

An electrical and thermodynamical view of microbial metabolism

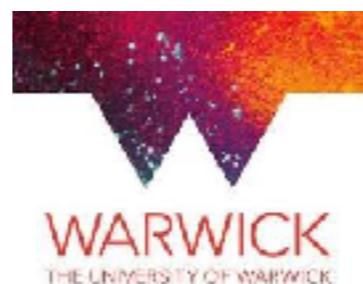
Orkun S Soyer

BEE Workshop
Warwick, 29 May 2018

OSS LAB



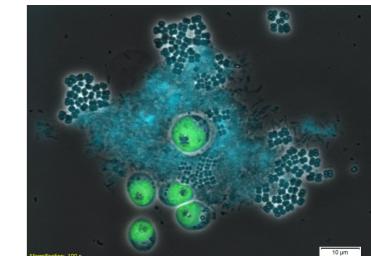
Bio Electrical Engineering
Innovation Hub @ Warwick



? Insights and Applications ?



BOTTOM-UP



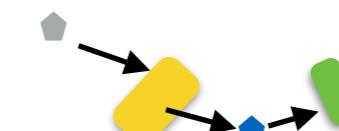
Engineer synthetic communities to learn about biochemical basis of communities

design principles
??

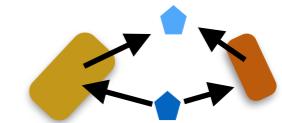


modules

Cross-Feeding



Metabolic Cycles



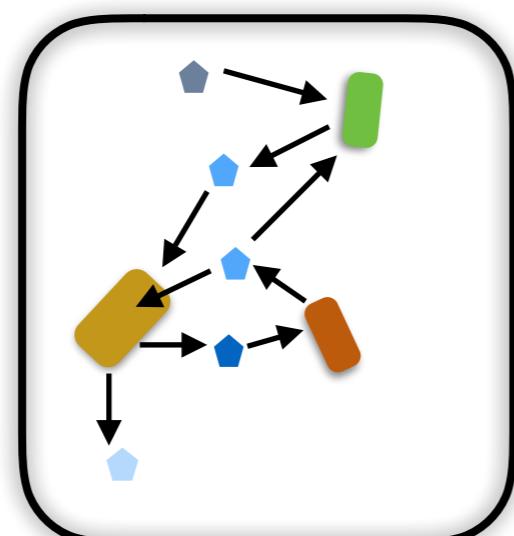
Auxotrophy



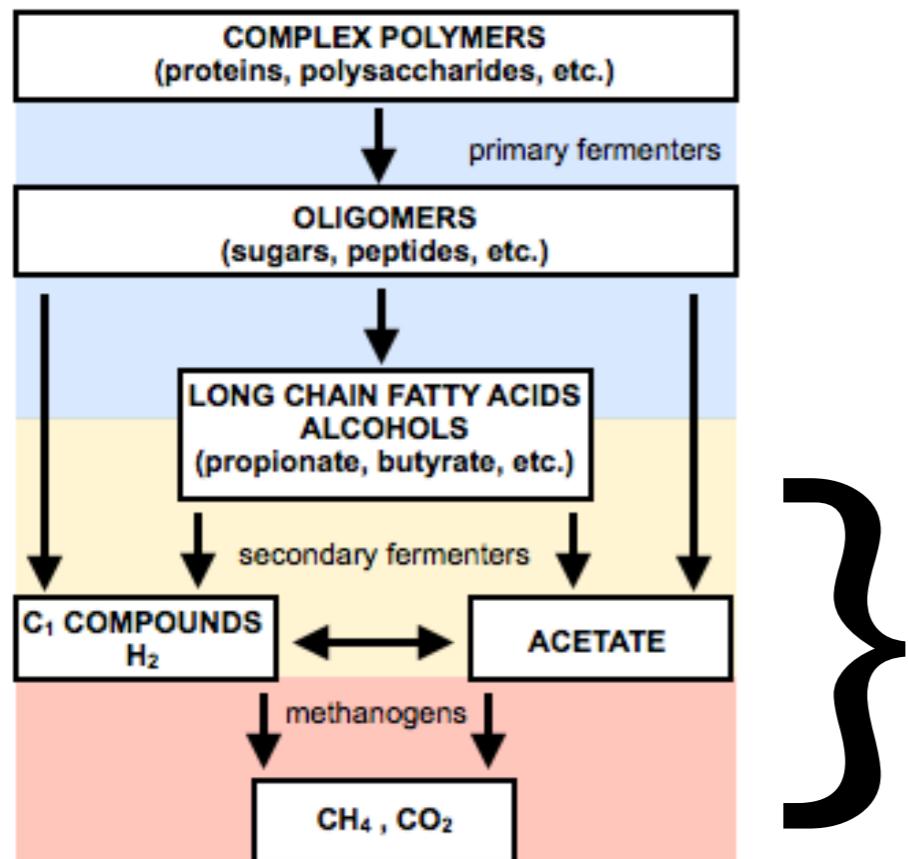
Syntropy



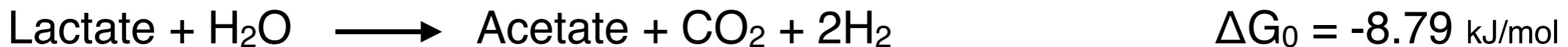
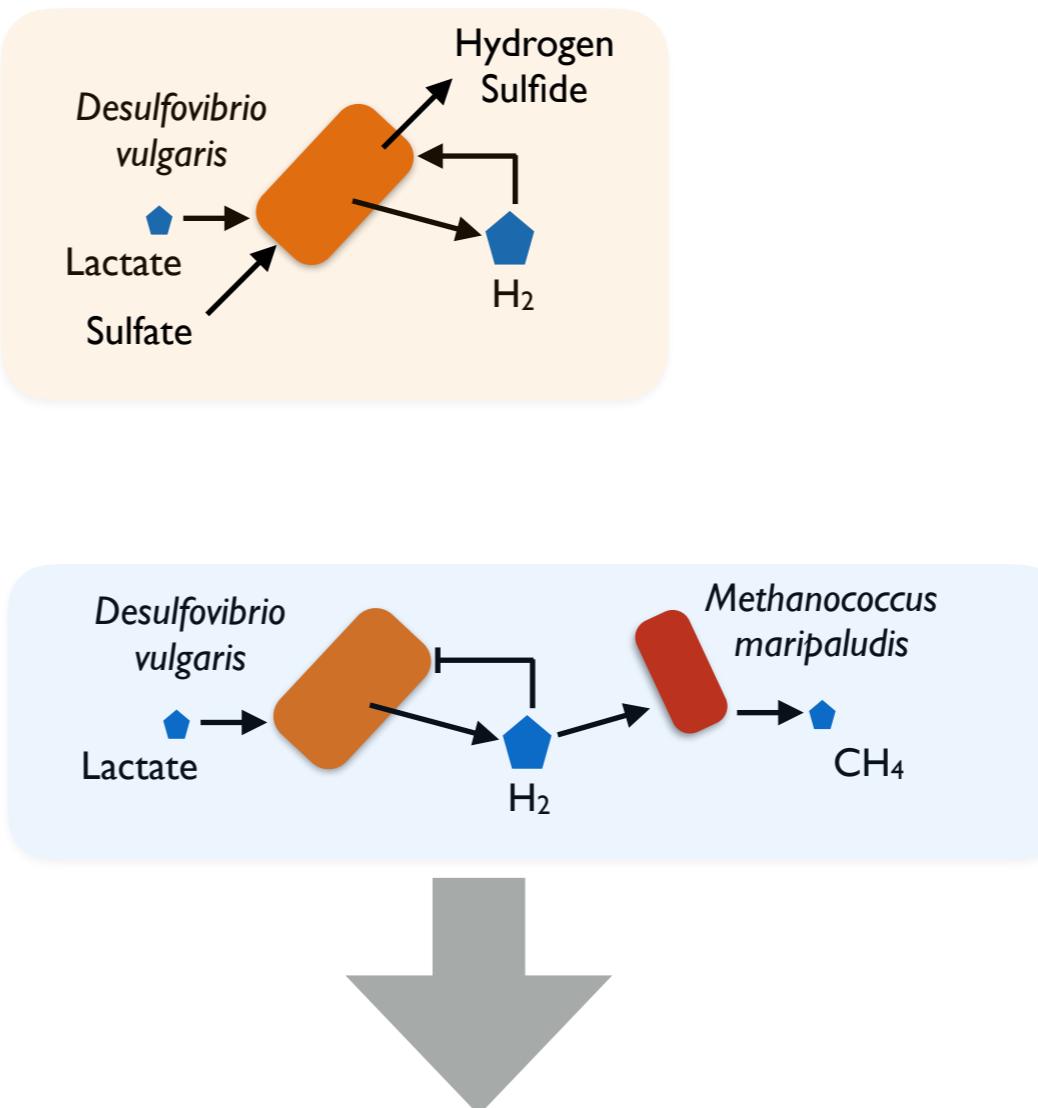
functional systems



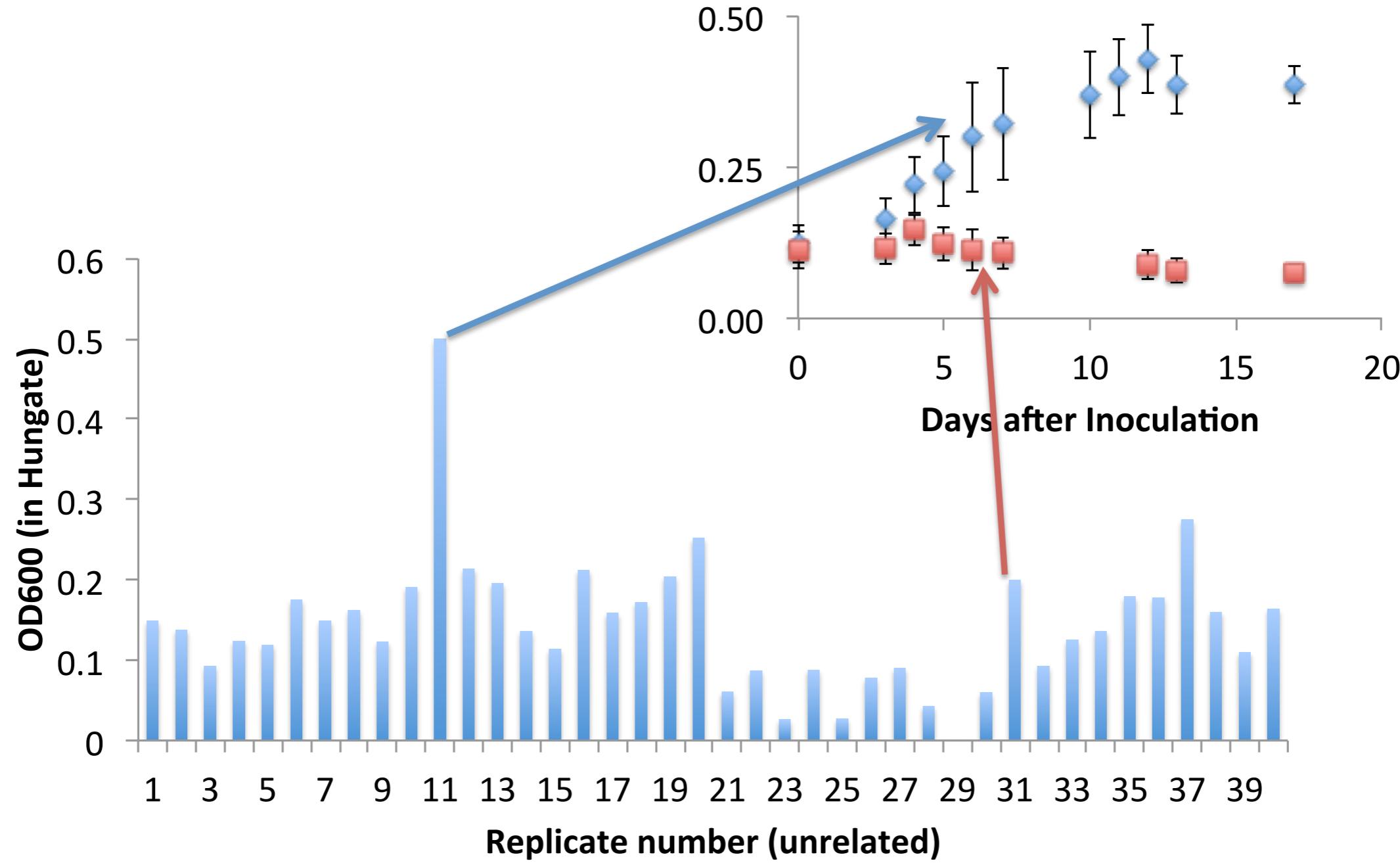
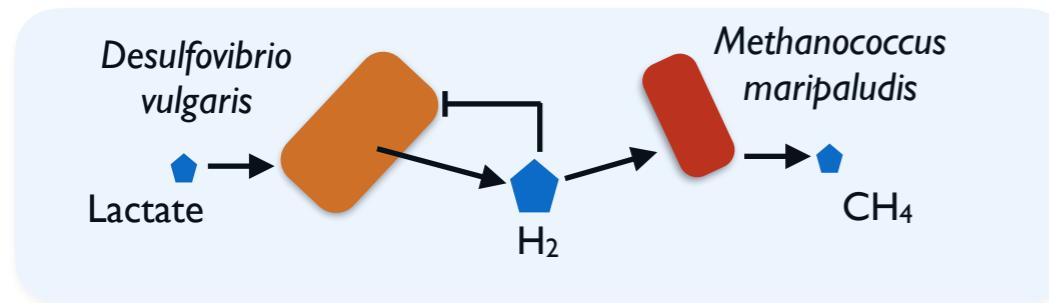
Syntrophy: Crucial in AD systems lacking strong terminal electron acceptors (TEAs)



