For the prediction of intracellular fluxes in *E. coli*

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Overview

- Biological question
- Modeling approach
- Biological answer

Biological question

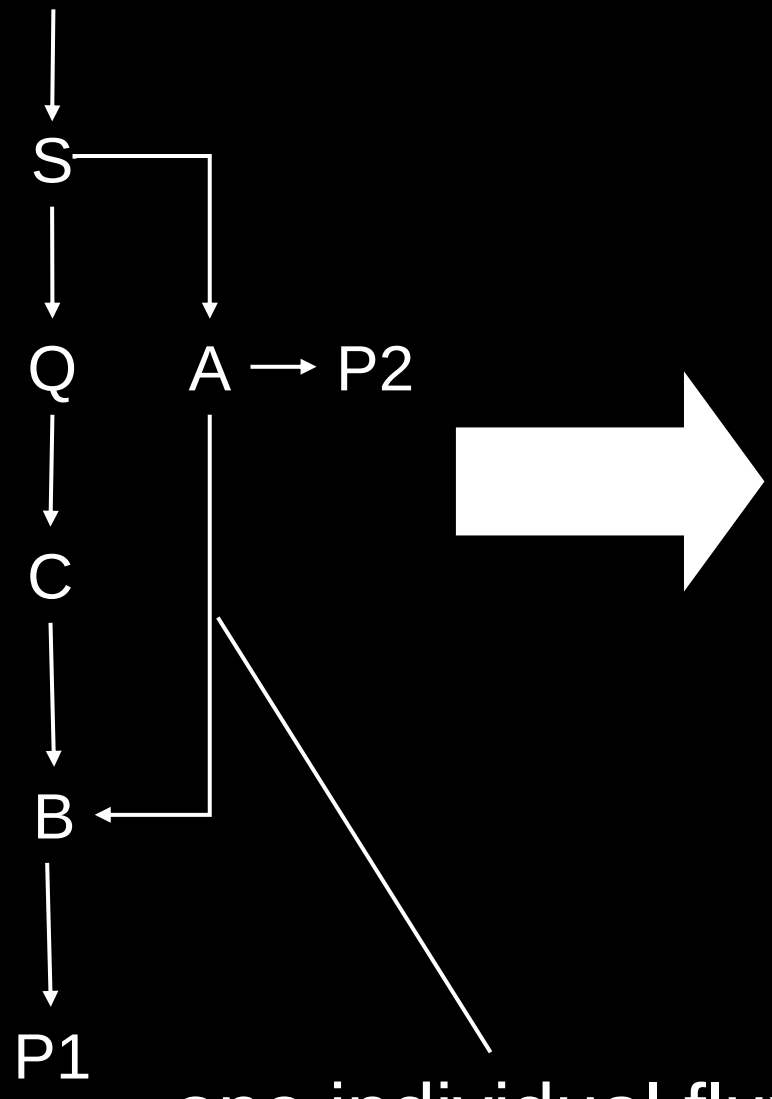
What is the underlying cellular strategy that explains the experimentally observed metabolic state ?

Cellular strategy

- Why do we observe what we observe?
- Benefit for the cell ?

