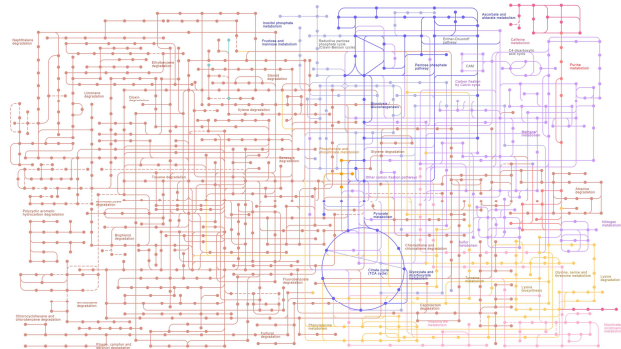
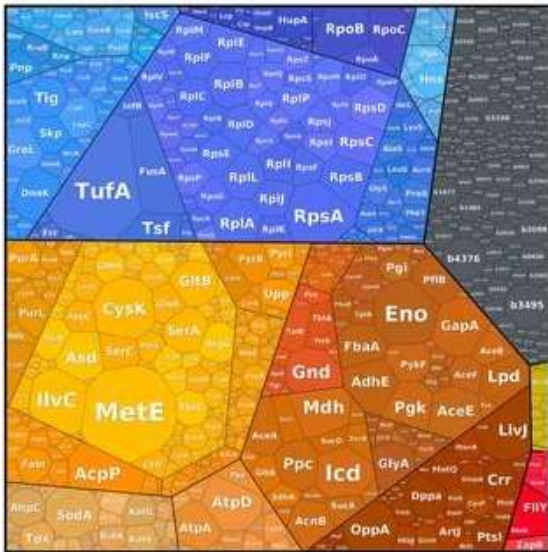
Basan et al. *Nature* (2015)

Fermentation is >50% more proteome-efficient at generating ATP than respiration.



Basan et al. *Nature* (2015)

# How does the cell implement optimality over its complex metabolic network?



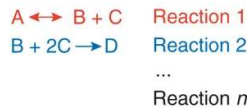
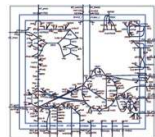
KEGG  
Liebermeister et al. PNAS (2014)

## Flux balance analysis

Genome-scale  
metabolic reconstruction

Mathematically represent  
metabolic reactions  
and constraints

Mass balance defines a  
system of linear equations



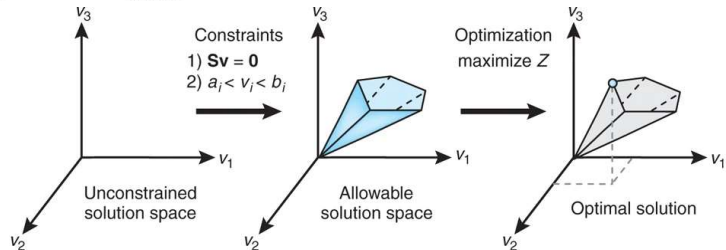
Metabolites	1	2	...	n	Biomass	Glucose	Oxygen
A	-1						
B	1	-1					
C	1	-2					
D				1			
...							
m					-1		

Stoichiometric matrix,  $S$

Fluxes,  $v$

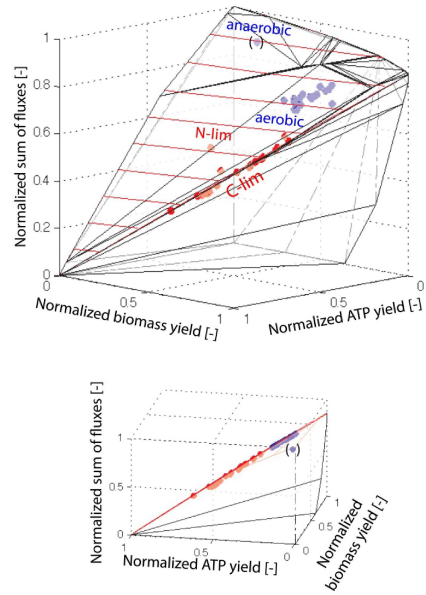
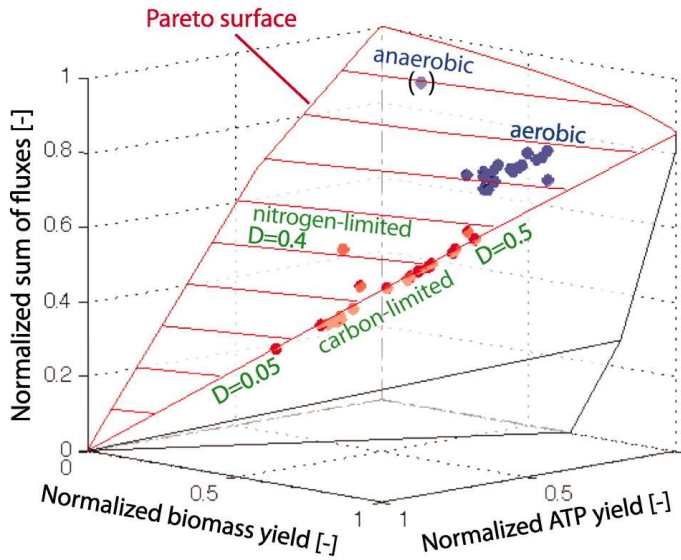
$$S \cdot v = 0$$

$$\begin{aligned}
 -v_1 + \dots &= 0 \\
 v_1 - v_2 + \dots &= 0 \\
 v_1 - 2v_2 + \dots &= 0 \\
 v_2 + \dots &= 0 \\
 \text{etc.}
 \end{aligned}$$



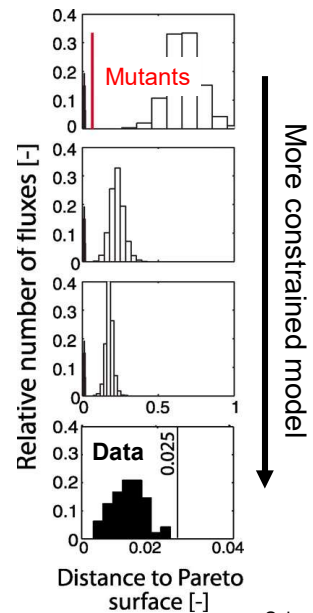
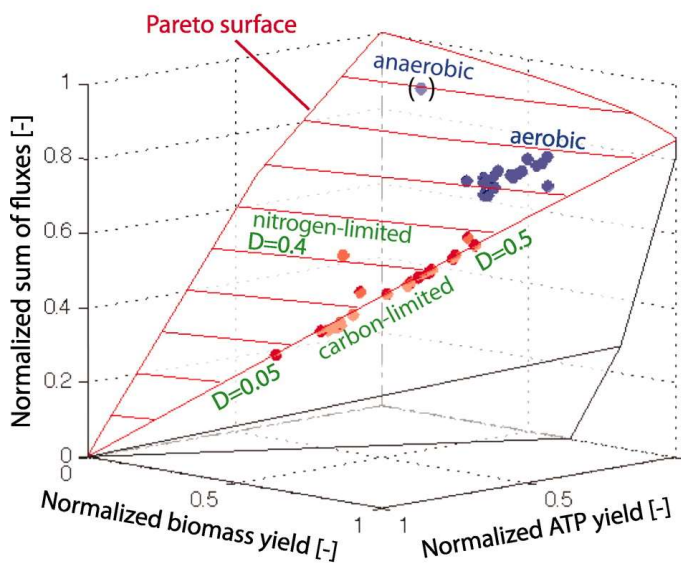
Orth et al. Nat Biotechnol (2010)

Metabolic fluxes are near optimal in multiple objectives.



