Using a hybrid approach to model central carbon metabolism across the cell cycle

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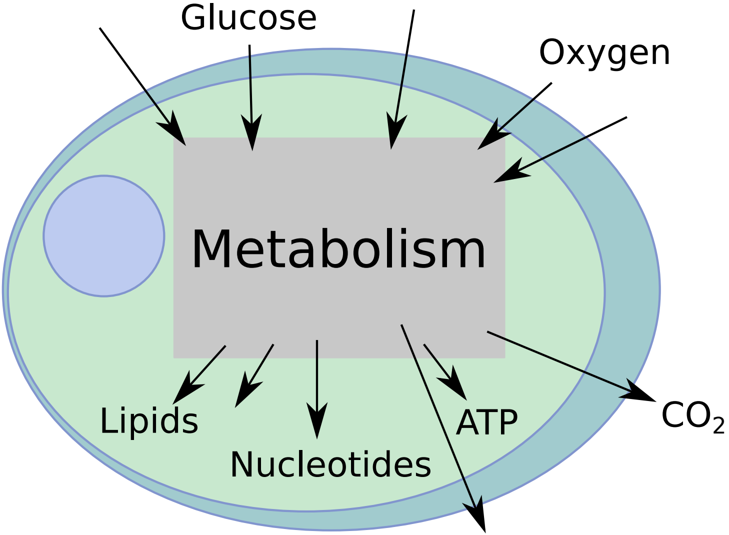
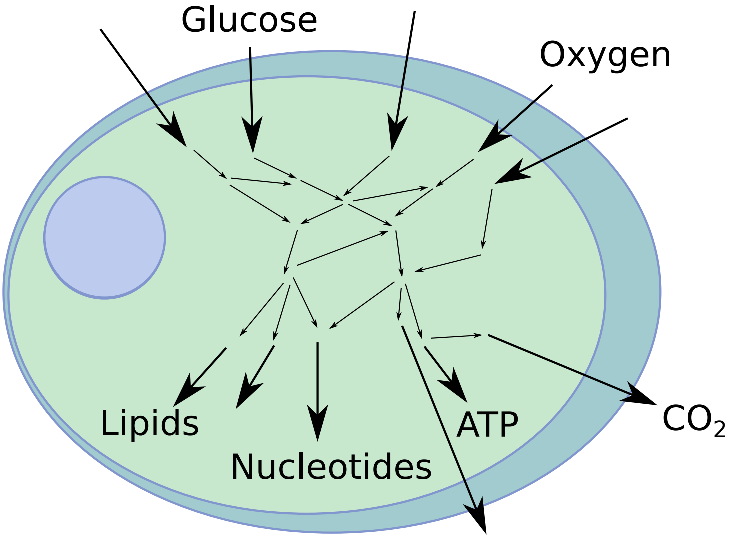
Metabolism is a production system

