Overflow- metabolism

What?

A metabolic phenomenon that is induced when the rate of glycolysis exceeds a critical value

Where?

In ”glucose sensitive yeast” species: aerobic ethanol formation

In *E. coli*: aerobic acetate formation

In mammalian cell cultures: aerobic lactate formation

Can be avoided by process control techniques

The Pasteur effect

”Oxygen inhibits fermentation and reduces the rate of glycolysis”

- Respiratory chain competes for ADP with PG kinase and Pyr kinase

The Crabtree effect **(” The glucose effect ”)**

”High rate of glycolysis reduces the respiration and induces fermentation”

- Catabolite repression of respiratory chain enzymes
- Slow response - gene level

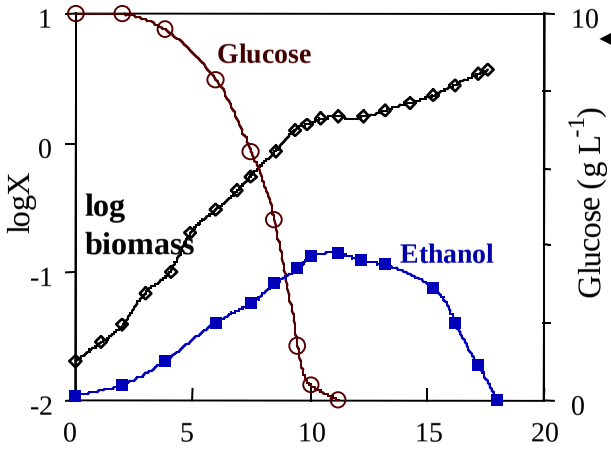
Overflow metabolism **(” The short-term Crabtree effect ”)**

”High rate of glycolysis results in by-product formation from pyruvate

- Unknown mechanisms . Different functions in yeasts and E. coli
- Fast response - enzyme regulation level

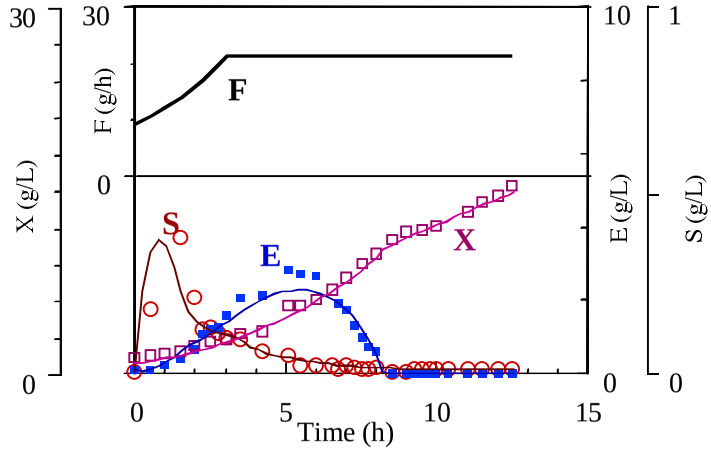
Crabtree positive yeasts:	*Crabtree negative yeasts:*
Saccharomyces cerevisiae	Saccharomyces fragilis
S. carlbergensis	Trichosporon fermentans
S. pasteurianus	Candida utilis
Schizosaccharomyses pompe	C. tropicalis
Debaromyces globosus	Pichia fermentans

