Synthetic Biology and Metabolic Engineering

Introduction and Outlook

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ITACA / Universidad Politécnica de Valencia

Valencia, 30th June 2017

Content

- About our motivation: Synthetic biology and engineering
- The role of Systems Biology and Metabolic Engineering
- Some examples from our research
  - Cyanodesign
  - Modeling at reactor scale

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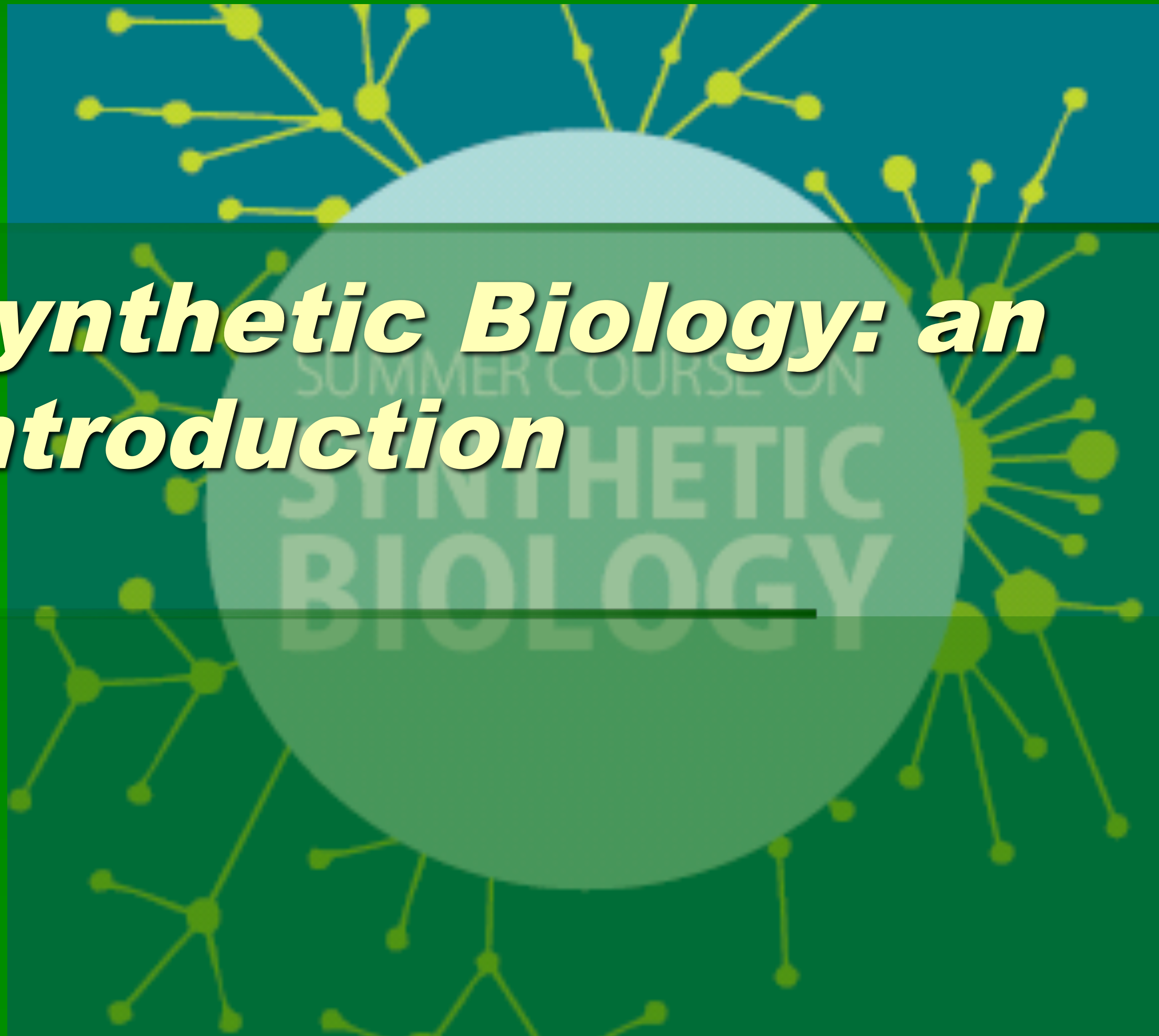
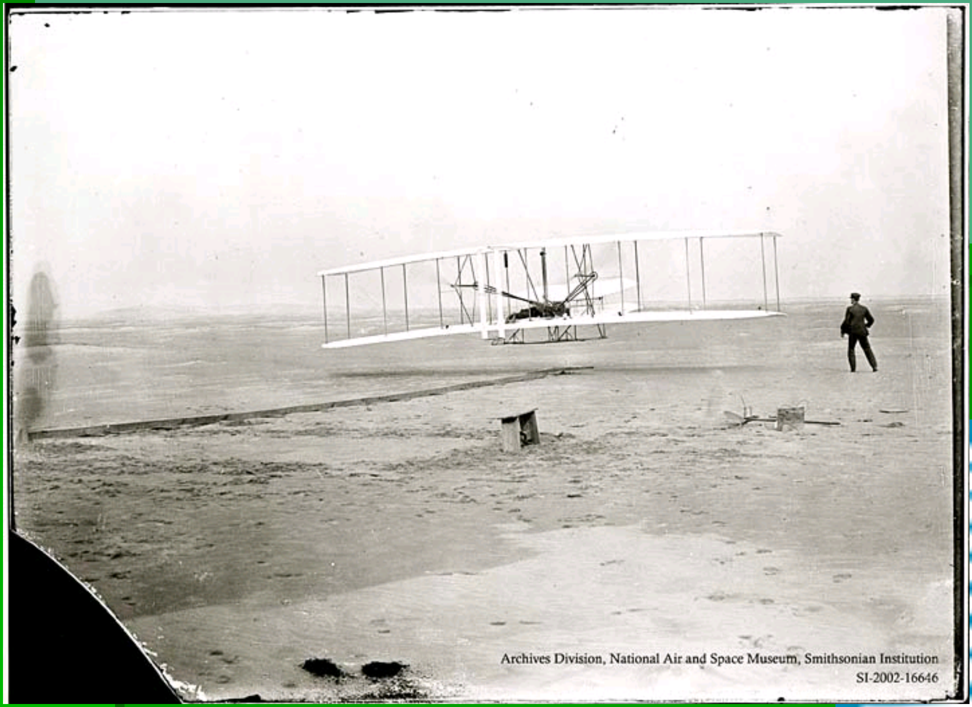
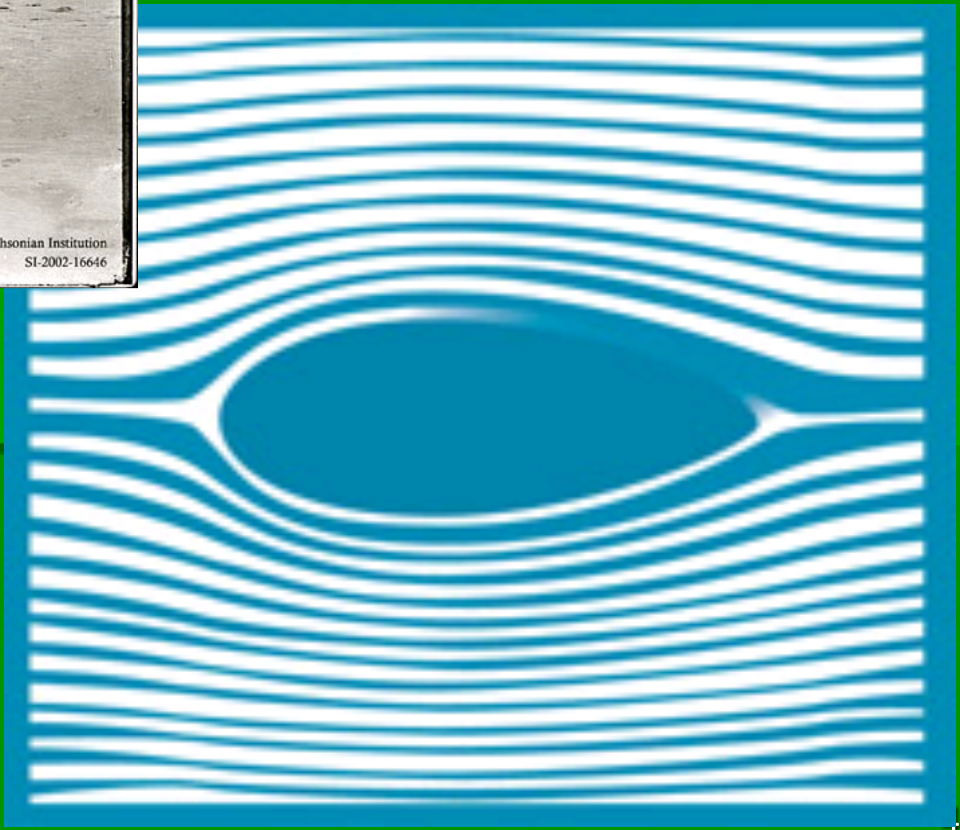
Synthetic Biology: an introduction







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About the name

- The term “Synthetic Biology” exists long ago
- Formerly SB was understood as “creating a living organism from scratch”
- Today the focus has changed towards a more engineering or industrial view, just as “adding new features to existing cells”
- The differences with conventional molecular biology and genetics is more methodological (how?) than intentional (what?).

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- Synthetic biology seeks to understand and design biological systems and their components to address a host of problems that cannot be solved using naturally occurin entities
- Design what?
  - Enzymes
  - Metabolic pathways
  - Genetic control systems
  - Signal transduction pathways
  - … a whole cell?

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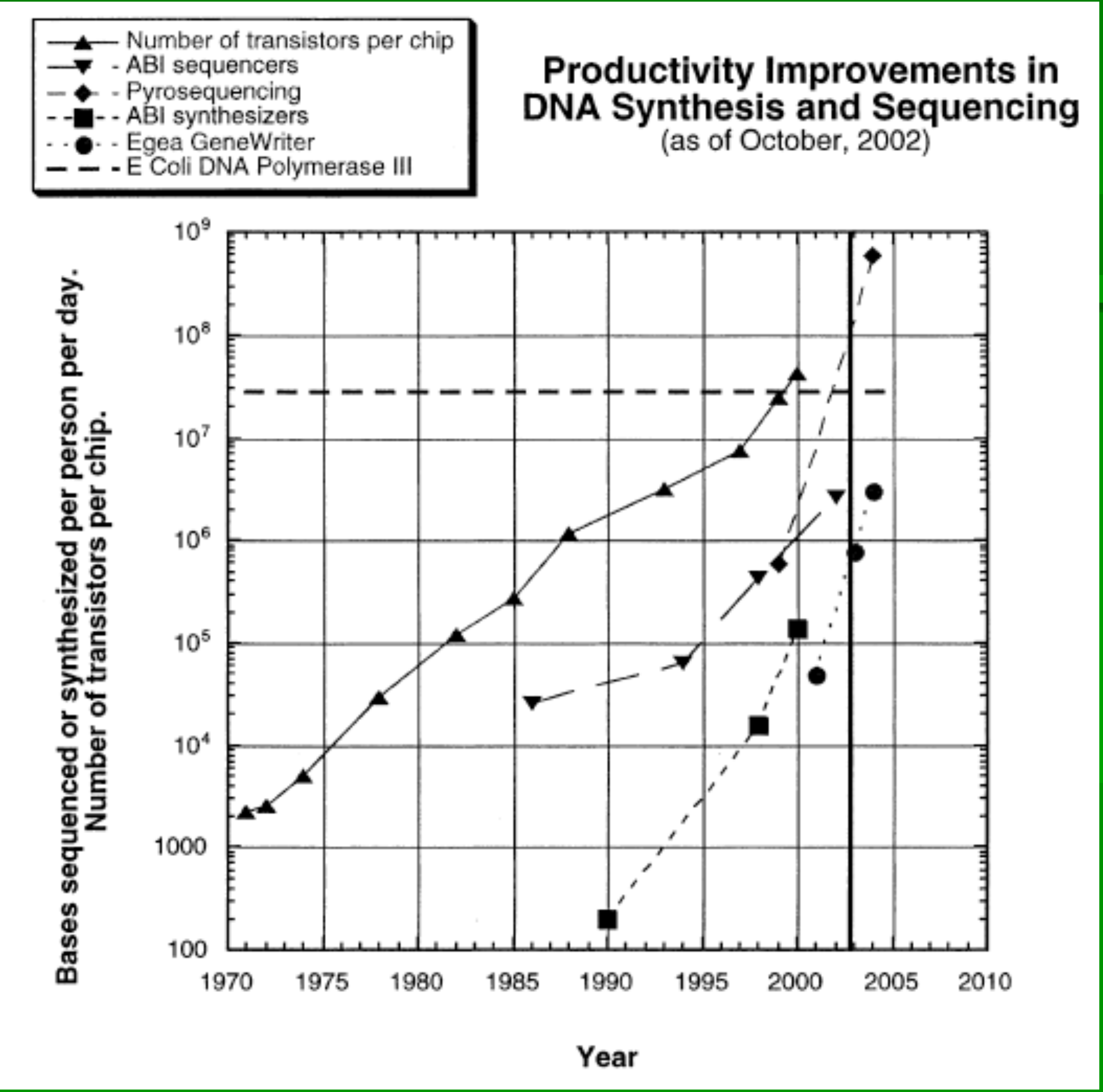
Why now?

- Advances in computing power…
- Internet
- Biological databases
- Genomic sequencing
- Availability of protein structures
- DNA synthesis, sequencing and other high-throughput technologies
- Repositories of genetic parts (genes)



Carlson, Pace & Proliferation of Biological Technologies, *Biosec. & Bioterror.* **1(3)**:1 (2003)

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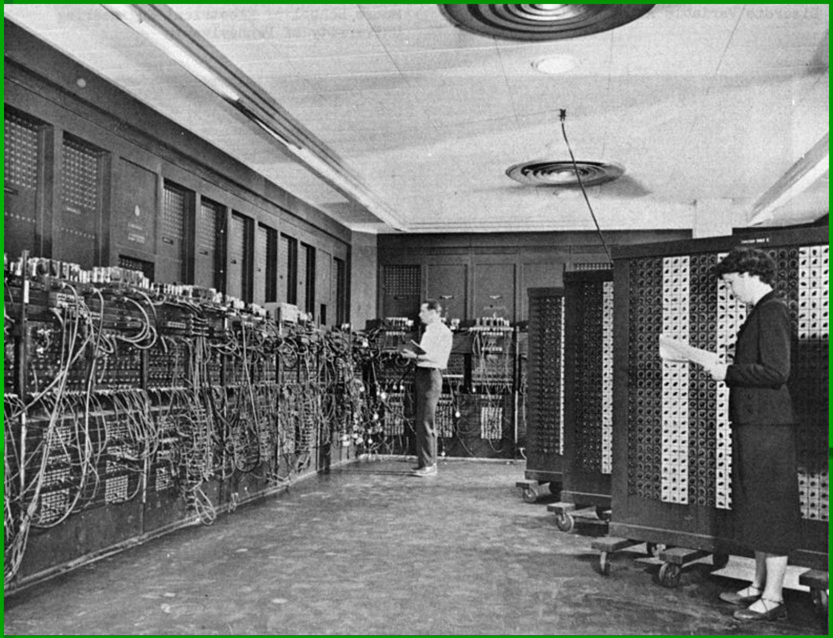
Designing a computer in the 40-60's



- Each computer: an original design
- Few people could understand it, not to say, repair it
- The designer had to understand the computer from bottom to top
- Only a few things were reusable for the next generation:

  SLOW PROGRESS!