- Objective function
- Optimality principle

Metabolic state



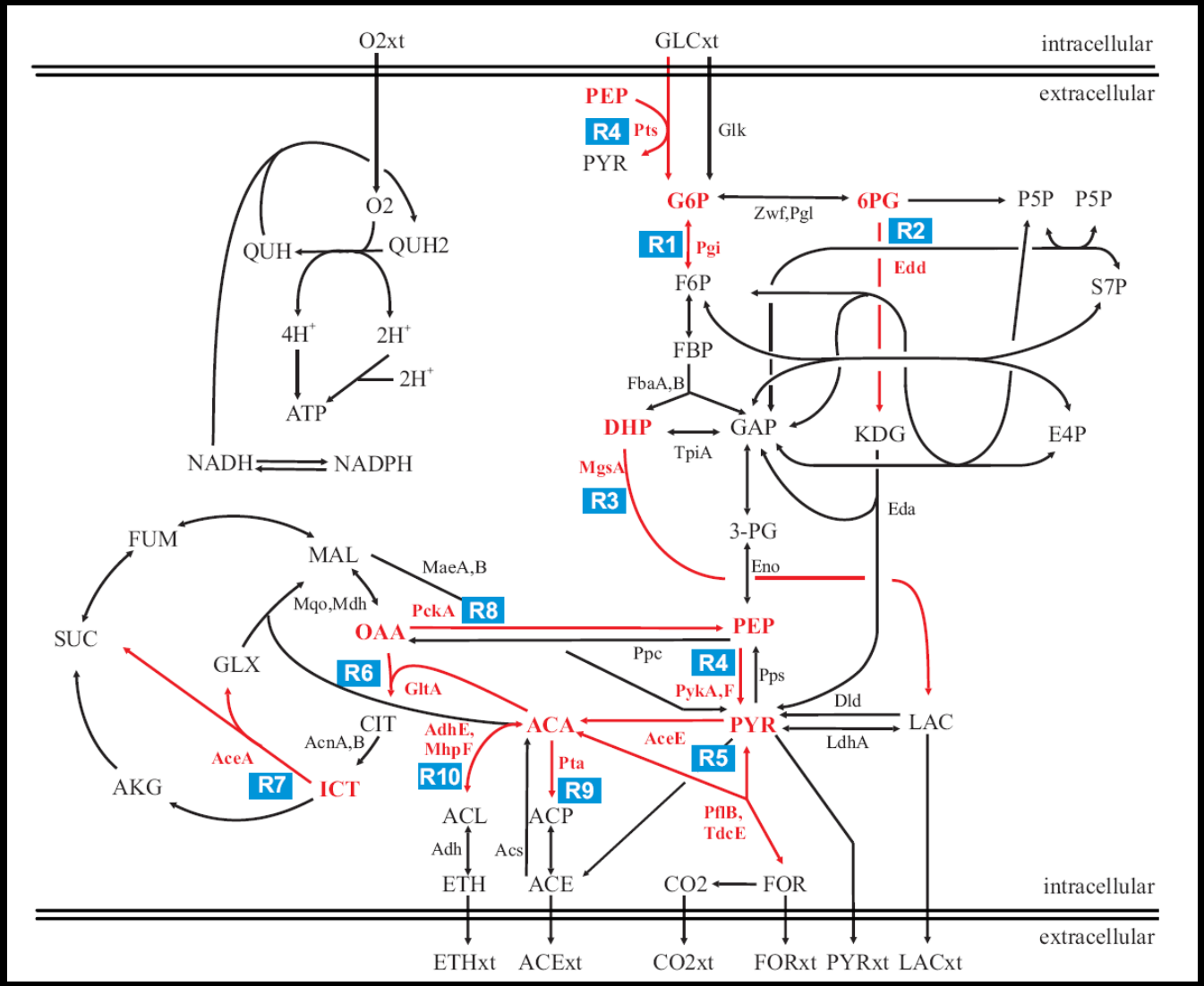
Distribution of all individual fluxes at given time point

one individual flux $\frac{mmol}{hr}$

Biological question

Why does the cell choose the experimentally observed intracellular flux distribution ?

