Modules in Hyper-Networks: an application to metabolic networks

Leen Stougie

In collaboration with Arne Reimers
Google, München

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- Life Sciences Group (CWI), ERABLE (CWI,INRIA, La Sapienza Rome)

Metabolic Network

- Network of chemical reactions
  together performing some constructive and destructive tasks in a living cell
  e.g. photosynthesis, glycolysis
- A reaction transforms some chemical molecules into others
- The molecules that describe a reaction are called chemical compounds or shortly compounds

Reactions

- Substrates - input compounds of a reaction
  - NH_3 and O_2
- Products - output compounds of a reaction
  - HNO_3 and H_2O
- Reactions are often reversible

Stoichiometry

Bipartite Graph and Hypergraph lack information

- $1NH_3 + 2O_2 \rightarrow 1HNO_3 + 1H_2O$

Numbers are important!

Stoichiometric Matrix

The stougiometric matrix is the compound-reaction matrix S describing a metabolic network

$s_{ir} = - \sharp$ compound i in reaction r,
if i is input compound (substrate) of r

$s_{ir} = + \sharp$ compound i in reaction r
if i is output compound (product) of r

$s_{ir} = 0$ otherwise

Stoichiometric Matrix

Example: $1NH_3 + 2O_2 \rightarrow 1HNO_3 + 1H_2O$

	R
·	0
·	0
NH_3	-1
O_2	-2
HNO_3	$+1$
H_2O	$+1$
·	0
·	0

Flux

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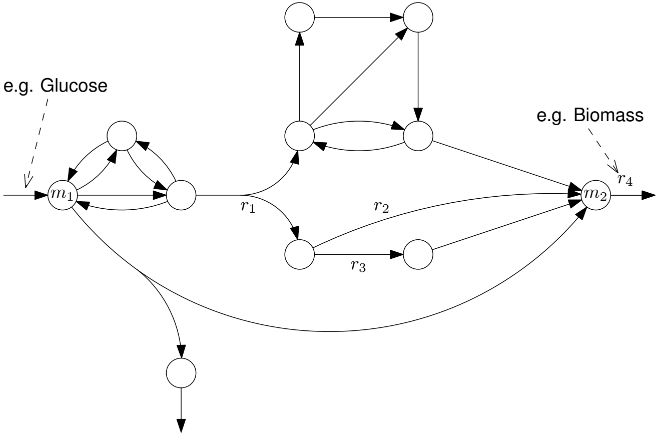
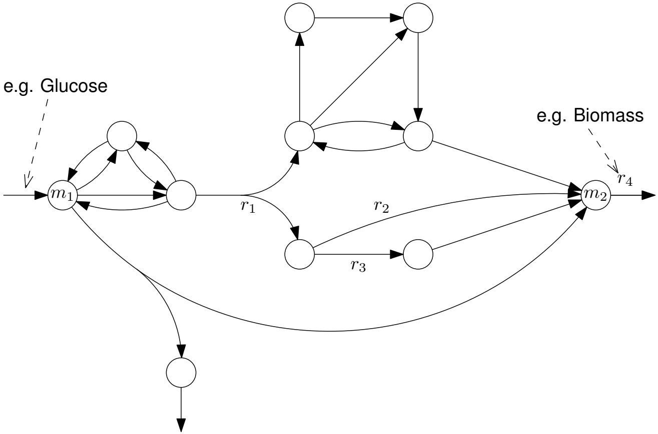
- If external compounds are included explicitly in the reaction, then steady state is imposed only on the internal compounds.

Running Example



Here all coefficients of the stoichiometric matrix are assumed to be $-1, 0, +1$.

Running Example



- Steady-State Assumption: e.g. $v_1 - v_2 - v_3 = 0$

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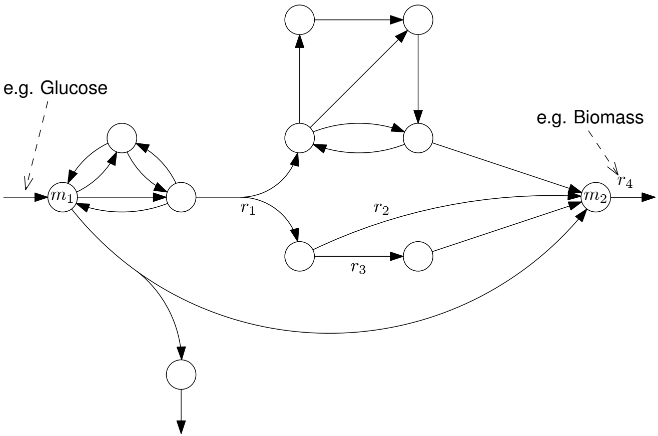

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- Flux Space: $\{v : Sv = 0\}$

