

Self-fabrication/autocatalysis in next-generation models of cellular growth

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Biochemical Network Analysis

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*Elementary vectors and autocatalytic sets for resource allocation
in next-generation models of cellular growth*

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S. Müller, C. Flamm, P.F. Stadler

What makes a reaction network chemical?

Journal of Cheminformatics 14:63, 2022

Outline

- Cellular growth
metabolism, gene expression & regulation, DNA replication & repair, cell division, signalling, ...

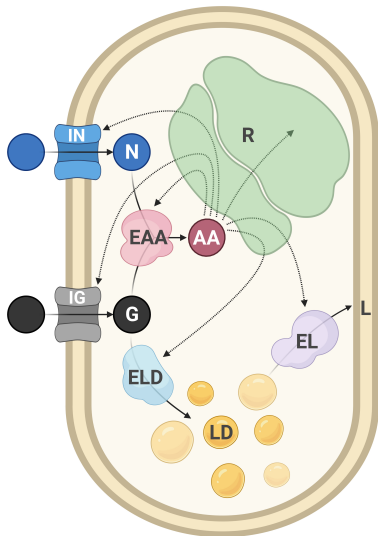
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Elementary growth modes/vectors

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Elementary growth modes/vectors
- Biological relevance
extreme phenotypes, “growth laws”, ribosome composition, ...

A small model of a self-fabricating cell



RBA: metabolism and macromolecule synthesis

$$\begin{array}{c}
 \text{G} \\
 \text{N} \\
 \text{AA} \\
 \text{LD} \\
 \text{L} \\
 \text{IG} \\
 \text{IN} \\
 \text{EAA} \\
 \text{ELD} \\
 \text{EL} \\
 \text{R}
 \end{array}
 \begin{pmatrix}
 r_{\text{IG}} & r_{\text{IN}} & r_{\text{EAA}} & r_{\text{ELD}} & r_{\text{EL}} & s_{\text{IG}} & s_{\text{IN}} & s_{\text{EAA}} & s_{\text{ELD}} & s_{\text{EL}} & s_{\text{R}} \\
 1 & 0 & -1 & -n_{\text{L}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 1 & 0 & 0 & -n_{\text{I}} & -n_{\text{I}} & -n_{\text{E}} & -n_{\text{E}} & -n_{\text{E}} & -n_{\text{R}} \\
 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\
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 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
 \end{pmatrix}
 = N_{\text{ng}}$$

$$(v_{\text{IG}}, v_{\text{IN}}, v_{\text{EAA}}, v_{\text{ELD}}, v_{\text{EL}}; w_{\text{IG}}, w_{\text{IN}}, w_{\text{EAA}}, w_{\text{ELD}}, w_{\text{EL}}, w_{\text{R}})^{\top} = v$$

FBA: metabolism

$$\begin{array}{c} \text{G} \\ \text{N} \\ \text{AA} \\ \text{LD} \\ \text{L} \end{array} \begin{pmatrix} r_{\text{IG}} & r_{\text{IN}} & r_{\text{EAA}} & r_{\text{ELD}} & r_{\text{EL}} & r_{\text{BM}} \\ 1 & 0 & -1 & -n_{\text{L}} & 0 & -\bar{\omega} x_{\text{G}} \\ 0 & 1 & -1 & 0 & 0 & -\bar{\omega} x_{\text{N}} \\ 0 & 0 & 1 & 0 & 0 & -\bar{\omega} x_{\text{AA}}^{\text{tot}} \\ 0 & 0 & 0 & 1 & -1 & -\bar{\omega} x_{\text{LD}} \\ 0 & 0 & 0 & 0 & 1 & -\bar{\omega} x_{\text{L}} \end{pmatrix} = N_{\text{bm}}$$

$$(v_{\text{IG}}, v_{\text{IN}}, v_{\text{EAA}}, v_{\text{ELD}}, v_{\text{EL}}; v_{\text{BM}})^{\top} = v$$

Metabolic modeling: “classical”

Stoichiometry:



metabolites A, B, C and enzyme $\mathcal{E}$

Kinetics:

$$v_{\mathcal{E}} = c_{\mathcal{E}} \cdot \kappa_{\mathcal{E}}(x_A, x_B, x_C; p)$$

(total) enzyme conc. $c_{\mathcal{E}} \geq 0$

metabolite conc. $x_A(t), x_B(t), x_C(t) \geq 0$

rate constants, external metabolite conc., etc. $p \geq 0$

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Network dynamics:

$$\frac{d}{dt} \begin{pmatrix} x_A \\ x_B \\ x_C \\ x_D \\ \vdots \end{pmatrix} = \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \\ \vdots \end{pmatrix} v_{\mathcal{E}} + \dots,$$

