CF-Induction applied to Metabolic Flux Analysis

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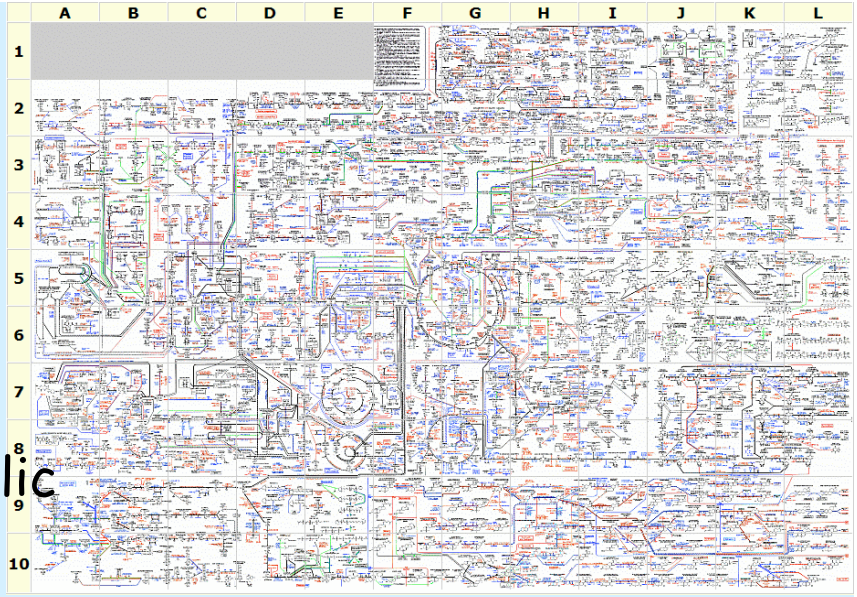
Goal



- Explain and predict the metabolic pathway into the cell

- Generic Model :
  - Saccharomyces erevisiae,
  - E-coli

- Inductive Logic Programming : can explain the biological knowledge

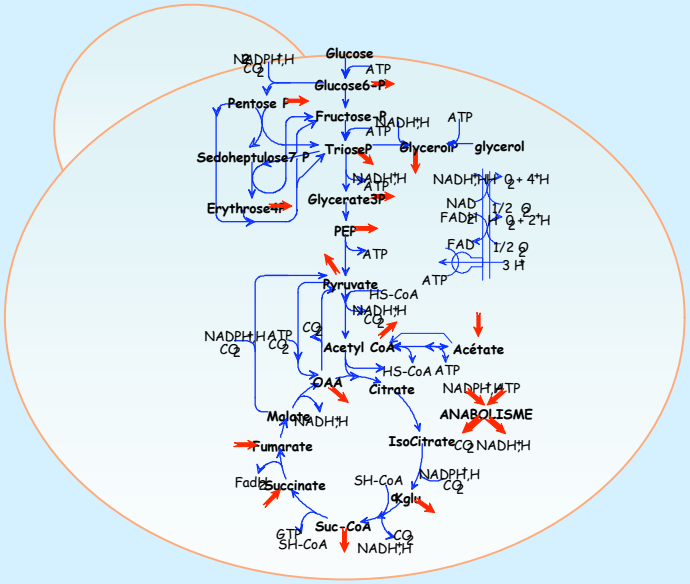
Metabolic Flux Analysis

- Definition :

Metabolic pathways **are sequences of enzyme-catalyzed reaction steps which convert the substrate to a variety of products to satisfy the needs of the cell.**

A huge set of biochemical reactions assume the *reproduction* and the *survey* of the cell.

Flux **is defined as the rate in which materials are processed trough a metabolic pathway. The fluxes are useful to determine the maximum theoretical yields.**



Simplification of metabolic pathway

- Michaelis-Menten Reaction

$$v = v_{\max} \frac{S}{K_m + S}$$

S=substrate
V=rate of reaction
K=constant

Explained by a logic rule

- Mono-molecular enzymes catalized reactions :

$$X_S \rightarrow X_P$$

substrate product

Metabolite Balancing

- Intracellular fluxes are determined as functions of the measurable extracellular fluxes using a stochiometric model for major intracellular reactions and applying a mass balance around each intracellular metabolite.