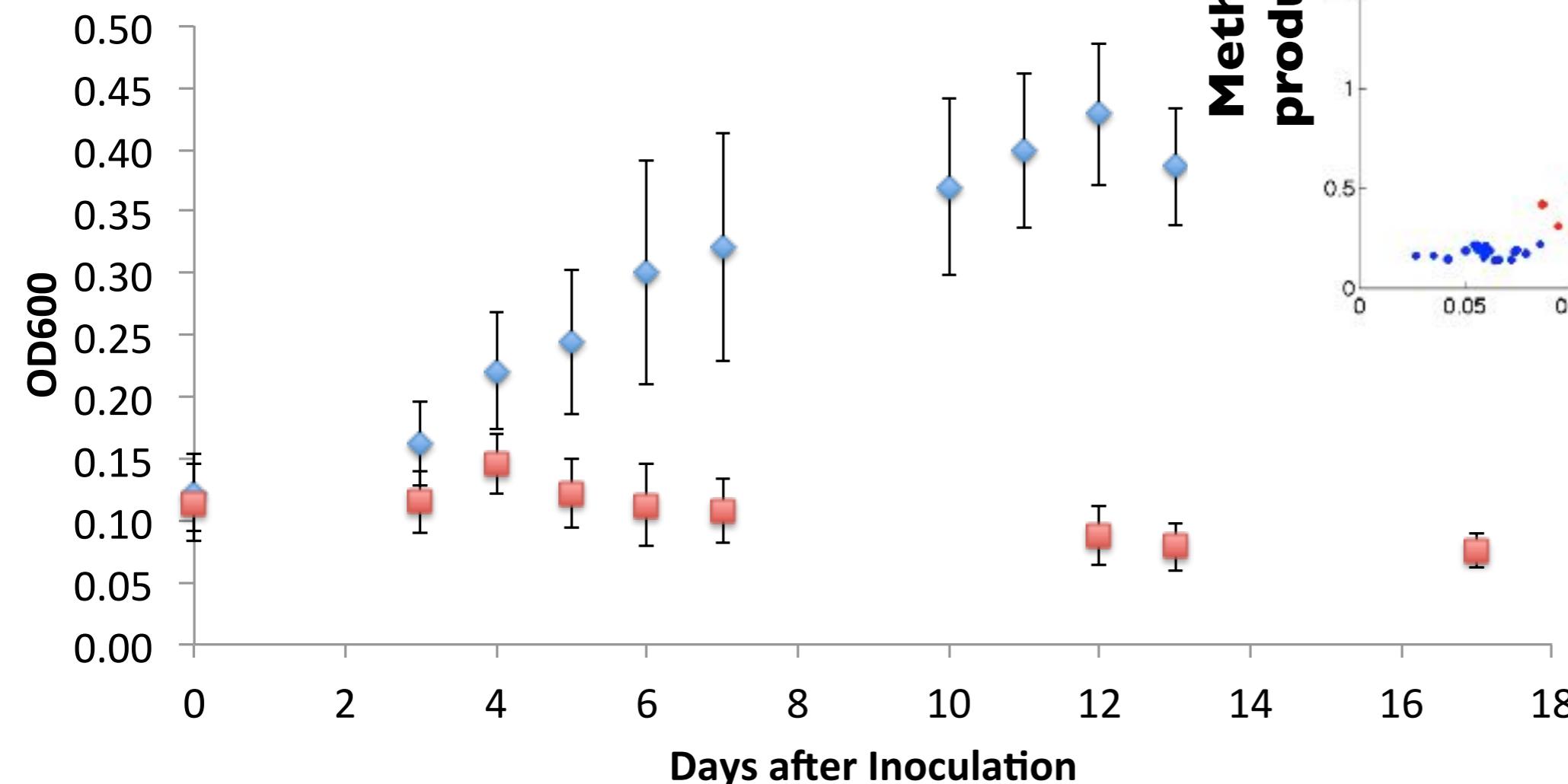
Schink B *Microbiol Mol Biol Rev* 61:2 (1997)



Does syntropy impact individual species' evolution?

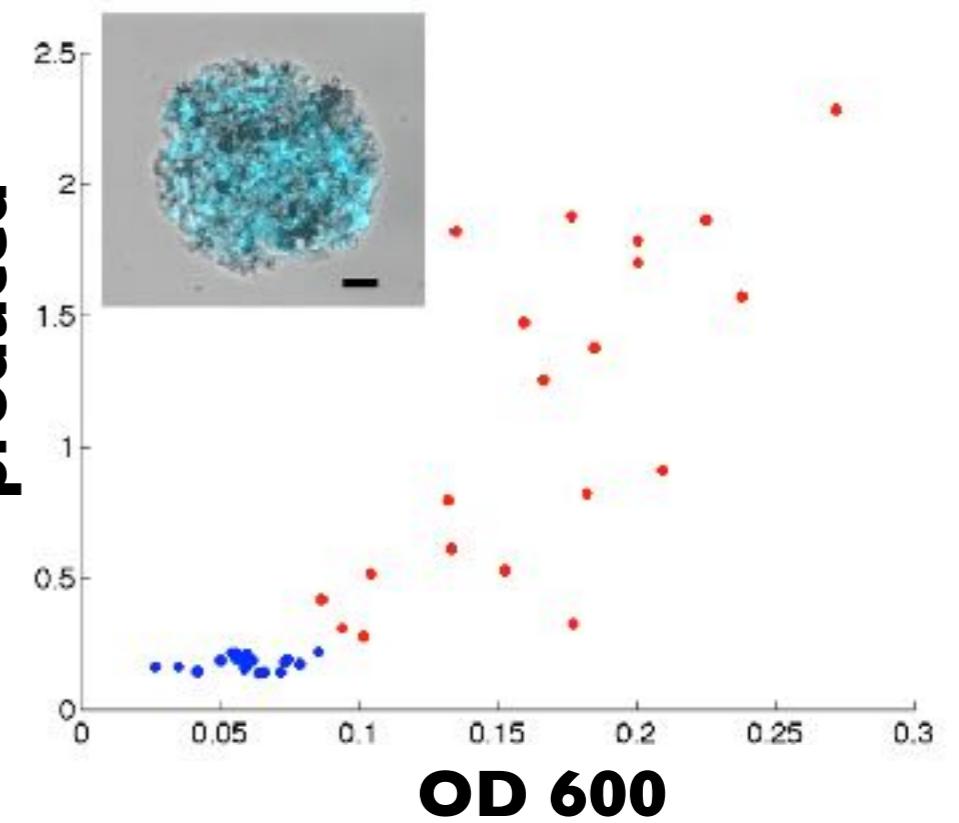


Isolates from co-culture are consistently “syntrophic”, while those from wild type are not



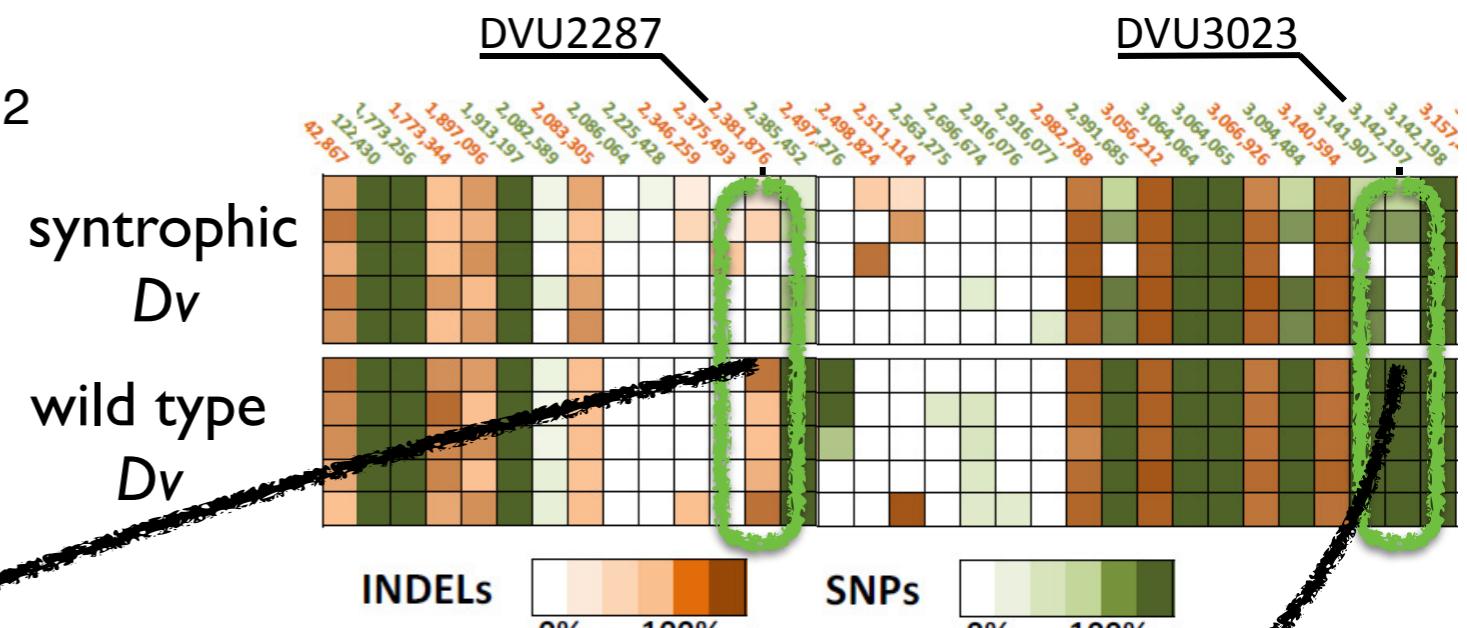
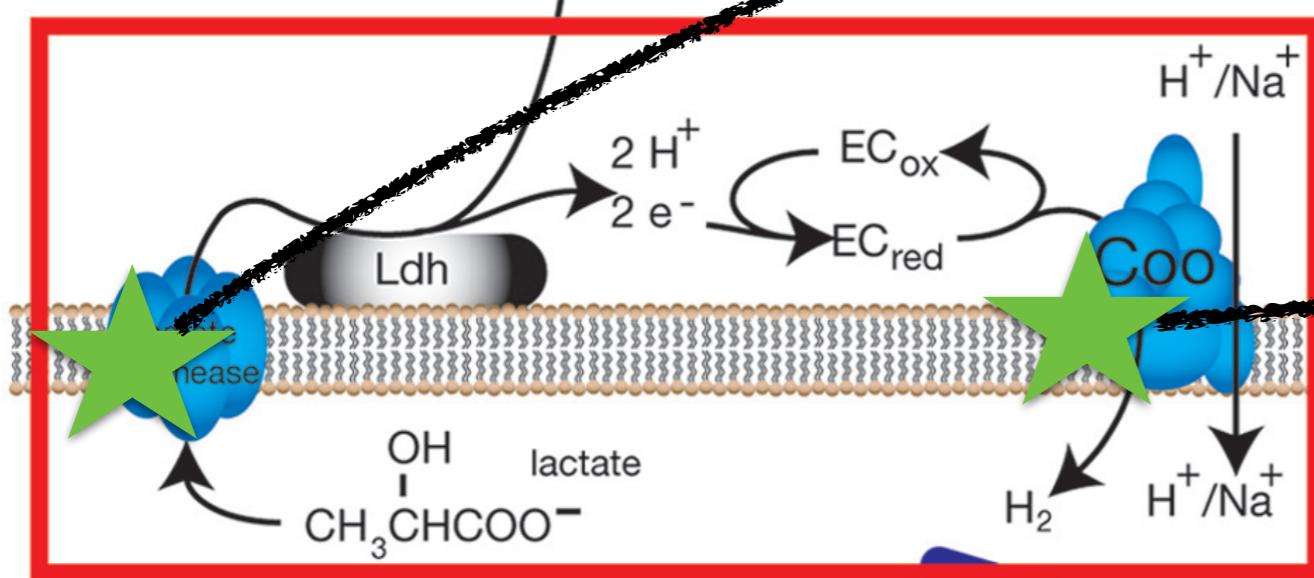
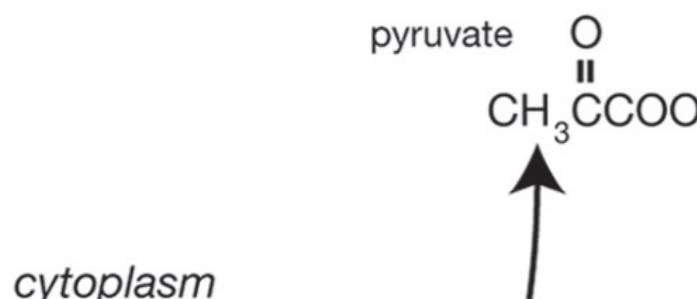
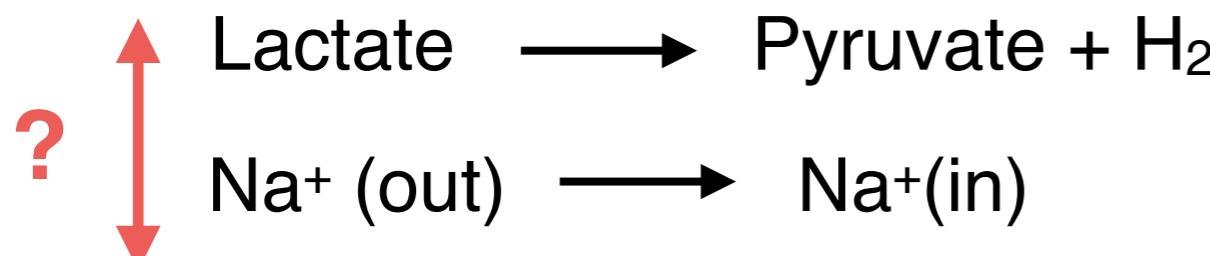
◆ Co-cultures using
isolate from
working co-culture

■ Co-cultures using
isolate from *Dv*
stock culture



Thermodynamics basis for genetic drivers of syntropy

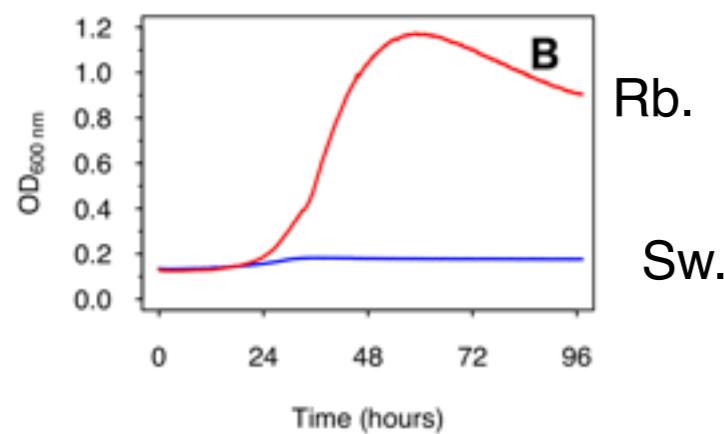
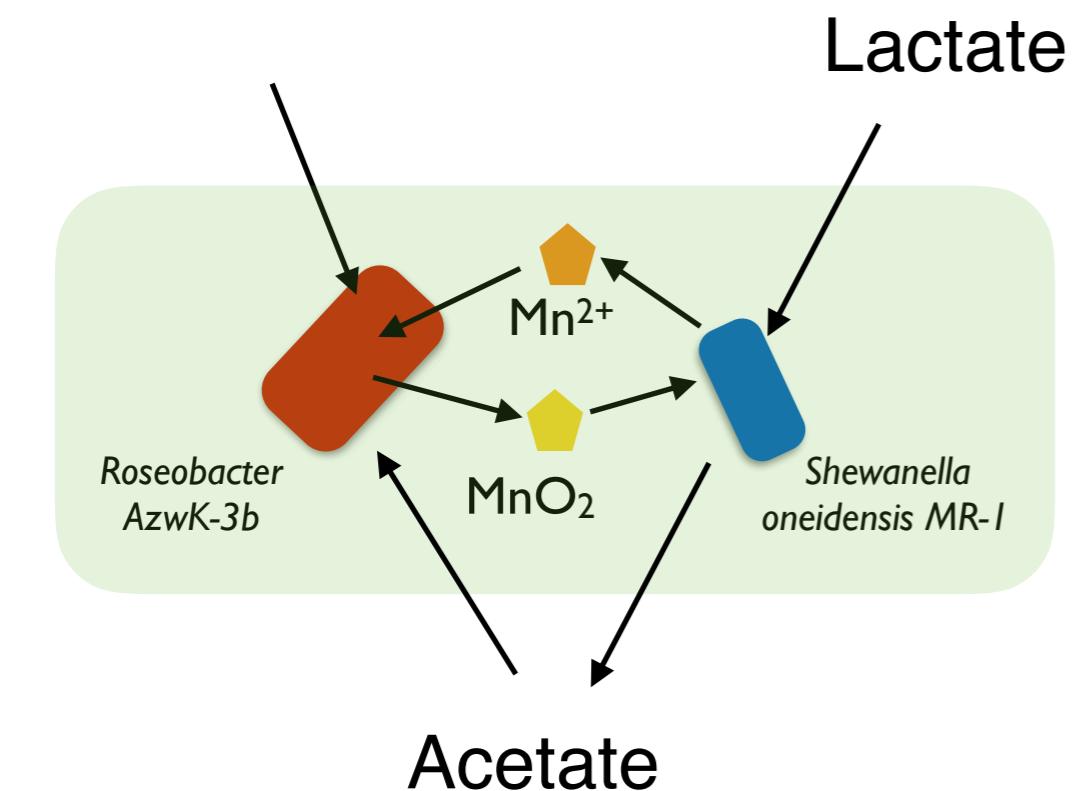
The syntropy enabling mutation allows energy investment to overcome thermodynamic hurdle:



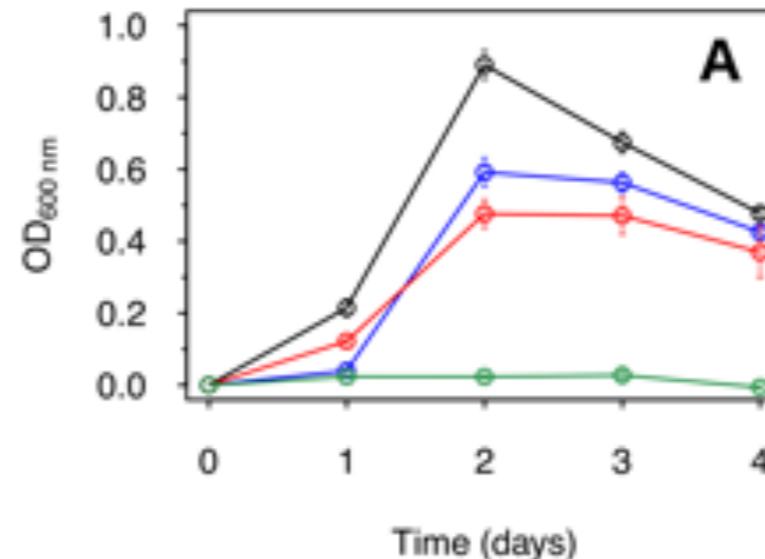
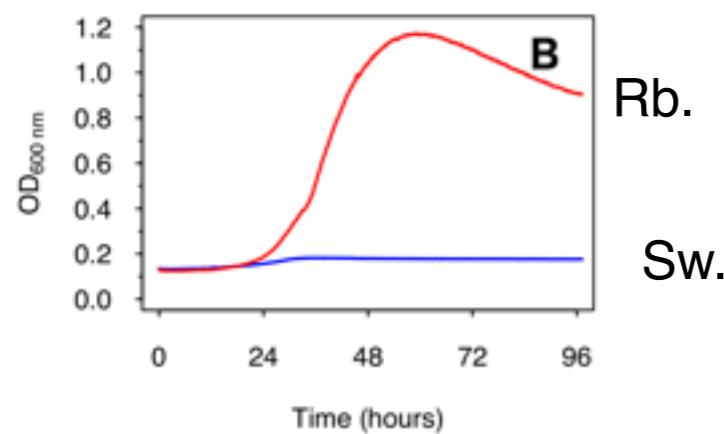
Lack of strong TEAs can enforce thermodynamic inhibition (i.e. redox reactions at the brink of energetic feasibility)

This limitation can be a key driver of evolution of metabolic systems (intra- and inter-cellular)

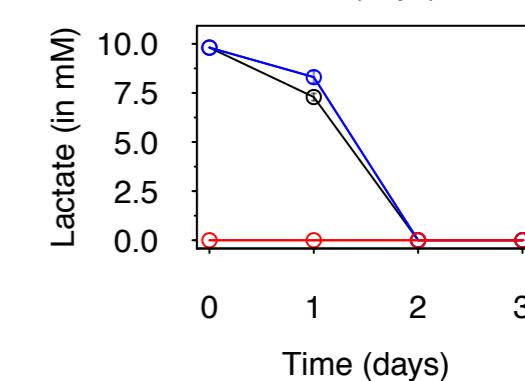
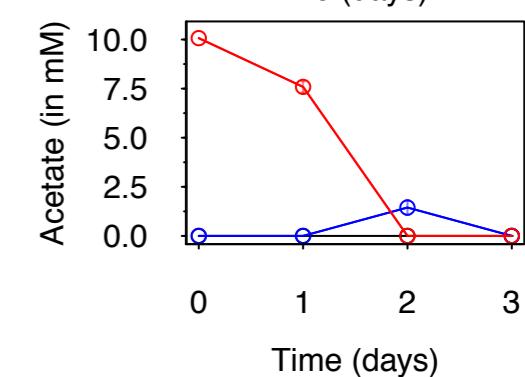
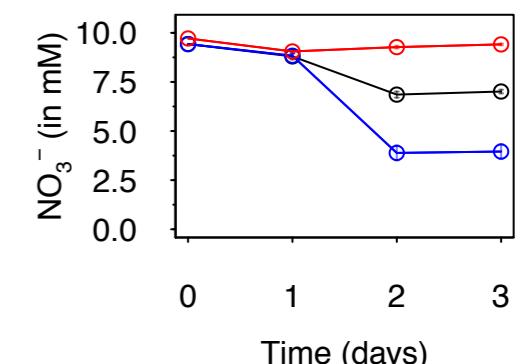
Cross-feeding: Even in the presence of TEAs!



Sw.



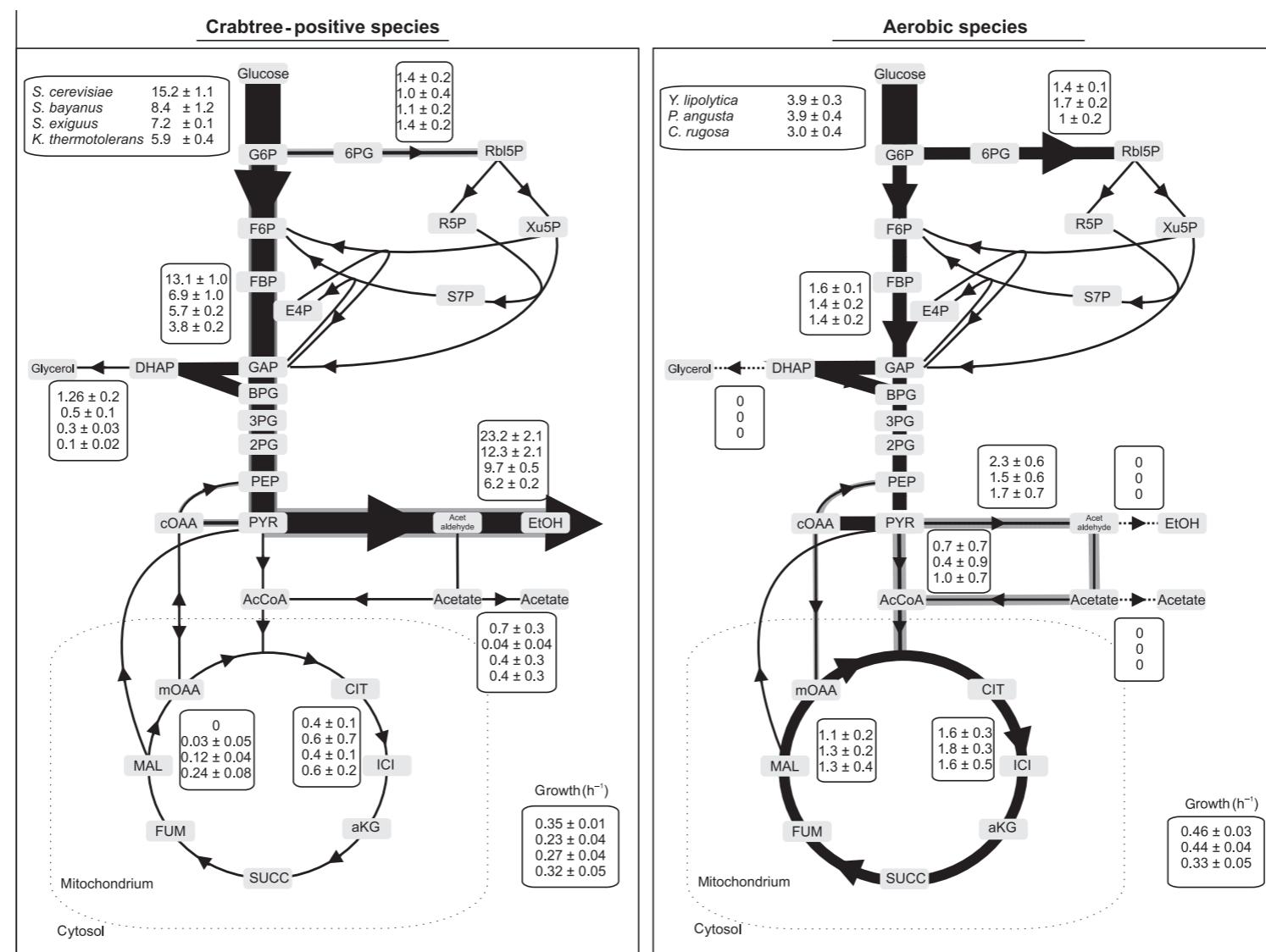
Cross-feeding allowing direct interaction in a bi-culture



Individual growth in bi-culture further confirmed by selective plating

Cross-feeding: Arising from metabolic overflow

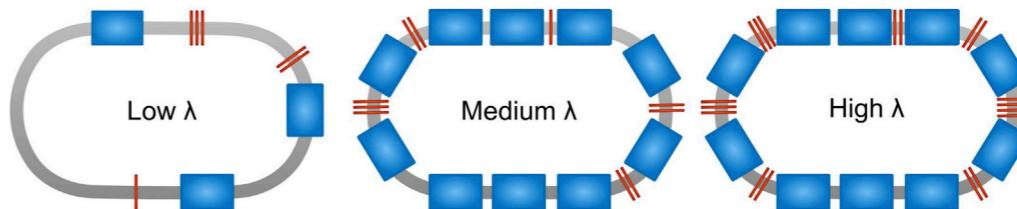
Cross-feeding can arise from ‘overflow metabolism’ (a.k.a Warburg effect and Crabtree effect in cancer and yeast cells). Seem to be present in all cells where it is studied.



Trade-offs in cellular metabolism could explain overflow metabolism (and cross feeding?)

Trade-offs in space/enzyme allocation

Szenk M, Dill KA, de Graaf AMR, *Cell Systems* 5 (2017)

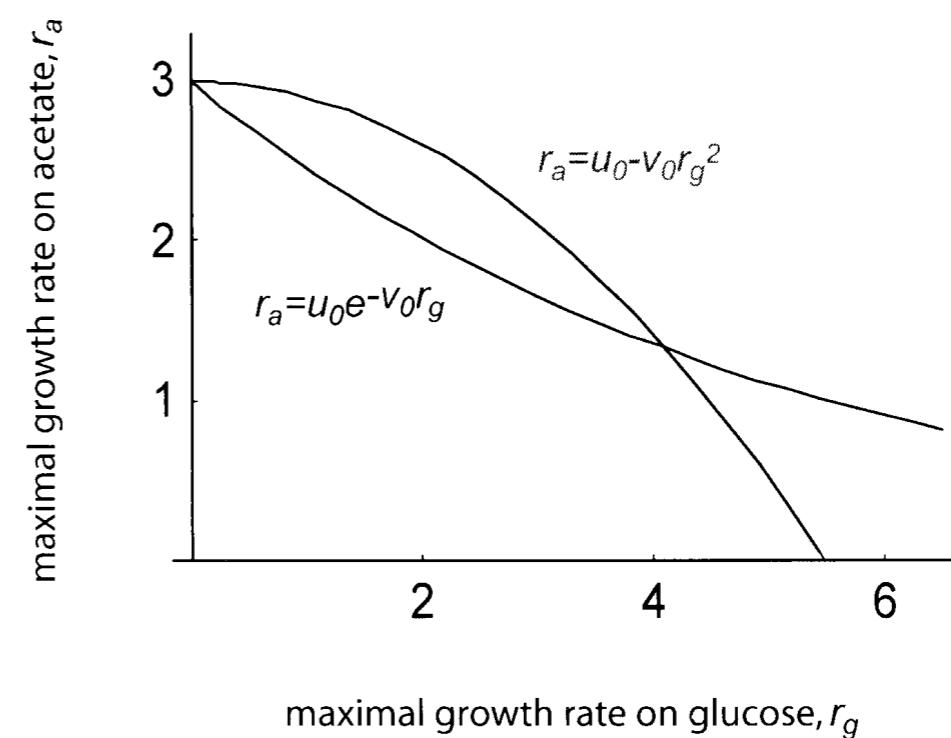


Costly intermediates and enzymes

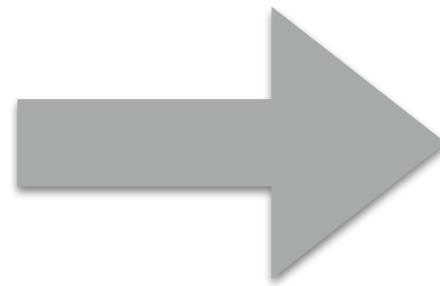
Pfeiffer T & Bonhoeffer S, *Curr. Am. Nat.* 163:6 (2004)

Trade-offs in substrate-based growth rates

Doebeli M, *Pop. Ecology* 44:2 (2002)



Can trade-offs lead to the evolution of cross-feeding?