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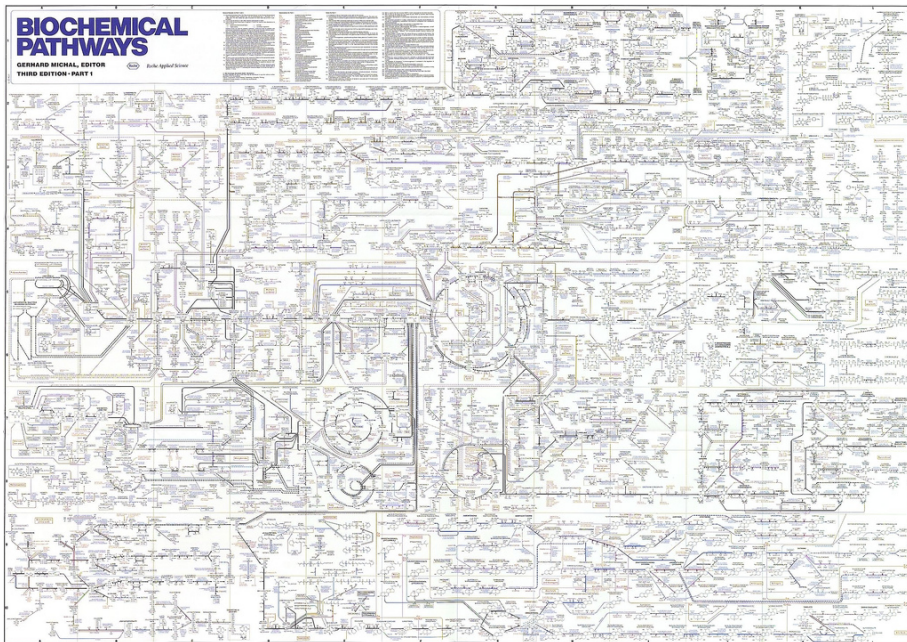
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stoichiometric matrix N , rate vector v
componentwise product $\circ$

Genome-scale metabolic models



Stoichiometric models

Based on $N \in \mathbb{R}^{1500 \times 2000}$, no kinetics

Flux vector v (vector of steady-state net reaction rates):

$$\frac{dx}{dt} = Nv = 0$$

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Linear methods:

- flux balance analysis (FBA):

flux polyhedron

$$P = \{v \mid Nv = 0, v^{\text{lb}} \leq v \leq v^{\text{ub}}\}$$

$$\max_{v \in P} a^{\top} v$$

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- elementary flux mode (EFM) analysis:

flux cone

$$C = \{v \mid Nv = 0, v_{\text{irr}} \geq 0\}$$

flux mode: $f \in C$

EFM: $e \in C$ with **minimal support**

Metabolic modeling: “next generation”

Model of self-fabrication:

$$N_{\text{ng}} = \begin{matrix} & \begin{matrix} r & s \end{matrix} \\ \begin{matrix} \text{Met} \\ \text{Mac} \end{matrix} & \begin{pmatrix} N & S \\ 0 & I \end{pmatrix} \end{matrix}$$

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$$\frac{dx}{dt} = N_{\text{ng}} v - \mu x$$

for concentrations $x = \frac{X}{M}$

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Fact:

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The biomass reaction as a simplification

Abuse of notation:

$$x = \begin{pmatrix} x_{\text{Met}} \\ x_{\text{Mac}} \end{pmatrix} = \begin{pmatrix} x \\ y \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} v_{\text{r}} \\ v_{\text{s}} \end{pmatrix} = \begin{pmatrix} v \\ w \end{pmatrix}$$

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Growth dynamics:

$$\frac{d}{dt} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} N & S \\ 0 & I \end{pmatrix} \begin{pmatrix} v \\ w \end{pmatrix} - \mu \begin{pmatrix} x \\ y \end{pmatrix}$$

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Steady state:

$$0 = Nv - \mu \underbrace{(Sy + x)}_{x^{\text{tot}}}$$

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Biomass “reaction”:

$$\sum_{i \in \text{Met}} \bar{\omega} x_i^{\text{tot}} \cdot i \rightarrow 1 \cdot \text{BM}$$

$$\bar{\omega} = \frac{1 \text{ g}}{1 \text{ mol}}$$

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Standard form:

$$0 = \underbrace{\begin{pmatrix} N & -n_{\text{bm}} \end{pmatrix}}_{N_{\text{bm}}} \begin{pmatrix} v \\ v_{\text{bm}} \end{pmatrix}$$

$$n_{\text{bm}} = \bar{\omega} x^{\text{tot}}, \quad v_{\text{bm}} = \mu / \bar{\omega}$$

Growth dynamics:

$$\frac{dx}{dt} = N_{\text{ng}} v - \mu x$$

Growth cone

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Growth cone:

$$C_{\text{g}} = \{v \in \mathbb{R}^{\text{Rxn}} \mid N_{\text{ng}}v \geq 0, v_{\text{lrr}} \geq 0\}$$

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Growth mode: $v \in C_{\text{g}}$

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Growth mode: $v \in C_{\text{g}}$ has associated

$$\mu(v) = \omega^{\top} N_{\text{ng}}v \quad \text{and} \quad x(v) = N_{\text{ng}}v / \mu(v)$$

Elementary growth modes

Definition (Flux cone)