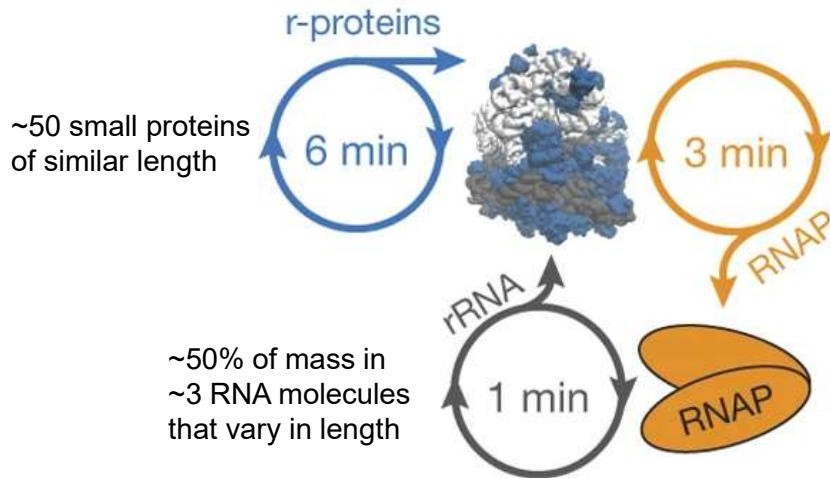
Schuetz et al. *Science* (2012)

Metabolic fluxes are near optimal in multiple objectives.



Schuetz et al. *Science* (2012)

Ribosome design is near optimal.



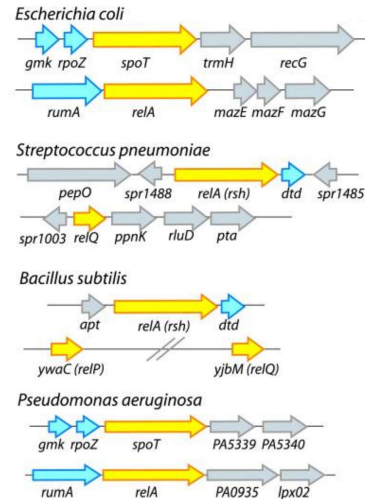
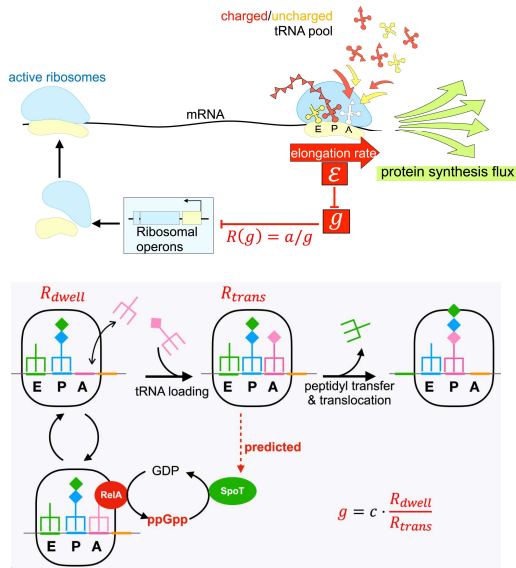
Reuveni et al. *Nature* (2017)

## Summary

- Bacterial growth is approximately optimal at multiple scales:
  - Ribosome design is parallelized.
  - Enzyme levels are regulated and achieve near optimal growth rate.
  - Coarse-grained laws emerge and make parameter-free predictions about growth in diverse scenarios.



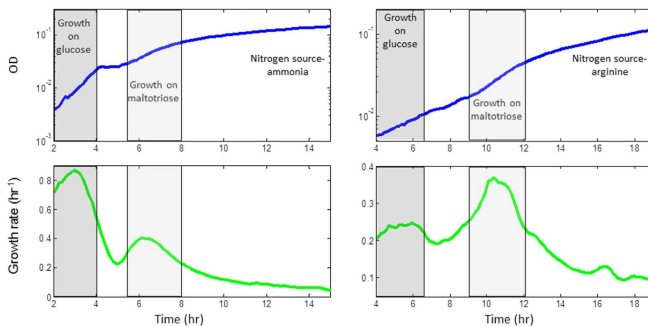
What is generalizable across species? Not the molecular components.



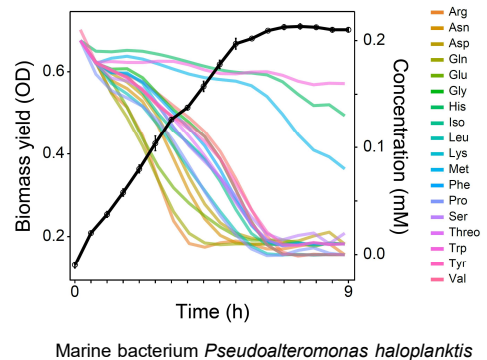
Battesti and Bouveret. *J Bacteriol* (2008)  
Wu et al. *PNAS* (2020)

What is generalizable across species? Not the exact algorithms.

**Two carbon sources and an amino acid**  
Sub-optimality

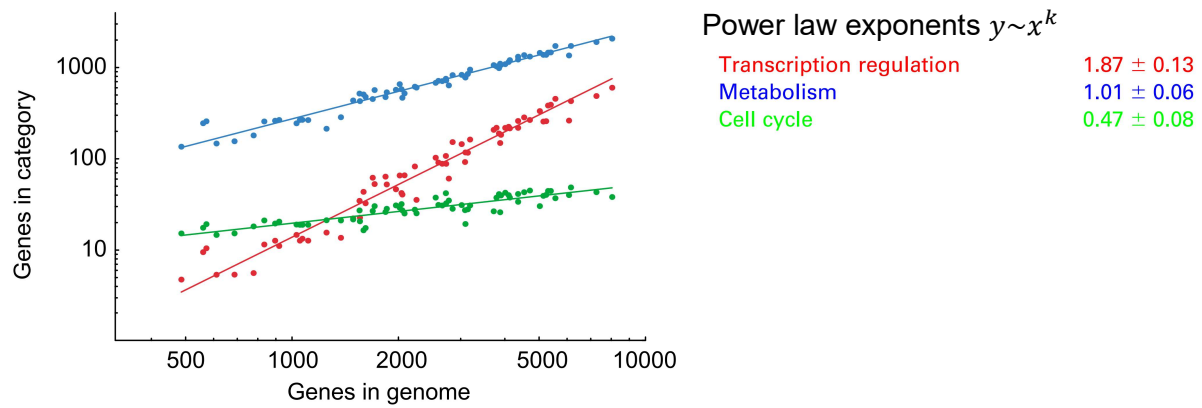


**All amino acids**  
Diauxie + Co-utilization



Bren et al. *Sci Rep* (2016)  
Perrin et al. *Nat Commun* (2020)

What is generalizable across species? Not even the networks themselves.



