# Semi-structured development of simple model for continuous cultivation

These slides give an introduction to setting up model equations for continuous cultivation processes
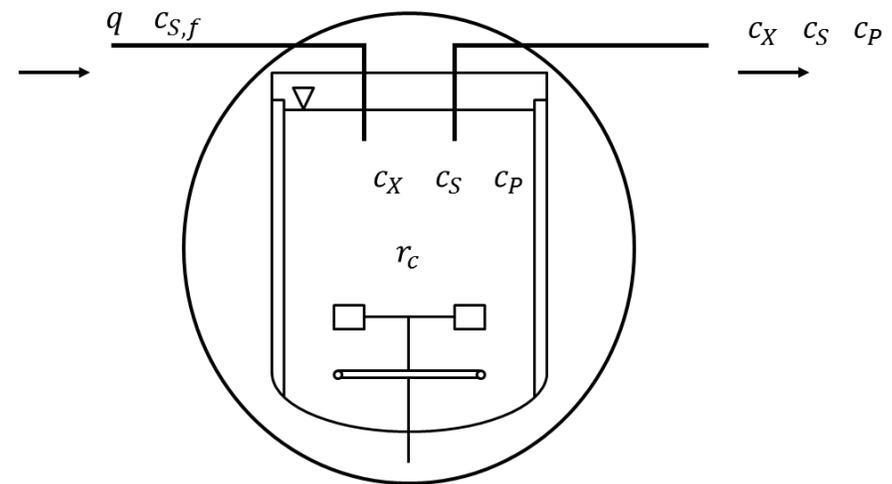
The first idea is to seperate strictly between different system boundaries.

The first one is the biomass / cell as such characterized by kinetcis and stoichiometry
The second one is the reactor characterized by material balances
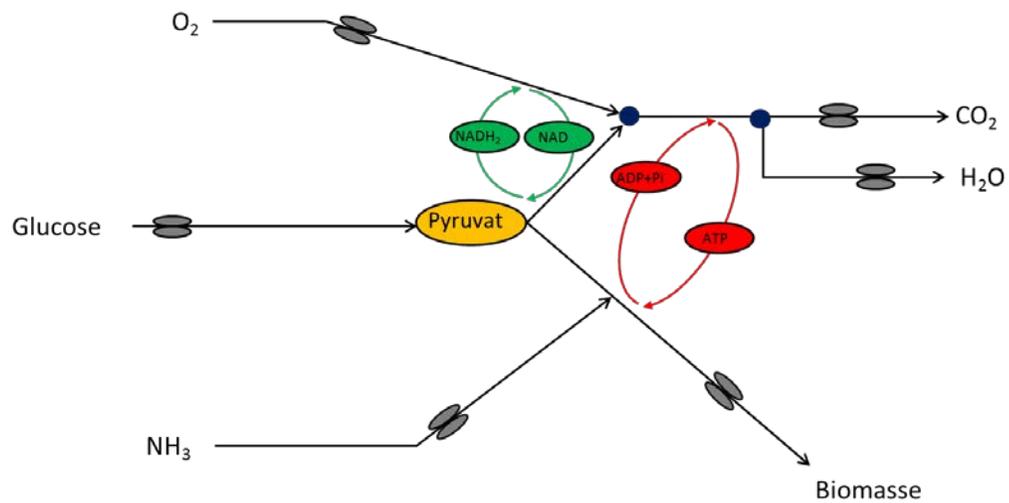
Simple structure of an aerobic organism

Balancing boundaries on the reactor level

On the cell level the idea is to think as much as possible about a reasonable sequence of metabolic steps in terms of kinetics and stoichiometry. That has advantages over collecting simply correlations from literature and leads to models which are not more complicated.

The easiest approach is to understand substrate uptake as an enzymatic step described by the specific substrate uptake rate r_S.

$$r_S = r_{S,max} * c_S / (c_S + k_S)$$ Michaelis-Menten (could be excahnged to other e.g. Haldane)

The specific growth rate r_X follows a balance between respiration and anabolism coupled by ATP or other stoichiometric constraints in the metabolism

$$r_X = y_{X,S} * r_S$$ Pirt $r_X = \mu$ (classic notation)

The Pirt equation is frequently proven by data.

$y_{X,S}$ is deduced from the ATP-balance, however, the single ATP-yields or demands of the metabolic steps do not have to be known explicitly, $y_{X,S}$ can be taken from data. For aerobic processes on Glucose it is usually 0,5 g/g. behind the ATP-balance there is of course a biological principle that the channeling of the two carbon-fluxes to repsiration or anabolism follows the attempt of the cell to the thermodynamic maximum.