$$S \bullet \underline{v} = \underline{r}$$

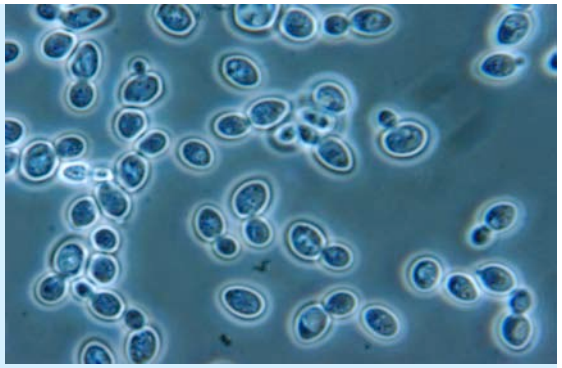
S[mxn] : stochiometric matrix of metabolic network
V : unknown fluxes at steady state
r : vector of extracellular metabolite accumulation rate

Machine Learning Approaches

- Steady state, ignoring the temporal variance of metabolite concentration : Tamadoni-Nezdah 2004

- Integrating abduction and induction on the problem of inhibition of metabolic pathway : Muggleton et al.2006

Modelling of Intracellular Enzyme Kinetics



- Let's take the reaction :

$$S \xrightarrow{r1} 2A \xrightarrow{r2} B \xrightarrow{r3} P$$

- The mass balance is :

$$\frac{dC_A}{dt} = 2.r1 - r2 \qquad \frac{dC_B}{dt} = r2 - r3$$

Where C is the metabolite concentration and r is the flux

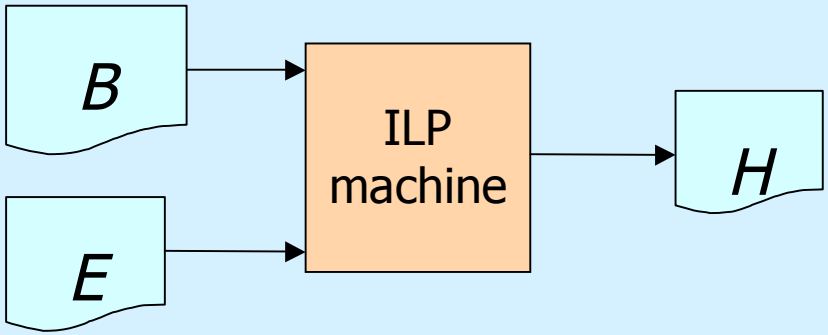
Abduction and Induction: Logical Framework

Input:

- *B* : background theory
- *E* : (positive) examples / observations

Output:

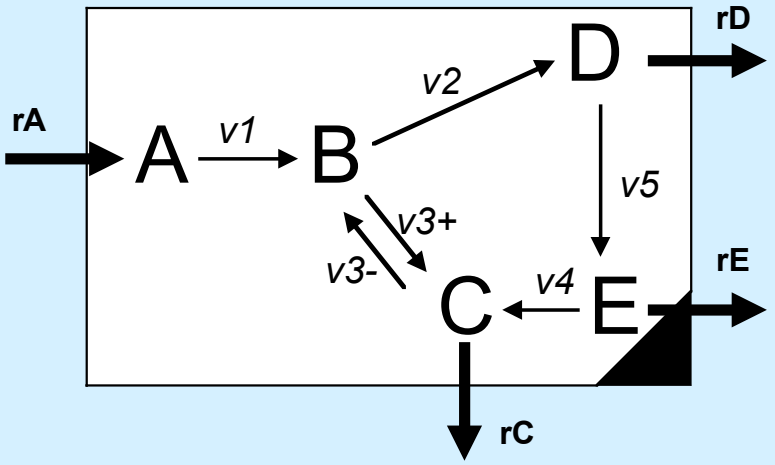
- *H* : hypothesis satisfying that
  - $B \wedge H \models E$
  - $B \wedge H$ is consistent.



Input of CF-induction

- **clause(e1,bg,[concentration(a,up)]).**
- **clause(e2,obs,[concentration(d,up)]).**
- **clause(e3,obs,[concentration(e,down)]).**
- **clause(e4,obs,[concentration(c,down)]).**
- **clause(e5,obs,[concentration(b,up)]).**

- The last clause in based on the fact that A and B are connected and
- the perturbation could be propagated from A to B.