Elementary flux modes (EFMs): support minimal

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Elementary growth modes (EGMs): conformally non-decomposable

Theorem

Every nonzero growth mode $v \in C_g$ is a finite, conformal sum of EGMs, that is, there is a finite set E of EGMs such that

$$v = \sum_{e \in E} e \quad \text{with} \quad \text{sign}(e) \leq \text{sign}(v).$$

Elementary growth modes

Definition (Flux cone)

Elementary flux modes (EFMs): **support minimal**

Definition (Growth cone)

Elementary growth modes (EGMs): **conformally non-decomposable**

Theorem

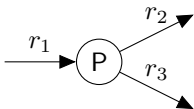
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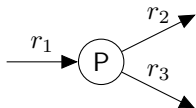
Let $v \in C_g$ with $\mu(v) =: \mu$. Then,

$$v = \sum_{e \in E_0} e + \sum_{e \in E_\mu} \lambda_e e \quad \text{with} \quad \text{sign}(e) \leq \text{sign}(v), \lambda_e \geq 0, \sum_{e \in E_\mu} \lambda_e = 1.$$

Subspace cone vs. (general) polyhedral cone

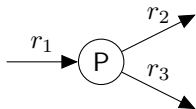


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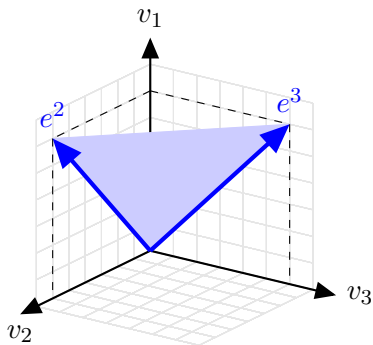


$$N = (1, -1, -1), \text{ } Nv = 0, v \geq 0$$

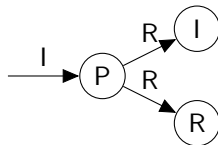
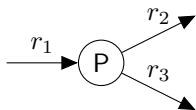
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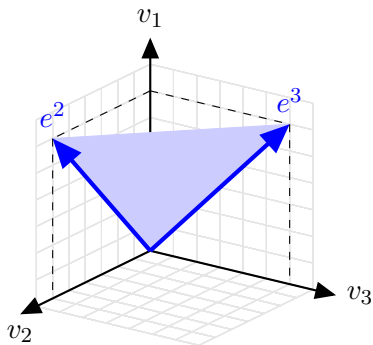
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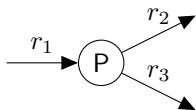
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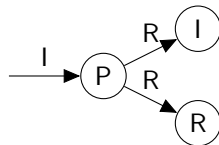
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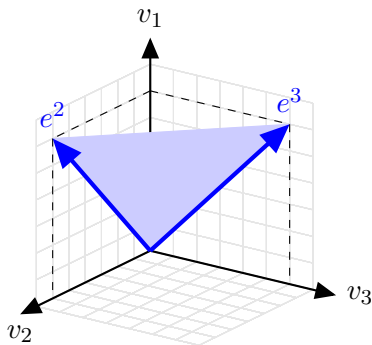
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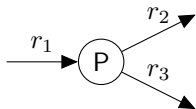
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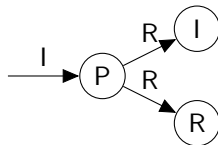
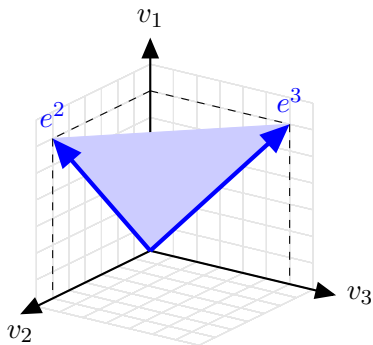
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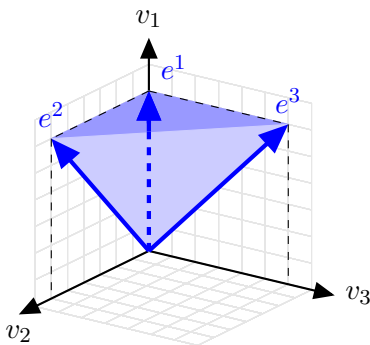
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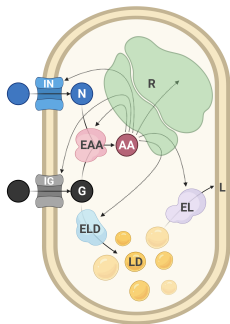
$$N = (1, -1, -1), \quad Nv = 0, \quad v \geq 0$$



$$N_{\text{ng}} = \begin{pmatrix} 1 & -1 & -1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad Nv_{\text{ng}} \geq 0, \quad v \geq 0$$