Designing a computer from the 70's (VLSI electronics)

- MODULARITY!!
- Different experts participate in the design in different levels
- Each one needs to understand only **his** part fully
- Most things are reusable

FAST PROGRESS!

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Now…

- ¿Can this idea translated to modern biology?
- ¿Is a rationalization of design possible?
- ¿Will nowadays biologist be seen by future bioengineers the same way ENIAC designers are seen by modern computer designers?

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Now…

- Or is an organism simply…

¿TO COMPLEX ?

- But even in this case:

¿isn't it worth trying?

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Design Principles in SB

- **Decoupling design from fabrication**
  - Rules insulating design process from details of fabrication
  - Enable parts, device, and system designers to work together
  - VLSI electronics, 1970s
- **Abstraction**
  - Insulate relevant characteristics from overwhelming detail
  - Simple artifacts that can be used in combination
- **Standardization**
  - Predictable performance
  - Off-the-shelf

Design principles in SB

- Engineering already deals usually with complex systems made up of interconnected devices and parts
- Modularized design is also a usual in nowadays Engineering
  - A modern plane is not much less complex than a simple bacteria
  - Use of modular programming languages is ideally suited to this requisites
- Standardization is essential in Engineering since 1800's
  - Example: standardization of screws

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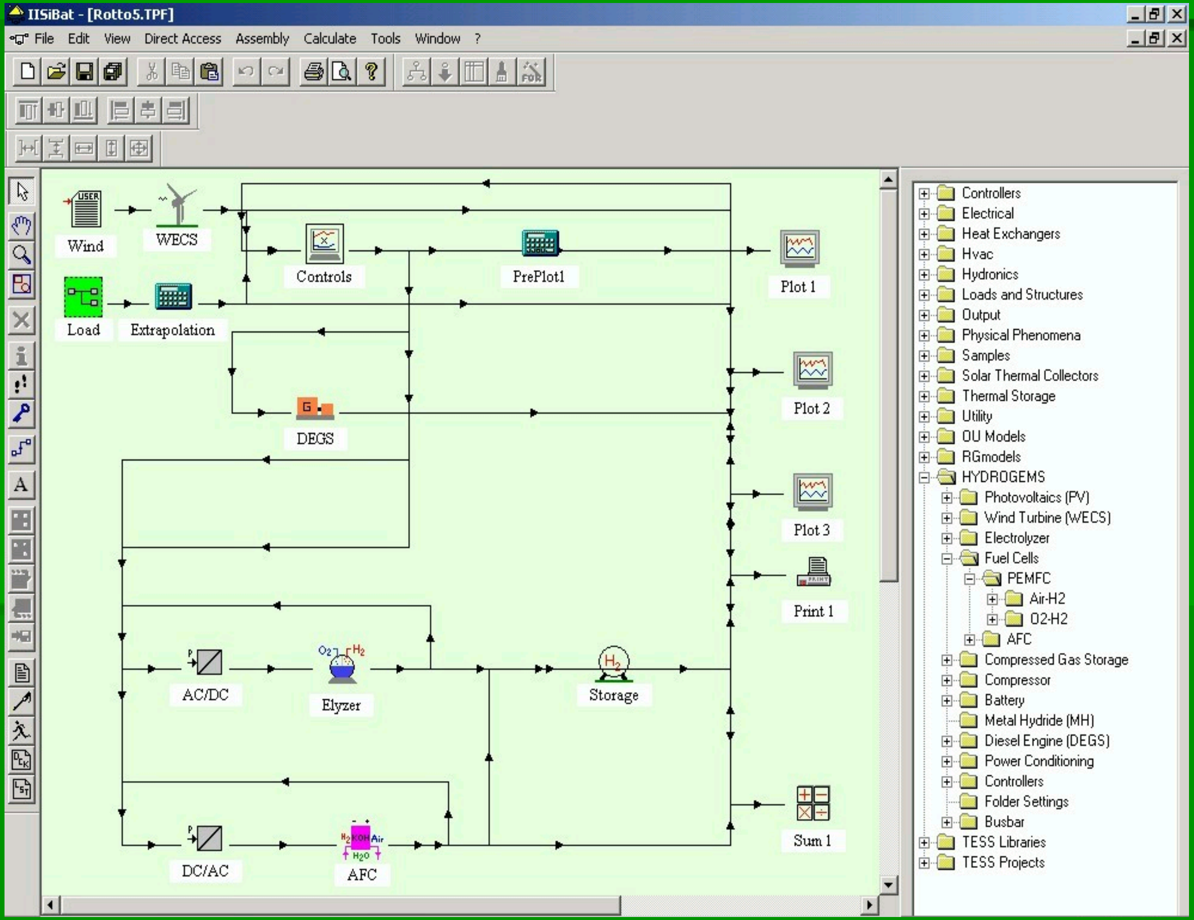
Example: windmill energy production coupled to a building with a fuel-cell based H2 storage modeled in TRNSYS



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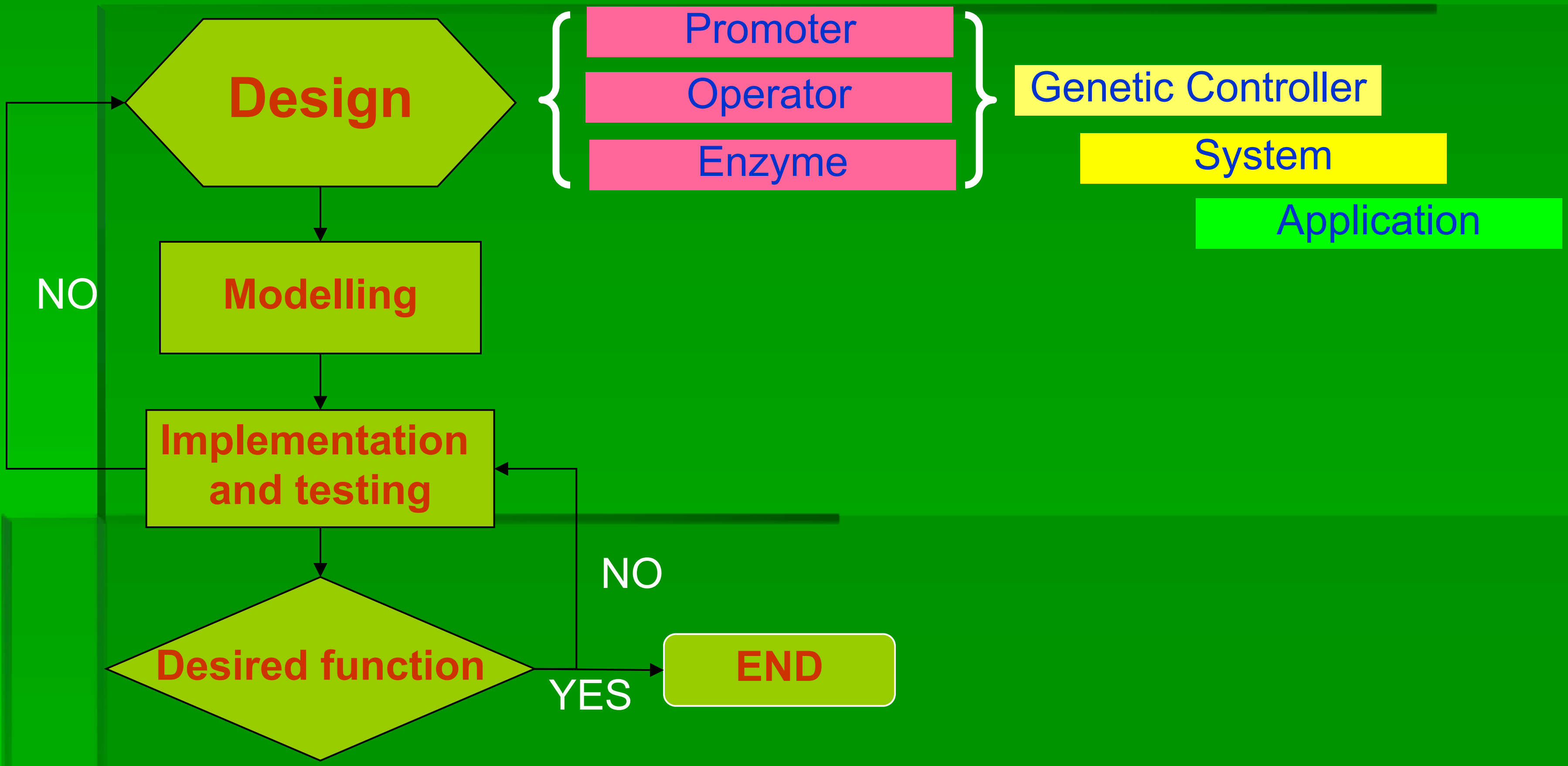
Design Principle 1
Decoupling design from fabrication



Design Principle 2
Abstraction

Systems

Devices

Parts

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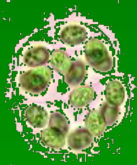
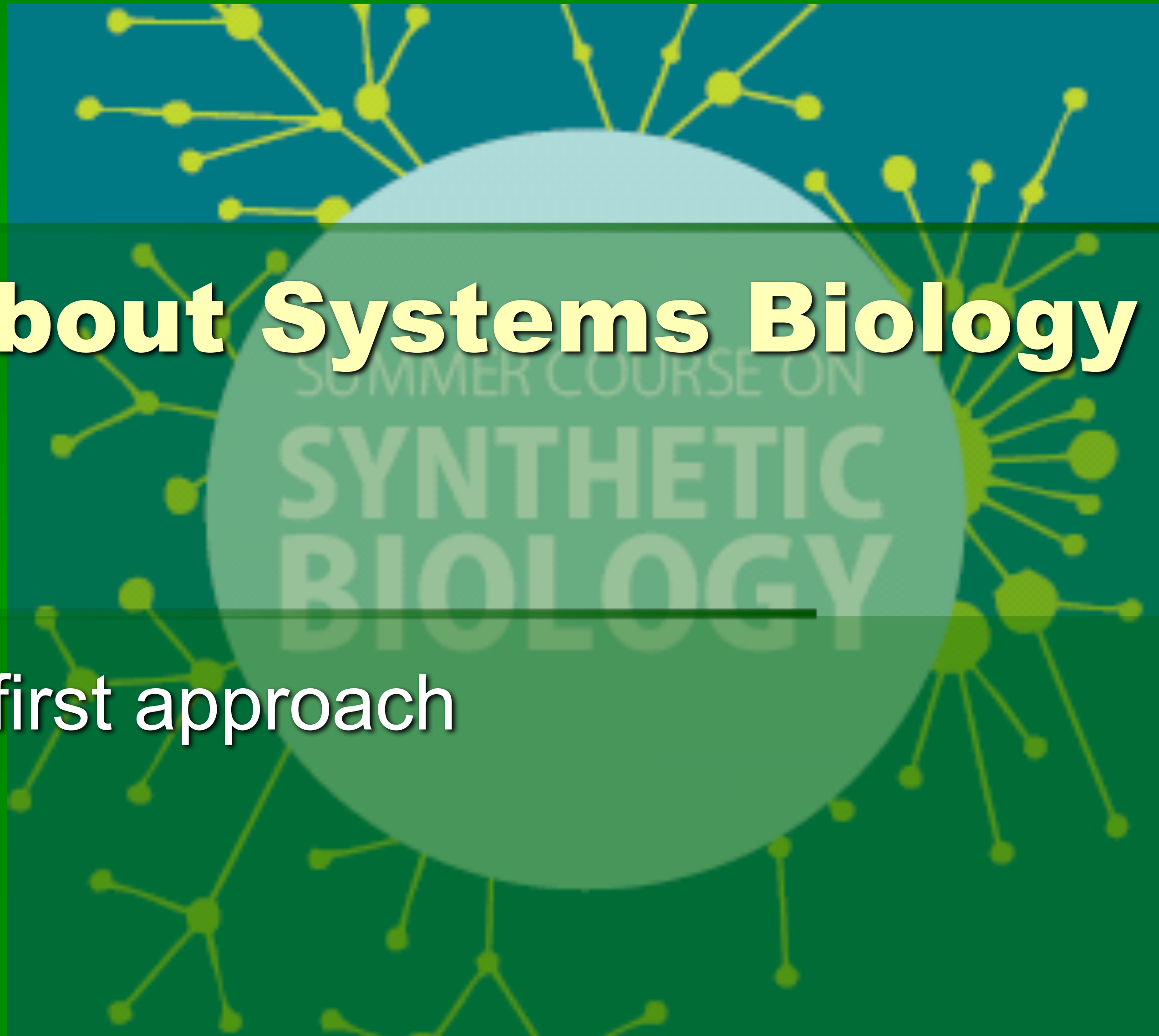


About Systems Biology



A first approach

What is Systems Biology?

- *To me, systems biology seeks to explain biological phenomenon not on a gene by gene basis, **but through the interaction of all the cellular and biochemical components in a cell or an organism**. Since, biologists have always sought to understand the mechanisms sustaining living systems, solutions arising from systems biology have always been the goal in biology. <u>Previously, however, we did not have the knowledge or the tools.</u>*

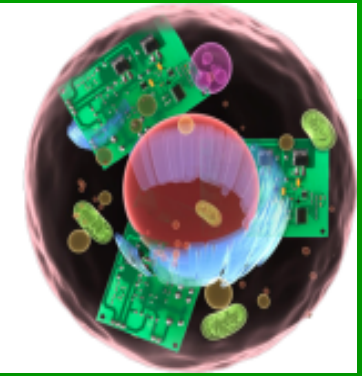
Edison T Liu

Genome Institute of Singapore

Systems vs. Synthetic Biology

- Understand life
  - Orientate experiments
- Study the whole cell

- Create life
- Experimental data
- Work within a device



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What is Systems Biology?

- *addresses the analysis of **entire** biological systems*
- ***interdisciplinary** approach to the investigation of all the components and networks contributing to a biological system*
- *[involves] new **dynamic computer modeling** programs which ultimately might allow us to simulate entire organisms based on their individual cellular components*
- *Strategy of Systems Biology is dependent on **interactive cycles of predictions and experimentation**.*
- *Allow[s Biology] to move from the ranks of a descriptive science to an **exact science**.*

(Quotes from SystemsX.ch website)

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What is Systems Biology?