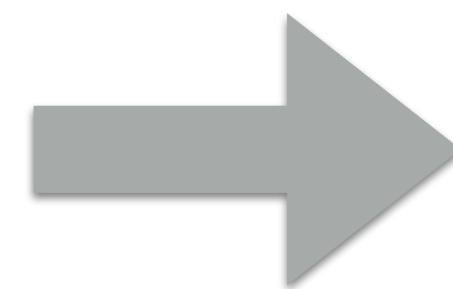
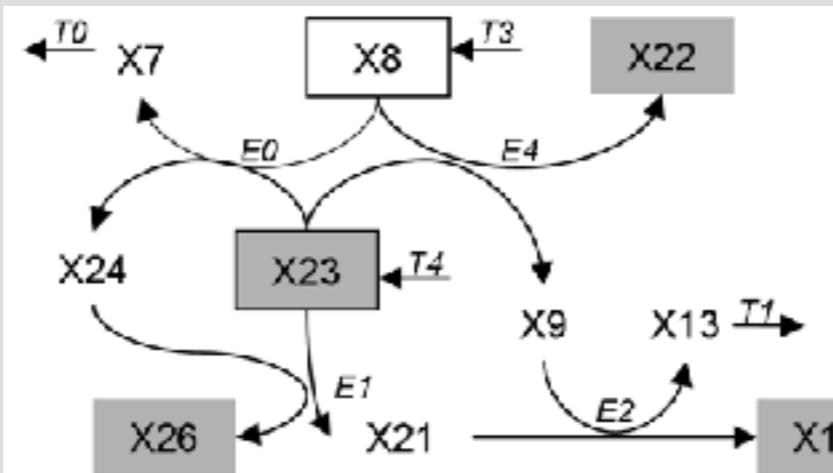


Constrain
substrate input

Assume steady
state

Create additional
constraints for
internal fluxes

FBA



Optimise for
“pseudoreaction”
mimicking cell
biomass

$$\frac{d[X]}{dt} = S \cdot r$$

$$0 = S \cdot r$$

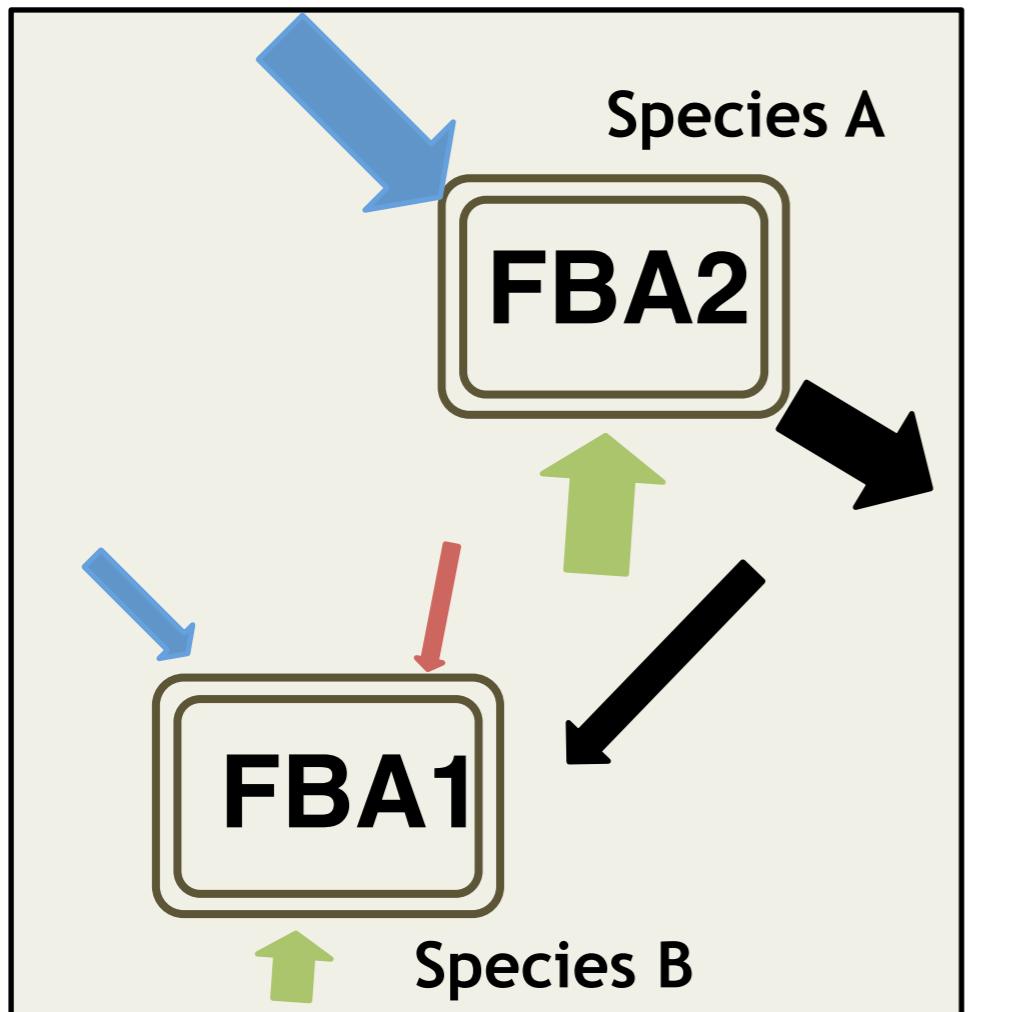
$$\alpha_i \leq r_i \leq \beta_i$$

$$c \cdot r = \text{Max!}$$

Can trade-offs lead to the evolution of cross-feeding?

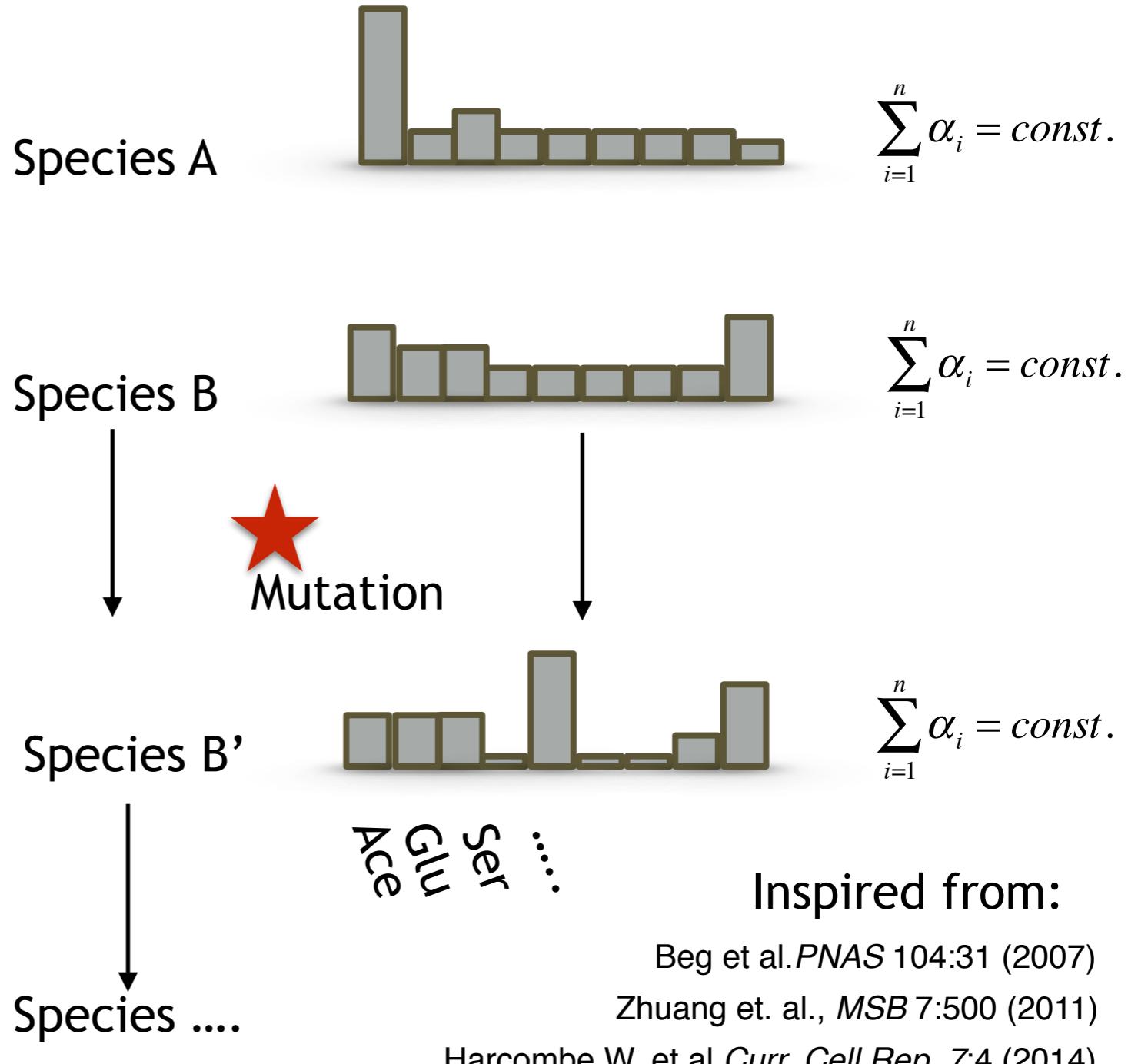
EvoFBA

available to download

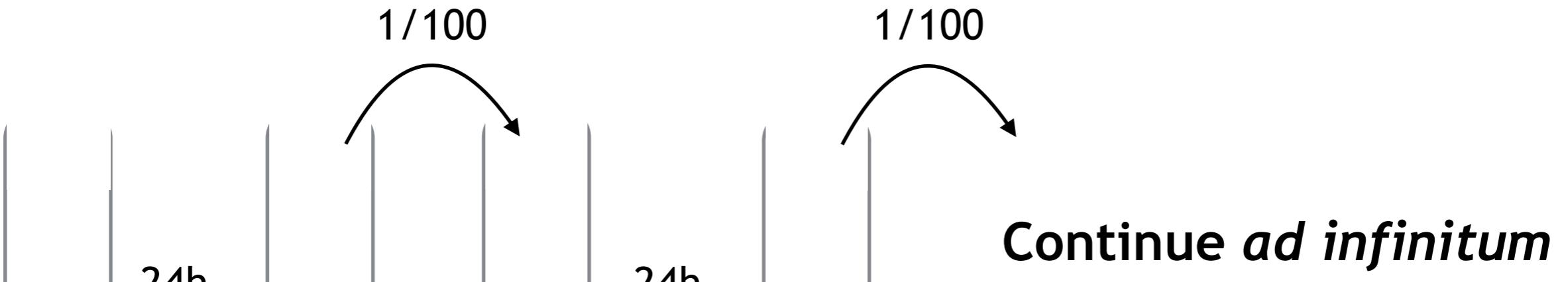


Continue ad
infinitum

Uptake Reaction Bounds



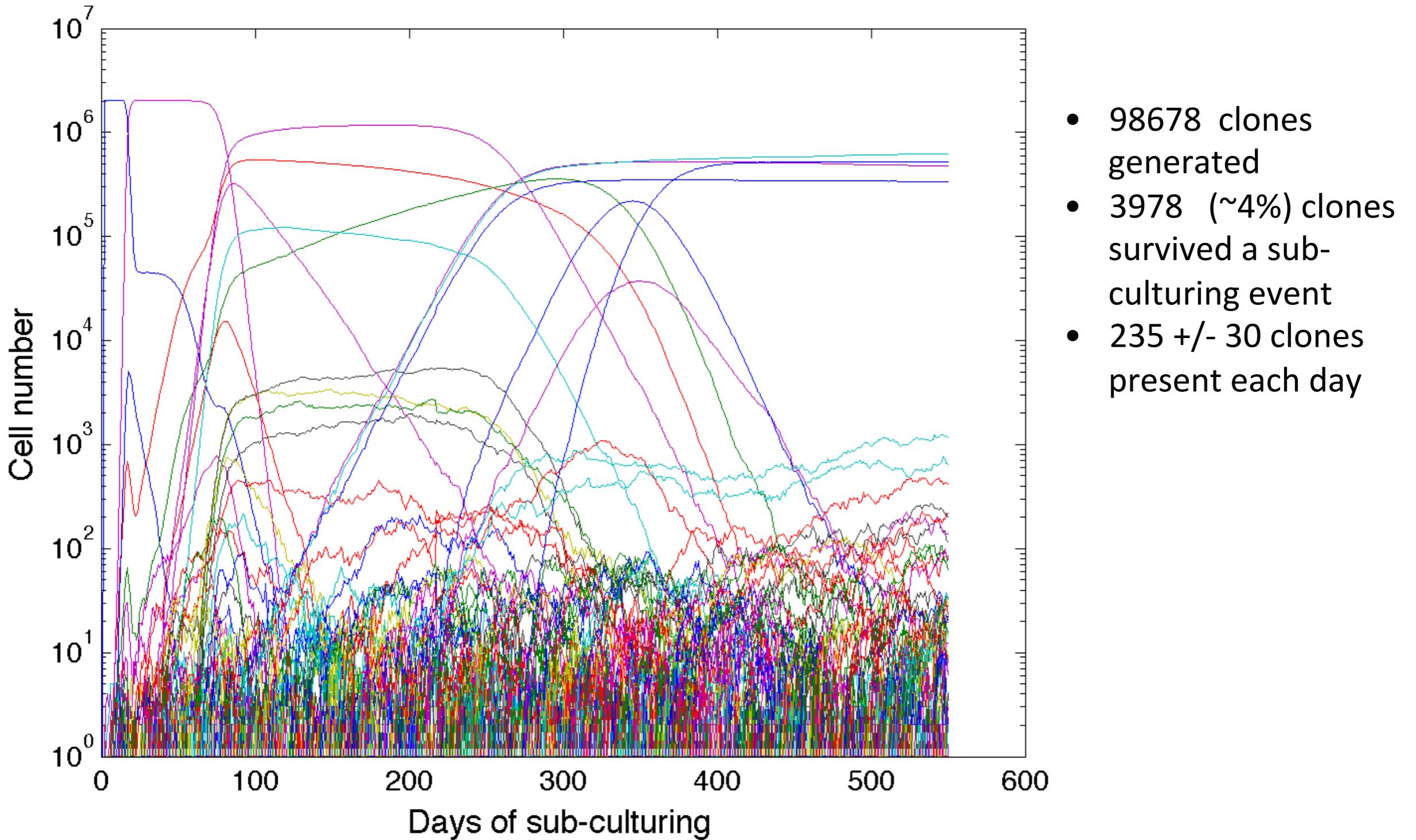
Directed evolution of *E.coli* using EvoFBA



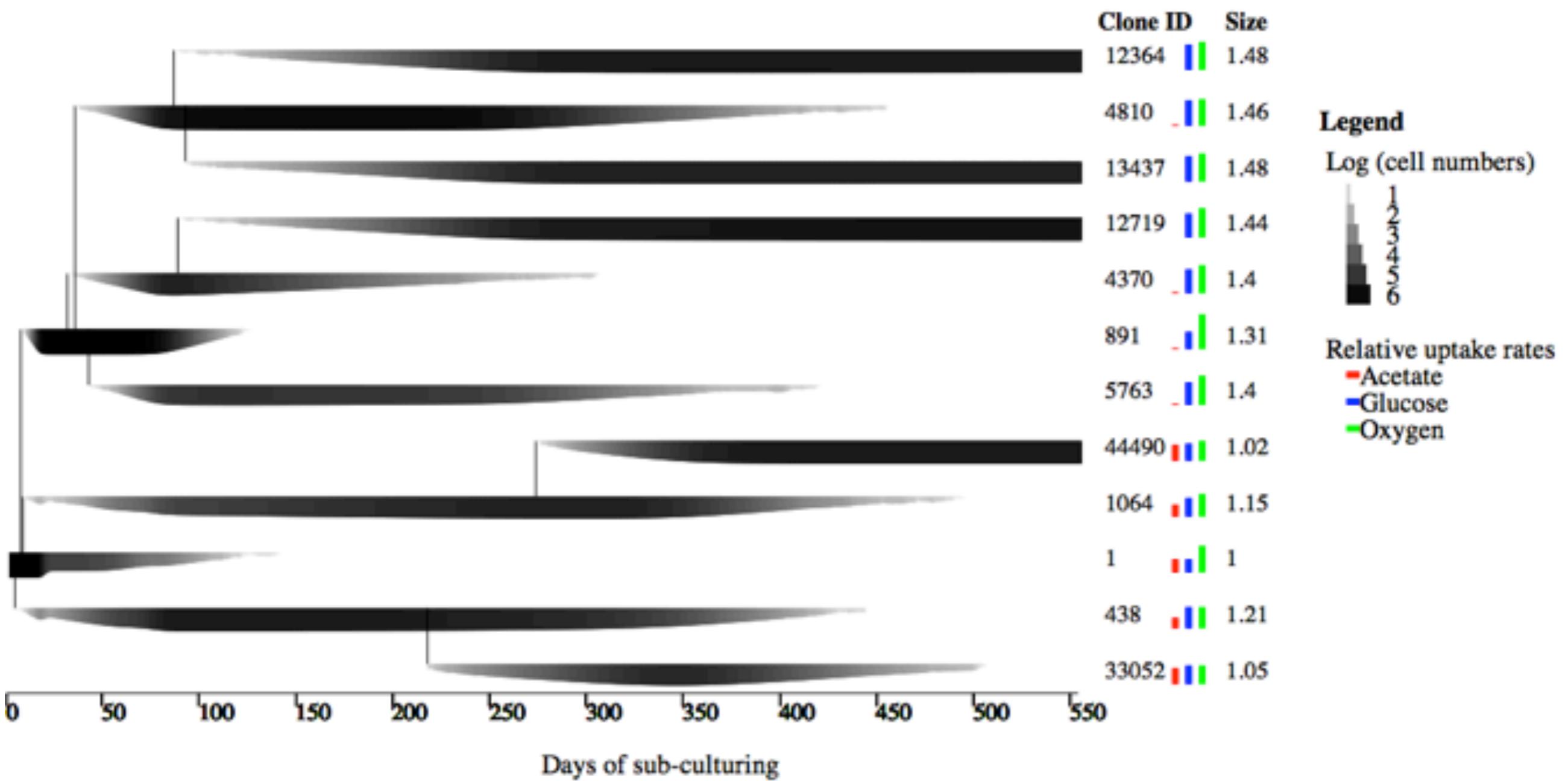
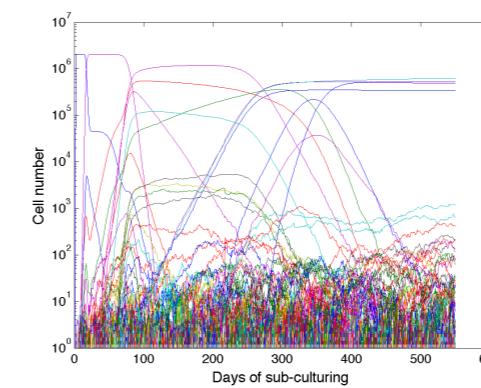
in silico version of

Lenski, R. et al., 1991. Long-term experimental evolution in *Escherichia coli*. I. Adaptation and divergence during 2,000 generations. *American Naturalist*, 138(6), pp.1315–1341.

