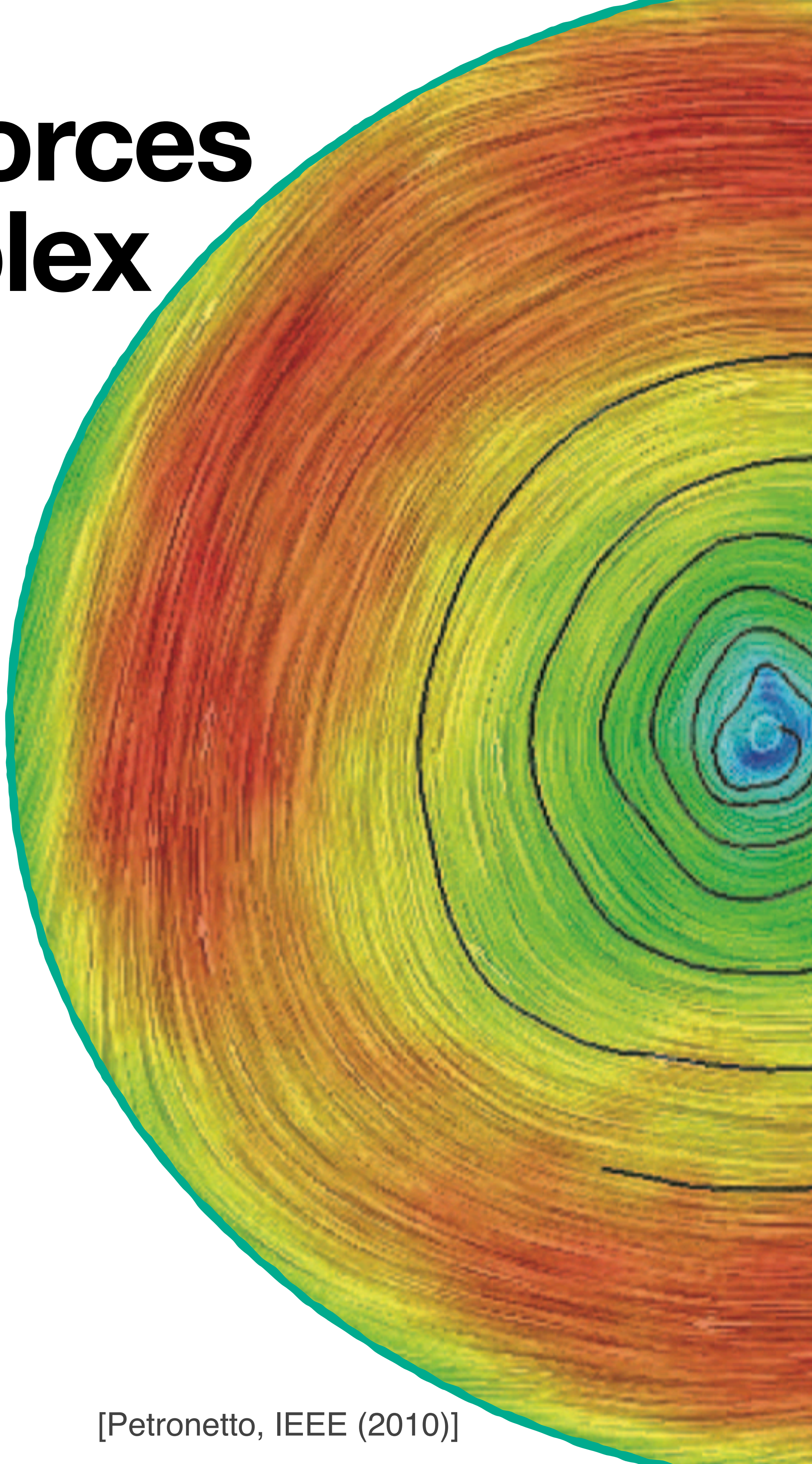
On the geometry of forces and currents in complex reaction networks


[Petronetto, IEEE (2010)]

Sara Dal Cengio
Vivien Lecomte
Matteo Polettini

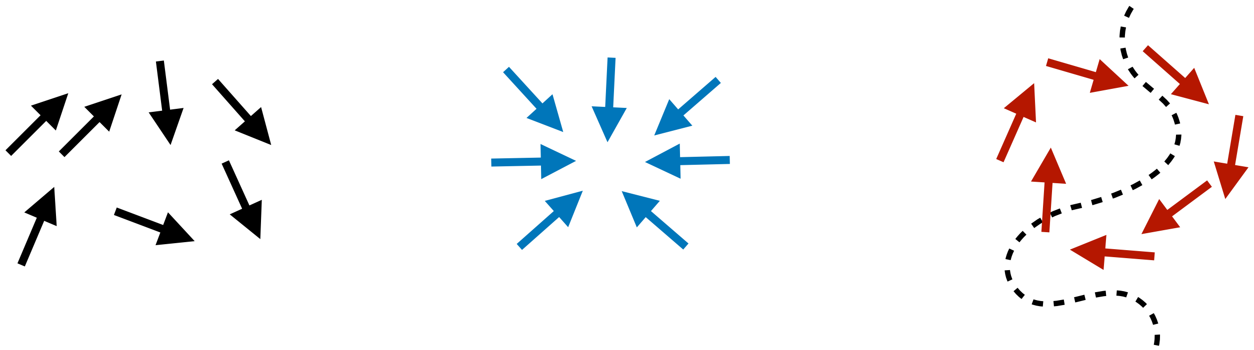
Physics of Life Summer School 2022
26/04/22

Identifying nonequilibrium forces

Identifying nonequilibrium forces

Helmholtz decomposition ($\mathbb{R}^2$, $\mathbb{R}^3$)

$$\mathbf{f} \quad = \quad -\nabla V \quad + \quad \nabla \times \mathbf{A}$$



Conservative

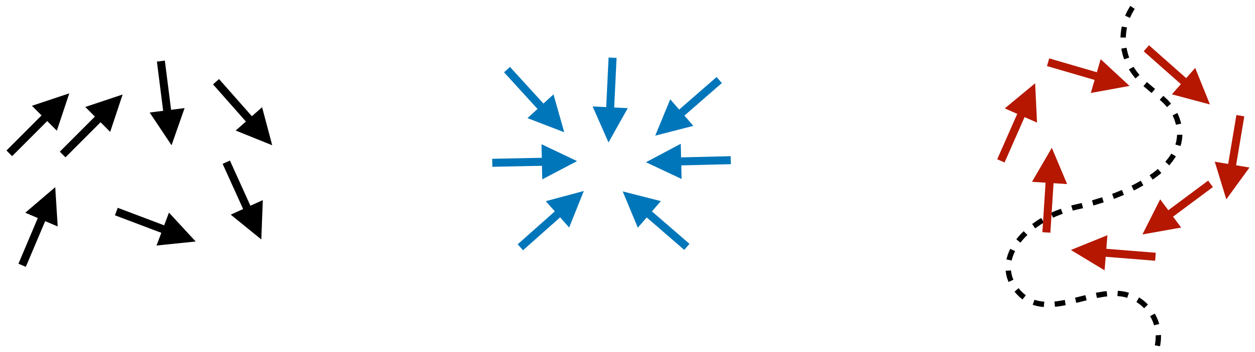
Non-conservative

In physics: $\mathbf{f}_{\mathrm{nc}} = 0$ $\Longleftrightarrow$ Equilibrium

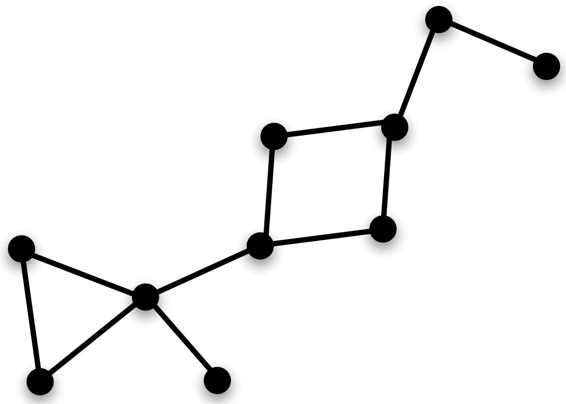
Identifying nonequilibrium forces

Helmholtz decomposition ($\mathbb{R}^2$, $\mathbb{R}^3$)

$$\mathbf{f} \quad = \quad -\nabla V \quad + \quad \nabla \times \mathbf{A}$$



Conservative Non-conservative

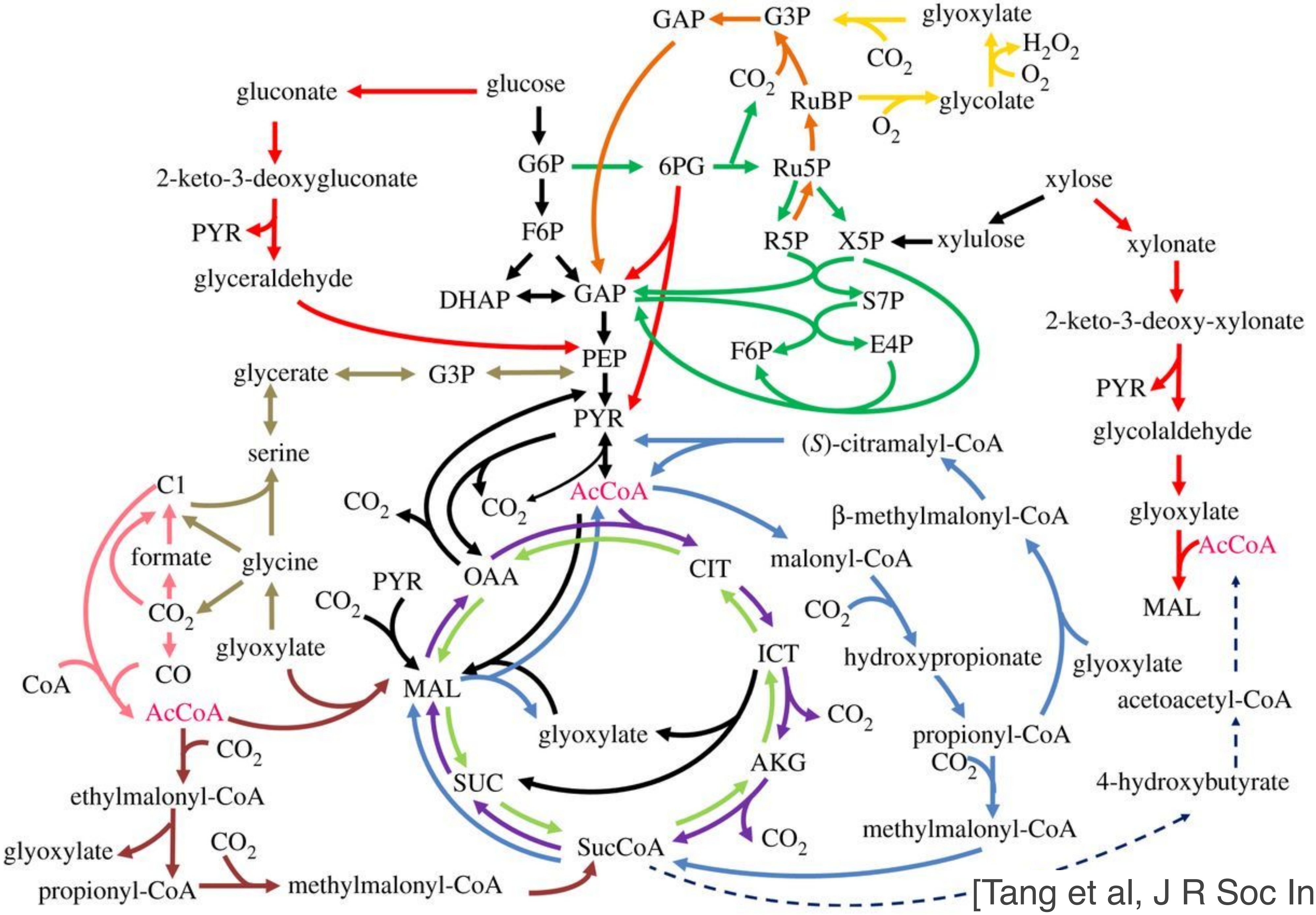


What if the space of configurations is a network?

What role for the network topology?

Chemical reaction networks (CRNs)

Nonequilibrium and topology ⟺ Functional to biological tasks



[Tang et al, J R Soc Interface (2012)]

Chemical reaction networks (CRNs)

How to identify nonequilibrium (chemical) forces in complex topology?

[Schnakenberg, Rev. Mod. Phys. (1976)]

Identification of nonequilibrium forces based on **graph theory**

[Polettini et al, J. Chem. Phys. (2014)]

Thermodynamics of CRNs based on **linear algebra**

Chemical reaction networks (CRNs)

How to identify nonequilibrium (chemical) forces in complex topology?