Metabolic network

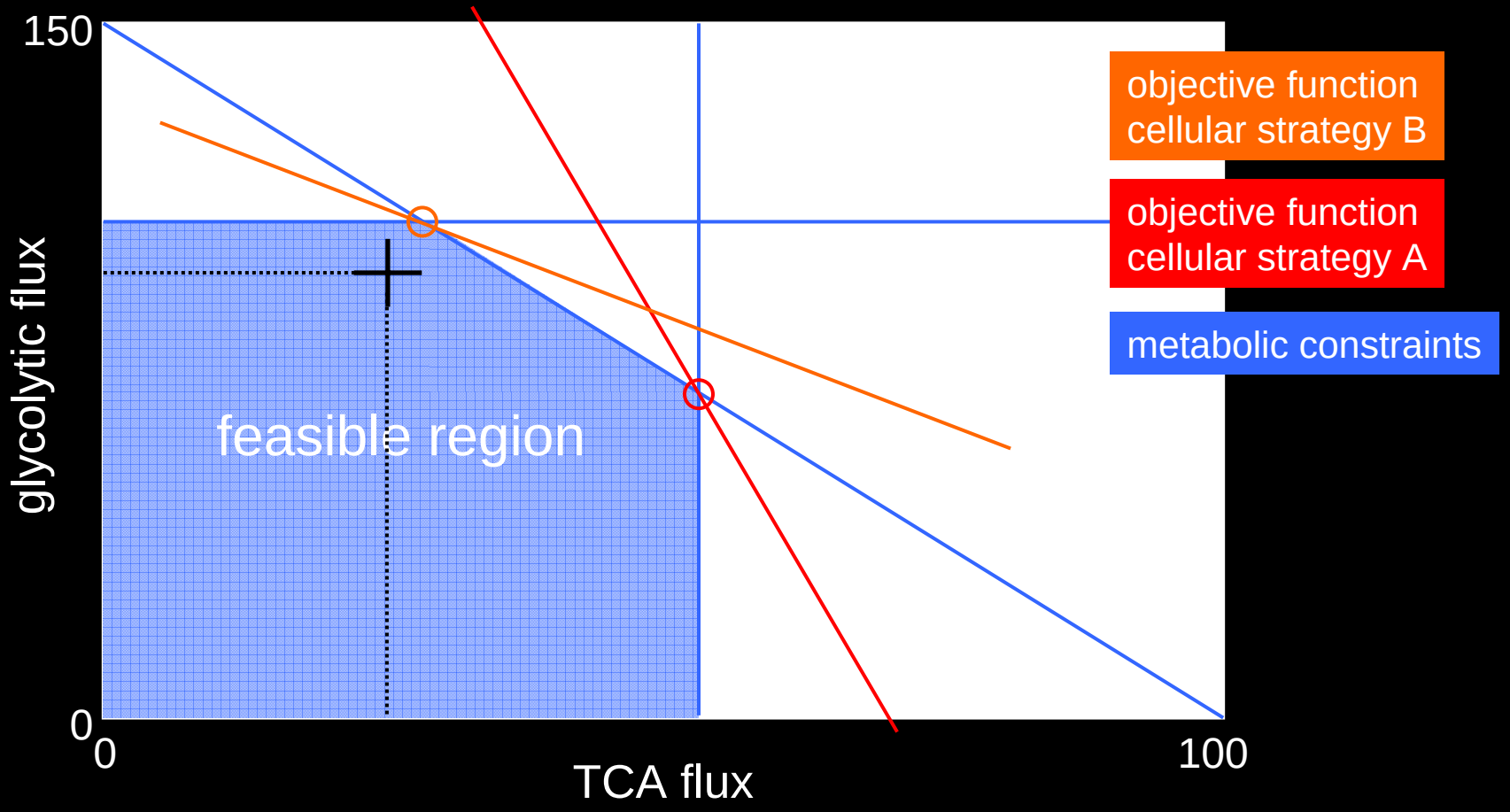


100 reactions
60 metabolites

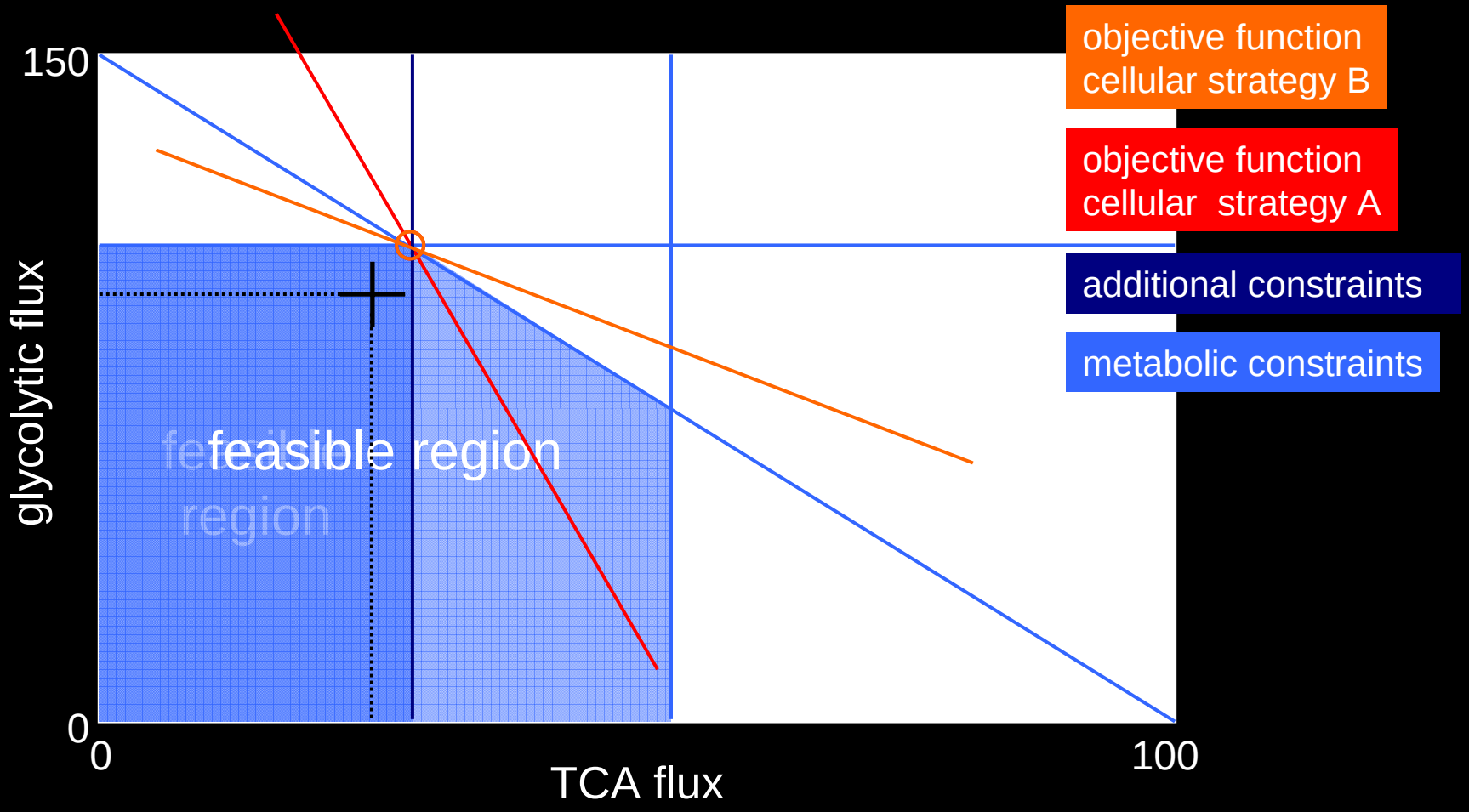
10 degrees of freedom

10 split ratios

Flux balance analysis



Flux balance analysis



Objective functions (cellular strategy)

1	Biomass maximization	Growth efficiency
2	ATP maximization	Energetic efficiency
3	Sum of fluxes minimization	Resource allocation efficiency
4	ATP per flux unit maximization	Combination of 2 and 3
5	Biomass per flux unit maximization	Combination of 1 and 3