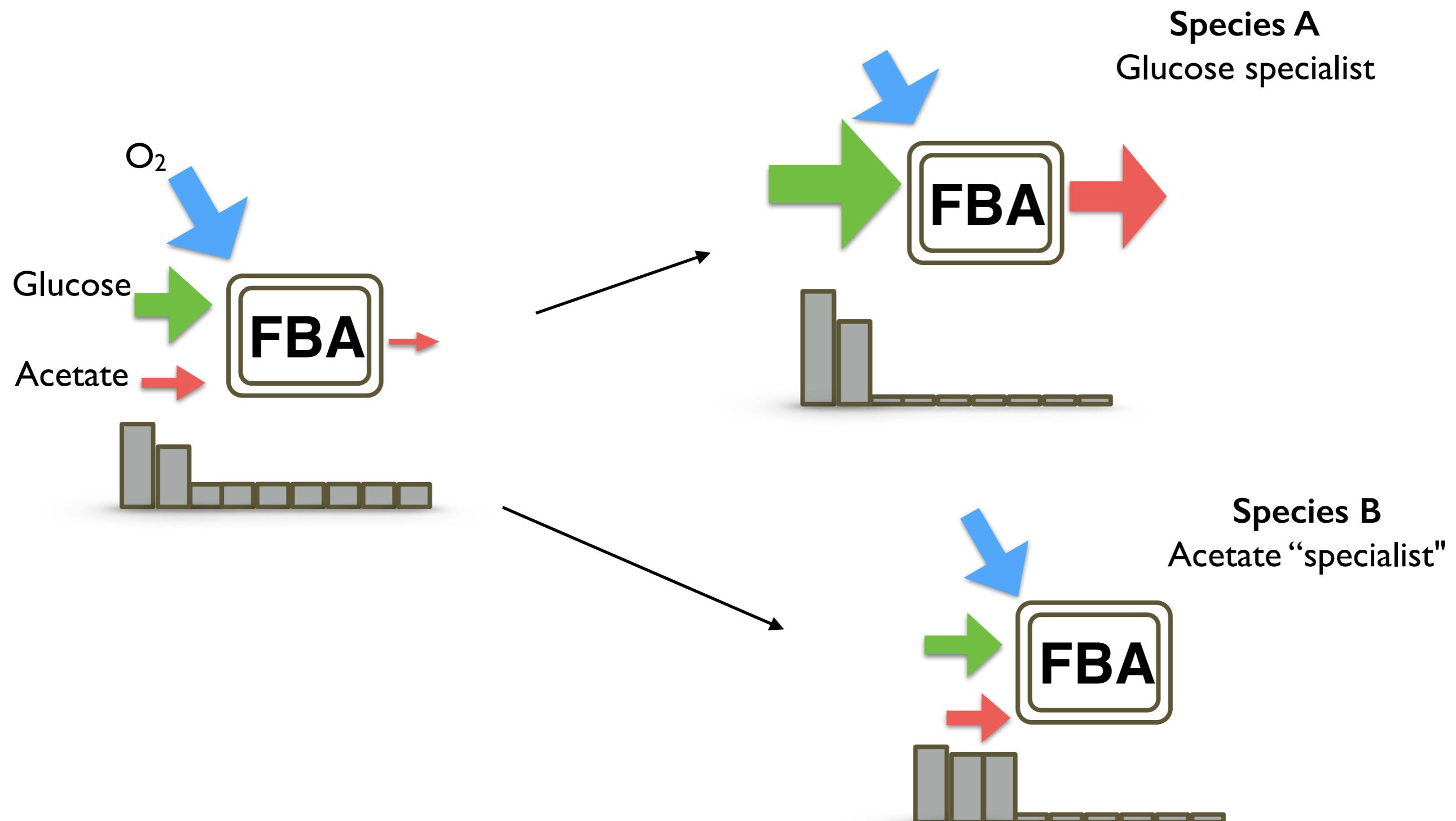
Many clones emerge over evolution



Two clones dominate...



Constraints in cellular resources lead to evolution of ‘cross-feeding’

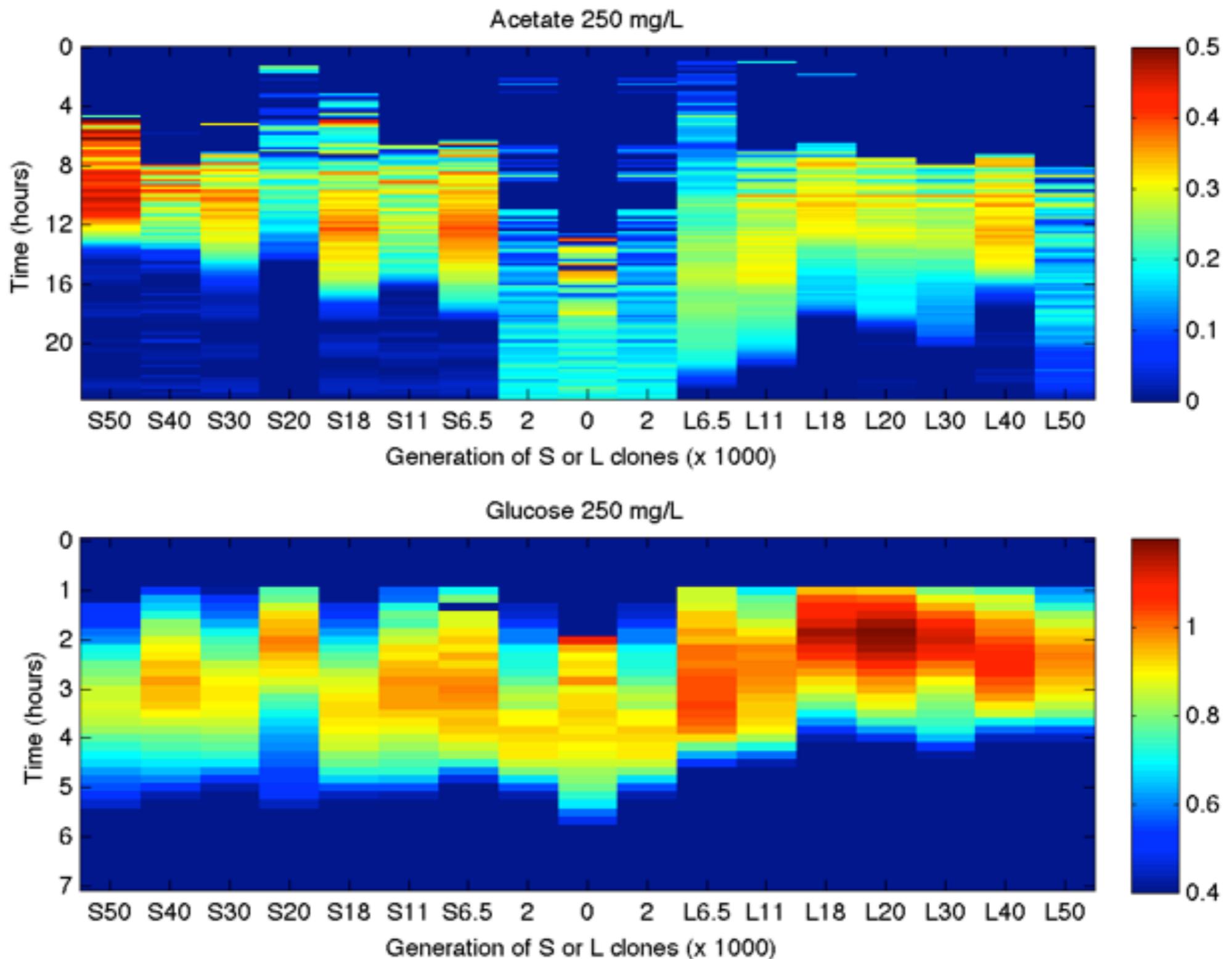


Constraints in cellular resources lead to evolution of ‘cross-feeding’

Ecological lineages of *Escherichia coli*

Mickaël Le Gac^{a,b}, Jérôme

divergence. This provides distinct niches or, evolution. Here we and S, that coexist by converging from a constrained phenotypic resource utilization on the catabolic prc

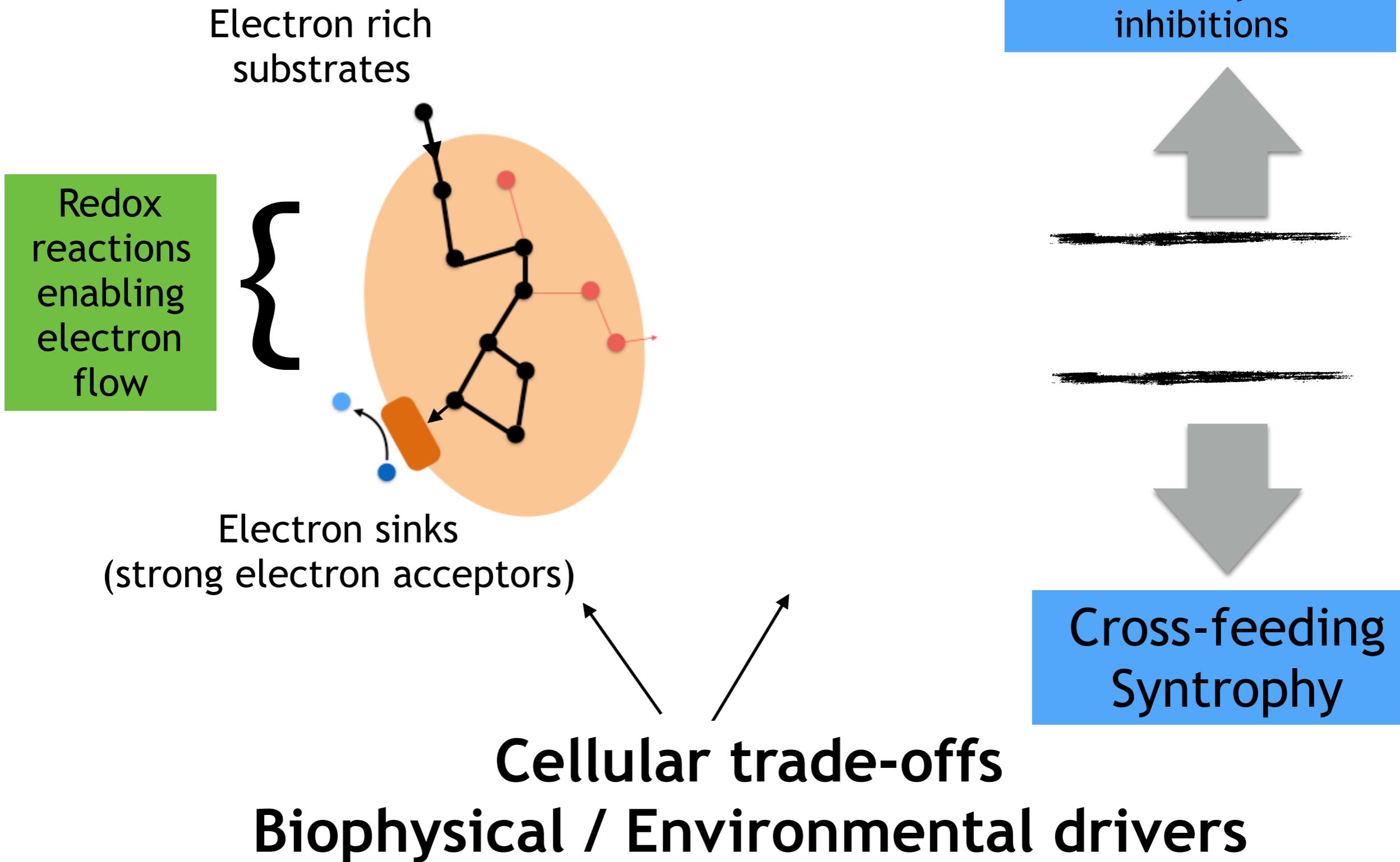


**Despite presence of strong TEAs,
metabolism can be forced into
overflows due to cellular limitations*
and trade-offs**

**It is possible that overflowing cells
can be evolutionarily stabilised by the
emergence of cross-feeding cells**

*e.g. toxic impacts of respiration (matter for another talk)

The story of metabolism: It is about electron flow



The story of metabolism: It is about electron flow

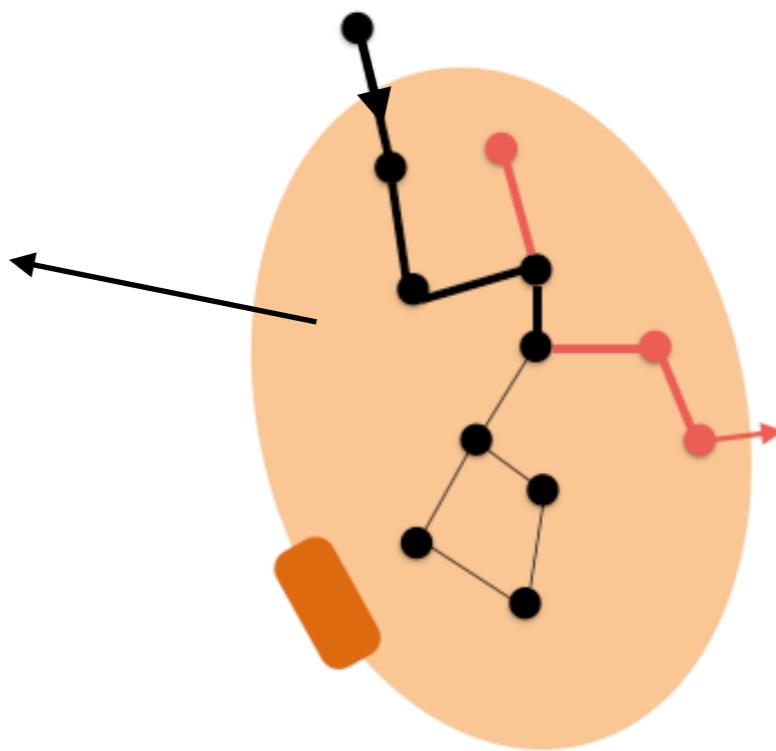
Electron-carrying compounds?

