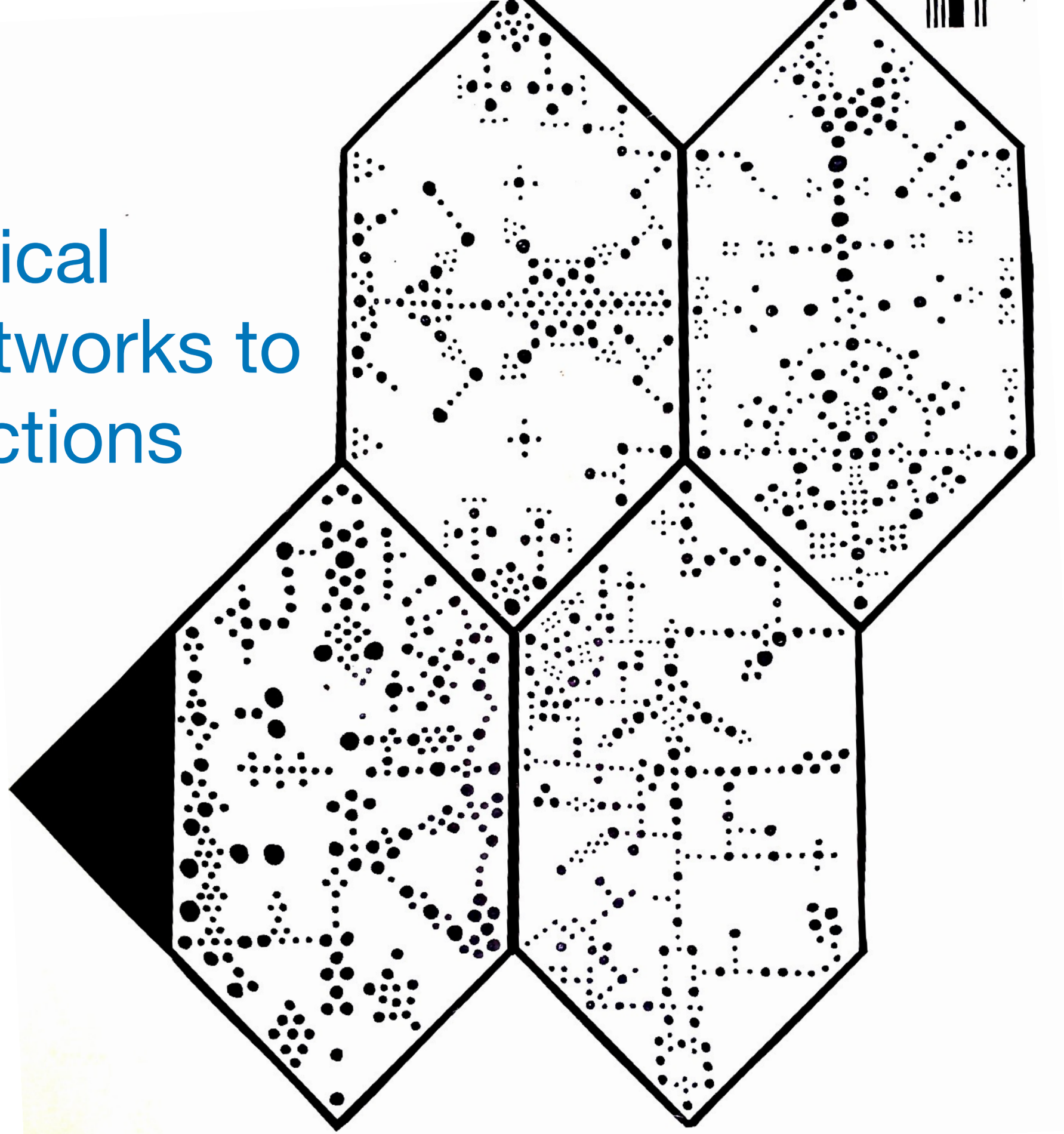
From chemical reaction networks to cellular functions

Sara Dal Cengio



Thermodynamic feasibility

- A closed system eventually relaxes to equilibrium with $(J_\rho\ , A_\rho) = 0 \quad \forall\, \rho$
- A nonzero A_ρ generates nonzero J_ρ of the same sign, s.t. $\dot{s}(t) = \sum J_\rho A_\rho \geq 0$