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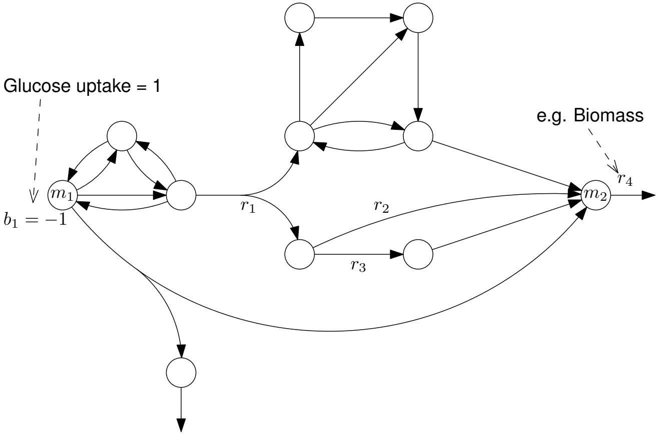

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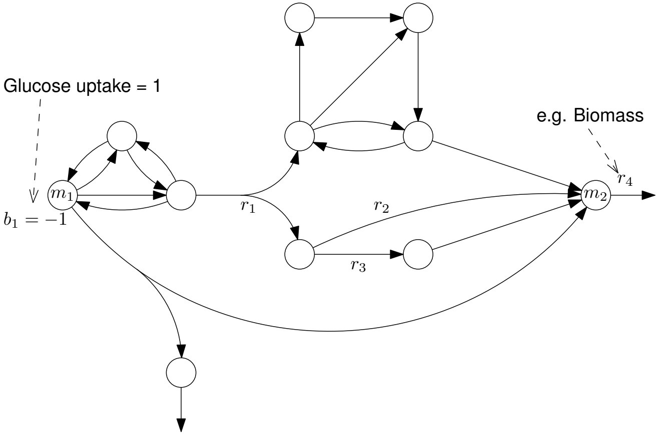

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$$\max v_{biomass} \quad \text{subject to } Sv = 0, \; v_{glucose} = 1$$

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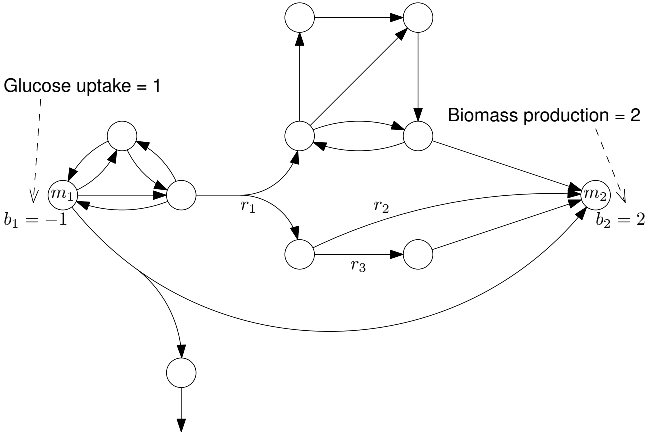

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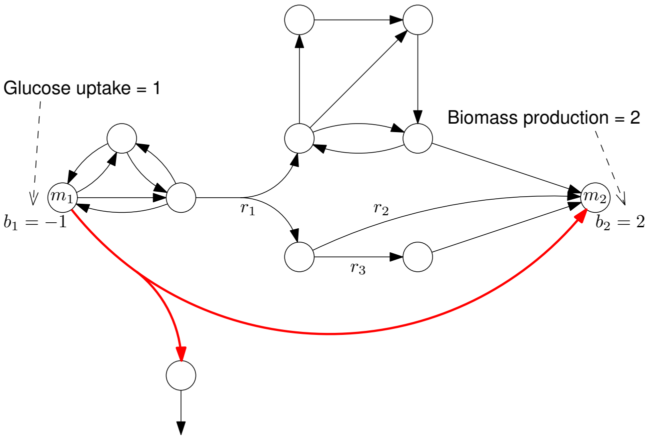

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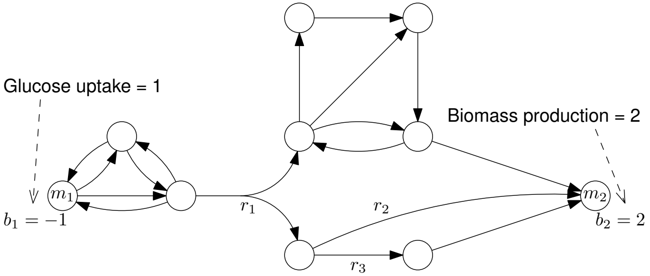

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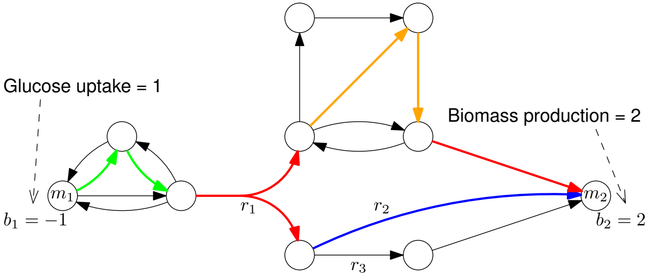

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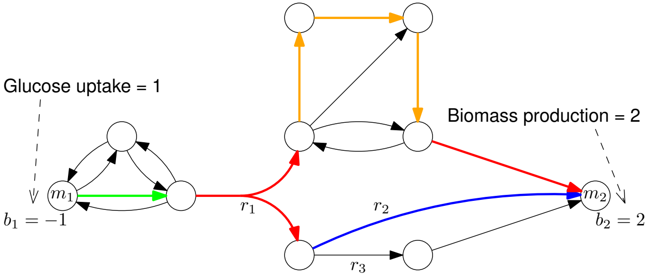

