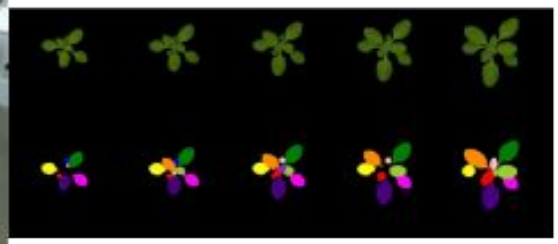
Predicting plant cell phenotypes using resource allocation based models

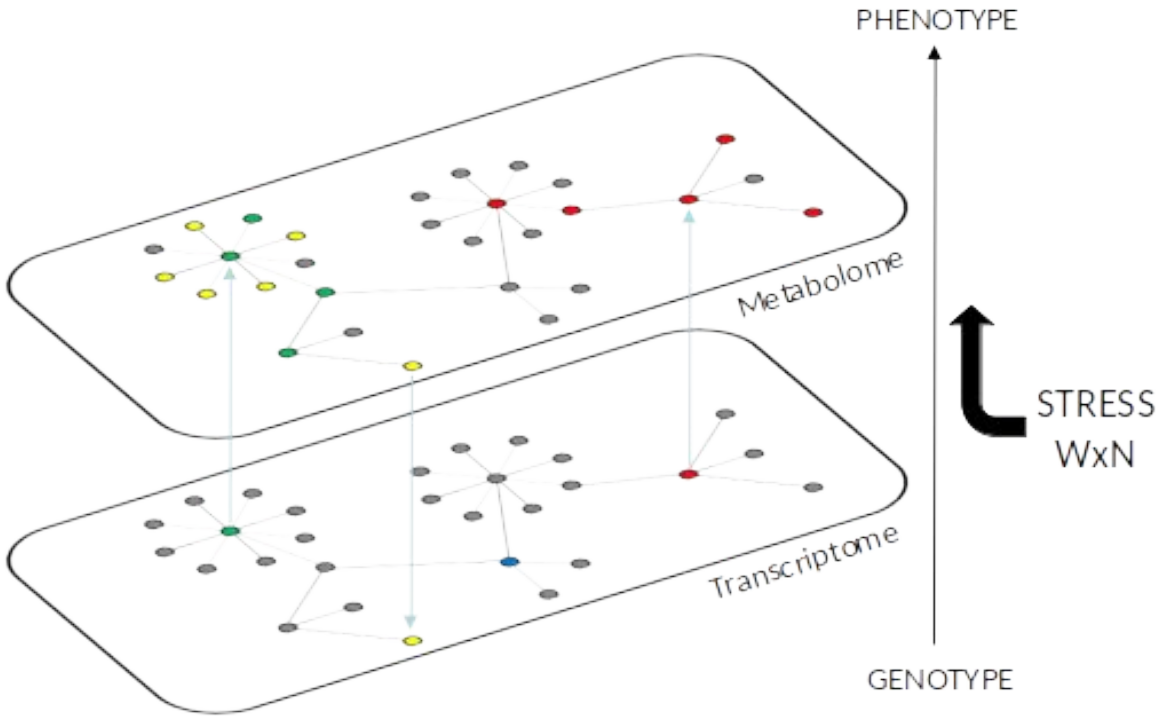
Anne Goelzer

(MIAT/MaIAGE)

Plant response to stress combinations (W x N)

Better explaining (and exploring) the response to stress from relationships between traits (network)

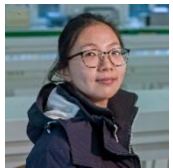




Response to stress combinations (W x N)

O. Loudet

Z. Xue



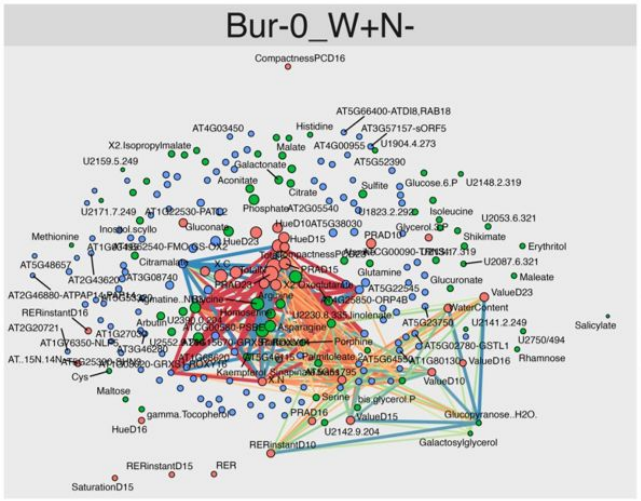
Marina Ferrand,
Anne Krapp,
Christian Meyer, …

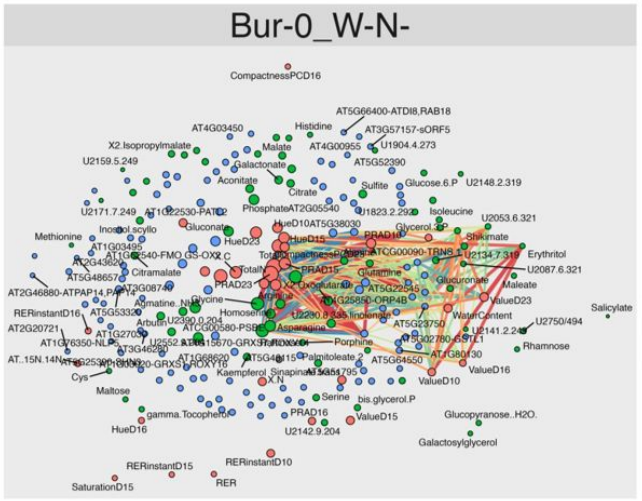
with the Phenoscope platform
https://phenoscope.versailles.inrae.fr