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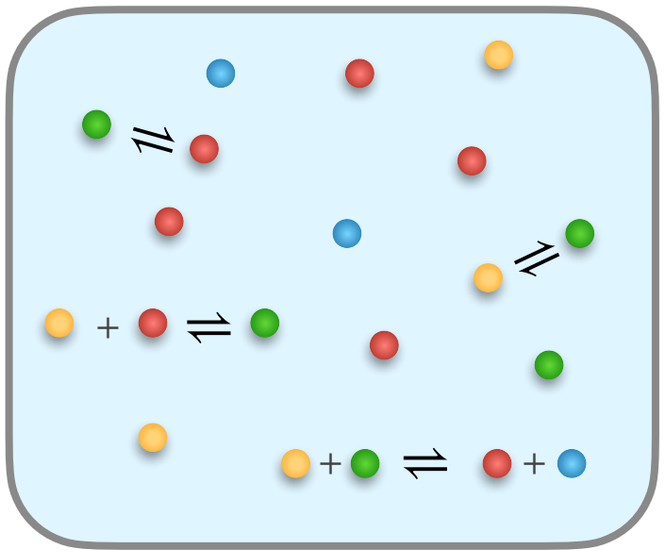
In the absence of chemostatting, affinities are conservative

$$\boldsymbol{A} = \sum_\gamma A_\gamma^c \boldsymbol{c}^\gamma = -\,\mathbb{S}^\top \boldsymbol{V}$$

$\boldsymbol{c}^\alpha \cdot \boldsymbol{A} = 0\ \forall \alpha$ for all internal cycles



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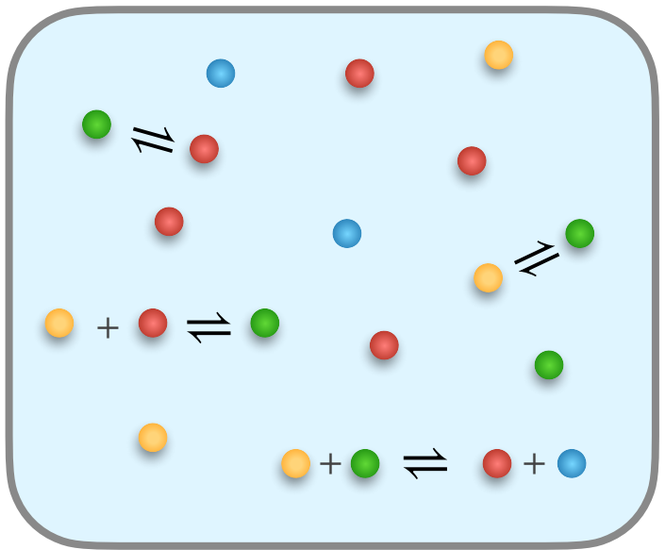
Using MAK:

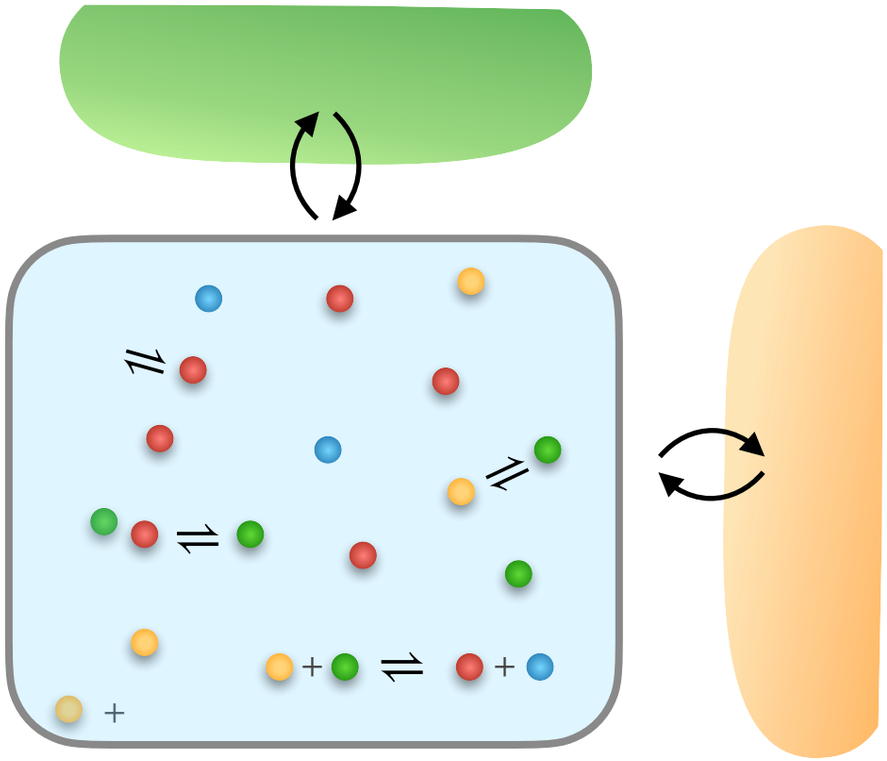
$$A_\rho(\boldsymbol{x}) = \log\left(\frac{j_\rho^+(\boldsymbol{x})}{j_\rho^-(\boldsymbol{x})}\right) = \log\left(\frac{k_\rho^+}{k_\rho^-}\boldsymbol{x}^{-\mathbb{S}_\rho}\right)$$