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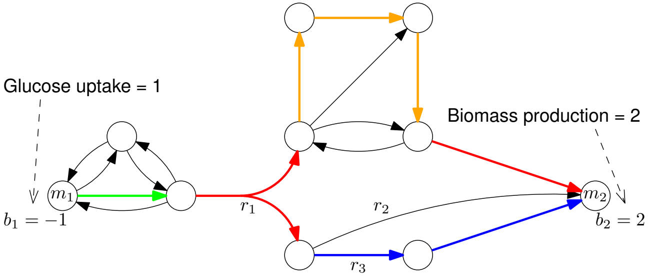

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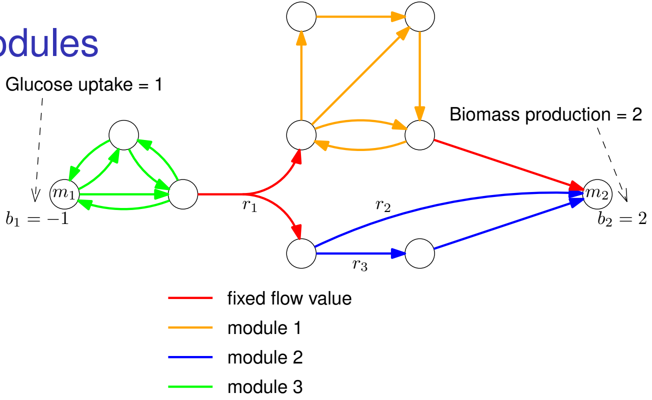
Flux-Modules



Observation (Kelk, Olivier, S., Bruggeman '12)

Reaction rates in the green module are independent from reaction rates in the orange module are independent from reaction rates in the blue module.

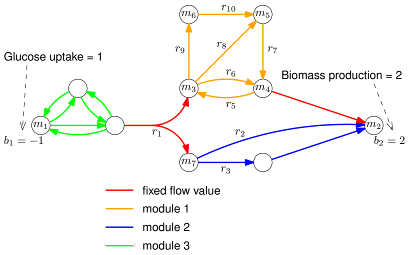
Kelk et al., Optimal flux spaces of genome-scale stoichiometric models are determined by a few subnetworks *Nature Scientific Reports*, 2:580, 2012.

Flux-Modules: A Definition

Notation:

- $\mathcal{R}$ reactions
- $\mathcal{M}$ metabolites
- S stoichiometric matrix
- $P \subseteq \mathbb{R}^{\mathcal{R}}$ flux space: In Ex.

  $\{v : Sv = 0, v_{glucose} = 1, v_{biomass} = 2\}$



Definition (Reimers '13)

$A \subseteq \mathcal{R}$ is a P-module if $\exists d \in \mathbb{R}^{\mathcal{M}}$ s.t. $S_A v_A = d$ for all $v \in P$.

- A module is a set of reactions A.
- The interface flux $d = S_A v_A$ of a module is constant for all feasible flux vectors ($v \in P$).

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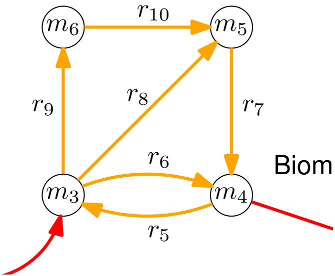

$$d_3 = -1, \; d_4 = 1, \; d_i = 0 \; \forall i \neq 3, 4$$

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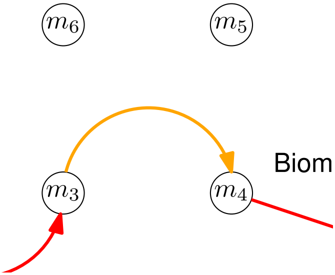

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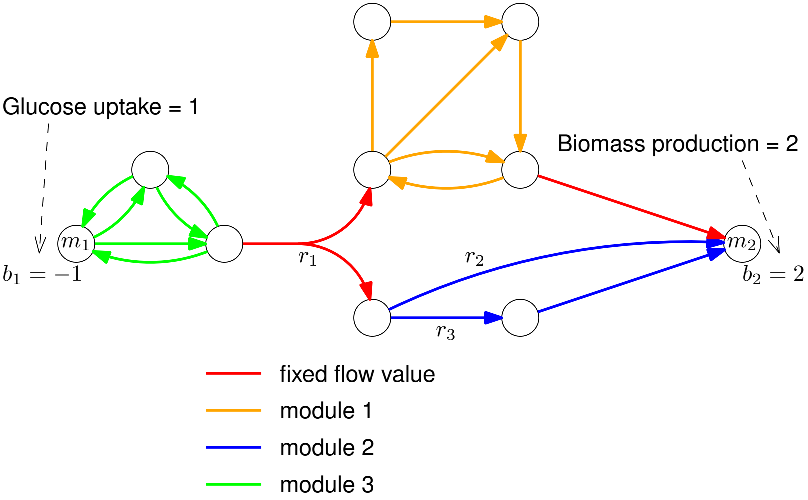
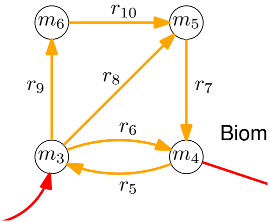
6) From 2 and 5 follows that A is a flux module if and only if $\mathcal{R} \setminus A$ is a flux module

Running example



Decomposition into flux models



Definition (Module)

$A \subseteq \mathcal{R}$ is a P-module if $\exists d \in \mathbb{R}^{\mathcal{M}}$ s.t. $S_A v_A = d$ for all $v \in P$.

