Photosynthesis and Phototrophic Growth: Modelling Life on Earth and elsewhere

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Fakulta informatiky MU
pondělí 14. 5. 2012, 14:00

outline

Part I

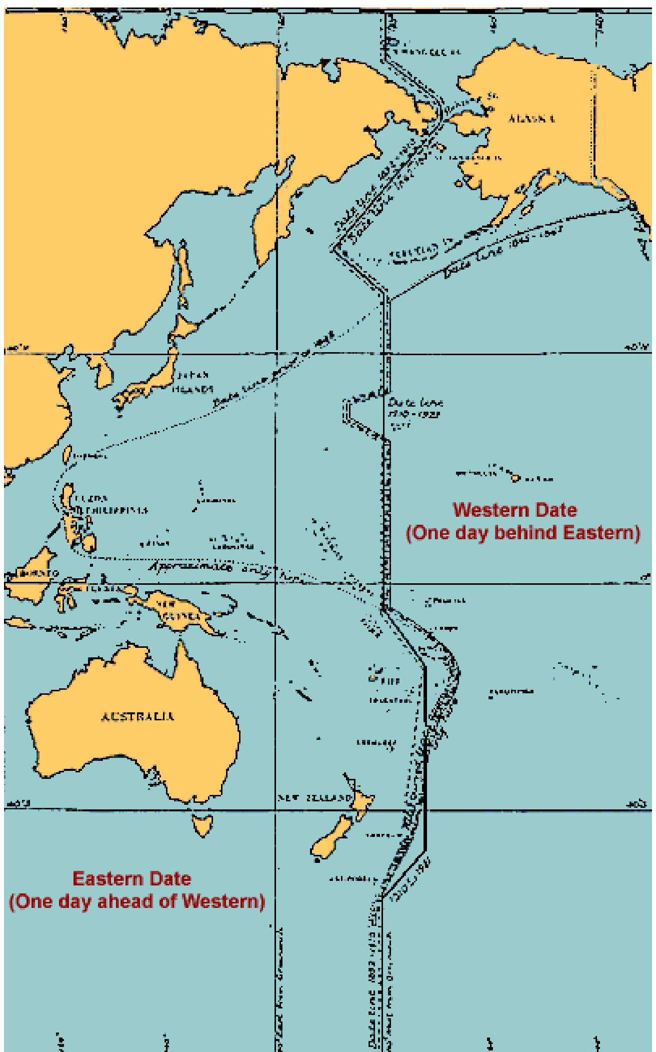
News and Events on May 14, 2012

Part II

Cyanobacteria: understanding phototrophic growth
Dynamics of large-scale networks
Applications to biotechnology

outline

May 14, 2012, 0am



outline

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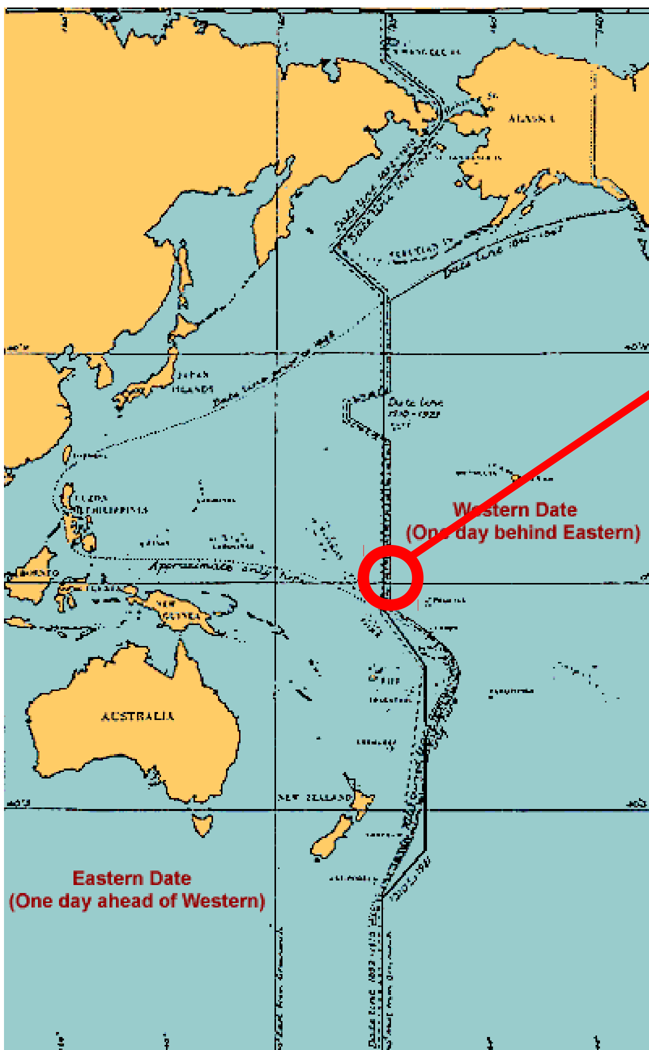
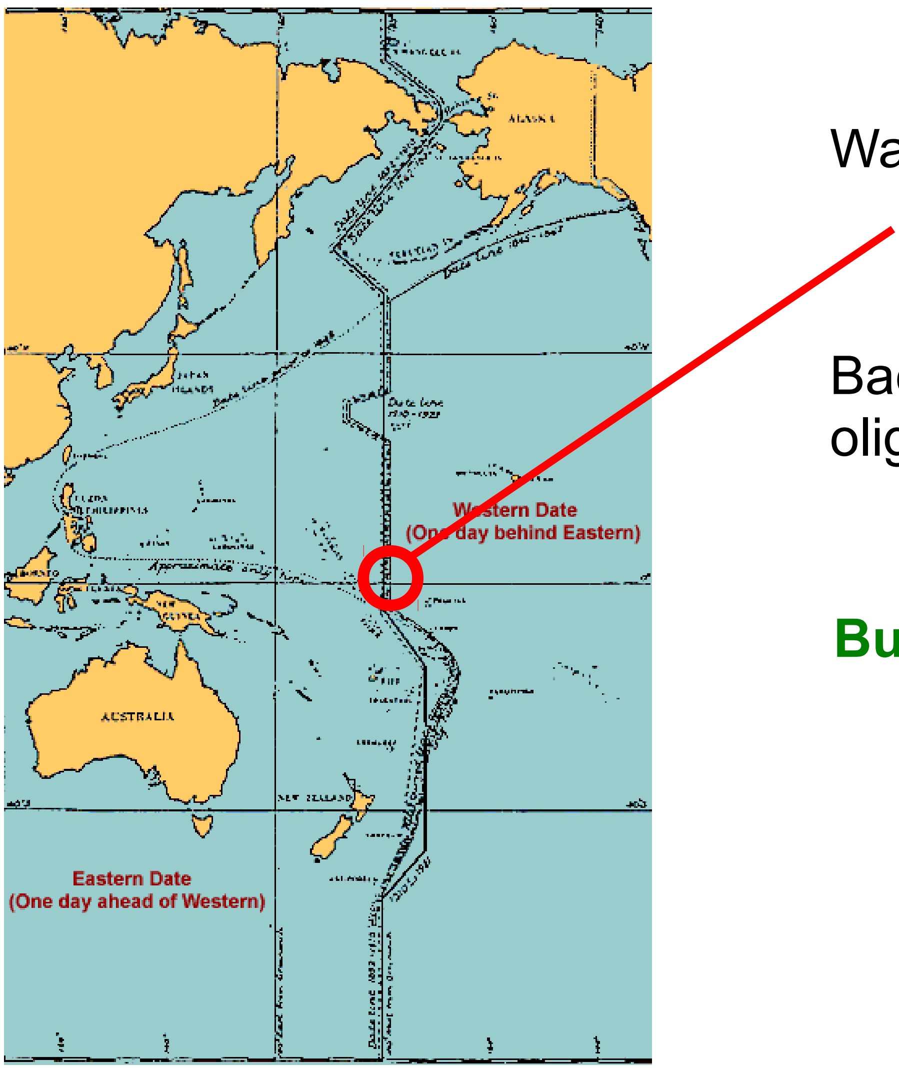


Water, water, everywhere, ...

Bacterial abundance in in stratified oligotrophic waters can be high (> 10^5 cells ml^{-1})

May 14, 2012, 0am

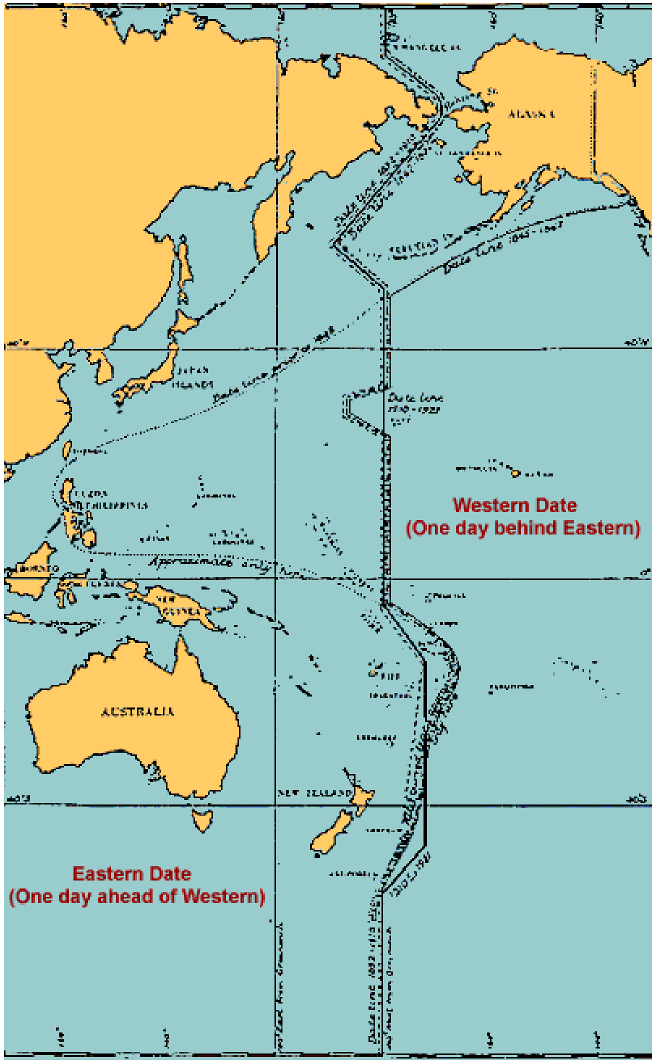


Water, water, everywhere, ...

Bacterial abundance in in stratified oligotrophic waters can be high (> 10^5 cells ml^{-1})

But no primary productivity ...

May 14, 2012, a few hours later ...

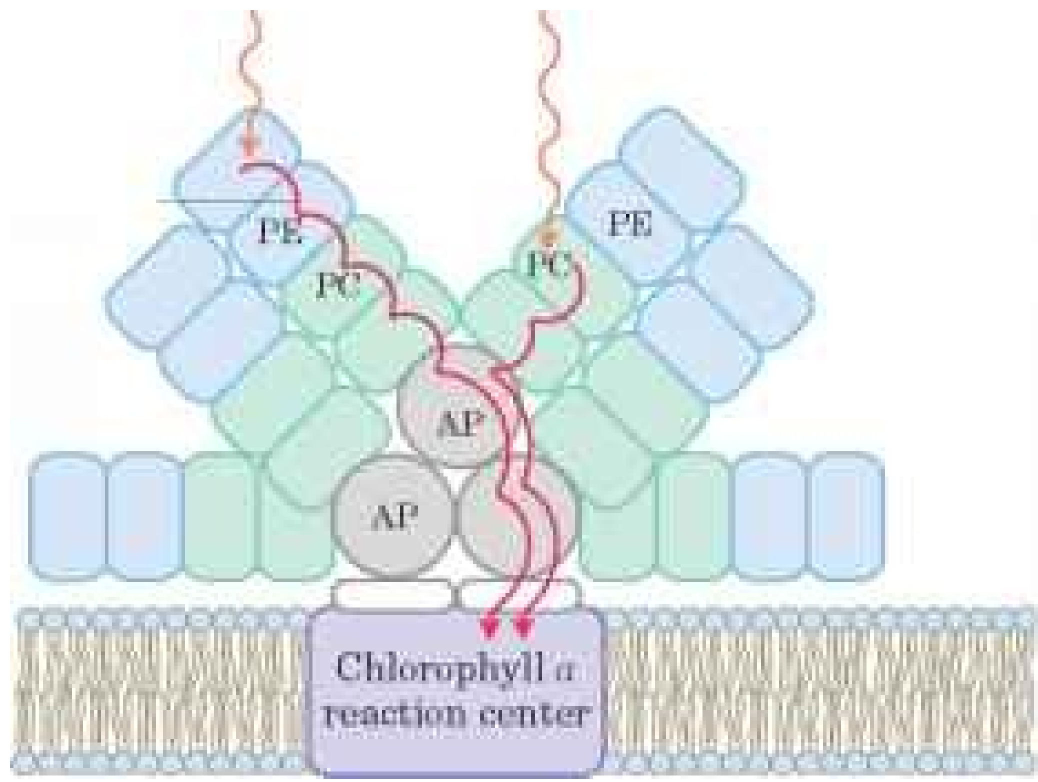


May 14, 2012, a few hours later ...

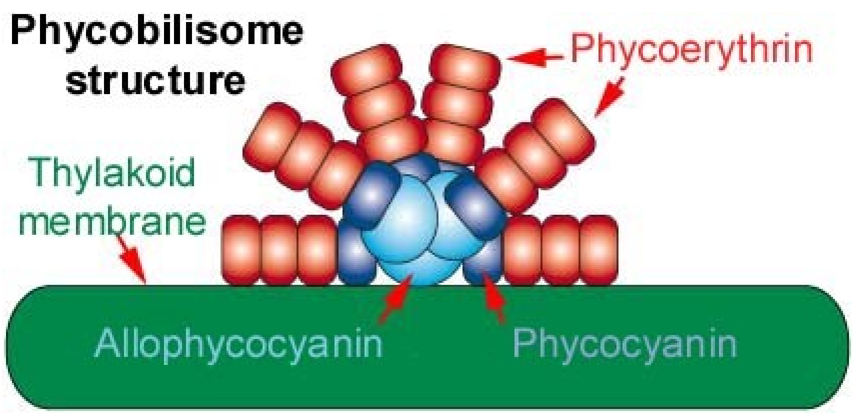
May 14, 2012, a few hours later ...

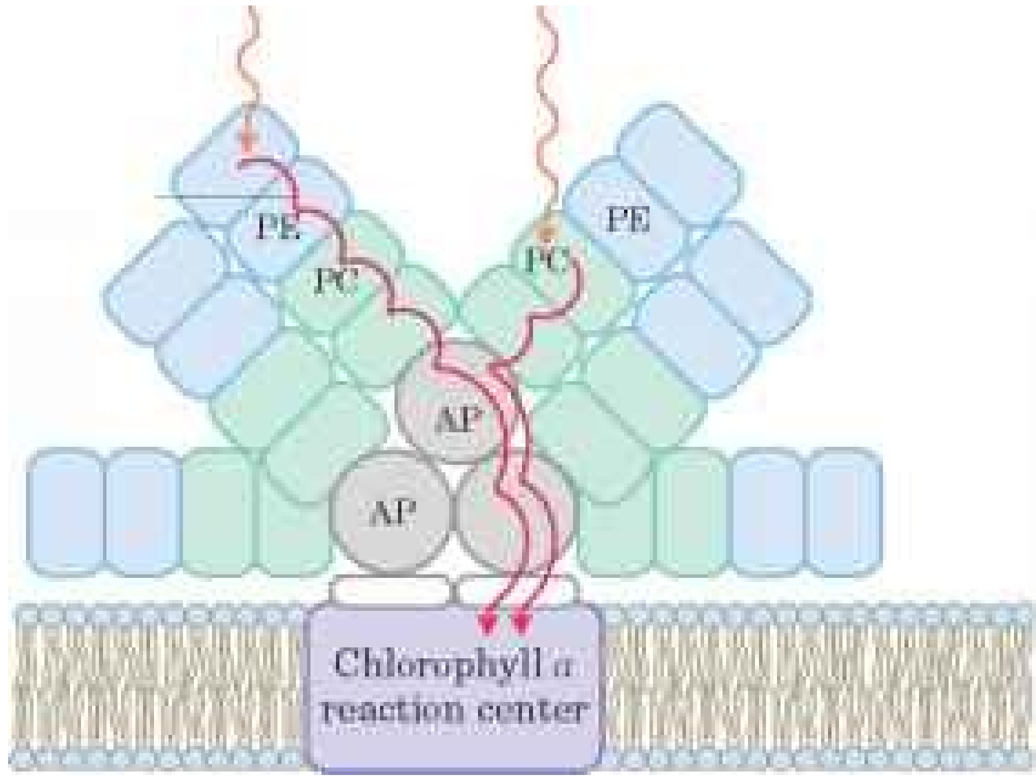
sunrise over pacific

May 14, 2012, and so Life begins ...

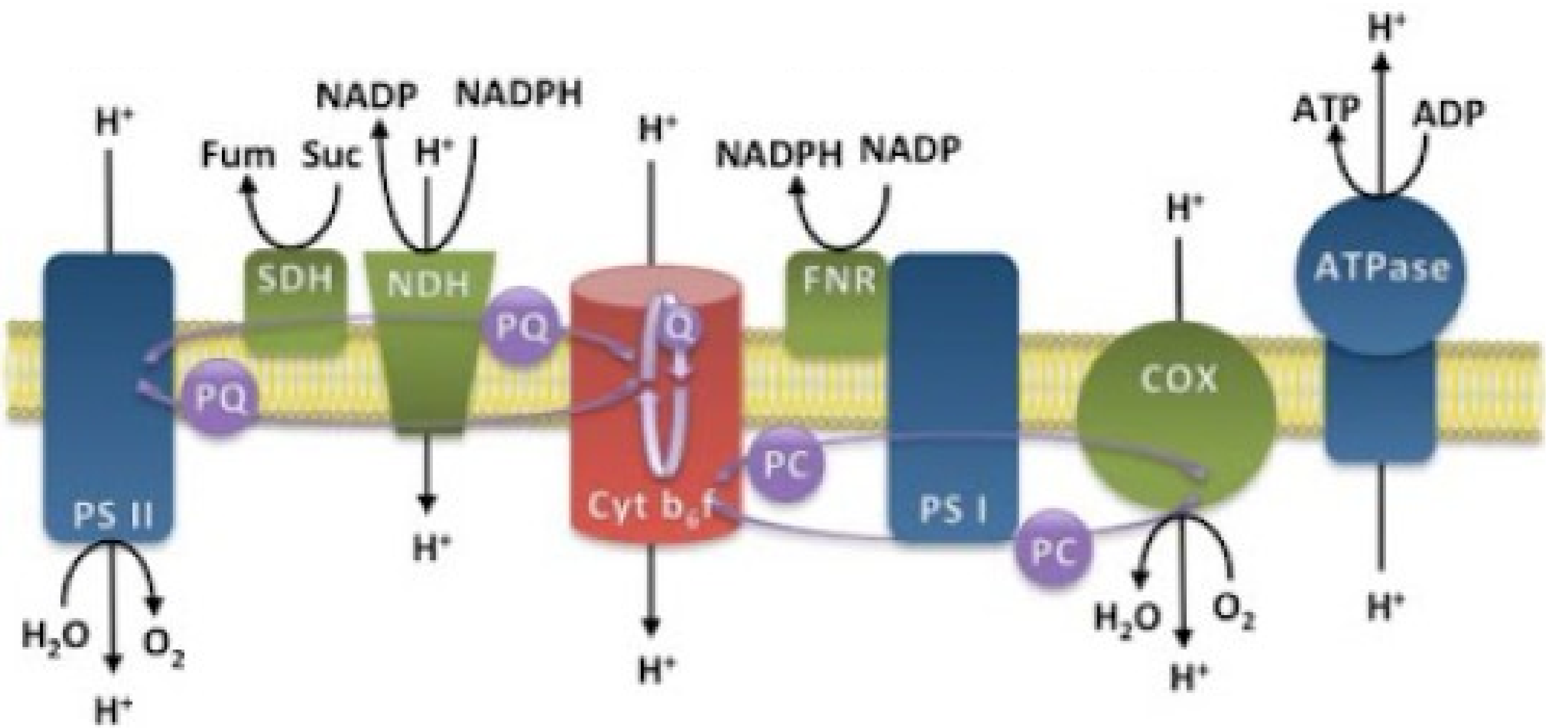


May 14, 2012, and so Life begins ...