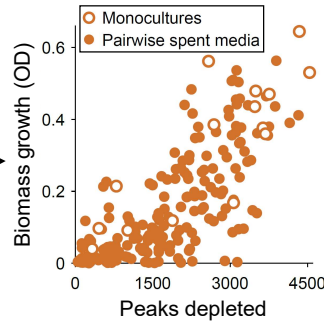
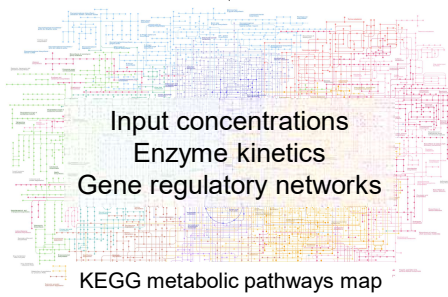
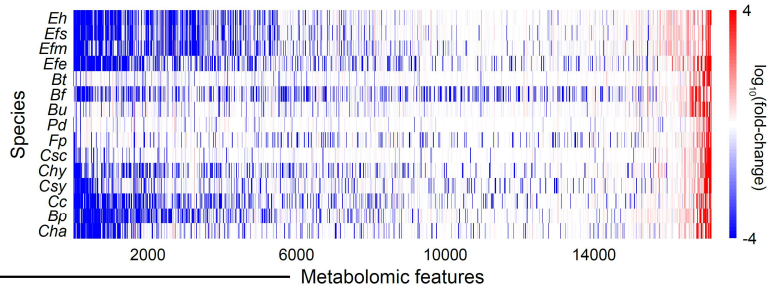
van Nimwegen. *Trends Genet* (2003)

Are there simple rules in bacterial growth across species and environments?

Biomass growth is proportional to the number of nutrients consumed.

Complex growth medium

- *Mimics* in vivo species relative abundances
- *Undefined*: peptone and digested tissue
- *Rich*: saturating amounts

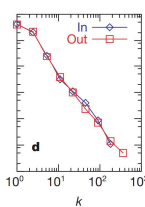
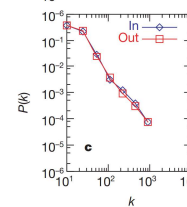
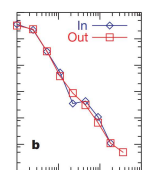
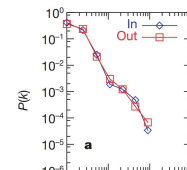
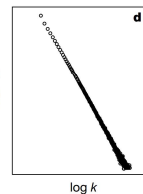
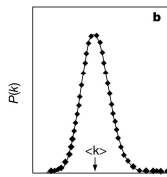
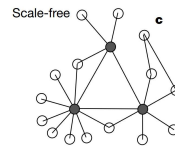
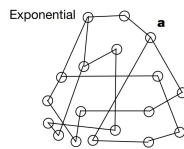
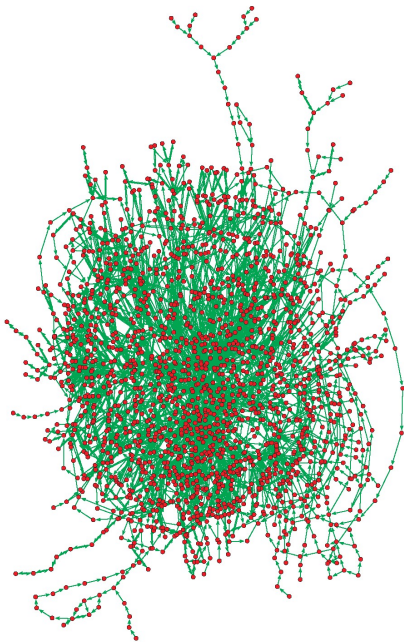


How might simple rules emerge from growth regulation under many nutrients?

Ho et al. *Nat Microbiol* (2024)

What is generalizable across species? Maybe the **network features**?

- Metabolic networks are scale-free. (hubs)

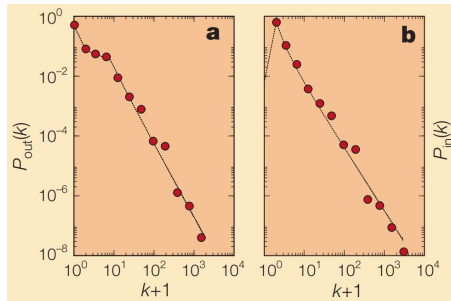


Jeong et al. *Nature* (2000)  
Maslov et al. *PNAS* (2009)

## Detour: Random walks on graphs and eigenvector centrality

- Consider a random surfer,

$$P_{ji} = (1 - d) \frac{1}{N} + d \frac{A_{ji}}{\sum_k A_{jk}}$$



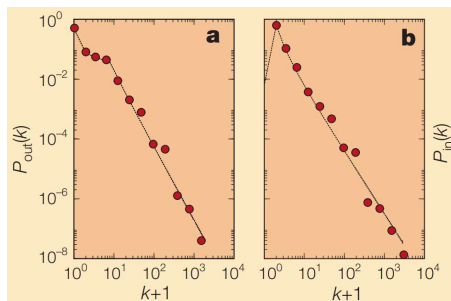
- What is the probability to arrive at a particular page after a large number of clicks?
- Simulate and average over random walks on graphs → Find the eigenvectors of the transition matrix  $P^T$ :

$$v_i^{t+1} = \sum_j v_j^t P_{ji}$$

- By the Perron-Frobenius theorem, the probability distribution is unique and stationary.