We concentrate on P is a polyhedron:

- Let $P := \{v \in \mathbb{R}^{\mathcal{R}} : Sv = b\}$.
- For optimal flux space of the example $P_F = \{v_{biomass} = 2, Sv = 0, v_{glucose} = 1\}$
- For module A with interface flux d define $P^A := \{v \in \mathbb{R}^A : S_A v = d\}$.

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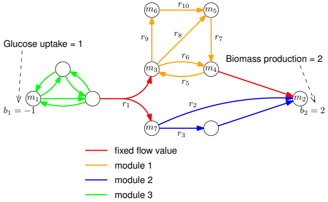

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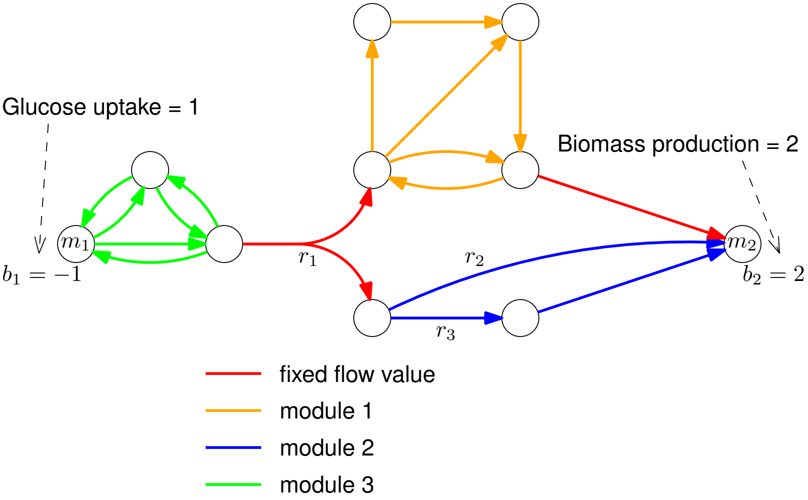
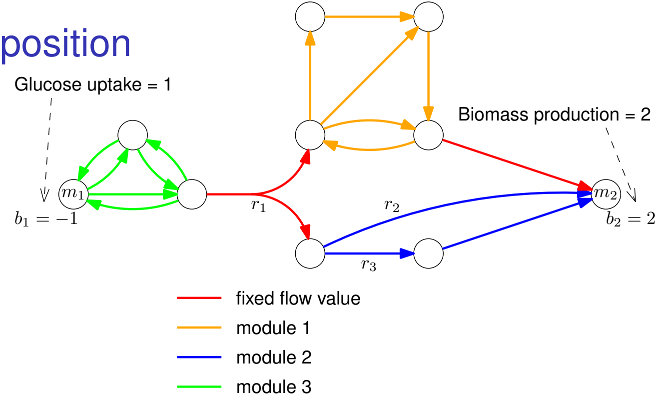


Decomposition



Theorem (Reimers '13)

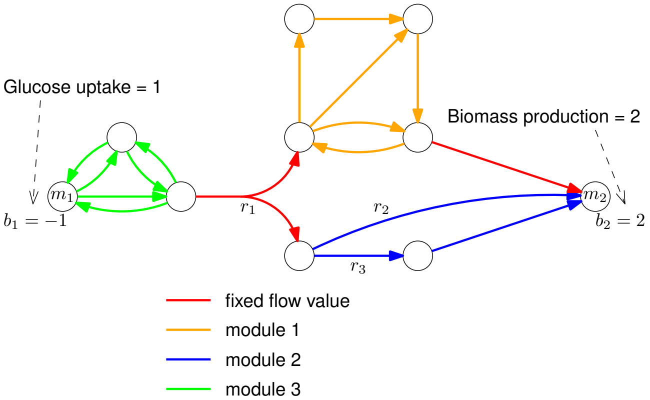
Let $\{A_1, \ldots, A_n\}$ be a partition of $\mathcal{R}$ into P-modules, then

$$P = \prod_{i=1}^{n} P^A := \left\{ v \in \mathbb{R}^{\mathcal{R}} : v_{A_i} \in P^{A_i} \; \forall i = 1, \ldots, n \right\}$$

Minimal flux-modules

Definition (Minimal Module)

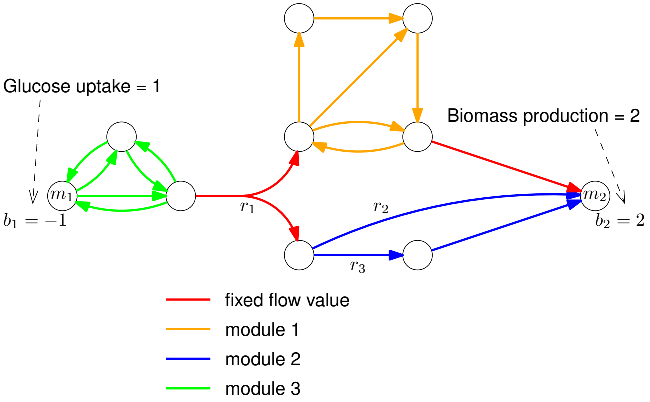
$A \subseteq \mathcal{R}$ is a minimal module if there does not exist another module $B \neq \emptyset$ with $B \subset A$.