Small model: EGMs



$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

$$e^{\text{G}} = \mu/\omega_{\text{G}} \cdot (1, 0, 0, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{N}} = \mu/\omega_{\text{N}} \cdot (0, 1, 0, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{AA}} = \mu/\omega_{\text{AA}} \cdot (1, 1, 1, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{LD}} = \mu/\omega_{\text{LD}} \cdot (n_{\text{L}}, 0, 0, 1, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{L}} = \mu/\omega_{\text{L}} \cdot (n_{\text{L}}, 0, 0, 1, 1; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{IG}} = \mu/\omega_{\text{IG}} \cdot (n_{\text{I}}, n_{\text{I}}, n_{\text{I}}, 0, 0; 1, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{IN}} = \mu/\omega_{\text{IN}} \cdot (n_{\text{I}}, n_{\text{I}}, n_{\text{I}}, 0, 0; 0, 1, 0, 0, 0, 0)^{\top}$$

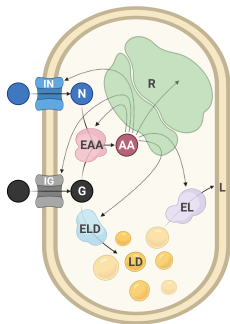
$$e^{\text{EAA}} = \mu/\omega_{\text{EAA}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 1, 0, 0, 0)^{\top}$$

$$e^{\text{ELD}} = \mu/\omega_{\text{ELD}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 0, 1, 0, 0)^{\top}$$

$$e^{\text{EL}} = \mu/\omega_{\text{EL}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 0, 0, 1, 0)^{\top}$$

$$e^{\text{R}} = \mu/\omega_{\text{R}} \cdot (n_{\text{R}}, n_{\text{R}}, n_{\text{R}}, 0, 0; 0, 0, 0, 0, 0, 1)^{\top}$$

Small model: EGMs



$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

$$e^{\text{G}} = \mu/\omega_{\text{G}} \cdot (1, 0, 0, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{N}} = \mu/\omega_{\text{N}} \cdot (0, 1, 0, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{AA}} = \mu/\omega_{\text{AA}} \cdot (1, 1, 1, 0, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{LD}} = \mu/\omega_{\text{LD}} \cdot (n_{\text{L}}, 0, 0, 1, 0; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{L}} = \mu/\omega_{\text{L}} \cdot (n_{\text{L}}, 0, 0, 1, 1; 0, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{IG}} = \mu/\omega_{\text{IG}} \cdot (n_{\text{I}}, n_{\text{I}}, n_{\text{I}}, 0, 0; 1, 0, 0, 0, 0, 0)^{\top}$$

$$e^{\text{IN}} = \mu/\omega_{\text{IN}} \cdot (n_{\text{I}}, n_{\text{I}}, n_{\text{I}}, 0, 0; 0, 1, 0, 0, 0, 0)^{\top}$$

$$e^{\text{EAA}} = \mu/\omega_{\text{EAA}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 1, 0, 0, 0)^{\top}$$

$$e^{\text{ELD}} = \mu/\omega_{\text{ELD}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 0, 1, 0, 0)^{\top}$$

$$e^{\text{EL}} = \mu/\omega_{\text{EL}} \cdot (n_{\text{E}}, n_{\text{E}}, n_{\text{E}}, 0, 0; 0, 0, 0, 0, 1, 0)^{\top}$$

$$e^{\text{R}} = \mu/\omega_{\text{R}} \cdot (n_{\text{R}}, n_{\text{R}}, n_{\text{R}}, 0, 0; 0, 0, 0, 0, 0, 1)^{\top}$$

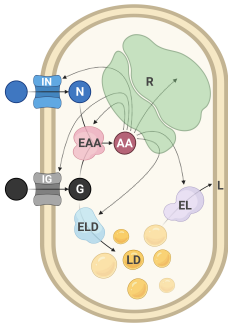
$$\mu(e^i) = \mu, x(e^i) \sim u^i$$

unit vector u^i

Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

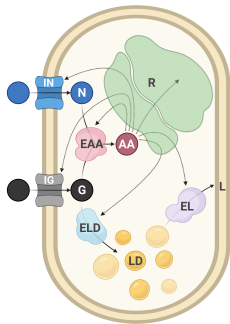
$$v = (*, *, *, 0, 0; *, *, 0, 0, 0, 0)^{\top}$$



Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

$$v = (*, *, *, 0, 0; *, *, 0, 0, 0, 0)^{\top}$$



Theorem:

$$v = \lambda_{\text{G}} e^{\text{G}} + \lambda_{\text{N}} e^{\text{N}} + \lambda_{\text{AA}} e^{\text{AA}} + \lambda_{\text{IG}} e^{\text{IG}} + \lambda_{\text{IN}} e^{\text{IN}}$$

with $\lambda_{\text{G}}, \lambda_{\text{N}}, \lambda_{\text{AA}} \geq 0$, $\lambda_{\text{IG}}, \lambda_{\text{IN}} > 0$,
and $\lambda_{\text{G}} + \lambda_{\text{N}} + \lambda_{\text{AA}} + \lambda_{\text{IG}} + \lambda_{\text{IN}} = 1$

Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

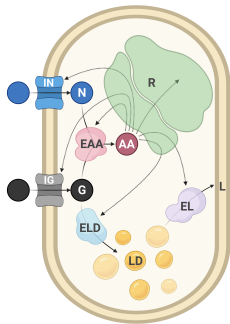
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not catalytically closed



Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

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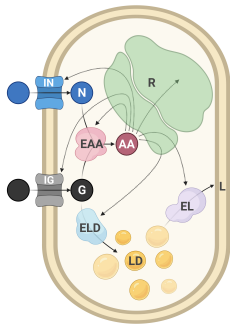
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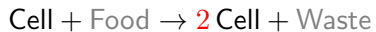
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not catalytically closed

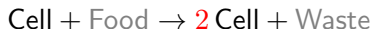
$$\begin{aligned} v' &= (*, *, *, 0, 0; *, *, *, 0, 0, *)^{\top} \\ &= (1 - \lambda_{\text{EAA}} - \lambda_{\text{R}}) v + \lambda_{\text{EAA}} e^{\text{EAA}} + \lambda_{\text{R}} e^{\text{R}} \end{aligned}$$



(Auto)catalysis



(Auto)catalysis

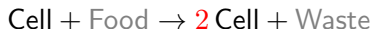


- Autocatalytic subnetworks

Barenholz et al, eLife, 2017; Blokhuis et al, PNAS, 2020

Andersen et al, J Syst Chem, 2020; Golnik et al, arXiv, 2025

(Auto)catalysis



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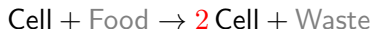
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- Network autocatalysis

Kauffman, Steel, Hordijk, ...

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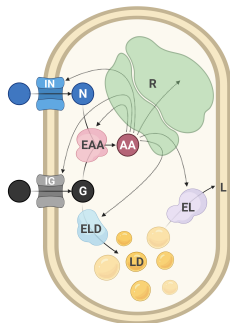
Definition

(BC) A growth mode $v \in C_g$ is *basically catalytic* if there is a catalytic reaction $r \in \text{supp}(v)$.

(CC) It is *catalytically closed* if, for every catalytic reaction $r \in \text{supp}(v)$ with catalyst s , $(N_{\text{ng}}v)_s > 0$.

(AC) It is *autocatalytic* if it is BC and CC.

Small model

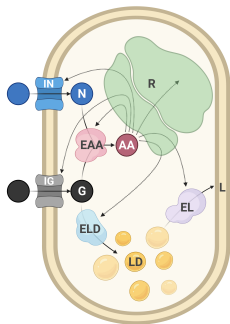


$$Rxn = \{r_{IG}, r_{IN}, r_{EAA}, r_{ELD}, r_{EL}; s_{IG}, s_{IN}, s_{EAA}, s_{ELD}, s_{EL}, s_R\}$$

$$v = (*, *, *, 0, 0; *, *, 0, 0, 0, 0)^T$$

BC, but **not** CC

Small model



$$Rxn = \{r_{IG}, r_{IN}, r_{EAA}, r_{ELD}, r_{EL}; s_{IG}, s_{IN}, s_{EAA}, s_{ELD}, s_{EL}, s_R\}$$

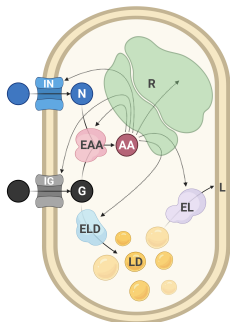
$$v = (*, *, *, 0, 0; *, *, 0, 0, 0, 0)^T$$

BC, but **not** CC

$$v' = (*, *, *, 0, 0; *, *, *, 0, 0, *)^T$$

BC and CC $\implies$ AC

Small model



$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

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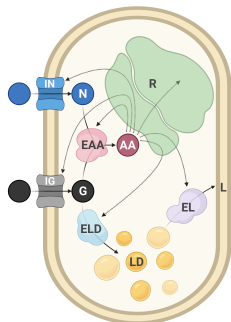
BC, but **not** CC

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$\text{supp}(v')$ is MAC set

Small model



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$$v = (*, *, *, 0, 0; *, *, 0, 0, 0, 0)^{\top}$$

BC, but **not** CC

$$v' = (*, *, *, 0, 0; *, *, *, 0, 0, *)^{\top}$$

BC and CC $\implies$ AC

$\text{supp}(v')$ is MAC set

Definition

(AC) A subset of reactions $S \subseteq \text{Rxn}$ is *autocatalytic* if there is a growth mode $v \in C_g$ with $S = \text{supp}(v)$ that is AC.

(MAC) A nonempty subset of reactions is *minimally autocatalytic* if it is AC and inclusion-minimal.