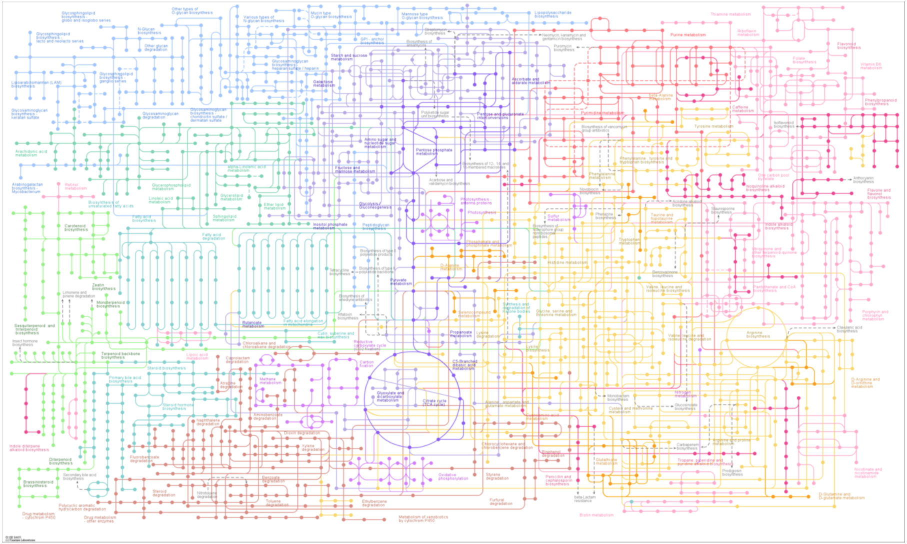


Metabolism is a reaction network

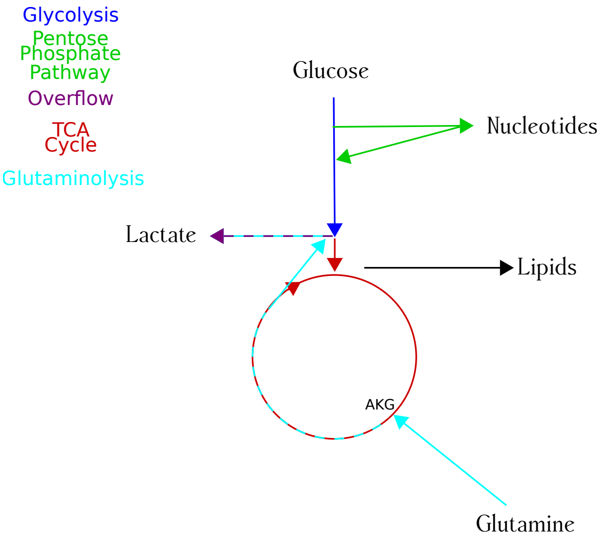


Metabolism is a huge network

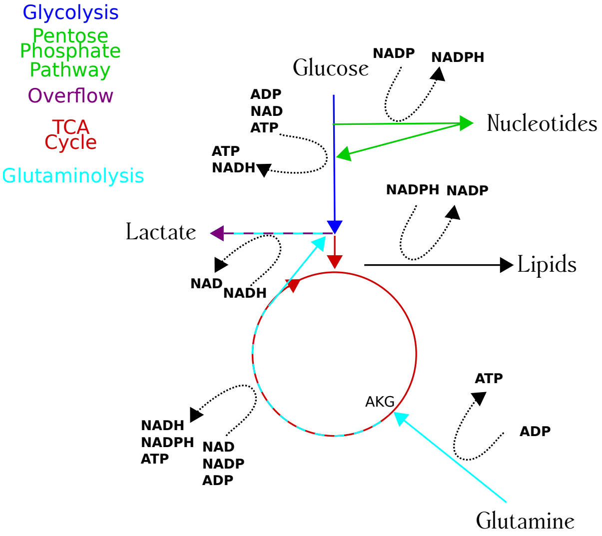
Recon3D:13 543 metabolic reactions, 4 140 unique metabolites (Brunk et al., 2018).
Kegg Map (metabolism global view):