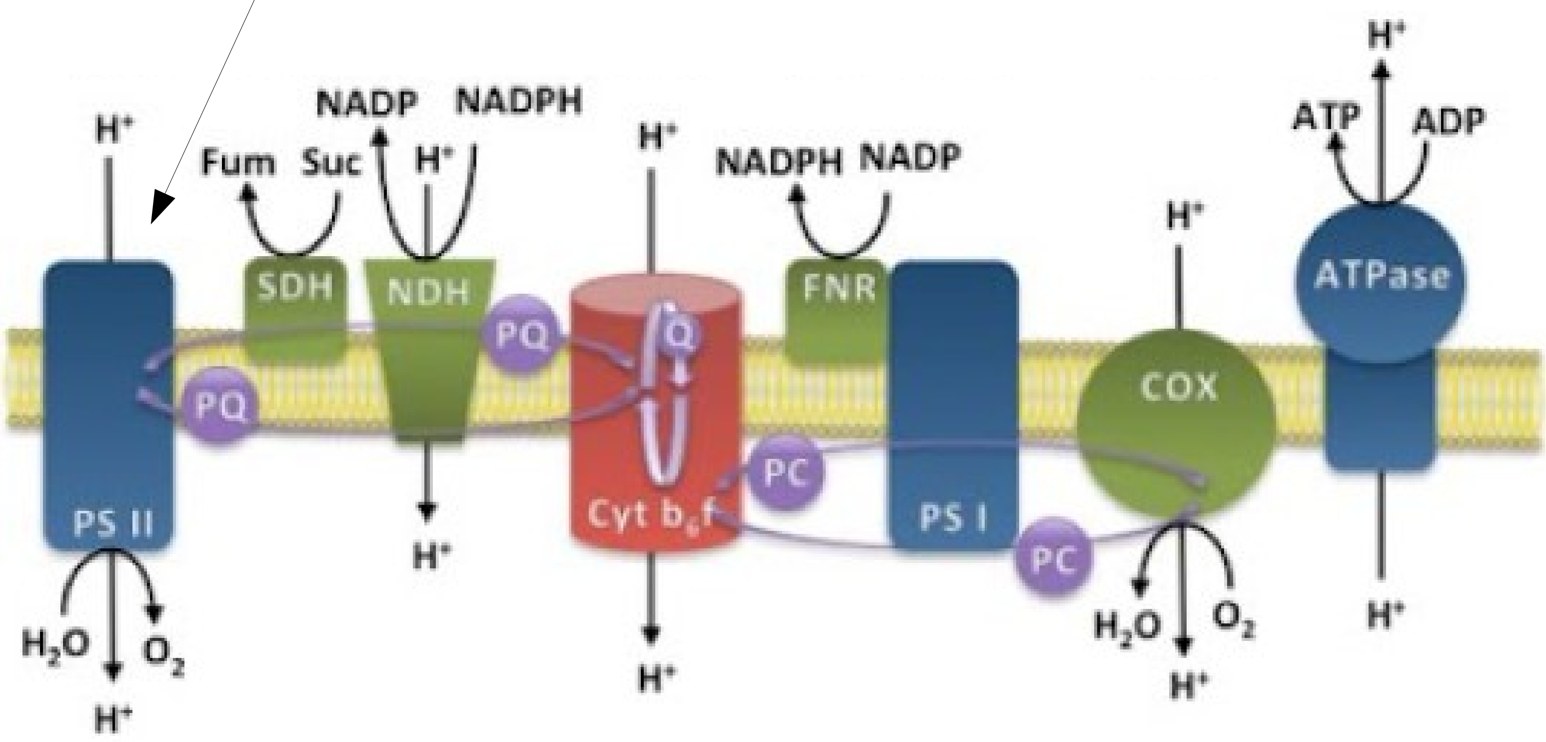


The light reactions

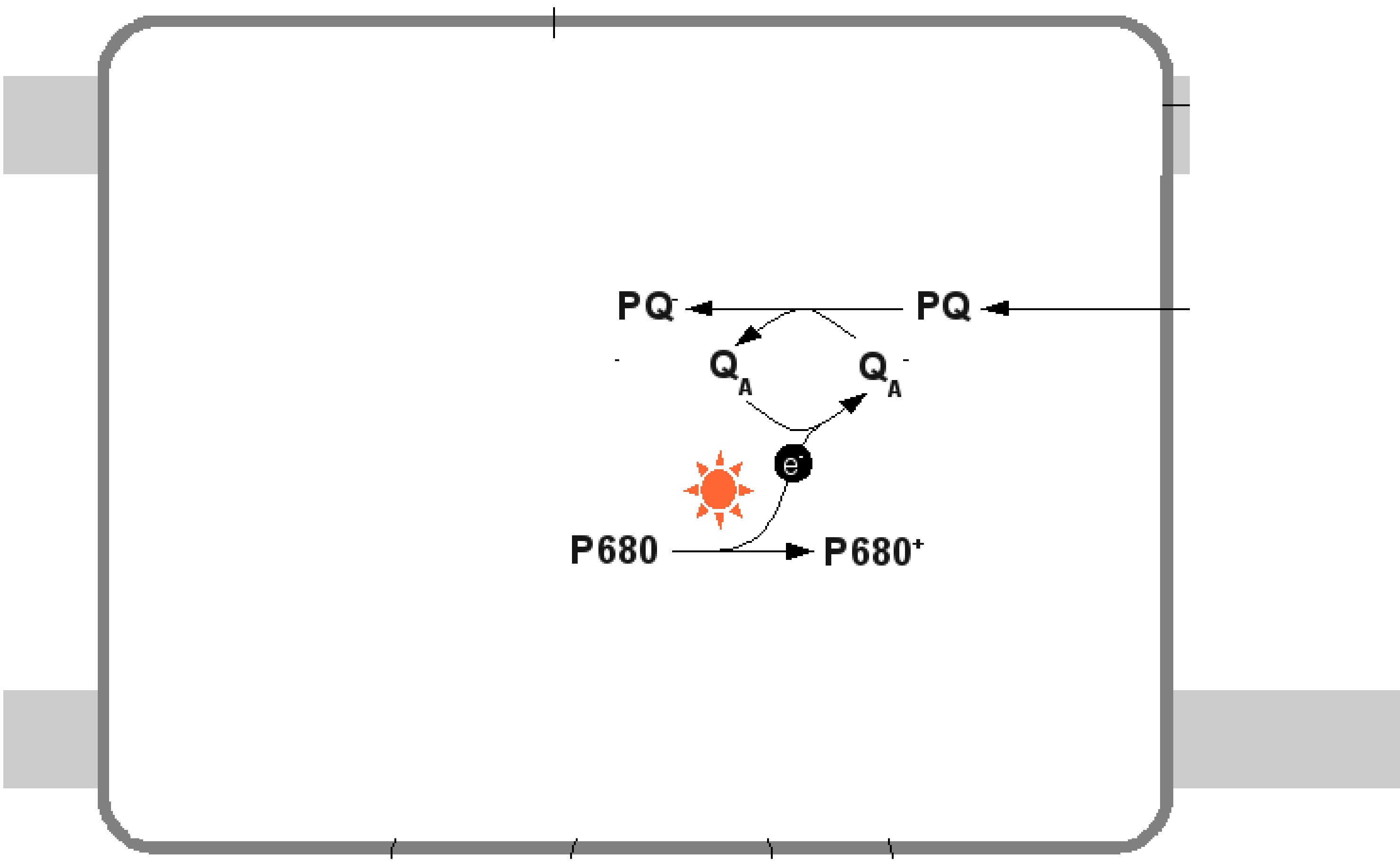


The light reactions

photosystem II



The light reactions: photosystem II



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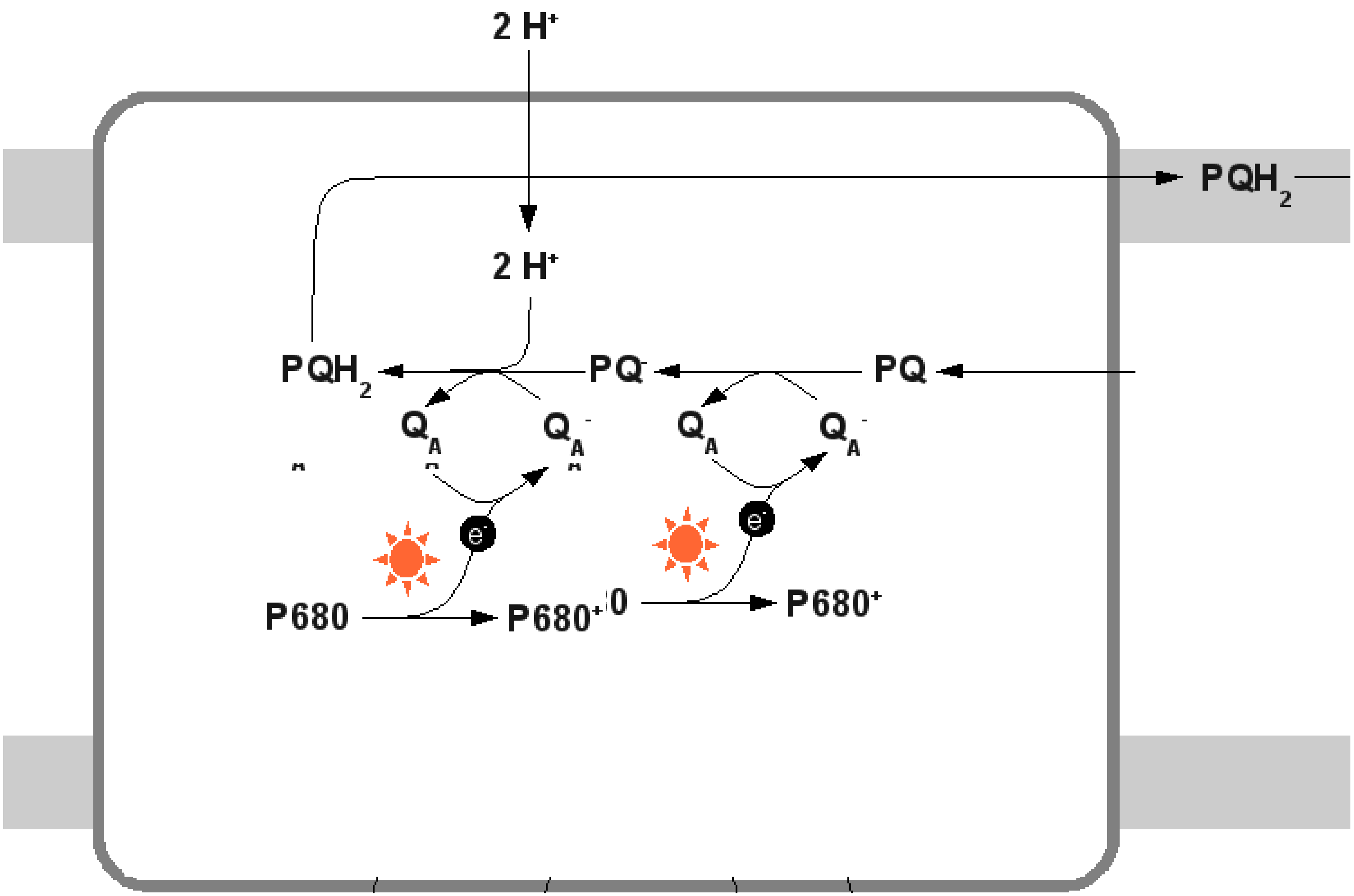

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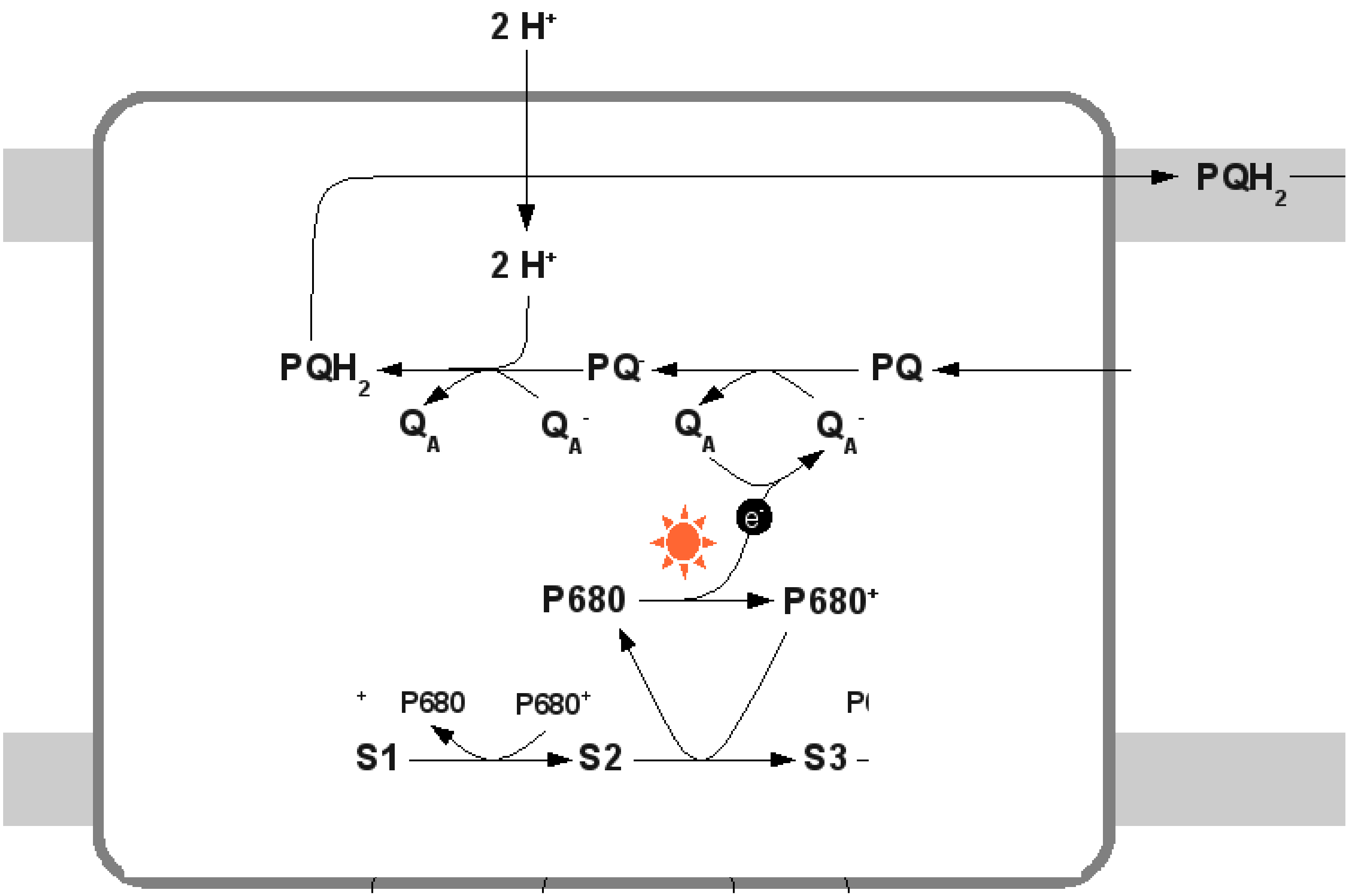

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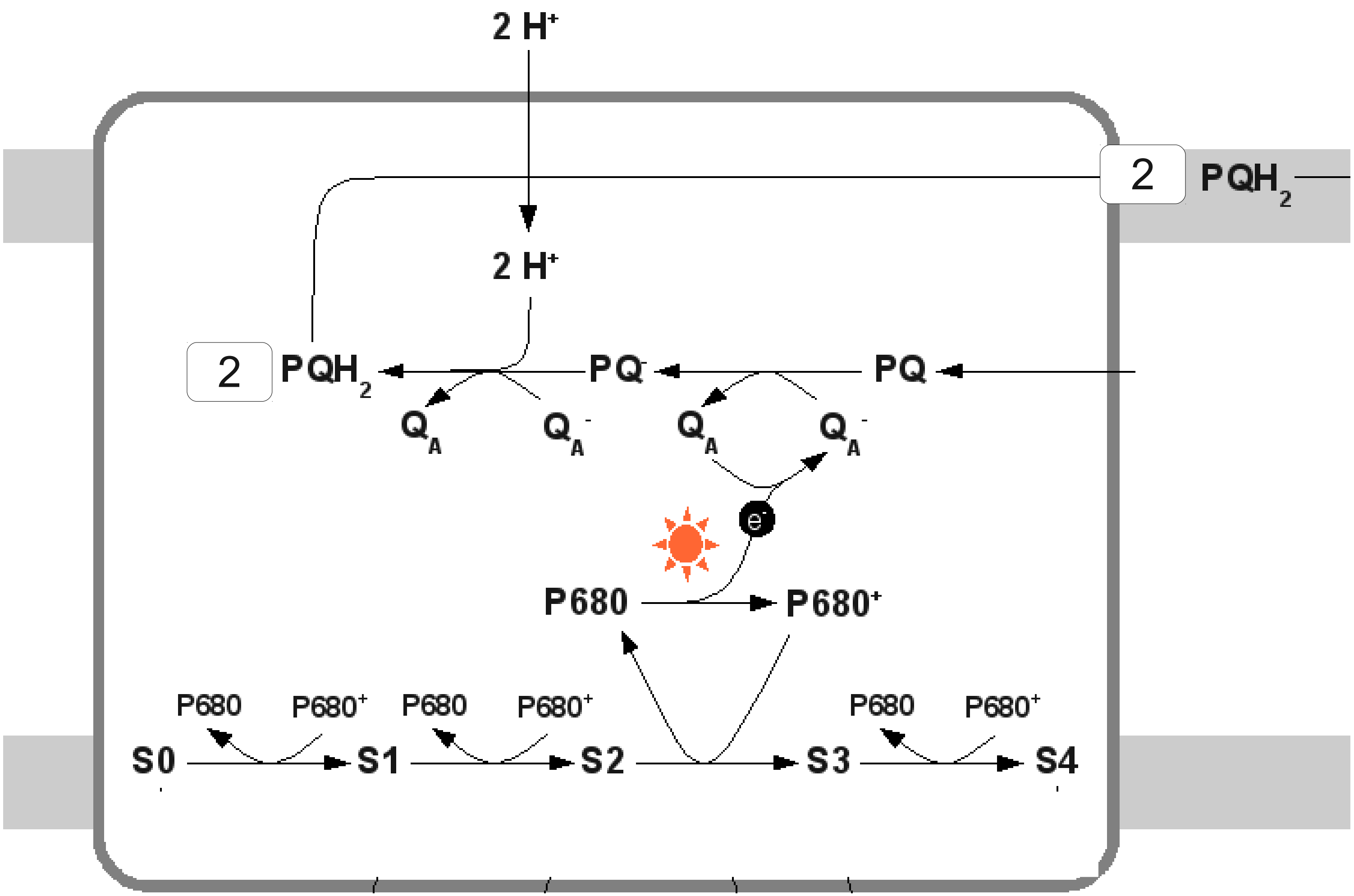

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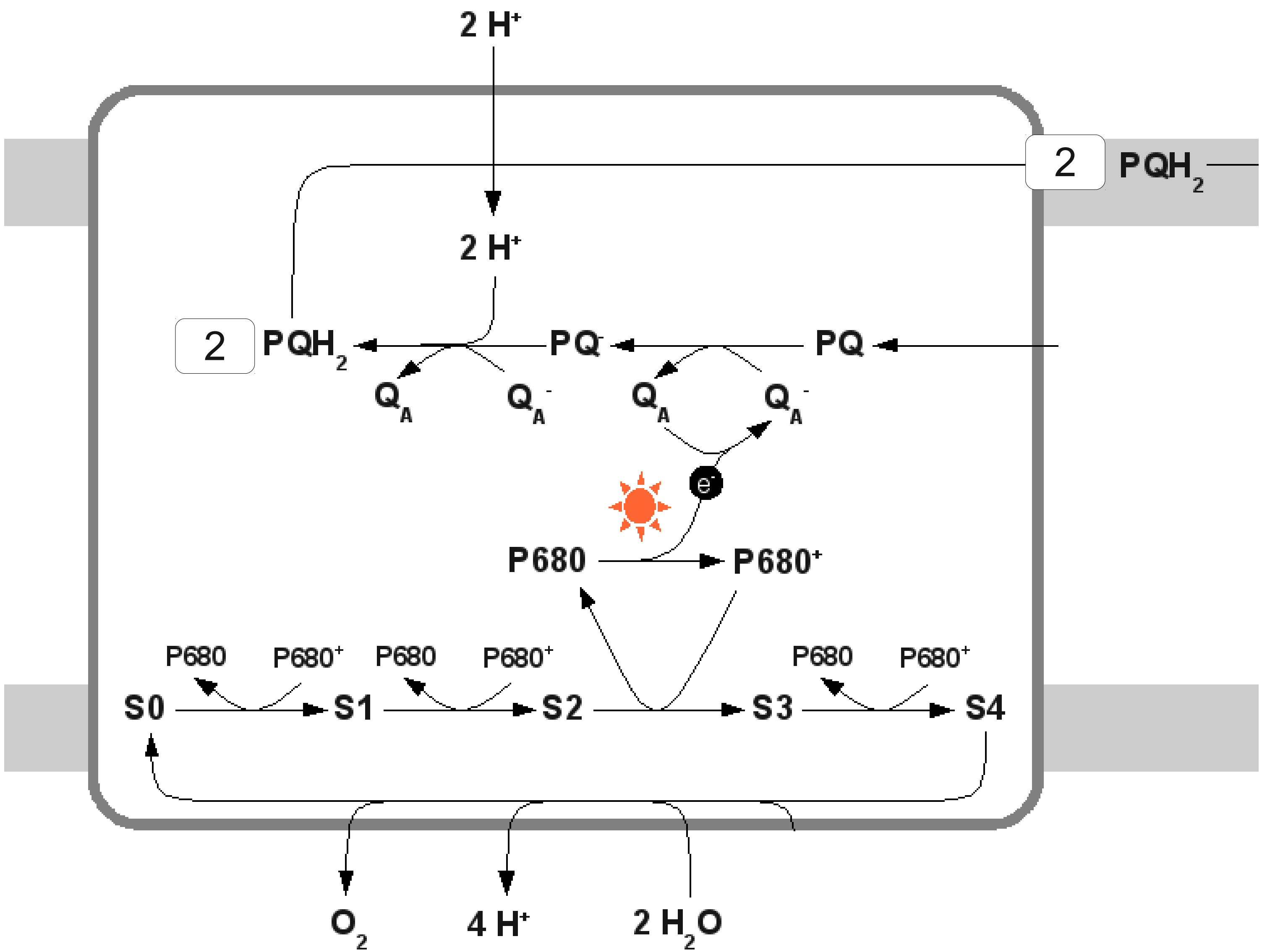

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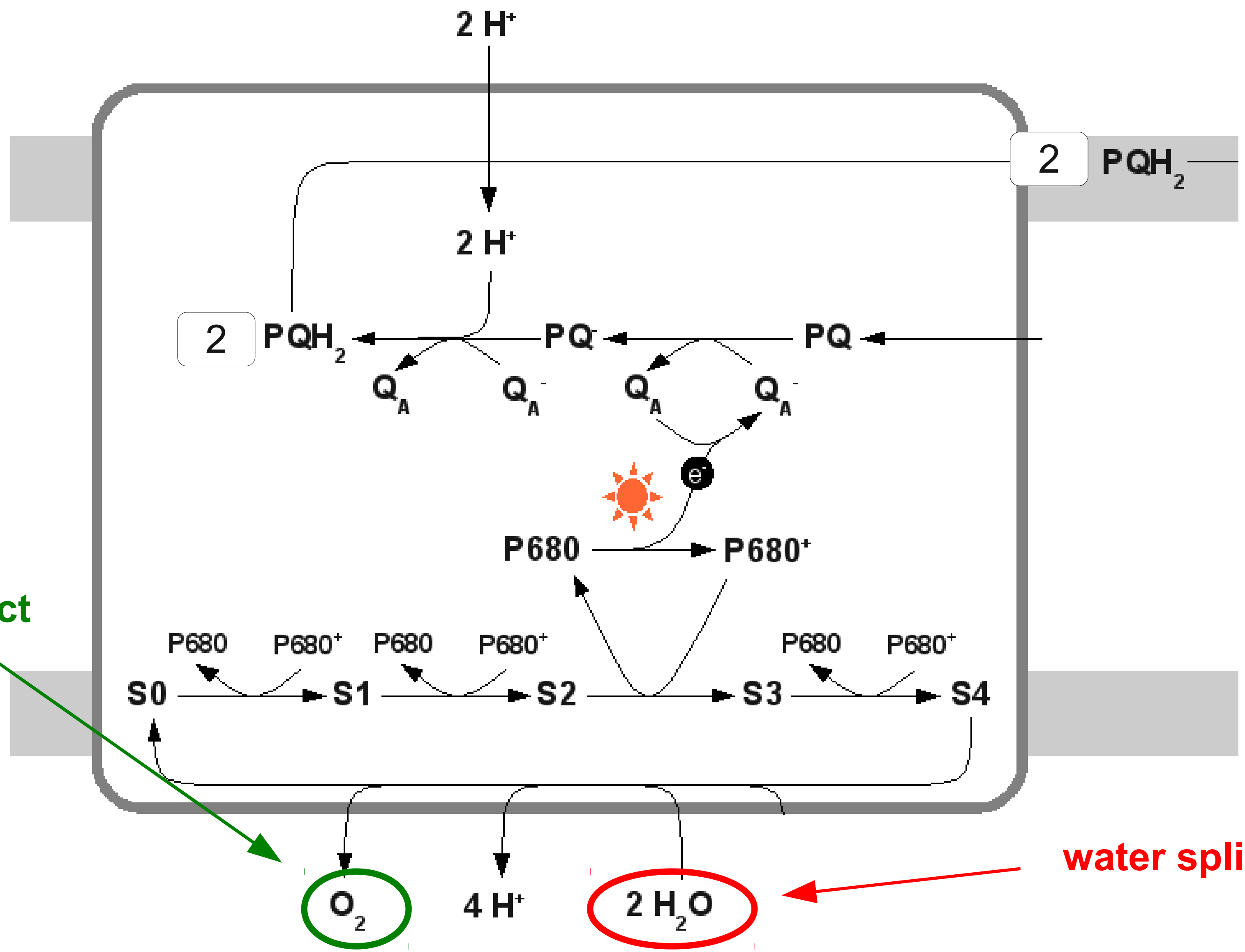
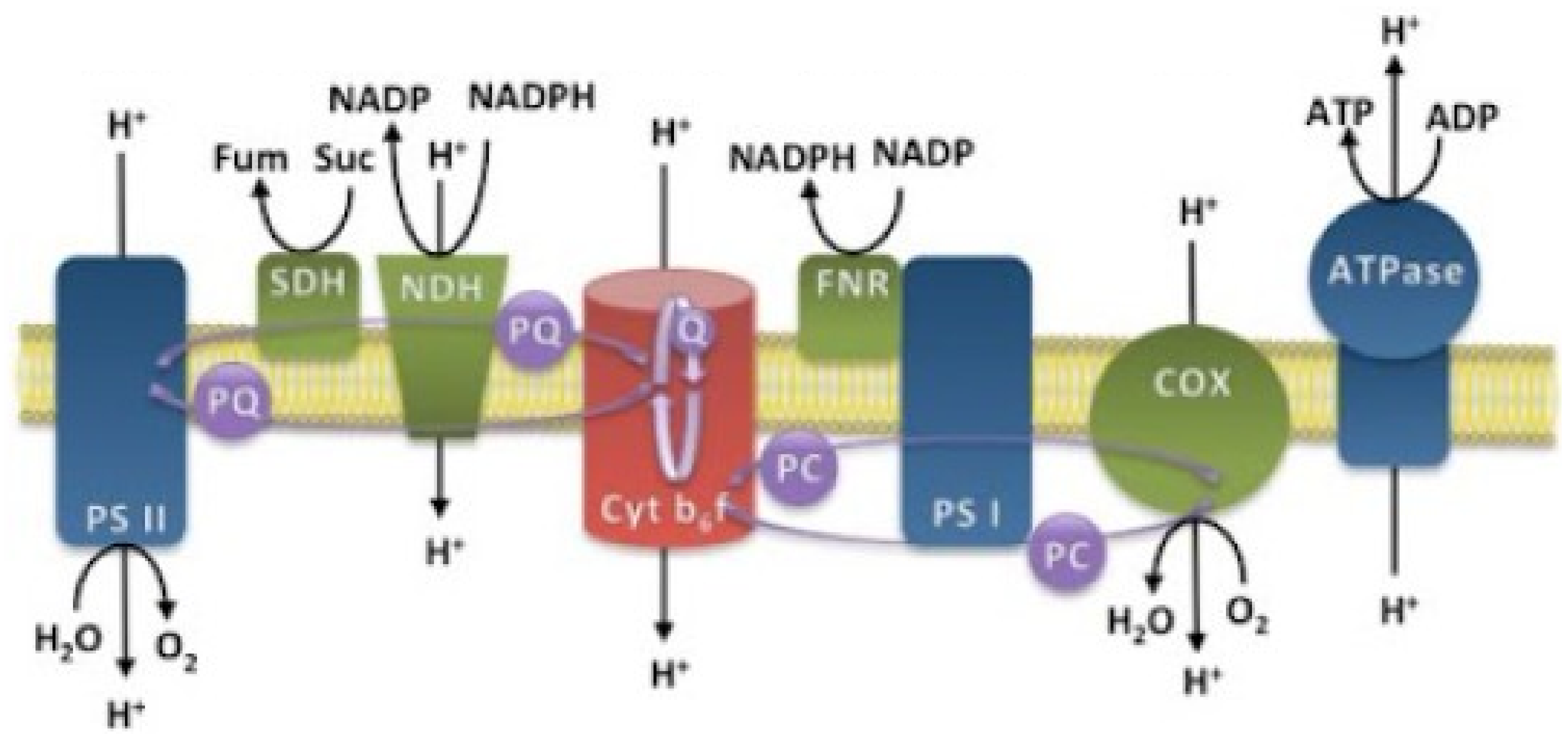