Electron-dense storage compounds?

Depositions on metals?

Direct electron exchanges with other microbes?

Electron rich substrates

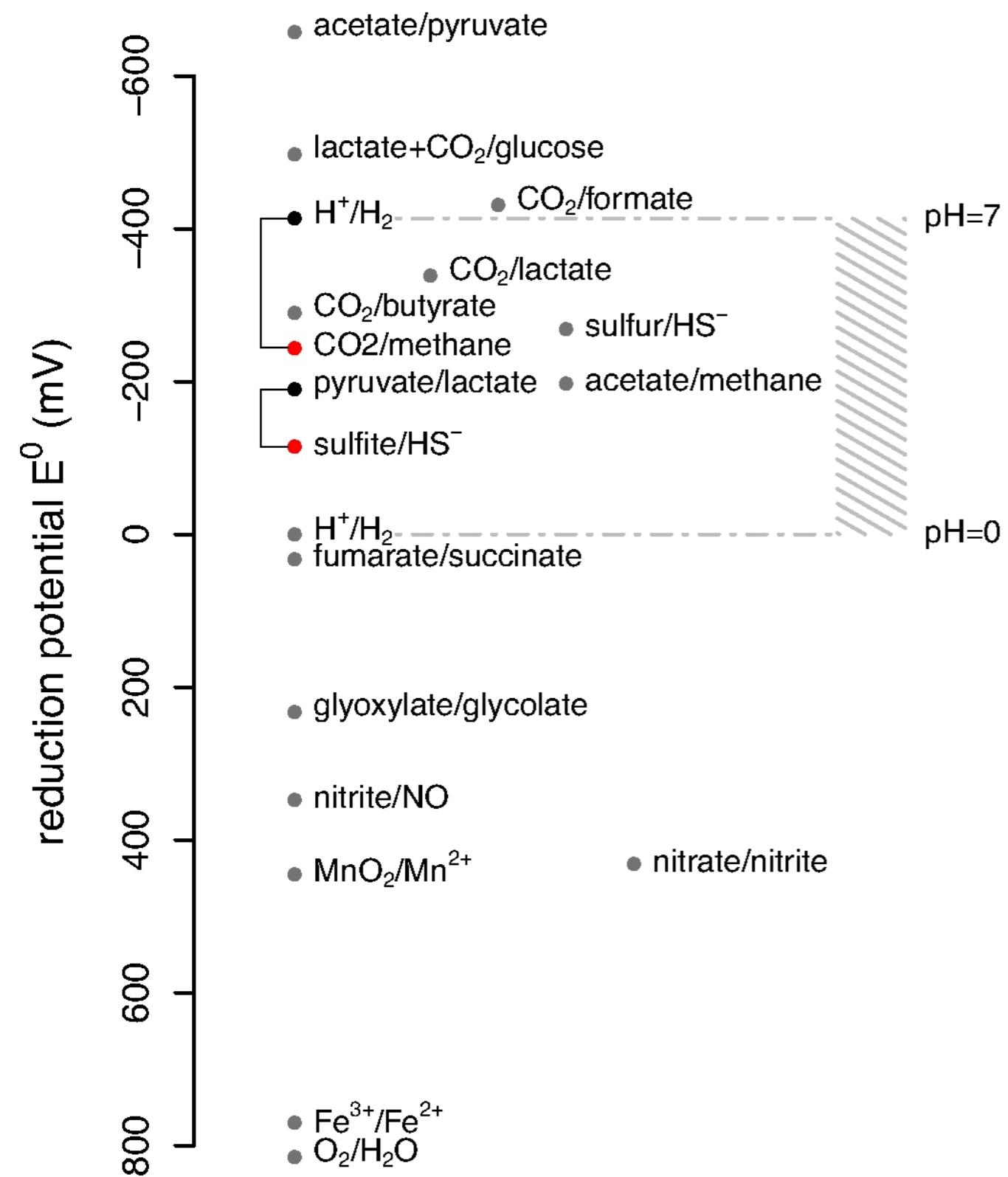


Diverse mechanisms of fermentation due to thermodynamic inhibitions

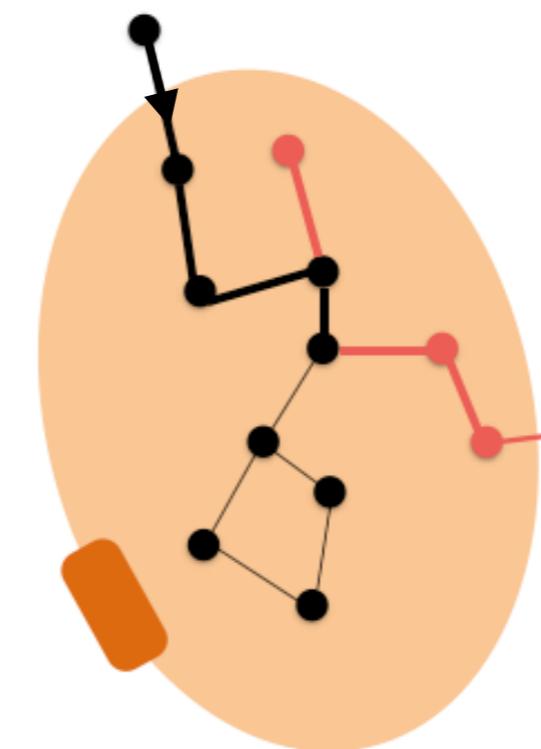
Organic acids,
H₂, ...

Cross-feeding
Syntropy

Metabolism as a redox ladder



Electron rich substrates

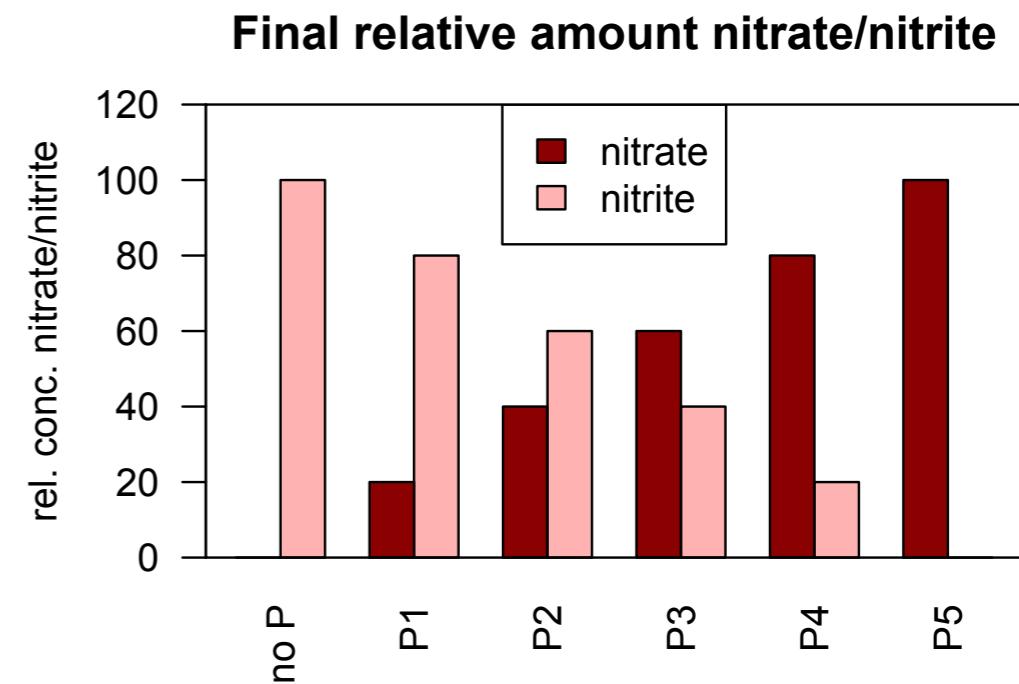
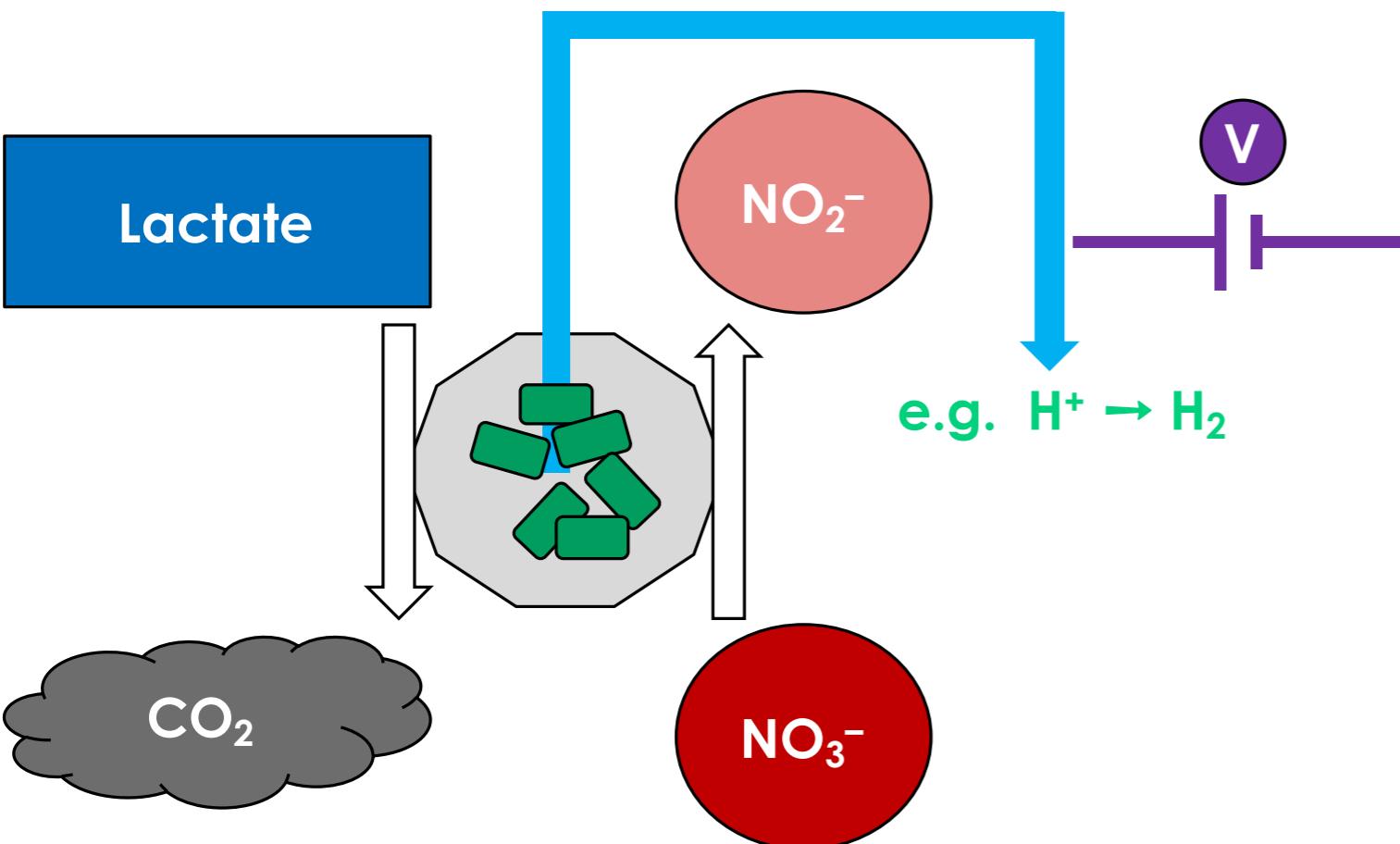


Organic acids,
H₂, ...

Is precise ‘electronic’ control
of cell metabolism possible?

"Electronic control" of cell metabolism?