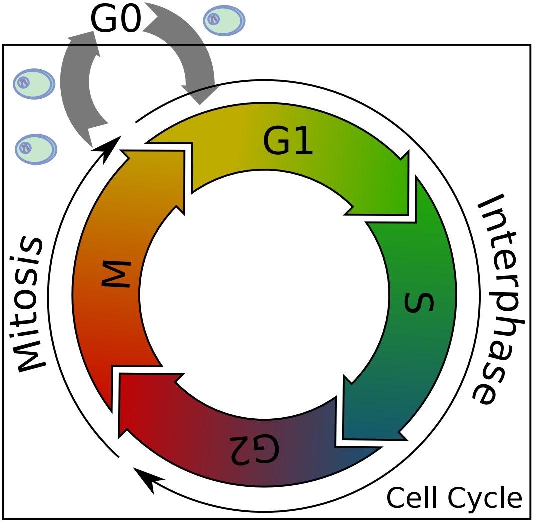
Solution: Metabolic Pathways



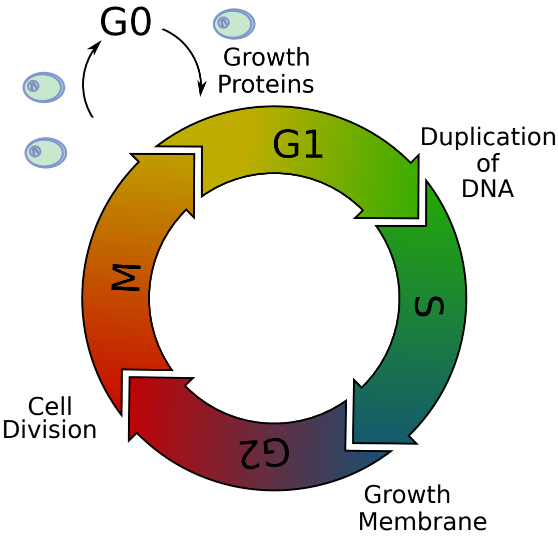
Metabolic pathways are coupled by currency metabolites



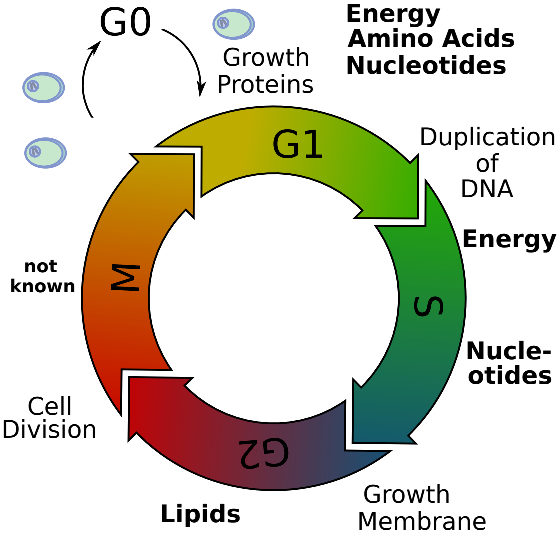
Eukaryotic cell cycle: From one mother cell to two daughter cells



Eukaryotic cell cycle: Divided into 4 phases

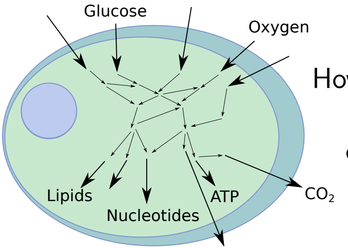


Eukaryotic cell cycle: Linked to the metabolism

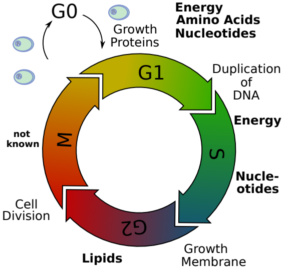


(da Veiga Moreira *et al.*, Theoretical Biology and Medical Modelling, 2015)

Goal: Create a model coupling metabolism and cell cycle



How do metabolism and cell cycle communicate?



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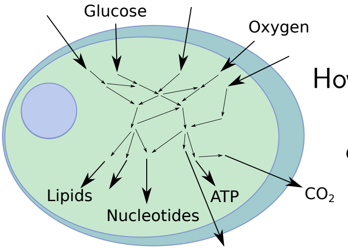
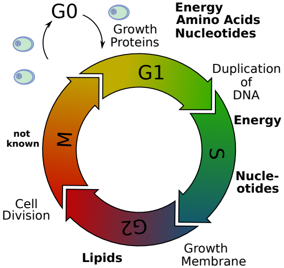


How do metabolism and cell cycle communicate?



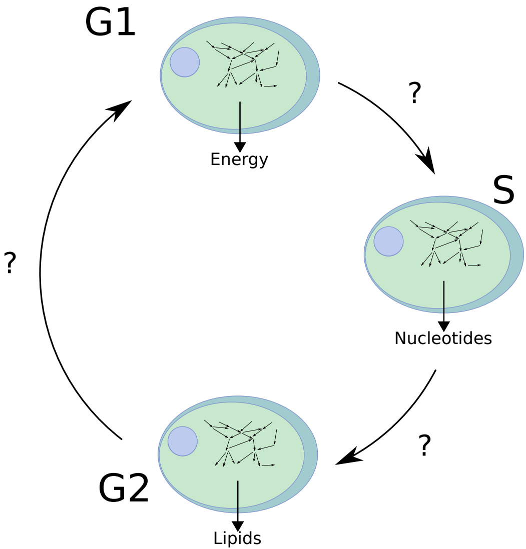
Challenges:

Different time scales

Which level of knowledge?