$$\forall \alpha \quad \prod_\rho \left(\frac{k_\rho^+}{k_\rho^-}\right)^{c_\rho^\alpha} = 1$$



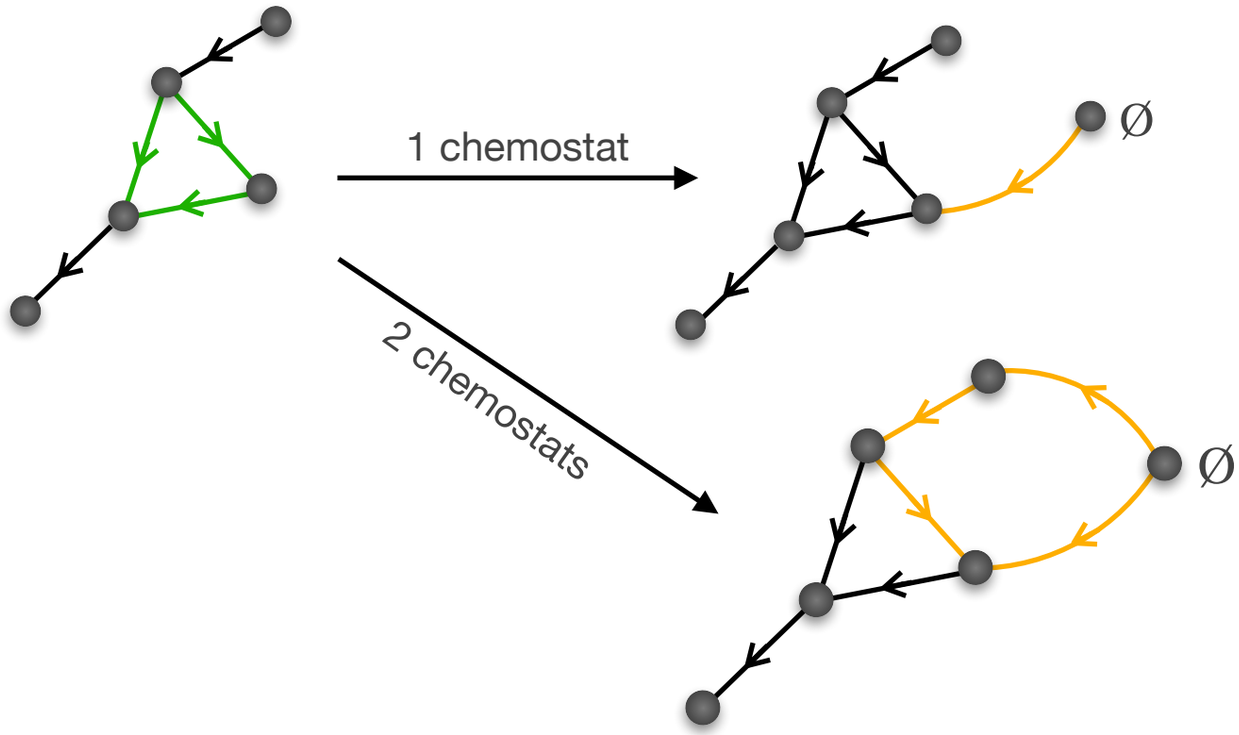
Kolmogorov condition for the rates

Thermodynamic feasibility



Open system

Adding chemostatting reactions $\emptyset \rightleftharpoons Y_i$
(may) introduce new *emergent* cycles