[Schnakenberg, Rev. Mod. Phys. (1976)]

Identification of nonequilibrium forces based on **graph theory**

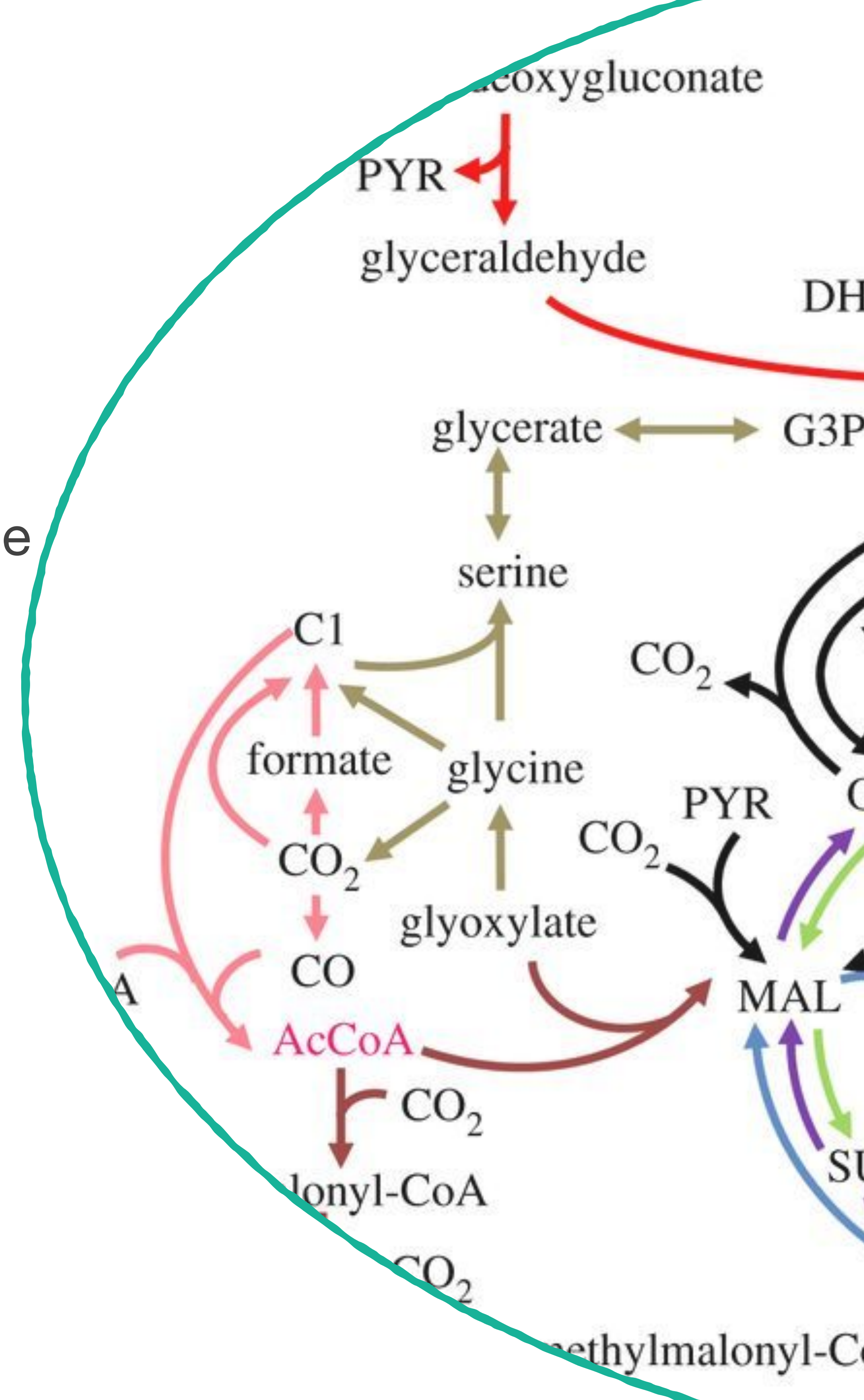
[Polettini et al, J. Chem. Phys. (2014)]

Thermodynamics of CRNs based on **linear algebra**

…Chemistry as a playground for stat. mech.?

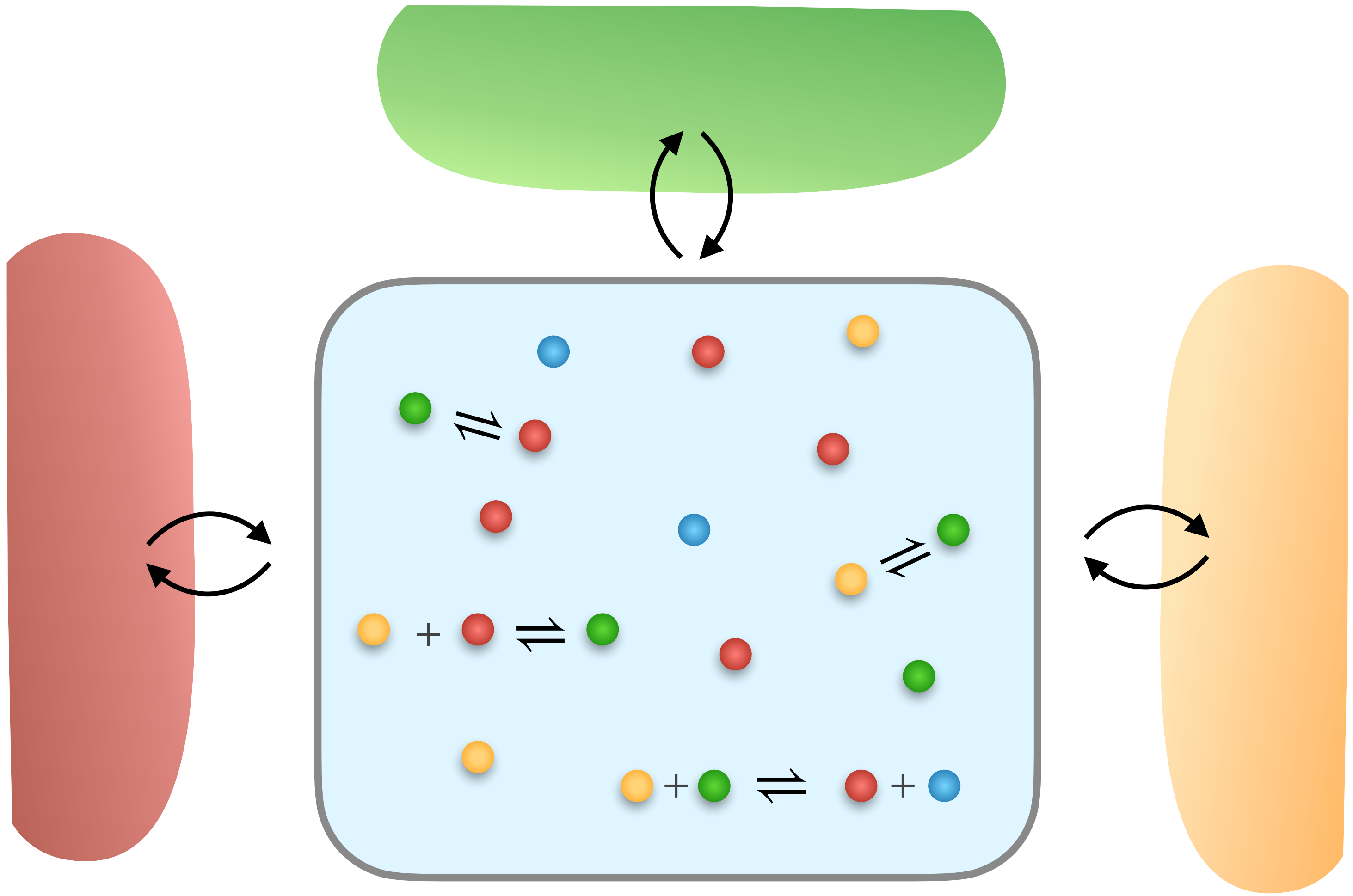
Outline

1. Equations first!
2. Graph theory and algebra: an example
3. Towards interacting CRNs
4. An application: linear response(s)
5. Perspectives and conclusions



General setting

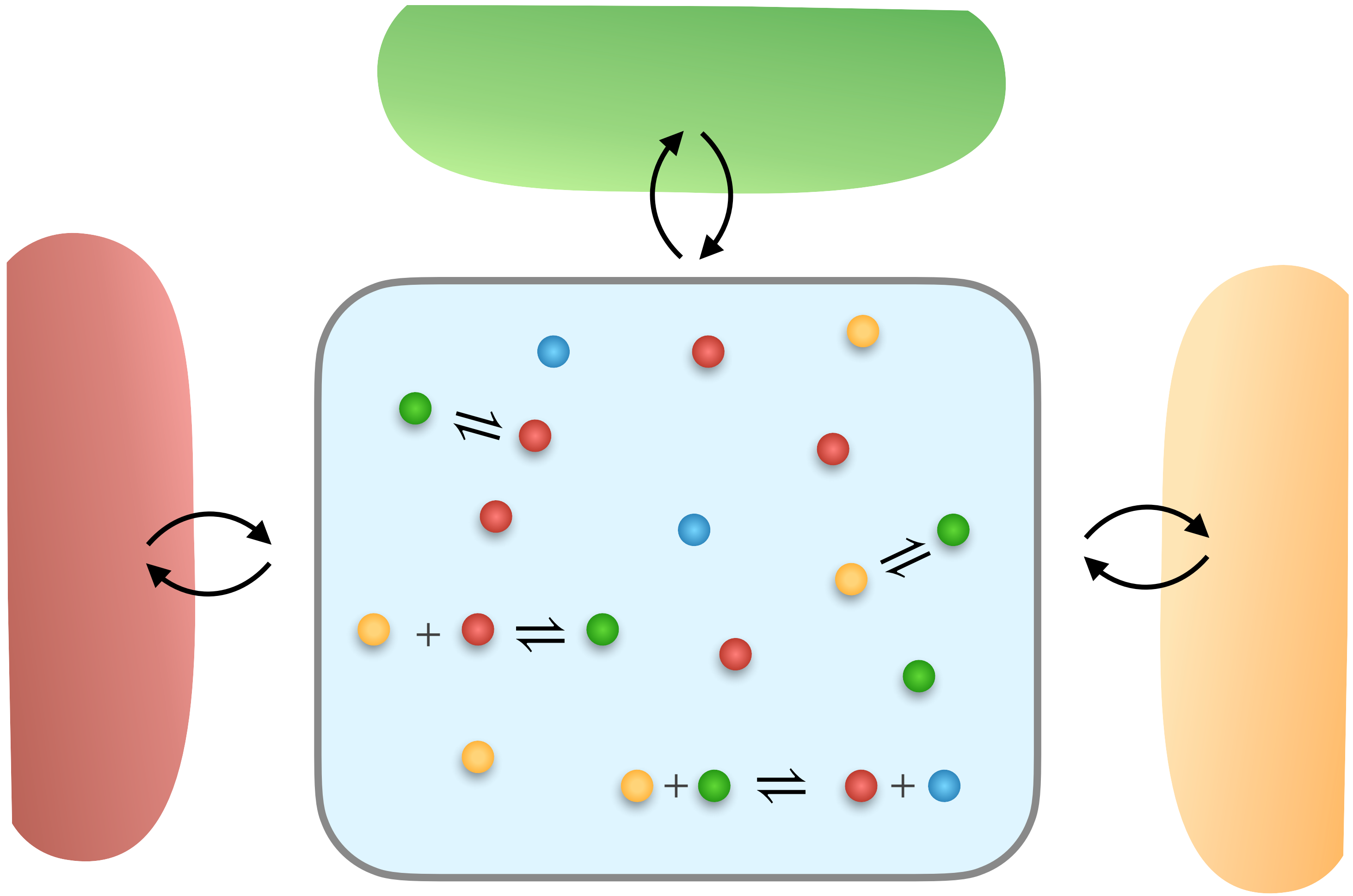
Open system, well-stirred, diluted with N species and R reactions



Ex. $X_A + X_B \rightleftharpoons X_C$

General setting

Open system, well-stirred, diluted with N species and R reactions



$$\nu^{+\rho} \cdot X \underset{k_\rho^-}{\overset{k_\rho^+}{\rightleftharpoons}} \nu^{-\rho} \cdot X$$

X : vector of the species

$\nu^{\pm\rho}$: stoichiometric coefficients

$k_\rho^{\pm}$: reaction rates

$$\mathbb{S}_\rho = \nu^{+\rho} - \nu^{-\rho}$$

$N \times R$ stoichiometric matrix

Ex. $X_A + X_B \rightleftharpoons X_C$

$$1 \leq \rho \leq R$$

Rate equation

For large systems: evolution at the average level $x_i \equiv \lim_{N,V\to\infty} \frac{N_i}{V}$

$$\partial_t x = \underbrace{\mathbb{S}\,J(x)}_{}$$

Deterministic rate equation

Linear combination of the microscopic currents $J_\rho(x)\ \forall \rho$

Rate equation

For large systems: evolution at the average level $x_i \equiv \lim_{N,V\to\infty} \frac{N_i}{V}$

$$\partial_t x = \underbrace{\mathbb{S}\, J(x)}$$

Deterministic rate equation

Linear combination of the microscopic currents $J_\rho(x)\ \forall \rho$

The stoichiometric matrix as a "<u>discrete divergence</u>"

→ It encodes the intrinsic topology of the network

Rate equation

For large systems: evolution at the average level $x_i \equiv \lim_{N,V \to \infty} \frac{N_i}{V}$

$$\partial_t x = \mathbb{S}\, J(x)$$

If $\ell \in$ Ker $\mathbb{S}^\top$ i.e. is a left-null eigenvector

$\Longrightarrow$ $\ell \cdot x =$ const Conservation law

Rate equation

For large systems: evolution at the average level $x_i \equiv \lim_{N,V\to\infty} \frac{N_i}{V}$

$$\boxed{\partial_t x = \mathbb{S}\, J(x)}$$

If $\ell \in \mathrm{Ker}\, \mathbb{S}^\top$ i.e. is a left-null eigenvector

$\Longrightarrow$ $\ell \cdot x = \mathrm{const}$ Conservation law

Counting degrees of freedom: $N = \underbrace{\mathrm{Rank}\, \mathbb{S}}_{} + \dim\left(\mathrm{Ker}\, \mathbb{S}^\top\right)$

independent degrees of freedom = M

Current-force relations

What are the microscopic reaction currents ?

$$J_\rho = \Lambda_\rho(x)\left(1 - e^{-A_\rho}\right)$$

Chemical affinity of reaction ρ

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

Current-force relations

$$\partial_t x = \mathbb{S}\, J(x)$$

What are the microscopic reaction currents ?

$$J_\rho = \Lambda_\rho(x)\left(1 - e^{-A_\rho}\right)$$

Chemical affinity of reaction ρ

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

It plays the role of a force!