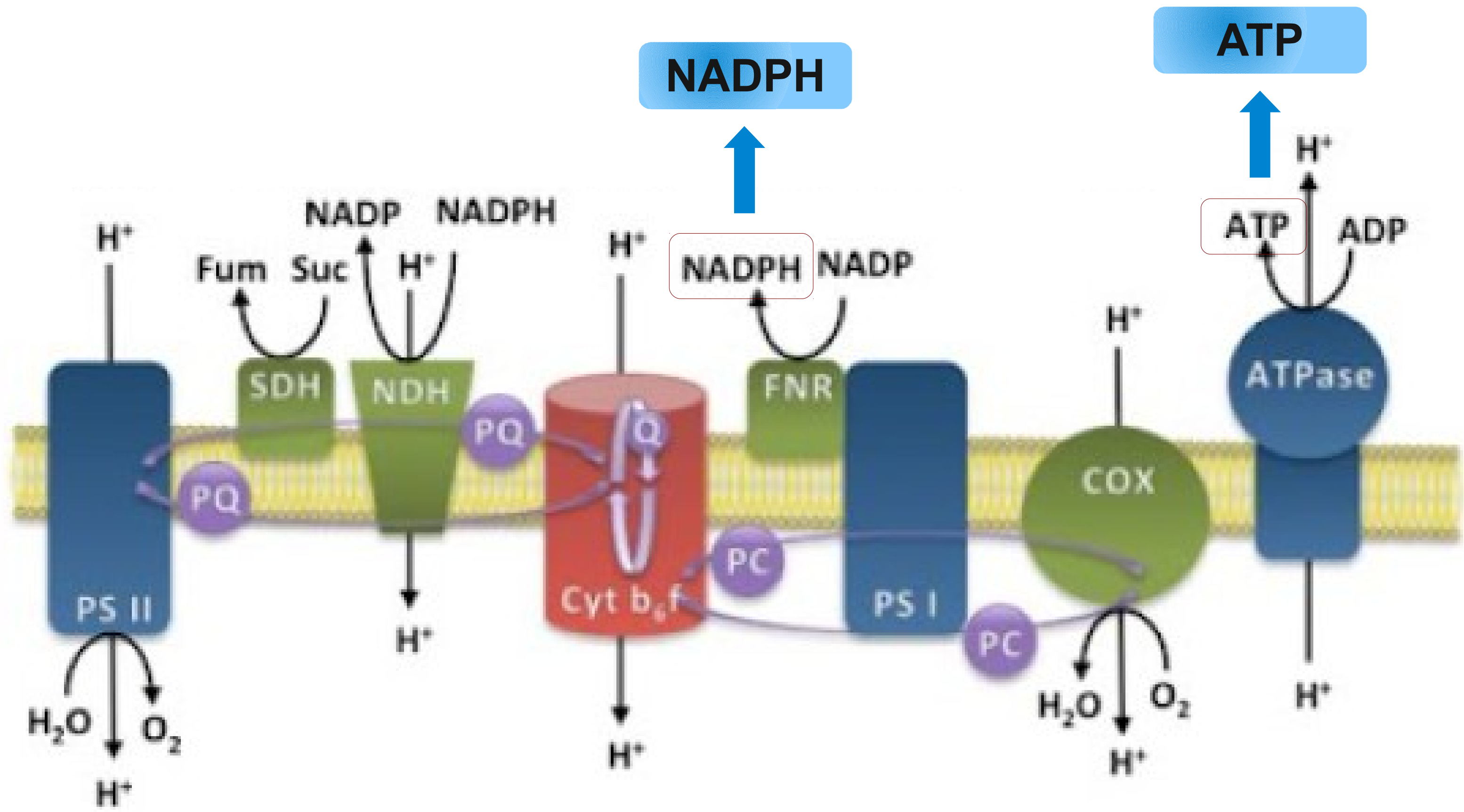
the waste product

water splitting ...

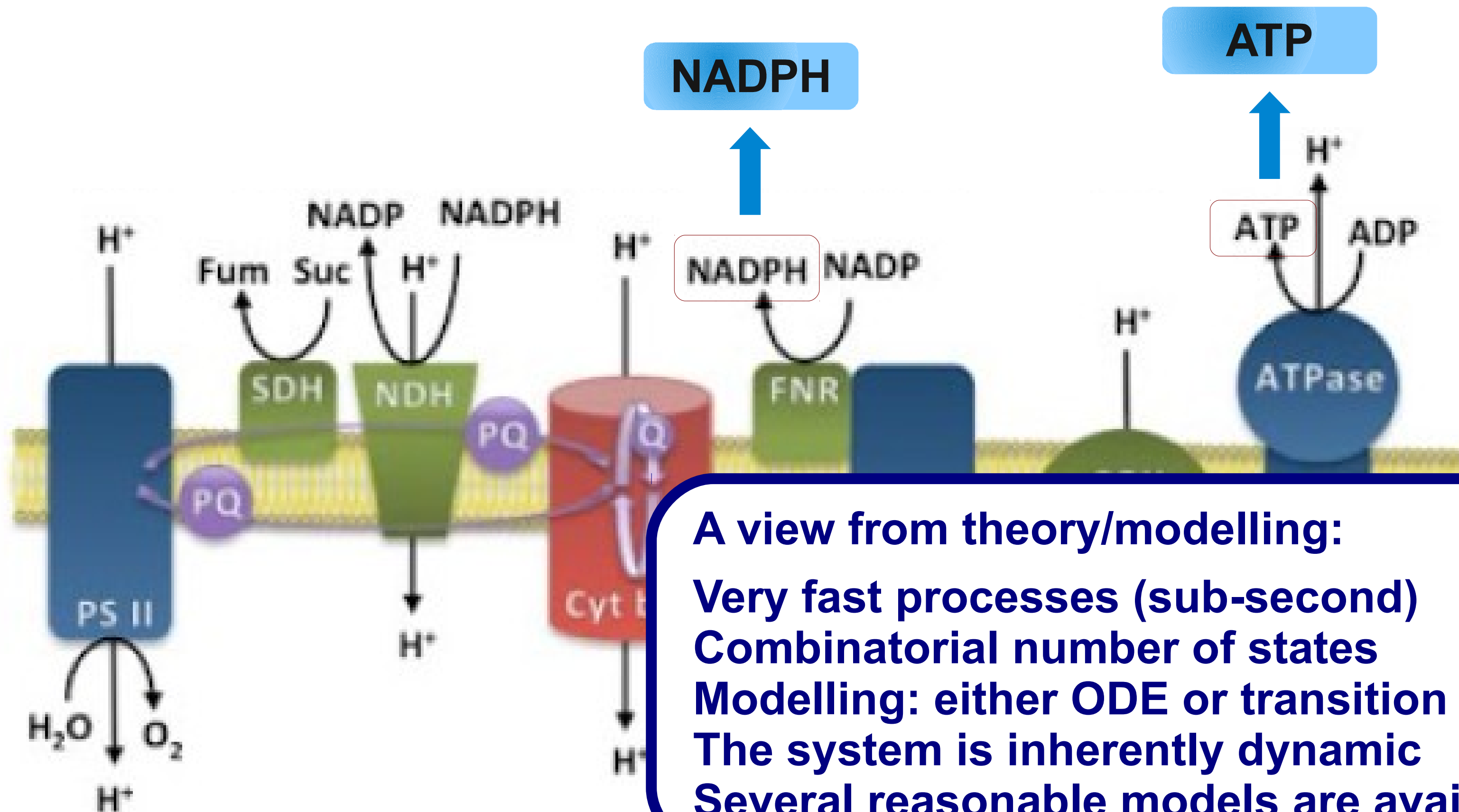
The light reactions: eating the sun



The light reactions: eating the sun



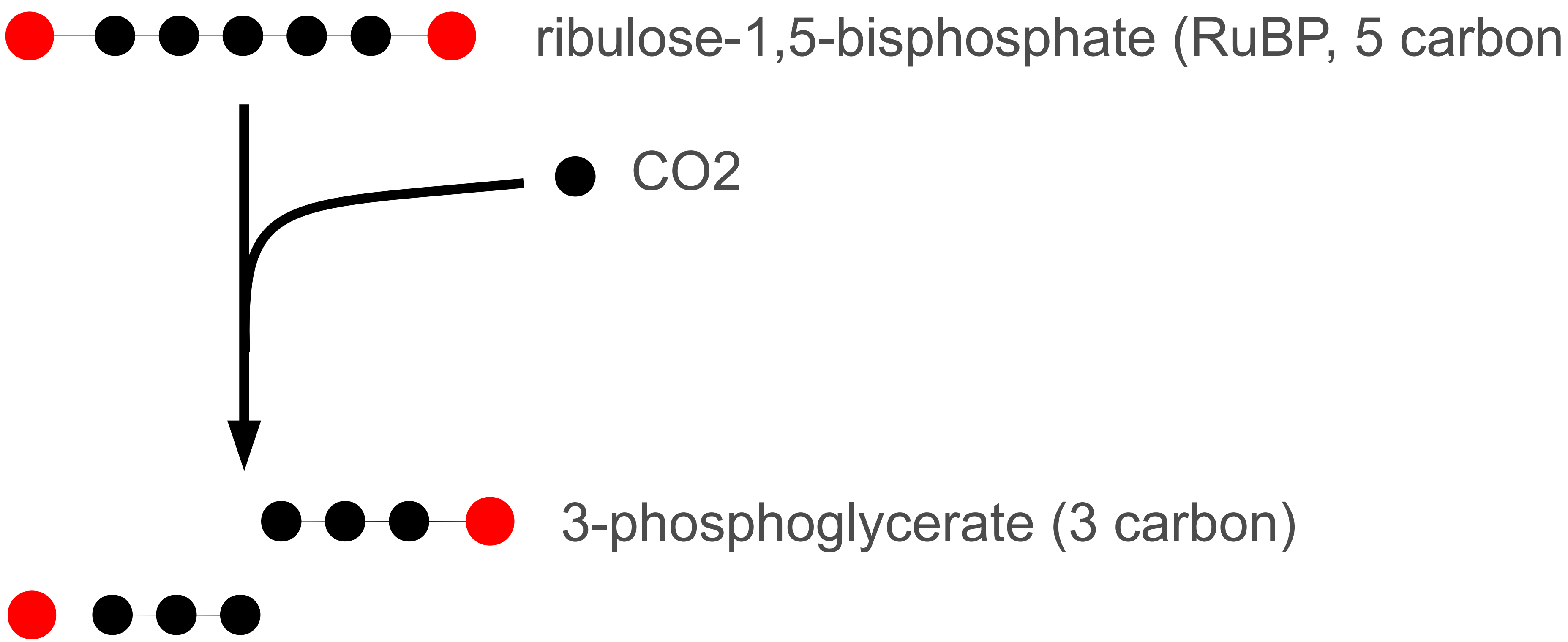
The light reactions: eating the sun



A view from theory/modelling:

Very fast processes (sub-second)
Combinatorial number of states
Modelling: either ODE or transition matrices
The system is inherently dynamic
Several reasonable models are available

Fixation of atmospheric CO_2 by RuBisCO



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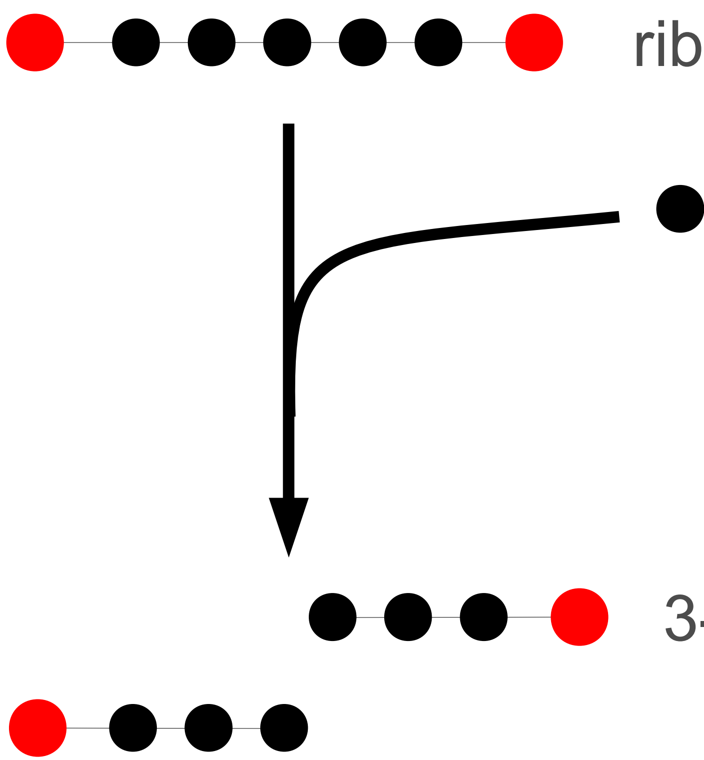

ribulose-1,5-bisphosphate (RuBP, 5 carbon)

A view from theory/modelling:

RubisCo is slow and sloppy
Only few interconversions per second
A limiting factor in phototrophic growth.
Low specificity to its substrate
Modelling: usually ODE/enzyme kinetics

3-phosphoglycerate (3 carbon)

The Calvin-Benson-Bassham (CBB) cycle: Regeneration

From: R. Steuer and B. H. Junker. (2009) Computational Models of Metabolism: Stability and Regulation in Metabolic Networks. Advances in Chemical Physics, Volume 142

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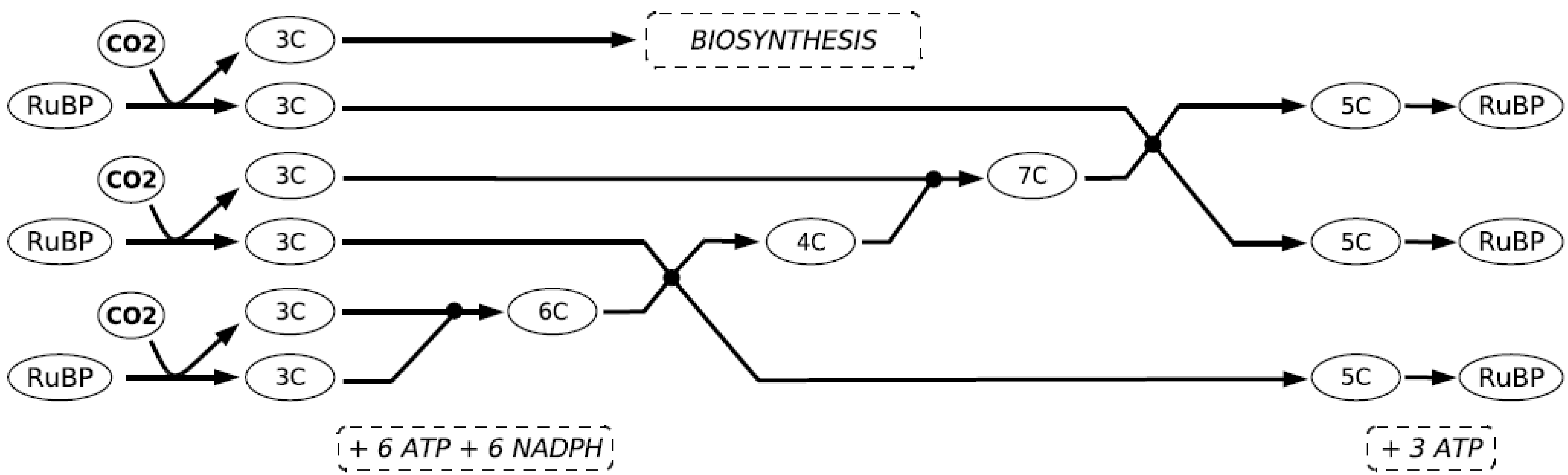

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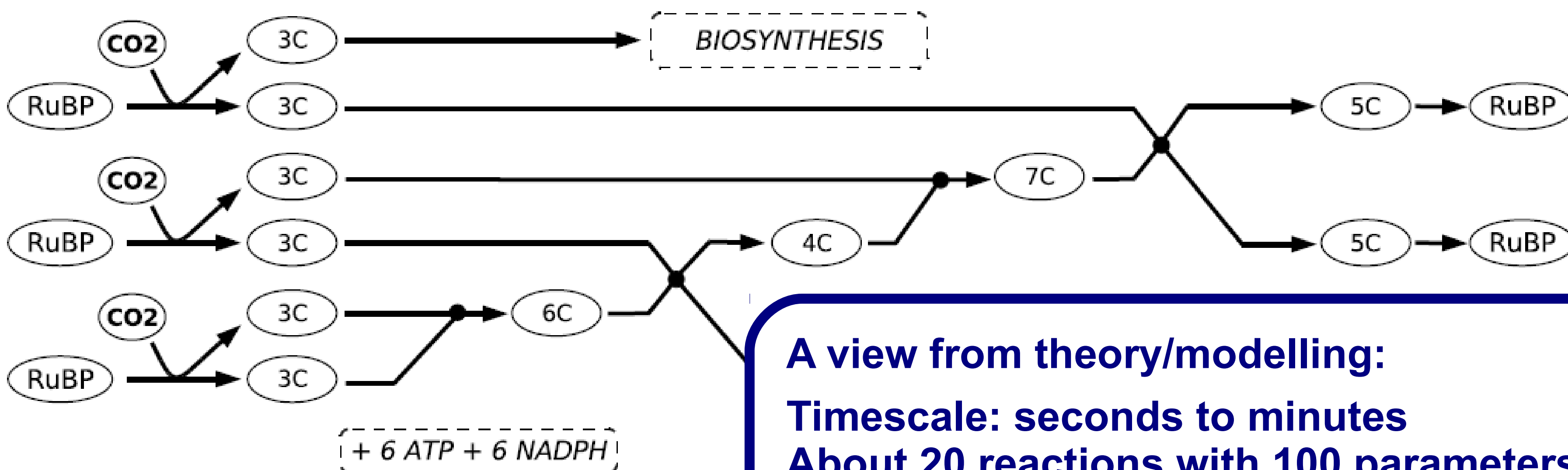

A view from theory/modelling:

Timescale: seconds to minutes
About 20 reactions with 100 parameters.
Typically implemented as ODE model
Q: are there alternative cycles?

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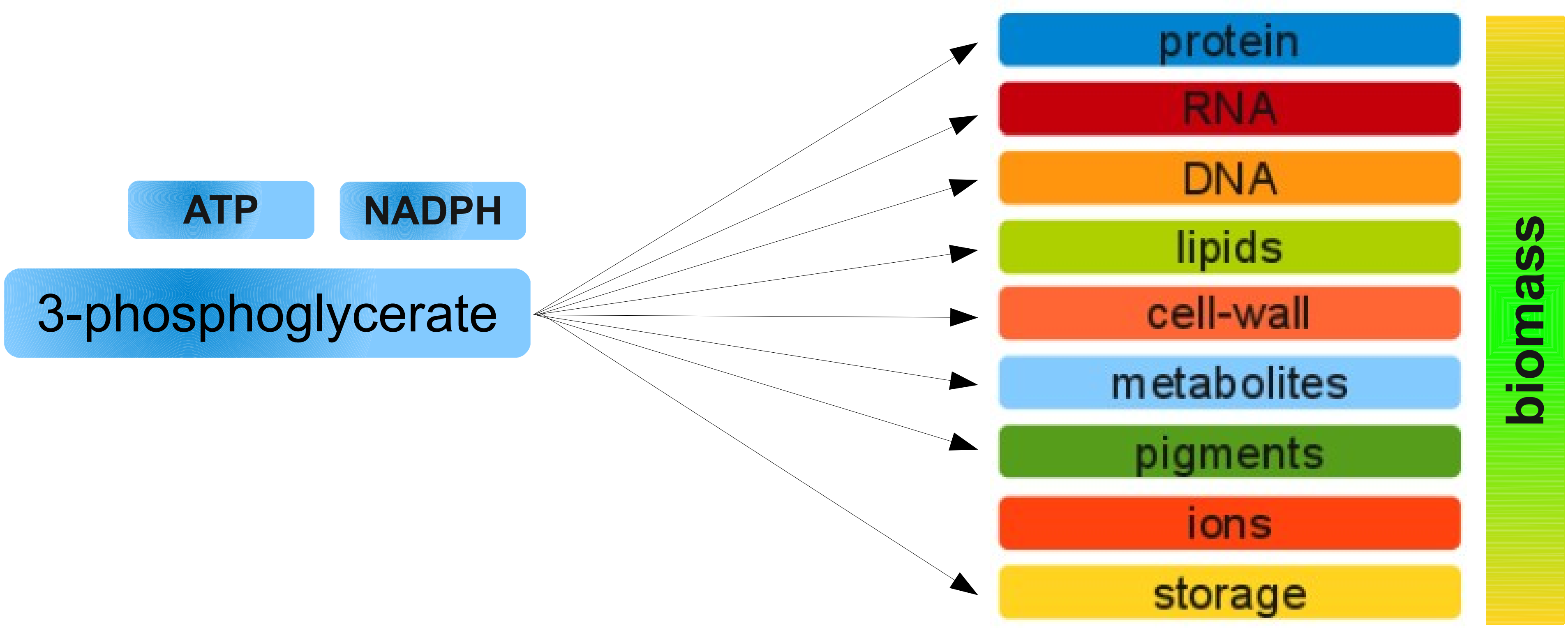
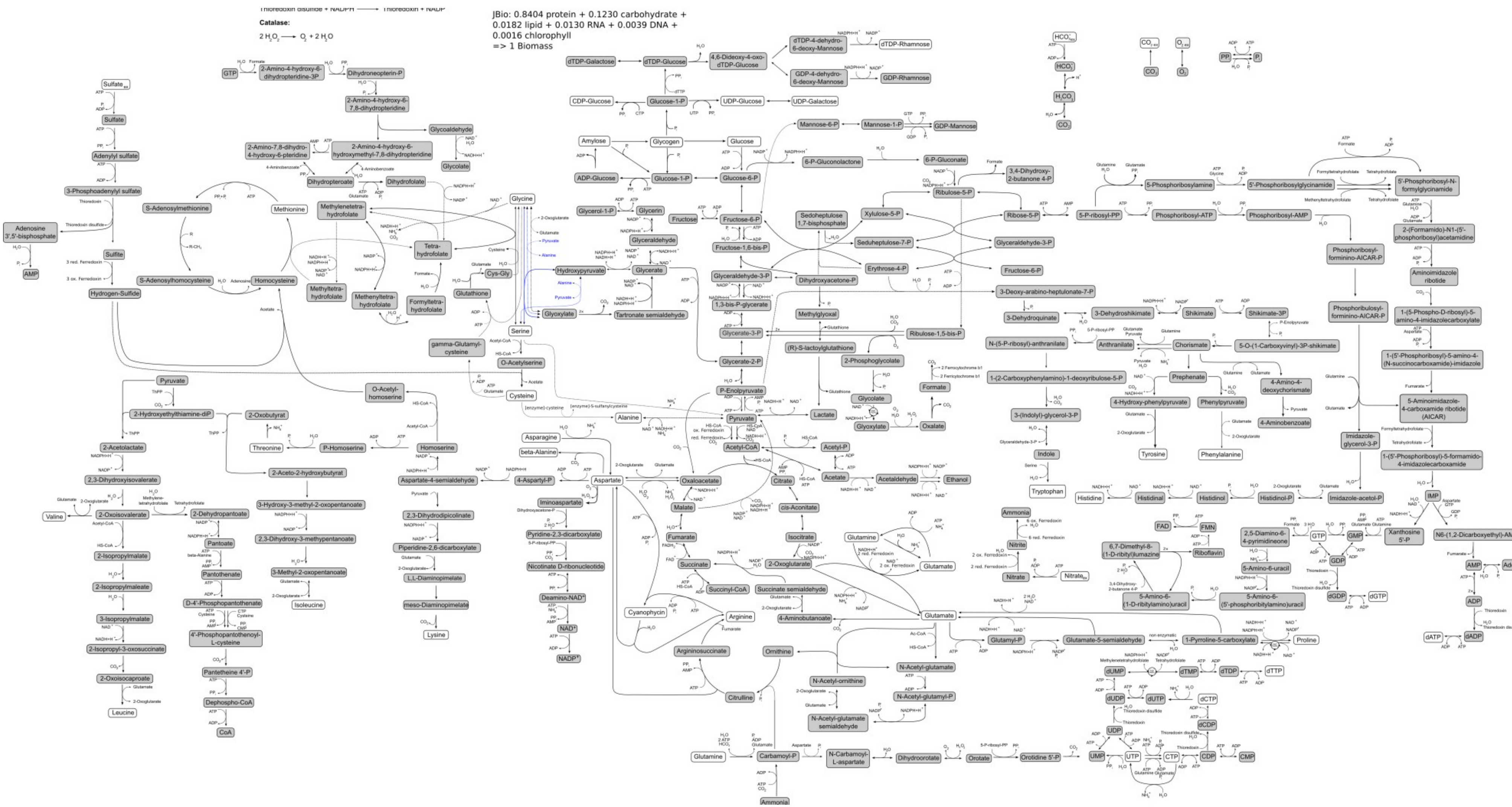
The Calvin-Benson-Bassham (CBB) cycle: Regeneration