- **identify *elements* (genes, molecules, cells, …)**
- **ascertain their *relationships* (co-expressed, interacting, …)**
- ***integrate* information to obtain view of system as a *whole***

Large (genomic) systems

- many uncharacterized elements
- relationships unknown
- *computational analysis* should:
  - improve annotation
  - reveal relations
  - reduce complexity

Small systems

- elements well-known
- many relationships established
- *quantitative modeling* of systems properties like:
  - Dynamics
  - Robustness
  - Logics

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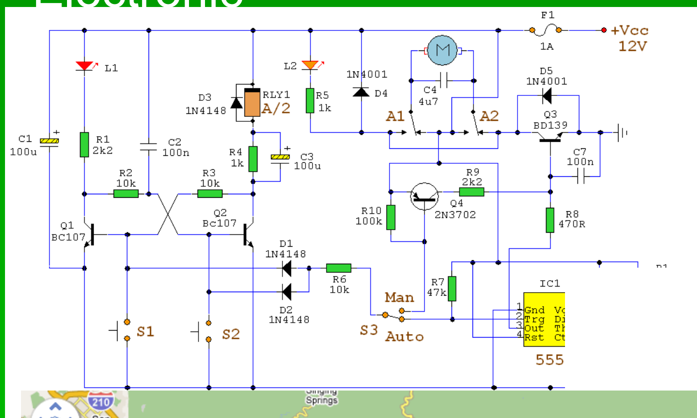
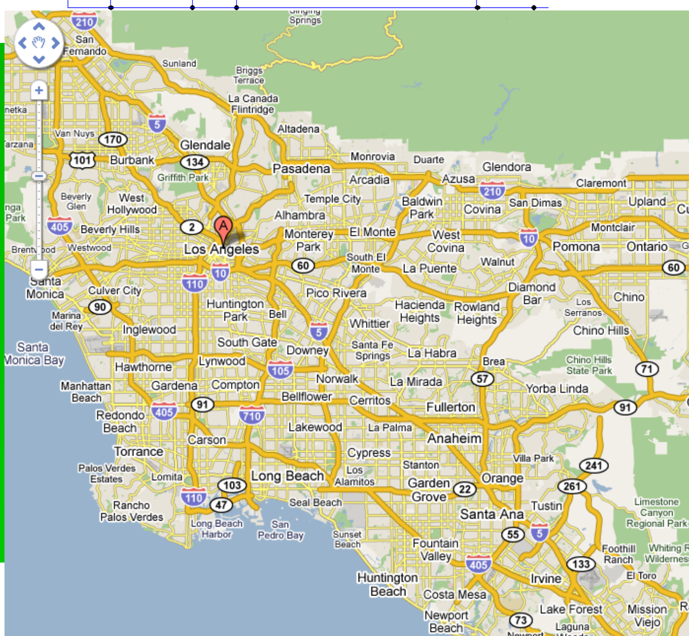
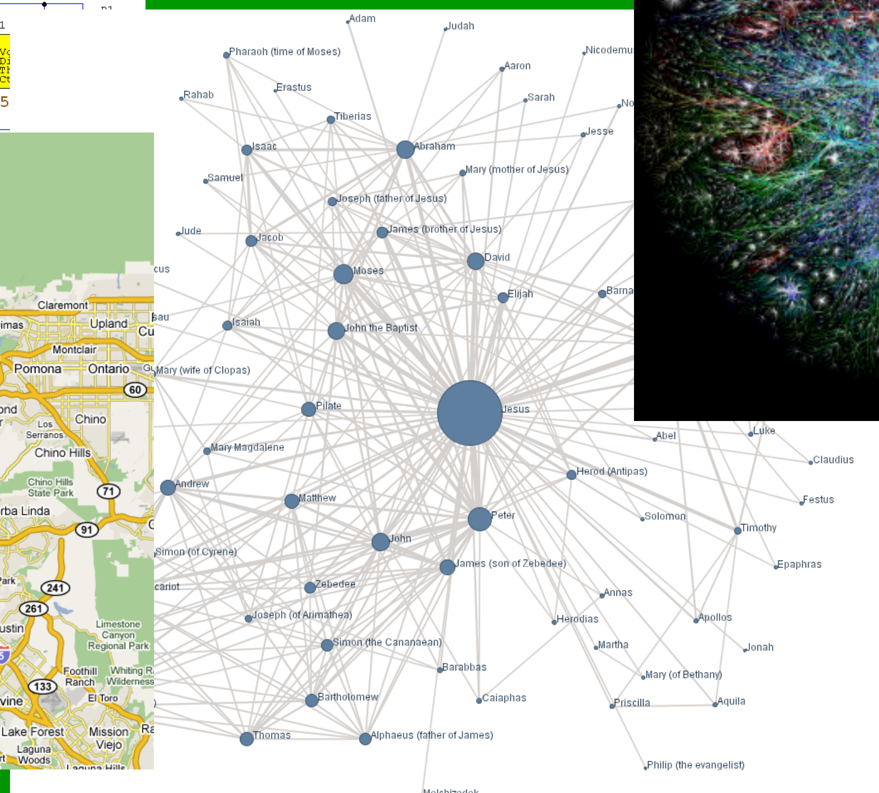
The world is full of networks

Electronic







WWW

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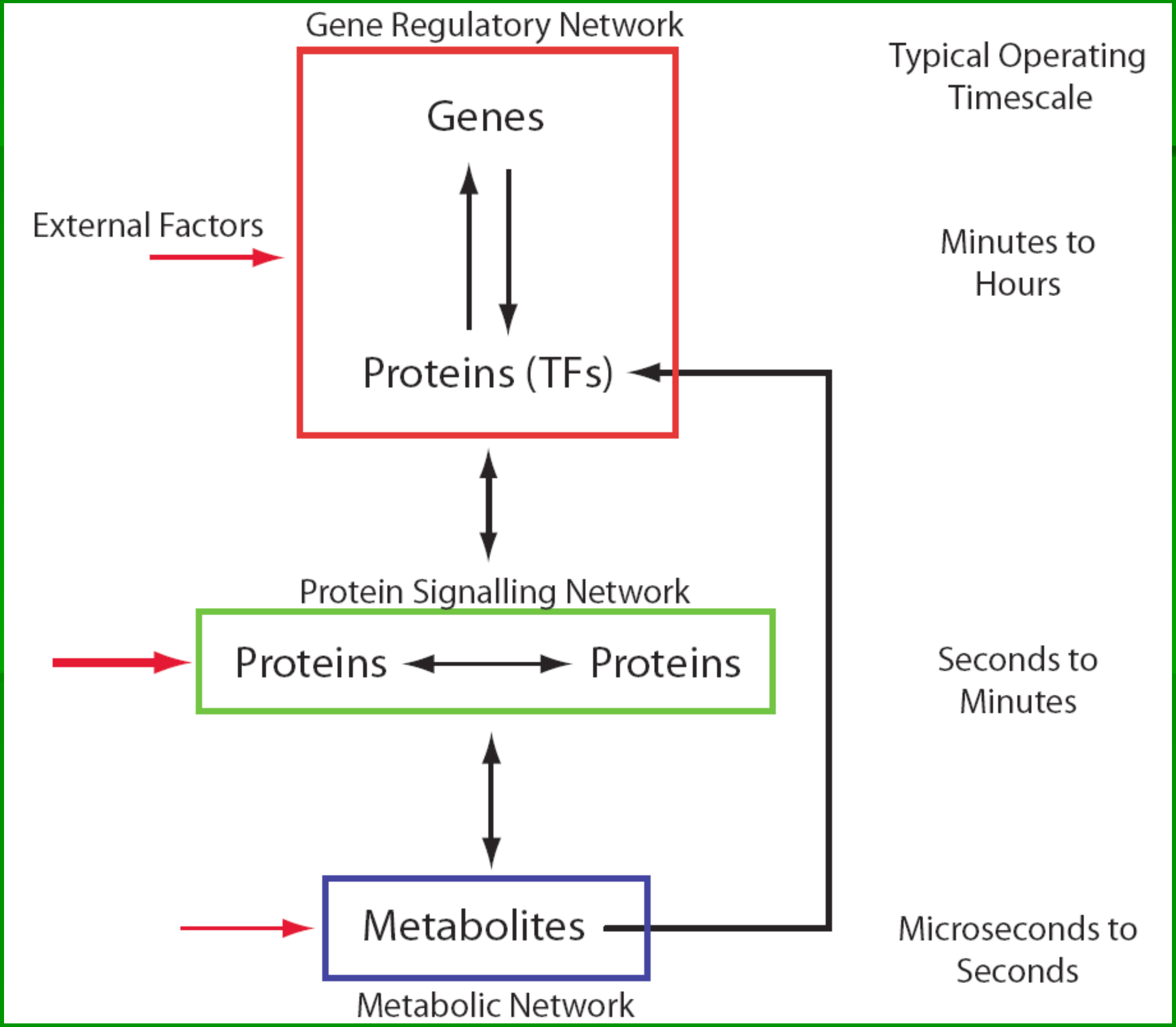
Biological Networks



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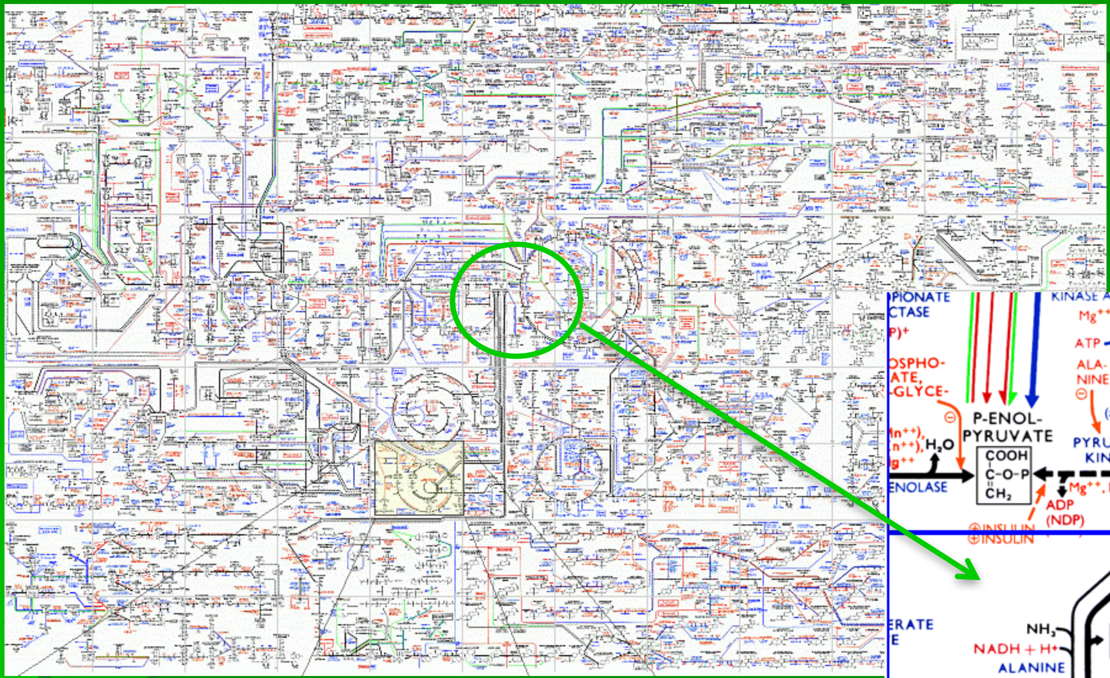
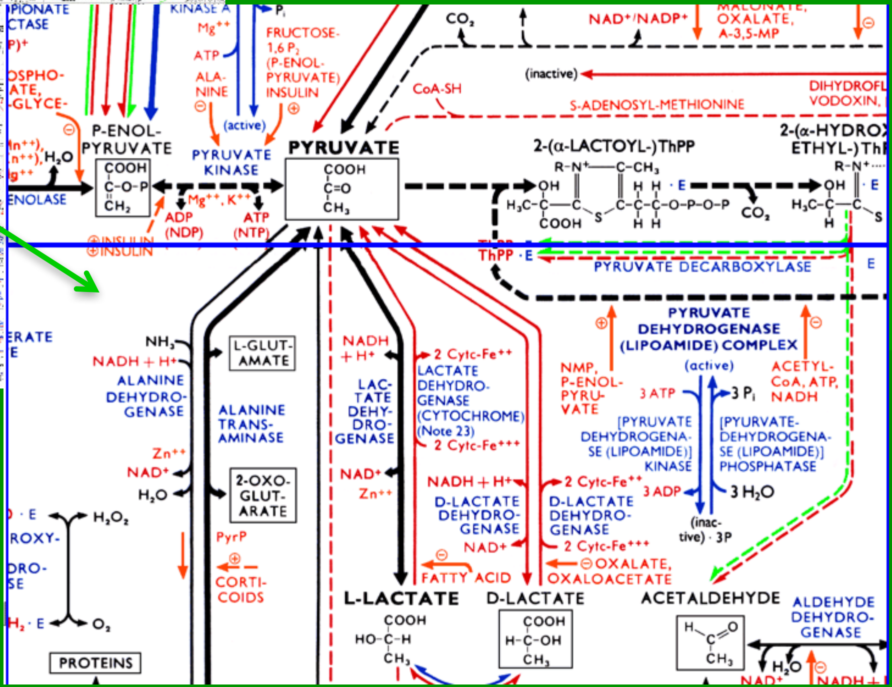
Metabolic Networks

Metabolic





About 1000-1400 genes that code for metabolic enzymes in E. coli (out of a total of about 4300 genes)