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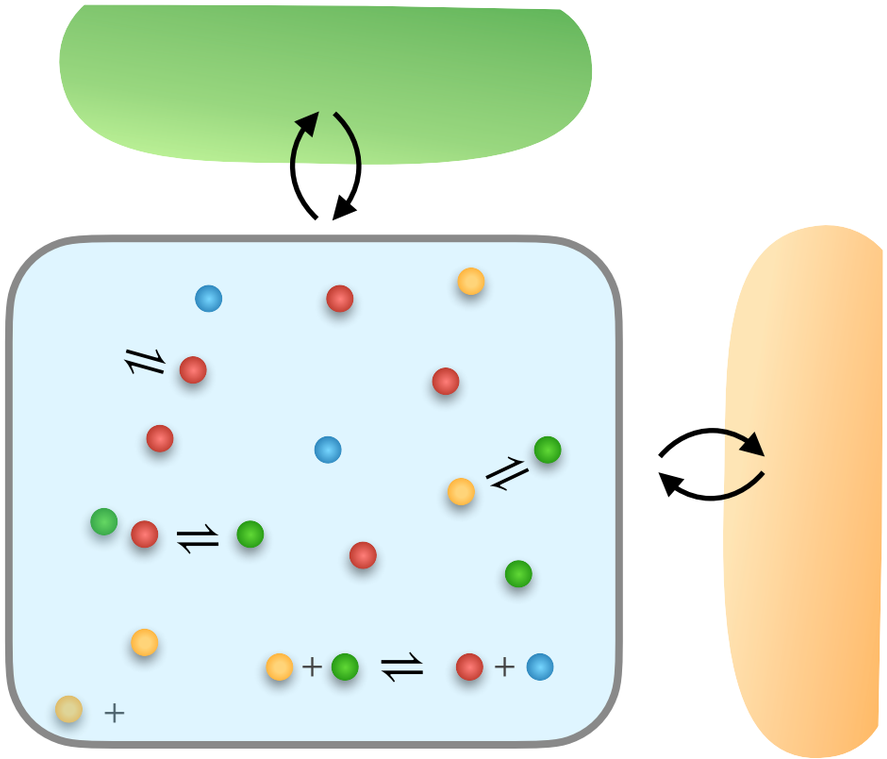

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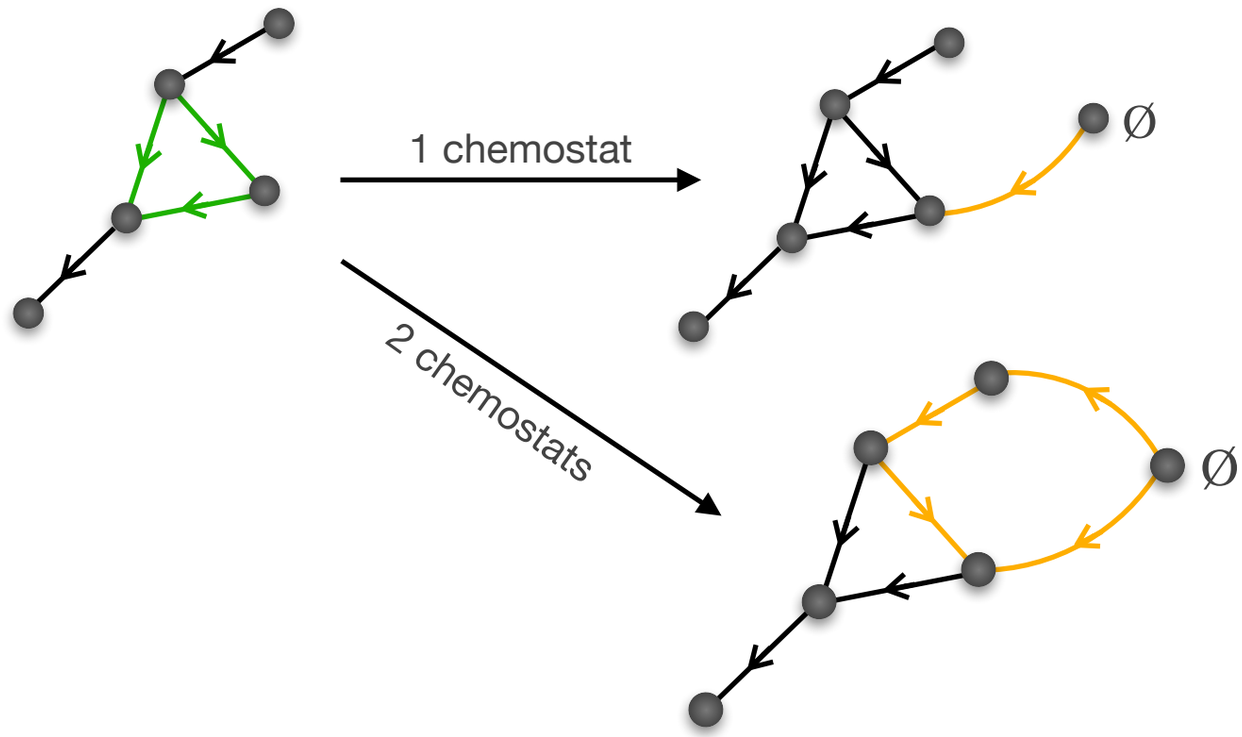