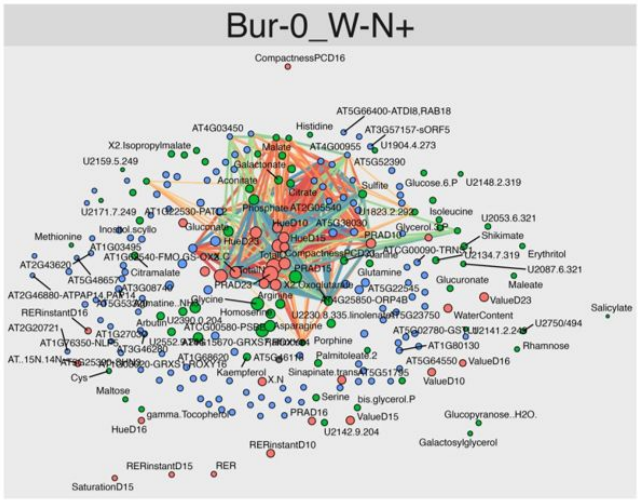
WxN stress interaction: network reconstruction

Bur-0 / mixomics networks

W+N- **W-N-** **W-N+**







A model for understanding
G x W x N interactions …

Xue et al. The Plant Cell. 2024

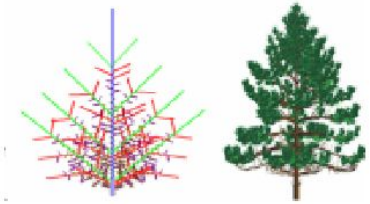
What kind of mechanistic plant models ?

Functional-structural plant growth models (FSPM) (plant scale)

- Simulate plant growth and development in time and 3D space
  - Plant architecture considered explicitly
  - Environment ==> plants adapt their functions but often also their structure ==> in turn, modifies the condition (e.g. light) in which functions operate.
  - Explicitly allow the feedbacks between structure and function to be captured.

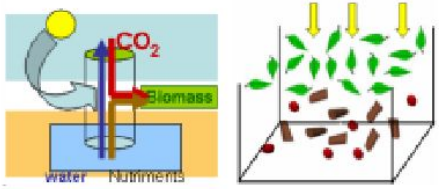
Vos et al (2010), Evers, Letort et al (2018)

Geometrical models : Simulation of 3D architectural development



Organogenesis + empirical geometry rules
Applications : video games, landscape/urbanism, design

Process-based models
Yield prediction as a function of environmental conditions



Biomass acquisition (Photosynthesis, root nutriment uptake) and allocation,. . .Compartment level

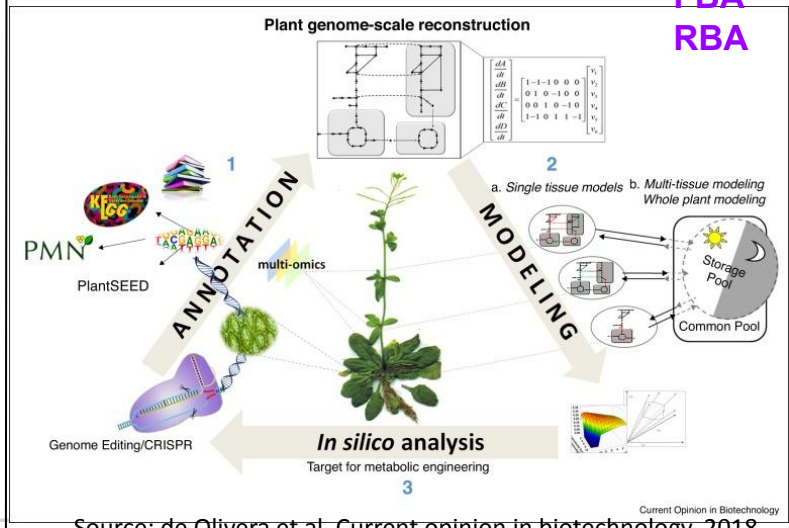
Constraint-based models (cellular scale)

Simulate the cell phenotype, usually in steady-state (i.e. during vegetative growth phase)