Equilibrium steady-state: $A_\rho(x^{eq}) = 0 \quad \Rightarrow \quad J_\rho(x^{eq}) = 0$

Current-force relations

$$\partial_t x = \mathbb{S}\, J(x)$$

What are the microscopic reaction currents ?

$$J_\rho = \Lambda_\rho(x)\left(1 - e^{-A_\rho}\right)$$

Chemical affinity of reaction ρ

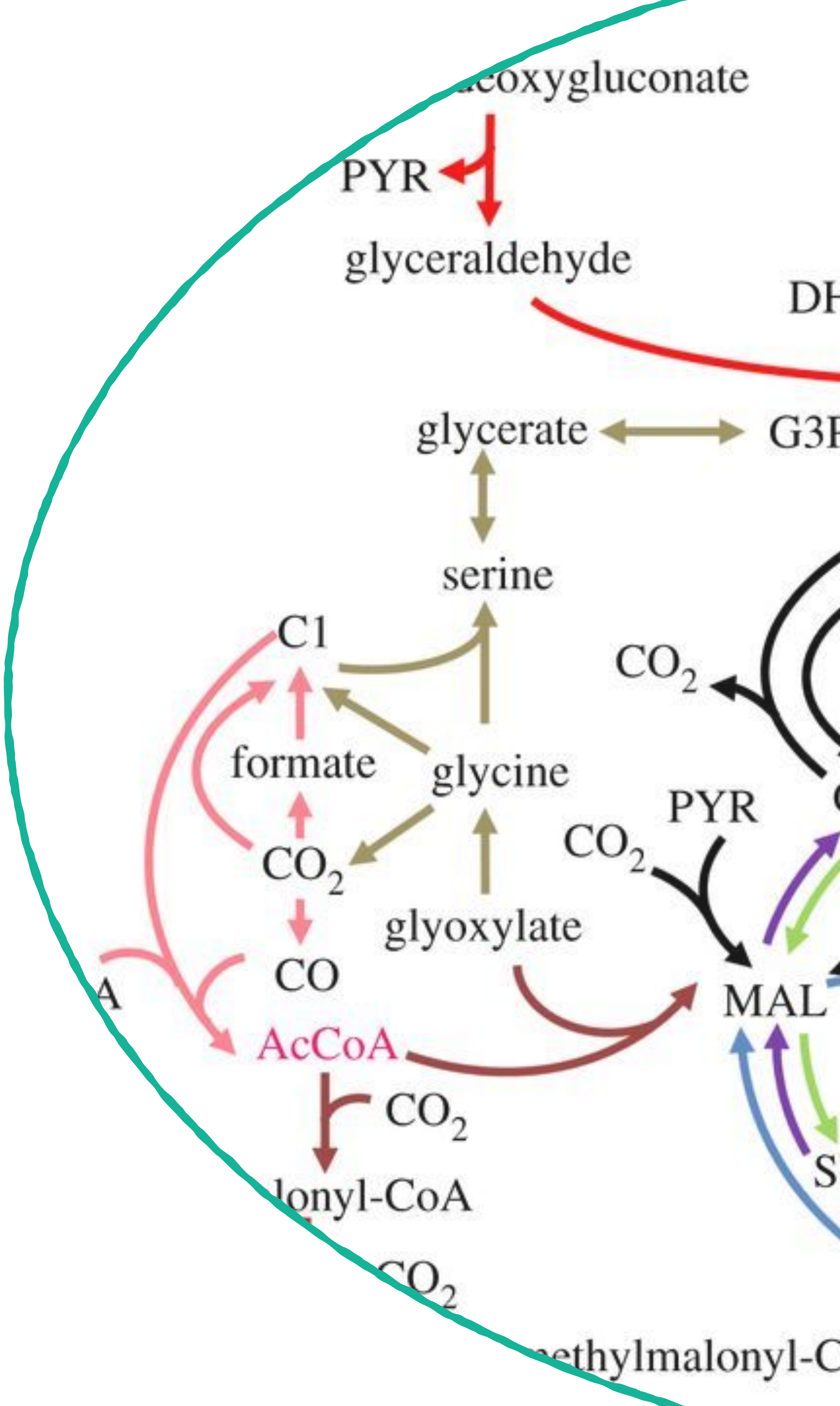
$$A_\rho = \log\left(\frac{k_\rho^+ x^{\nu^{+\rho}}}{k_\rho^- x^{\nu^{-\rho}}}\right) = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) + \left(\log x\right)^{-\mathbb{S}_\rho}$$

It plays the role of a force!

…How to decompose it?

Outline

2. Graph theory and algebra: an example



Noninteracting CRNs

Unimolecular reactions: $X_i \rightleftharpoons X_j$

Ex.
$$X_1 \rightleftharpoons X_2$$
$$X_2 \rightleftharpoons X_3$$
$$X_4 \rightleftharpoons X_2$$
$$X_3 \rightleftharpoons X_4$$
$$X_5 \rightleftharpoons X_4$$

Noninteracting CRNs

Unimolecular reactions: $X_i \rightleftharpoons X_j$

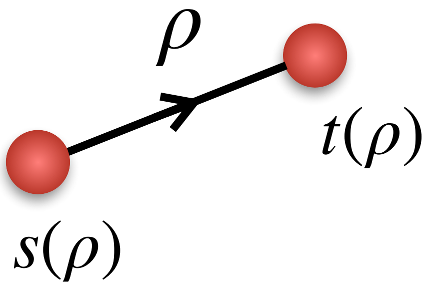
Ex.

$$X_1 \rightleftharpoons X_2$$
$$X_2 \rightleftharpoons X_3$$
$$X_4 \rightleftharpoons X_2$$
$$X_3 \rightleftharpoons X_4$$
$$X_5 \rightleftharpoons X_4$$

Stoichiometric matrix as an incidence matrix:

$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

$\mathbb{S}^{\mathsf{T}}$ as a discrete gradient



Noninteracting CRNs

Unimolecular reactions: $X_i \rightleftharpoons X_j$

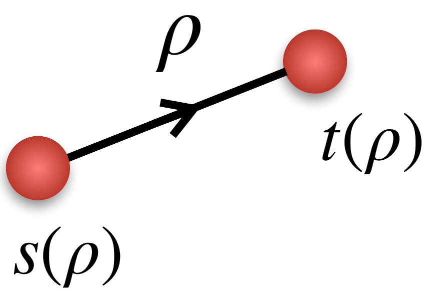
Ex.

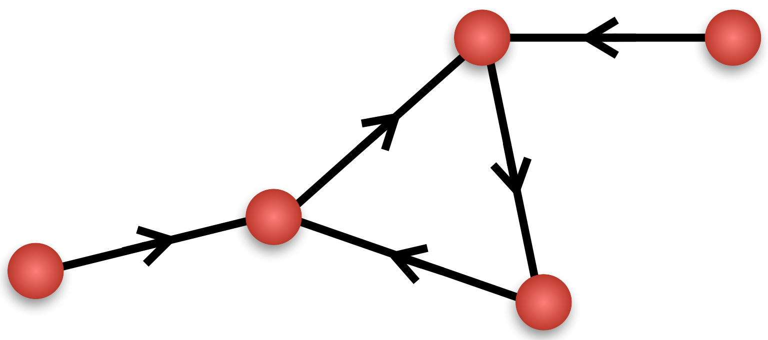
$$X_1 \rightleftharpoons X_2$$
$$X_2 \rightleftharpoons X_3$$
$$X_4 \rightleftharpoons X_2$$
$$X_3 \rightleftharpoons X_4$$
$$X_5 \rightleftharpoons X_4$$

Stoichiometric matrix as an incidence matrix:

$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

$\mathbb{S}^{\mathsf{T}}$ as a discrete gradient





N Nodes $\Longleftrightarrow$ Species

R Edges $\Longleftrightarrow$ Reactions

Noninteracting CRNs

$X_i \rightleftharpoons X_j$

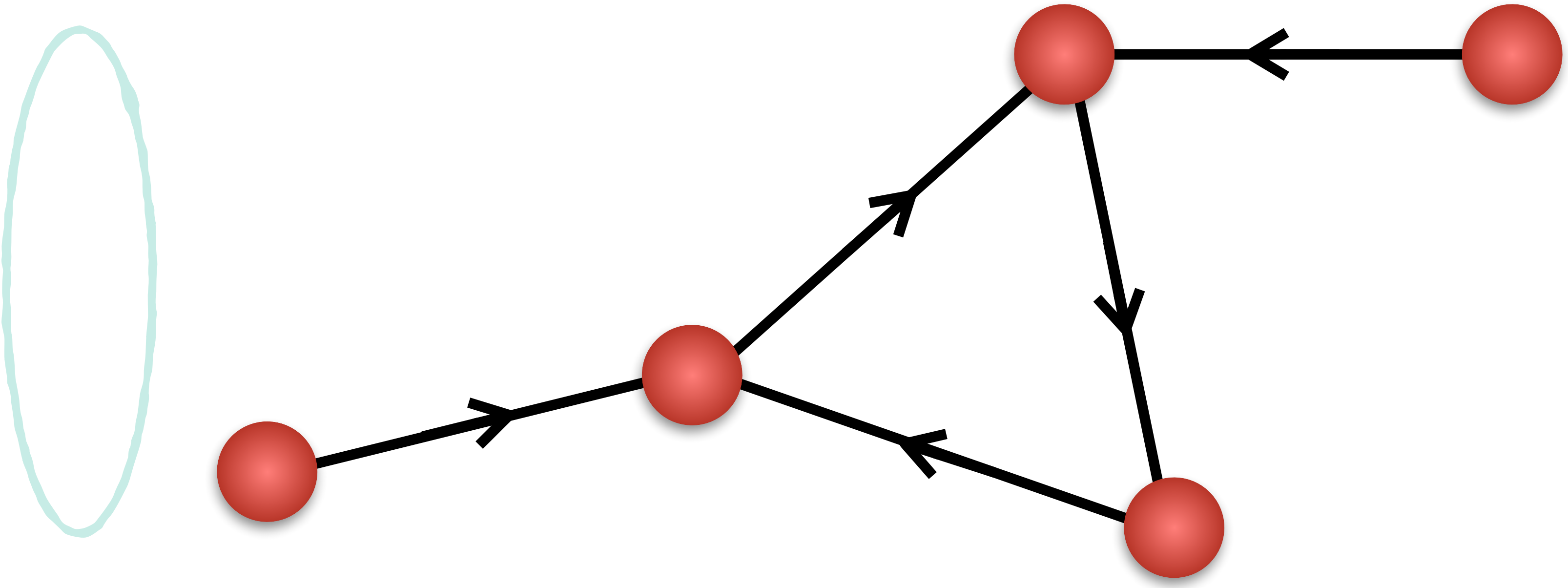
$X_1 \rightleftharpoons X_2$

$X_2 \rightleftharpoons X_3$

$X_4 \rightleftharpoons X_2$

$X_3 \rightleftharpoons X_4$

$X_5 \rightleftharpoons X_4$



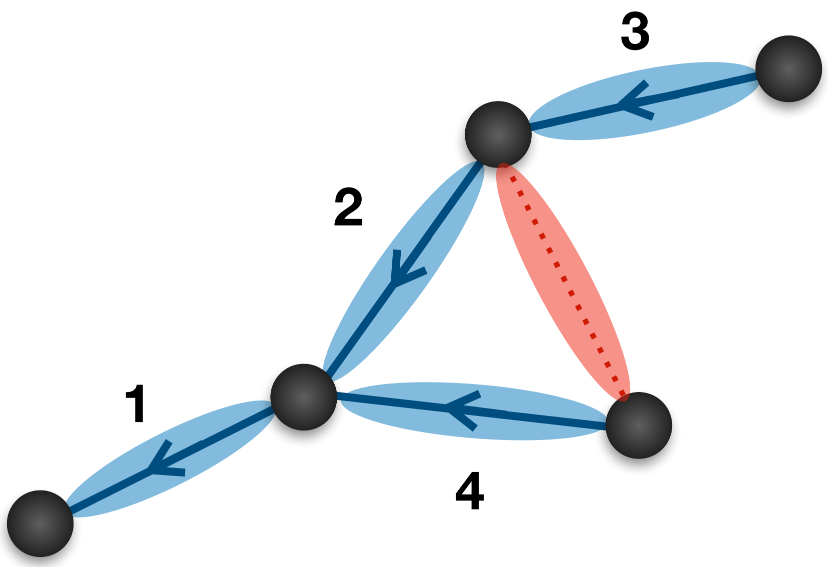
Let’s focus on the graph!