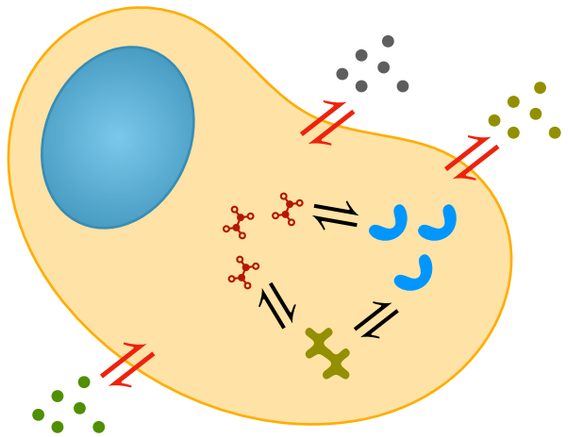
Even if the system is open, internal constraints are still there

$\boldsymbol{c}^{\alpha} \cdot \boldsymbol{A} = 0 \; \forall \alpha$ for all internal cycles

Metabolic reconstruction

Genome-based metabolic networks: stoichiometry is known

Experimentally one has access to some external exchange currents



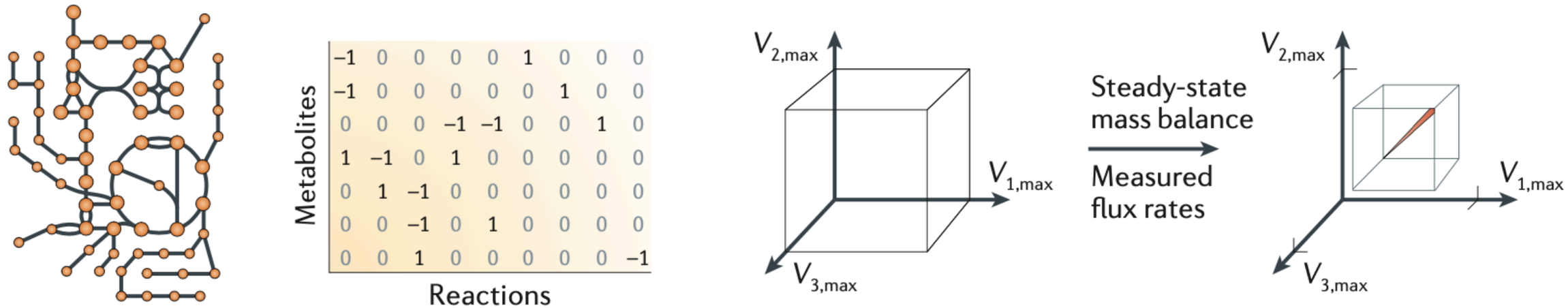
$\boldsymbol{J}^{\text{ext}}$: known exchange currents

$\boldsymbol{J}$: Unknown internal metabolic currents

Q: How to reconstruct the internal currents $\boldsymbol{J}$ in the cell?

$$\mathbb{S}_X \boldsymbol{J} = -\mathbb{S}_Y \boldsymbol{J}^{\text{ext}}$$ (Rate equation at stationarity)

Constrained-based models



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- Flux Balance Analysis (FBA): optimizing some cellular objective function under the hypothesis of stationarity
- Unbiased sampling via MCMC of the solution space + currents bounds

Imposing thermodynamic feasibility is hard

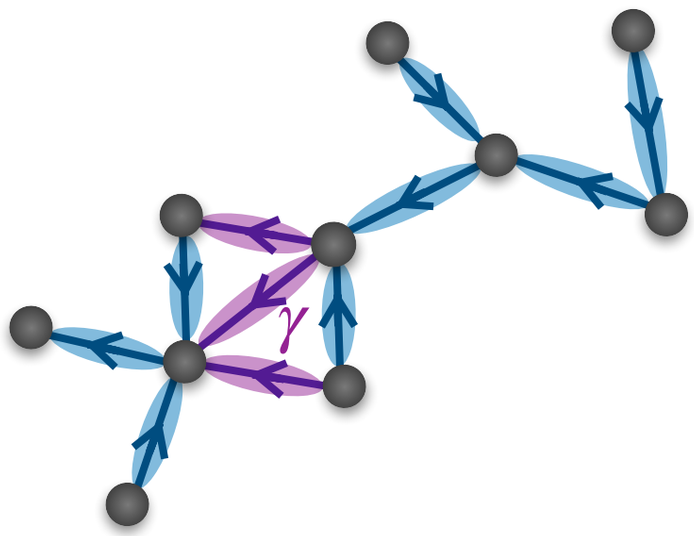
A geometric approach to reconstruction

Recalling the current decomposition: $\boldsymbol{J} = \sum_{\gamma} J^e_\gamma \boldsymbol{e}^\gamma + \sum_{\alpha} J^c_\alpha \boldsymbol{c}^\alpha$