Metabolic reactions are considered explicitly

Genome-scale

FBA
RBA

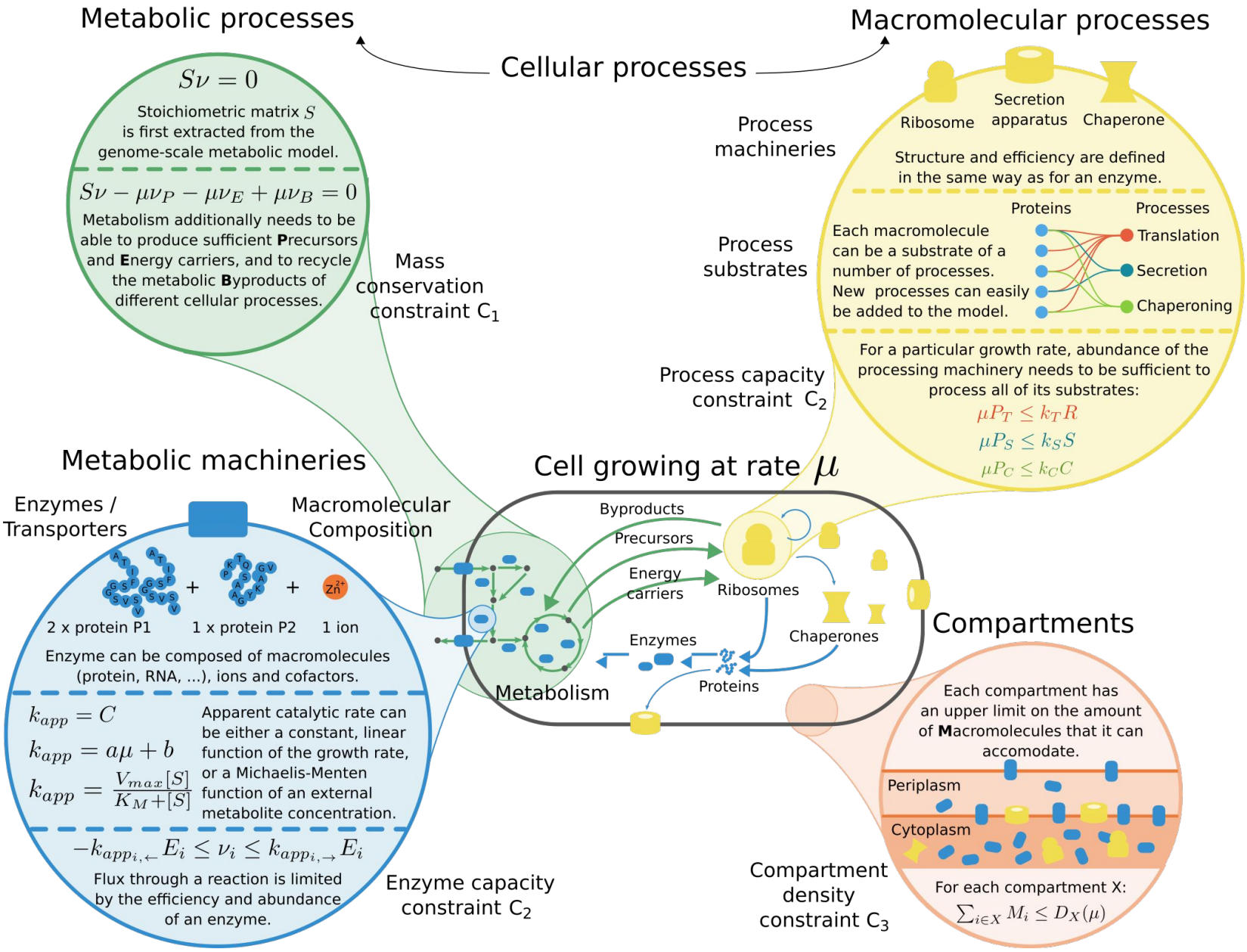


Source: de Olivera et al. Current opinion in biotechnology. 2018

FBA: Flux Balance Analysis
RBA: Resource Balance Analysis

In steady-state

Resource Balance Analysis in a nutshell



An RBA optimization problem

Concentration of molecular machines

Compartment size

Growth rate

Concentration of housekeeping proteins

Metabolic fluxes

$$\underset{Y \in \mathbb{R}^{N_y}_{\geq 0}, \nu \in \mathbb{R}^{N_m}, f \in \mathbb{R}^{N_c}_{\geq 0}}{\text{maximize}} \quad \mu \in \mathbb{R}_{\geq 0},$$

$$(C_1) \quad -\Omega\nu + \mu(C^S_Y Y + C^S_G P_G + C^S_B \bar{B} + C^S_F f \hat{B}) = 0$$

$$(C_2) \quad \mu(C^M_Y Y + C^M_G P_G) - K_T Y \leq 0$$

$$-K^{'}_E Y \leq \nu \leq K_E Y$$

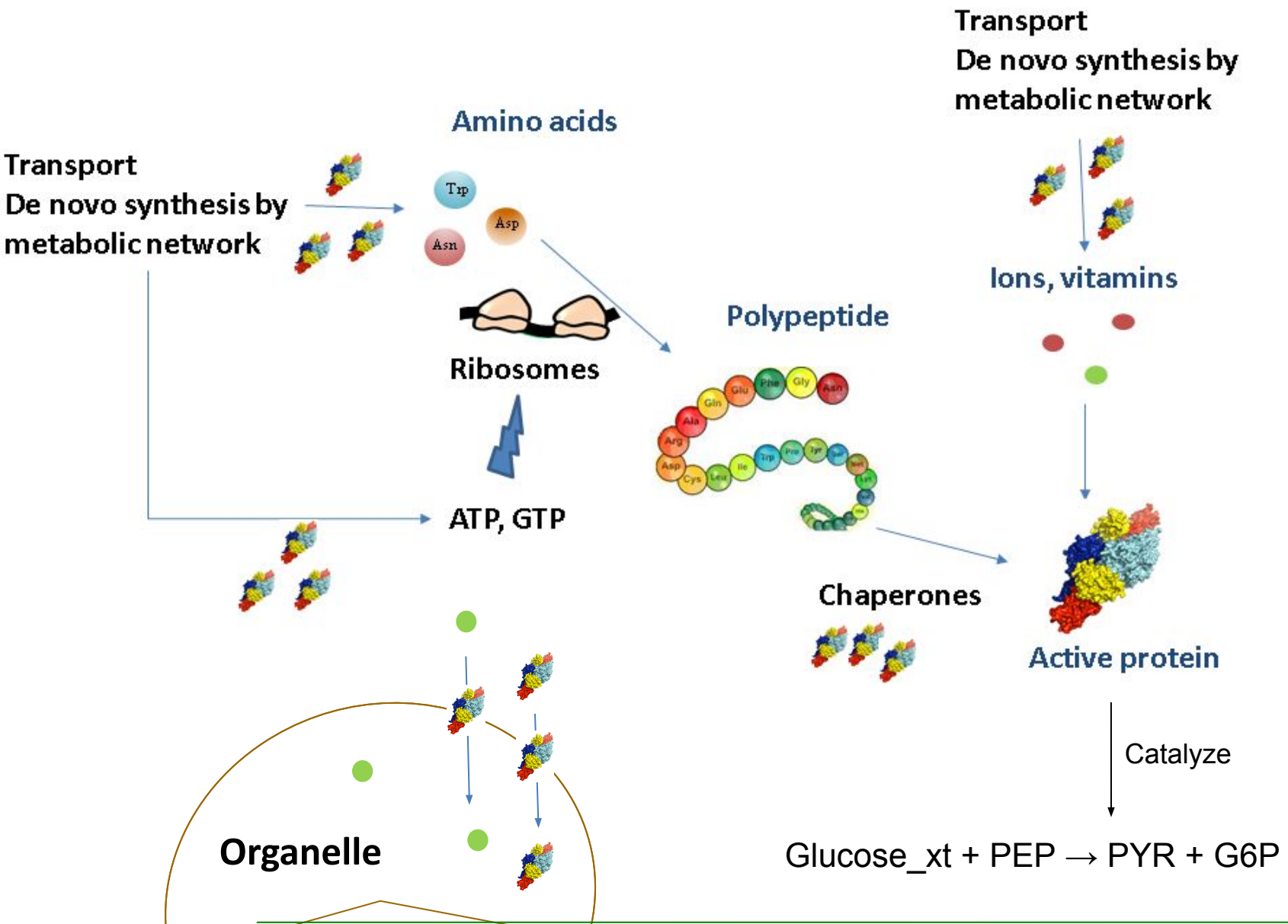
$$(C_3) \quad C^D_Y Y + C^D_G P_G - C^D_F f \leq 0$$