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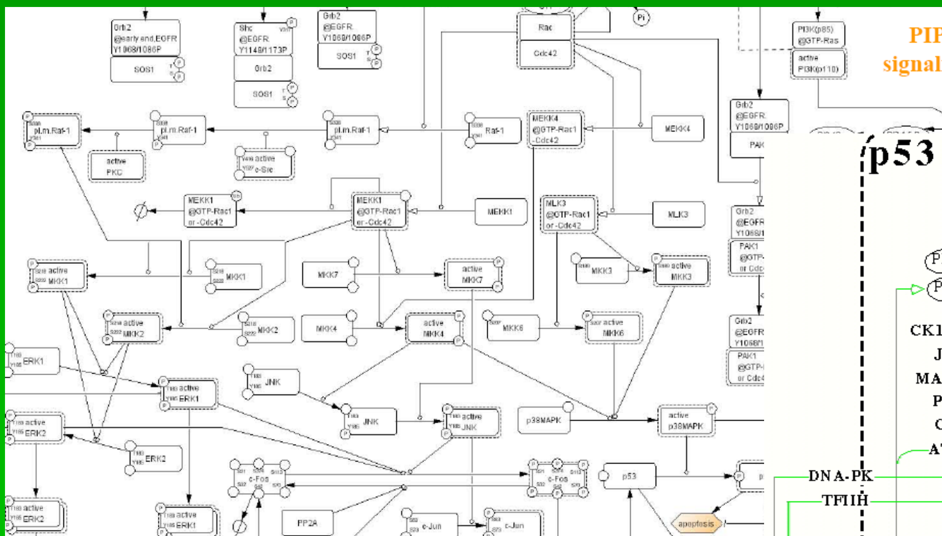
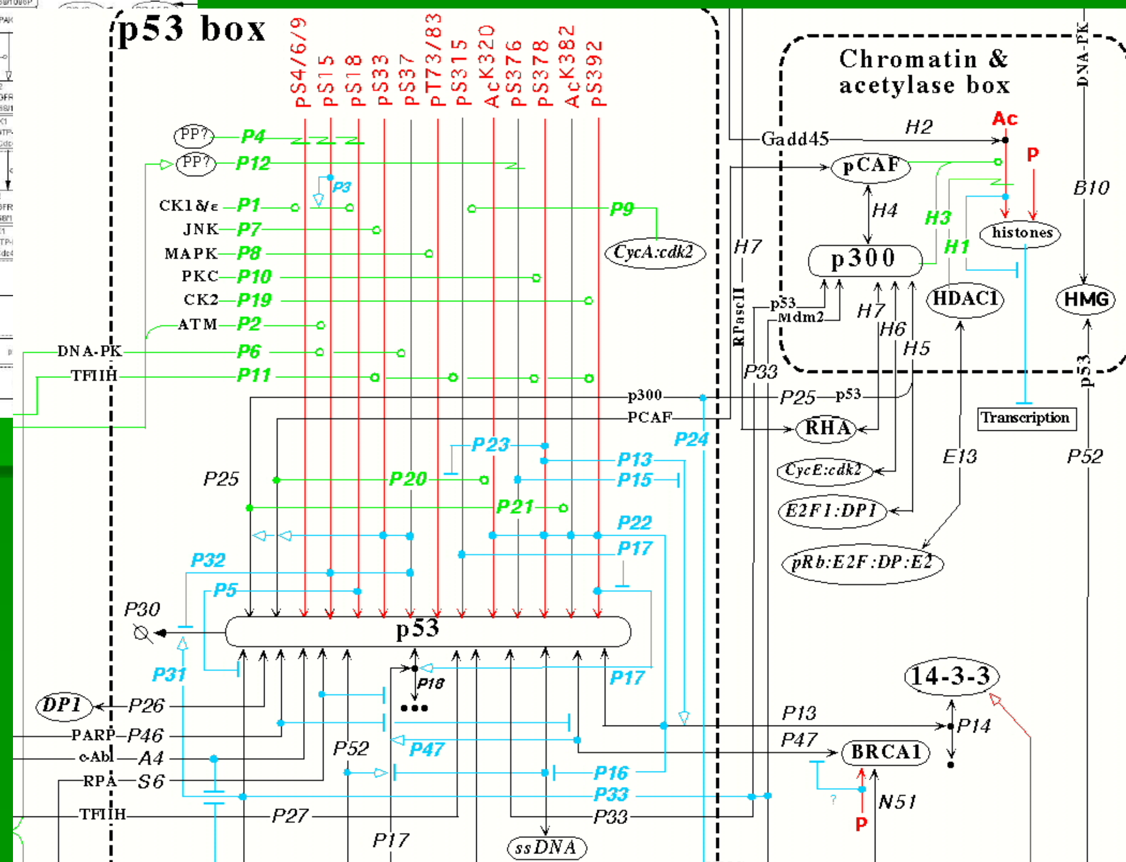
Protein-Protein Networks

Protein Signaling Network: CellDesigner



Kohn MIMS



20% of the human protein-coding genes encode components of signaling pathways, including transmembrane proteins, guanine-nucleotide binding proteins (G proteins), kinases, phosphatases and proteases.

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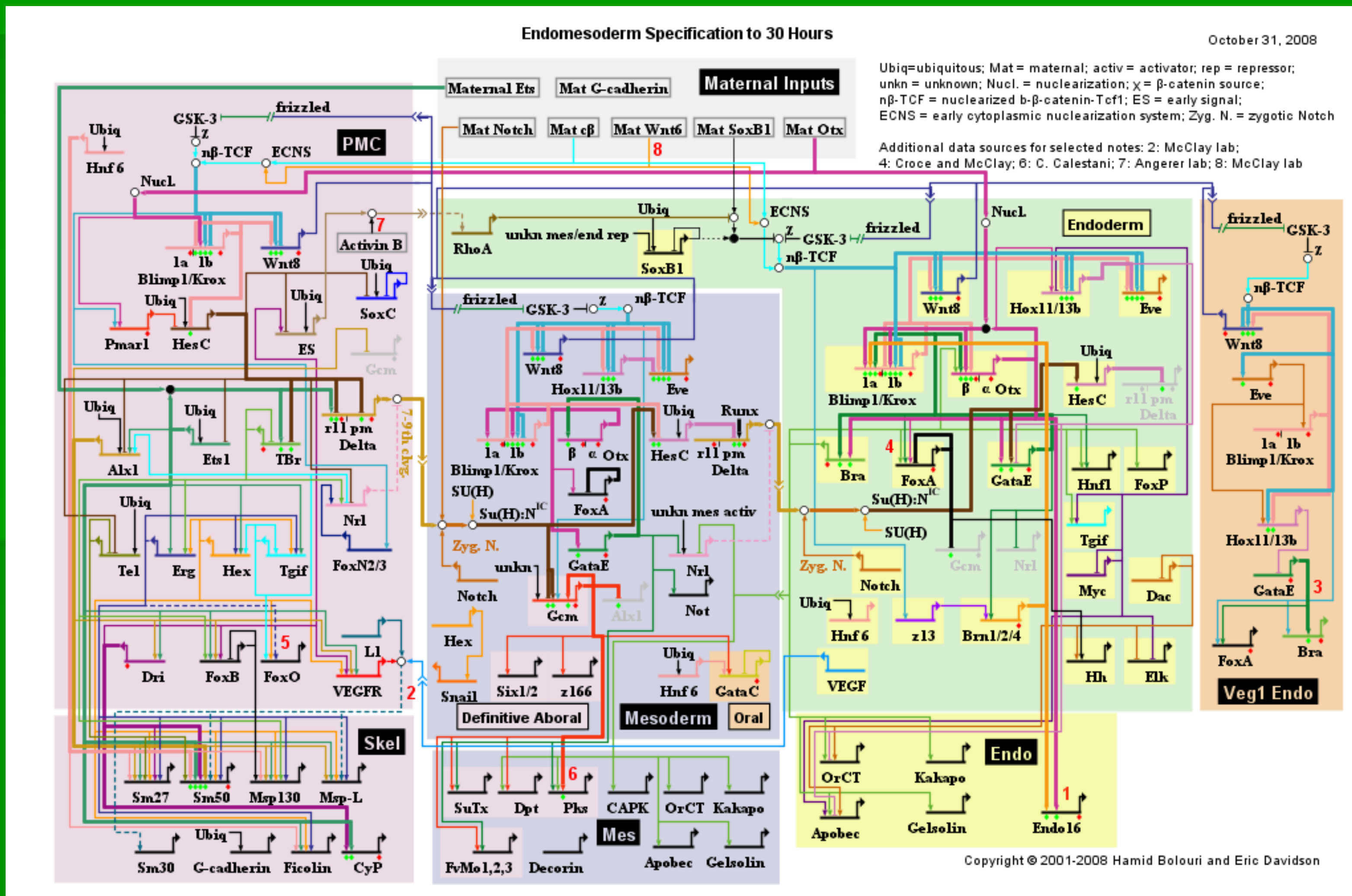
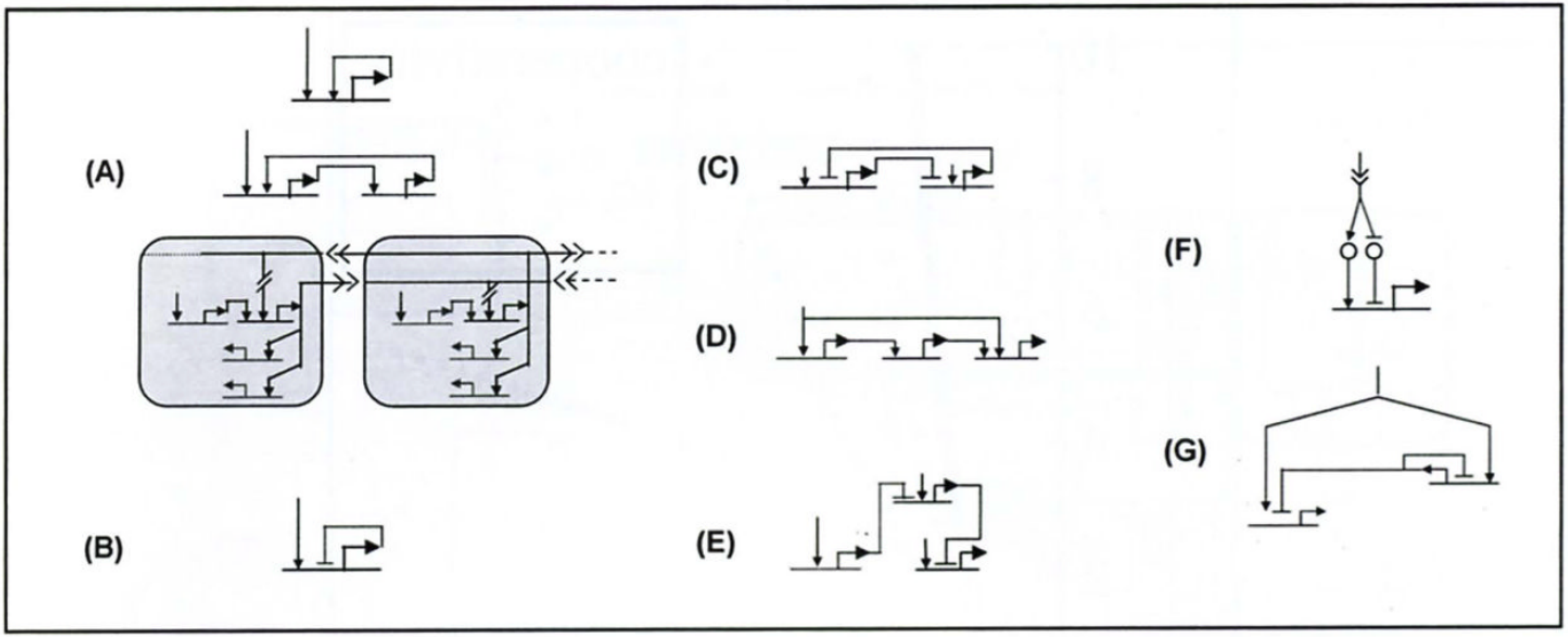
Genetic Networks

Gene Regulatory Networks: BioTapestry

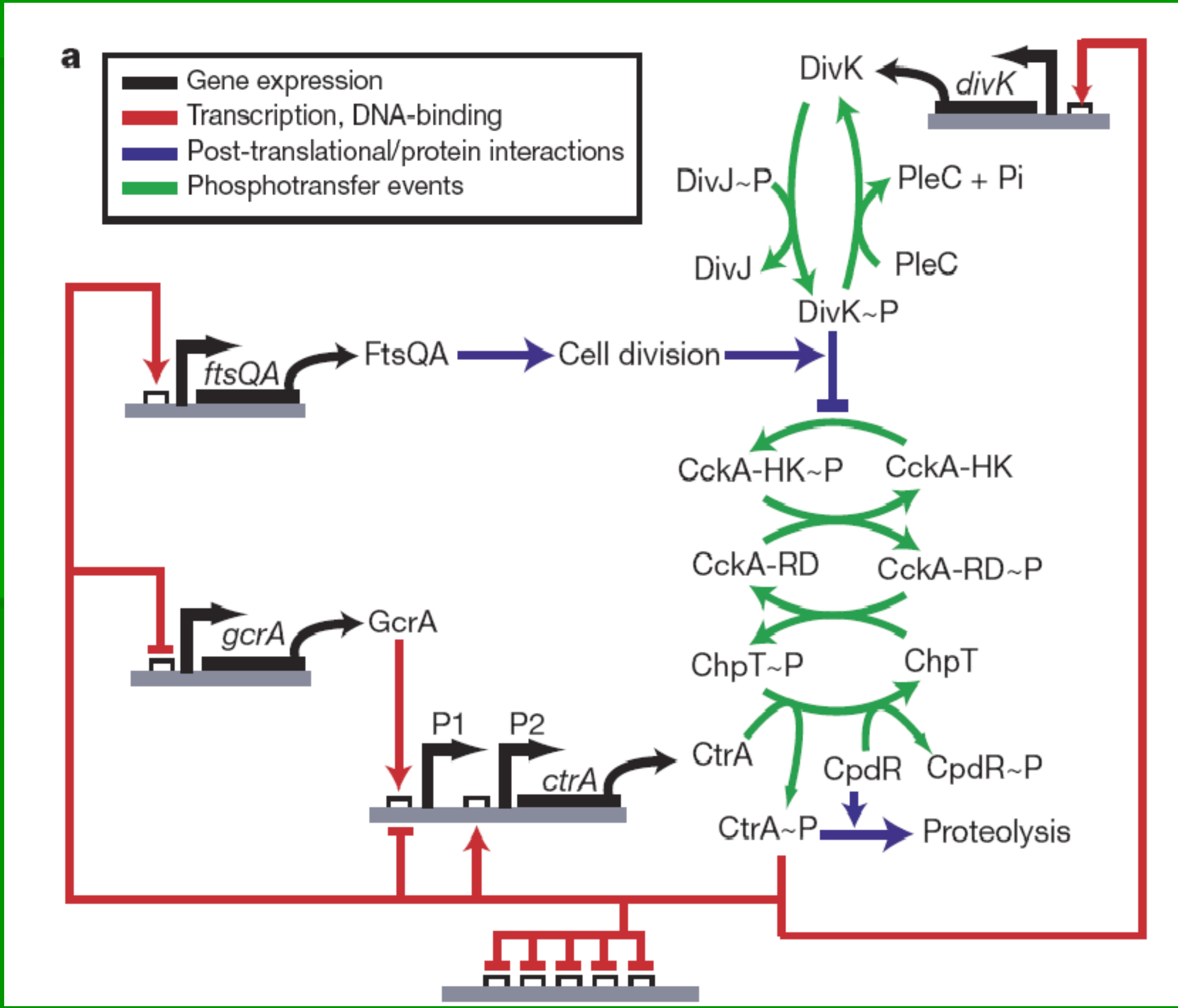


Genetic Units



Understanding the Dynamic Behavior of Genetic Regulatory Networks by Functional Decomposition. William Longabaugh and Hamid Bolouri Curr Genomics. Author manuscript; available in PMC 2007 December 12. Published in final edited form as: Curr Genomics. 2006 November; 7(6): 333–341.