With $J^e_\gamma \equiv \boldsymbol{c}^\gamma \cdot \boldsymbol{J}$

and $J^c_\alpha \equiv \boldsymbol{e}^\alpha \cdot \boldsymbol{J}$

Notion of cocycle: $\forall \gamma\,,\, \boldsymbol{c}^\gamma = -\,\mathbb{S}_X^{\mathsf{T}}\, \boldsymbol{v}^\gamma$



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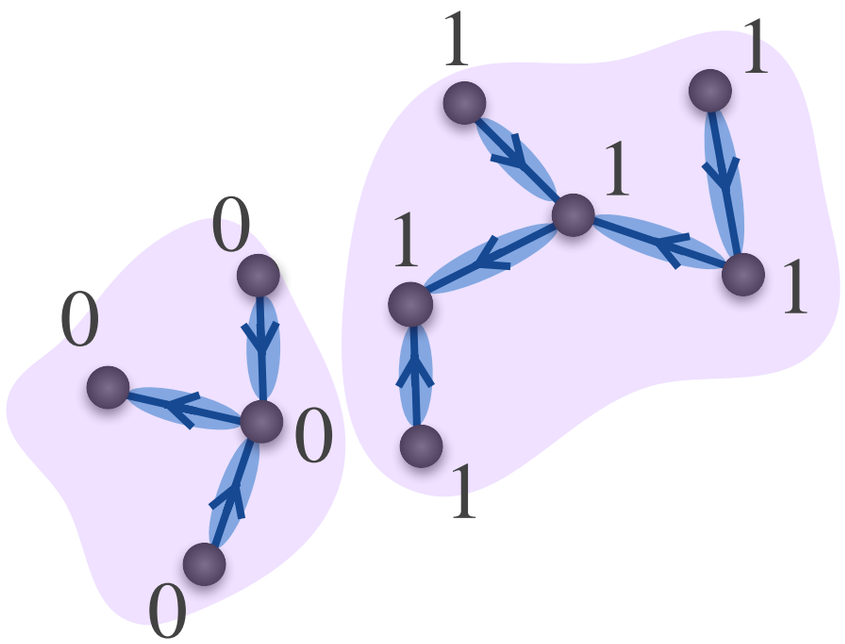

- Emergent conservation laws whenever a cochord γ is removed
- Potential landscape on the hypergraph
- They constitute the columns of the matrix of row-reduction $\mathbb{G}_{M}$

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$$\boxed{\boldsymbol{J}^e_\gamma = \left(\mathbb{G}_M \mathbb{S}_Y \boldsymbol{J}^{\text{ext}}\right)_\gamma}$$

Set of $M =$ rank $\mathbb{S}_X$ linear constraints between (cocycle) internal currents and external ones

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The cocycle currents are not constrained by thermodynamic feasibility

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$$\begin{pmatrix} \boldsymbol{J}^e \\ \boldsymbol{J}^c \end{pmatrix} = \begin{pmatrix} \mathbb{G}_M \mathbb{S}_Y \boldsymbol{J}^{\text{ext}} \\ \text{function}(\boldsymbol{J}^{\text{ext}}) \end{pmatrix}$$

R-M Cycle currents are the one affected by thermodynamic feasibility

A geometric approach to reconstruction

In full generality: $J_\rho = \underbrace{\Lambda(A_\rho)}_{>0} A_\rho$ and $J_\rho = 0$ iff $A_\rho = 0$

Thermodynamic feasibility:

$$\underbrace{\left(-\mathbb{T}^\top \quad \mathbf{1}_{R-M}\right)}\boldsymbol{A} = \left(-\mathbb{T}^\top \quad \mathbf{1}_{R-M}\right)\left(\Lambda[\boldsymbol{A}]\right)^{-1}\boldsymbol{J} = 0$$