$$C^F_F f - \bar{C} = 0$$

$$\underline{f}_V \leq I_V f \leq \bar{f}_V$$

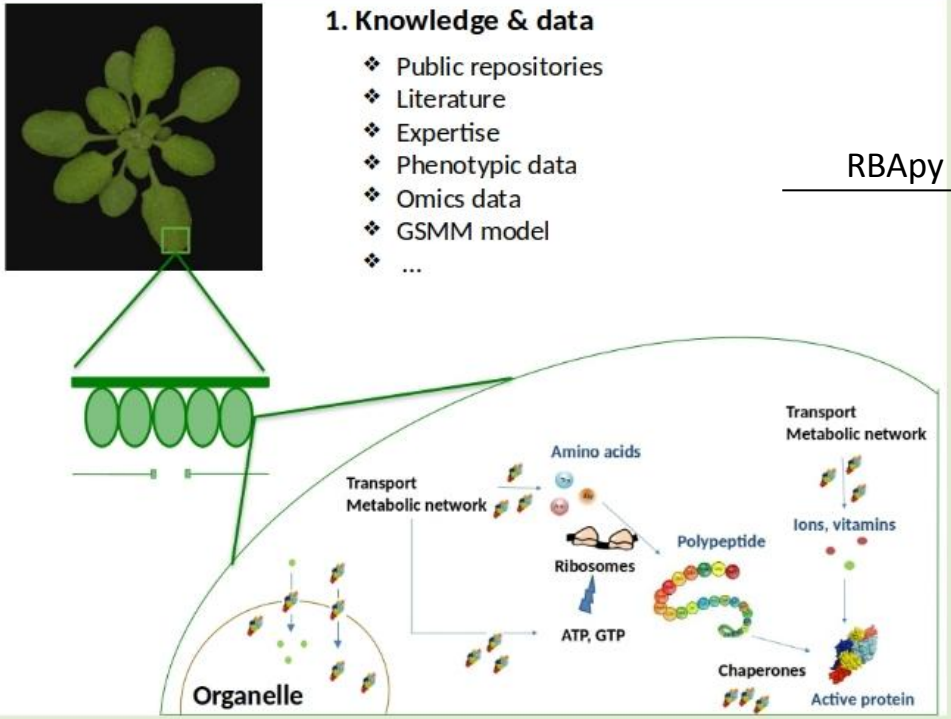
Constraints (C_1, C_2, C_3) define the set of all possible cell phenotypes (i.e. variables *Y,v,f*) at given relative growth rate μ

Description of molecular machines



A RBA model of the photosynthetic cell of Arabidopsis

Objective : Investigate if the principle of parsimonious use of cellular resources leads to realistic plant cell phenotypes

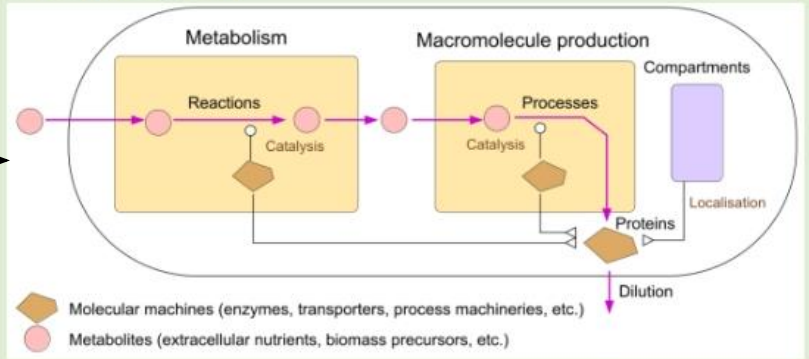


1. Knowledge & data

- Public repositories
- Literature
- Expertise
- Phenotypic data
- Omics data
- GSMM model
- ...

RBApy

2. Leaf RBA model



Original Aracore GSMM reaction number (Arnold et al. 2014)	549
Updated Aracore GSMM reaction number (this paper)	794
RBA metabolic reaction number (isoreaction included)	1599
RBA molecular machine number (isoenzyme included)	1622
Total parameter number (using default efficiency for enzymes and transporters except for RuBisCO and PSII)	108

3. Model simulation

Define the environmental condition :

- Concentrations of nutrients at the interface of the leaf cell
- Temperature

+

Assumption : parcimonious allocation of cellular resources
→ Compute the cell configuration maximizing the relative growth rate

4. Biological prediction for an environmental condition

- Relative growth rate
- Quantitative traits as the C:N ratio
- Protein distribution among cellular compartments
- Protein abundances including cofactor content for activity
- Metabolic fluxes including
  - ✓ Rubisco activity
  - ✓ Exchange fluxes (CO_2 assimilation rate, ...)