Then on the reactor level simple quasi-stationary material balances can be set up.

$$dc_S / dt = D * (c_{S,f} - c_S) - r_S * c_X = 0 \qquad \text{for substrate}$$

$$dc_X / dt = -D * c_X + r_X * c_X = 0 \qquad \text{for biomass}$$

This system of algebraic equations consiting of the physiological equations and the reactor equations and has (in the simplest case) two solutions, as can easiliy be seen from the biomass balance:

First solution (wash-out case):

$$c_S = c_{S,f}; \quad c_X = 0$$

Second solution (normal operation with $r_X = D$):

$$c_S = -D*k_S/(-r_{S,max}*y_{X,S}+D)$$

$$c_X = y_{X,S}*(-c_{S,f}*r_{S,max}*y_{X,S}+c_{S,f}*D+D*k_S)/(-r_{S,max}*y_{X,S}+D) \quad \rightarrow \quad c_X = y_{X,S}*(c_{S,f} - c_S)$$

This system of equations can be further developed for

Maintenance n the stoichiometric level $\qquad r_X = y_{X,S} * r_S - \mu_e$

Note: Sometimes in literature modelling starts with Monod and continues with rs = my/yxs + re to Consider maintenance. But that leads to a positive substrate uptake for $c_S = 0$.

Another variation is Haldane kinetics for substrate inhibition $\qquad r_S = r_{S,max} * c_S / (c_S + k_S + k_{i,S} / c_S^2)$
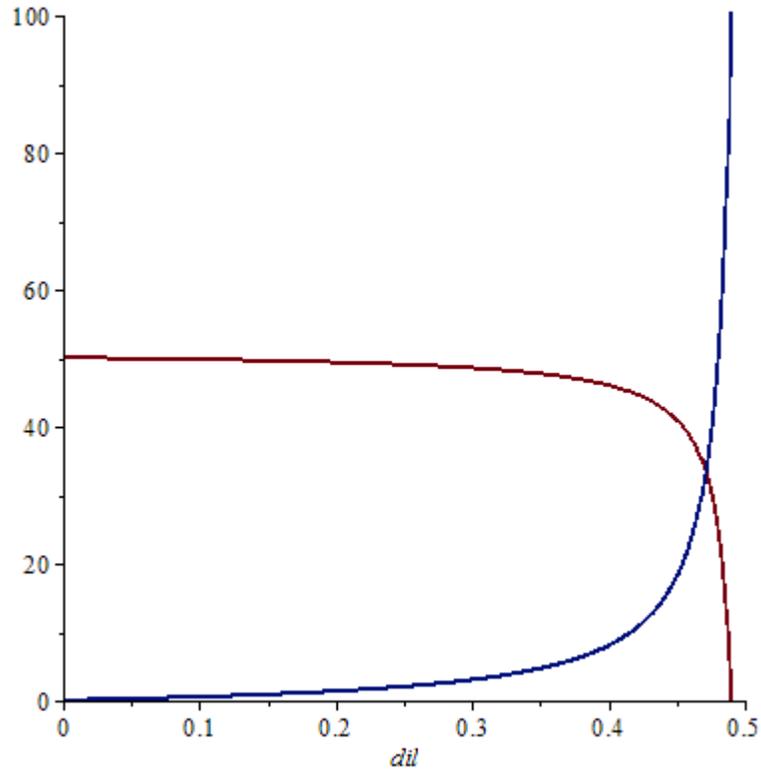In that case three solutions are mathematically and practically possible,
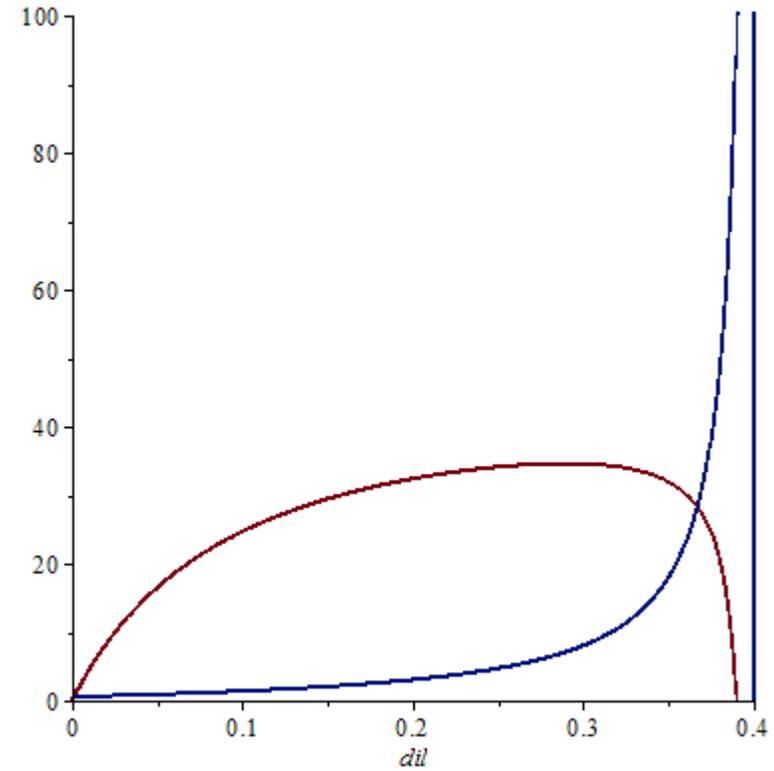the wash-out case,
substrate limited case
unstable substrate inhibited case

Plots with Maple

No maintenance
Note that wash-out occurs shortly before the
theoretical $\mu_{max} = y_{X,S} * r_{S,max}$ due to $k_S > 0$ and therefore
r_S always $< r_{S,max}$

With maintenance
Wash-out occurs even earlier
Low biomass concentration for low growth rates
due to relative higher substrate demand per growth.