Metabolic modeling: additional constraints

Constraints for v :

$$N_{\text{ng}}v \geq 0, v_{\text{lrr}} \geq 0 \implies \mu(v), x(v)$$

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Constraints for v, x, μ :

- Steady state

$$N_{\text{ng}}v = \mu x \geq 0$$

- (Dry) mass

$$\mu = \omega^{\top} N_{\text{ng}}v$$

- Irreversibility

$$v_{\text{lrr}} \geq 0$$

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$$\text{e.g. } A + B + \mathcal{E} \rightarrow C + \mathcal{E}: \quad v_{\mathcal{E}} \leq k_{\text{cat},\mathcal{E}} x_{\mathcal{E}}$$

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- Biophysics

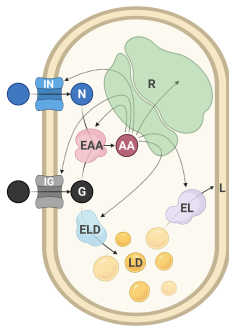
e.g. membrane

Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

Importer/Enzyme

$$v_i \leq k_{\text{cat},i} x_i \quad \text{for } i = \text{IG, IN, EAA, ELD, EL}$$



Small model

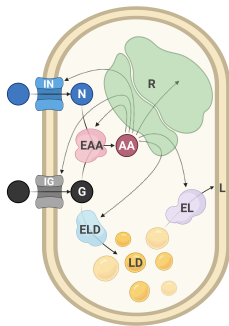
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$$v_i \leq k_{\text{cat},i} x_i \quad \text{for } i = \text{IG, IN, EAA, ELD, EL}$$

Ribosome

$$\sum_{i=\text{IG,IN,EAA,ELD,EL,R}} n_i w_i \leq k_{\text{el}} x_{\text{R}}$$



Small model

$$\text{Rxn} = \{r_{\text{IG}}, r_{\text{IN}}, r_{\text{EAA}}, r_{\text{ELD}}, r_{\text{EL}}; s_{\text{IG}}, s_{\text{IN}}, s_{\text{EAA}}, s_{\text{ELD}}, s_{\text{EL}}, s_{\text{R}}\}$$

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$$v_i \leq k_{\text{cat},i} x_i \quad \text{for } i = \text{IG, IN, EAA, ELD, EL}$$

Ribosome

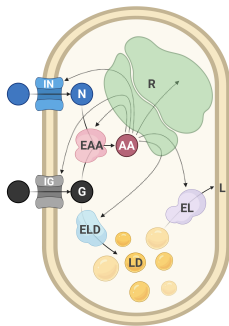
$$\sum_{i=\text{IG,IN,EAA,ELD,EL,R}} n_i w_i \leq k_{\text{el}} x_{\text{R}}$$

Membrane area

$$A_{\text{L}} x_{\text{L}} + A_{\text{I}} (x_{\text{IG}} + x_{\text{IN}}) = C$$

$$A_{\text{L}} x_{\text{L}} \geq \alpha C$$

$$C = C(A/V, \rho), \quad 0 < \alpha < 1$$



Growth polyhedron

Summarize constraints (for v and c):

$$\tilde{P}_g(\mu) = \left\{ (v, x) \in \mathbb{R}^{\text{Rxn}} \times \mathbb{R}^{\text{Mol}} \mid N_{\text{ng}}v = \mu x \geq 0, \mu = \omega^\top N_{\text{ng}}v, v_{\text{lrr}} \geq 0, \right. \\ \left. Ax + Bv \geq c \right\}$$

Growth polyhedron

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$$\tilde{P}_g(\mu) = \left\{ (v, x) \in \mathbb{R}^{R \times n} \times \mathbb{R}^{\text{Mol}} \mid N_{\text{ng}}v = \mu x \geq 0, \mu = \omega^\top N_{\text{ng}}v, v_{\text{lrr}} \geq 0, \right. \\ \left. Ax + Bv \geq c \right\}$$

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$$P_g(\mu) = \left\{ v \in \mathbb{R}^{R \times n} \mid N_{\text{ng}}v \geq 0, \mu = \omega^\top N_{\text{ng}}v, v_{\text{lrr}} \geq 0, \right. \\ \left. (AN_{\text{ng}}/\mu + B)v \geq c \right\}$$

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Growth vector: $v \in P_g(\mu)$

Elementary growth vectors

Definition (Growth polyhedron)

Elementary growth vectors (EGVs): **convex-conformally non-decomposable**
or conformally non-decomposable elements of the recession cone

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Elementary growth vectors (EGVs): **convex-conformally non-decomposable**
or conformally non-decomposable elements of the recession cone

Theorem

Let $v \in P_g$ with $\mu(v) =: \mu$. Then,

$$v = \sum_{e \in E_0} e + \sum_{e \in E_\mu} \lambda_e e \quad \text{with} \quad \text{sign}(e) \leq \text{sign}(v), \lambda_e \geq 0, \sum_{e \in E_\mu} \lambda_e = 1.$$

Small model: EGVs

	EGV																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
mb G	>								>								>									
mb LD		>								>								>								
mb N			>								>								>							
mb AA				>								>								>						
cap IG									>	>	>	>	>	>	>	>		>	>	>	>	>	>	>	>	
cap IN																	>	>	>	>	>	>	>	>	>	>
cap EAA					>							>									>					
cap ELD						>							>									>				
cap EL							>							>									>			
cap R								>							>									>		
memb L	>	>	>	>	>	>	>	>																	>	>
G	*								*								*									
LD		*								*								*								
N			*								*								*							
AA				*								*								*						
μ									L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	H	H