Cellular processes in the RBA plant cell model

Cellular compartments. cytoplasm (c), nucleus (n), mitochondrion (m), chloroplast (p), thylakoid, vacuole, peroxisome, golgi, endoplasmic reticulum, extracellular matrix. Fine description integrating organelle membranes.

Non-metabolic processes (NMP)

- Replication : n, m, p
- Transcription : n, m, p
- Translation: c, m, p
- Folding : c, m, p
- Protein, RNA translocation : n, m, p
- RNA degradation : c
- Protein degradation : c

} To be refined

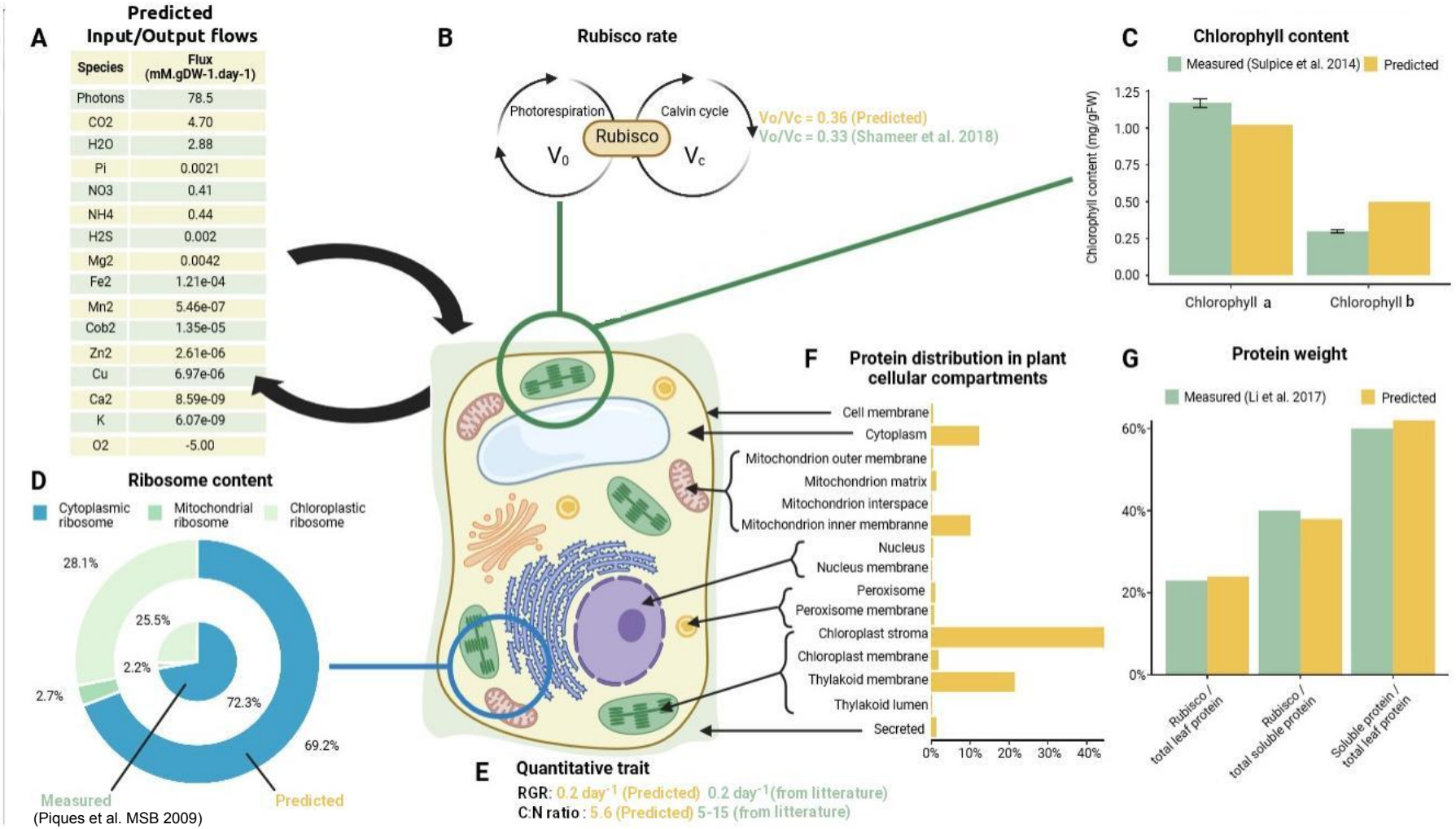
Metabolic processes (or reactions)

- Photosynthesis
- Calvin cycle, photorespiration, gluconeogenesis/glycolysis, PPP
- TCA cycle, oxidative phosphorylation
- Starch & sucrose synt./deg
- Amino acid, (deoxy)-nucleotide synt., nucleotide salvage pathways
- Cofactors synt (Chlorophyll A and B, Riboflavin, NAD(P), Pyridoxal-5P)
- Transport of metabolites in/out of the cell and of organelles

Total RBAv1: 728 metabolites, 1599 reactions, 27 NMP, 1332 proteins, 108 parameters (from literature)