Albert et al. *Nature* (1999)

## Detour: Random walks on graphs and eigenvector centrality

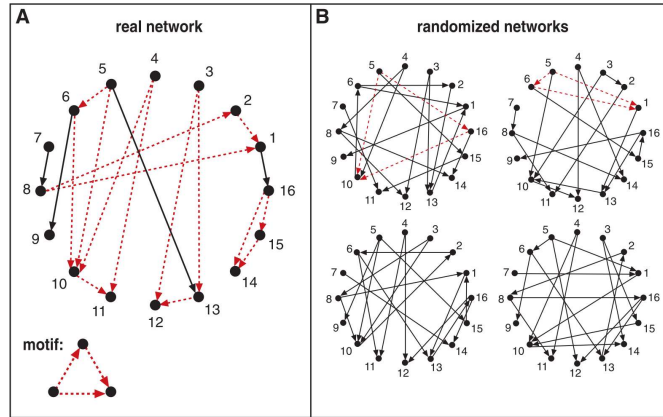
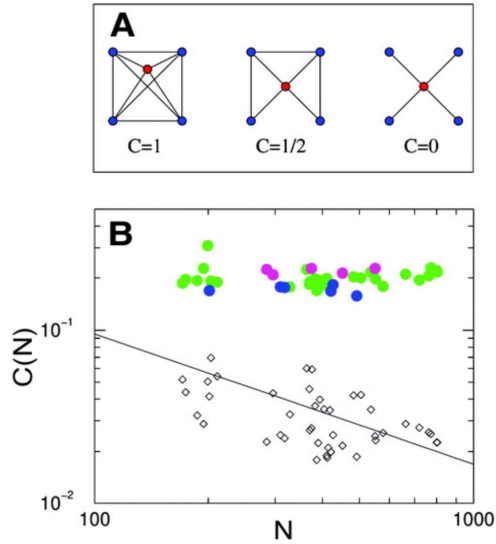


Web Page	PageRank (average is 1.0)
Download Netscape Software	11589.00
<a href="http://www.w3.org/">http://www.w3.org/</a>	10717.70
Welcome to Netscape	8673.51
Point: It's What You're Searching For	7930.92
Web-Counter Home Page	7254.97
The Blue Ribbon Campaign for Online Free Speech	7010.39
CERN Welcome	6562.49
Yahoo!	6561.80
Welcome to Netscape	6203.47
Wusage 4.1: A Usage Statistics System For Web Servers	5963.27
The World Wide Web Consortium (W3C)	5672.21
Lycos, Inc. Home Page	4683.31
Starting Point	4501.98
Welcome to Magellan!	3866.82
Oracle Corporation	3587.63

Page. (1997)  
Albert et al. *Nature* (1999)

What is generalizable across species? Maybe the **network features**?

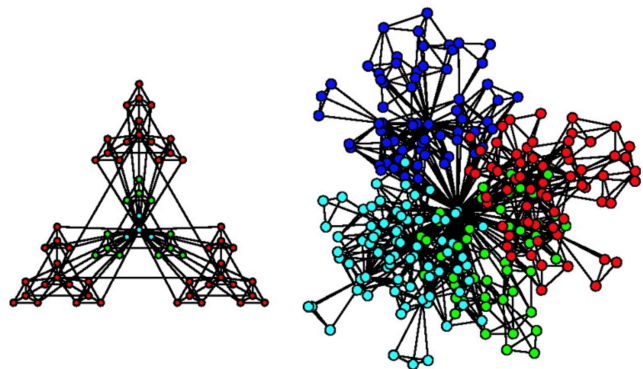
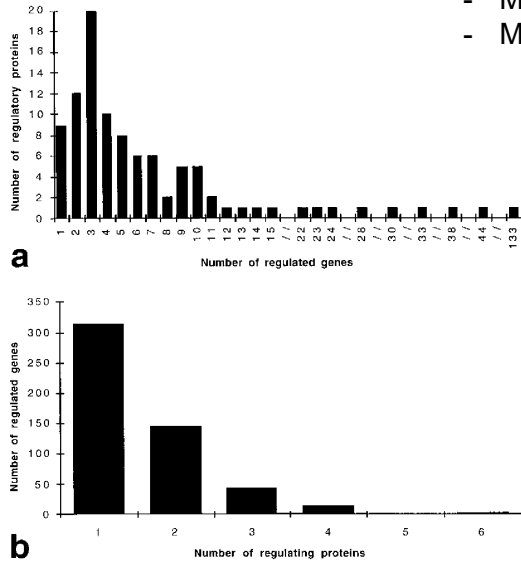
- Metabolic networks are scale-free. (hubs)
- Metabolic networks are modular. (motifs)



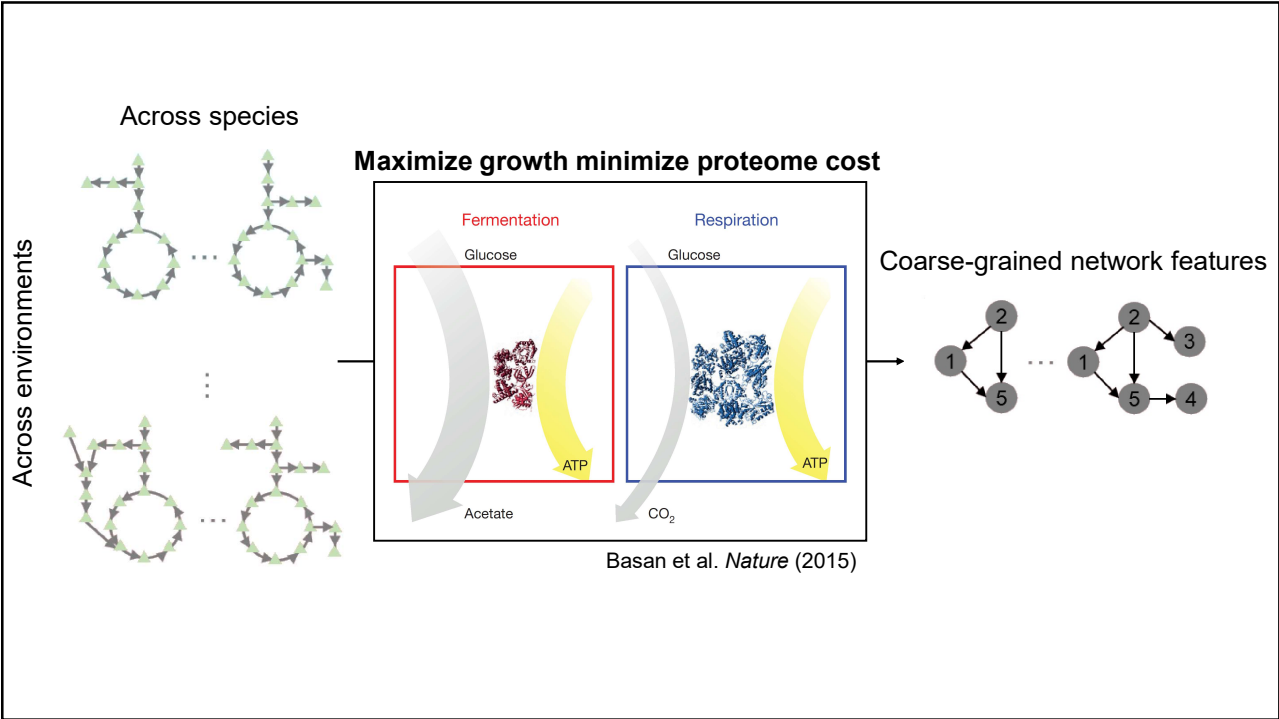
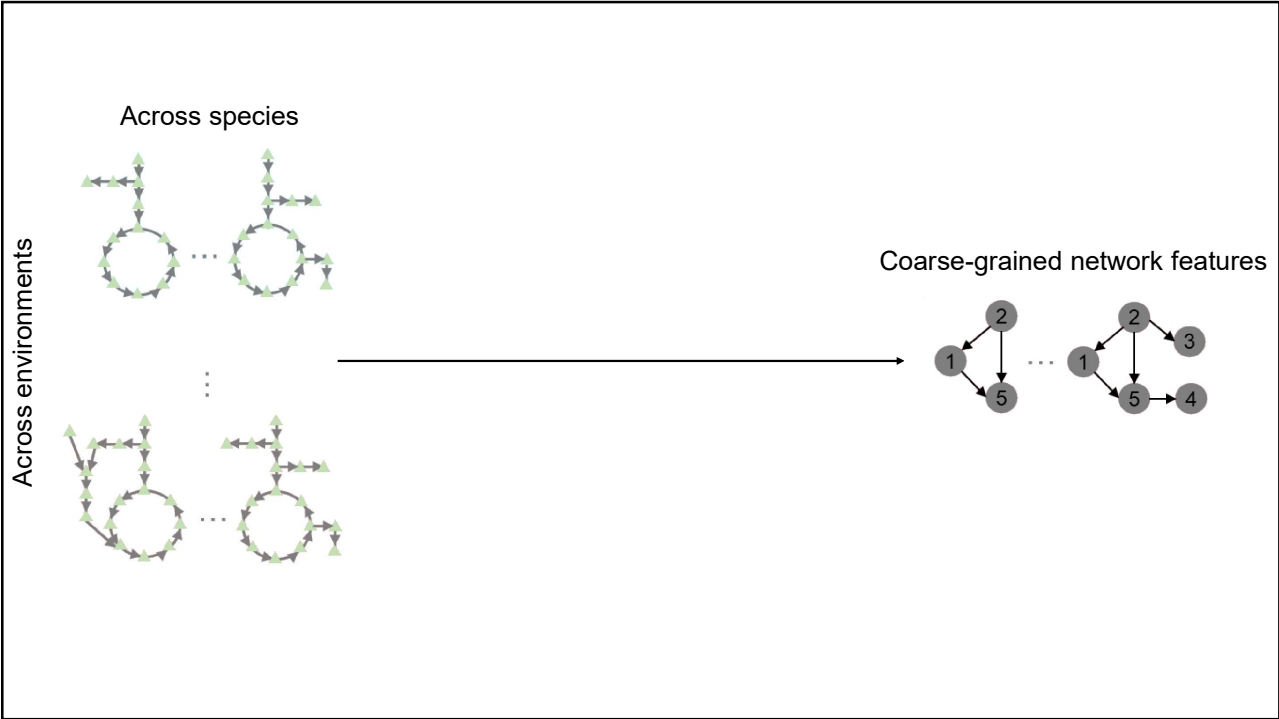
Milo et al. *Science* (2002)  
Ravasz et al. *Science* (2002)