Decomposition into minimal flux-modules

Theorem (Reimers '13)

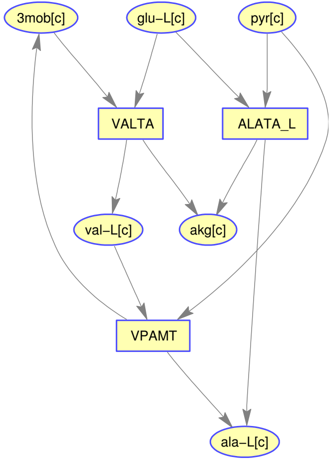
The decomposition of P into minimal flux modules is unique.



What is it good for?

- reactions that in every possible optimal pathway carry always the same flux
- subnetworks that are of a size (hopefully) small enough to study alternative optimal pathways

Module in all *E. coli* Networks



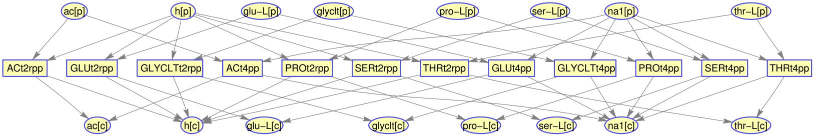
Interface-Flux*:
3-Methyl-2-oxobutanoate:
`3mob[c]` $= -0.3118$,
2-Oxoglutarate:
`akg[c]` $= 0.7412$,
L-Alanine:
`ala-L[c]` $= 0.4294$,
L-Glutamate:
`glu-L[c]` $= -0.7412$,
Pyruvate:
`pyr[c]` $= -0.4294$,
L-Valine:
`val-L[c]` $= 0.3118$

- `ALATA_L`: L-alanine transaminase
- `VALTA`: valine transaminase
- `VPAMT`: valine-pyruvate aminotransferase

* *E. coli* iAF1260, grown on glucose, aerobic

Another Module

from *E. coli* iAF1260, grown on glucose, aerobic



Interface Flux:

- H^+ (cytosol): `h[c]` $= -0.00349$
- H^+ (periplasm): `h[p]` $= 0.00349$
- Sodium (cytosol): `na1[c]` $= 0.00349$
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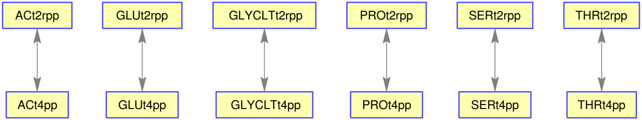

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- It allows to provide biologists with lots of information:
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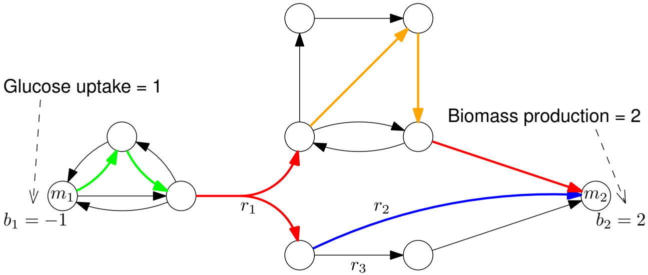
- But biologists like to know more!

Elementary Flux Modes (EFM)

$$P := \{v \in \mathbb{R}^{\mathcal{R}} : Sv = b, \ell \leq v \leq u\}$$

- Description of polyhedron P in terms of linear inequalities (facets)



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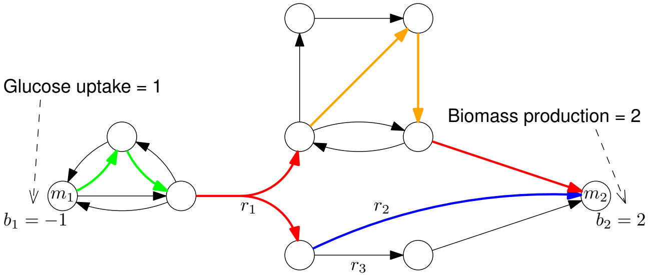

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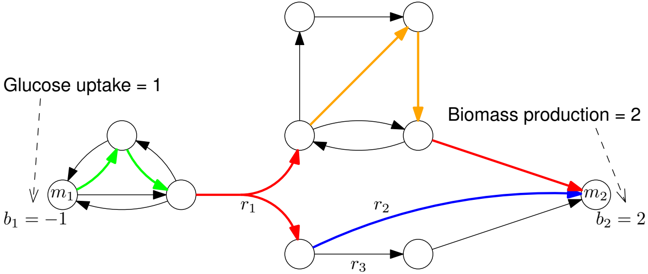