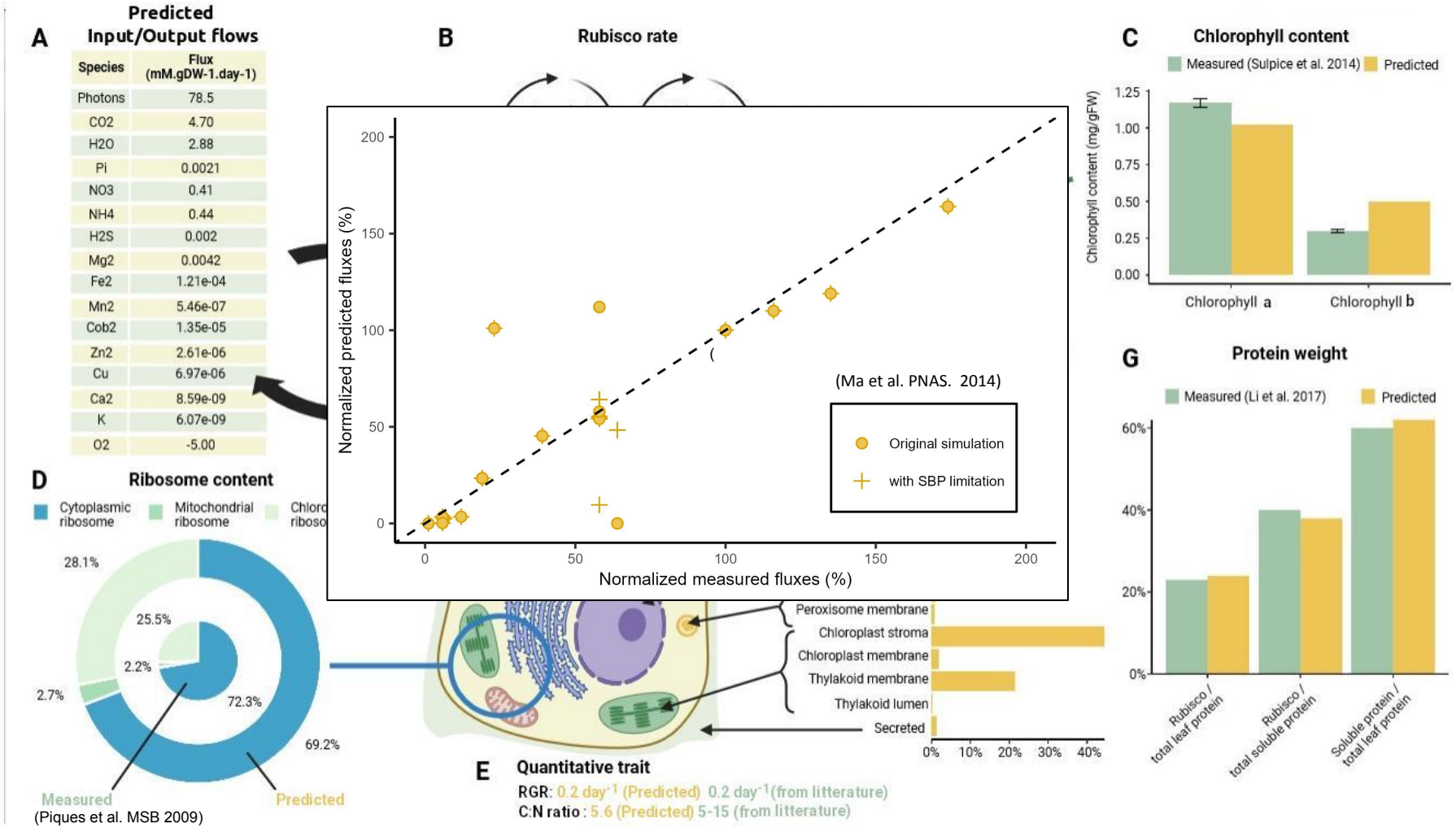
AraCore : Arnold et al. Plant Physiology. 2014; 165:1380-1391