Kinetics in aerobic batch and fed-batch cultures of *S. cerevisiae*

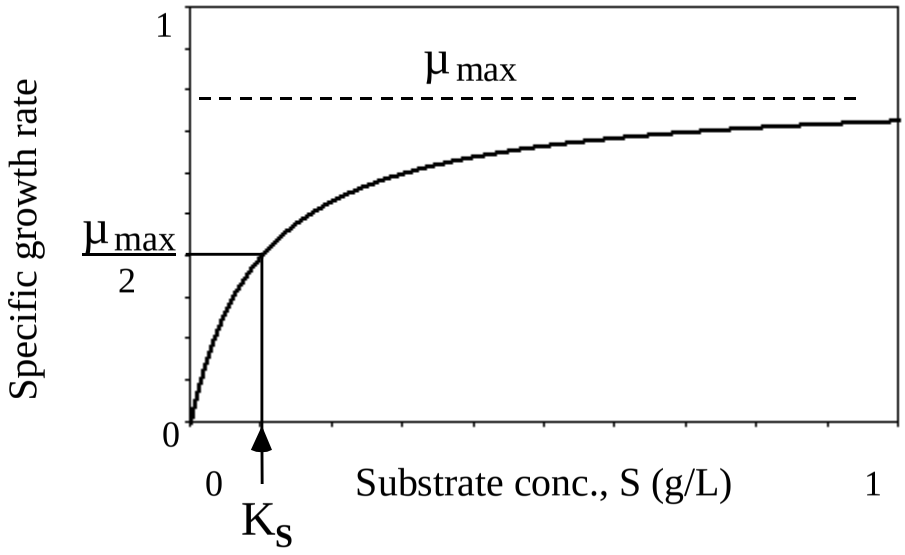


Batch:**Diauxic lag phase** between ethanol production and consumption

Fed-batch: Concomitant consumption of ethanol and glucose



The Monod model



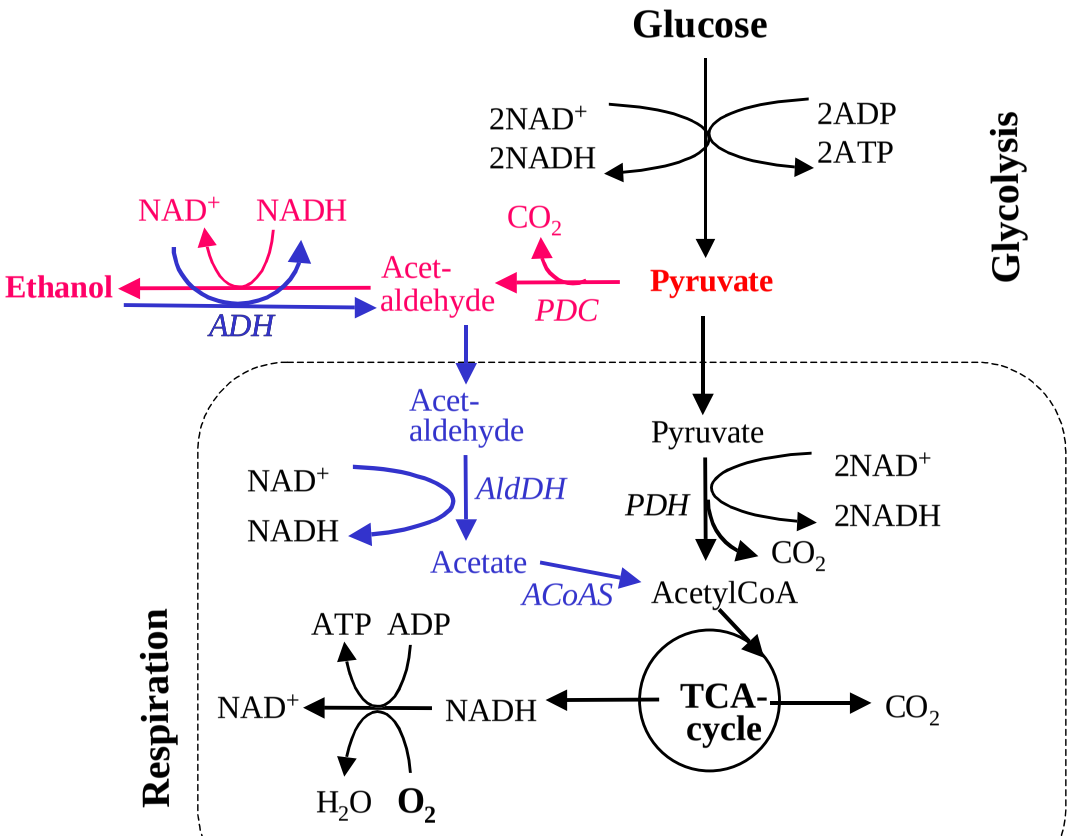
For growth:

$$\mu = \mu_{max} \frac{S}{S + K_s}$$

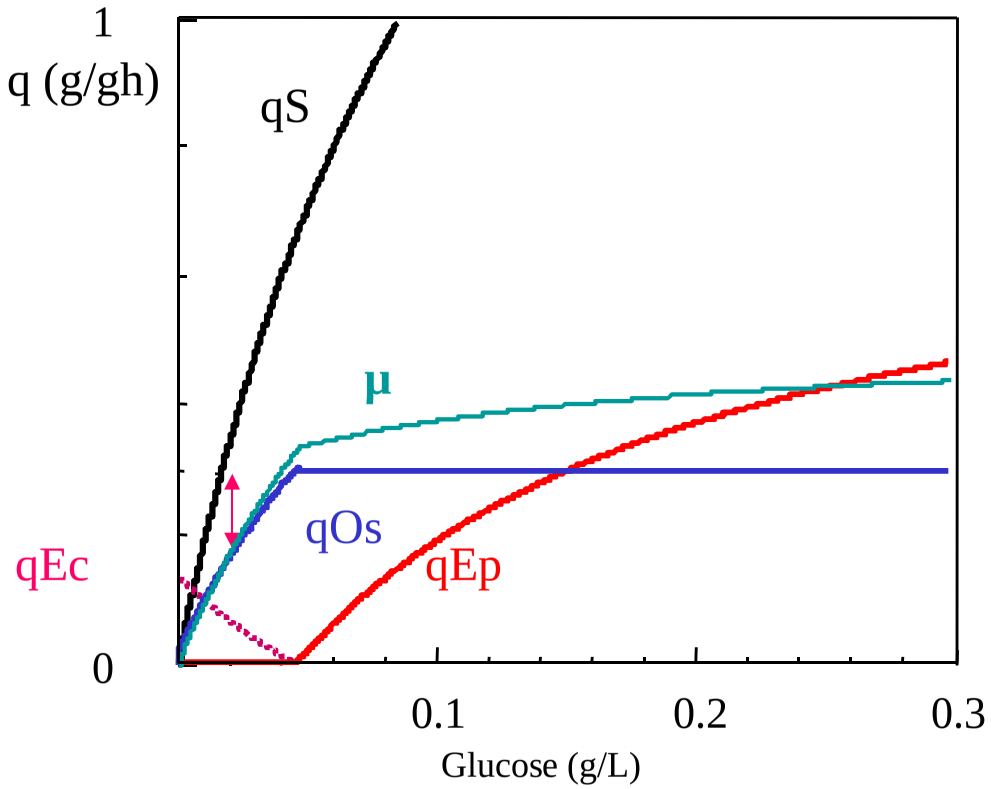
For substrate uptake:

$$q_S = q_{S,max} \frac{S}{S + K_s} = \frac{\mu}{Y_{X/S}}$$

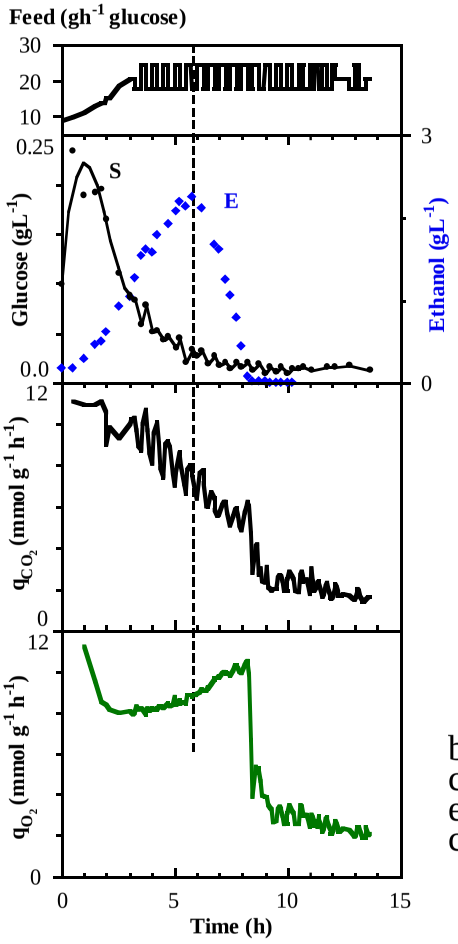
Energy metabolism of S. cerevisiae



Kinetic model of yeast over-flow metabolism



Experimental verification of the overflow mrtabolism model for yeast



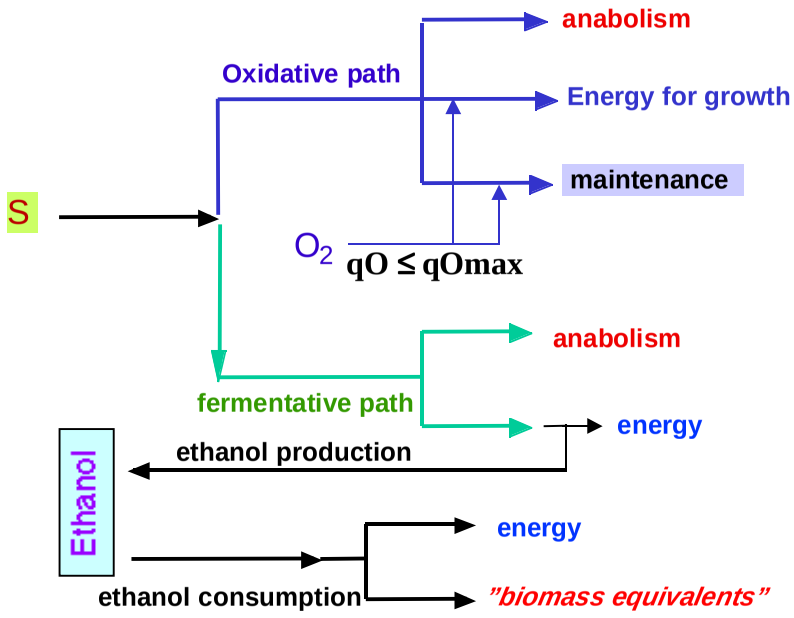
Oscillating glucose feed

results in oscillating sugar concentration

and oscillating CO2 production

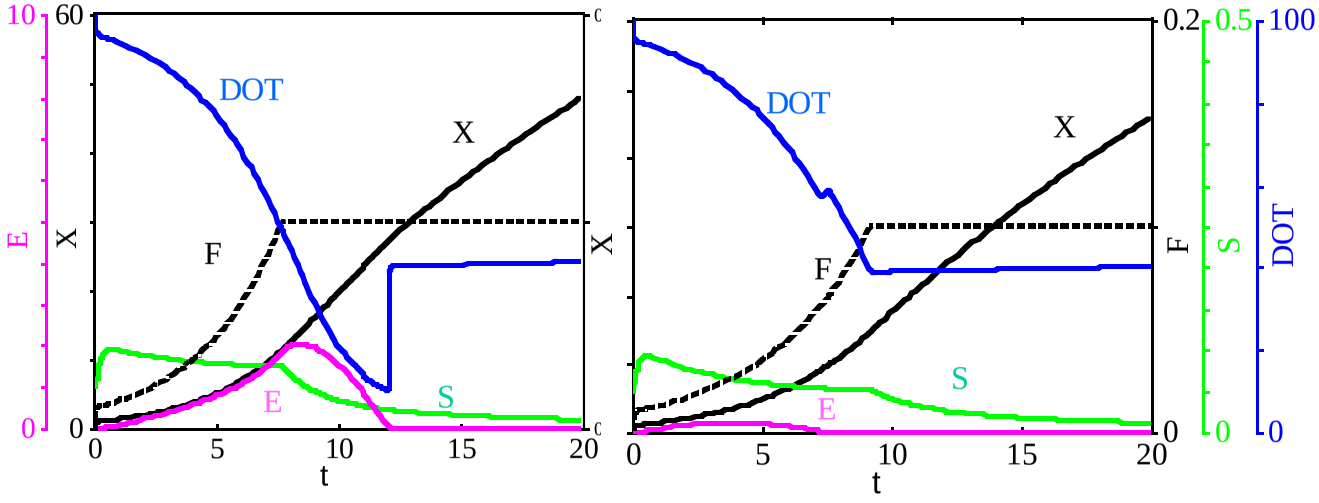
but no oscillation in O2 consumption, as long as ethanol is produced or consumed