Reaction

- **clause(bR1,bg,[reaction(a,b)]).**
- **clause(bR2,bg,[reaction(b,d)]).**
- **clause(bR3,bg,[reaction(d,e)]).**
- **clause(bR4,bg,[reaction(e,c)]).**
- **clause(bR5,bg,[reaction(c,b)]).**
- **clause(bR6,bg,[reaction(b,c)]).**

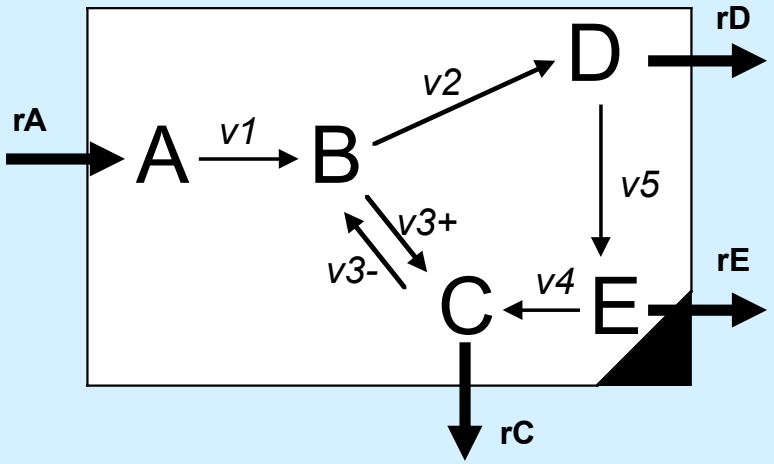
Explanation :

clause(be1,bg,[-reaction(Y,X),-reaction(X,Z),inhibited(Y,X),-inhibited(Y,Z),concentration(X,up)])
clause(be2,bg,[-concentration(Y,down),-reaction(Y,X),inhibited(Y,X),concentration(X,down)]).

Output of CF-induction

Hypotheses:

- **1.[concentration(b, up), inhibited(b, c), inhibited(b, d), inhibited(c,b), inhibited(a, b), -concentration(a, up)]**
- **2.[concentration(e, down),inhibited(c, b), inhibited(a, b),-concentration(a, up)]**
- **3.[concentration(c, down), -inhibited(e, c), inhibited(c, b),inhibited(a, b),-concentration(a,up)]**
- **4.[concentration(d, up), inhibited(c, b), inhibited(a, b),-concentration(a, up)]**

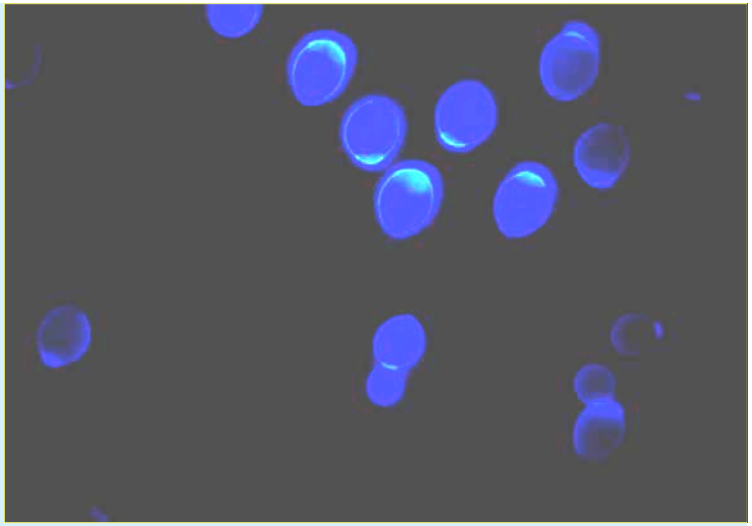


• The result obtained shows the possible inhibitions in the case where metabolites D,E,C are measured and an hypothesis is done about the concentration of the metabolite B.

• The interest result is obtain on the pathway B-D which explains why the metabolite concentration level in D is bigger than E, based on the non-inhibition between A-B and B-D.

• Another interesting result is the explanation of the low level concentration in C due to the inhibition on the pathway E-C.

Conclusion



- CF-induction is able to explain metabolic pathway in a dynamic context
- The next step **diagnosis** of intracellular Enzyme Kinetics.