"Wherever continuous and discrete dynamics interact, hybrid systems arise."

(Heemels *et al.*, **Handbook of Hybrid Systems Control**, 2009)



Outline

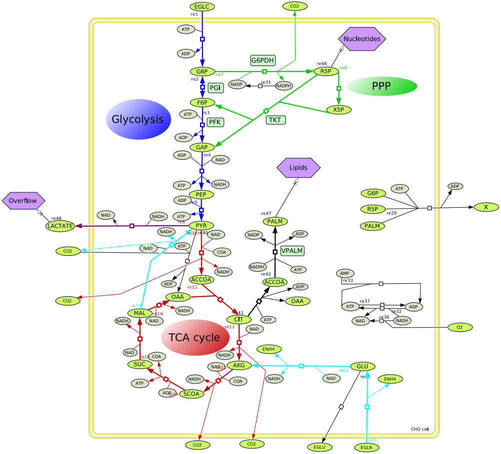
1. The metabolic model
   - Introduction of the model
   - Test the model with cell cycle inputs
2. The hybrid model
   - Parameters selection
   - Behavior of the hybrid model

Extended mammalian Central Carbon Metabolism model

The original models:

Robitaille *et al.*, PLOS ONE, 2015 (CHO)

da Veiga Moreira *et al.*, Scientific Reports, 2019 (mice)



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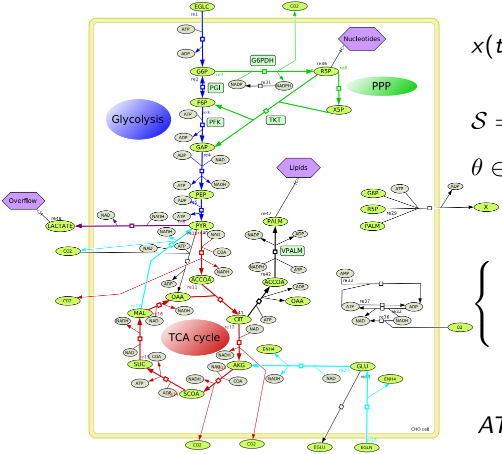


$$x(t) = \begin{pmatrix} x_I(t) \\ x_{II}(t) \\ x_{biomass}(t) \end{pmatrix} \begin{matrix} 16 \\ 7 \\ 1 \end{matrix}$$

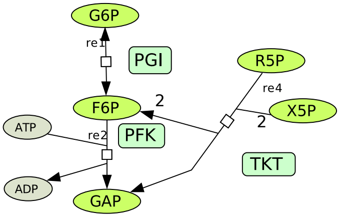
$$\mathcal{S} = \begin{pmatrix} \mathcal{S}_I \\ \mathcal{S}_{II} \end{pmatrix} \in \mathbb{Q}^{23\times 30}$$

$$\theta \in \mathbb{R}_+^{\sim 100}$$

$$\begin{cases} \dot{x}_I & = \mathcal{S}_I \nu_\theta(x(t)) - \mu_\theta(x(t)) x_I(t), \\ \dot{x}_{II} & = \mathcal{S}_{II} \nu_\theta(x(t)), \\ \dot{x}_{biomass} & = \mu_\theta(x(t)) x_{biomass}(t). \end{cases}$$

$$ATP + G6P + R5P + PALM \rightarrow X + ADP$$

Example: production/consumption of fructose 6-phosphate (F6P)



$$\frac{dF6P}{dt} = \nu_{pgi\_f}(t) - \nu_{pgi\_b}(t) - \nu_{pfk}(t) + 2\nu_{tkt}(t) - \mu(t)F6P(t).$$

(Robitaille *et al.*, PLOS ONE, 2015)

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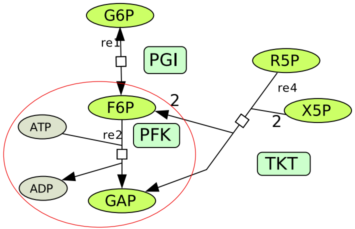

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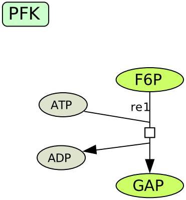