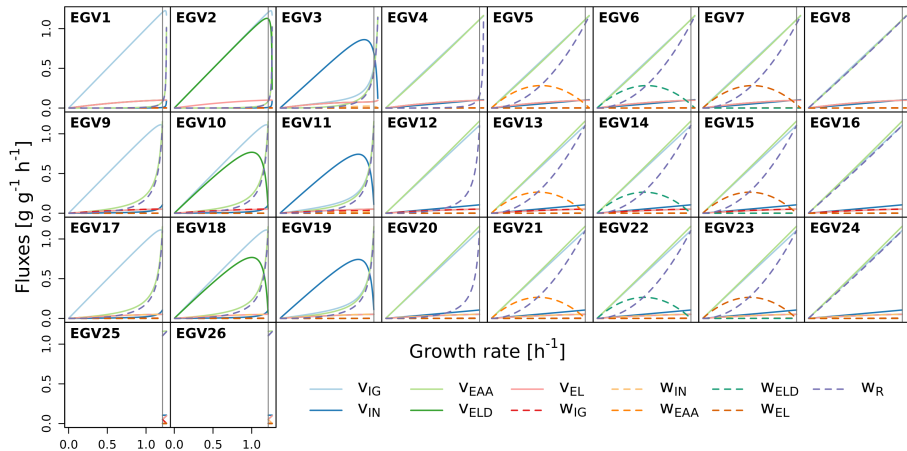
26 EGVs: 8 for all μ , 16 for low μ (L), 2 for high μ (H)

every EGV has full support $\implies$ only MAC set is Rxn

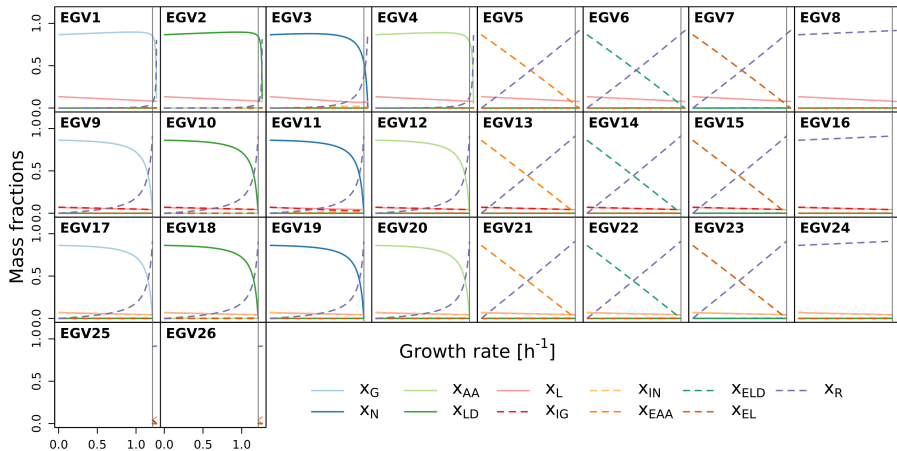
every EGV has two inactive constraints (>)

concentrations of macromolecules, lipids, and at most one other metabolite nonzero (*)

Details: fluxes vs. growth rate



Details: concentrations/mass fractions vs. growth rate

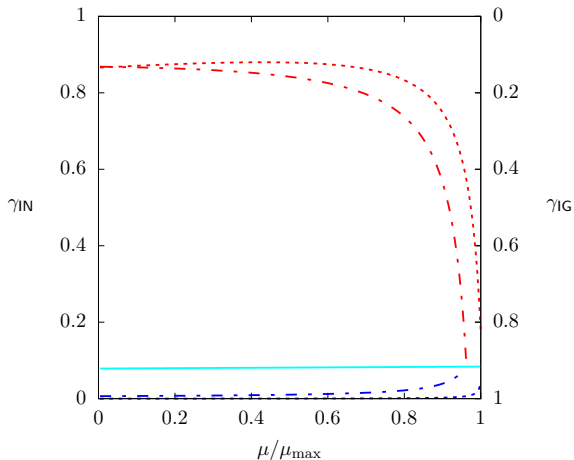


Bio relevance: ammonium (vs. glucose) uptake

$$\gamma_{IG} = \frac{\omega_G v_{IG}}{\mu}, \gamma_{IN} = \frac{\omega_N v_{IN}}{\mu} : \gamma_{IG} + \gamma_{IN} = 1$$