Cellular metabolism: facilitated by a network of reactions



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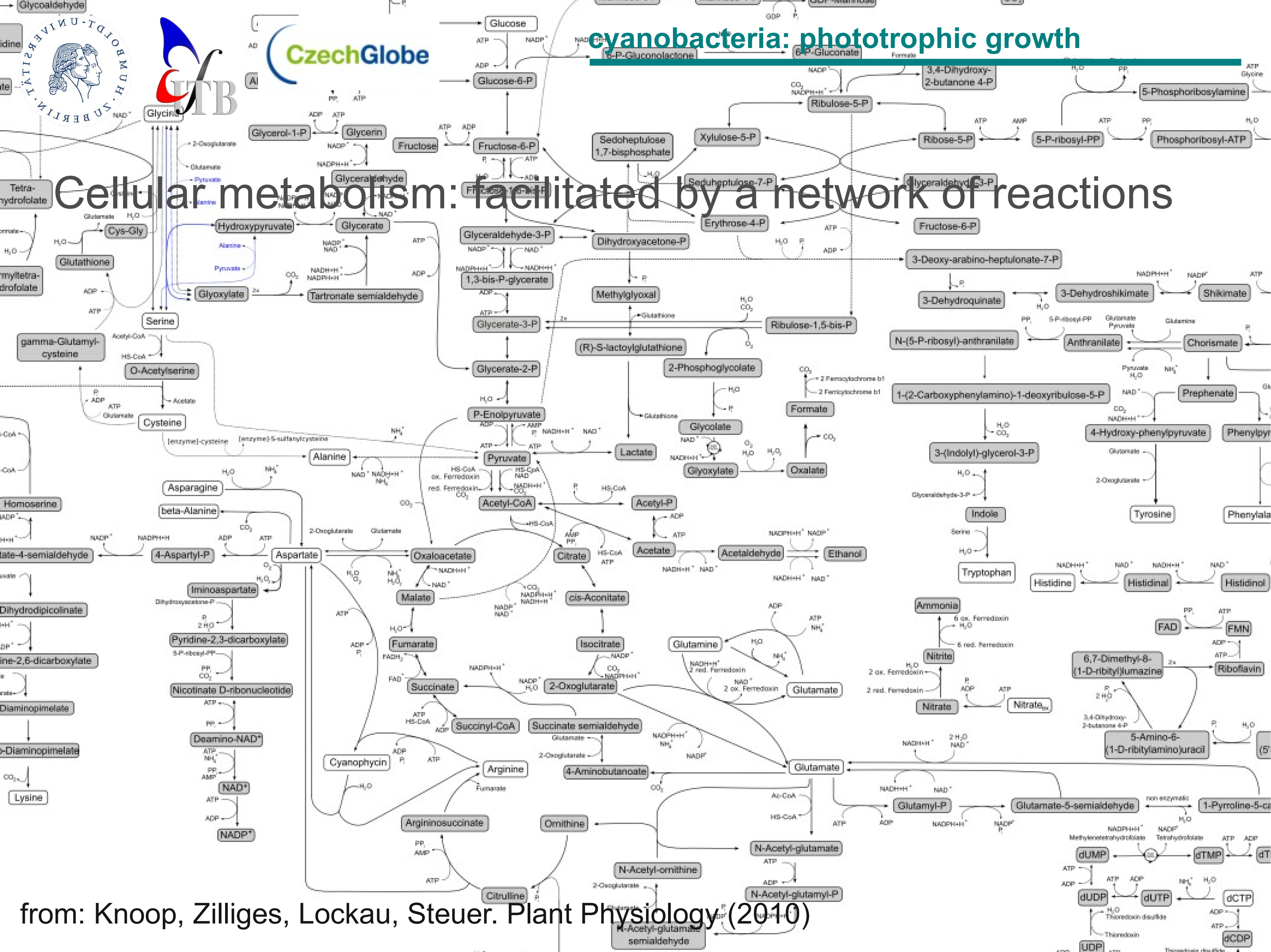

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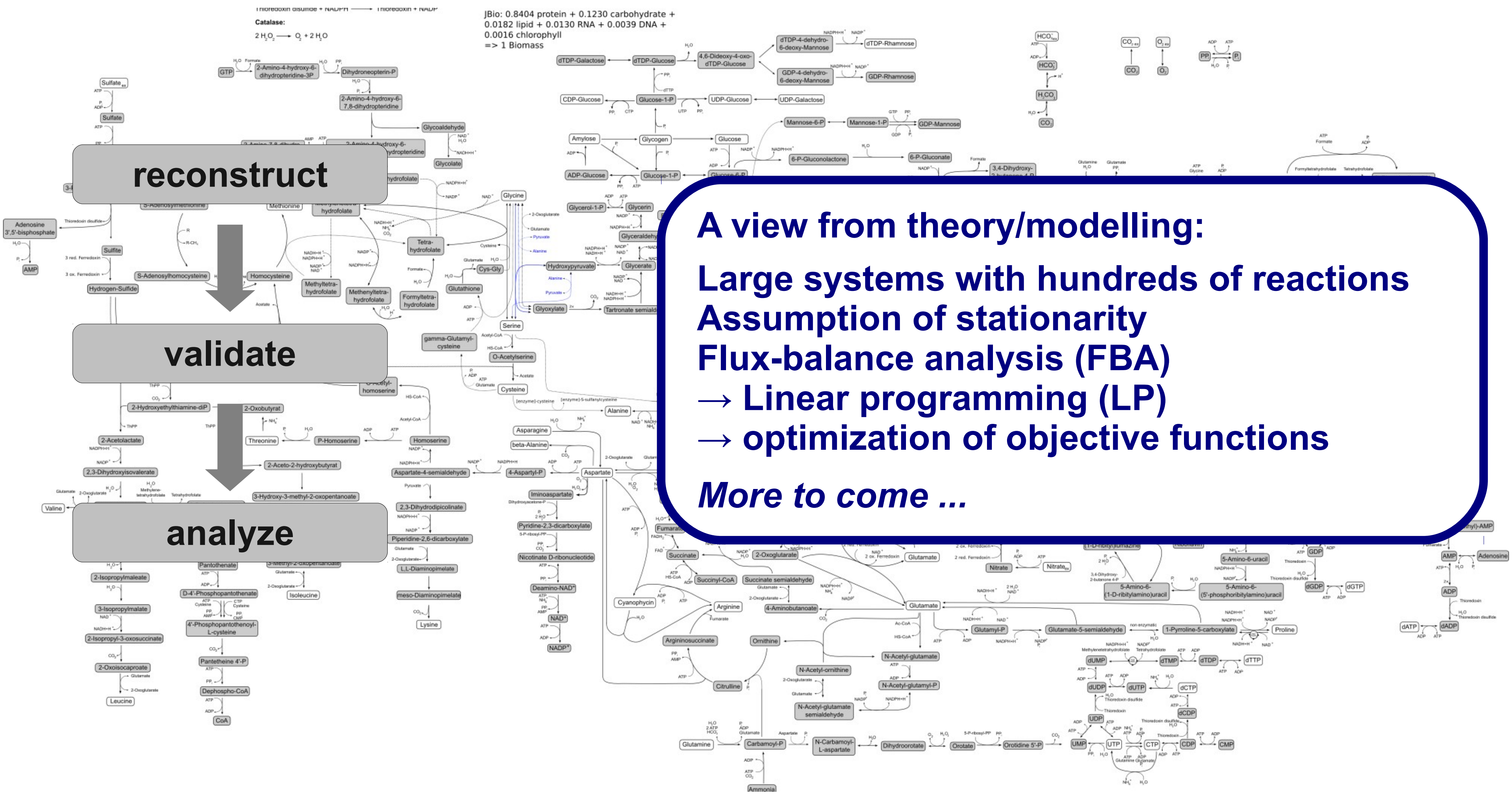

reconstruct

validate

analyze

A view from theory/modelling:

Large systems with hundreds of reactions
Assumption of stationarity
Flux-balance analysis (FBA)
→ Linear programming (LP)
→ optimization of objective functions

More to come ...

from: Knoop, Zilliges, Lockau, Steuer. Plant Physiology (2010)

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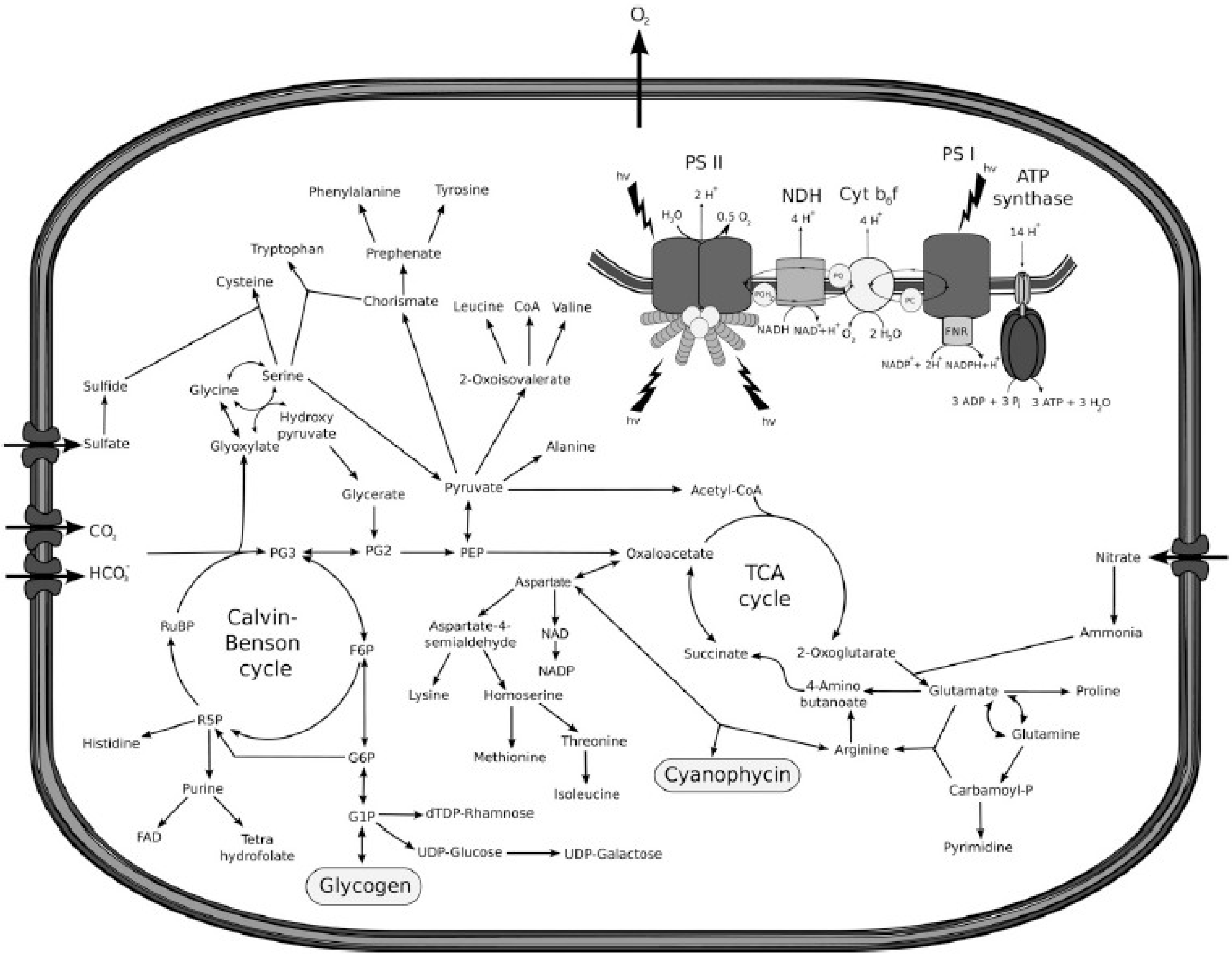

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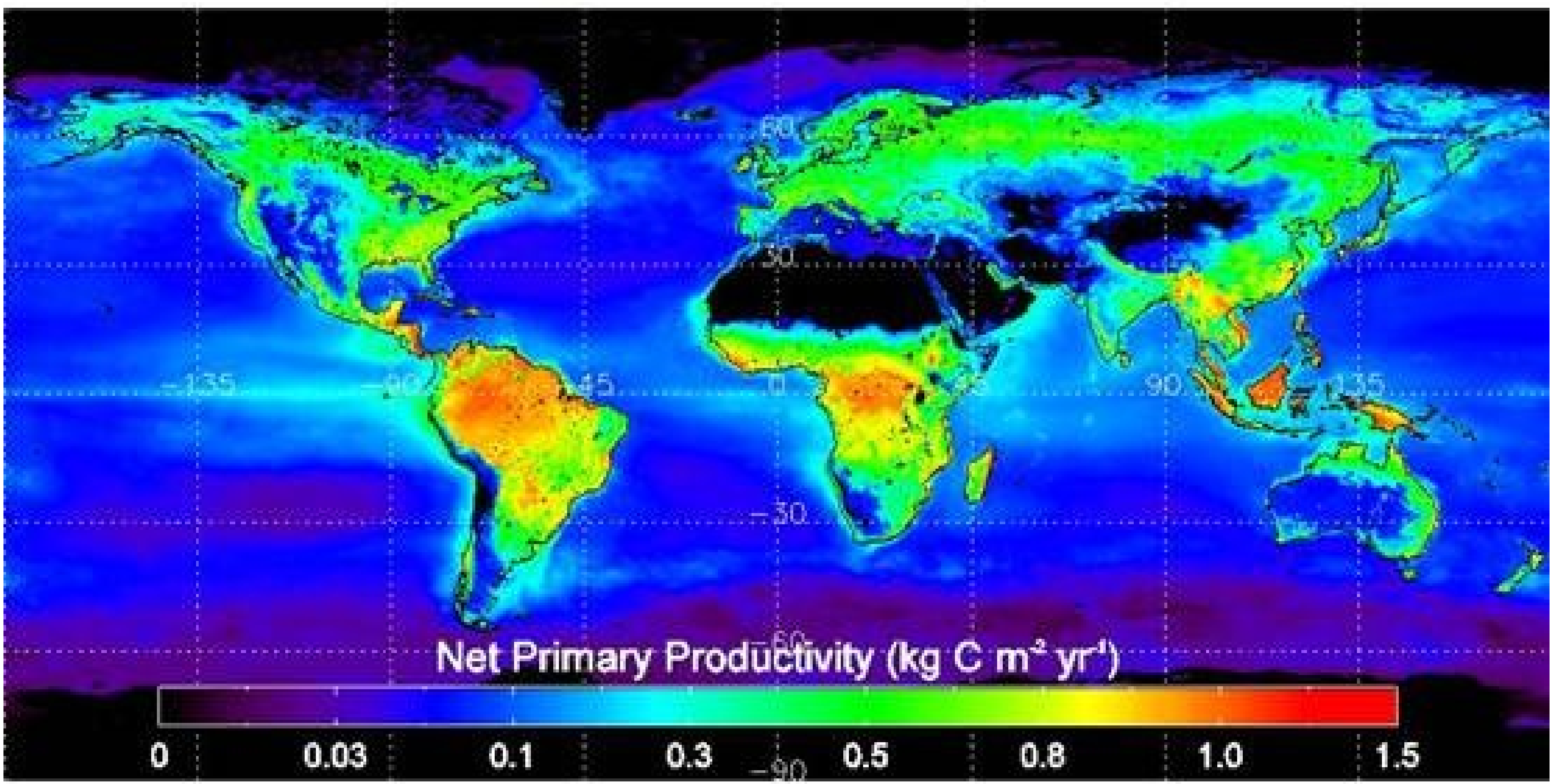
Phototrophic growth and the environment:



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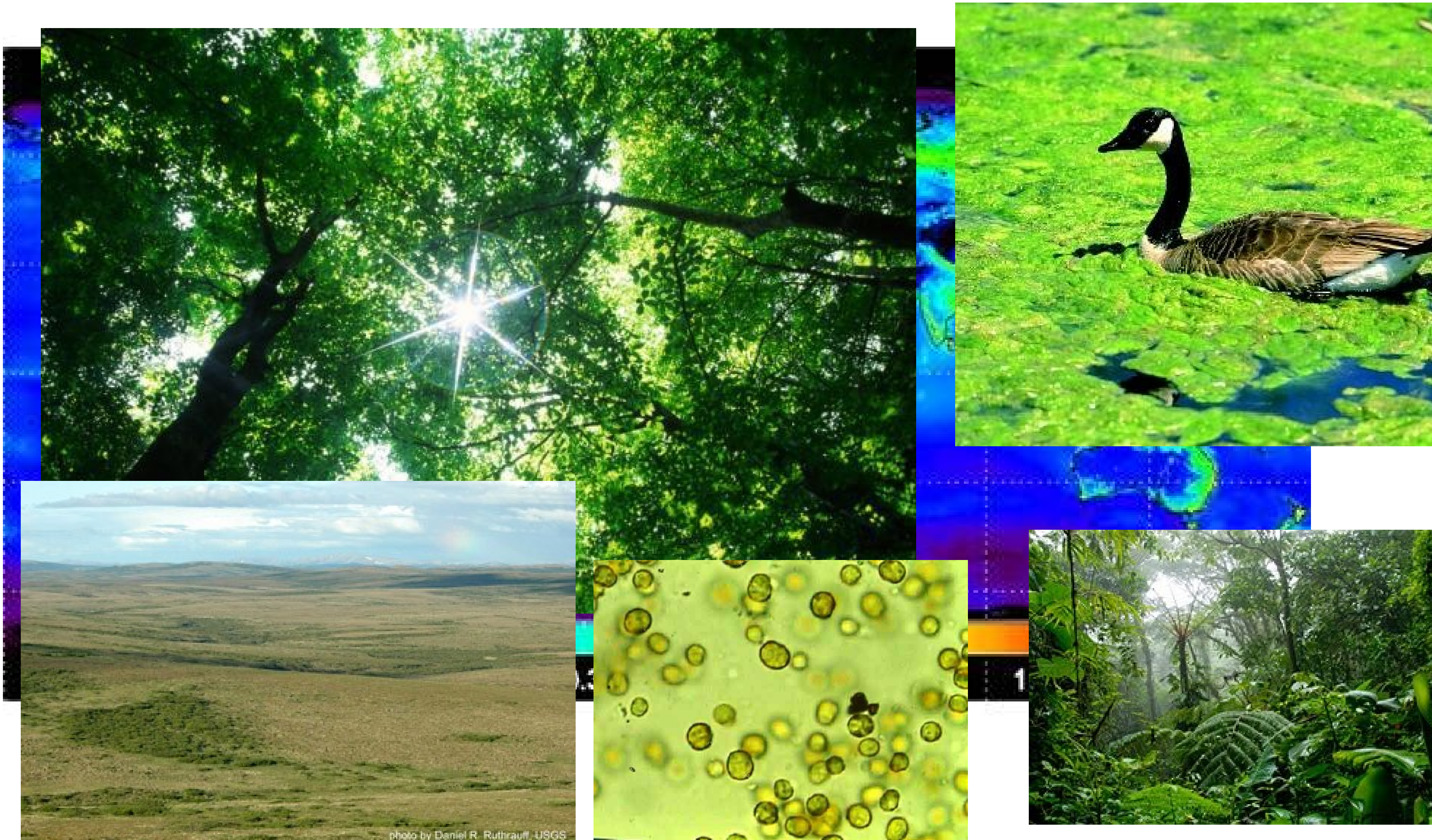
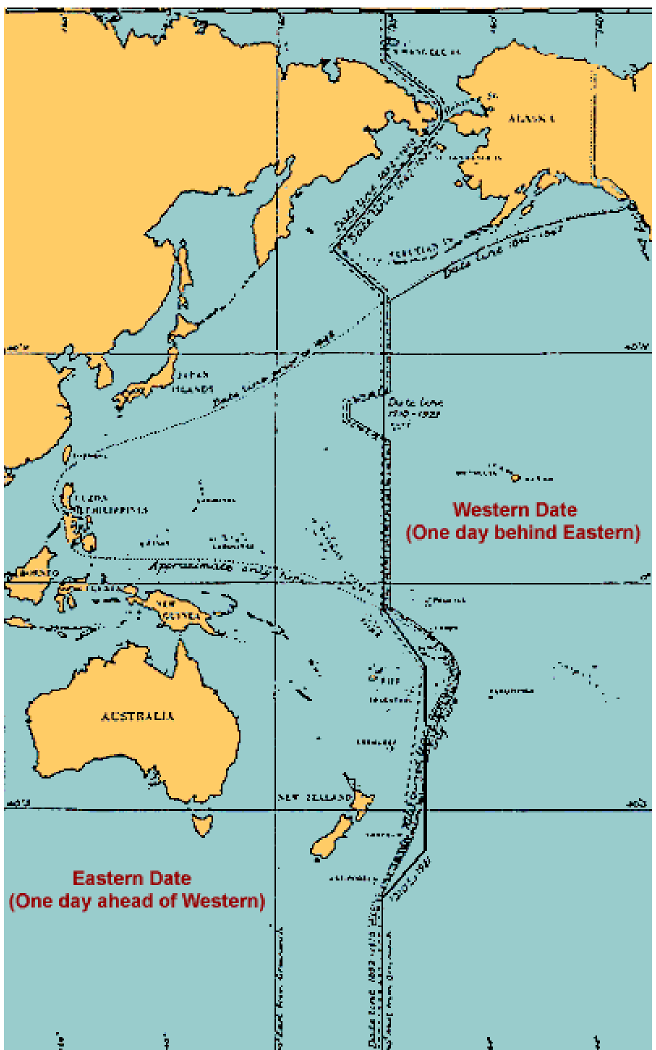


May 14, 2012, 11:59pm, by the end of the day ...



1.1×10^{19} joule solar energy is absorbed by Earth's atmosphere, oceans and land masses per day …

600 000 000 tons of carbon fixed by photosynthesis

120 Gt carbon per year (land)

90 Gt carbon per year (ocean)

Cyanobacteria: a hierarchy of processes

We aim to understand the life and growth of cyanobacteria

Cyanobacteria: a hierarchy of processes

We aim to understand the life and growth of cyanobacteria

The CyanoTeam and CyanoNetwork

An association between several groups from EU, Israel, and USA to model and understand a cyanobacterial cell *in silico*.