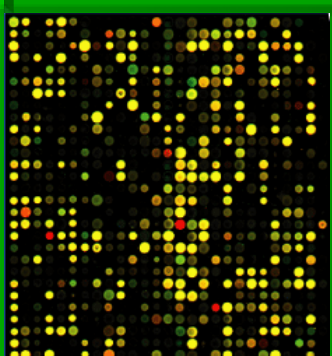
Hybrid Network: Cell Cycle Control is Bacteria

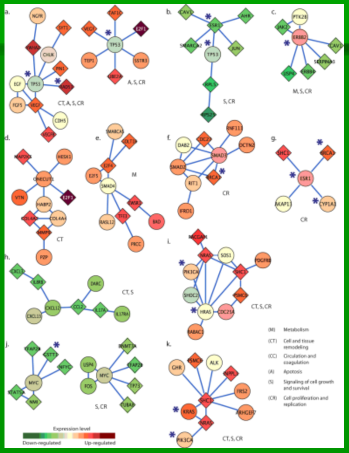


Top Down and Bottom Up

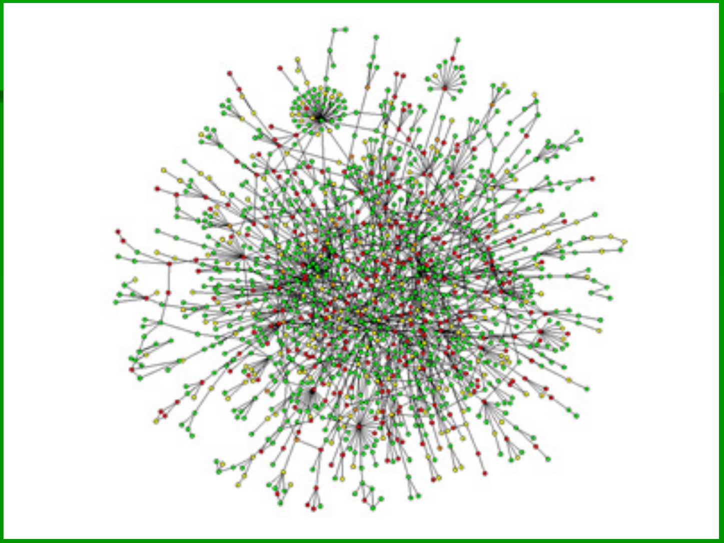
Top Down "-omics"

System	• Whole cell
Model	• Statistical Correlations
Data	• High-throughput





Yeast Protein-Protein Interaction Map



Top Down and Bottom Up

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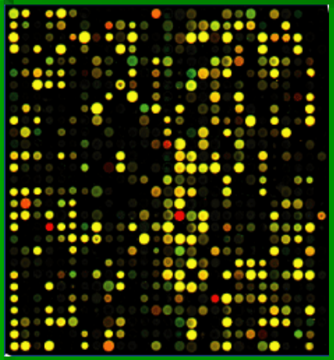
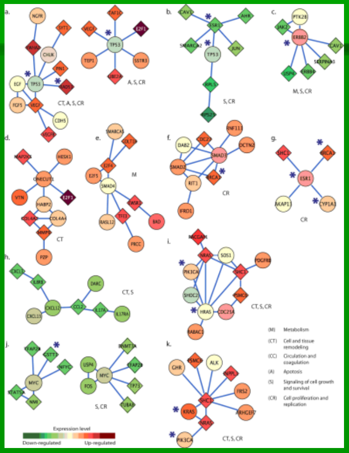
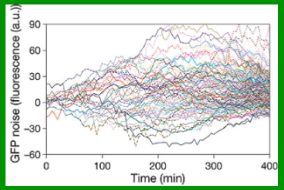
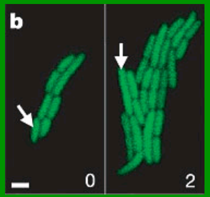
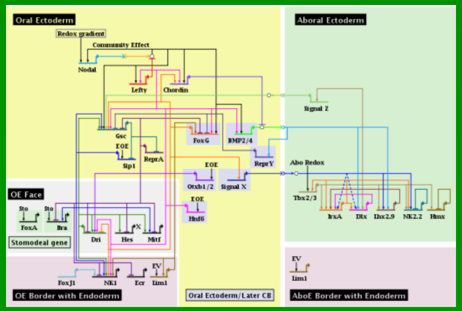



Bottom Up "mechanistic"

System	• Networks/Pathways
Model	• Mechanistic, biophysical
Data	• Quantitative, single-cell







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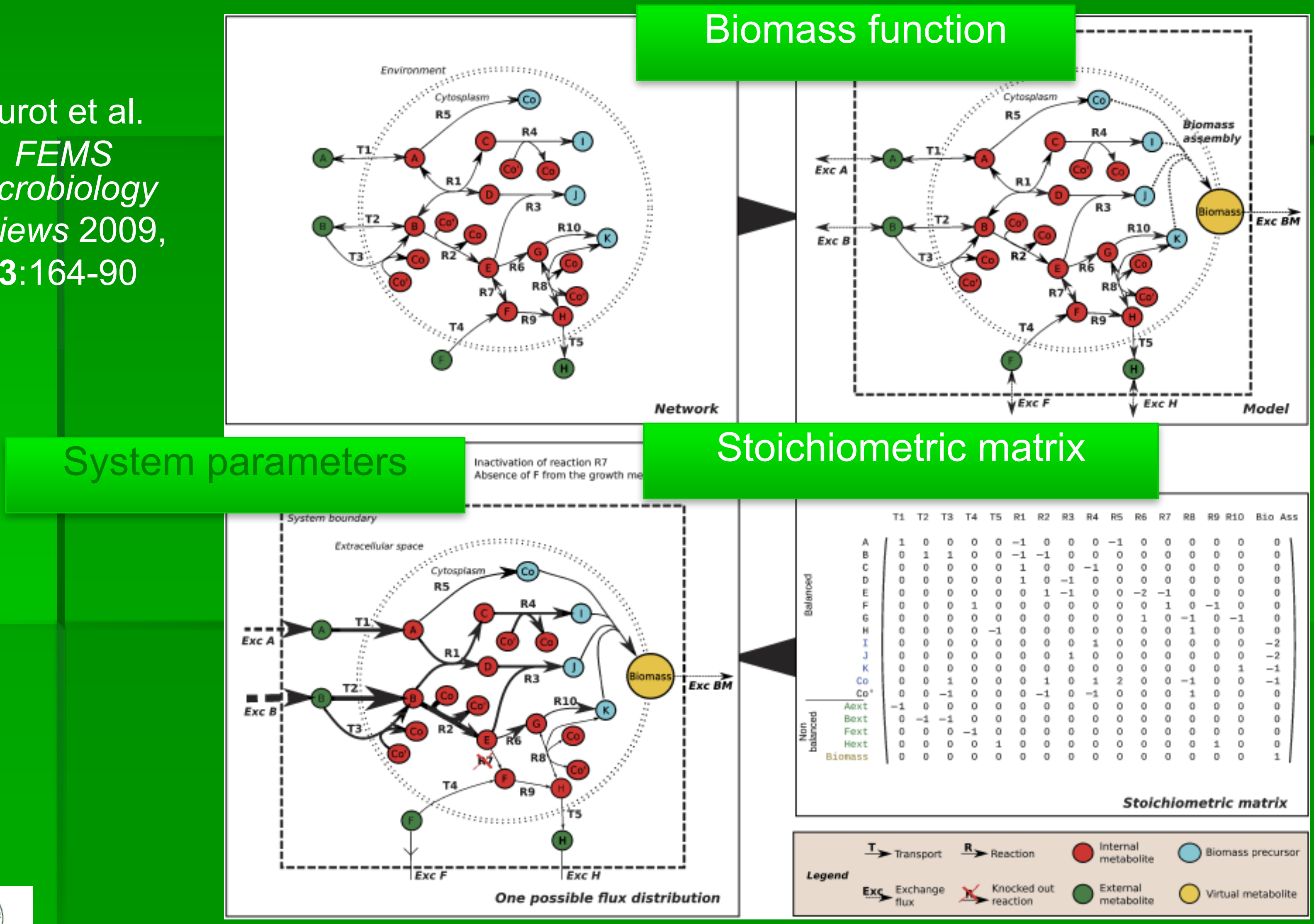
Metabolic modelling: a primer.. from network to mathematical model

Durot et al. *FEMS microbiology reviews* 2009, **33**:164-90



	T1	T2	T3	T4	T5	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Bio Ass
A	1	0	0	0	0	−1	0	0	0	−1	0	0	0	0	0	0
B	0	1	1	0	0	−1	−1	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	1	0	0	−1	0	0	0	0	0	0	0
D	0	0	0	0	0	1	0	−1	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	1	−1	0	0	−2	−1	0	0	0	0
F	0	0	0	1	0	0	0	0	0	0	0	1	0	−1	0	0
G	0	0	0	0	0	0	0	0	0	0	1	0	−1	0	−1	0
H	0	0	0	0	−1	0	0	0	0	0	0	0	1	0	0	0
I	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	−2
J	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	−2
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	−1
Co	0	0	1	0	0	0	1	0	1	2	0	0	−1	0	0	−1
Co'	0	0	−1	0	0	0	−1	0	−1	0	0	0	1	0	0	0
Aext	−1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bext	0	−1	−1	0	0	0	0	0	0	0	0	0	0	0	0	0
Fext	0	0	0	−1	0	0	0	0	0	0	0	0	0	0	0	0
Hext	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
Biomass	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

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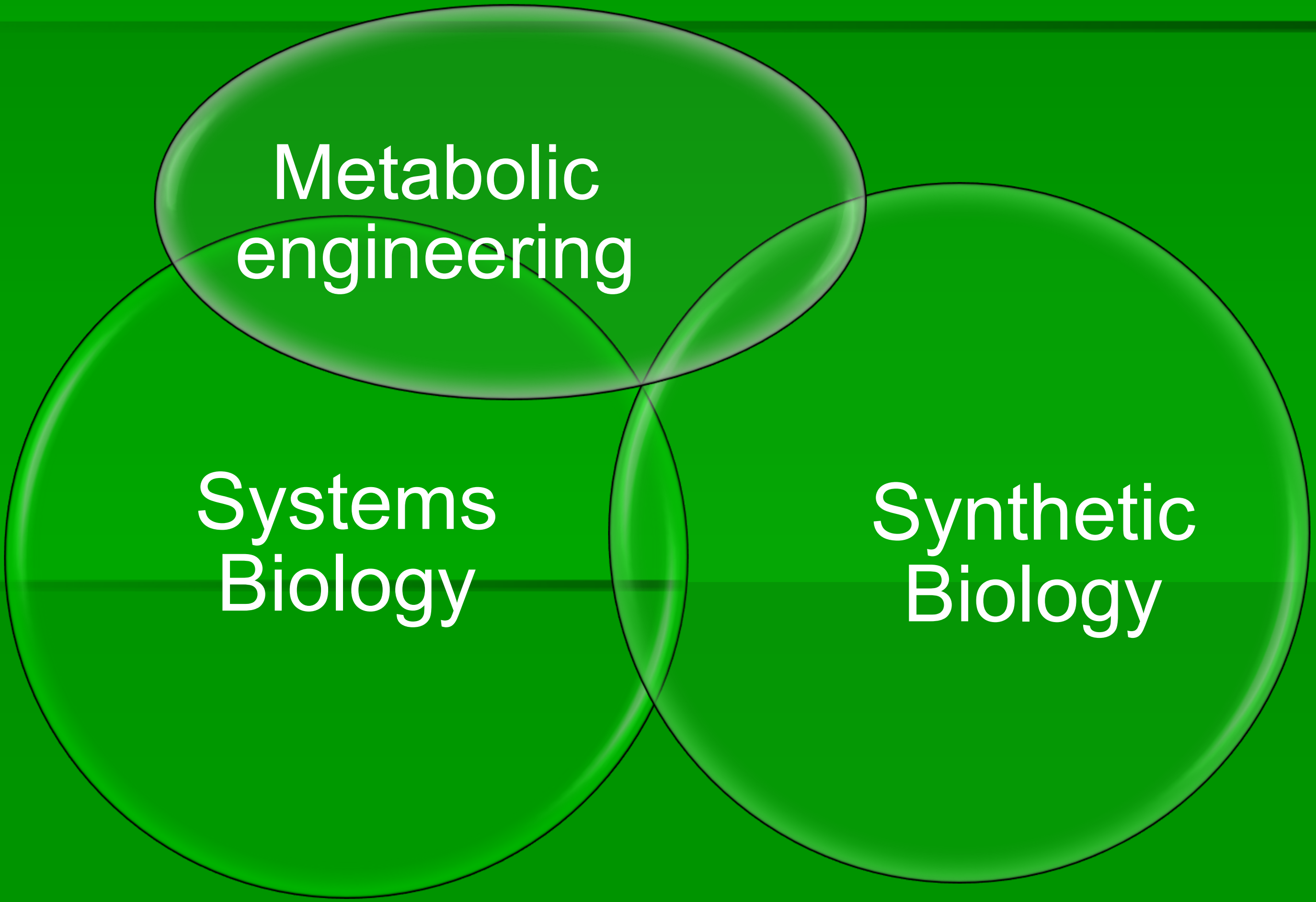
An overall picture…



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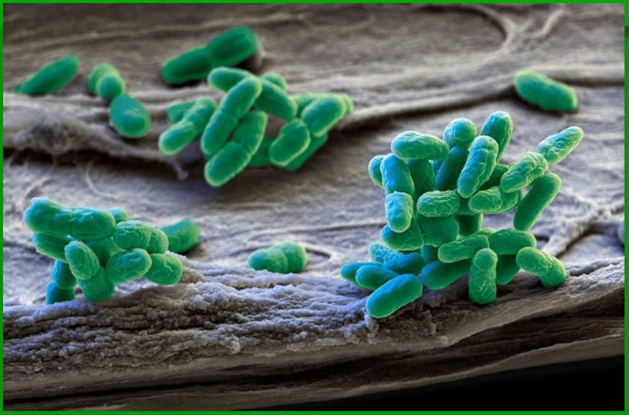
What is CyanoFactory

- FP7 EU Research Project on:
  - Development of alternative biofuels
  - Improving hydrogen production