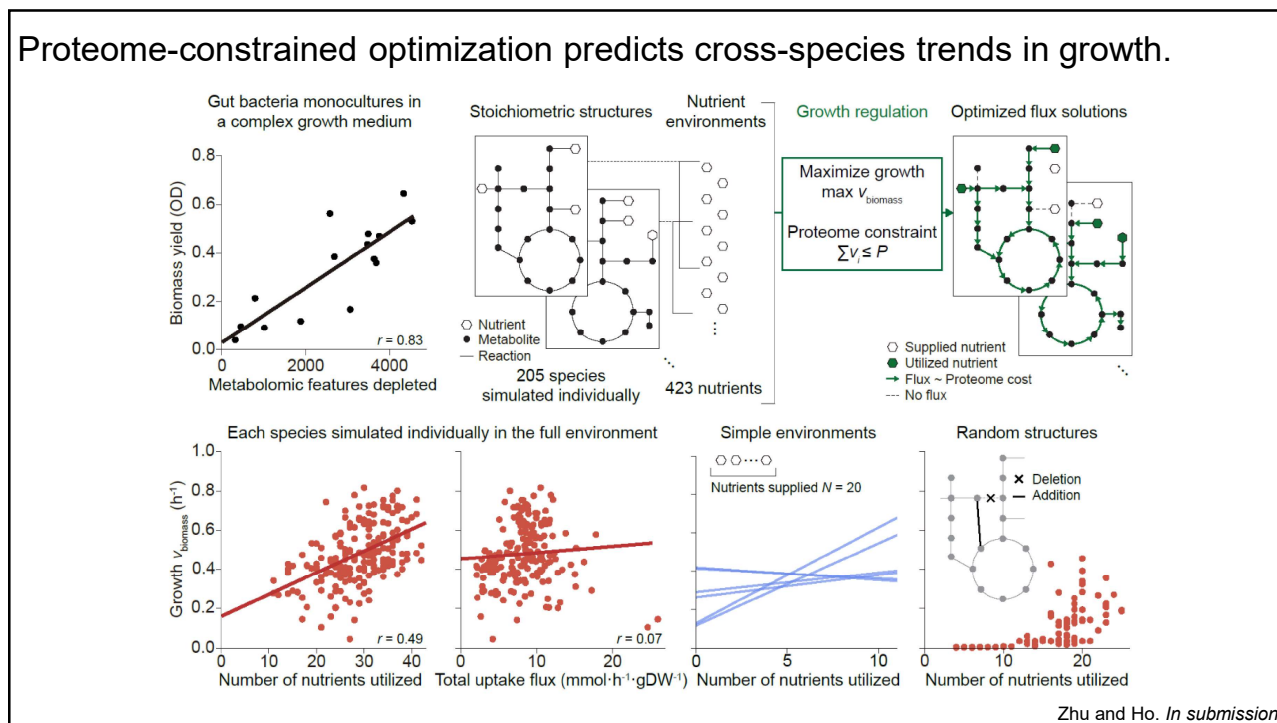
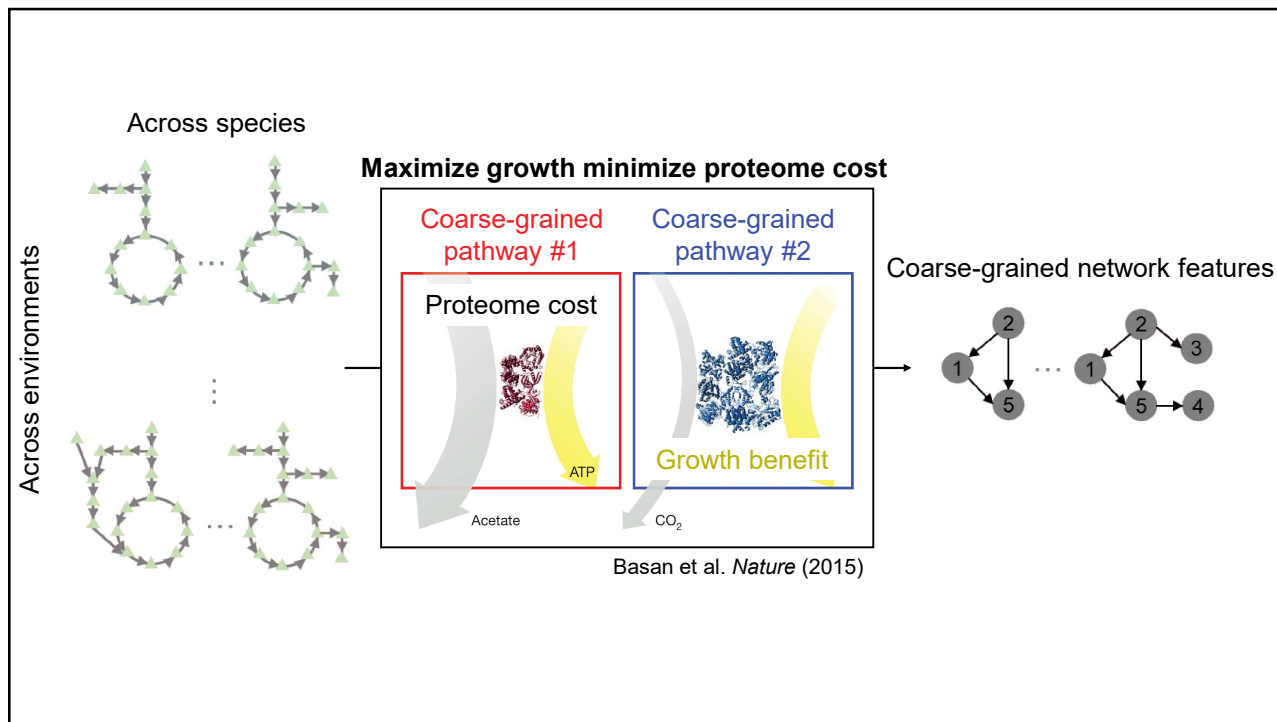
What is generalizable across species? Maybe the **network features**?