$\Longleftrightarrow$

$\Longleftrightarrow$

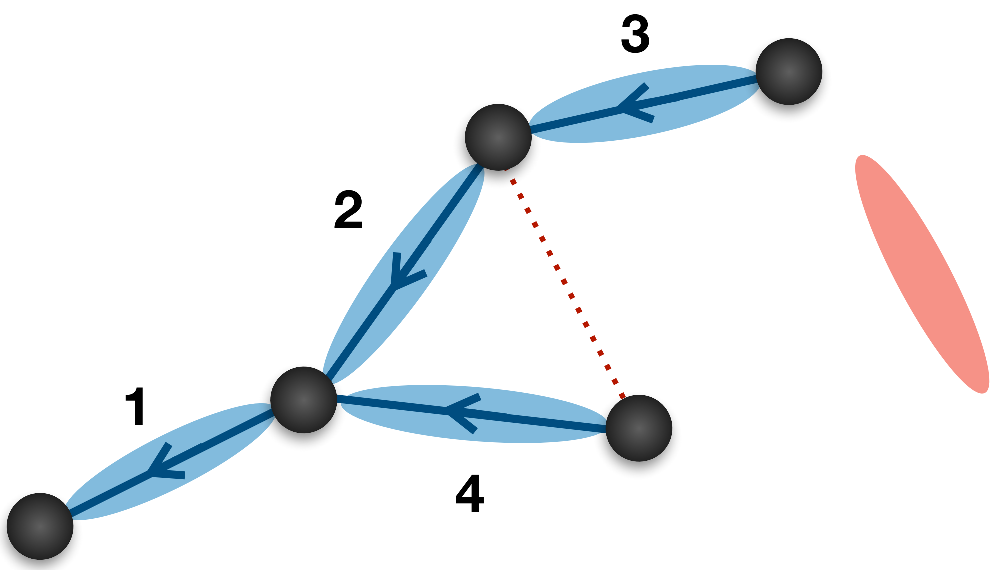
A handful of graph theory

Choosing a spanning tree…



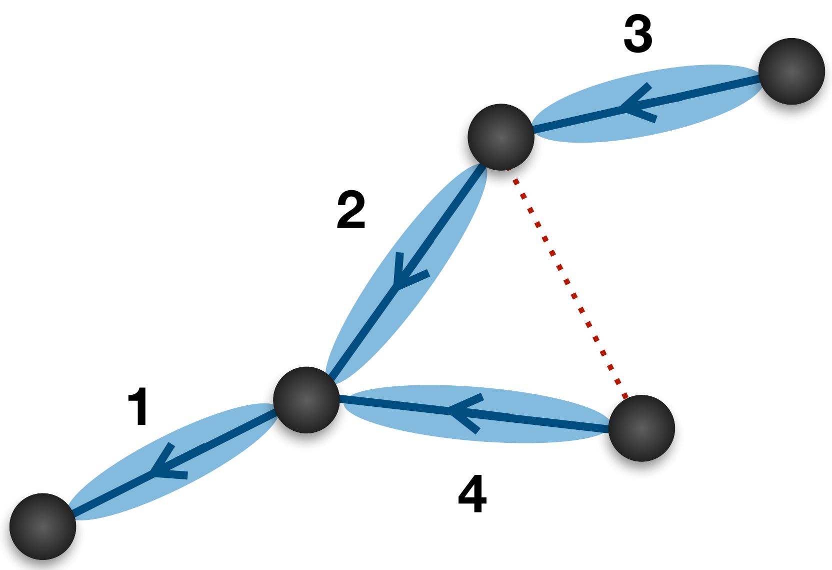
A handful of graph theory

Choosing a spanning tree…



A handful of graph theory

Choosing a spanning tree…



$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

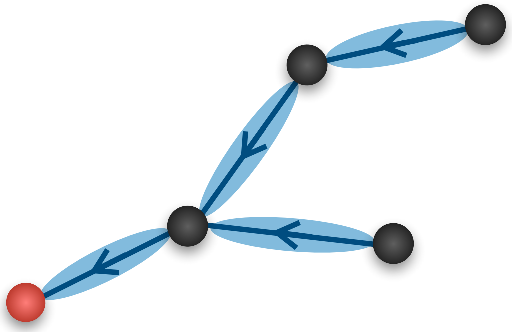
M independent reactions

Depending reactions

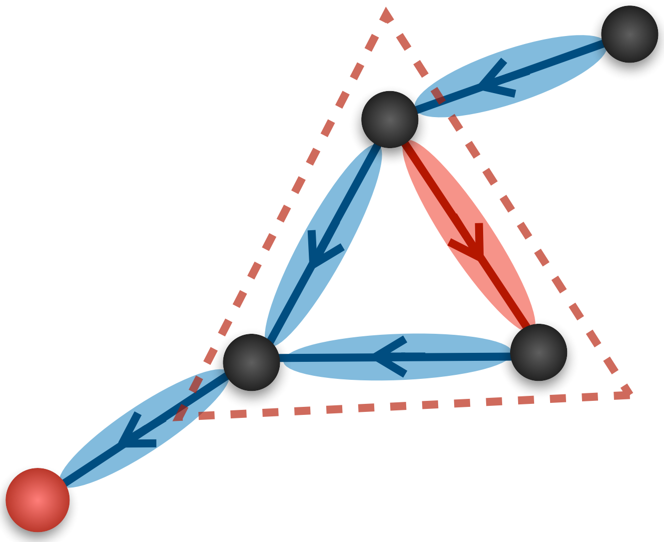
Counting degrees of freedom:

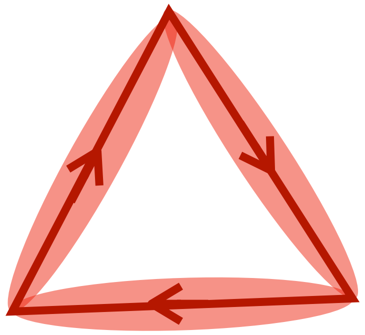
$$R = \underbrace{\mathrm{Rank}\,\mathbb{S}}_{1 \leq \gamma \leq M} + \underbrace{\dim\left(\mathrm{Ker}\,\mathbb{S}\right)}_{M+1 \leq \alpha \leq M + \dim \mathrm{Ker}}$$

A handful of graph theory



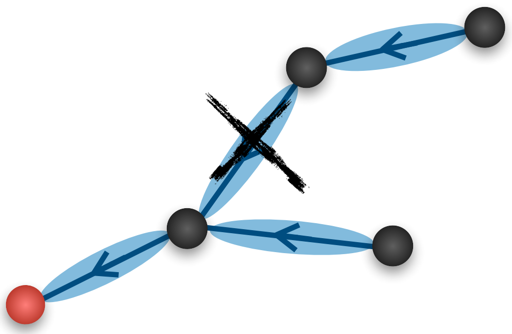
Adding an edge back:



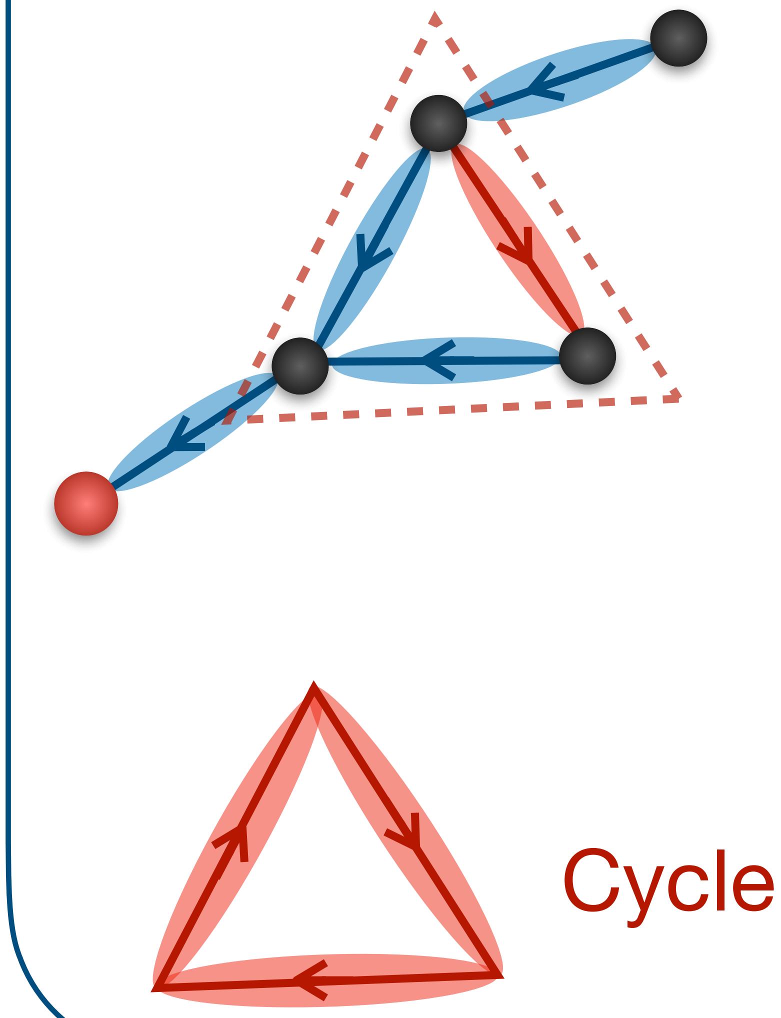


Cycle

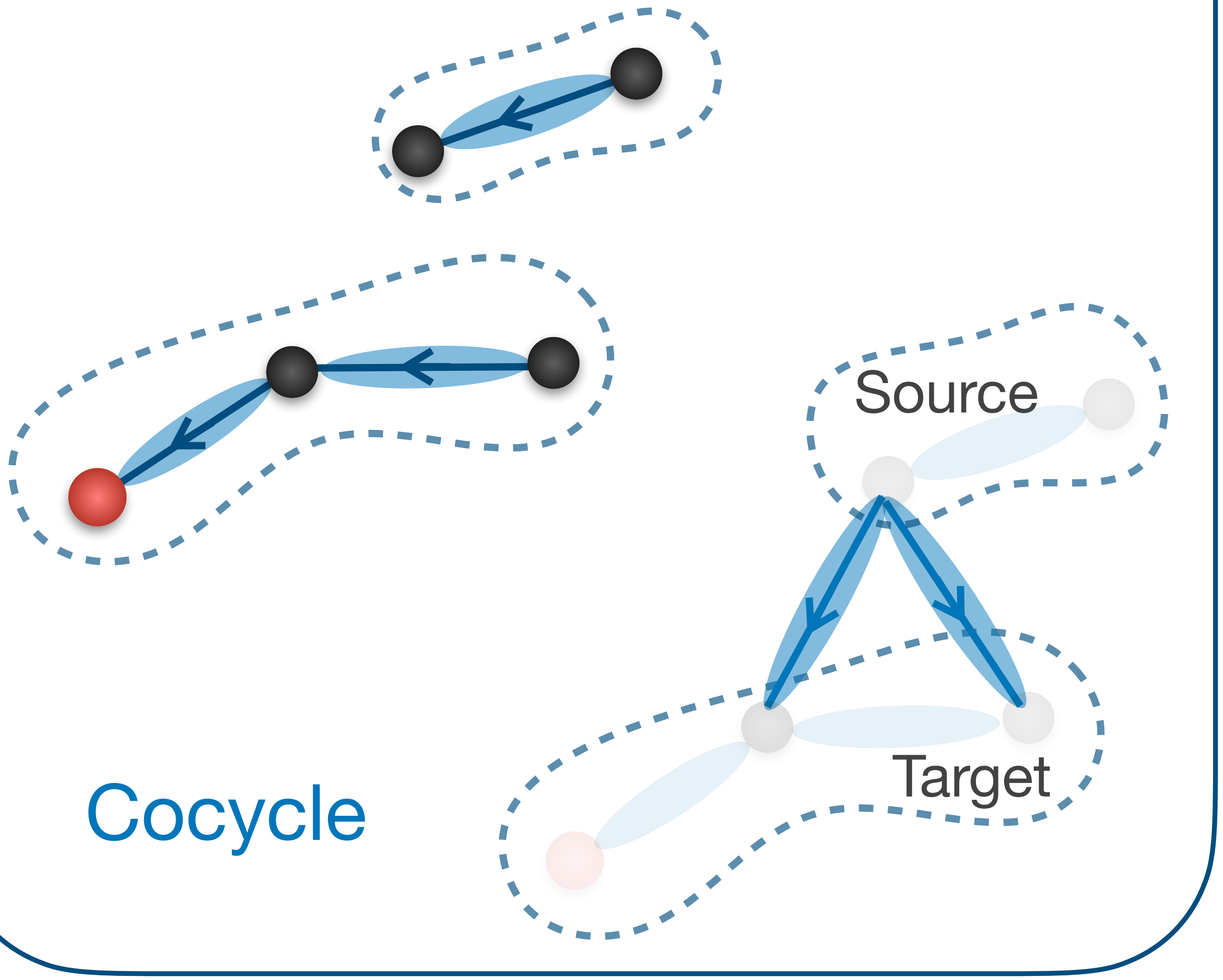
A handful of graph theory



Adding an edge back:



Removing a edge:



A handful of graph theory

About counting…

cycles = $\dim\left(\mathrm{Ker}\,\mathbb{S}\right)$

cocycles = M = $\mathrm{Rank}\,\mathbb{S}$

A handful of graph theory

About counting…

…About spaces

cycles = $\dim\left(\mathrm{Ker}\,\mathbb{S}\right)$

$|c^{\alpha}\rangle \in \mathbb{R}^{R}$

cocycles = M = $\mathrm{Rank}\,\mathbb{S}$

$|c^{\gamma}\rangle \in \mathbb{R}^{R}$

A handful of graph theory

About counting…

…About spaces

cycles = $\dim\left(\mathrm{Ker}\,\mathbb{S}\right)$

cocycles = M = Rank $\mathbb{S}$

span $\left(|c^{\alpha}\rangle\right) = \mathrm{Ker}\,\mathbb{S}$

span $\left(|c^{\gamma}\rangle\right) = \mathrm{Im}\,\mathbb{S}^{\top}$ (Coimage)

A handful of graph theory

About counting…

…About spaces

cycles = $\dim\left(\mathrm{Ker}\,\mathbb{S}\right)$

$\mathrm{span}\left(|c^{\alpha}\rangle\right) = \mathrm{Ker}\,\mathbb{S}$

cocycles = M = $\mathrm{Rank}\,\mathbb{S}$

$\mathrm{span}\left(|c^{\gamma}\rangle\right) = \mathrm{Im}\,\mathbb{S}^{\top}$ (Coimage)