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CyanoFactory

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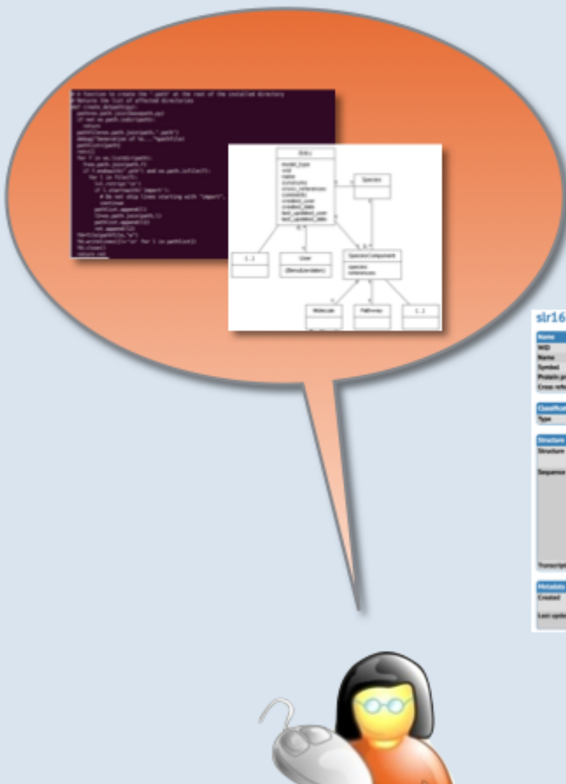
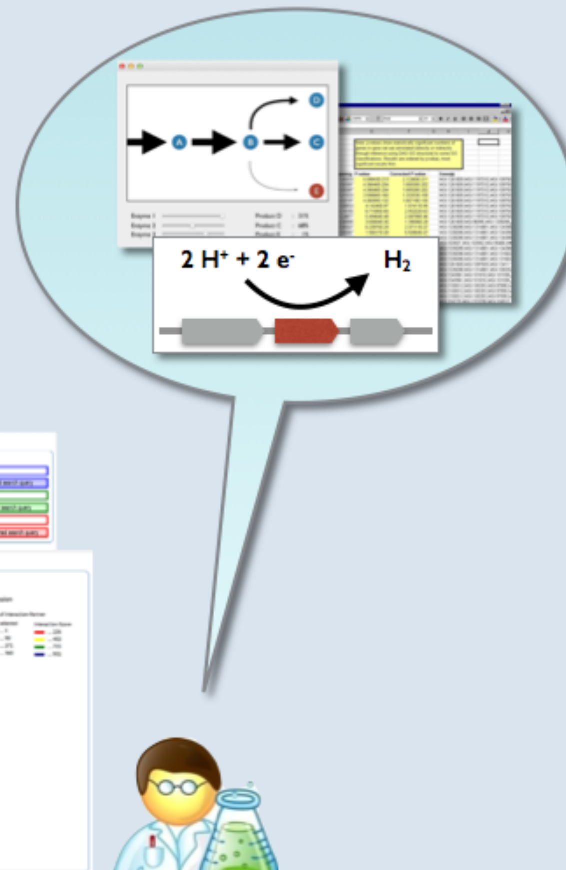
Computer Scientist vs. Life Scientist

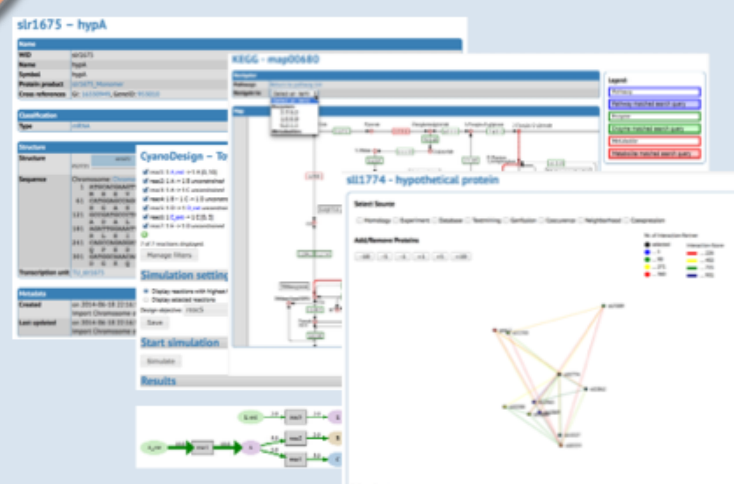
CyanoFactory KB



Both have different expectations when talking about data.

CyanoFactory KB tries to make both happy.





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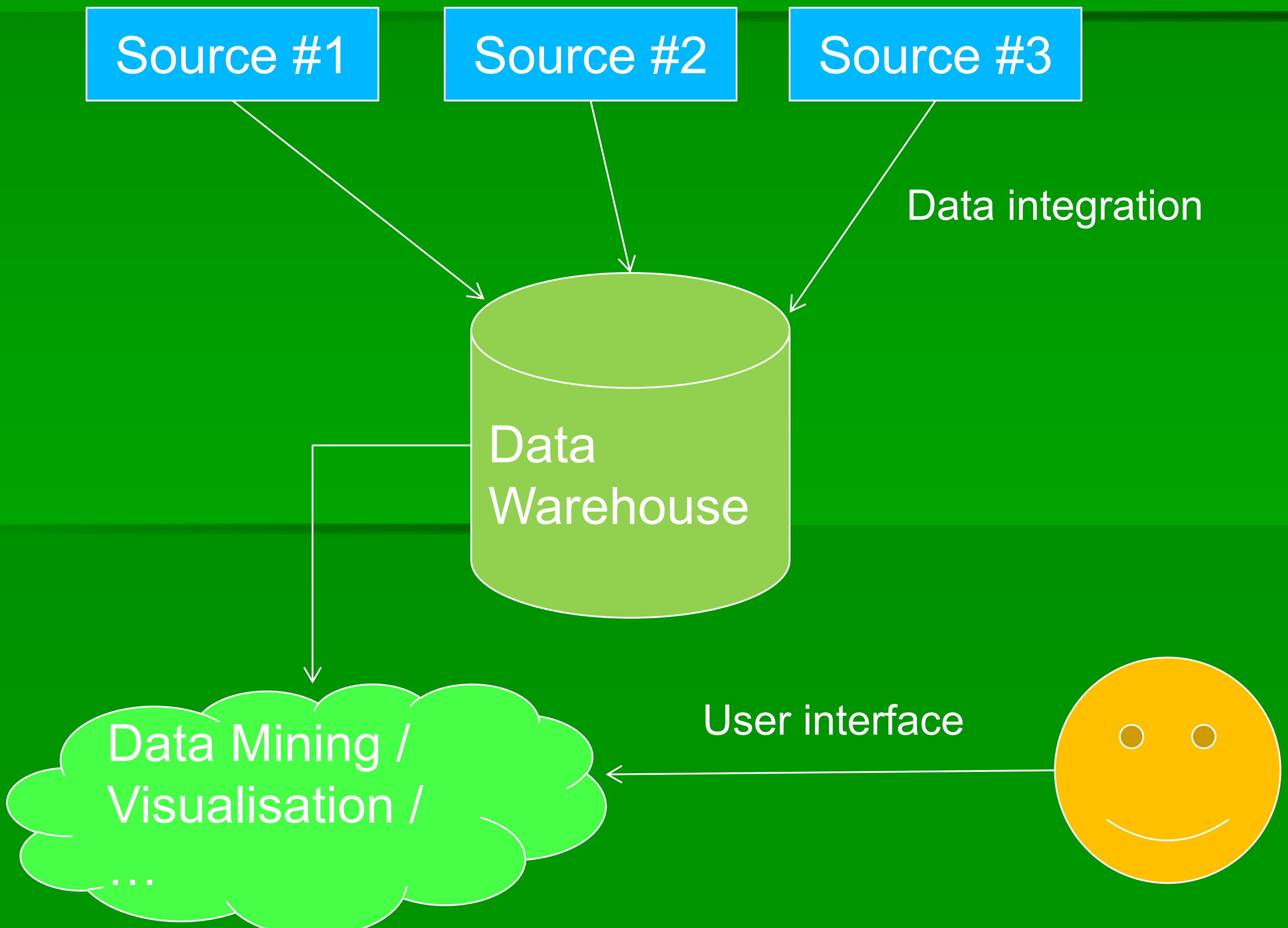
Data Warehouse



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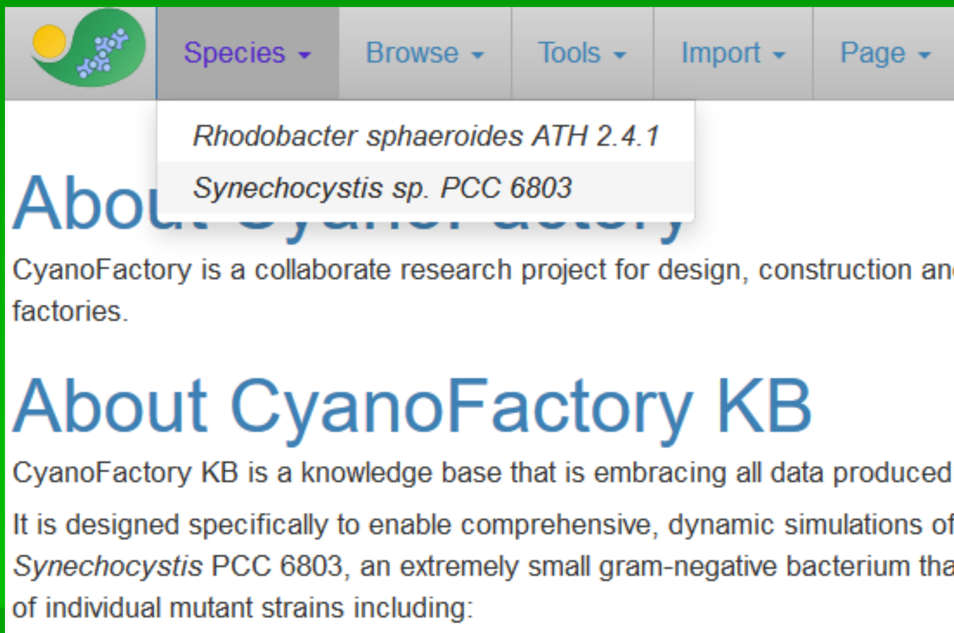
CyanoFactory KB



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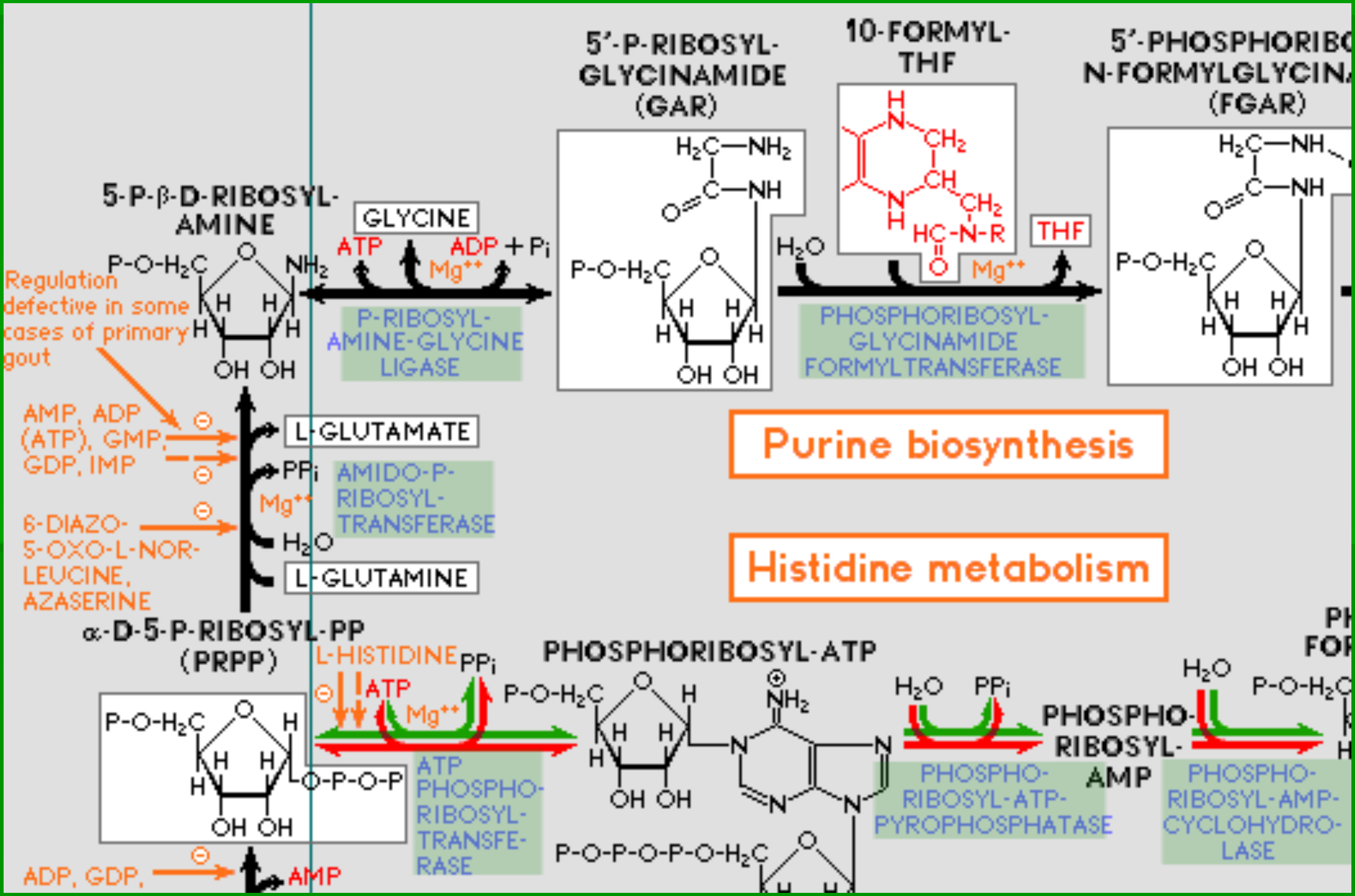
Boehringer Biochemical Pathways