- Metabolic networks are scale-free. (hubs)
- Metabolic networks are modular. (motifs)

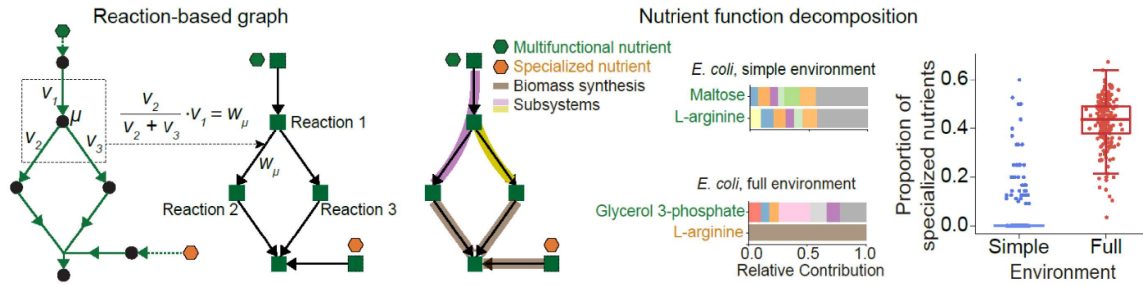


Thieffry et al. *BioEssays* (1998)  
Ravasz et al. *Science* (2002)



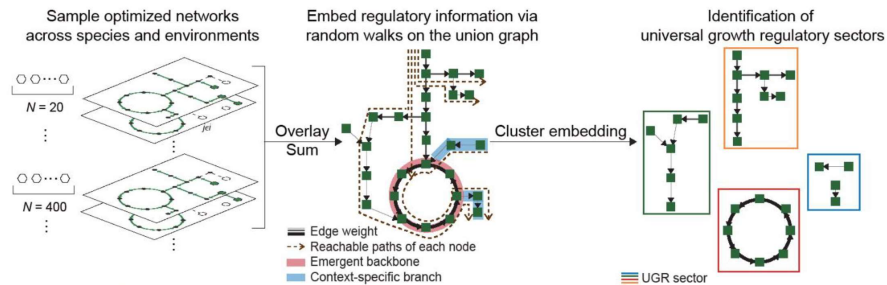


## Division of labor among input nutrients increases in complex environments.



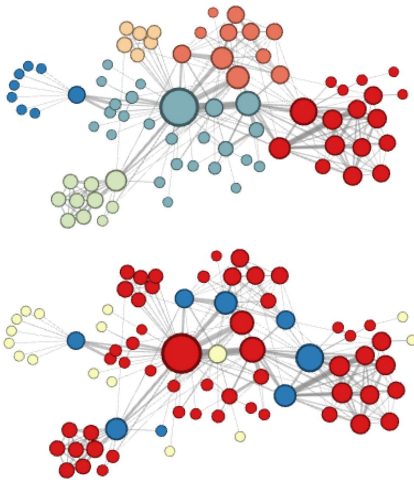
Zhu and Ho. *In submission*

## Coarse-grain metabolic networks via representation learning:



Zhu and Ho. *In submission*

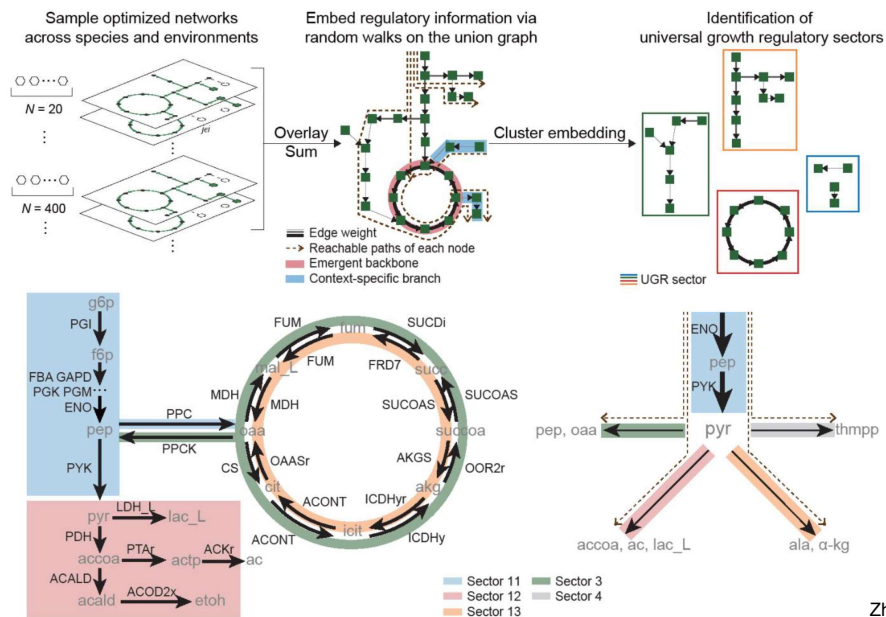
## Detour: Random walks on graphs and flexible neighborhood similarity



- Define the neighborhood  $N(u)$  of a node  $u$  as the collection of nodes sampled via random walks starting from node  $u$ .
- Find a vector representation  $f(u)$  of node  $u$  by maximizing over  $f$  the similarity  $f(n_i) \cdot f(u)$  of the representations of nodes  $n_i \in N(u)$  in the same neighborhood.