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1a: EGV1-2

2a: EGV3

3a: EGV4-8

1b: EGV9-10/17-18

2b: EGV11/19

3b: EGV12-16/20-24 + 25-26

Bio relevance: ammonium uptake and carbon storage

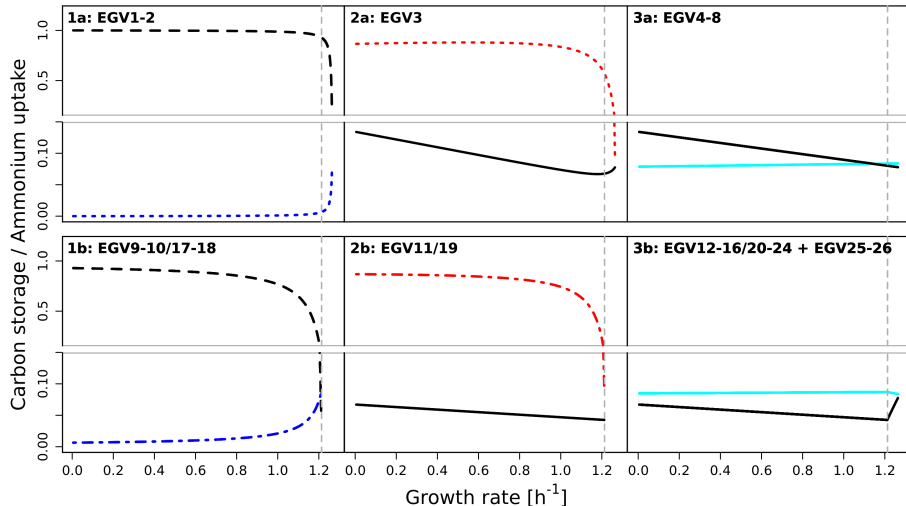
ammonium uptake: $\gamma_{\text{IN}} = \frac{\omega_{\text{N}} v_{\text{IN}}}{\mu}$ (color)

carbon storage: $s_{\text{C}} = \omega_{\text{G}} x_{\text{G}} + \omega_{\text{LD}} x_{\text{LD}} + \omega_{\text{L}} x_{\text{L}}$ (black)

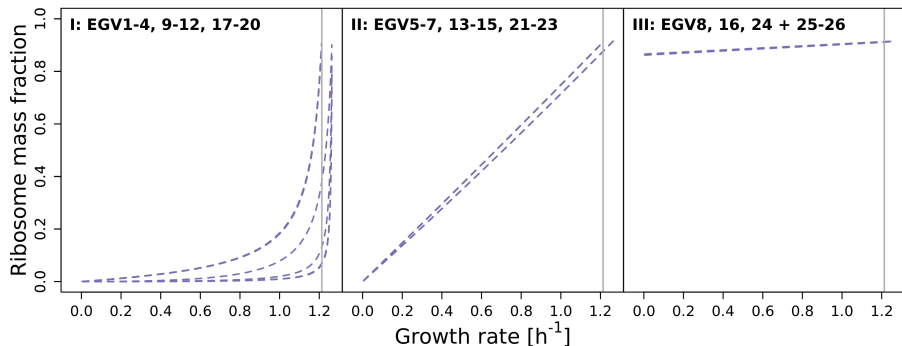
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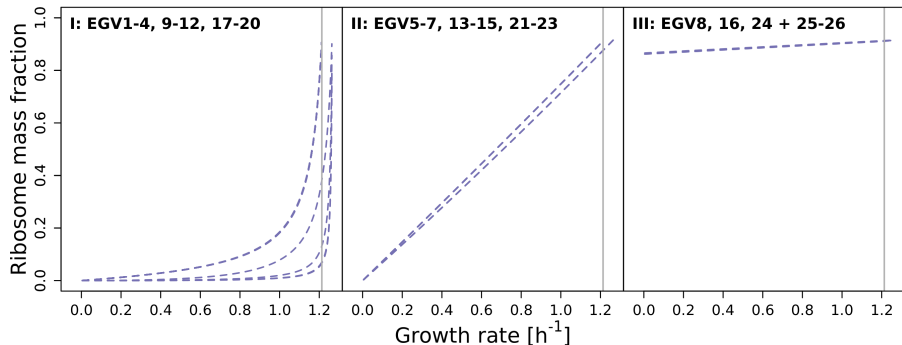
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Bio relevance: ribosome mass fraction



Bio relevance: ribosome mass fraction



M. Scott, C.W. Gunderson, E.M. Mateescu, Z. Zhang, T. Hwa
Interdependence of cell growth and gene expression: origins and consequences
Science 330, 2010

Scott M, Klumpp S, Mateescu EM, Hwa T
Emergence of robust growth laws from optimal regulation of ribosome synthesis
Mol Syst Biol 10:747, 2014

Bio relevance: “optimal” ribosome composition

S. Kostinski, S. Reuveni

Ribosome composition maximizes cellular growth rates in E. coli

Phys Rev Lett 125:028103, 2020

D. Széliová, S. Müller, J. Zanghellini

Costs of ribosomal RNA stabilization affect ribosome composition at maximum growth rate

Communications Biology 7:196, 2024

Economic Principles in Cell Biology

- Online seminar (monthly)
- Summer school
- A collaborative open-access textbook

<https://principlescellphysiology.org>

Mathematics of Reaction Networks (MoRN)

- Online seminar (every two weeks)

<https://researchseminars.org/seminar/MoRN>

Thank you for your attention!