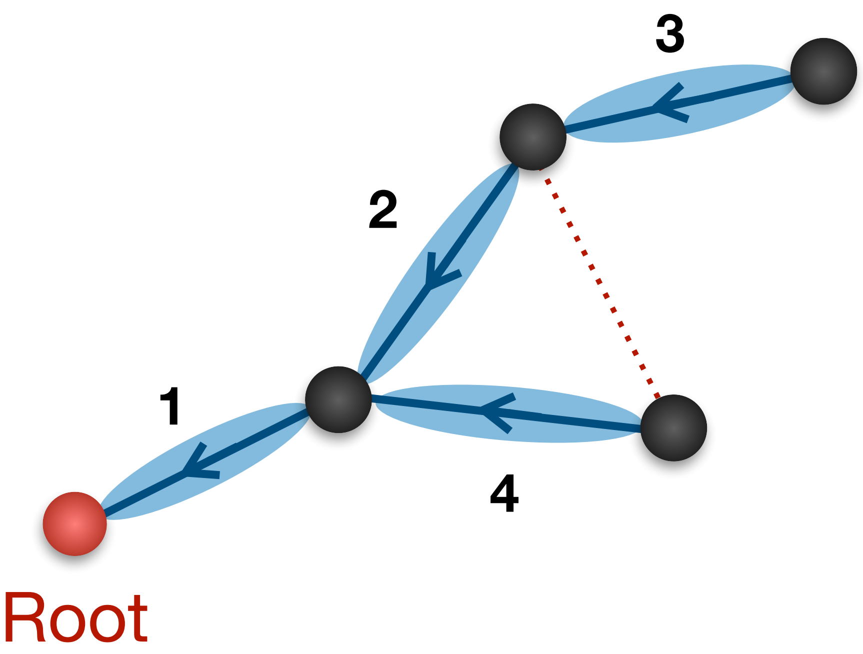
$$\Downarrow$$

They form a non-canonical basis in the space of the reactions $\mathbb{R}^{R}$:

$$\underline{\mathrm{Ker}\,\mathbb{S}} \perp \underline{\mathrm{Im}\,\mathbb{S}^{\top}}$$

A handful of graph theory

Canonical basis in the space of the reactions $\mathbb{R}^R$:



$$\big(\,|e^{\gamma}\rangle, |e^{\alpha}\rangle\big) = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$|e^{\gamma}\rangle \qquad 1 \leq \gamma \leq M$

$|e^{\alpha}\rangle \qquad M+1 \leq \alpha \leq M + \text{dim ker } \mathbb{S}$

A handful of graph theory

1) Picking a spanning tree $\Longleftrightarrow$ Choosing M independent reactions

2) Building cycles & cocycles $\Longleftrightarrow$ The cycles span the Ker $\mathbb{S}$

The cocycles span the Im $\mathbb{S}^T$

…Physical significance?

Back to physics

How to decompose the affinity?

Back to physics

How to decompose the affinity?

Non-orthogonal decomposition of the affinity $|A\rangle \in \mathbb{R}^R$:

$$|A\rangle = A^c_\gamma \, |c^\gamma\rangle + A^e_\alpha \, |e^\alpha\rangle \qquad \langle c^\gamma | e^\alpha \rangle \neq 0$$

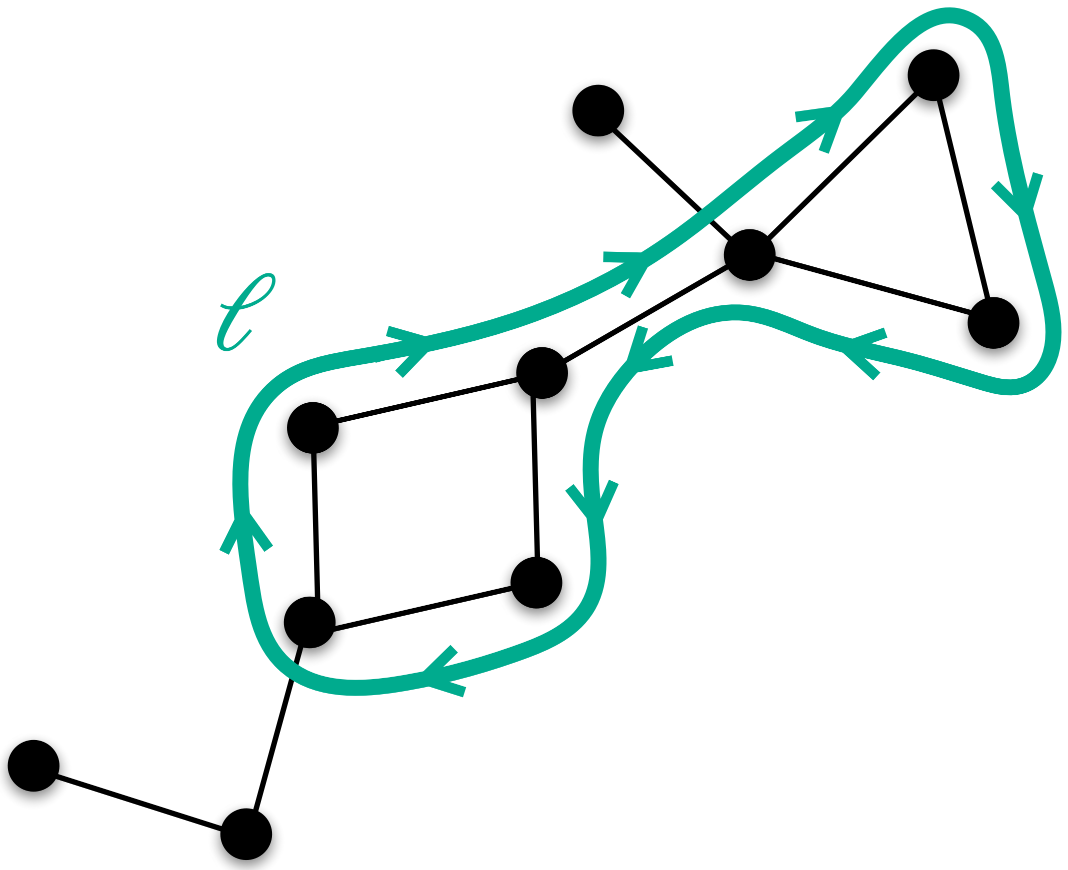
Conservative Non-conservative

Claim: Analogy with the Helmholtz decomposition for graphs

Conservativeness

$$|A\rangle = A^c_\gamma\,|\,c^\gamma\rangle + A^e_\alpha\,|\,e^\alpha\rangle$$

A generic loop on the graph is a linear combination its cycles



Conservativeness

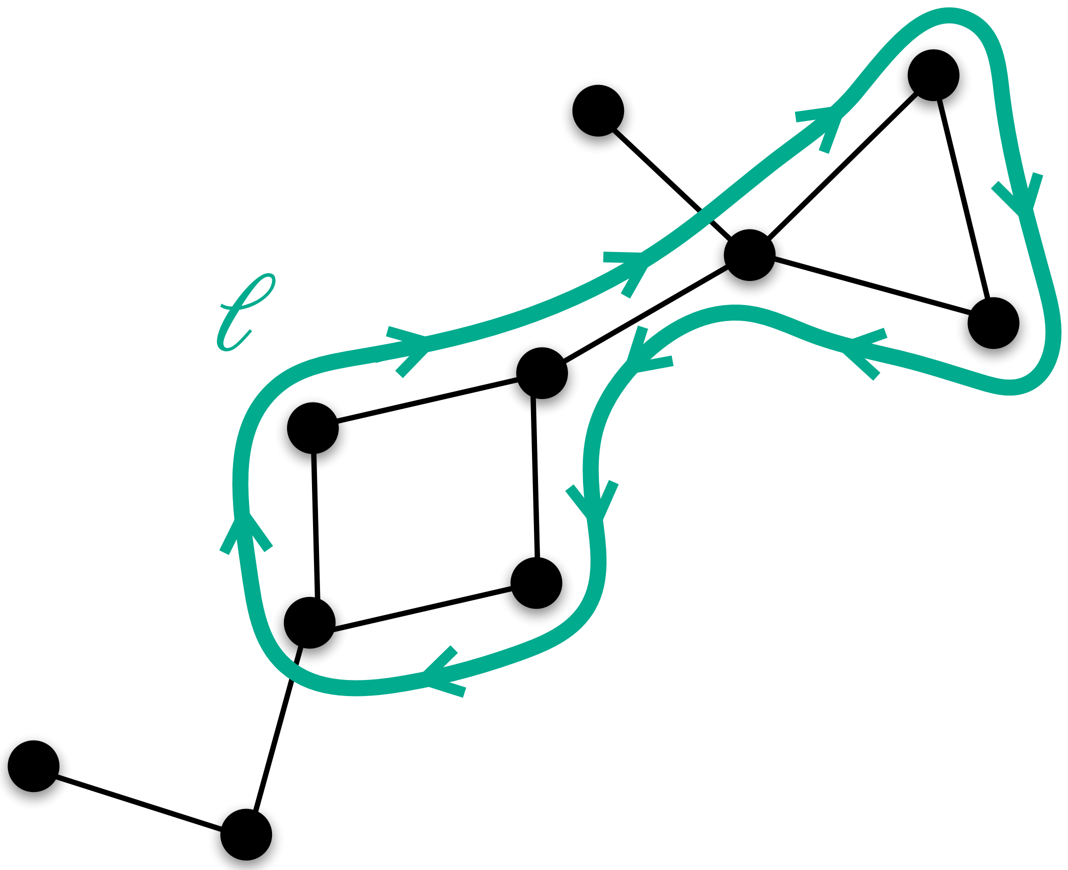
$$|A\rangle = A^c_\gamma \,|\, c^\gamma\rangle + A^e_\alpha \,|\, e^\alpha\rangle$$

A generic loop on the graph is a linear combination its cycles

Circulation of the affinity:

$$\langle A \,|\, c^\alpha\rangle = A^c_\alpha$$

Non-local circulations of the affinity



$$A^e_\alpha = 0 \quad \forall\alpha \iff$$ **Conservative affinity**

Conservative dynamics

In the case of conservative dynamics:

$$|A\rangle = A^c_\gamma \,|c^\gamma\rangle + \cancel{A^e_\alpha \,|e^\alpha}\rangle$$

At all times

M conservative affinities $\in \operatorname{Im} \mathbb{S}^\top$

$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

$\mathbb{S}^\top$ as a discrete gradient

Conservative dynamics

In the case of conservative dynamics:

At all times

$$|A\rangle = A^c_\gamma \,|c^\gamma\rangle + \cancel{A^e_\alpha \,|e^\alpha}\rangle$$

M Conservative affinities $\in \mathrm{Im}\ \mathbb{S}^\top$

$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

$\mathbb{S}^\top$ as a discrete gradient

…Underlying potential landscape?

$(F = -\,\mathrm{grad}\ V)$

…Connection to reversibility?

A decomposition for the currents

From the rate equation: $\partial_t x = \mathbb{S}\, J(x)$

For $t \to \infty$ $\mathbb{S}\,|\,J^{ss}\rangle = 0 \quad \in \ker \mathbb{S}$

A decomposition for the currents

From the rate equation: $\partial_t x = \mathbb{S}\, J(x)$

For $t \to \infty$ $\quad \mathbb{S}\,|\,J^{ss}\rangle = 0 \quad \in \ker \mathbb{S}$

Non-orthogonal decomposition of the current $|\,J\rangle \in \mathbb{R}^R$:

$$|\,J\rangle = J^e_\gamma\,|\,e^\gamma\rangle + J^c_\alpha\,|\,c^\alpha\rangle$$

A decomposition for the currents

From the rate equation: $\partial_t x = \mathbb{S}\, J(x)$

For $t \to \infty$ $\quad \mathbb{S}\,|\,J^{ss}\rangle = 0 \quad \in$ ker $\mathbb{S}$

Non-orthogonal decomposition of the current $|\,J\rangle \in \mathbb{R}^R$:

At infinite time

$$|\,J\rangle = J^e_\gamma\,|\,e^\gamma\rangle + J^c_\alpha\,|\,c^\alpha\rangle \implies |\,J^{ss}\rangle = \cancel{J^{e,ss}_\gamma}\,|\,e^\gamma\rangle + J^{c,ss}_\alpha\,|\,c^\alpha\rangle$$

M transient currents

cy Steady-state currents

$\in$ Ker $\mathbb{S}$

[Schnakenberg]

Back to chemistry?

Back to chemistry?

The chemical affinity:

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

Back to chemistry?

The chemical affinity:

$$A_\rho = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) + (\log x)^{-\mathbb{S}_\rho} = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) - \underbrace{\left(\mathbb{S}^\top \log x\right)}_{\in \operatorname{Im} \mathbb{S}^\top}{}_\rho$$

Conservative: $\langle A \,|\, c^\alpha \rangle \overset{?}{=} 0$

Back to chemistry?

The chemical affinity:

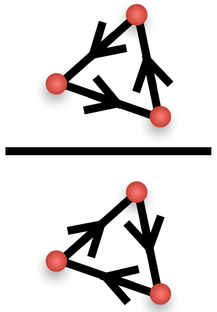
$$A_\rho = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) + (\log x)^{-\mathbb{S}_\rho} = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) - \underbrace{(\mathbb{S}^\top \log x)_\rho}_{\in \operatorname{Im} \mathbb{S}^\top}$$

Conservative: $\langle A \,|\, c^\alpha \rangle \overset{?}{=} 0$

$\big\downarrow$ Condition on the rates!

Wegscheider- Kolmogorov (WK) condition

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



Back to chemistry?

The chemical affinity:

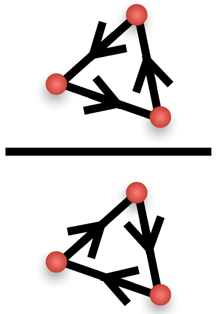
$$A_\rho = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) + (\log x)^{-\mathbb{S}_\rho} = \log\left(\frac{k_\rho^+}{k_\rho^-}\right) - \underset{\in \mathrm{Im}\ \mathbb{S}^\intercal}{\underline{(\mathbb{S}^\intercal \log x)_\rho}}$$

Conservative: $\langle A \,|\, c^\alpha \rangle \overset{?}{=} 0$

Condition on the rates!

Conservativeness is fully equivalent to **stochastic reversibility** and **detailed balance**

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



Back to chemistry?