1. Michaelis-Menten
   $\nu_{max} = k_{cat}[E]$

$$\nu_{pfk} = \nu_{max} \frac{F6P}{K_{m1} + F6P}$$

(Robitaille *et al.*, PLOS ONE, 2015)
(Ghorbaniaghdam *et al.*, Bioprocess and Biosystems Engineering, 2013)
(Segel, **Enzyme kinetics**, 1993)

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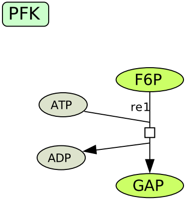

1. Michaelis-Menten
   $\nu_{max} = k_{cat}[E]$
2. Currency Metabolites

$$\nu_{pfk} = \nu_{max} \frac{F6P}{K_{m1} + F6P} \frac{\frac{ATP}{ADP}}{K_{m2} + \frac{ATP}{ADP}}$$

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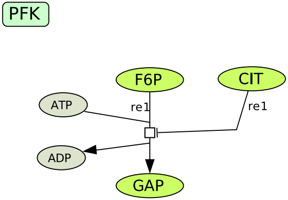
Example: production/consumption of fructose 6-phosphate (F6P)



1. Michaelis-Menten
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2. Currency Metabolites
3. Non-competitive inhibition

$$\nu_{pfk} = \nu_{max} \frac{F6P}{K_{m1} + F6P} \frac{\frac{ATP}{ADP}}{K_{m2} + \frac{ATP}{ADP}} \frac{K_i}{K_i + CIT}$$

(Robitaille *et al.*, PLOS ONE, 2015)
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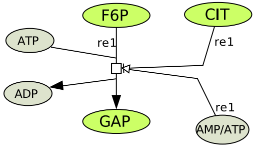
Example: production/consumption of fructose 6-phosphate (F6P)

PFK



1. Michaelis-Menten
   $\nu_{max} = k_{cat}[E]$
2. Currency Metabolites
3. Non-competitive inhibition
4. Non-essential activation

$$\nu_{pfk} = \nu_{max} \frac{F6P\left(1 + \frac{\beta}{\alpha K}\frac{AMP}{ATP}\right)}{K_{m1}\left(1 + \frac{1}{K}\frac{AMP}{ATP}\right) + F6P\left(1 + \frac{1}{\alpha K}\frac{AMP}{ATP}\right)} \frac{\frac{ATP}{ADP}}{K_{m2} + \frac{ATP}{ADP}} \frac{K_i}{K_i + CIT}$$

(Robitaille *et al.*, PLOS ONE, 2015)
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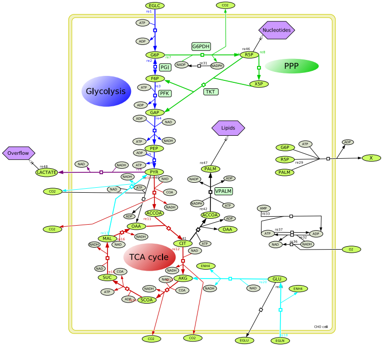
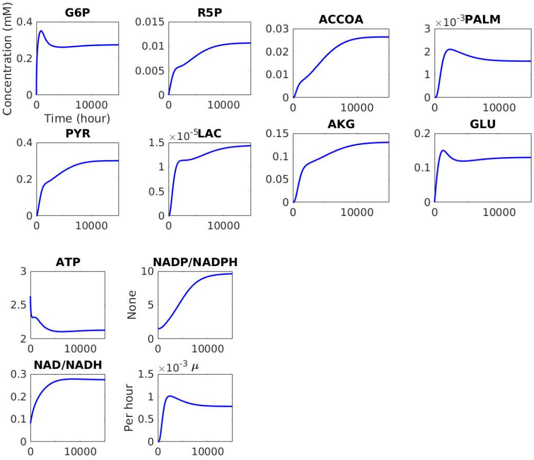
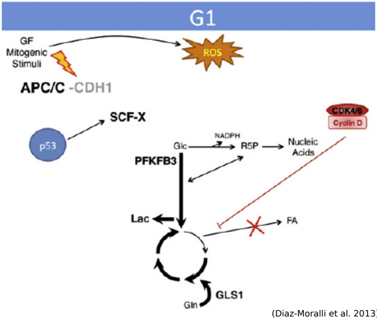
The model reaches a stationary regime

$$\theta \in \mathbb{R}_{+}^{\sim 100}$$





The model responds correctly to G1 inputs



(Diaz-Moralli et al. 2013)