Metabolic flux model of S. cerev isiae



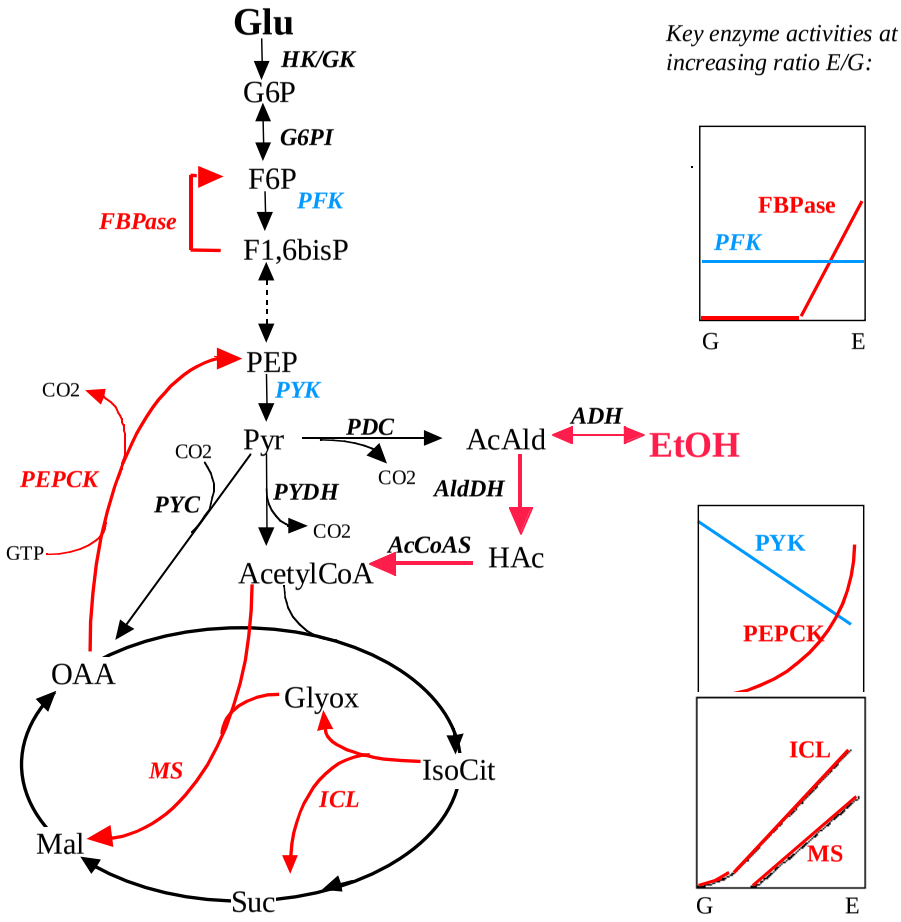
Each arrow (flux) can be expressed as a rate and then used for process simulation

Control of over-flow metabolism by exponential feed in S.cerevisiae fed-batch cultures



The only difference in the two processes is that the one to the left is run with exponent 0.3h^{-1} and the right hand process wit exponent 0.25 h^{-1} which resulted in less ethanol.

Gluconeogenesis induced by low glucose/high ethanol in S. cerevisiae



Overflow metabolism and **mixed-acid-fermentation** *in E. coli*