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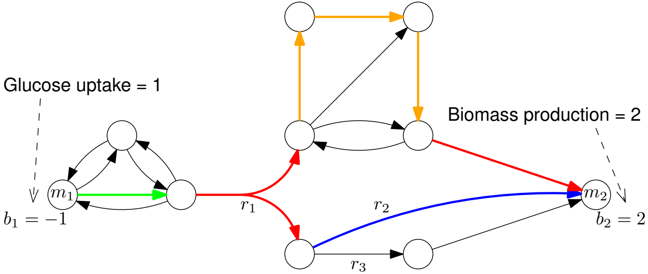

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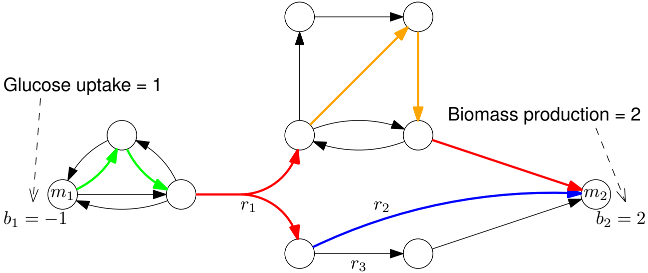

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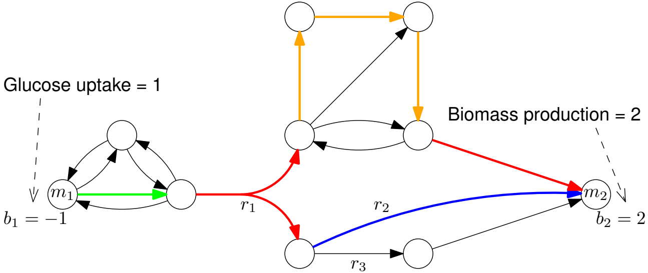

Elementary Flux Modes (EFM)

$P := \{v \in \mathbb{R}^{\mathcal{R}} : Sv = b, \ell \leq v \leq u\}$

- Finitely many optimal solutions from which all others can be combined
- P has finitely many extreme points
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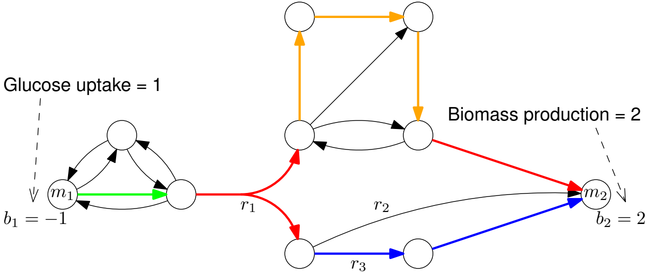

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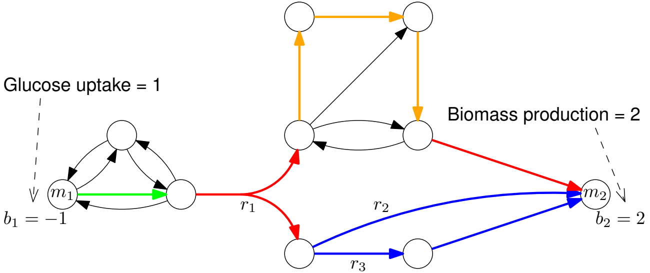

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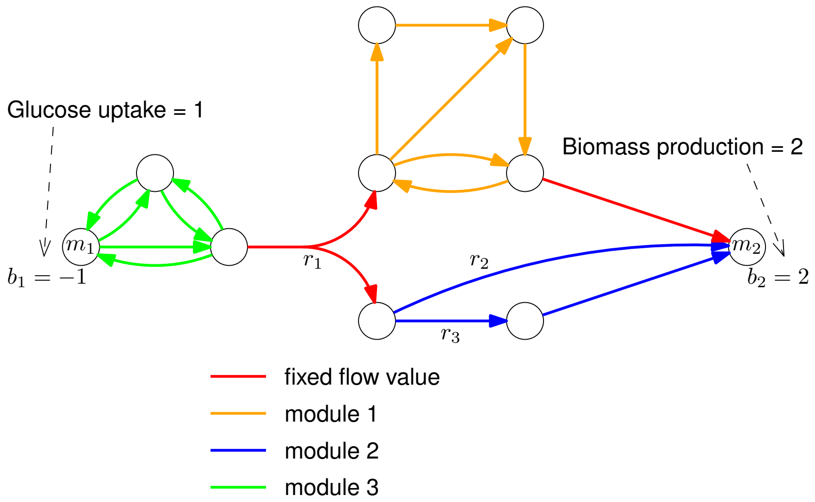
Theorem (Reimers '13)

Let $\mathcal{X} = \{A_1, \ldots, A_n\}$ be a partition of $\mathcal{R}$ into modules, then

$$\mathrm{EFM}(P) = \prod_{A \in \mathcal{X}} \mathrm{EFM}(P^A),$$

Decomposition of Elementary Flux Modes (EFM)