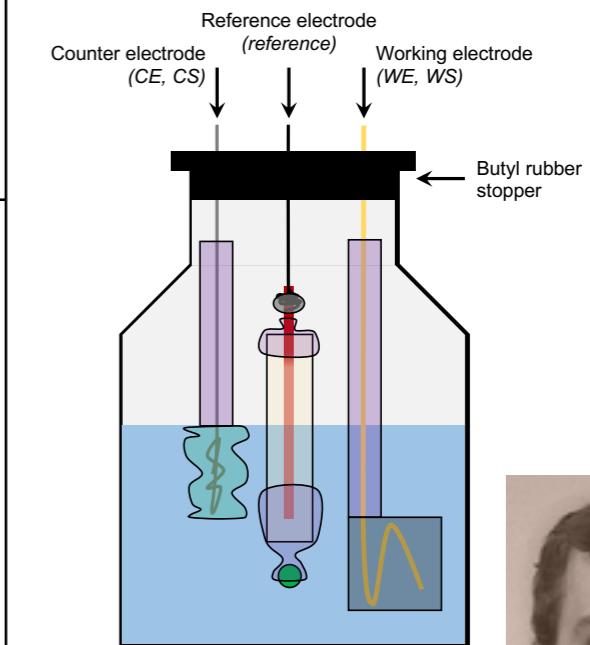
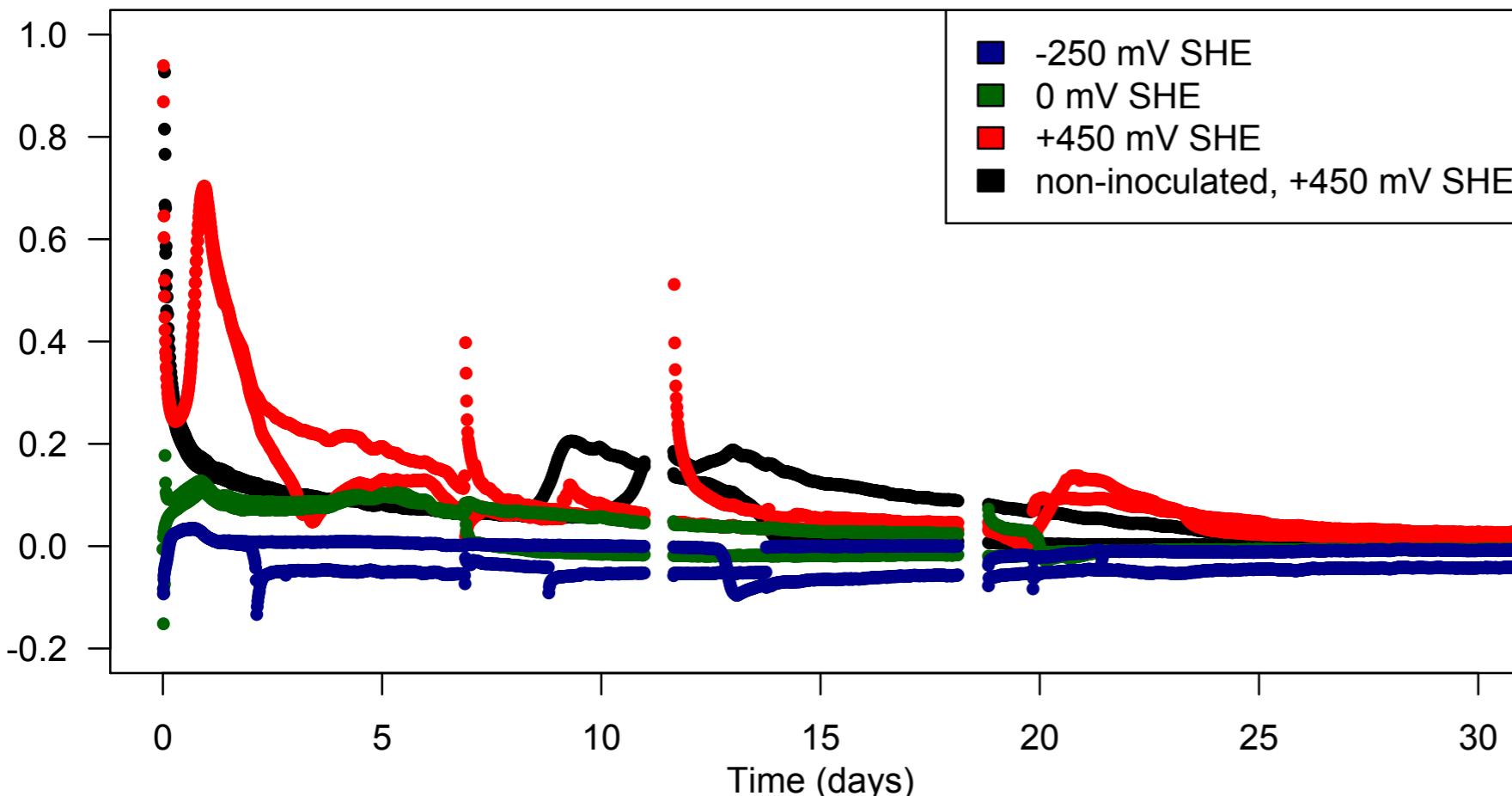
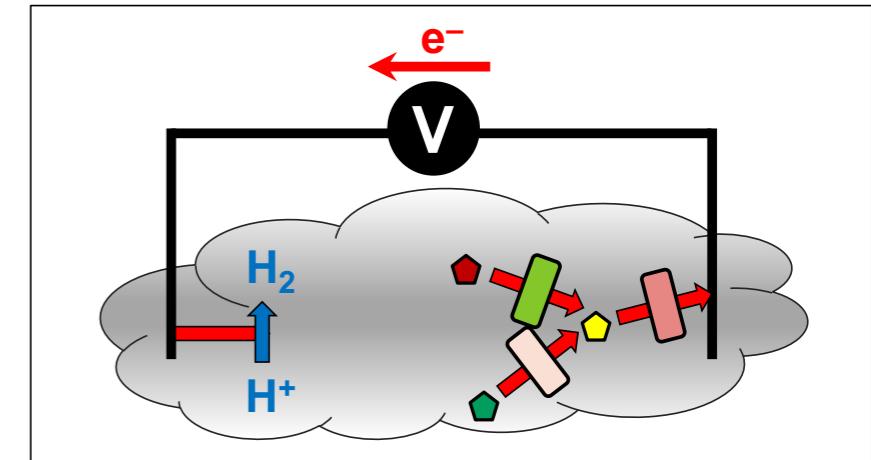
Control of respiration vs. fermentation in *Shewanella oneidensis* using electrodes poised at specific potentials



Christian Zerfass

"Electronic control" of community metabolism?

Control of community composition using electrodes poised at specific potentials

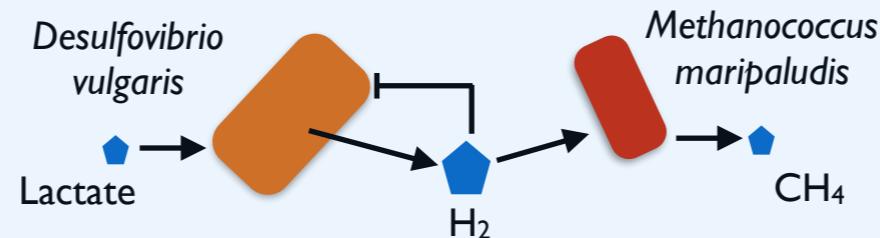


Christian Zerfass

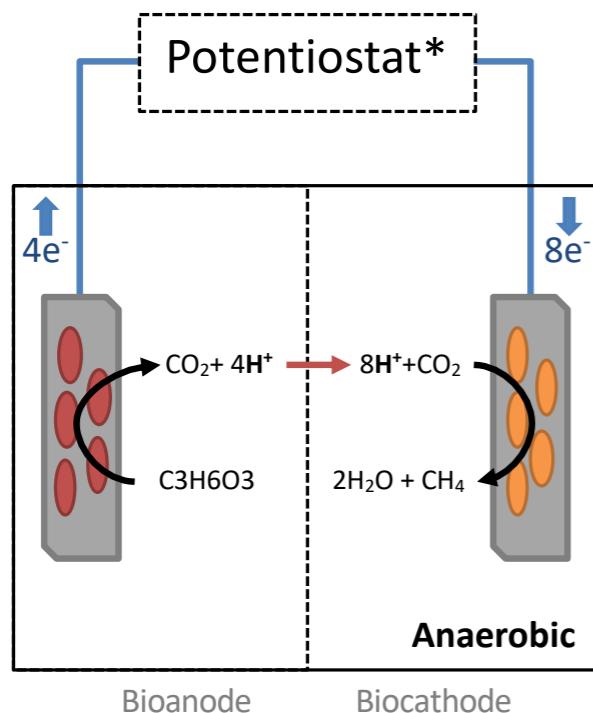
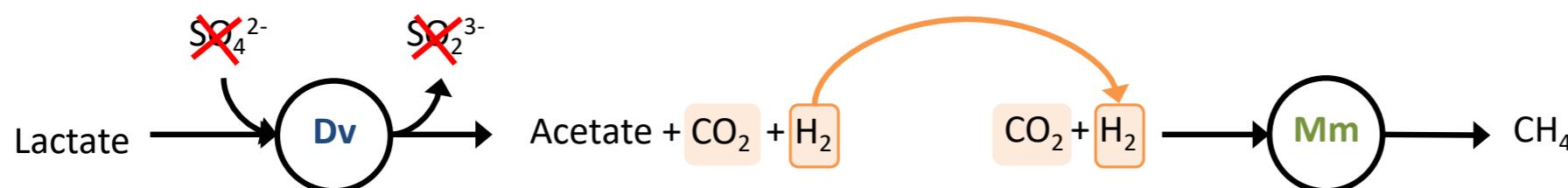
"Wiring" of cells via metabolism?



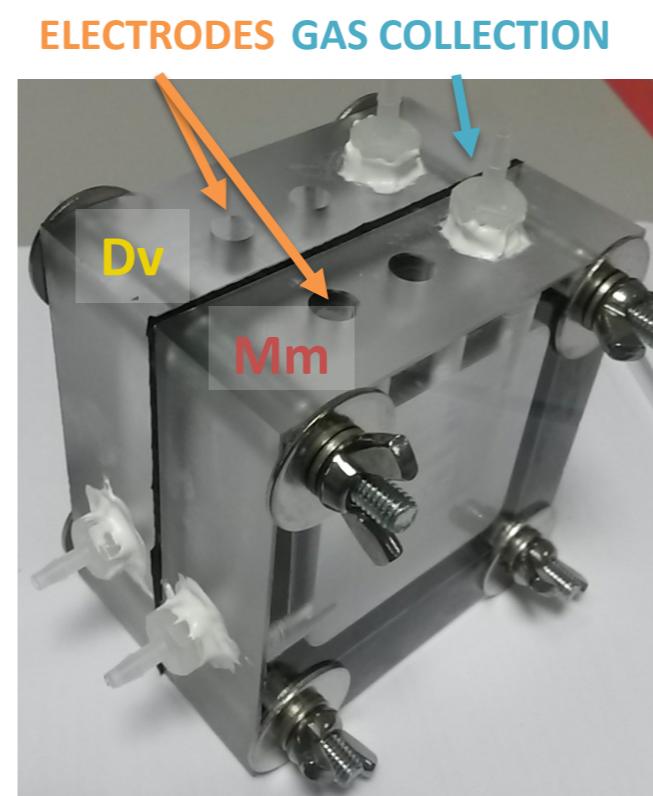
Andrea
Martinez-Vernon



Control/study of syntropy across wires!