[...] **the accumulation of PFK/FB3** leads to the activation of glycolysis and an increase in lactate production. [...] Moreover cyclin D1 is able to **downregulate the expression of lipogenic enzymes** [...] preventing pyruvate consumption in lipogenesis and contributing to lactate formation.

(Diaz-Moralli *et al.* Pharmacology & Therapeutics, 2013)

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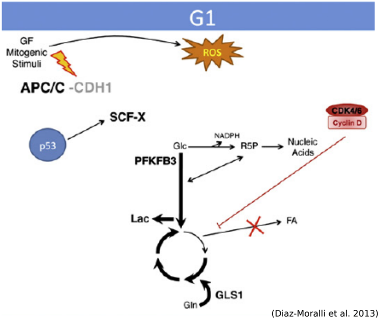

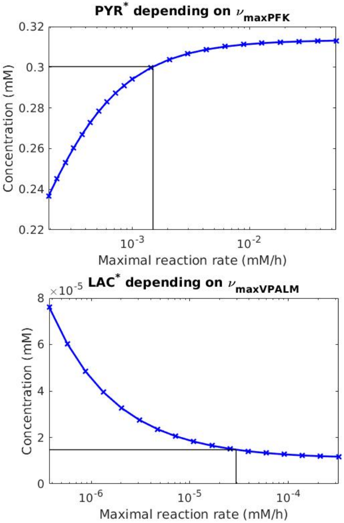

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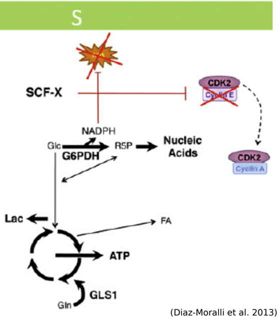
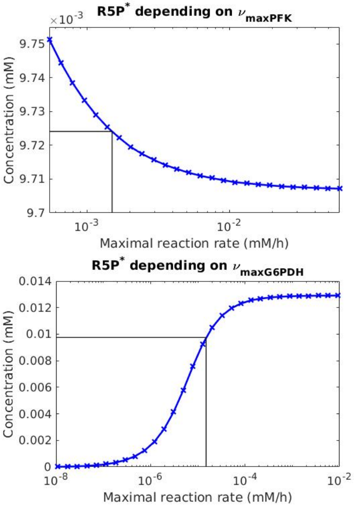
The model responds correctly to S inputs



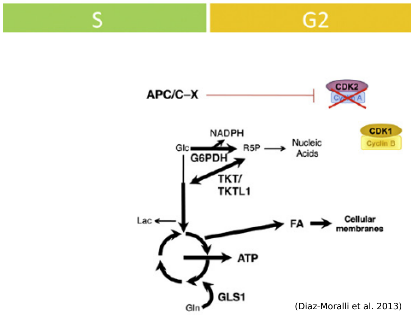
(Diaz-Moralli et al. 2013)

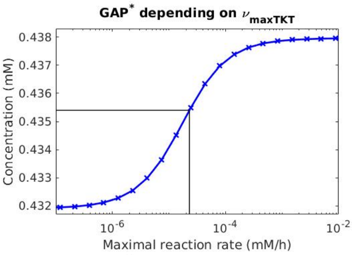


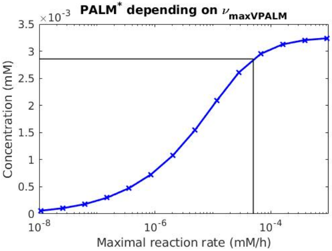
[...] proliferating cells **increase G6PD activity** during late G1- and S-phases [...]. Moreover, during S-phase the activation of the SCF ubiquitin ligase [...] allows **[the proteasome degradation of]** PFKFB3. [...] Through these mechanisms cells redirect the glucose flux from the direct glycolytic pathway to the PPP [...]