A graphical visualization of all 12 EFMs in the example network



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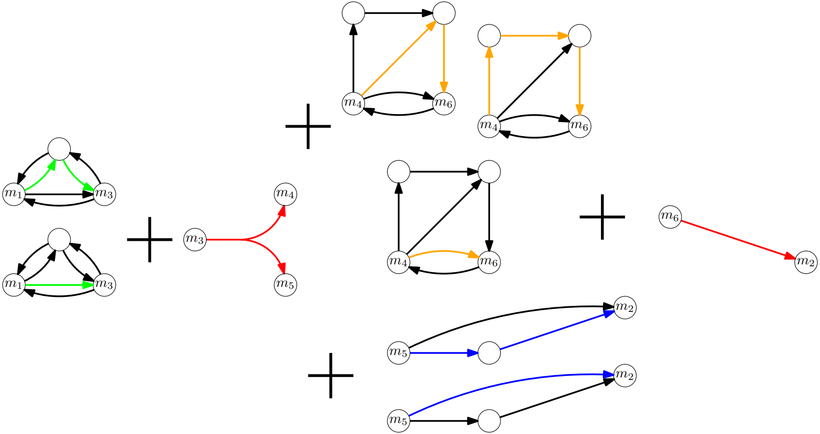
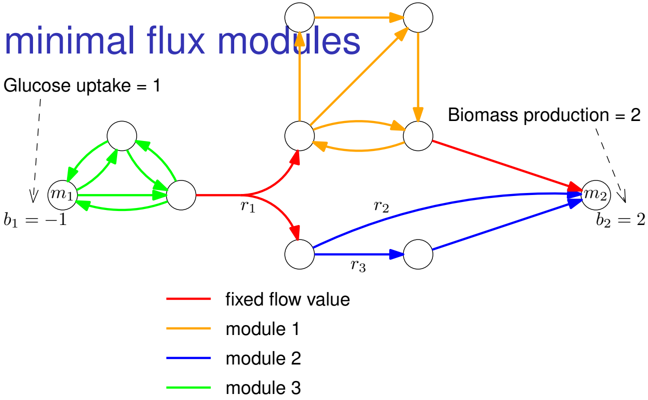


Finding minimal flux modules



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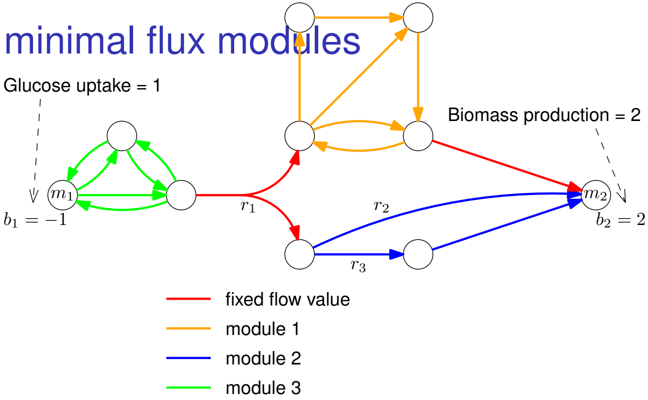
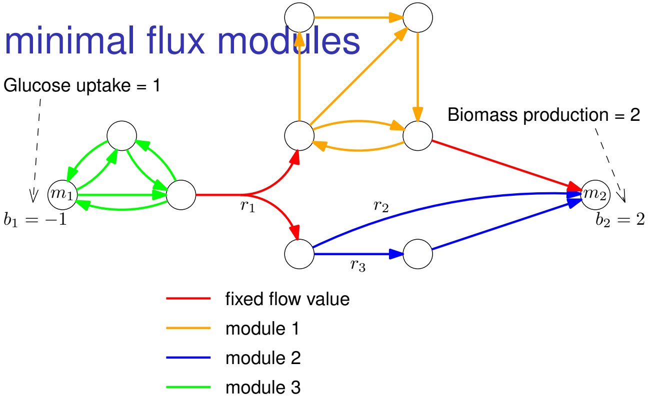


Step 1. Find all the red reactions: reactions with fixed flux.

Finding minimal flux modules



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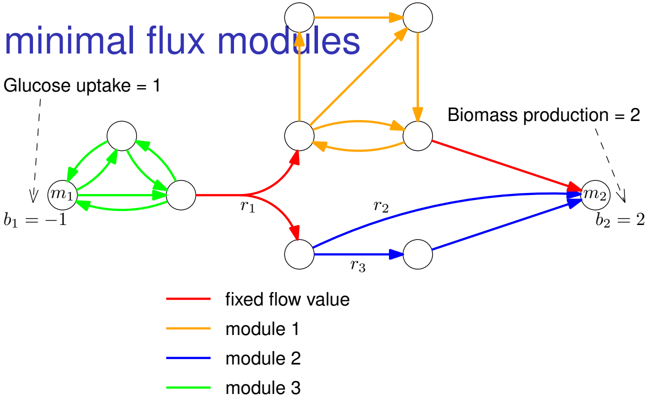
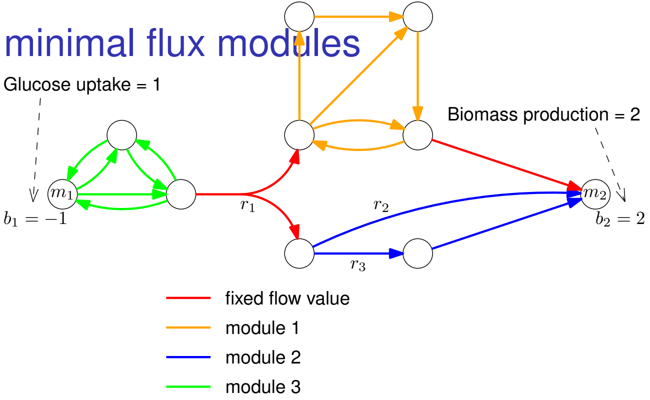


Step 1. Find all the red reactions: reactions with fixed flux.