Systematic approach

9 additional constraints
mass / energy
thermodynamic
environmental
regulatory

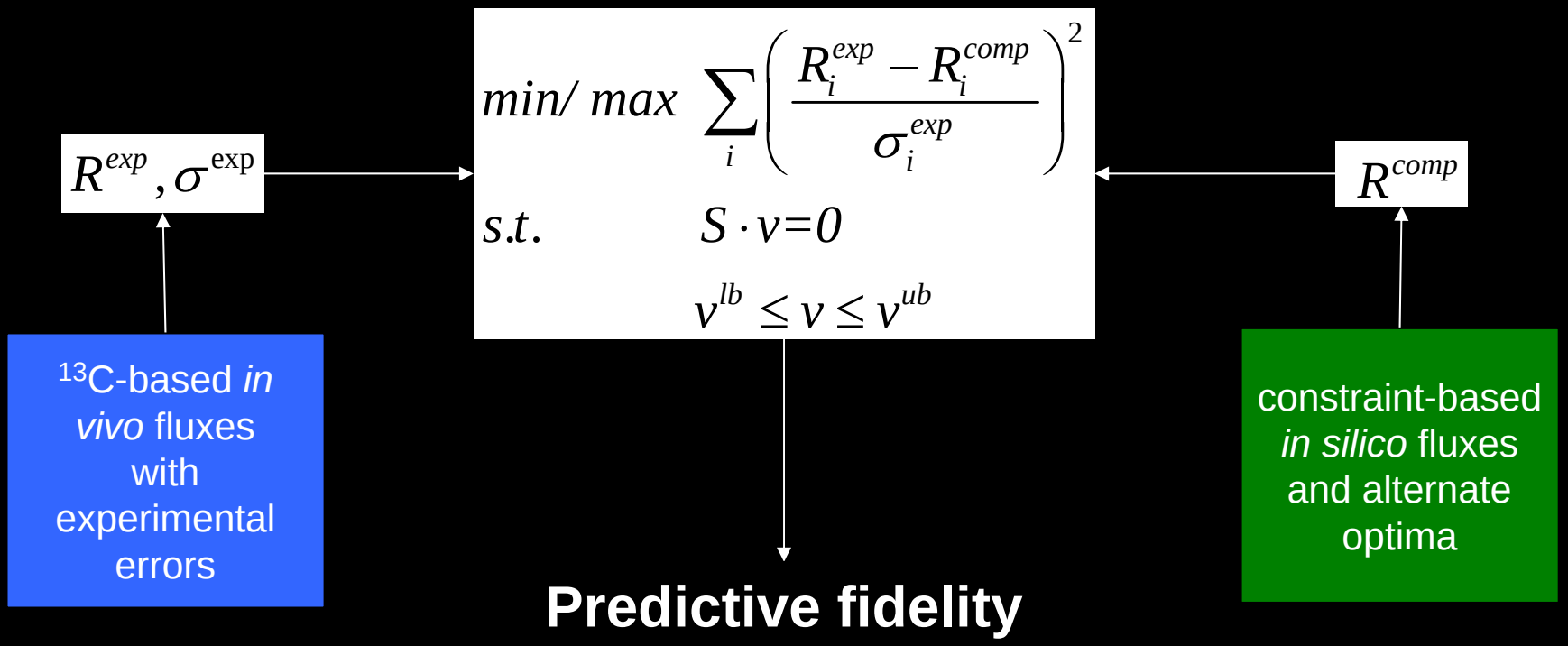
11 objective functions
linear
non-linear
quadratic
mixed-integer

6 environmental conditions
3 batch cultures[1]
3 chemostat cultures[2,3]