(Diaz-Moralli *et al.* Pharmacology & Therapeutics, 2013)

The model responds correctly to G2 inputs







[...]**transketolase activity showed an acute increase** in late S. This shift allows [...] recycling the excess of R5P back to glycolysis in late S- and G2-phases, when lipid synthesis [... is highly demanded]. Moreover, [...] the **activation of transcription of lipogenic enzymes** [contributes] to this process [...].

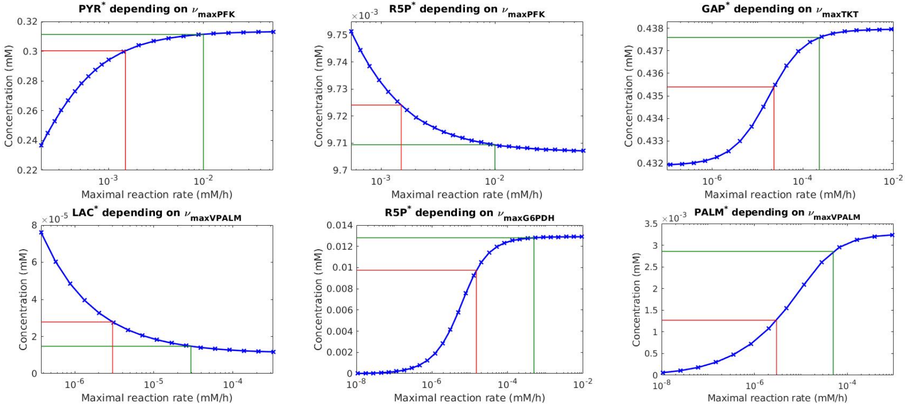
(Diaz-Moralli *et al.* Pharmacology & Therapeutics, 2013)

Creation of the three sub-models: G1, S, G2

G1 $\nearrow$ PFK: $\nearrow$ glycolysis
G1 $\searrow$ VPALM: $\nearrow$ LAC
S $\searrow$ PFK: $\nearrow$ PPP

S $\nearrow$ G6PDH: $\nearrow$ PPP
G2 $\nearrow$ TKT: $\nearrow$ end of PPP
G2 $\nearrow$ VPALM: $\nearrow$ PALM

	G1	S	G2
PFK	+	-	-
G6PDH	-	+	+
TKT	-	-	+
VPALM	-	-	+

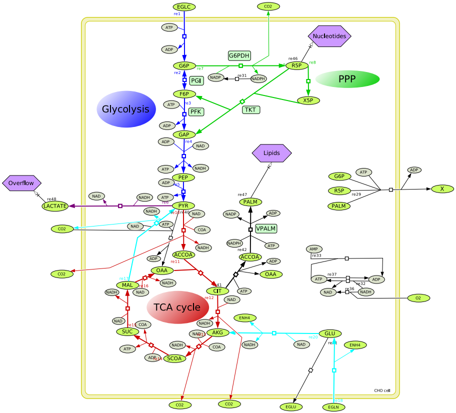


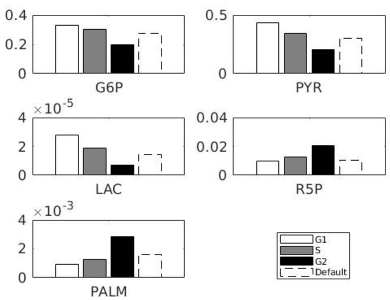
Validation of the sub-models

G1: High Glycolysis activity and Lactate production ✓

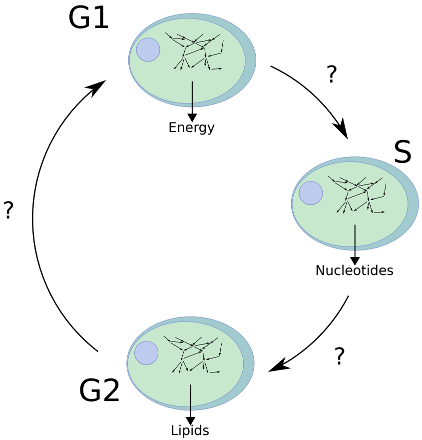
S: High beginning of Pentose Phosphate Pathway activity ✓