International team led by John Whitmarsh
Coordinator local experimental team: Ladislav Nedbal
Coordinator local modelling team: Ralf Steuer

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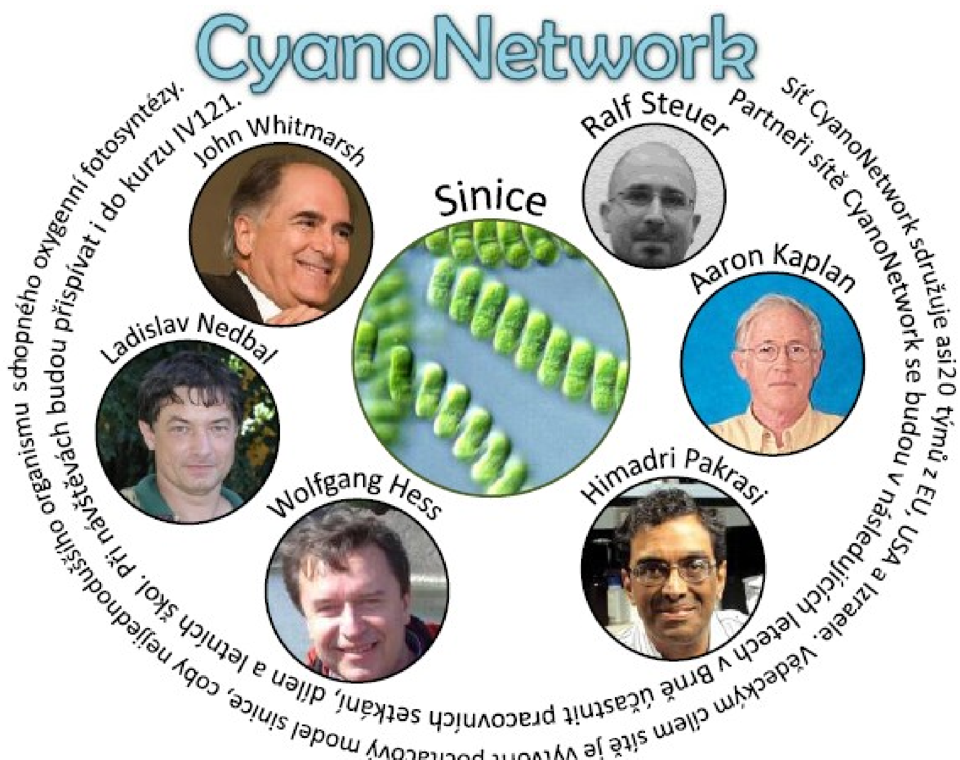
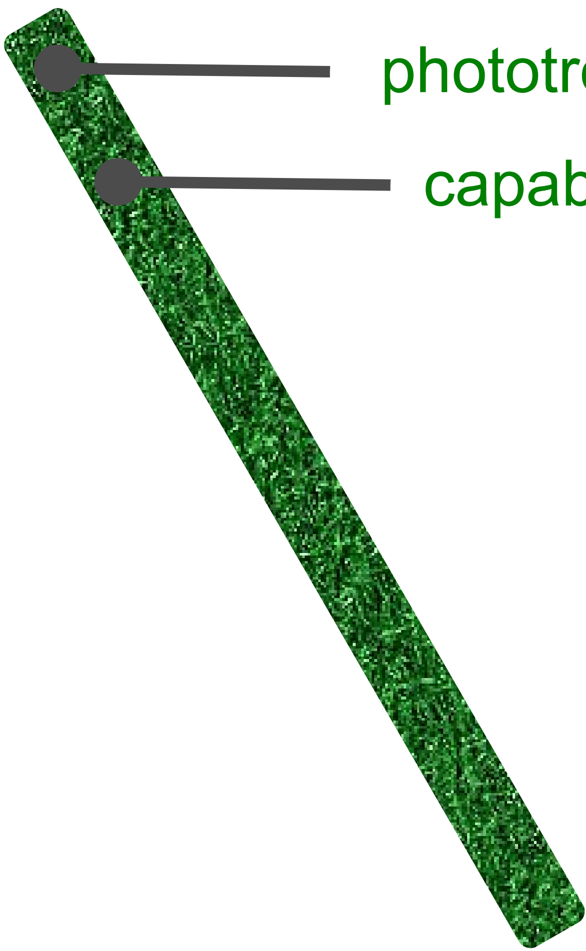


Cyanobacteria: understanding phototrophic growth



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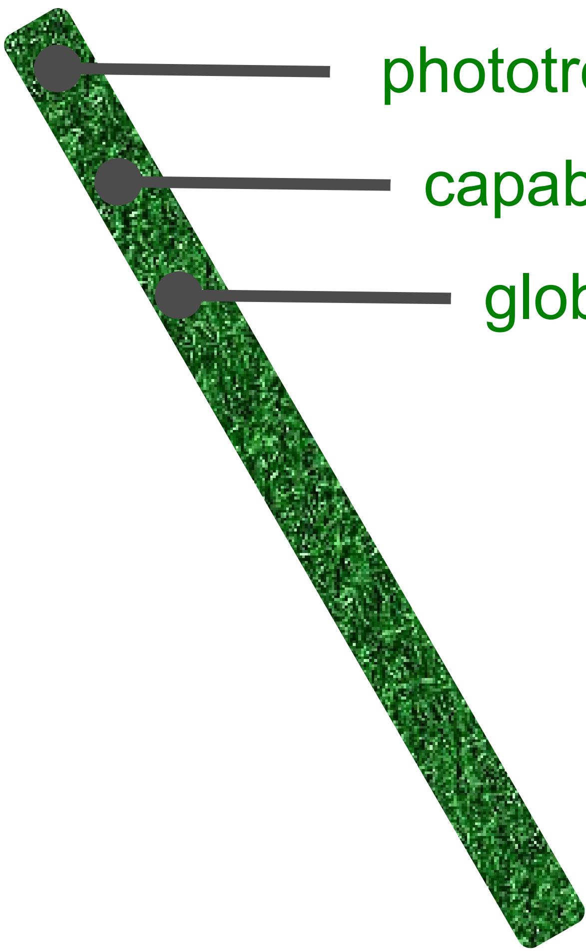


phototrophic micro-organisms (prokaryotes)

capable of oxygen-evolving photosynthesis

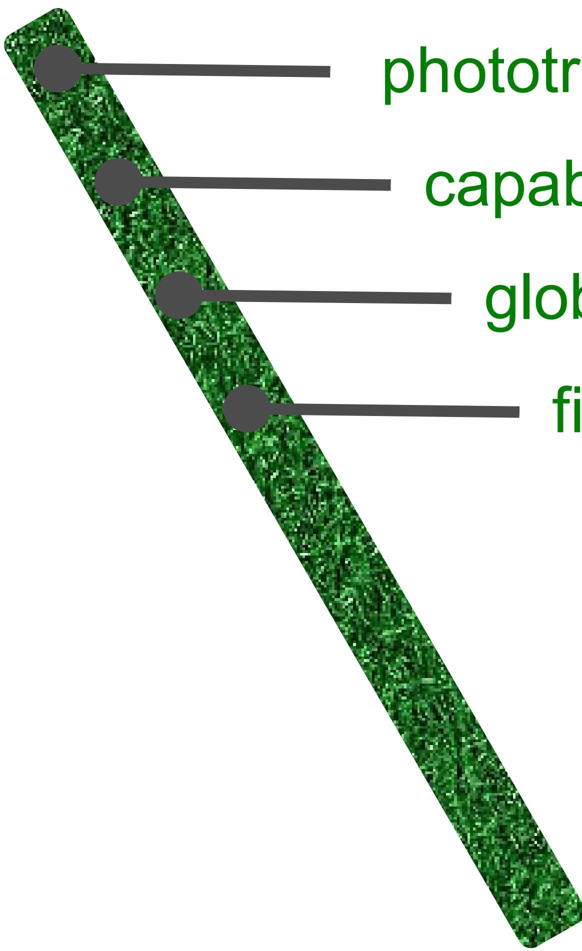
globally extremely abundant

The cyanobacterium Prochlorococcus is the numerically dominant phototroph in some oceans (up to half of the photosynthetic biomass).

Cyanobacterial abundance in in stratified oligotrophic waters can be high (> 10^5 cells ml^{-1})

from: Sullivan et al. Nature (2003)

Cyanobacteria: understanding phototrophic growth

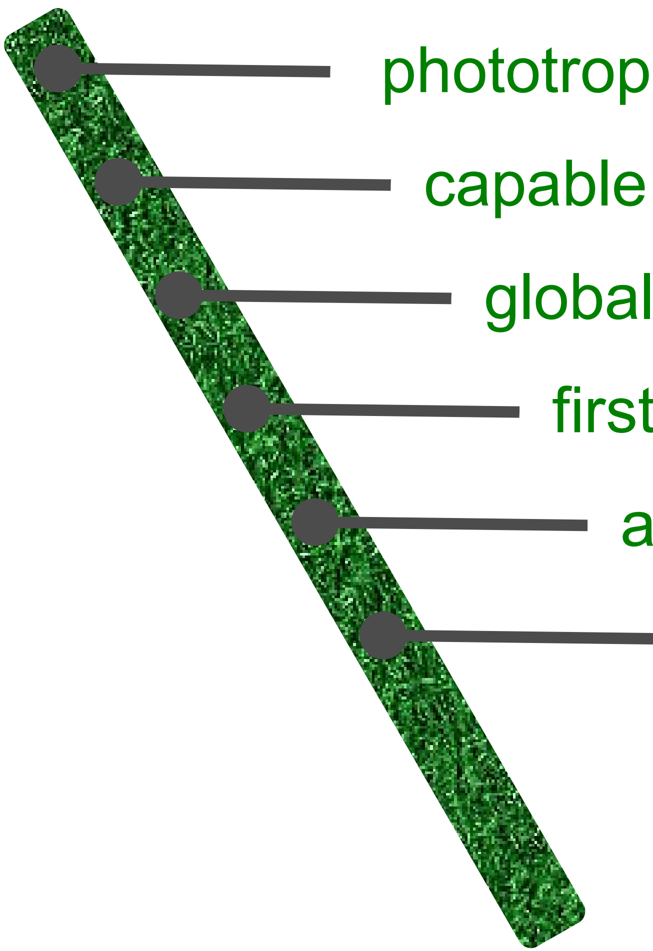


- phototrophic micro-organisms (prokaryotes)
- capable of oxygen-evolving photosynthesis
- globally extremely abundant
- first mass-producers of free molecular oxygen

↓

responsible for the Great Oxygenation Event (GOE) around 2.4 billion years ago.

Cyanobacteria: understanding phototrophic growth



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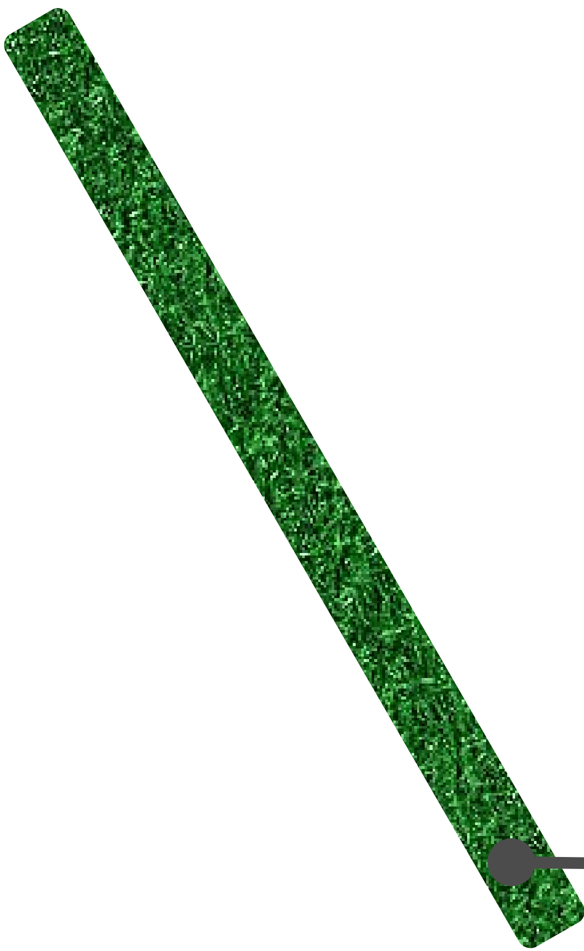
- ancestors of modern day chloroplasts
- relevant for the global carbon cycle

Cyanobacteria: understanding phototrophic growth

- phototrophic micro-organisms (prokaryotes)
- capable of oxygen-evolving photosynthesis
- globally extremely abundant
- first mass-producers of free molecular oxygen
- ancestors of modern day chloroplasts
- relevant for the global carbon cycle
- live as symbionts and in communities
- relevance for biotechnology (biofuels)

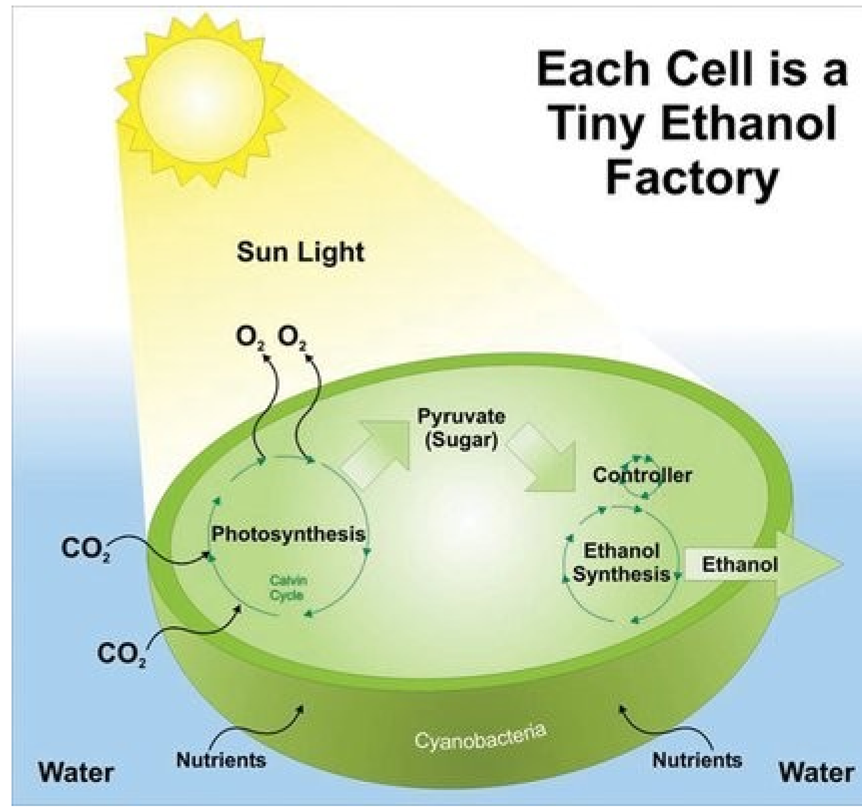
Cyanobacteria: understanding phototrophic growth



An open pond Spirulina farm:

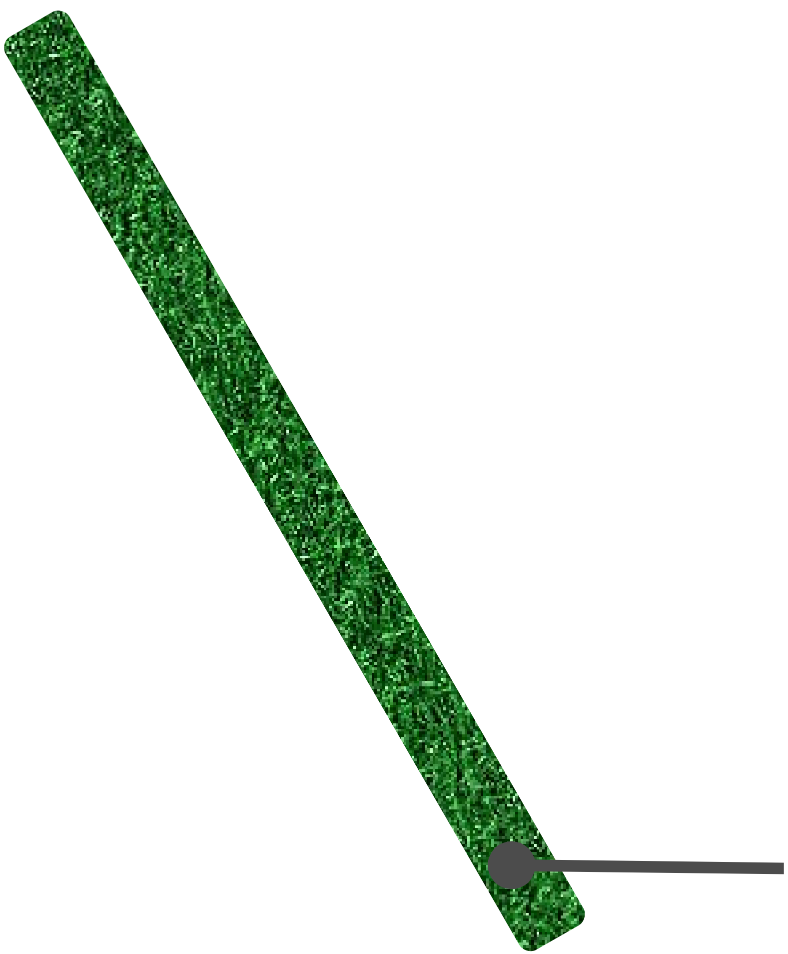
relevance for biotechnology (biofuels)

Cyanobacteria: understanding phototrophic growth



relevance for biotechnology (biofuels)

Cyanobacteria: understanding phototrophic growth

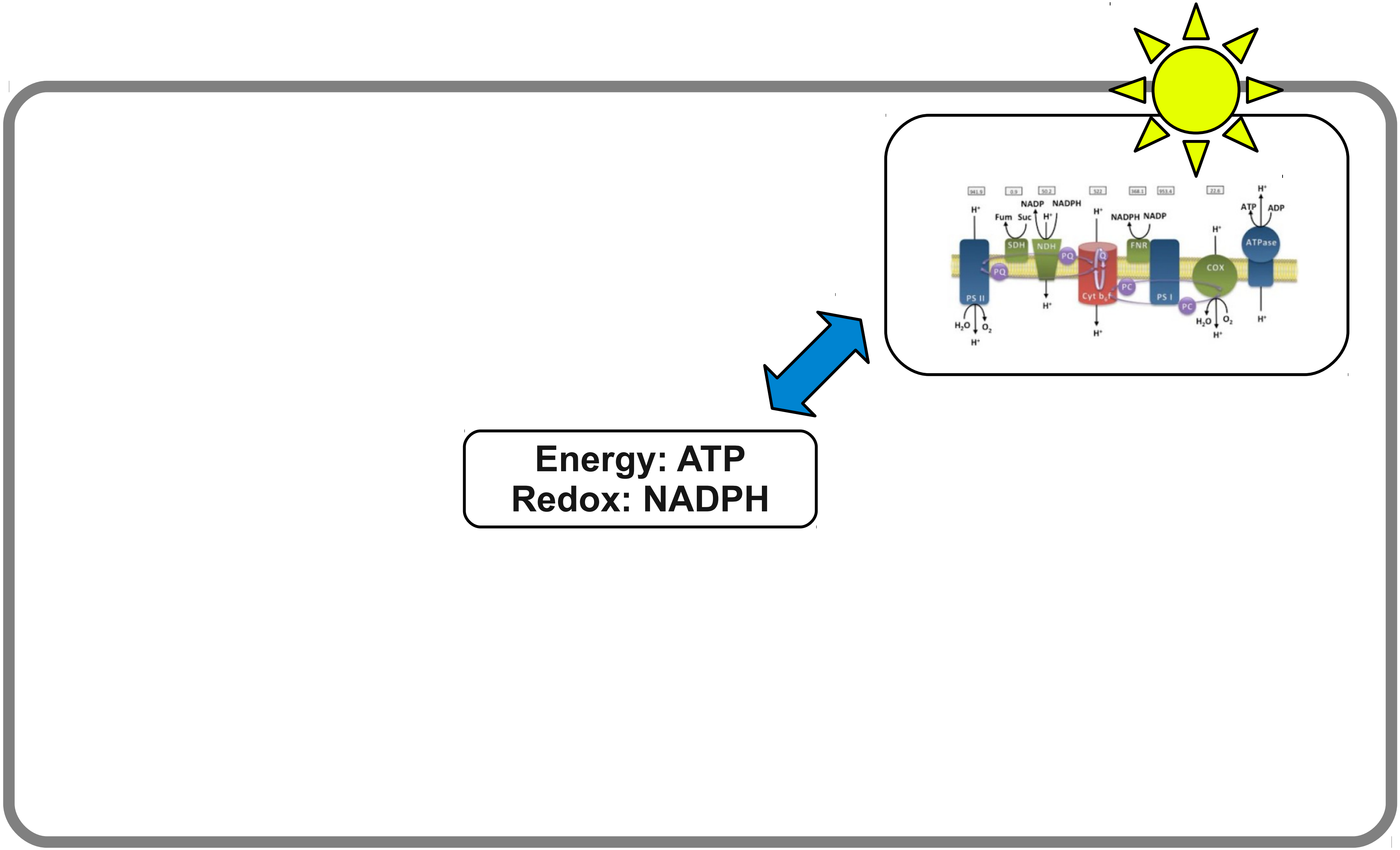


relevance for biotechnology (biofuels)