If WK is fulfilled the total affinity is conservative

$A \in \mathrm{Im}\, \mathbb{S}^{\top}$ (No circulation)

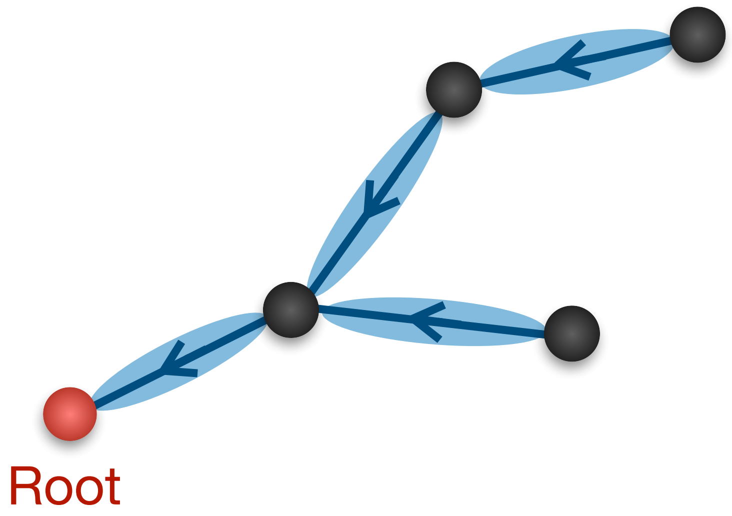
…Underlying potential landscape?

Back to chemistry?

If WK is fulfilled the total affinity is conservative

$A \in \mathrm{Im}\, \mathbb{S}^{\top}$ (No circulation)

…Underlying potential landscape?



Integrating the affinity along the spanning tree

$$\sum_{[i \to \mathrm{root}]} A_\rho = \mu_i$$

Chemical potential

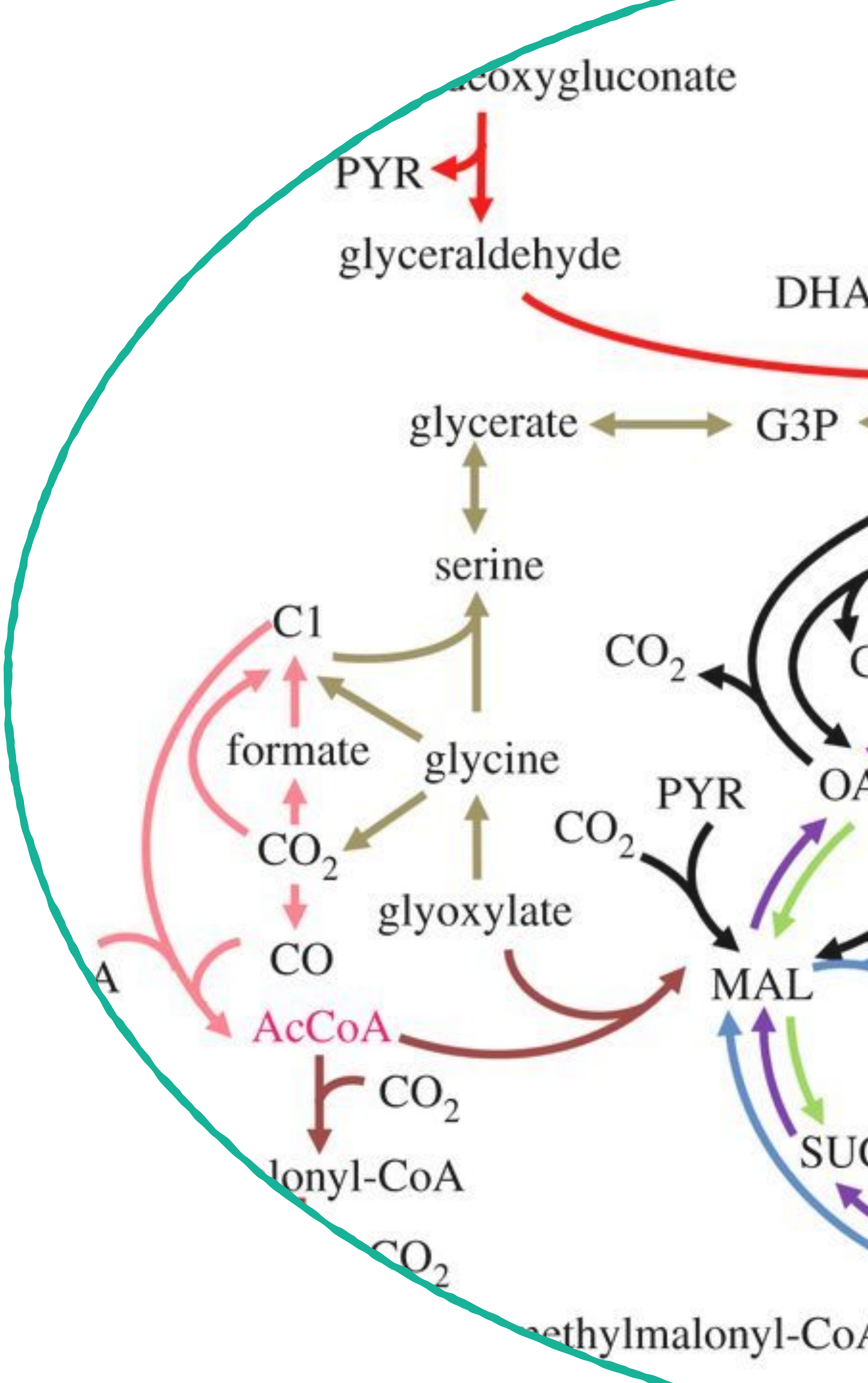
$$\sum_{[i \to \mathrm{root}]} \log\left(\frac{k_\rho^-}{k_\rho^+}\right) = \mu_i^{\ominus}$$

Standard chemical potential

Constructive way to get the chemical potentials!

Outline

3. Towards interacting CRNs



Interacting CRNs

Example

$$2X_1 \rightleftharpoons X_2$$

$$X_2 + 2X_3 \rightleftharpoons 2X_4$$

$$X_4 \rightleftharpoons X_2 + X_5$$

$$X_4 \rightleftharpoons X_1 + X_3$$

Stoichiometric matrix is no longer an incidence matrix

$$\mathbb{S} = \begin{pmatrix} -2 & 0 & 0 & +1 \\ +1 & -1 & +1 & 0 \\ 0 & -2 & 0 & +1 \\ 0 & +2 & -1 & -1 \\ 0 & 0 & +1 & 0 \end{pmatrix}$$

Ex. Autocatalytic networks, epidemic dynamics…

Interacting CRNs

Example

$2X_1 \rightleftharpoons X_2$

$X_2 + 2X_3 \rightleftharpoons 2X_4$

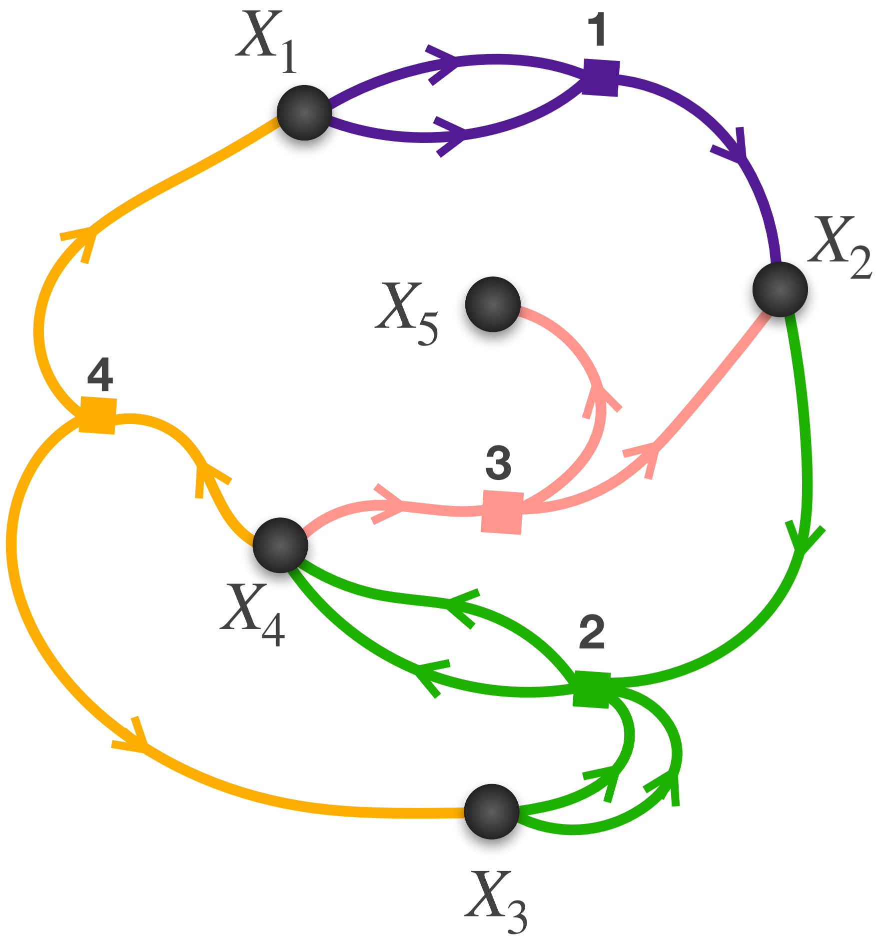
$X_4 \rightleftharpoons X_2 + X_5$

$X_4 \rightleftharpoons X_1 + X_3$

Stoichiometric matrix is no longer an incidence matrix

$$\mathbb{S} = \begin{pmatrix} -2 & 0 & 0 & +1 \\ +1 & -1 & +1 & 0 \\ 0 & -2 & 0 & +1 \\ 0 & +2 & -1 & -1 \\ 0 & 0 & +1 & 0 \end{pmatrix}$$

Hypergraph representation:



Ex. Autocatalytic networks, epidemic dynamics…

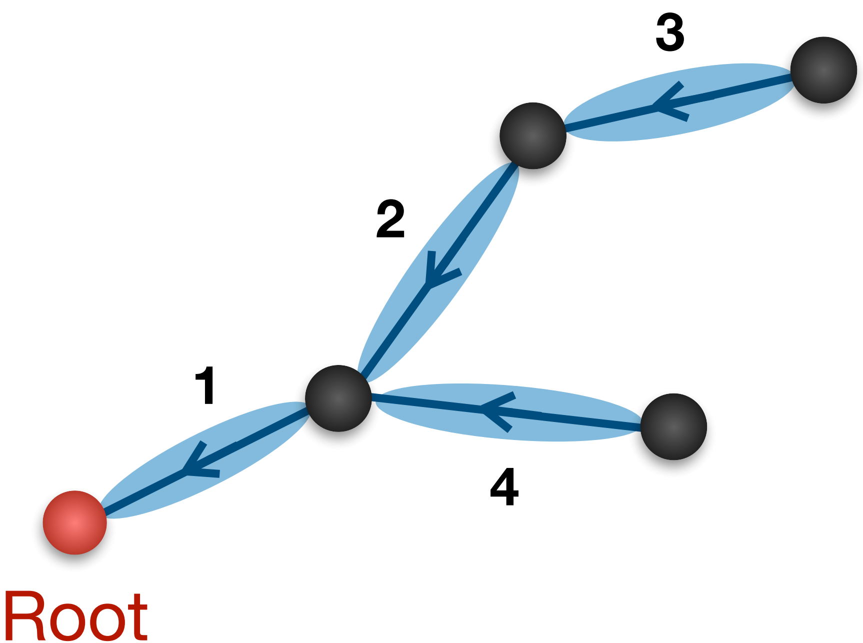
No longer a spanning tree… what about cycles and cocycles?

Cycles & cocycles

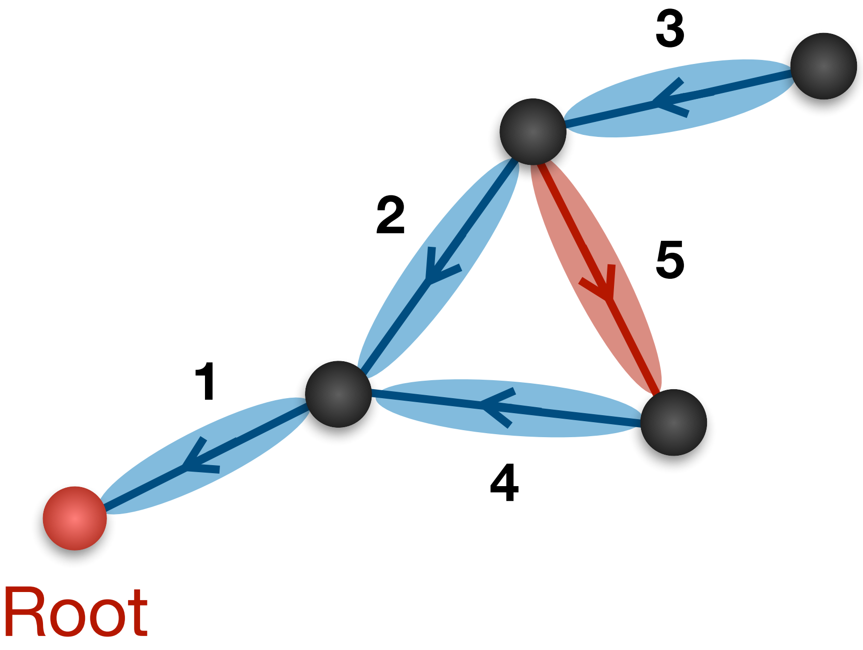
Vectorial representation:

$$\big(\,|\,c^{\gamma}\rangle, |\,c^{\alpha}\rangle\big) = \,?$$

Spanning tree:



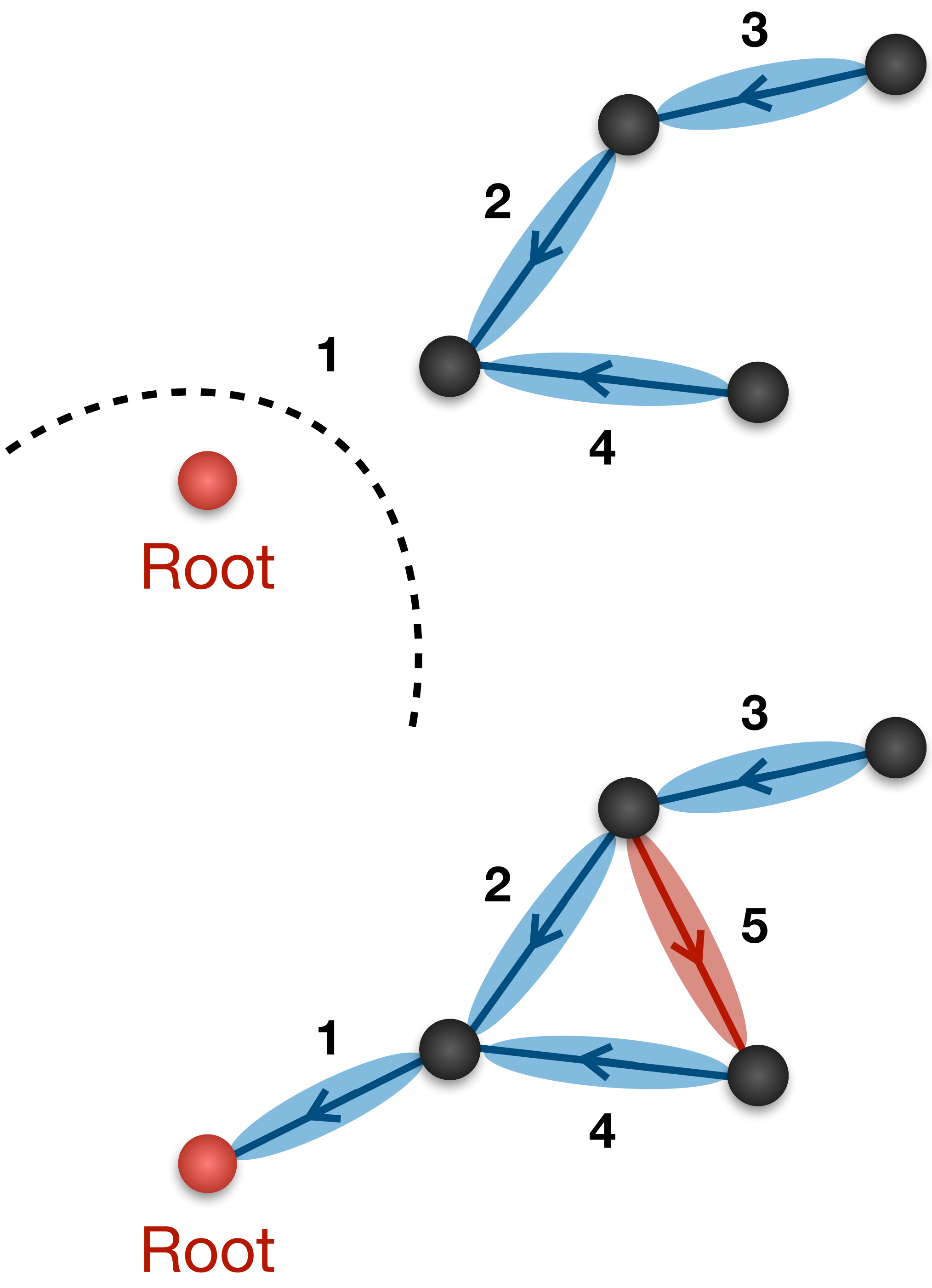
Full graph:



Cycles & cocycles

Vectorial representation:

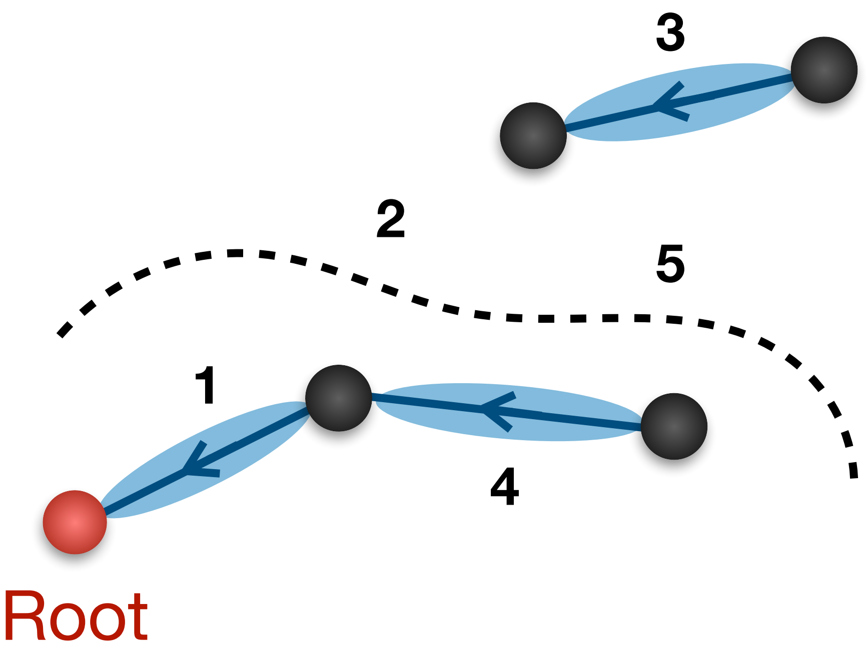
$$\big(\,|c^{\gamma}\rangle, |c^{\alpha}\rangle\big) = \begin{pmatrix} 1 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \end{pmatrix}$$

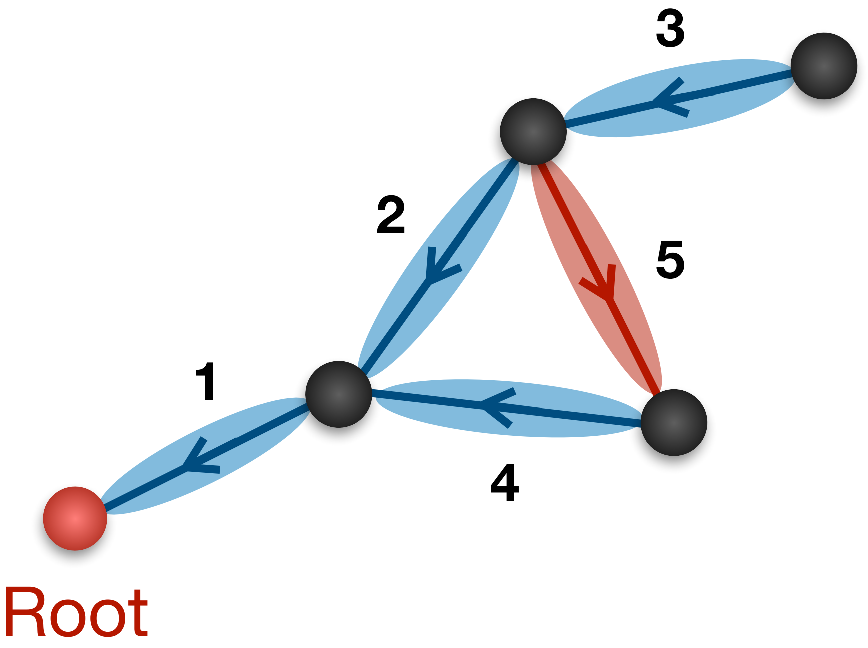


Cycles & cocycles

Vectorial representation:

$$\big(\,|\,c^{\gamma}\rangle,|\,c^{\alpha}\rangle\big)=\begin{pmatrix}1 & 0 & & \\ 0 & 1 & & \\ 0 & 0 & & \\ 0 & 0 & & \\ 0 & 1 & & \end{pmatrix}$$

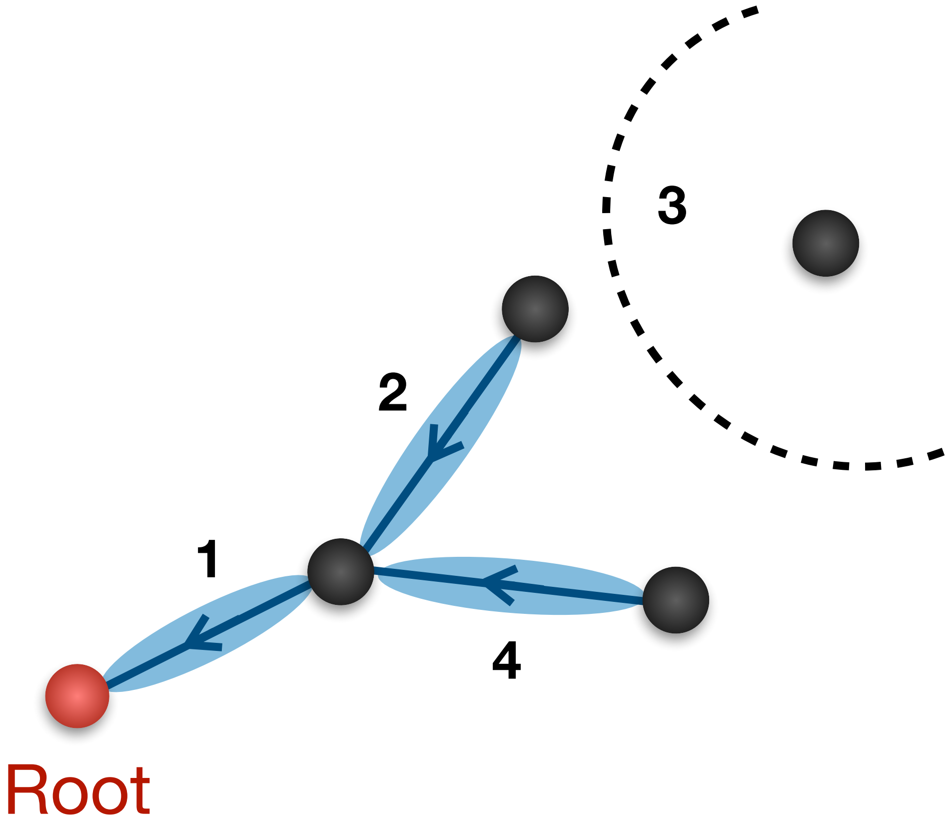


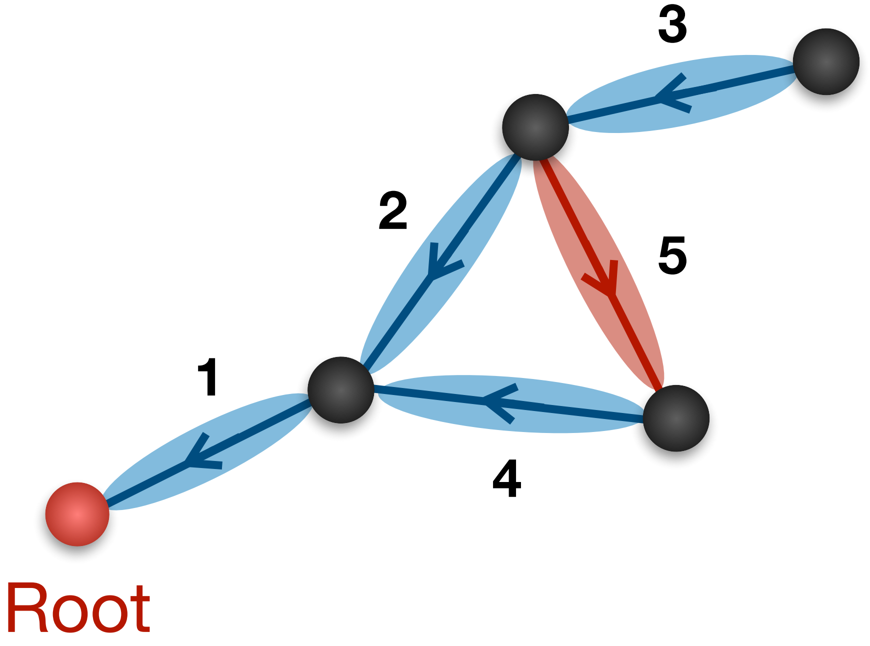


Cycles & cocycles

Vectorial representation:

$$\big(\,|\,c^{\gamma}\rangle, |\,c^{\alpha}\rangle\big) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}$$