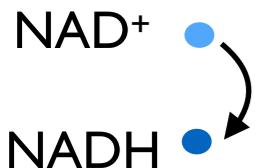


Electrochemical set up
*voltage control

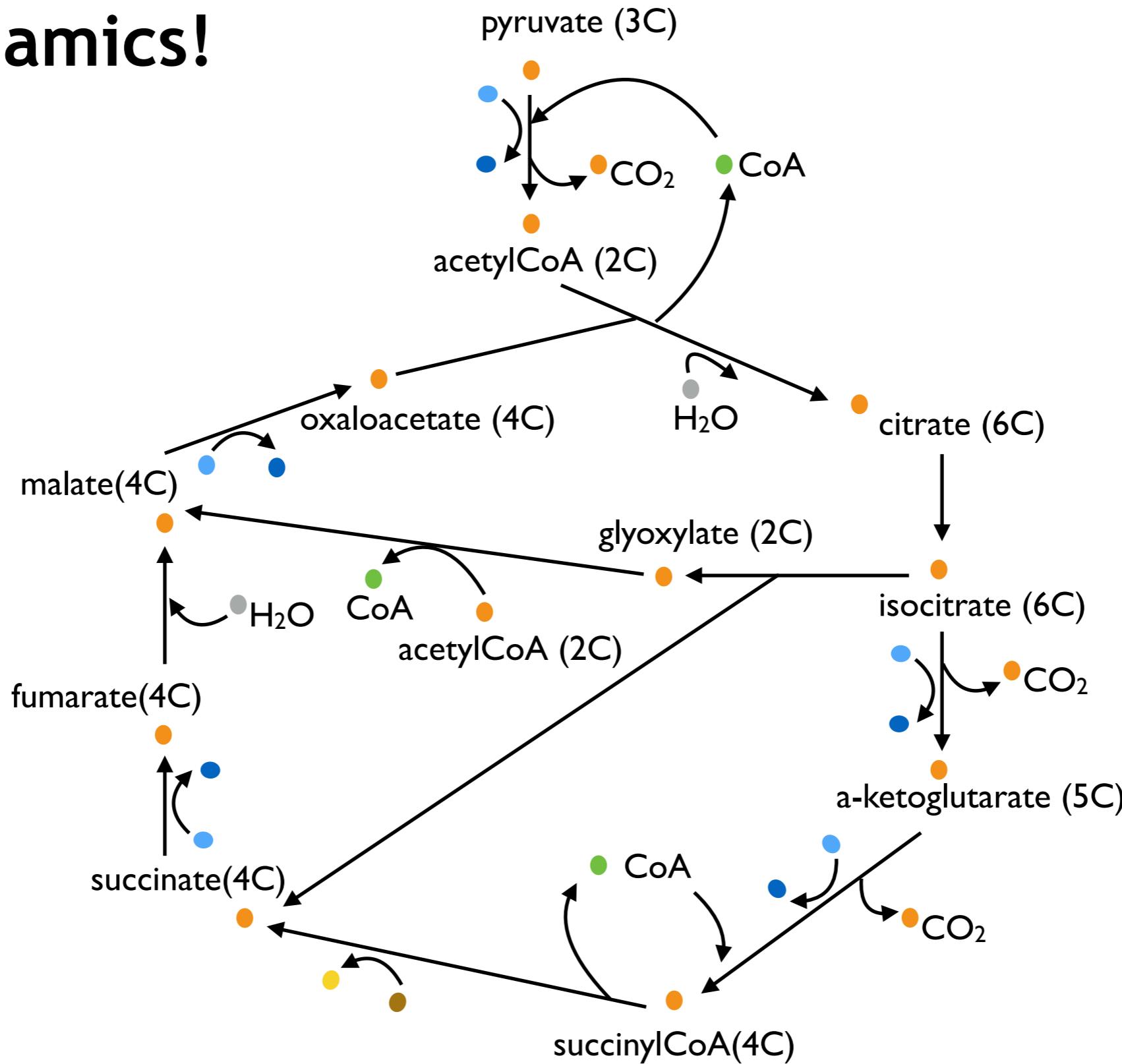


Electrochemical cell

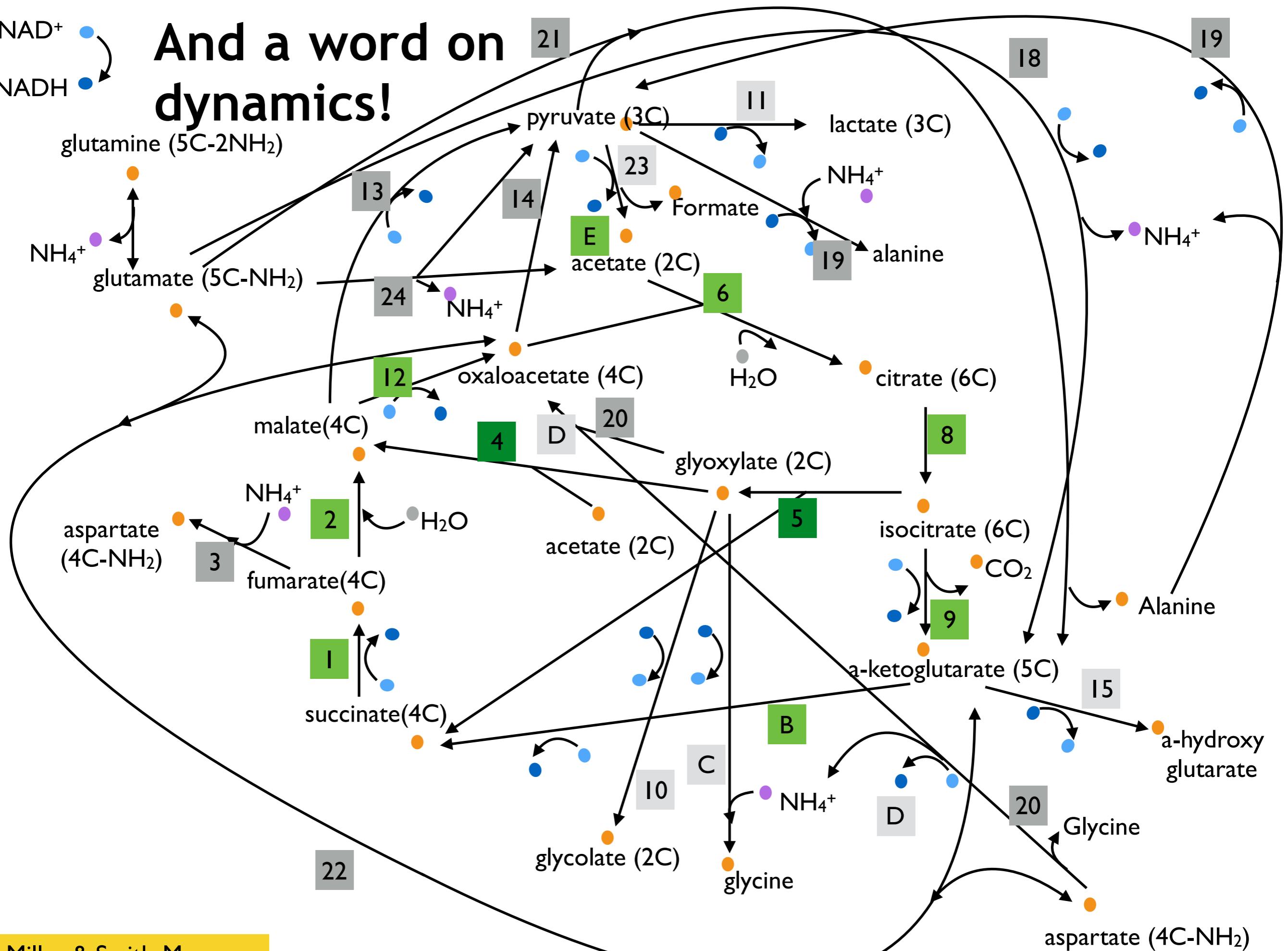




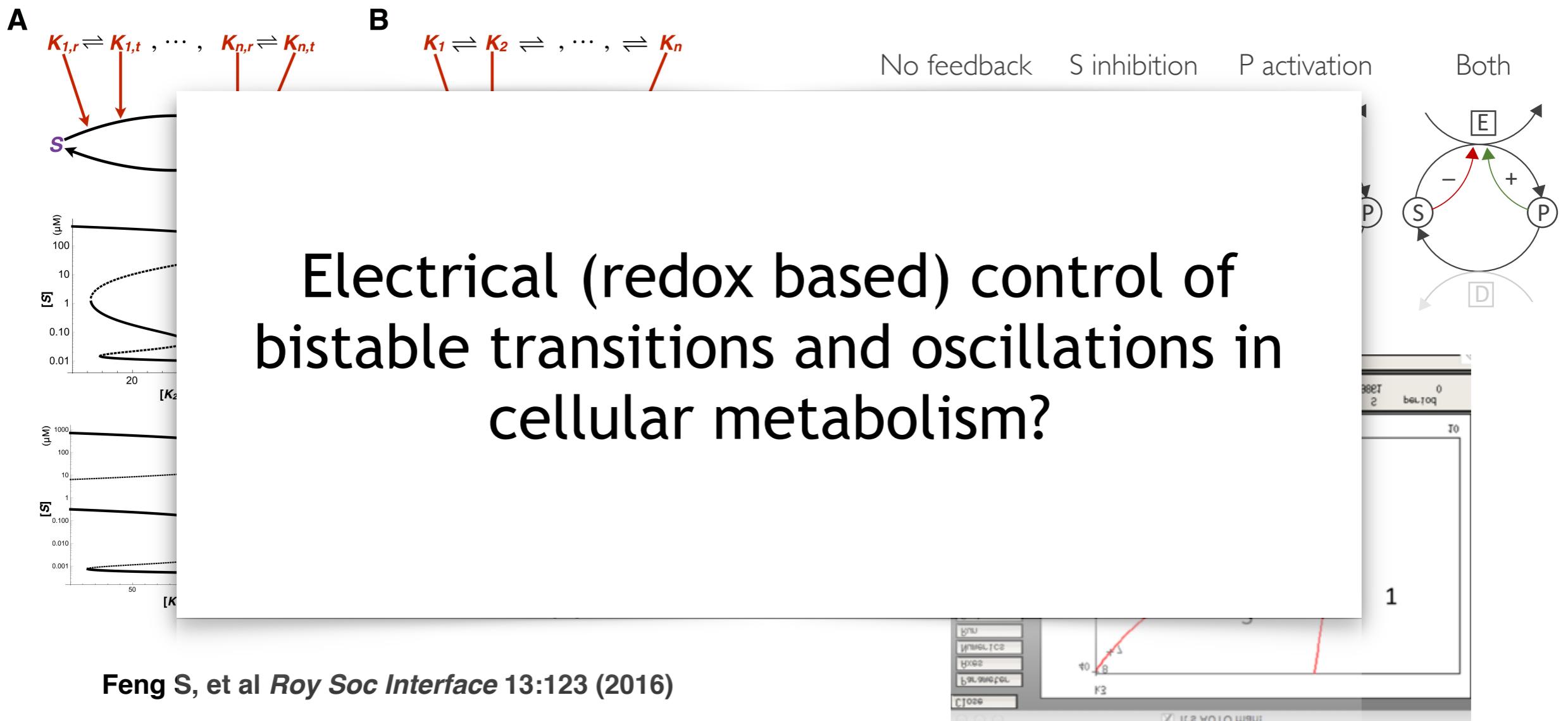
And a word on dynamics!



And a word on dynamics!



Cycles competing through common substrates/enzymes can generate multistabilities and oscillations

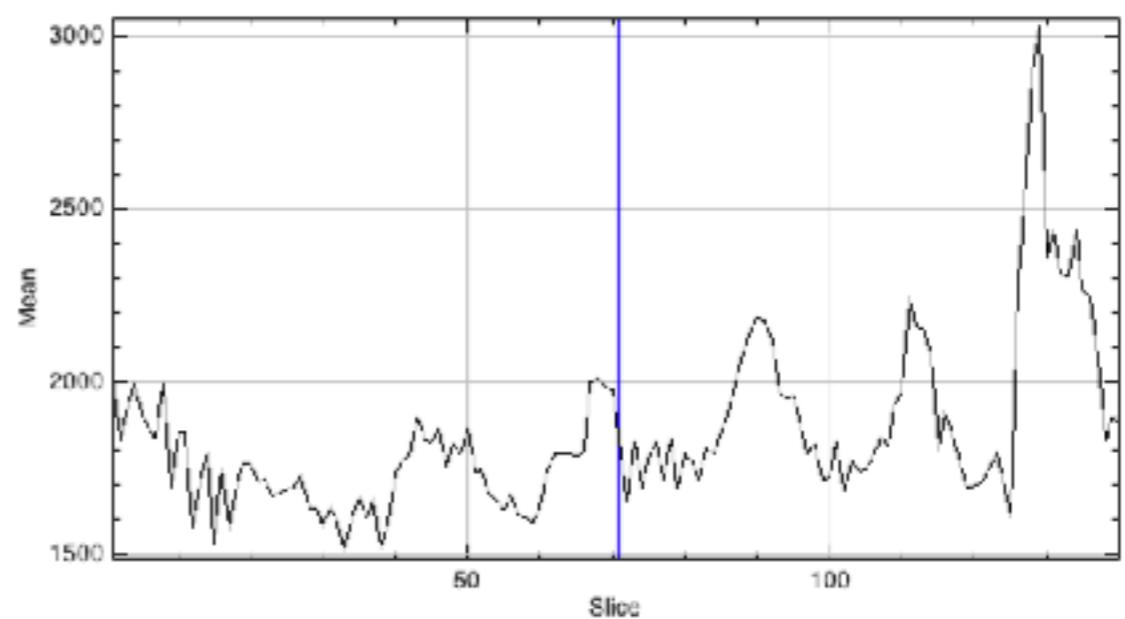
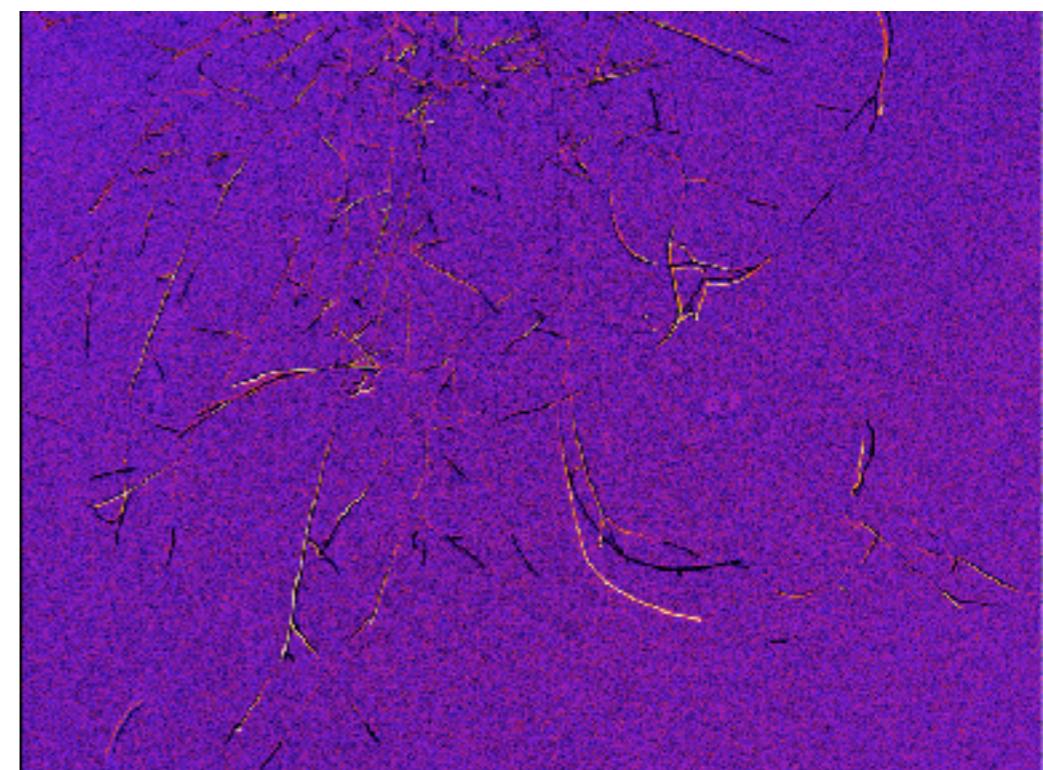
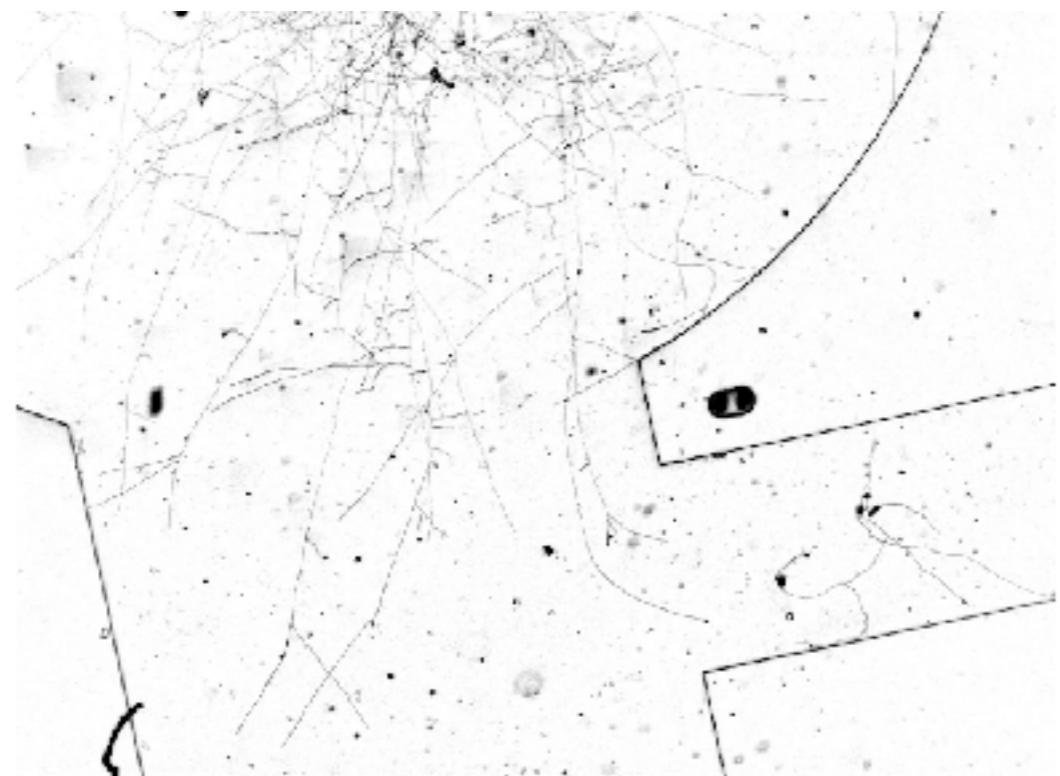


Number of steady-states
by region

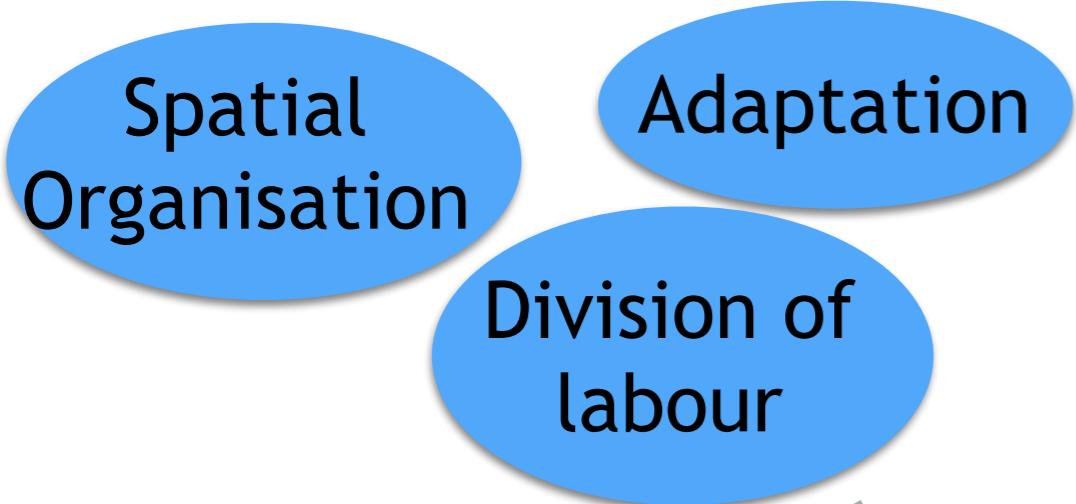


Hayes C.,
ongoing work

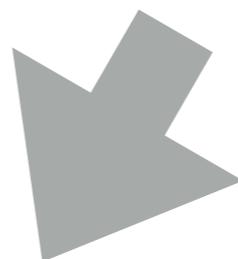
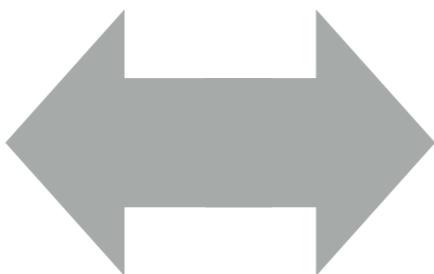
Electrical (redox based) control of bistable transitions and oscillations in cellular metabolism?



Ecology & Evolution



Biophysical Drivers



Towards a Simplified Theory of Cellular Metabolism

THANK YOU



<http://osslab.lifesci.warwick.ac.uk>

Kalesh Sasidharan
Christian Zerfass
Jing Chen

Xue Jiang
Clare Hayes
Andrea Martinez-Vernon
Sean Aller

Open PhD and PDRA positions

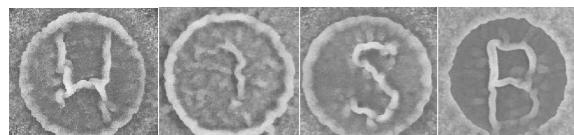
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Dominique Schneider (University of Grenoble)

Funders



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Training in Synthetic Biology