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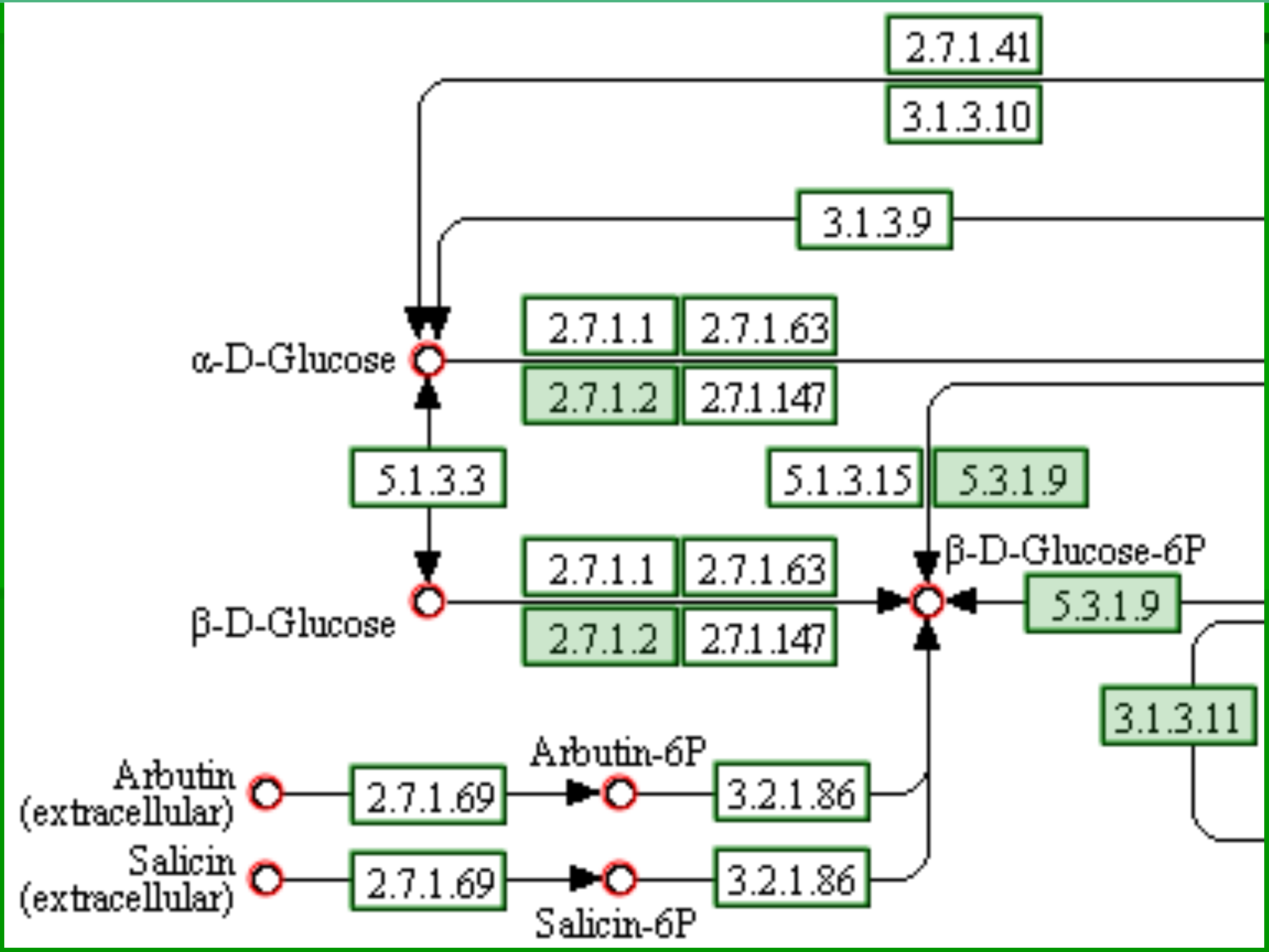
KEGG



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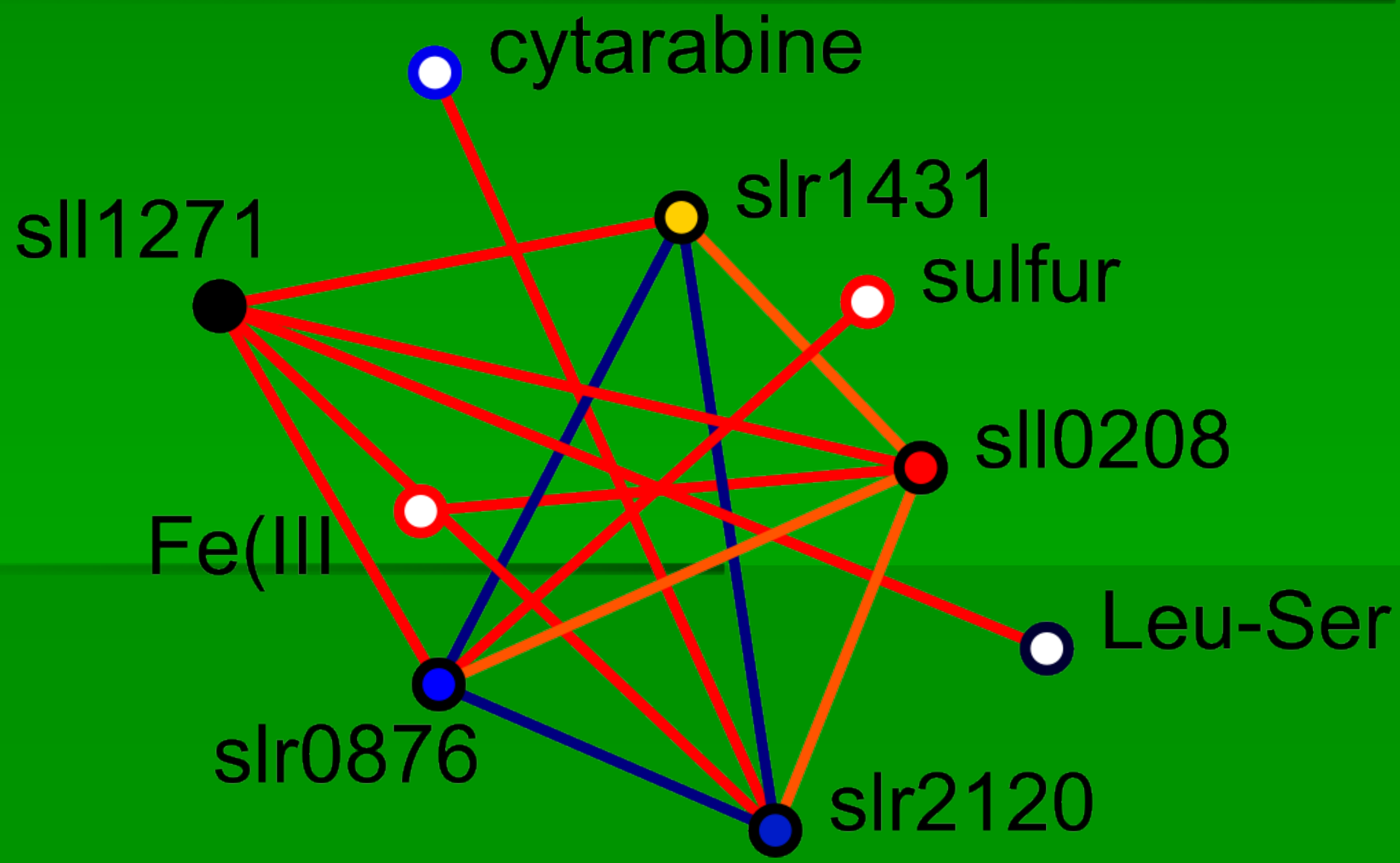
Interaction visualisation



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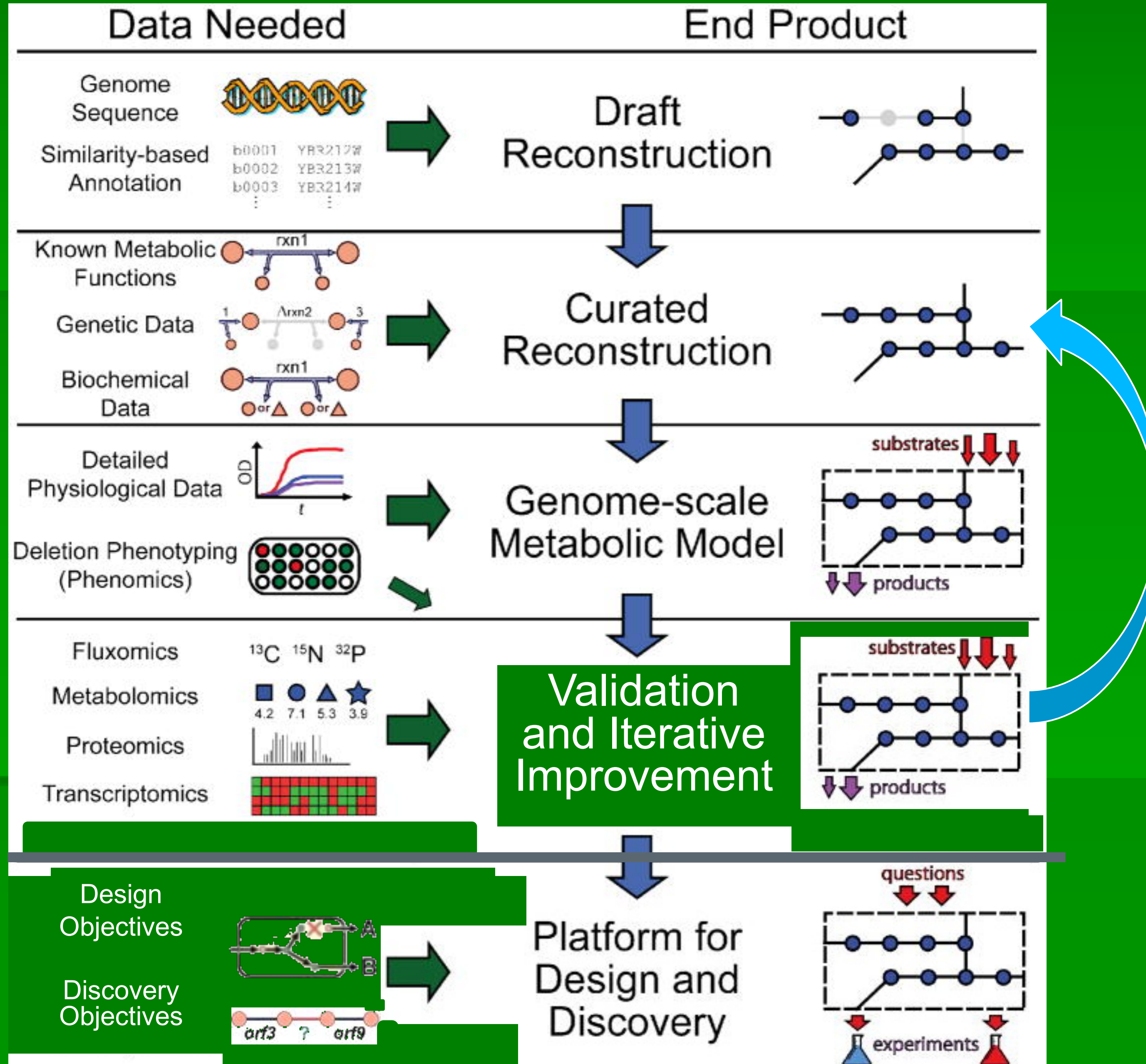
Automated generation of components

Manual reconstruction refinement

Conversion to a mathematical model

Network evaluation and debugging



Adapted from: Feist et al.
Nat Rev Microbiol. 2009; **7**(2):129-143

CyanoDesign

CyanoDesign – Toy Model

Reactions | Metabolites | Settings | Simulation

Show 25 entries | Search:

Filter reactions No filter applied | Search with RegExp

Name	Reaction	Constraint	Active	
reac1	1 A_ext → 2 A	[0.0, 5.0]	✓ Enabled	Delete
reac2	1 A ↔ 1 B		✓ Enabled	Delete
reac3	1 A → 1 C		✓ Enabled	Delete
reac4	1 B + 1 C → 1 D		✓ Enabled	Delete
reac5	1 D → 1 D_ext		✓ Enabled	Delete
reac6	1 E_ext → 1 E	[0.0, 3.0]	✓ Enabled	Delete
reac7	2 E → 1 D		✓ Enabled	Delete

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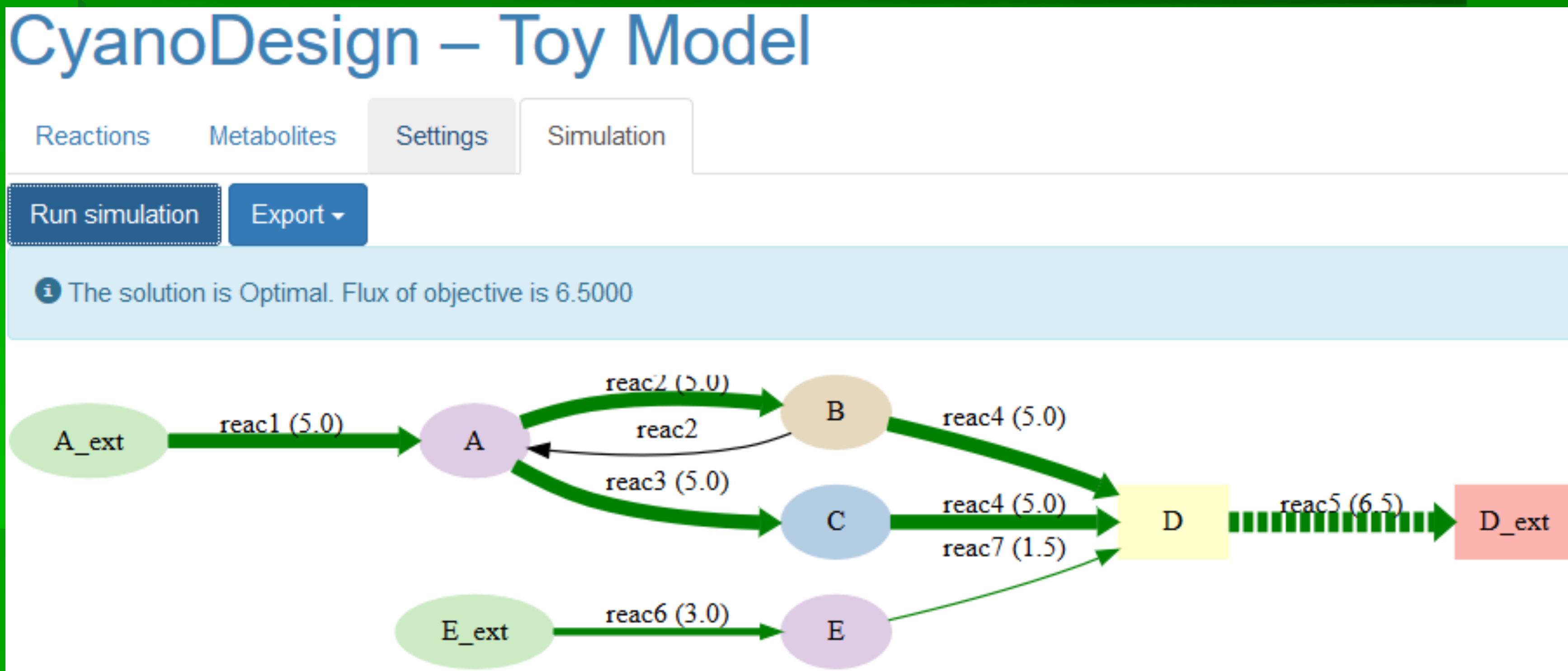
CyanoDesign