With Λ positive real matrix

$\Lambda_{\rho\rho} \equiv \Lambda(A_\rho)$

Each line of this matrix is a cycle, i.e. they form a basis for the Nullspace of $\mathbb{S}_X$

+ Algebra of oblique projectors

A geometric approach to reconstruction

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$$\boldsymbol{J}^c = \mathbb{L}_P^{-1}\mathbb{T}^\top\Lambda_M^{-1}\mathbb{G}_M\mathbb{S}_Y\boldsymbol{J}^{\text{ext}}$$

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- For metabolic reconstruction, the Λ_ρ's are the free parameters which parametrize the space of feasible solutions

  # Λ_ρ = # reactions which belongs to internal chemical cycles (no bridges)

Outlook

Working with Delphine Ropers (INRIA) for application to the metabolism of *Escherichia Coli*

79 internal currents $\boldsymbol{J}$, 15 external (fixed) currents $\boldsymbol{J}^{\mathrm{ext}}$, 12 internal cycles $\boldsymbol{c}^{\alpha}$

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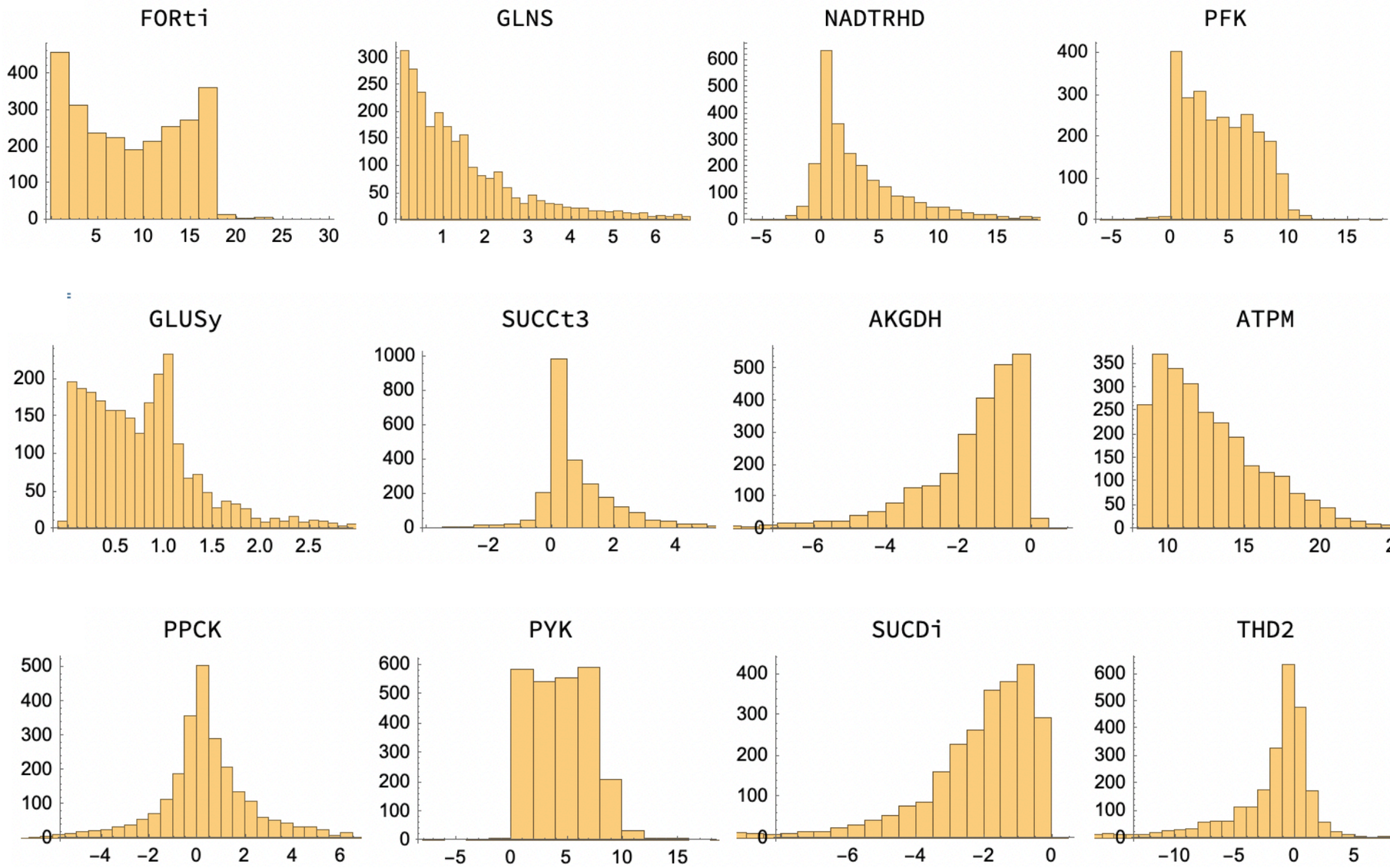