- By flux variability analysis:
- For every reaction r:
  compute $\bar{v}_r = \max v_r \text{subject to } v \in P$
  compute $\underline{v}_r = \min v_r \text{subject to } v \in P$
  Reaction r is red only if $\bar{v}_r = \underline{v}_r$

Finding minimal flux modules



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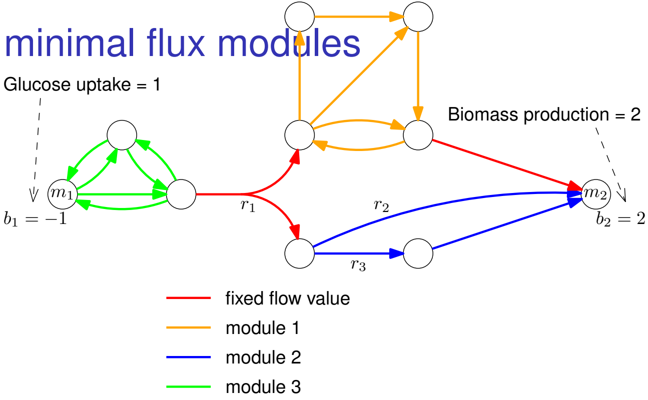

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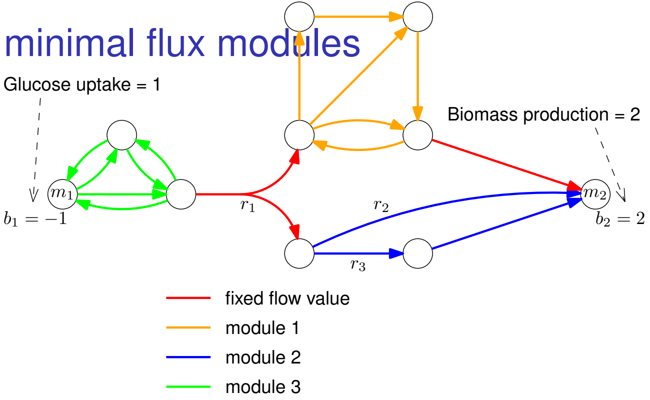

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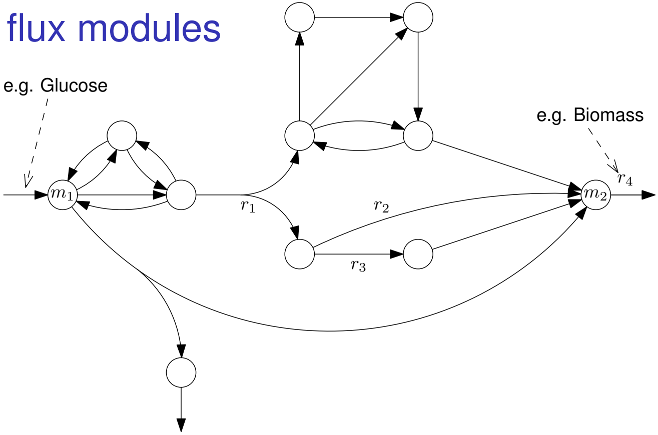
- A circuit is a minimal set A of reactions whose columns in S have the property that $S_A v_A = 0$ has a non-zero solution
- Or alternatively: The circuits are the minimal dependent sets of the matroid made up by the columns of the matrix S, with the columns of red reactions deleted.

Beyond flux modules



Suppose r_1 is split into two, each input 1, output 1.
Then optimal biomass rate is 1 and only two minimal modules survive. The green one and the rest.

But the old flux-modules are some sort of modules again if we allow some more flexibility

k-modules

Definition (module)

$A \subseteq \mathcal{R}$ is a P-module if there exists a $d \in \mathbb{R}^{\mathcal{M}}$, s.t. for all $v \in P$

$$S_A v_A = d \qquad .$$

k-modules

Definition (*k*-module)

$A \subseteq \mathcal{R}$ is a P-k-module if there exists a $d \in \mathbb{R}^{\mathcal{M}}$, $D \in \mathbb{R}^{\mathcal{M} \times k}$ s.t. for all $v \in P$ exists a $\alpha \in \mathbb{R}^k$ with

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- Hierarchic decomposition into *k*-modules
  $\rightsquigarrow$ branch decomposition / branch width

$\Rightarrow$ total polynomial time EFM enumeration algorithm for metabolic networks with bounded branch width.

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Summary

Flux modules: $S_A v_A = d$

- decomposition theorems
- characterization by variable reactions

$\Rightarrow$ Include experimental data only as reaction knock-outs

k-modules: $S_A v_A = d + D\alpha$

- capture functions of a subnetwork
- nice computational properties
- biological interpretation?