Modeling light utilization for photosynthetic production

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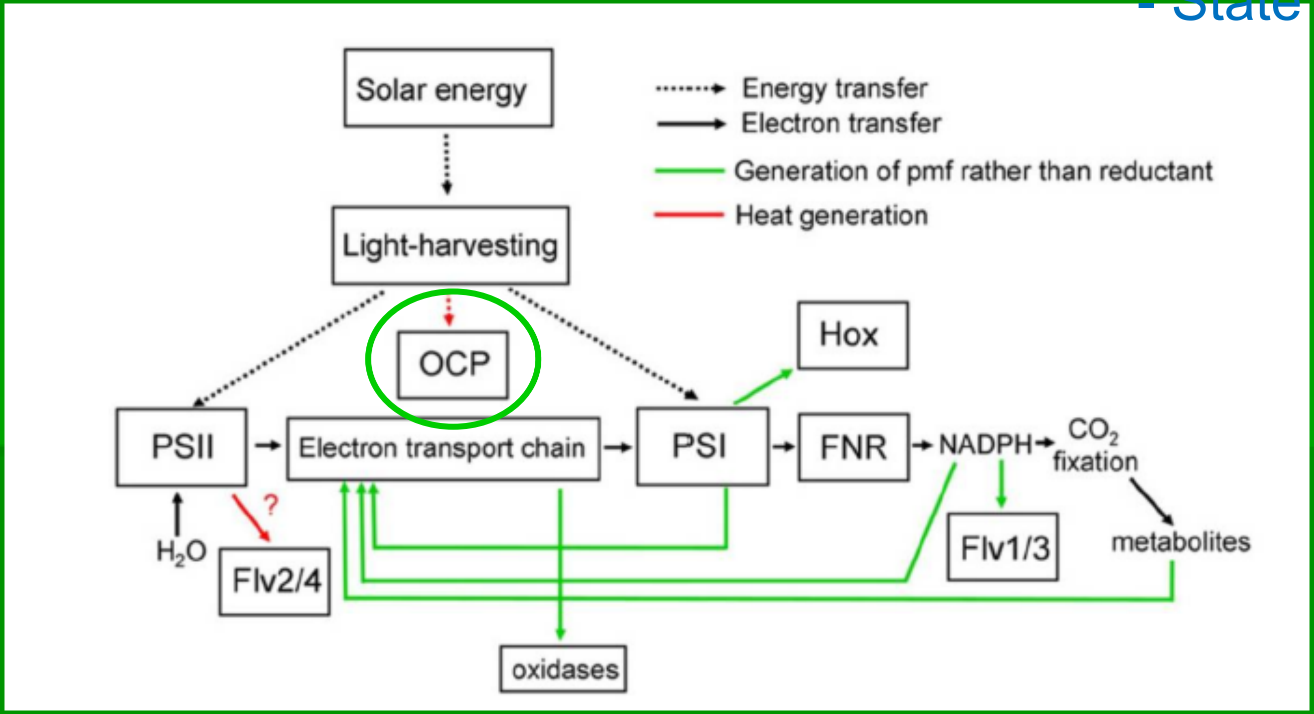
Photosynthesis in cyanobacteria

- Scheme

- Non photochemical Quenching

- State transitions

St. Trans.



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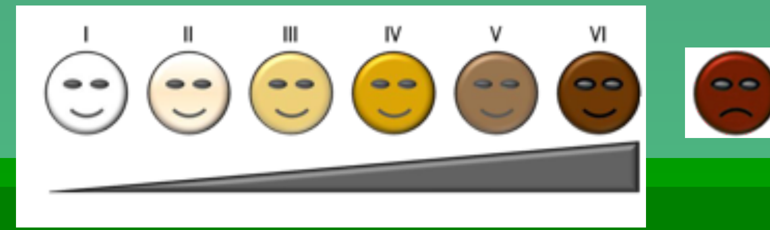
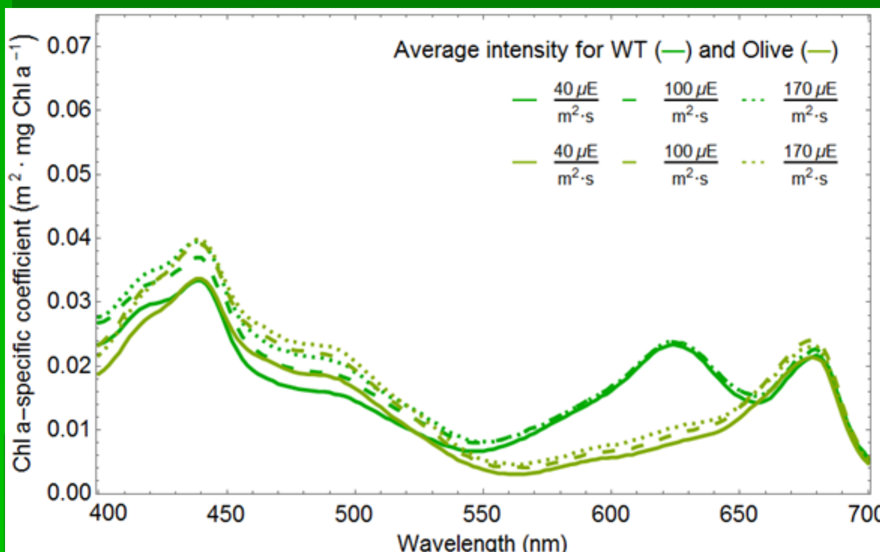
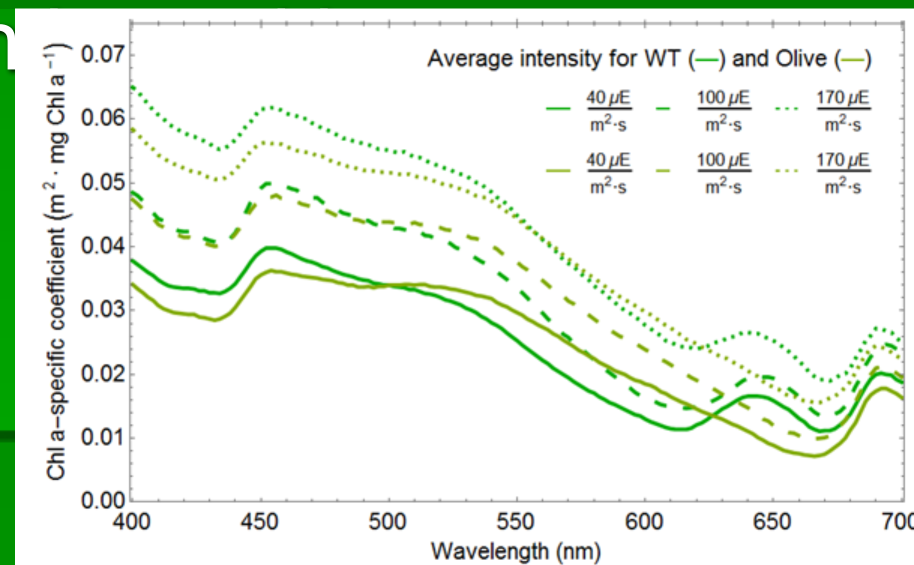
Light model input



- Absorption and scattering coefficient at





WT (dark colour) - Olive (light colour)

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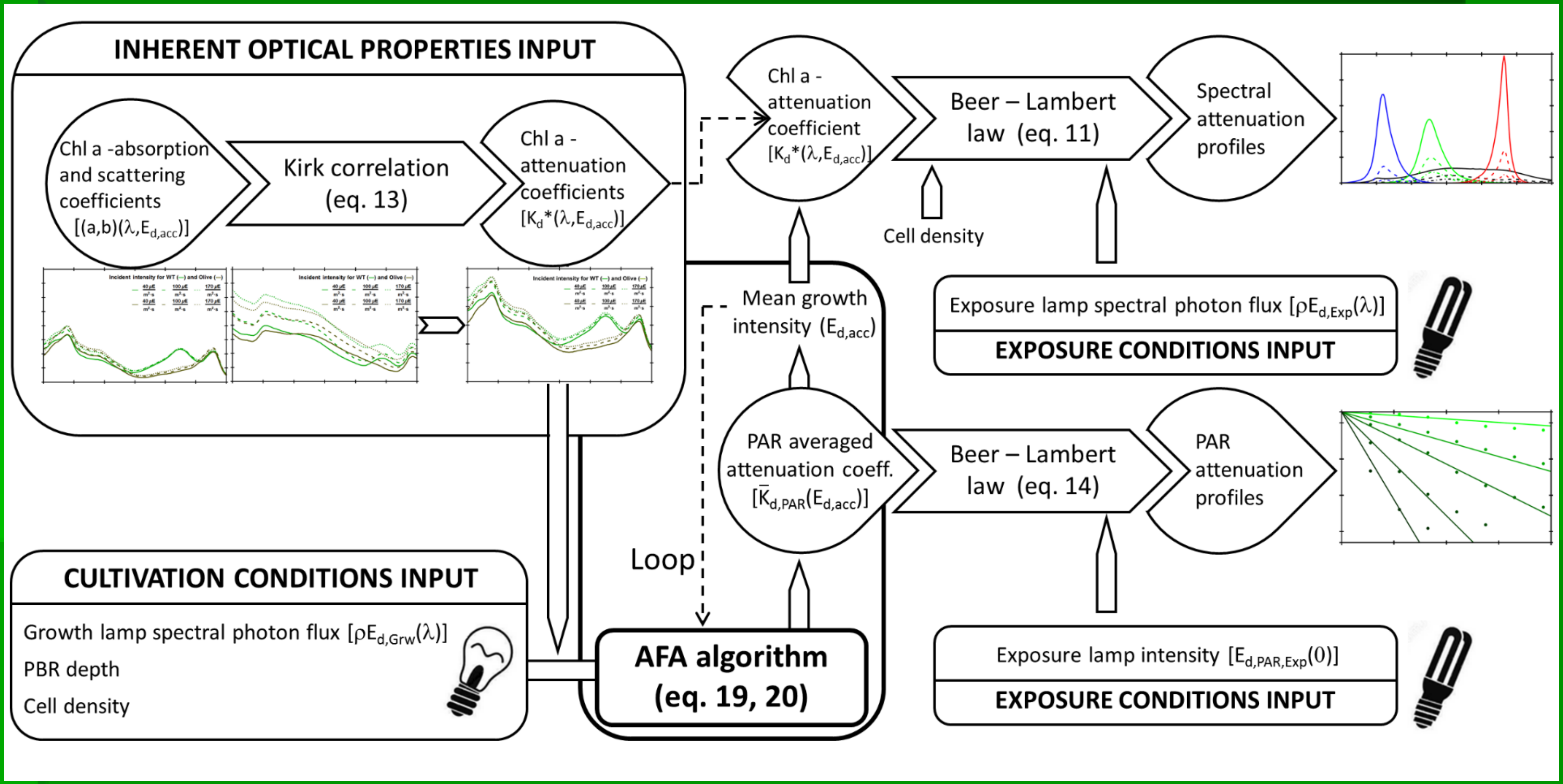
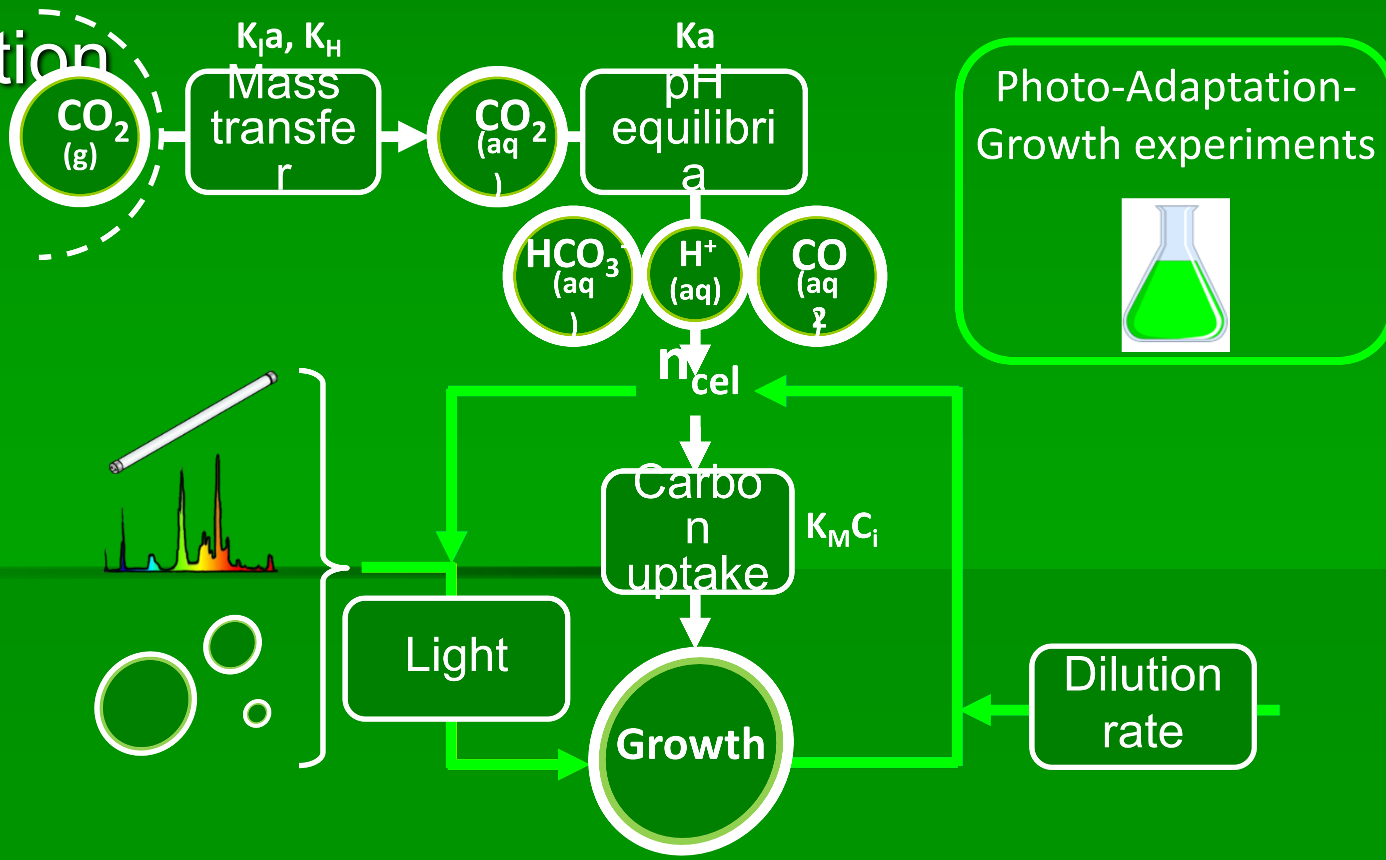
Light model calculation scheme



PBR model

- Definition



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Gracias por su atención

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