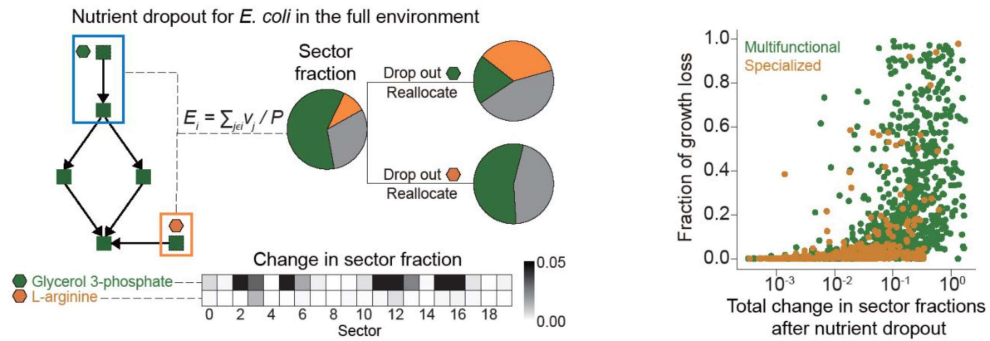
Grover and Leskovec. *arXiv* (2016)

## Coarse-grain metabolic networks via representation learning:



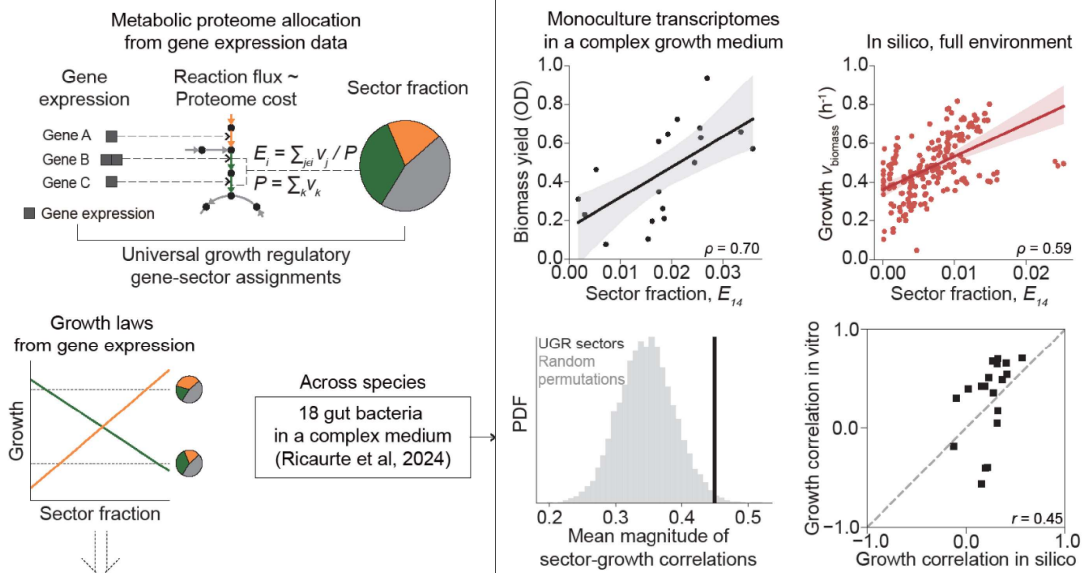
Zhu and Ho. *In submission*

## Coarse-grained sectors link network structure and nutrient function.



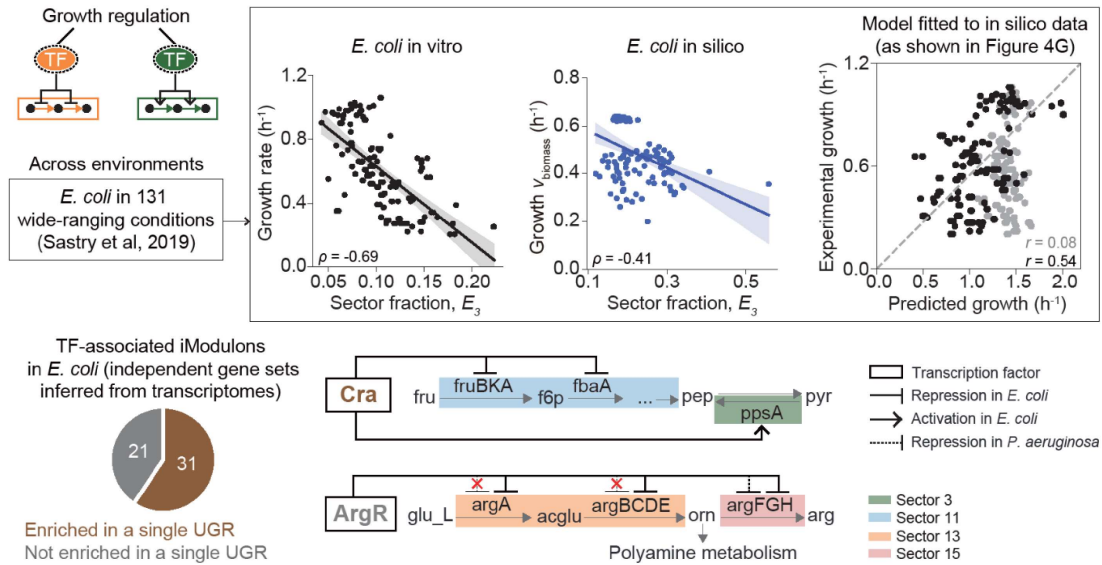
Zhu and Ho. *In submission*

## Coarse-grained sectors reveal growth laws across species.



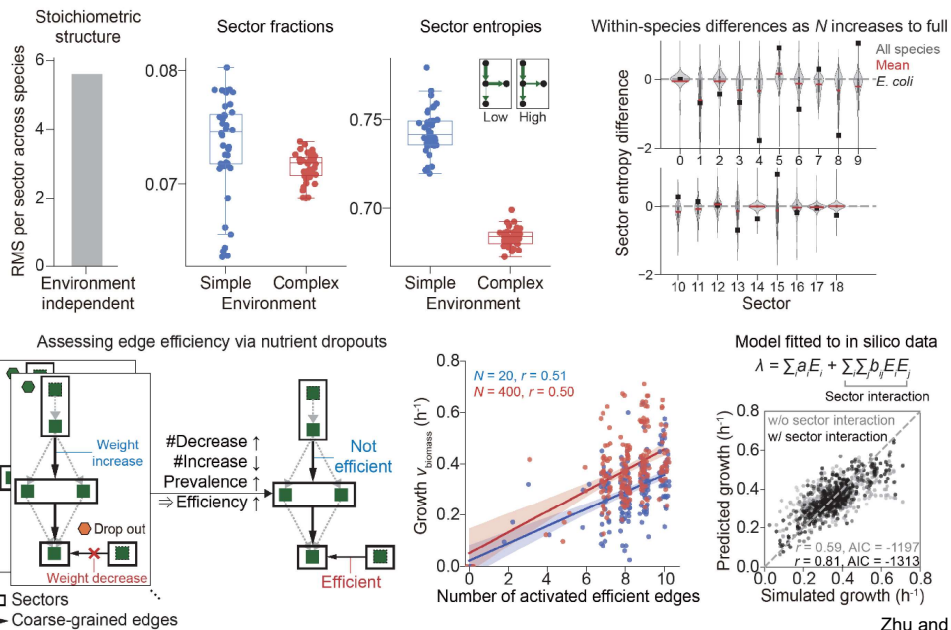
Zhu and Ho. *In submission*

# Coarse-grained sectors reveal growth laws across species and environments.



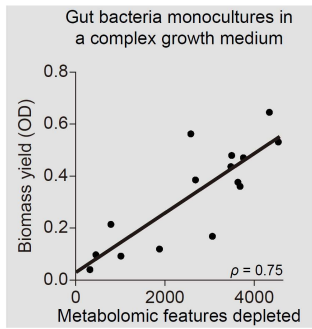
Zhu and Ho. *In submission*

# Coarse-grained network features are key determinants of growth.

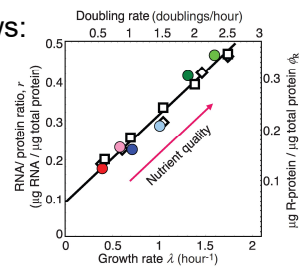