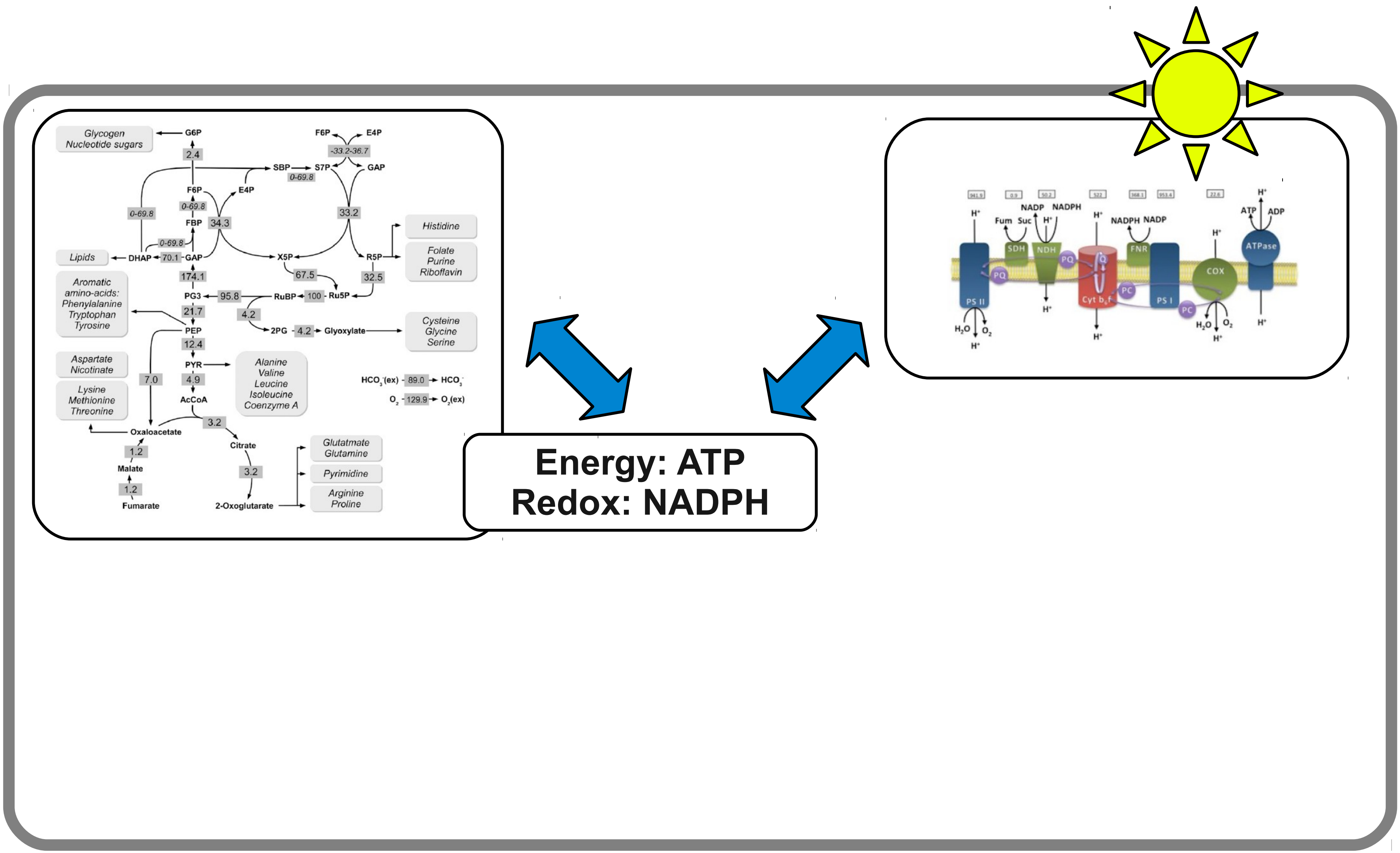
Cyanobacteria: a modular approach

We aim to understand the life and growth of cyanobacteria

Cyanobacteria: a modular approach



Cyanobacteria: a modular approach



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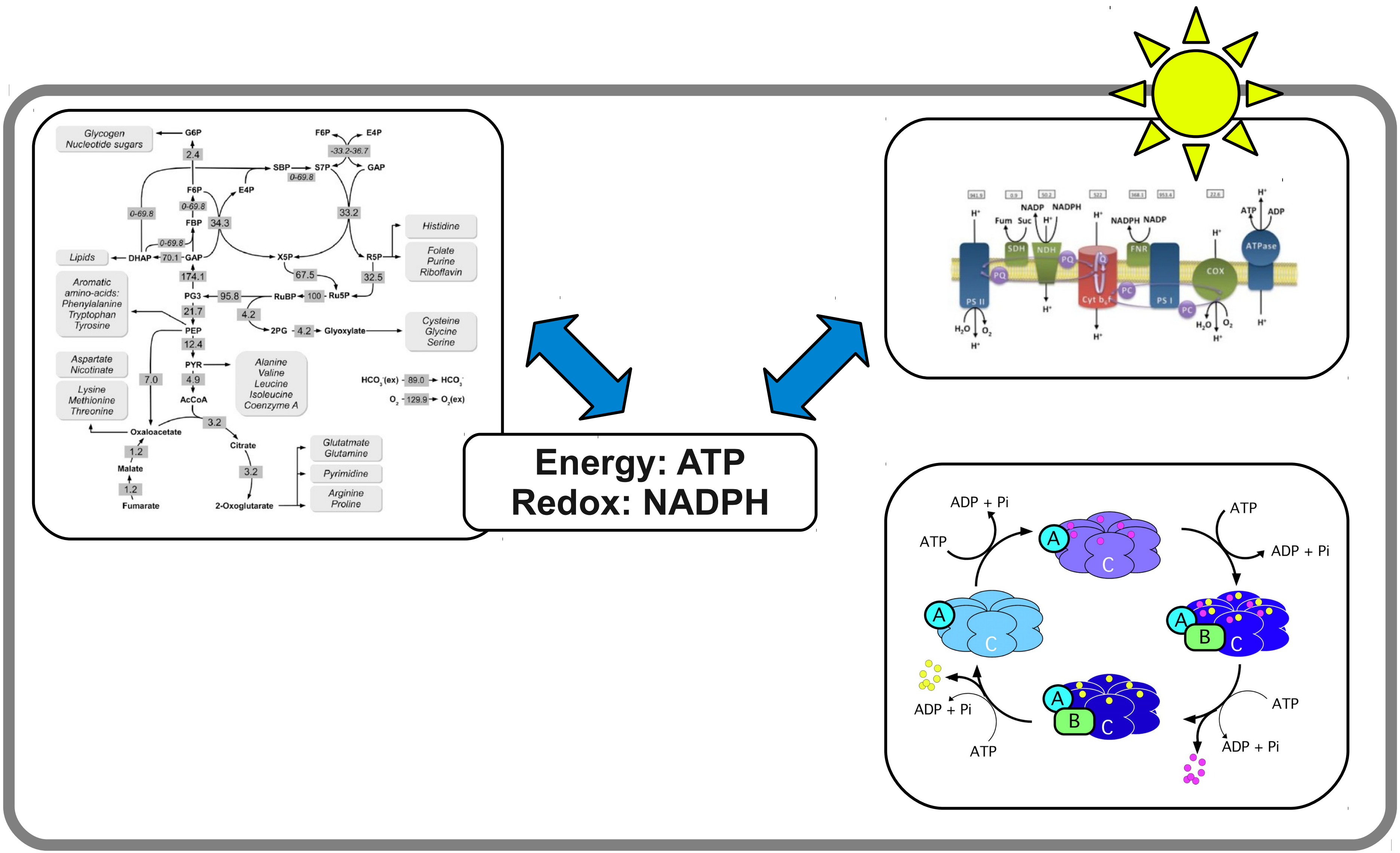

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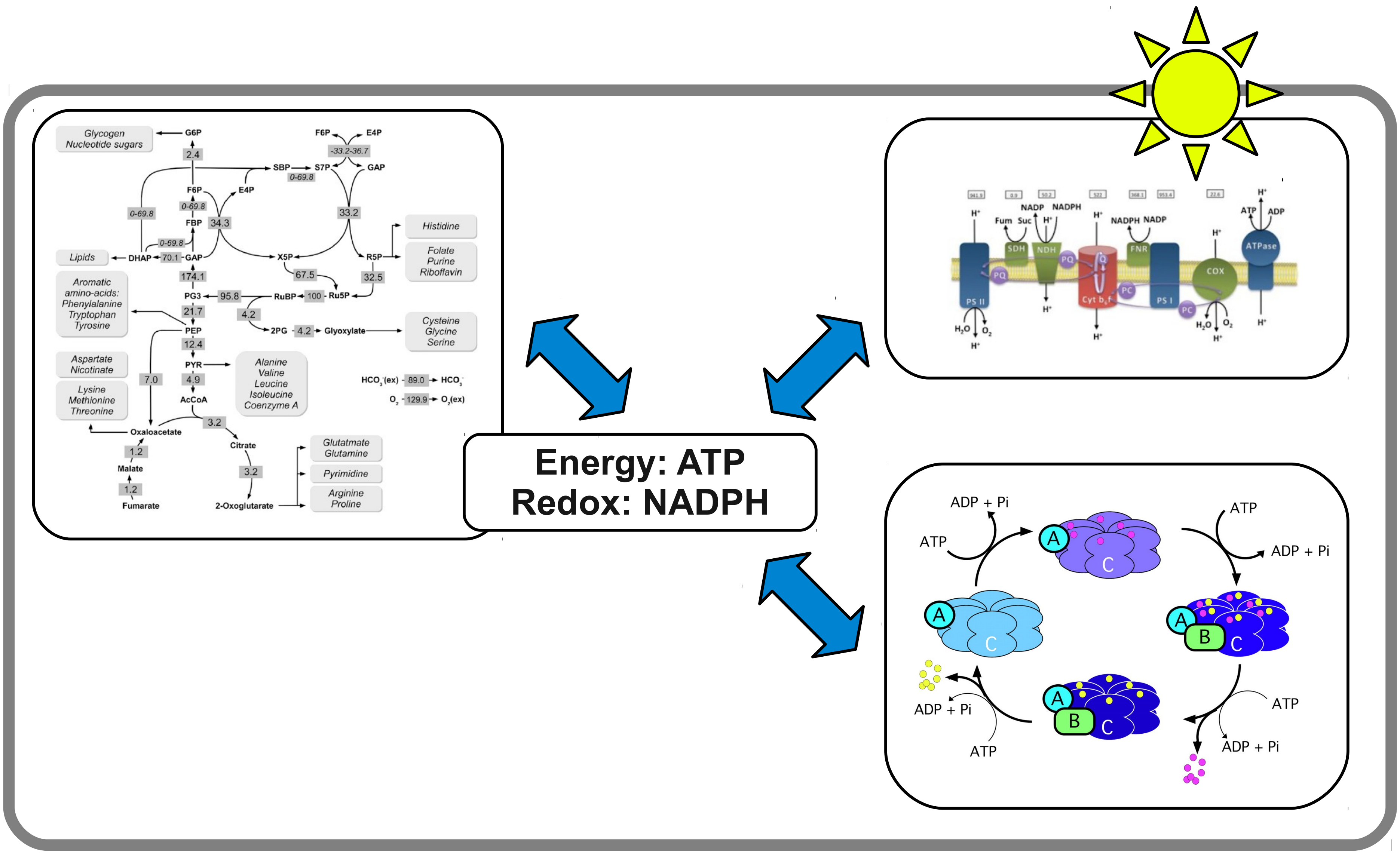

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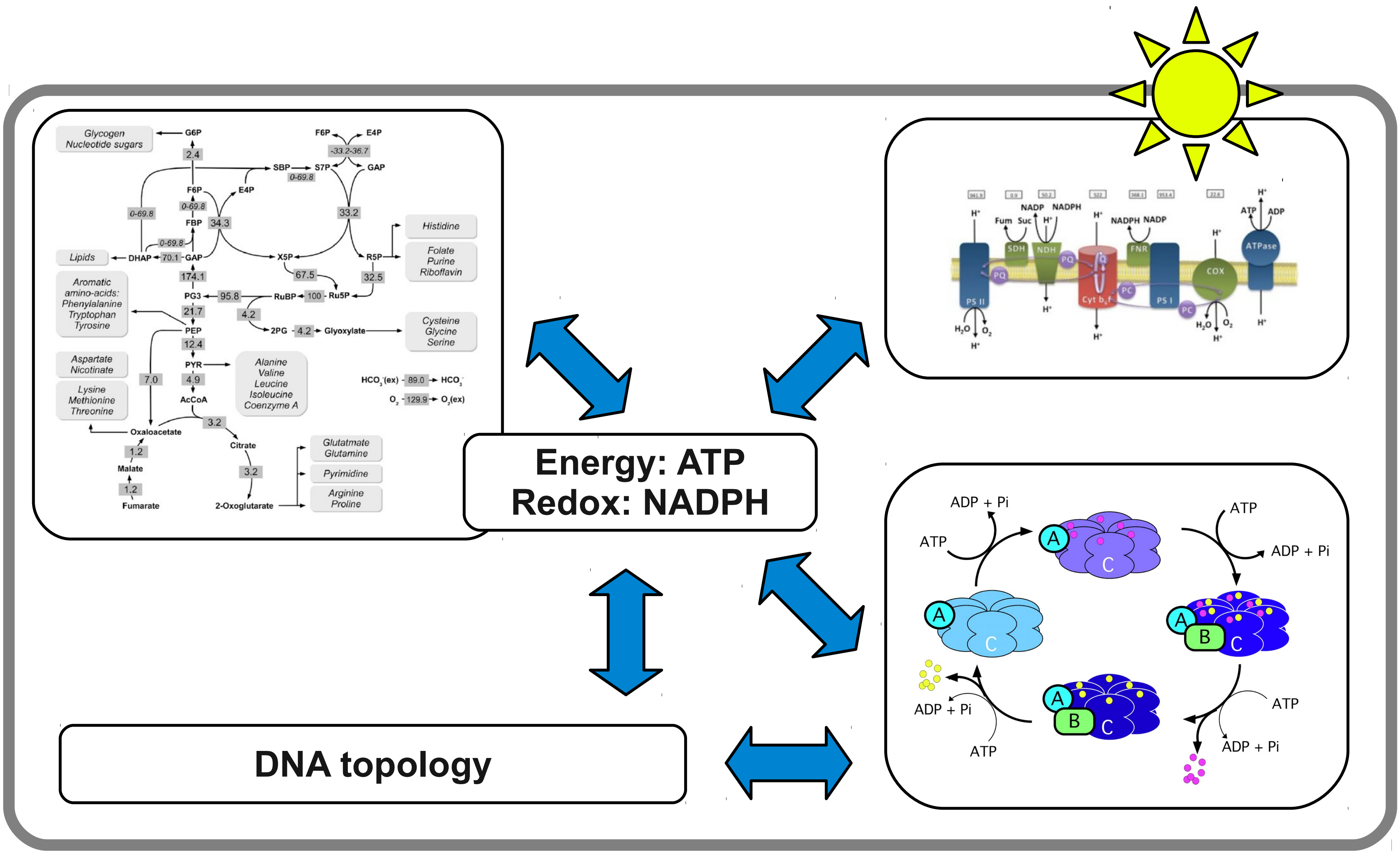

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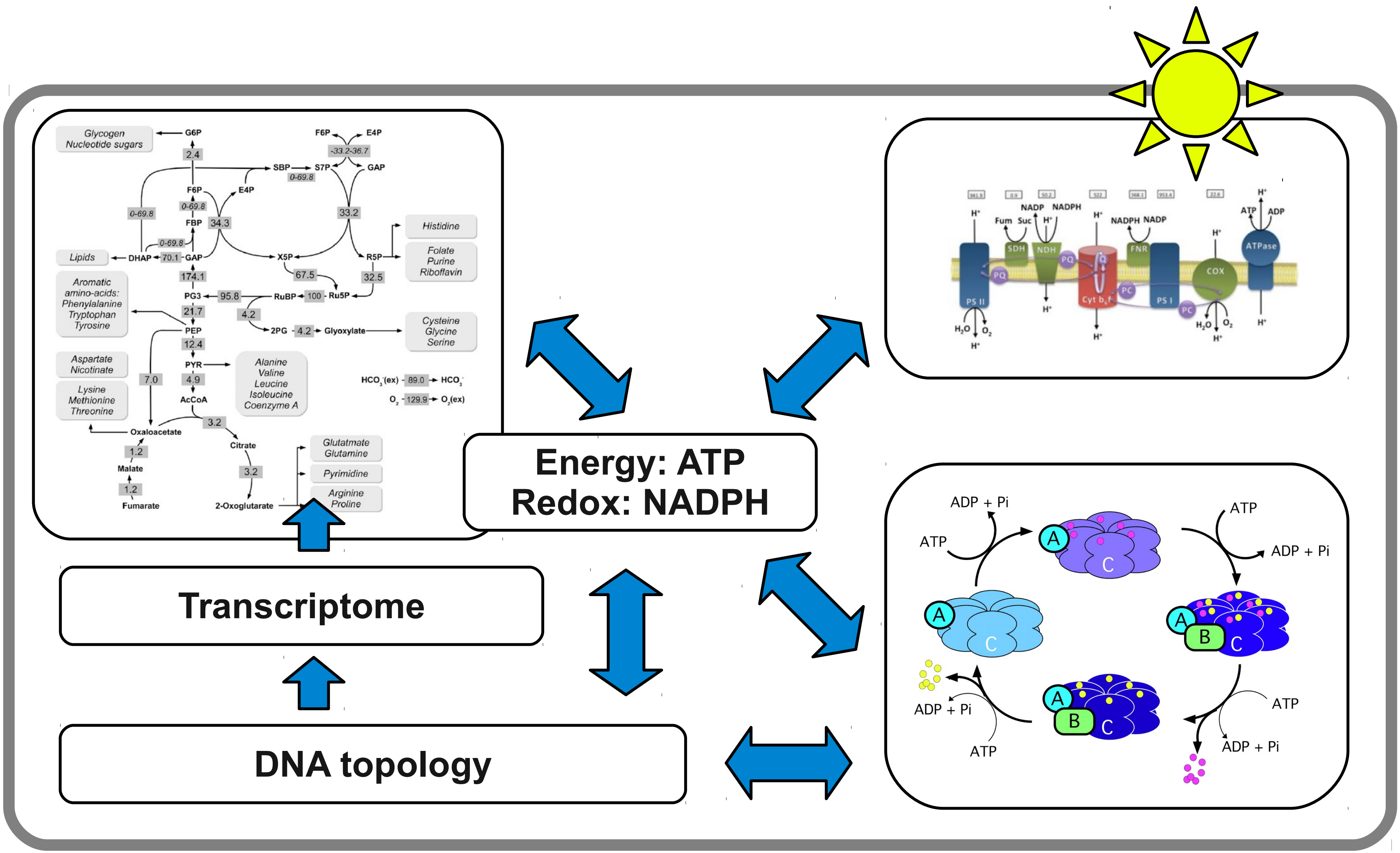

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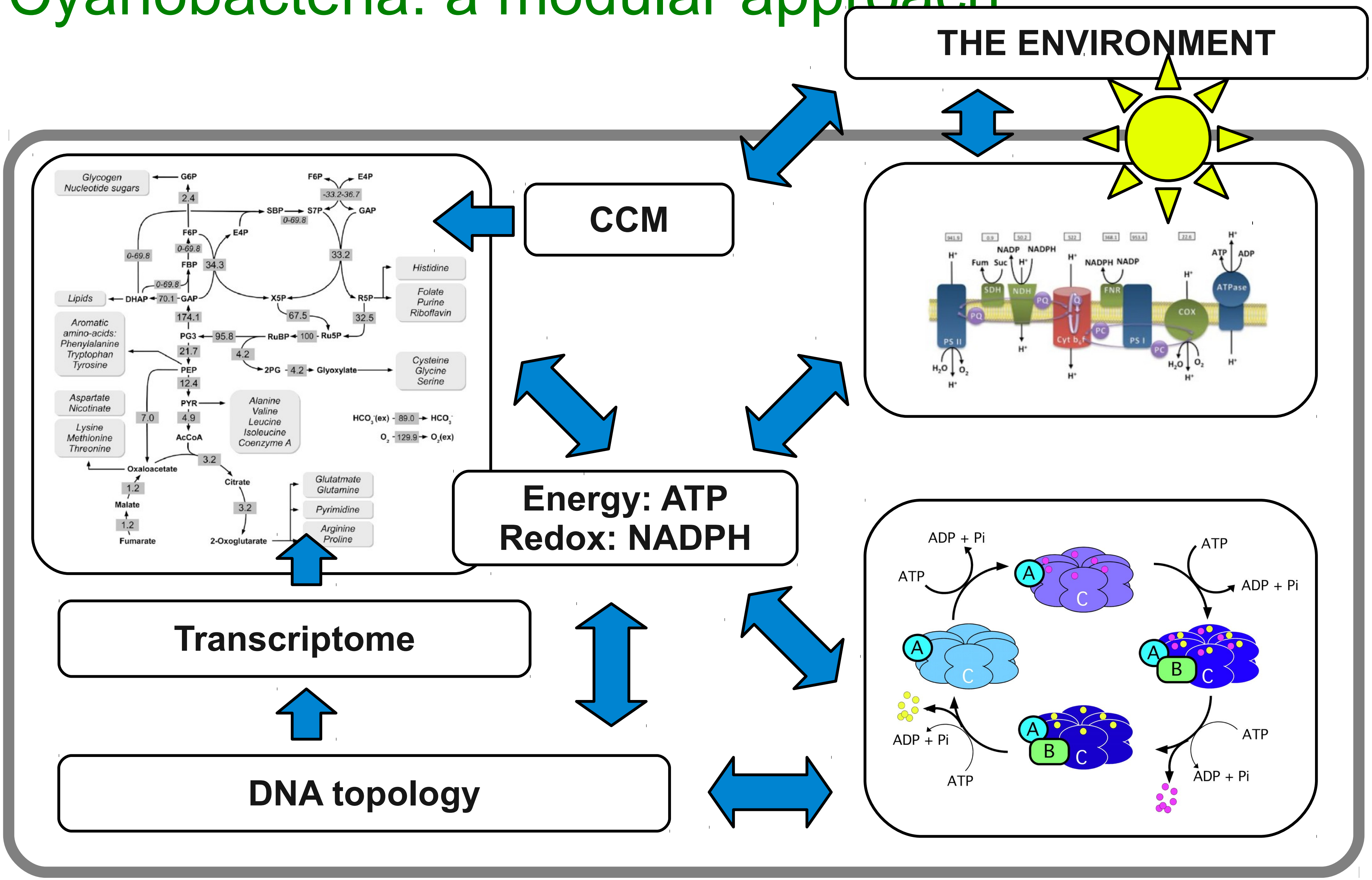
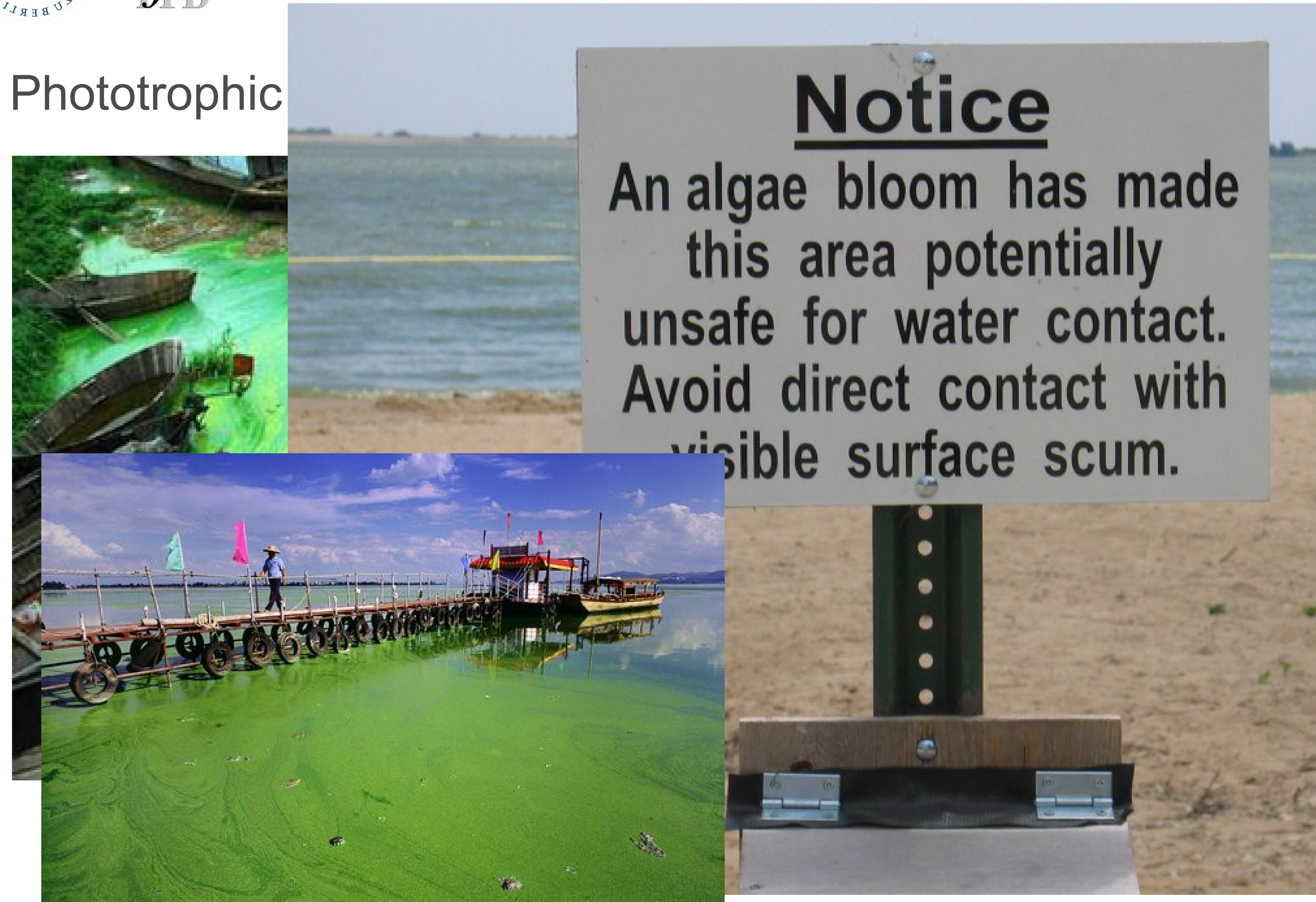


Cyanobacteria: a hierarchy of processes

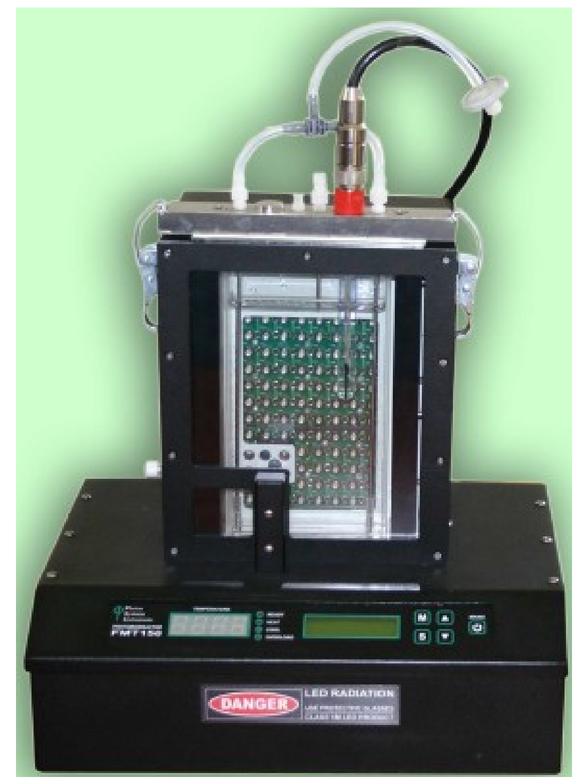
Phototrophic growth and the environment

Phototrophic



Cyanobacteria: a hierarchy of processes

Phototrophic growth and the environment



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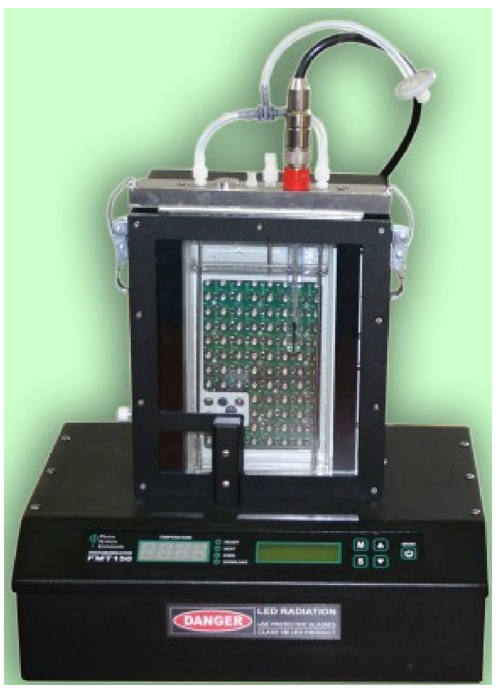
Phototrophic growth and the environment



Traditional ODE model for gas-liquid mass transfer:

$$\frac{\mathrm{d}c_l}{\mathrm{d}t} = \underbrace{k_{L,b}\,\frac{A_b}{V_l}\,(k_H\,c_b - c_l)}_{\alpha} + \underbrace{k_{L,h}\,\frac{A_h}{V_l}\,(k_H\,c_h - c_l)}_{\beta} + \underbrace{q_{cell}}_{\gamma}$$

$$\frac{\mathrm{d}c_b}{\mathrm{d}t} = \frac{\Phi}{V_b}\,(c_{in} - c_b) - \underbrace{k_{L,b}\,\frac{A_b}{V_b}\,(k_H\,c_b - c_l)}_{\alpha}$$

$$\frac{\mathrm{d}c_h}{\mathrm{d}t} = \frac{\Phi}{V_h}\,(c_b - c_h) - \underbrace{k_{L,h}\,\frac{A_h}{V_h}\,(k_H\,c_h - c_l)}_{\beta}$$

plus carbonate chemistry and a light gradient.

