EPCP Summer School - self replicator cell models

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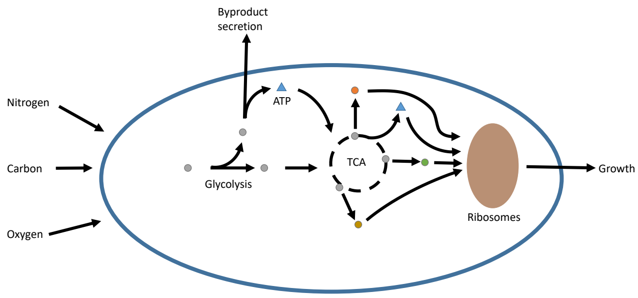
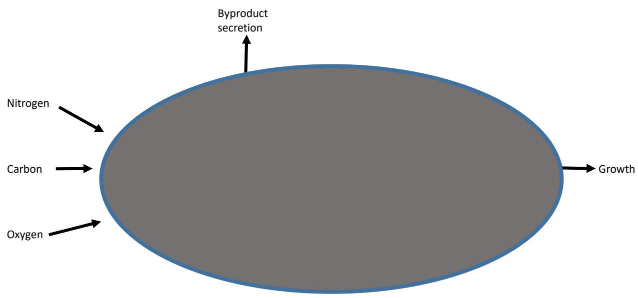
1 Introduction

Detailed view of metabolism



Main question: *What does this system do?*.

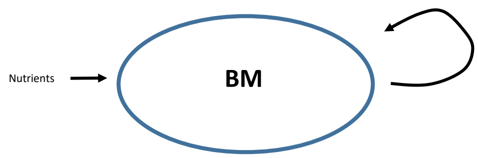
Metabolism from basic principles



What is metabolism?

2 Mathematical definition of metabolic system

A system that takes in nutrients from the environment and uses it to sustain itself and grow



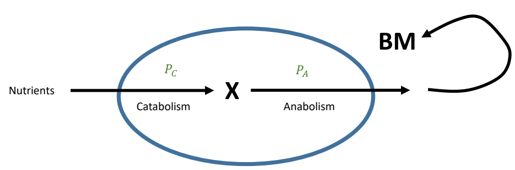
$\frac{dBM}{dt} = \lambda BM$

λ - growth rate

Solution: $BM = BM_0 e^{\lambda t}$

Reduced question: what determines the growth rate λ ?

Basic metabolic system



X - intermediate metabolite.

P_C - proteome sector that carries out the catabolic reaction.
P_A - proteome sector that carries out the anabolic reaction.

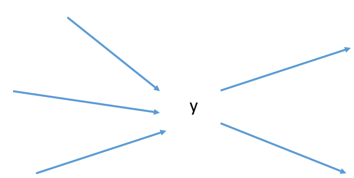
3 Constraints and assumptions

- **Flux balance constraint and steady state assumption**

  Flux balance - law of conservation of mass. The change in metabolite concentration is equal to the incoming metabolite flux minus outgoing metabolite flux.

  for some metabolite y:
  $\frac{dy}{dt} = \sum_{incoming fluxes\, i \to y} J_{i \to y} \quad - \sum_{outgoing fluxes\, y \to k} J_{y \to k}$

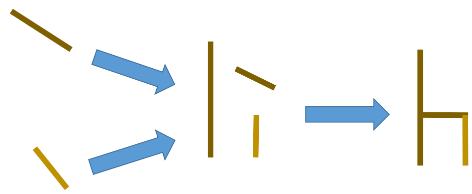
  $J_{i \to j}$ - flux going from metabolite pool i to metabolite pool j.

  Basic metabolic system example:
  $dx/dt = J_{n \to x} - J_{x \to BM}$

  Steady state assumption
  All metabolite concentrations are constant in time:
  $\frac{dy}{dt} = 0 \; \forall \; metabolitepool \; y$

  Analogy to economics: factory production line.

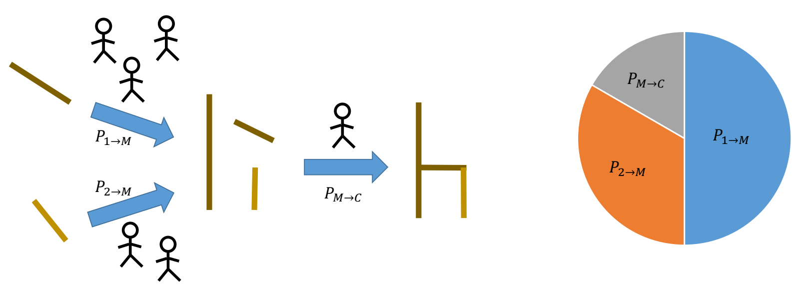


- **Proteome allocation constraint**
  Allocation of the proteome to the different reactions of the metabolic system.