Predicted phenotype in non-limiting growth condition

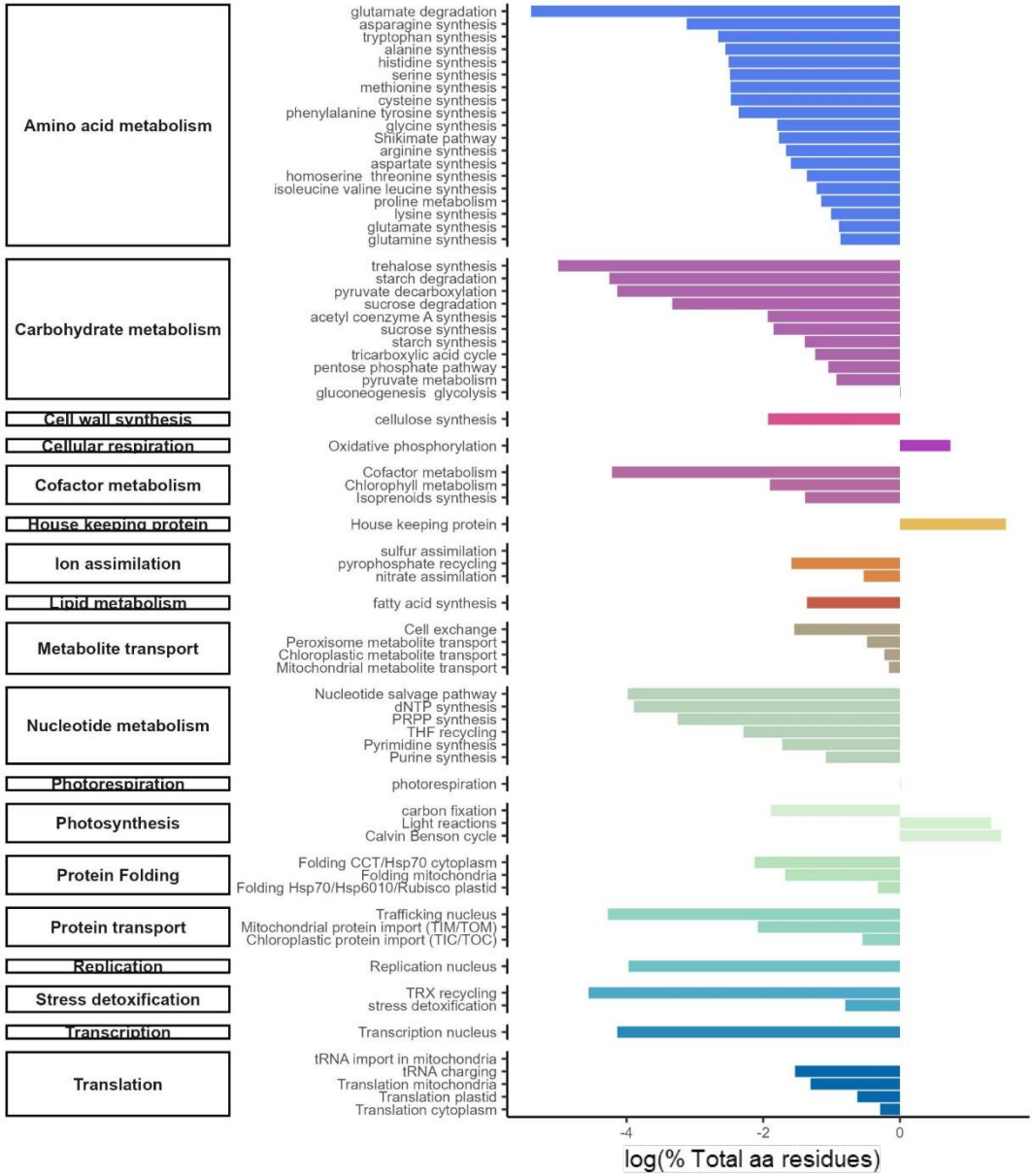


(Piques et al. MSB 2009)

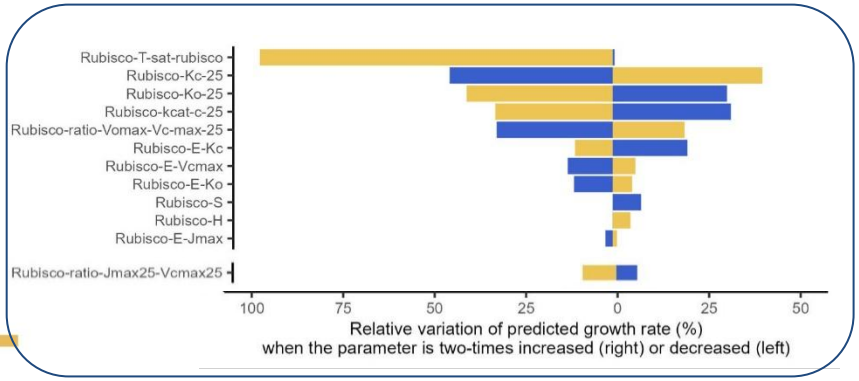
Predicted phenotype in non-limiting growth condition



Protein cost of cellular functions

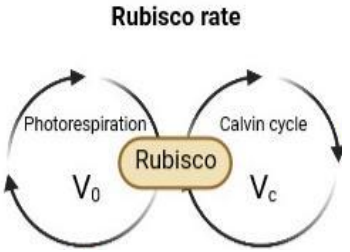


Protein cost of cellular functions



yellow: RGR is decreasing | blue: RGR is increasing

$K_o(T)$
V_{omax}/V_{cmax}

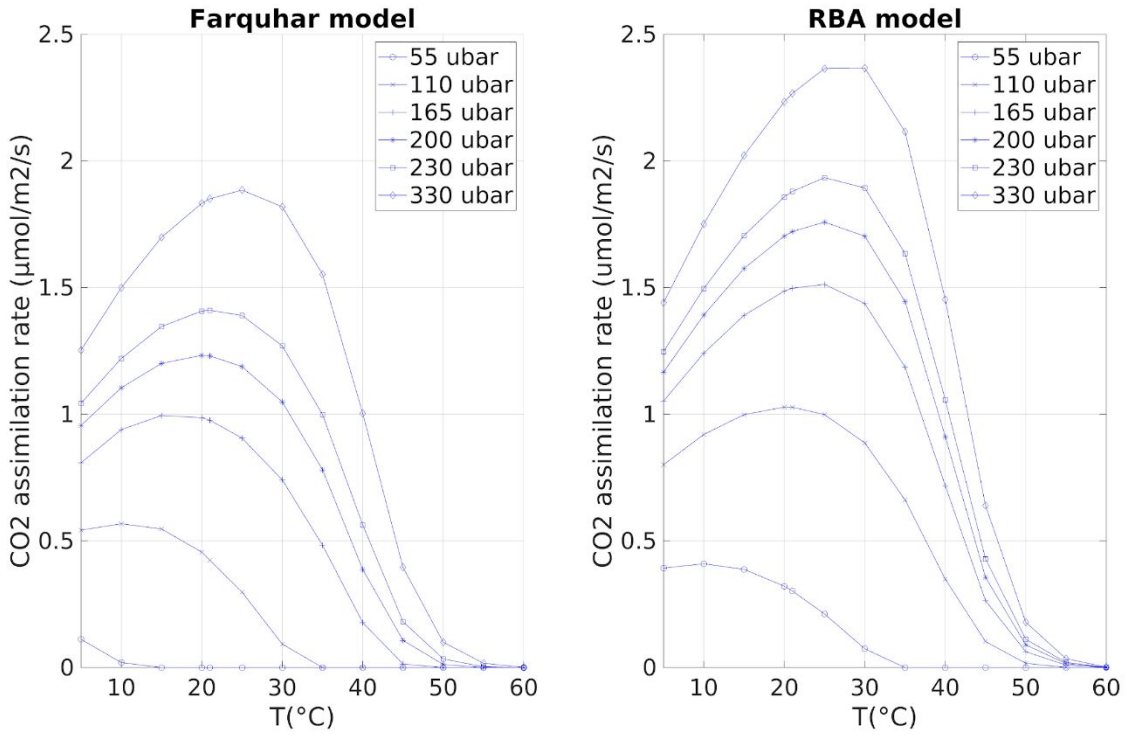


$K_c(T)$ $kcat_c(T)$

Comparison with the Farquhar model of carbon fixation

Simulations under varying environmental conditions:

- Partial pressure of CO2
- Partial pressure of O2
- Irradiance
- Temperature

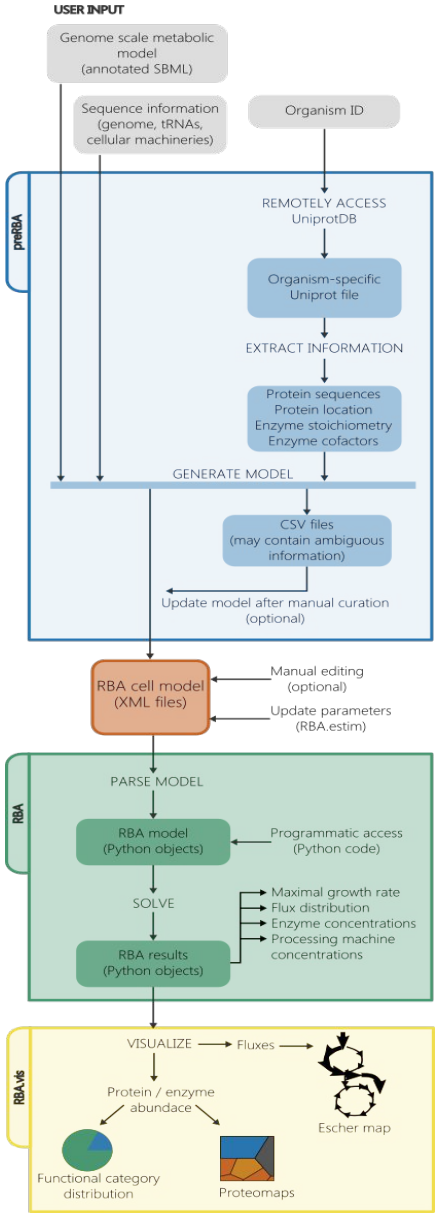


1 point = 1 simulation

Farquhar et al. Planta 1980; 149, 78-90
Walker et al. Plant Cell Env 2013; 36.12:2108-2119

Goelzer et al., Metabolic Engineering, 83: 86-101. 2024

How to generate an RBA model ?



Input (mandatory)

- Metabolic model having a description
- of enzymatic complexes
- NCBI identifier of the organism

Additional inputs (specialization)

- Definition of other molecular machines (e.g. ribosomes)
- Composition of rRNA, tRNA

Additional inputs (calibration)

- Quantitative proteomics
- Fluxomics (or an estimator of metabolic fluxes)

Outputs

- A RBA model available in XML
- Simulations (text format)


A. Bulovic


S. Fischer

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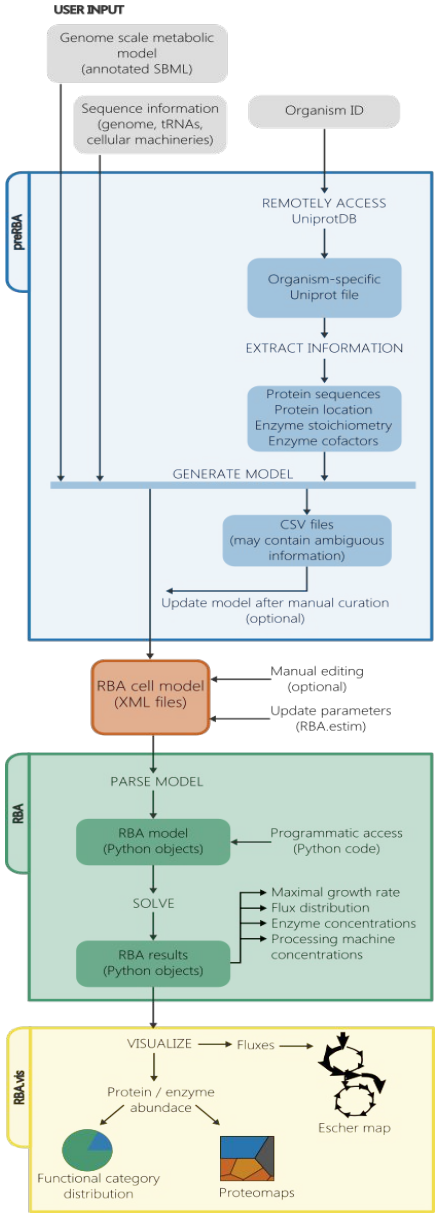
Protein Factory

A. Bulovic et al. *Metabolic Engineering*, 55:12-22. **2019**

How to generate an RBA model ….



Originally developed for bacteria, now under adaptation for eukaryotes

Input (mandatory)

- Metabolic model having a description of enzymatic complexes
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A. Bulovic et al. *Metabolic Engineering*, 55:12-22. **2019**

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Ongoing and future works

1. Model calibration - validation in combined abiotic stress and for several accessions

INRAE Digitbio *PlantRBA* [2021-2023]

Accessions
Col, Bur, Sha, Cvi, Tsu

Data acquisition
- High-throughput phenotyping
- Multi-omics (metab, prot.)
- Elemental analyses
- Aass, R rates of CO2

Nitrate \ Water			
W+N+	W-N+	W--N+
W+N-	W-N-	W--N-
W+N--	W-N--	W--N--

→ The challenge of absolute quantification for mechanistic modeling !!!

2. Extension to the whole plant during the vegetative growth phase in dynamical regimen (ANR *ModLSys* 2023-2028)

ModLSys

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