Stefan Mueller et al. An integrated model of photosynthetic growth in a bioreactor: gas-liquid mass transfer, carbonate chemistry, and cellular fluxes (to be completed soon).

Cyanobacteria: a hierarchy of processes

We aim to understand the life and growth of cyanobacteria

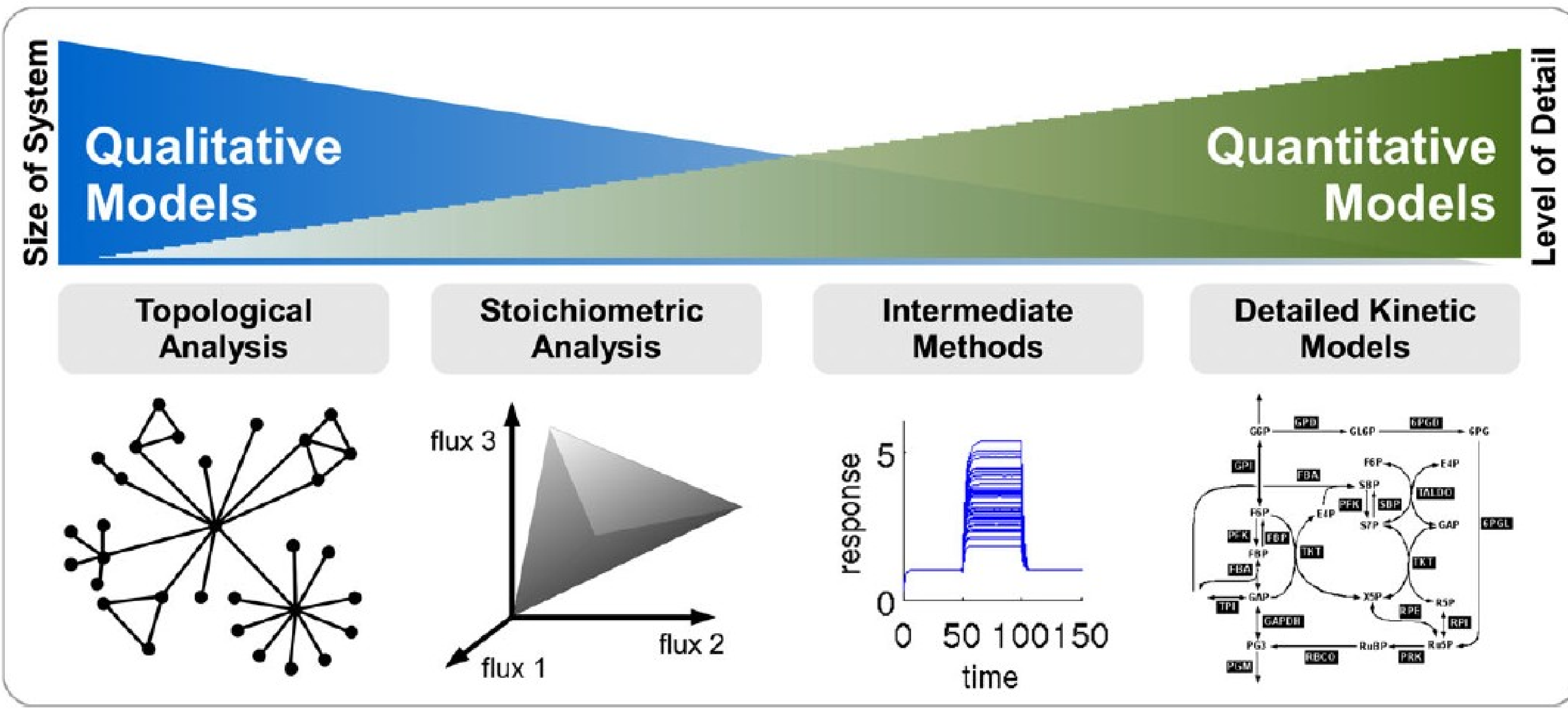
- Biophysics of photosynthesis and the light reactions
- ODE models of cellular metabolism and CCMs
- Integration of the cyanobacterial circadian clock
- Integration of gene expression and signalling
- Need to integrate diverse computational methodologies to describe sub-processes
- Necessitates a community approach: The international CyanoTeam

Modelling cellular metabolism

Understanding phototrophic growth in a complex environment

Modelling cellular metabolism

Understanding phototrophic growth in a complex environment



Journal of Experimental Botany

Steuer, Knoop, Machne. Journal of Experimental Botany (2012)

Modelling cellular metabolism

Mechanistic versus teleological models

Based on mechanistic details of the underlying processes (bottom-up)

Modelling cellular metabolism

Mechanistic versus teleological models

↓

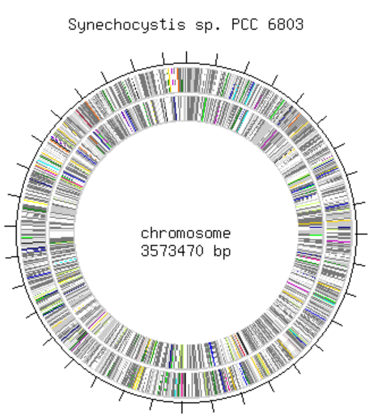
Based on constraints and optimization principles (top-down).

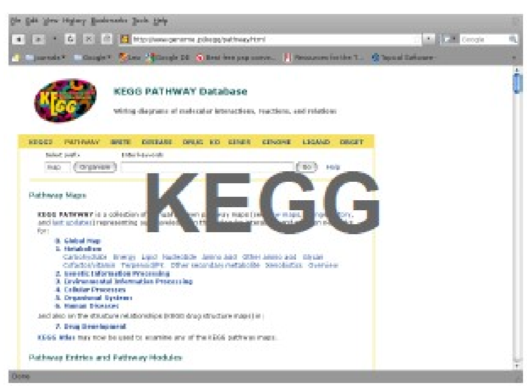
Widely applied to study flux distributions in metabolic network

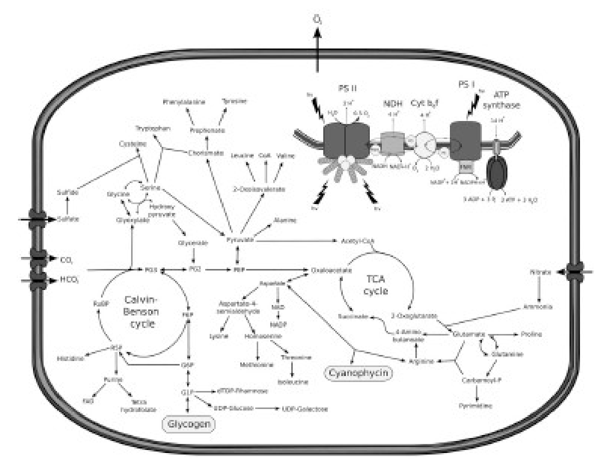
Modelling cellular metabolism

Mechanistic versus teleological models

All results are based on a high-quality reconstruction of the underlying network of biochemical interconversions.







Modelling cellular metabolism

Mechanistic versus teleological models

⬇

All results are based on a high-quality reconstruction of the underlying network of biochemical interconversions.

Metabolic reconstruction: a compendium of all biochemical interconversions of small molecules within a cell.

Modelling cellular metabolism

A stoichiometric model of *Synechocystis* sp. PCC6803

[1] Start with databases and genome sequence: Initial draft network

[2] Identify gaps and inconsistencies: manual curation and literature mining

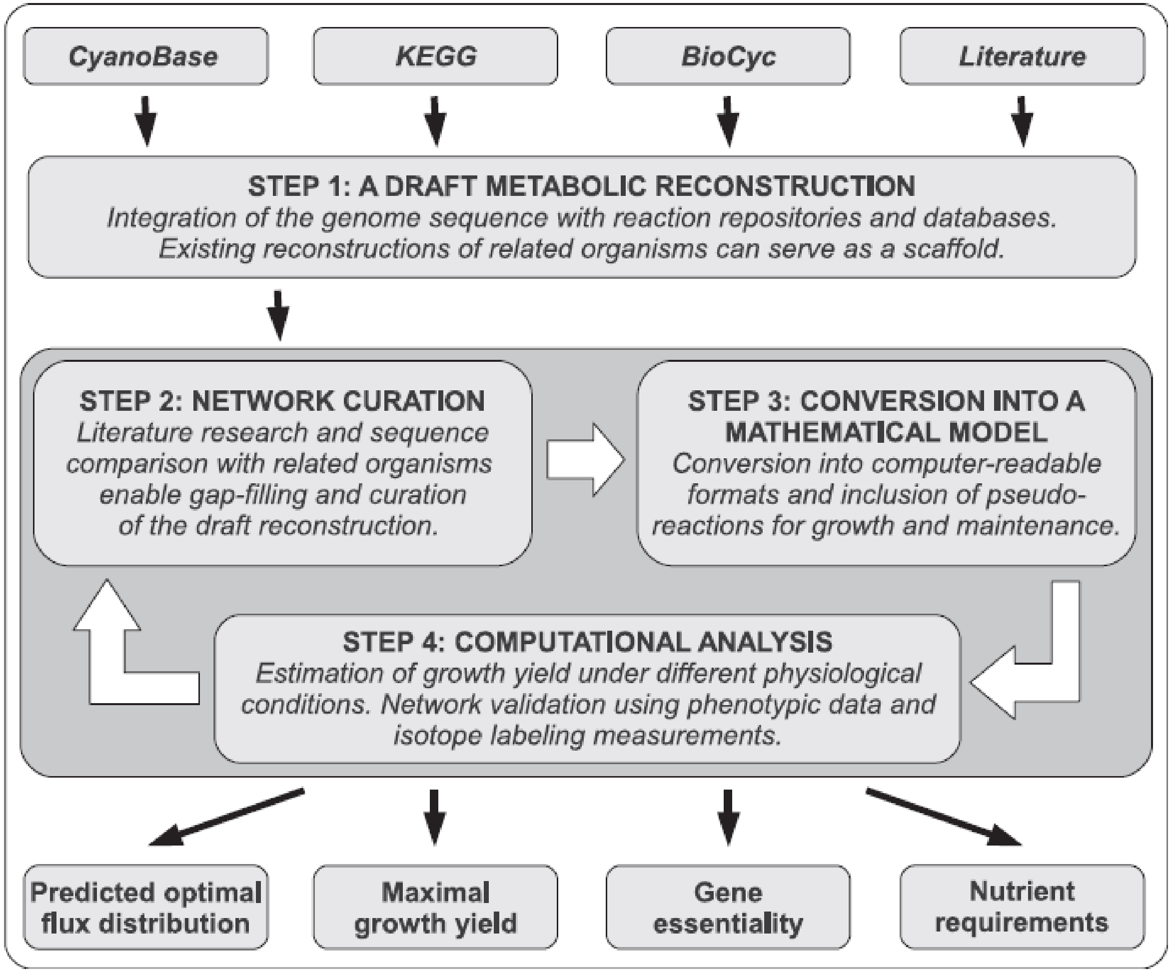
[3] Convert to mathematical model: Include pseudo-reactions for cellular maintenance

[4] Analyse the model using contraint-based optimization

The whole process is iterative and is repeated several times!

Modelling cellular metabolism

A stoichiometric model of *Synechocystis* sp. PCC6803



From: Steuer et al. JXB (2012)

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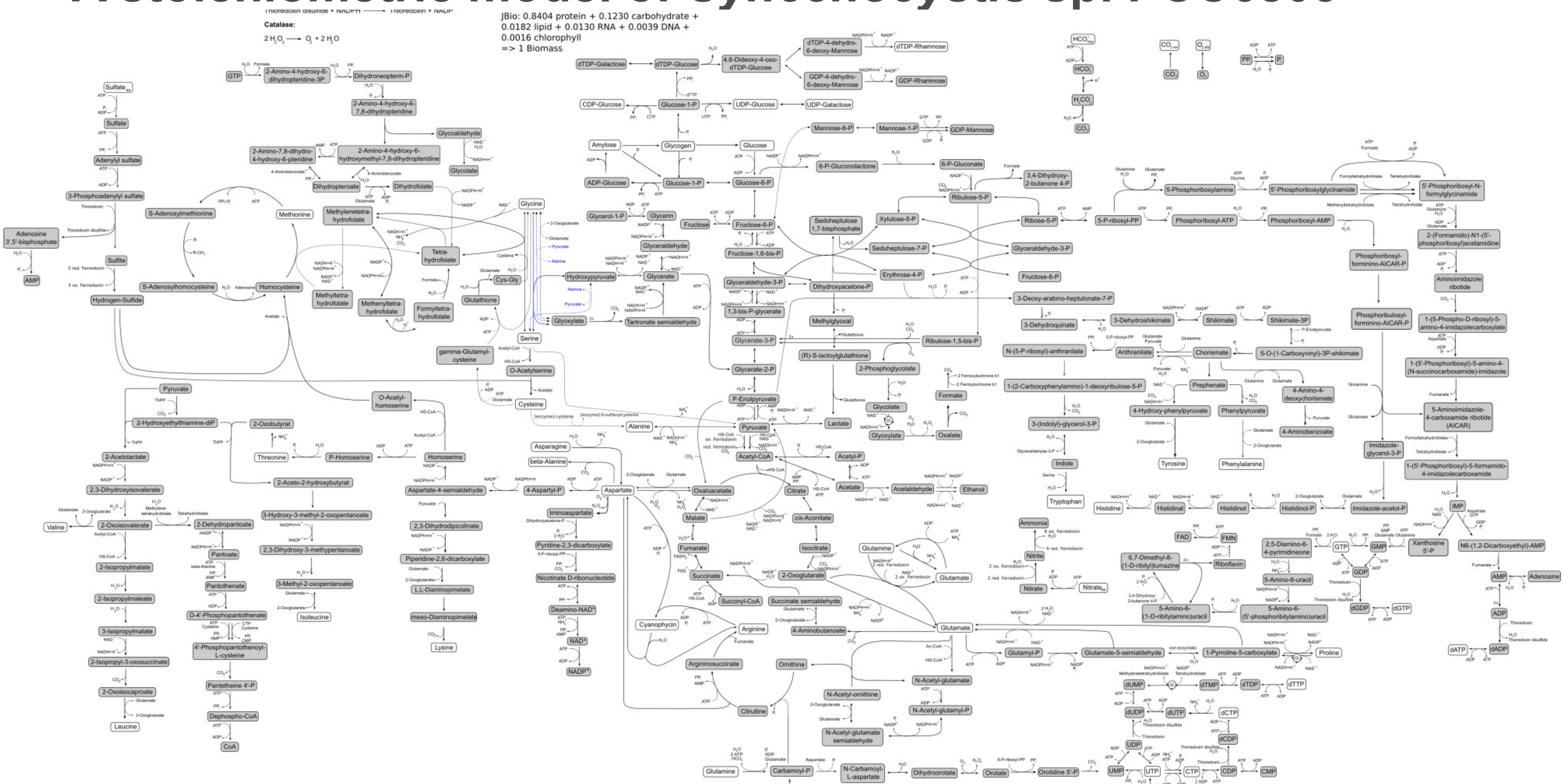

Plot by H. Knoop (HU Berlin), see also Knoop et al. Plant Physiology (2010)

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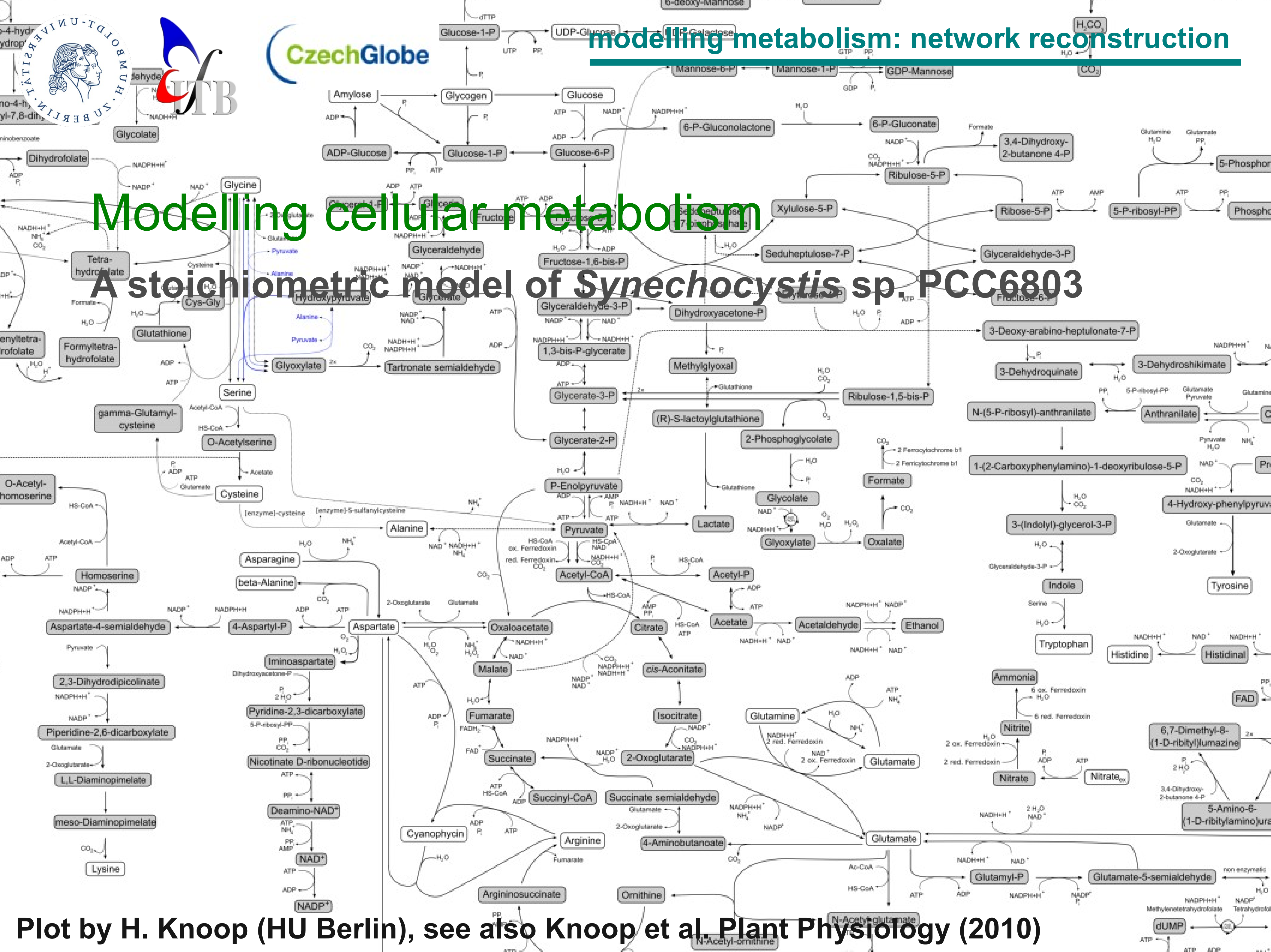

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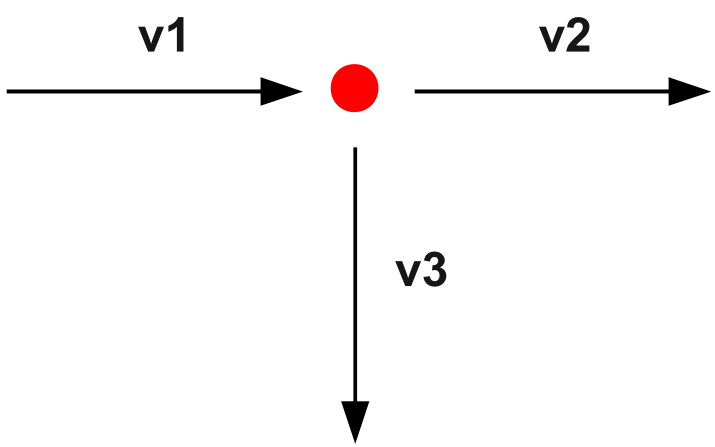
Analyse the model using contraint-based optimization



Assuming stationary conditions:

v1 – v2 – v3 = 0

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Analyse the model using contraint-based optimization

More general:

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = N\nu(\mathrm{S},\mathrm{k})$$

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = 0 \quad \Rightarrow \quad N\nu(\mathrm{S}^0,\mathrm{k}) = 0$$

2rd assumptions: metabolic fluxes are organized such that a given (usually linear) objective function Z is maximized.