G2: High Pentose Phosphate Pathway activity and Lipids production ✓





Hybrid model: transition between phases



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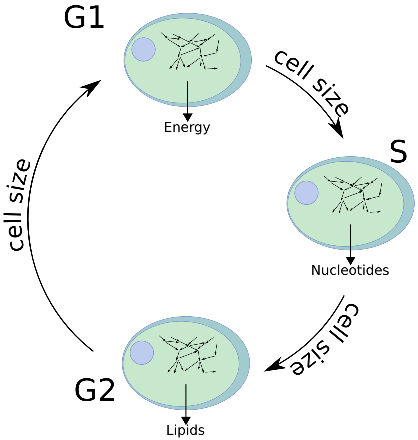


Rules

G1 ends when:

$$x_{biomass}(t) := (1+\alpha)x_b^0$$

S ends when:

$$x_{biomass}(t) := (1+\beta)x_b^0$$

G2 ends when:

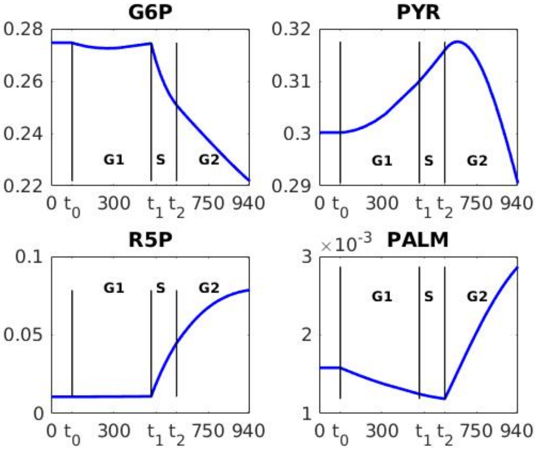
$$x_{biomass}(t) := (1+\gamma)x_b^0$$

New parameters:

$$\alpha, \beta, \gamma := 1$$

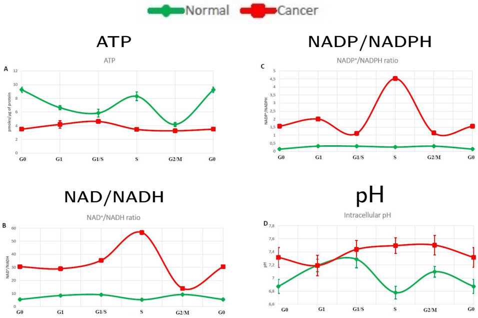
Validation of the hybrid model

Duration of phases $\times$
G1: High Glycolysis activity ✓
S: High beginning of Pentose Phosphate Pathway activity ✓
G2: High Pentose Phosphate Pathway activity and Lipids production ✓
$x_b^0 = 1.1 \cdot 10^{-4} L, \alpha = 0.3, \beta = 0.4$

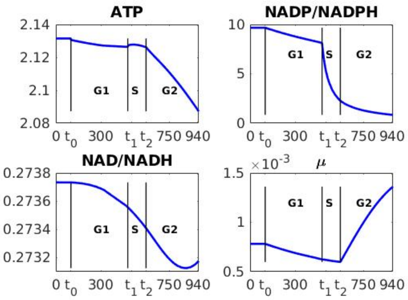


Comparison with experimental data

NAD/NADH variations $\times$
NADP/NADPH decrease in S $\checkmark$
ATP variations $\checkmark$



(da Veiga Moreira *et al.*, Metabolites, 2016)

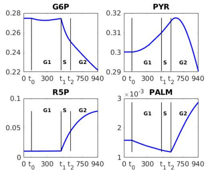


Conclusion and Perspectives

From a metabolic model to a **hybrid model,** representing **metabolism through cell cycle**.

Succession of phases:

- G1: Glycolysis activity
- S: Nucleotides production
- G2: Lipids production



Toward the understanding of the **interconnections** between **cell cycle** and **metabolism**

- Are these changes minimum ?
- Other areas of the Central Carbon Metabolism (Amino-Acids)
- Change biomass function (supply and demand)
- Adaptations to cancer metabolism