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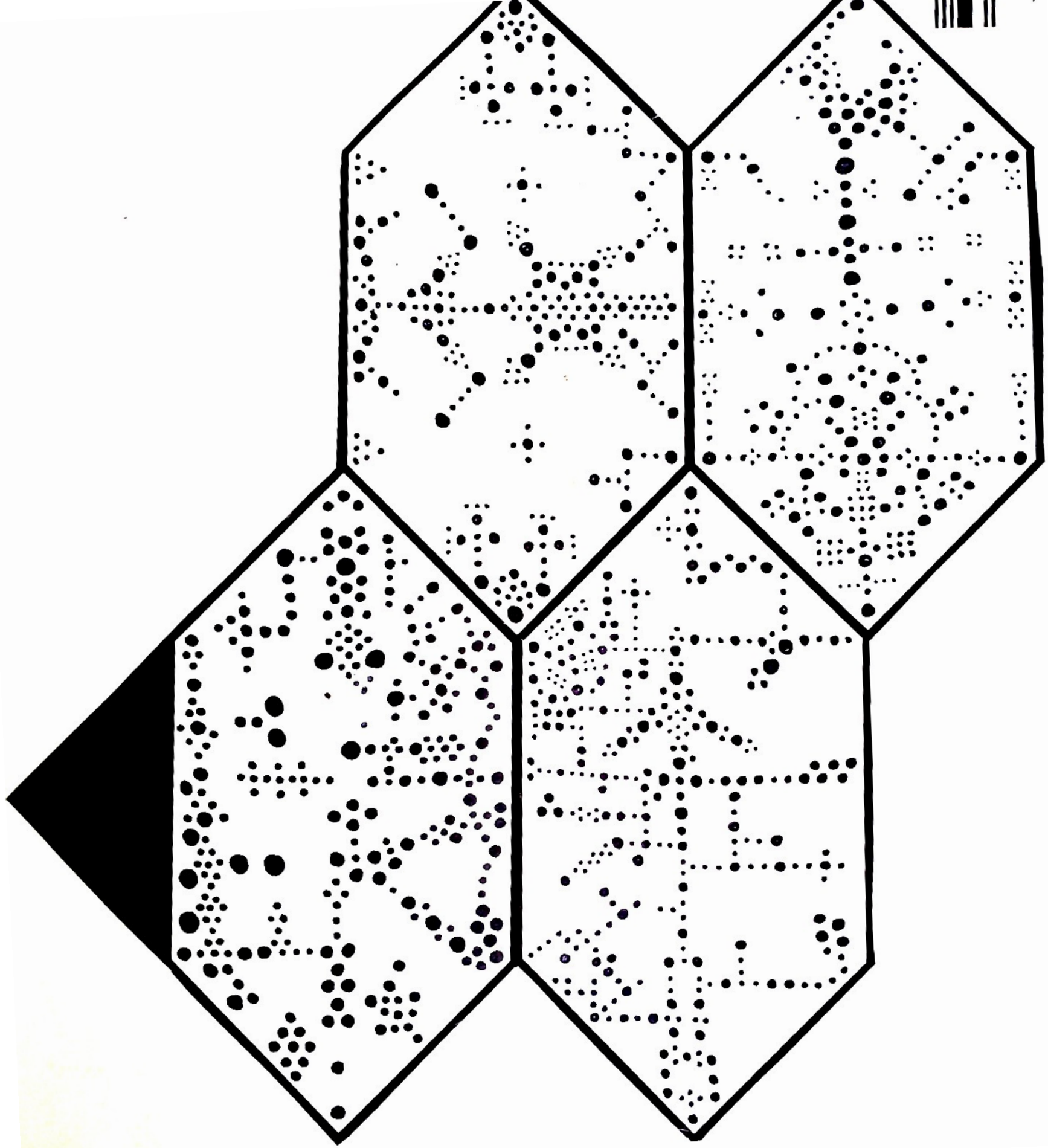
- A criterion to check thermodynamical feasibility given a set of currents $\boldsymbol{J}$. Applications?
  - How to integrate bounds on internal currents systematically in our approach?
    - How do these bounds relate to thermodynamic feasibility?
    - Comparison with other algorithms like cycle-free fluxes?

Thank you!



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