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Analyse the model using contraint-based optimization

Constraint-based stoichiometric modeling

maximize $Z = \boldsymbol{w}^T \cdot \boldsymbol{\nu}^0$

subject to: $\boldsymbol{N\nu}^0 = \mathbf{0}$

and $\nu_i^{\min} \leq \nu_i^0 \leq \nu_i^{\max}$
with $i = 1, \ldots, r$

See: Steuer and Junker. Advances in Chemical Physics (2009)

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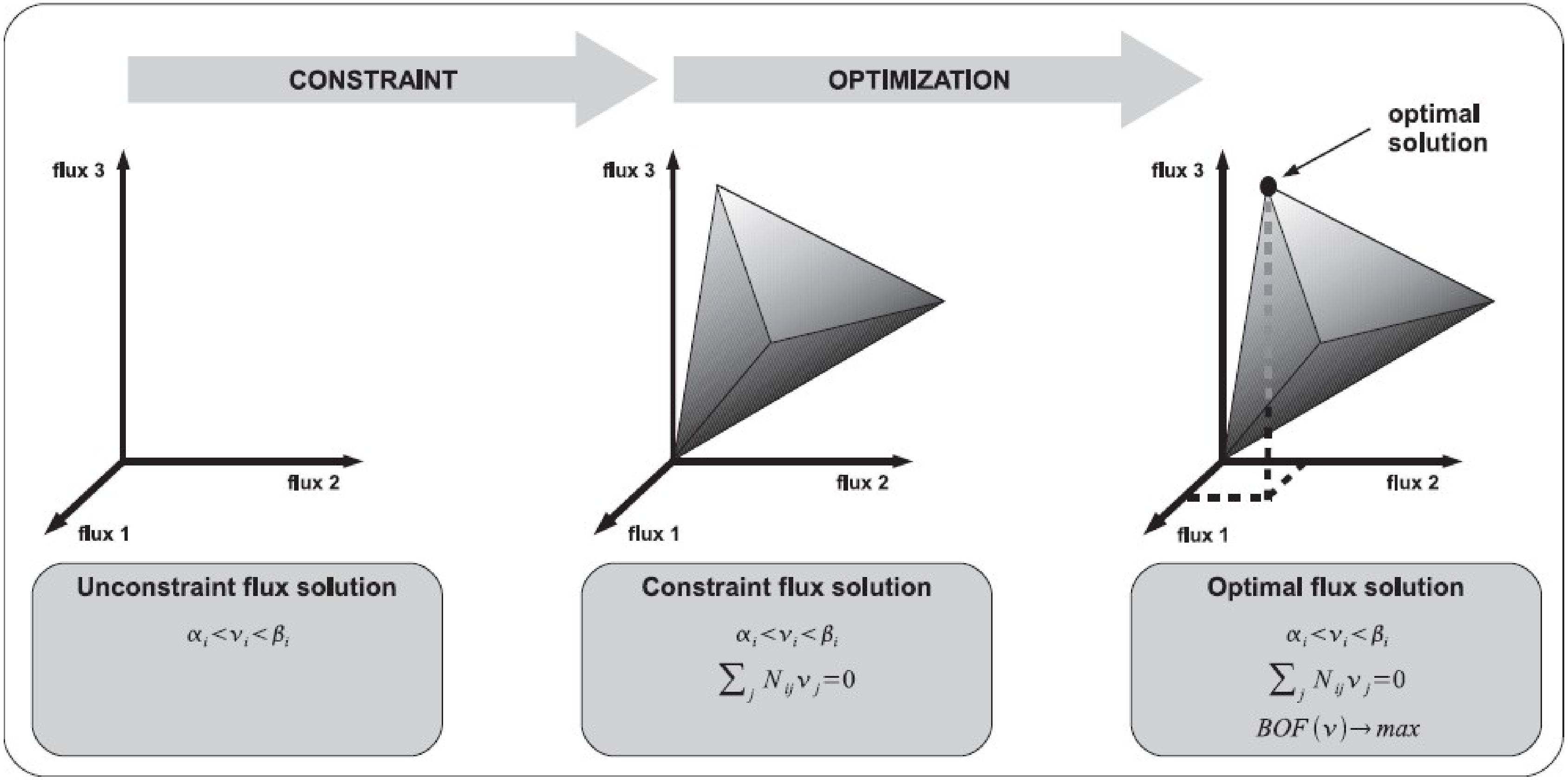


From: Steuer et al. JXB (2012)

A stoichiometric model of *Synechocystis* 6803

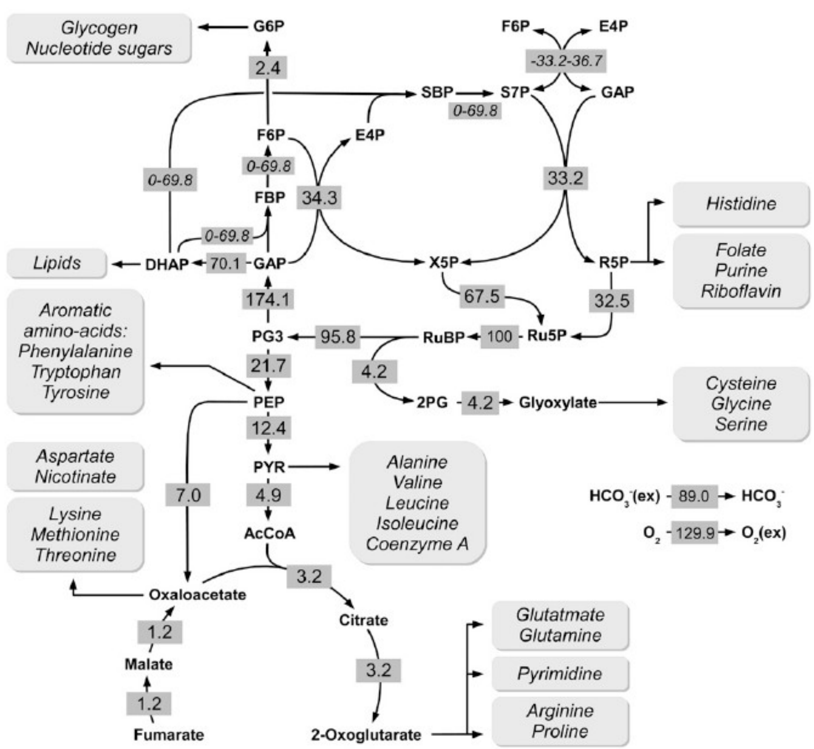
Applications of constraint-based optimization

- Optimal flux patterns (maximal biomass yield)
- Flux-variability analysis
- Gene essentiality analysis
- Reaction coupling (with A. Bockmayr, FU Berlin)

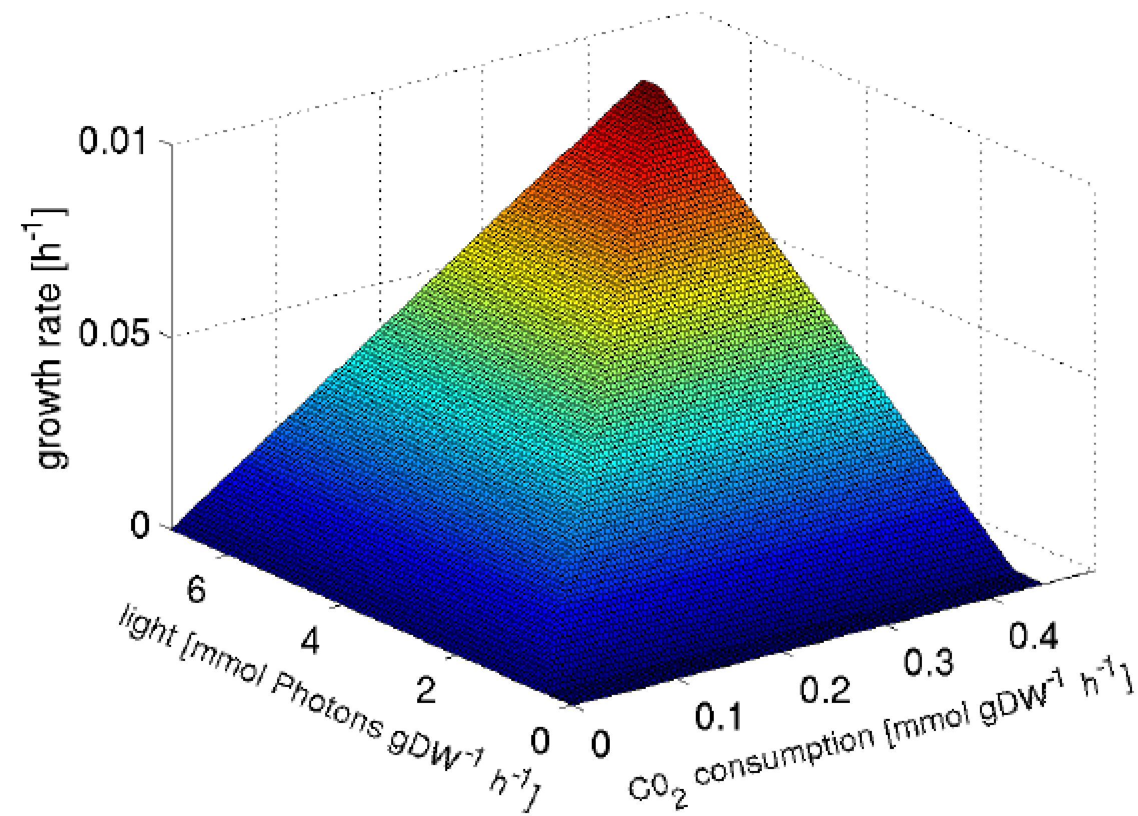
A stoichiometric model of *Synechocystis* 6803

Optimal flux patterns (maximal biomass yield)

flux distribution:



growth rate/yield:



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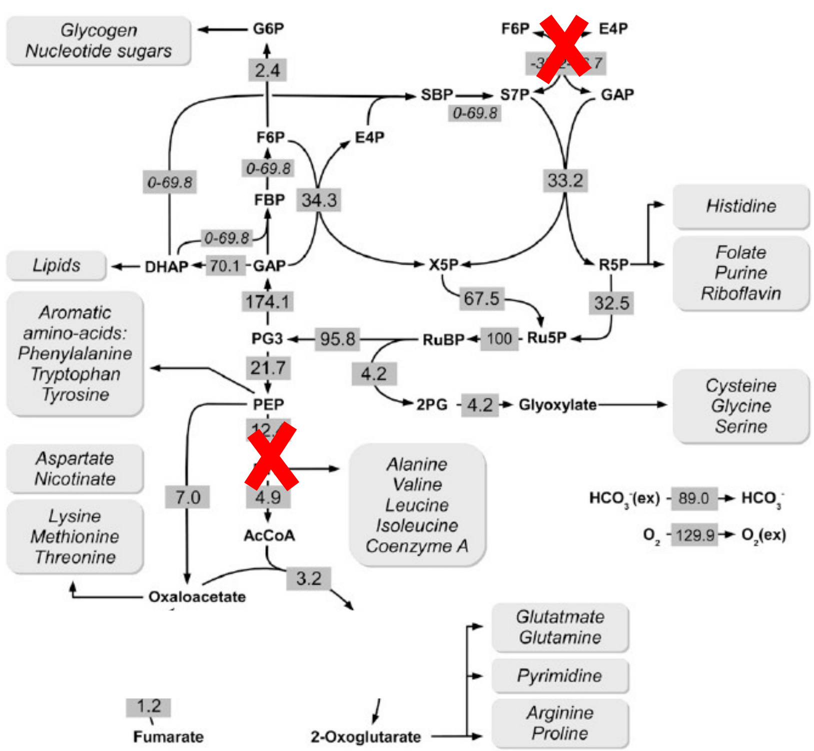
Gene essentiality analysis: network validation



still viable?

126 (of 337) genes are classified as essential for biomass formation: Comparison with CyanoMutants

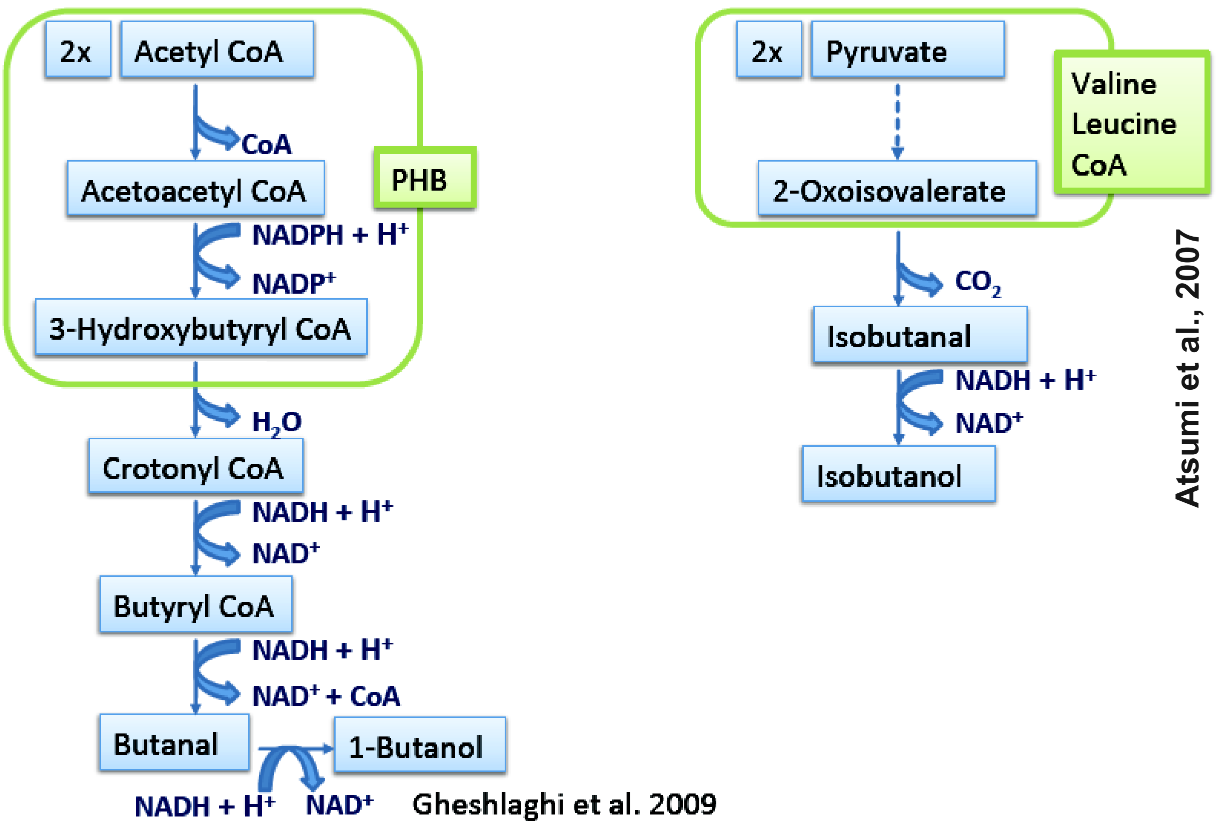
new hypotheses/questions!

A stoichiometric model of *Synechocystis* 6803

Applications of constraint-based optimization: Biofuels

A stoichiometric model of *Synechocystis* 6803

The model as a platform for strain improvement

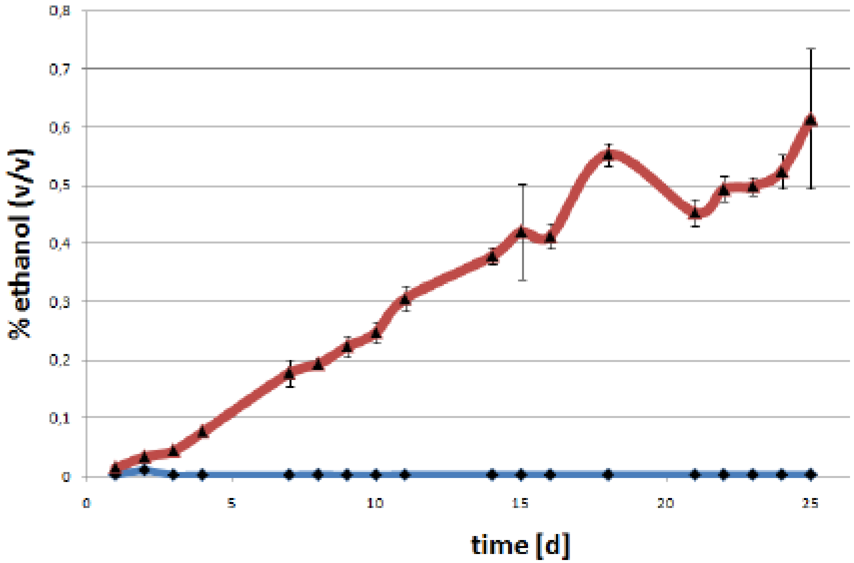


A stoichiometric model of *Synechocystis* 6803

The model as a platform for strain improvement

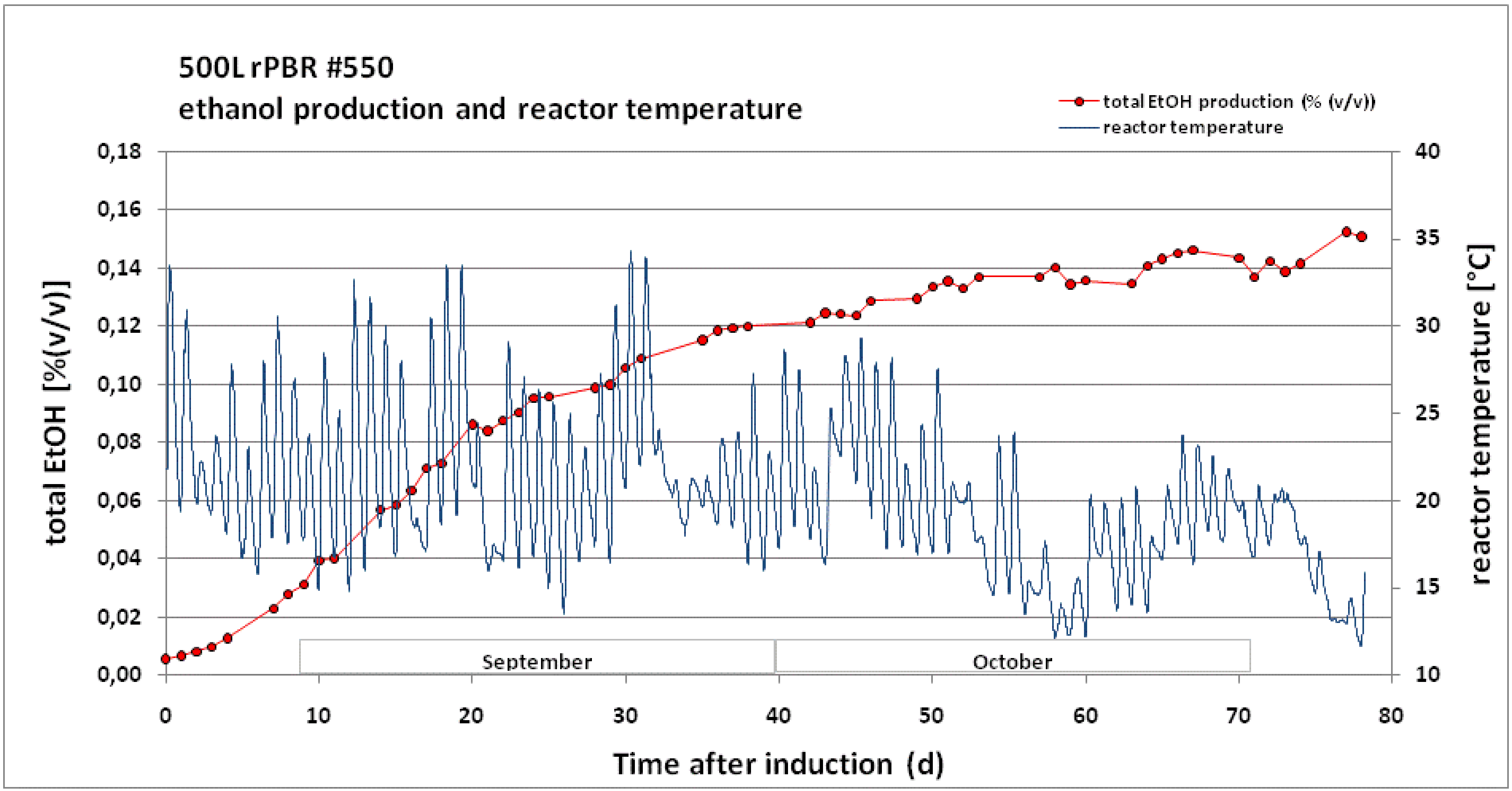
product	CO2	ATP	NAD(P)H	"photons"
ethanol	2	8	6	24.33
ethylene	2.5	23.5	12	64.92
isobutanol	4	18	12	51
isoprene	5	22	13	60.66

From lab to applications: large-scale cultivation of Synechocystis sp. PCC 6803



From lab to applications: large-scale cultivation of Synechocystis sp. PCC 6803

Culture Duration: 79 days/Final EtOH Conc. : 0.15 %(v/v)



A stoichiometric model of *Synechocystis* 6803

Applications of constraint-based optimization: Biofuels

Introduce fuel pathways into the stoichiometric reconstruction

- contributions to host optimization and metabolic streamlining
- identify main routes of synthesis for precursor metabolites
- prediction of optimal knockout targets for product formation

Direct Fuel

Direct biological conversion of solar energy to volatile hydrocarbon fuels by engineered cyanobacteria

An EU FP7 collaborative project (grant no. 256808)

SEVENTH FRAMEWORK PROGRAMME

www.directfuel.eu

A stoichiometric model of *Synechocystis* 6803

CHALLENGES AND EXTENSIONS OF FBA

- Thermodynamic consistency
- The costs of pathways: minimum-cost flow problems
- Temporal coordination of metabolism

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Temporal coordination of metabolism

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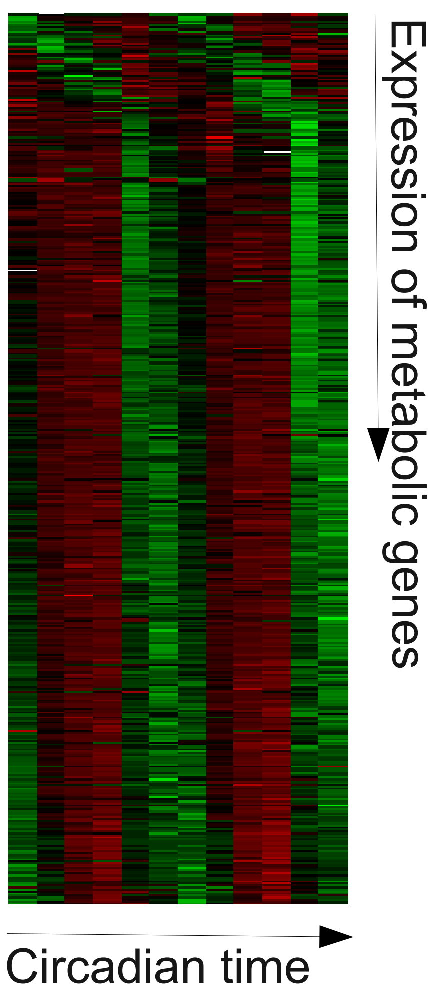
Temporal coordination of metabolism



Indeed, cyanobacterial metabolism follows a complex circadian program

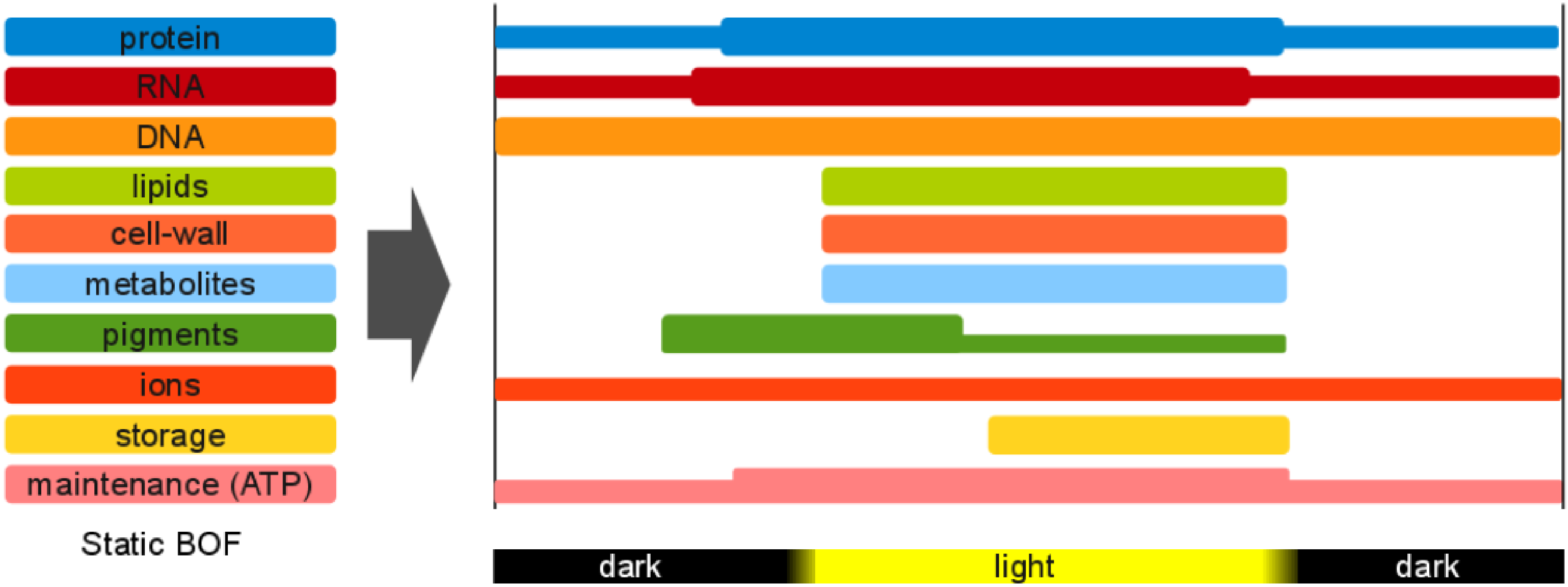
Most genes expressed during light period

Data: group of I. Axmann (ITB, Berlin)
Clustering/Data analysis: Rob Lehmann, Rainer Machne
submitted

A stoichiometric model of *Synechocystis* 6803

Temporal coordination of metabolism

A time-dependent objective function:



Modelling cellular metabolism: summary

Understanding phototrophic growth in a complex environment

- Biological systems typically involve multiple temporal and spatial scales: need for different methodologies.
- It is a conceptual and computational challenge to integrate diverse systems into a coherent whole.
- Of most interest are intermediate methods that allow to deal with incomplete and uncertain data.
- Large-scale predictive models of cells are possible: computational biology needs to integrate parts into a coherent whole

Thanks for your attention!

And thanks to the group in Berlin:

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Sabrina Hoffmann
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Raik Otto
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Ettore Murabito (Manchester)
Hans Westerhoff (Manchester)
Lada Nedbal (Brno, CZ)
Wolfgang Hess (ALU-FR)
Patrik Jones (Turku)