  $\sum_{proteome\,sectors} P_{i\to j} = 1$

  Where $P_{i\to j} = 1$ is the ratio of the total proteome that carries out reaction $i \to j$.

  Analogy to economics: factory production line.



The workers make up the overall proteome and they are allocated to the different tasks. The proteome sector is the number of workers out of the

total number of workers allocated to the task. In this example:
$P_{1\to M} = 3/6, P_{2\to M} = 2/6, P_{M\to C} = 1/6$

The sum of all the proteome sectors together is equal to 1:
$P_{1\to M} + P_{2\to M} + P_{M\to C} = 1$

Basic metabolic system example:
$P_{Nutrient\to x} + P_{x\to BM} = 1$

- **Mathematical description of flux rates**
  The flux between different metabolite pools is the rate at which one proteome sector is turning one metabolite into another. It is determined by a combination of the allocated proteome sector, the concentration of the substrates necessary for the reaction and possible allosteric regulation that is carried out by other metabolites in the system.

  Examples:

  1. **Linear correlation to proteome sector**
     $J_{i\to j} = P_{i\to j}\beta_{i\to j}$

     Where $\beta_{i\to j}$ is a parameter describing the efficiency of proteome sector $P_{i\to j}$.

     No allosteric interactions and i is in excess.

     Analogy to economics: This parameters describes the efficiency of each worker.

     Basic metabolic system example:
     $J_{Nutrient\to X} = P_{Nutrient\to X}\beta_{Nutrient\to X}$
     $J_{X\to BM} = P_{X\to BM}\beta_{X\to BM}$

  2. **Limited substrate concentration and effect of allosteric interactions**
     Taking into account the effect of allosteric interactions and the effect of having lower concentration of substrate i. Two functions are introduced to the flux – one for the effect of the concentration of substrate i and one for the effect of allosteric interaction or some other metabolite l:

     $J_{i\to j} = P_{i\to j}\beta_{i\to j}f(i)g(l)$

Where $f(i)$, $g(l)$ are the regulating functions describing the effects of the concentrations of metabolites i and l on the reaction rate. $f(i)$ and $g(l)$ return values between 0 and 1:
$0 < f(i), g(l) < 1$

Typically we take Michaelis-Menten kinetics:
$f(i) = \frac{i}{k_{i \to j} + i}$

In this case, when the concentration of i is in excess so that $i >> k_{i \to j}$, the Michaelis-Menten function gives 1 and a linear assumption is sufficient.

3. **Non-linear correlation to the proteome sector**

- **Volume and surface area constraints**

4 Examples of theoretical models of metabolic systems

1. **Example 1 - Basic metabolic system with linear mechanistic reaction rates**

Constraint equations:

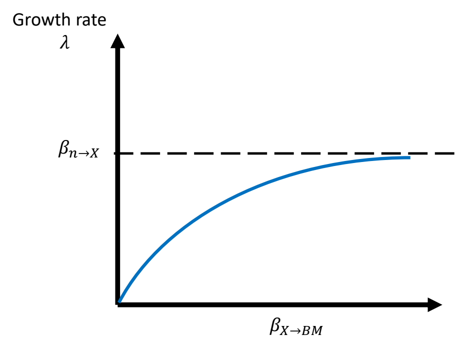
Flux balance and steady state:
$*J_{X \to BM} = J_{Nutrient \to X}$

Linear flux assumption:
$J_{Nutrient \to X} = P_{Nutrient \to X} \beta_{Nutrient \to X}$
$J_{X \to BM} = P_{X \to BM} \beta_{X \to BM}$

Proteome allocation:
$P_{Nutrient \to x} + P_{x \to BM} = 1$

Growth rate is equal to the flux into BM: $\lambda = J_{x \to BM}$

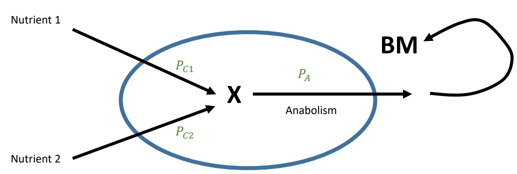
Solution: $\lambda = \frac{\beta_{x \to BM} \beta_{n \to x}}{\beta_{x \to BM} + \beta_{n \to x}}$



Growth rate is limited by rate limiting step.