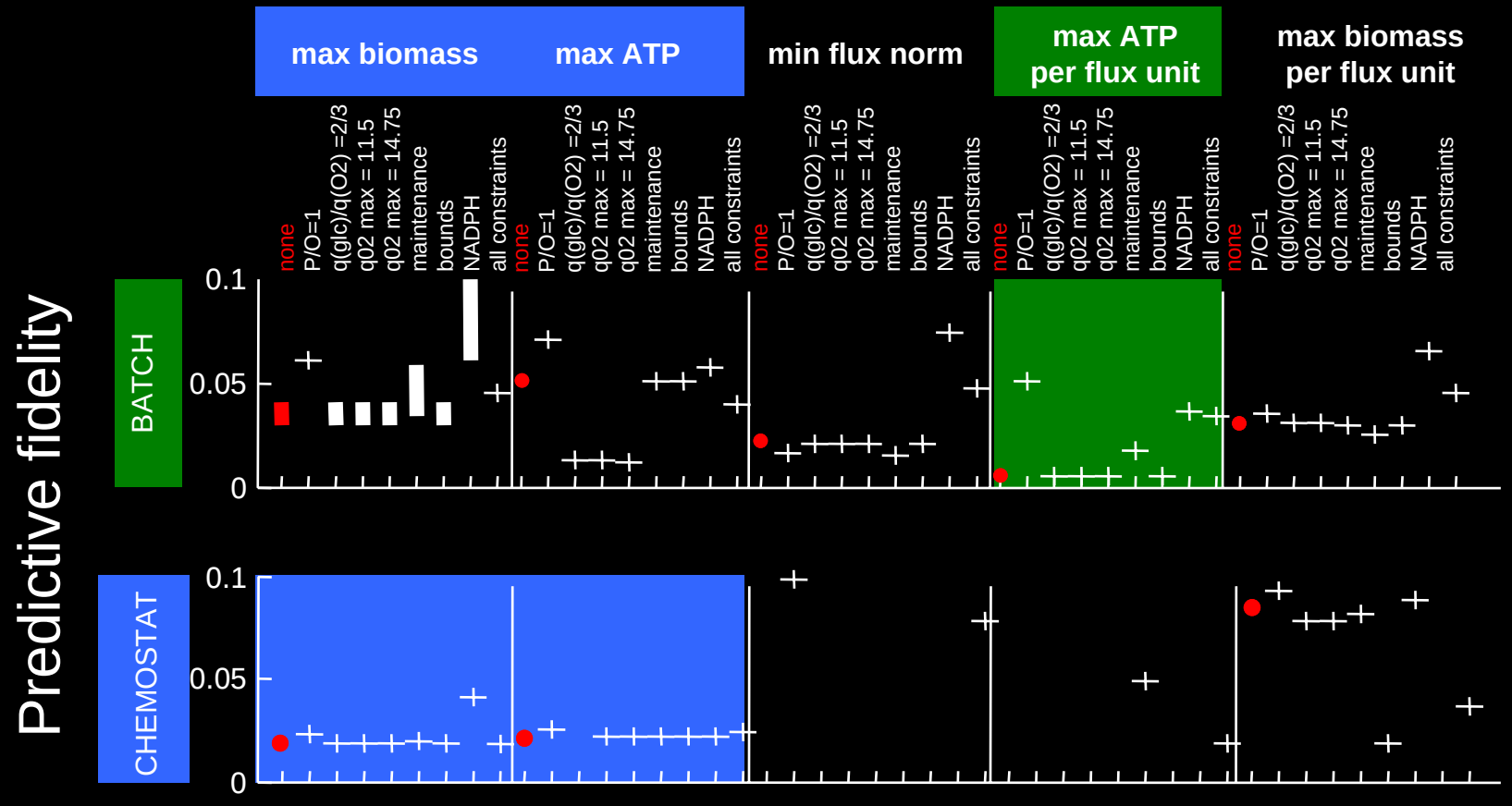
~600 permutations

[1] Perrenoud *et al* (2005) *J Bacteriol* **187** 3171 - 3179
[2] Nanchen *et al* (2006) *Appl Environ Microbiol* **72** 1164 – 1172
[3] Emmerling *et al* (2002) *J Bacteriol* **184** 152 – 164

Predictive fidelity describes the accuracy of flux predictions



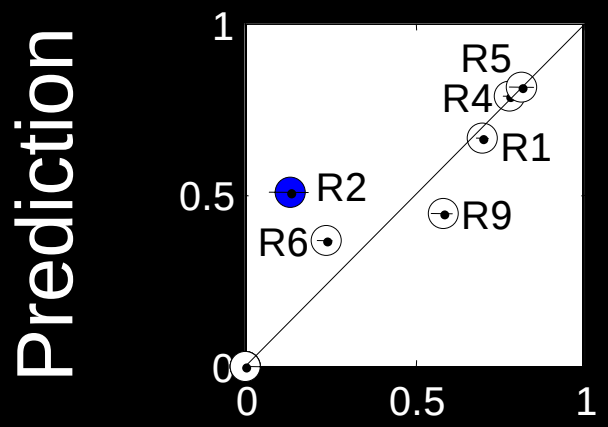
Two metabolic states identified in *E. coli*



Two metabolic states identified in *E. coli*

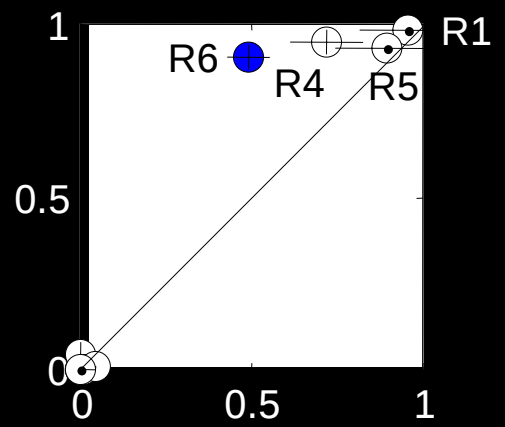
BATCH

max ATP / flux unit



CHEMOSTAT

max ATP (biomass)



Experiment

Conclusions

1. **Assumption so far still valid?**

   Maximization of biomass (growth) widely accepted

   Two metabolic states operational in *E. coli*

2. **Evolutionary selection of metabolic network regulation?**

   No additional, potentially artificial constraints

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