Zhu and Ho. *In submission*

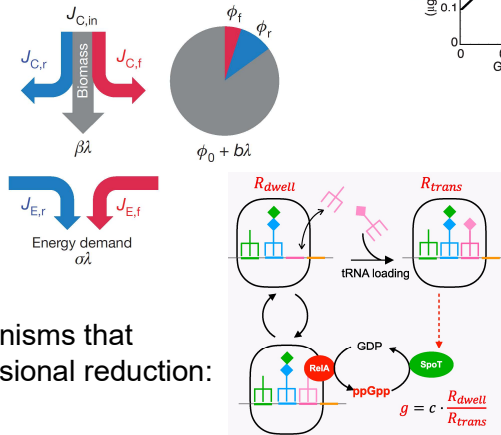
# Bacterial growth laws – from quantitative phenomenon to understanding:



Phenomenological laws:



Coarse-grained models:

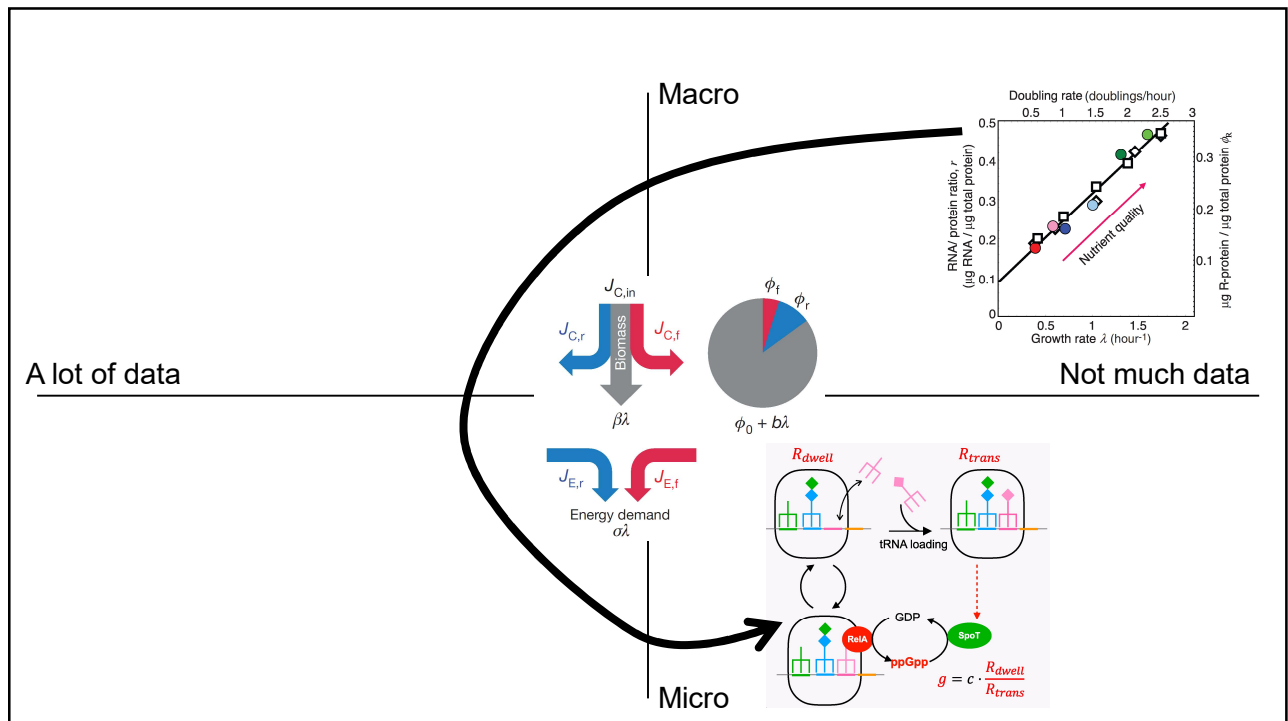


Molecular mechanisms that implement dimensional reduction:

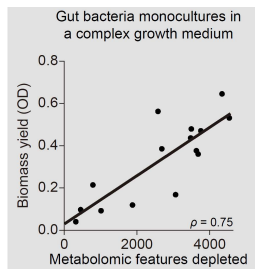
Scott et al. *Science* (2010)  
 Basan et al. *Nature* (2015)  
 Wu et al. *PNAS* (2022)

A lot of data

Not much data

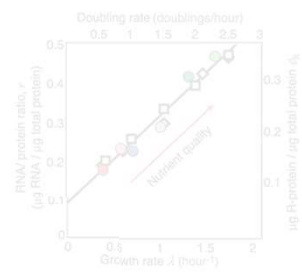
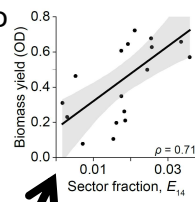


# Biological diversity is a key engine for generating fundamental questions.

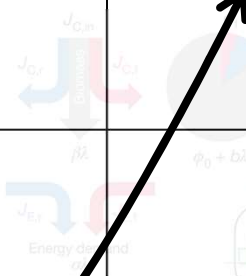
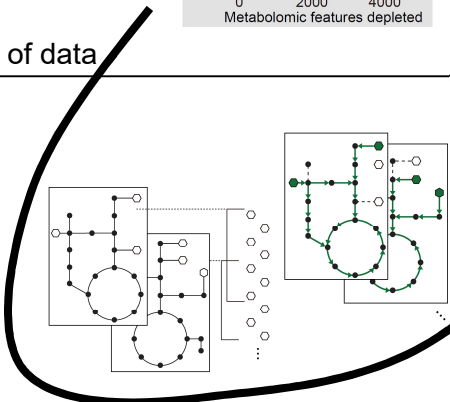


A lot of data

Macro



Not much data



Micro