Mechanistic model - assumptions and constraints are based only on mechanistic properties.

2. **Example 2 - Growth on two nutrient sources**
The metabolic system grows on two different nutrient sources. Both are catabolized to the same metabolite x but at different rates. The anabolic reaction is the same as in example model 1:



Constraint equations:

Flux balance and Steady state:
$J_{n_1\to x} + J_{n_2\to x} = J_{x\to BM}$

Linear flux assumptions:
$J_{n_1 \to X} = P_{n_1 \to X} \beta_{n_1 \to X}$
$J_{n_2 \to X} = P_{n_2 \to X} \beta_{n_2 \to X}$
$J_{X \to BM} = P_{X \to BM} \beta_{X \to BM}$

For simplicity, let's take it so that:
$\beta_{n_1} < \beta_{n_2}$

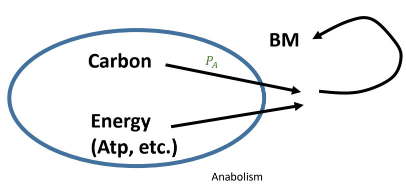
Proteome allocation:
$P_{n_1 \to x} + P_{n_2 \to x} + P_{x \to BM} = 1$

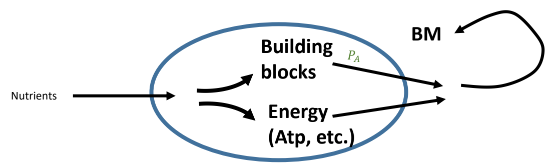
growth rate is equal to the flux into BM:
$\lambda = J_{x \to BM}$

Solution:
$\lambda = \frac{\beta_{x \to BM} \beta_{n_2 \to x}}{\beta_{x \to BM} + \beta_{n_2 \to x}} - P_{n_1 \to x} \left(\frac{\beta_{n_2 \to x} \beta_{n_1 \to x}}{\beta_{n_2 \to x} + \beta_{n_1 \to x}} \right) \beta_{x \to BM}$

Growth rate optimization assumption - cell growth strategy is set to maximize the growth rate λ:
$\lambda -> max : P_{n_1 \to x} = 0$

3. **Example 3 - Metabolic system that requires multiple substrates** In biological systems, multiple substrates are simultaneously necessary for biomass biosynthesis - amino acids, nucleic acids and energy molecules (ATP, NADH etc.). This example - carbon precursor and energy are necessary simultaneously for growth.





Constraint equations

Flux balance and Steady state:

Flux balance of two nutrient pools - building blocks and energy.

$J_{in}^{nutrient} = J_{n \to BB}^{C} + J_{n \to E}^{C}$
$J_{n \to BB}^{C} = J_{BB \to BM}^{C}$

Flux into BM - stoichiometric coefficients:

$J_{E \to BM}^{E} = \sigma_E \lambda$
$J_{BB \to BM}^{C} = \sigma_C \lambda$

Proteome allocation:

$P_{n \to BB} + P_{n \to E} + P_{x \to BM} = 1$

Solution:

$\frac{\sigma_C \lambda}{\beta_{n \to BB}^{C}} + \frac{J_{in} - \sigma_C \lambda}{\beta_{n \to E}^{C}} + P_{x \to BM} = 1$

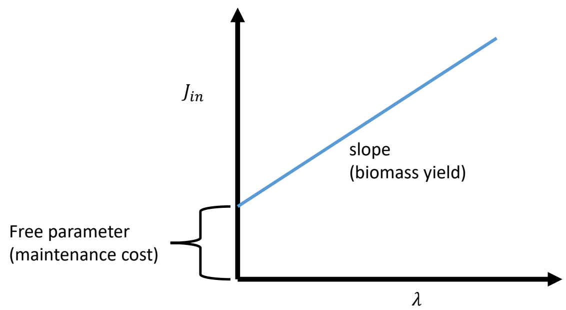
Another equation is necessary. Phenomenological assumption - growth rate is linear to anabolic proteome sector:

$P_{x \to BM} = P_{x \to BM,0} + \sigma_B M \lambda$

Phenomenological assumption: an assumption or constraint based on experimental observations.

Solution:

$J_{in} = (1 - P_{x \to BM,0})\beta_{n \to E}^{C} + \lambda((1 - \frac{\beta_{n \to E}^{C}}{\beta_{n \to BB}^{C}})\sigma_C - \beta_{n \to E}^{C} M \sigma_B)$



5 Examples from the literature