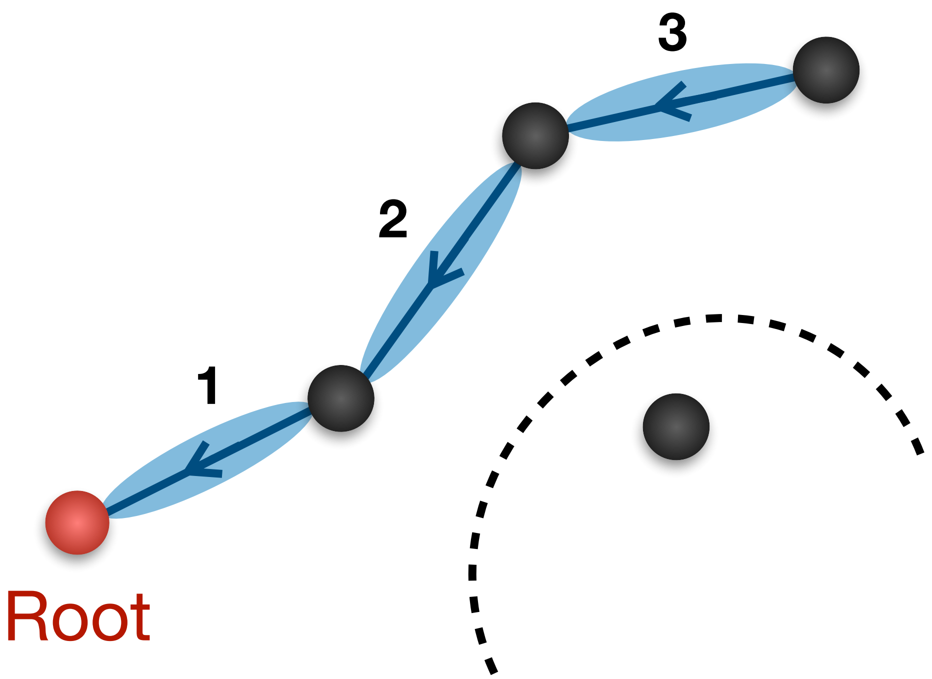


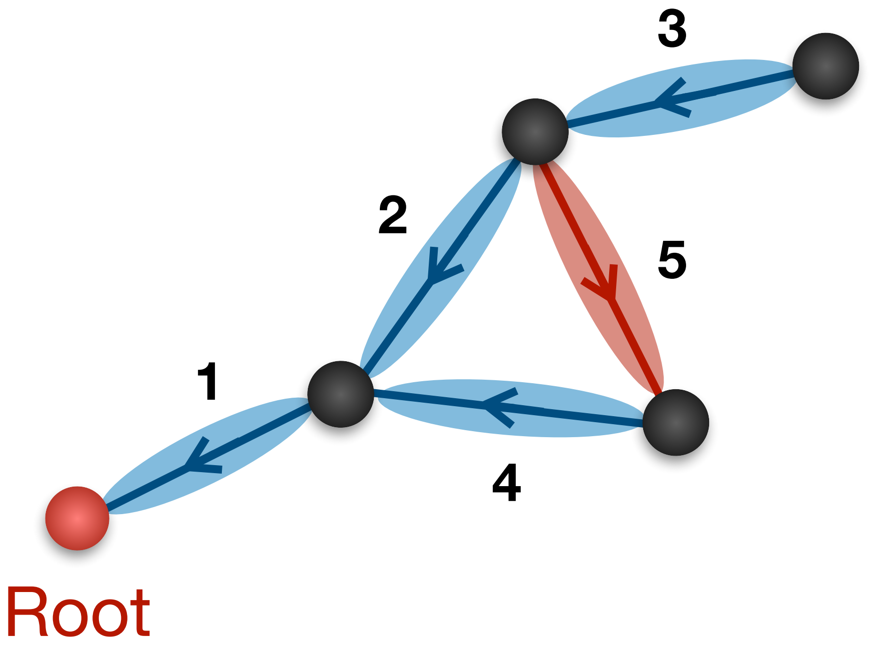


Cycles & cocycles

Vectorial representation:

$$\big(\,|\,c^{\gamma}\rangle,|\,c^{\alpha}\rangle\big) = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & -1 \end{pmatrix}$$

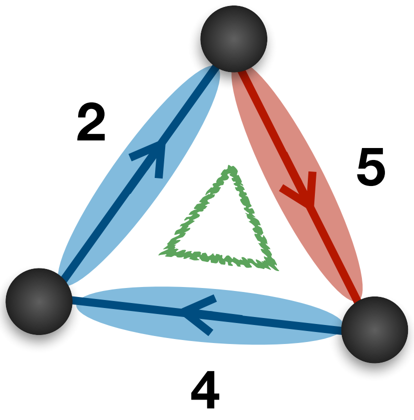


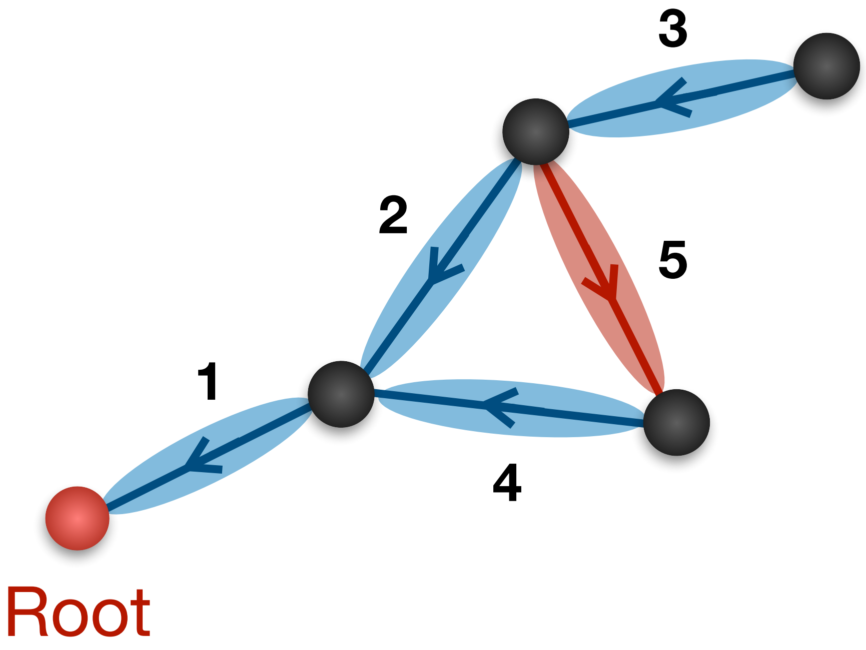


Cycles & cocycles

Vectorial representation:

$$\left(|c^{\gamma}\rangle,|c^{\alpha}\rangle\right)=\left(\underbrace{\begin{matrix}1&0&0&0\\0&1&0&0\\0&0&1&0\\0&0&0&1\\0&1&0&-1\end{matrix}}_{|c^{\gamma}\rangle}\quad\underbrace{\begin{matrix}0\\-1\\0\\1\\1\end{matrix}}_{|c^{\alpha}\rangle}\right)$$



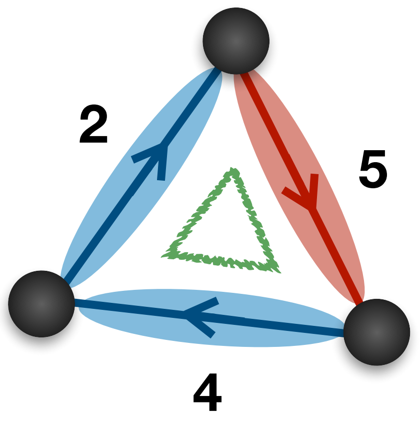


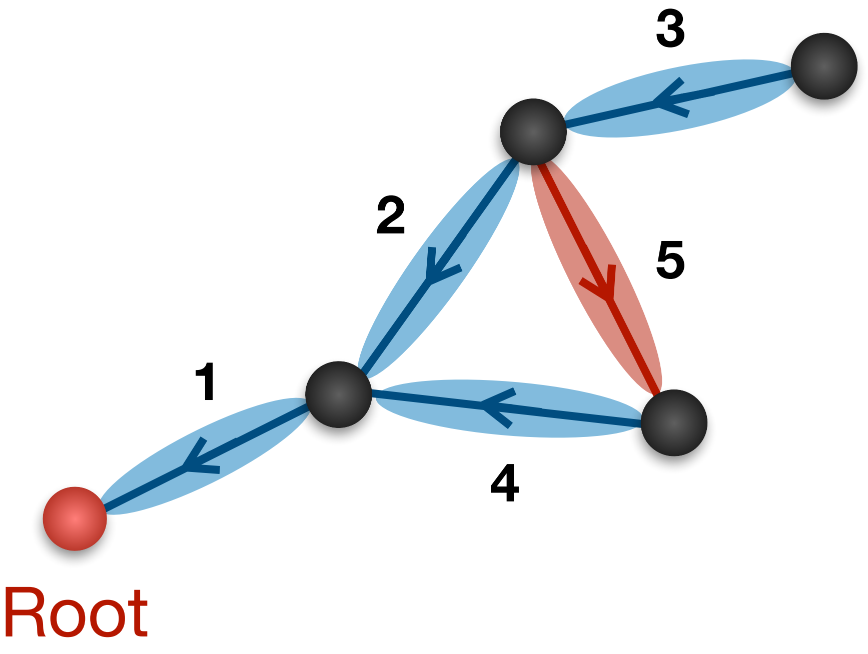
Cycles & cocycles

Vectorial representation:

$$\big(\,|c^{\gamma}\rangle, |c^{\alpha}\rangle\big) = \left(\begin{array}{cccc|c} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ \hline 0 & 1 & 0 & -1 & 1 \end{array}\right)$$

$$\underbrace{\hphantom{0 \quad 1 \quad 0 \quad -1}}_{|c^{\gamma}\rangle} \quad \underbrace{\hphantom{1}}_{|c^{\alpha}\rangle}$$





Cycles & cocycles

$$\big(\,|c^\gamma\rangle, |c^\alpha\rangle\big) = \left(\begin{array}{cccc|c} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ \hline 0 & 1 & 0 & -1 & 1 \end{array}\right)$$

$$\underbrace{\qquad\qquad\qquad\qquad}_{|c^\gamma\rangle}\;\underbrace{\qquad}_{|c^\alpha\rangle}$$

From the geometrical construction

$$\xrightarrow{\qquad\qquad}$$

$$\begin{pmatrix} \overbrace{\mathbf{1}_M}^{M\,=\,\text{Rank}\,\mathbb{S}} & \overbrace{-\mathbb{T}}^{\#\text{cy}} \\ \underbrace{\mathbb{T}^\top}_{|c^\gamma\rangle} & \underbrace{\mathbf{1}_{\#\text{cy}}}_{|c^\alpha\rangle} \end{pmatrix}$$

Cycles & cocycles

$$\left(|c^\gamma\rangle, |c^\alpha\rangle\right) = \left(\begin{array}{cccc|c} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ \hline 0 & 1 & 0 & -1 & 1 \end{array}\right)$$

$$\underbrace{\qquad\qquad\qquad}_{|c^\gamma\rangle} \quad \underbrace{\quad}_{|c^\alpha\rangle}$$

From the geometrical construction

$$\xrightarrow{\qquad}$$

$$\begin{array}{cc} \overbrace{\qquad}^{M = \text{Rank}\,\mathbb{S}} & \overbrace{\qquad}^{\#\text{cy}} \end{array}$$

$$\begin{pmatrix} \mathbf{1}_M & -\mathbb{T} \\ \mathbb{T}^\top & \mathbf{1}_{\#\text{cy}} \end{pmatrix}$$

$$|c^\gamma\rangle \qquad |c^\alpha\rangle$$

In the example:

$$\mathbb{S} = \begin{pmatrix} +1 & 0 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 & 0 \\ 0 & -1 & +1 & 0 & -1 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & +1 \end{pmatrix}$$

$$\mathbb{S}_{\text{indep}} \qquad\qquad \mathbb{S}_{\text{dep}}$$

$$\mathbb{S}_{\text{dep}} = \mathbb{S}_{\text{indep}}\,\mathbb{T}$$

$$(N \times \#\text{cy}) = (N \times M)(M \times \#\text{cy})$$

Cycles & cocycles

$$\left(\,|c^{\gamma}\rangle, |c^{\alpha}\rangle\right) = \left(\begin{array}{cccc|c} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ \hline 0 & 1 & 0 & -1 & 1 \end{array}\right)$$

From the geometrical construction $\longrightarrow$

$$\begin{pmatrix} \overbrace{\begin{matrix} \mathbf{1}_{M} \\ \mathbb{T}^{\top} \end{matrix}}^{M = \text{Rank}\,\mathbb{S}} & \overbrace{\begin{matrix} -\mathbb{T} \\ \mathbf{1}_{\#\text{cy}} \end{matrix}}^{\#\text{cy}} \end{pmatrix}$$

What is the matrix $\mathbb{T}$ in the case of an interacting complex CRNs?

In the example:

$$\mathbb{S} = \left(\underbrace{\begin{matrix} +1 & 0 & 0 & 0 \\ -1 & +1 & 0 & +1 \\ 0 & -1 & +1 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & -1 \end{matrix}}_{\mathbb{S}_{\text{indep}}} \quad \underbrace{\begin{matrix} 0 \\ 0 \\ -1 \\ 0 \\ +1 \end{matrix}}_{\mathbb{S}_{\text{dep}}}\right)$$

$$\mathbb{S}_{\text{dep}} = \mathbb{S}_{\text{indep}}\,\mathbb{T}$$

$$(N \times \#\text{cy}) = (N \times M)(M \times \#\text{cy})$$

Gauss-Jordan elimination

Row reduced Echelon form for $\mathbb{S}$:

$$\mathrm{G}\,\mathbb{S} = \begin{pmatrix} \mathbf{1}_M & \mathbb{T} \\ 0 & 0 \end{pmatrix}$$

Algebraic tool

Gauss-Jordan elimination

Row reduced Echelon form for $\mathbb{S}$:

$$\mathrm{G}\,\mathbb{S} = \begin{pmatrix} \mathbf{1}_M & \mathbb{T} \\ 0 & 0 \end{pmatrix}$$

Fractional entries, unique

Algebraic tool

$$\Downarrow$$

$$\big(\,|\,c^\gamma\rangle, |\,c^\alpha\rangle\big) = \begin{pmatrix} \mathbf{1}_M & -\mathbb{T} \\ \mathbb{T}^\top & \mathbf{1}_{\#\mathrm{cy}} \end{pmatrix}$$

$|\,c^\alpha\rangle$ Still a basis for Ker $\mathbb{S}$

$|\,c^\gamma\rangle$ Still a basis for Im $\mathbb{S}^\top$

Gauss-Jordan elimination

Row reduced Echelon form for $\mathbb{S}$:

$$\mathrm{G}\,\mathbb{S} = \begin{pmatrix} \mathbf{1}_M & \mathbb{T} \\ 0 & 0 \end{pmatrix}$$

Fractional entries, unique

Algebraic tool

$$\Downarrow$$

$$\left(|c^\gamma\rangle, |c^\alpha\rangle\right) = \begin{pmatrix} \mathbf{1}_M & -\mathbb{T} \\ \mathbb{T}^\top & \mathbf{1}_{\#\mathrm{cy}} \end{pmatrix}$$

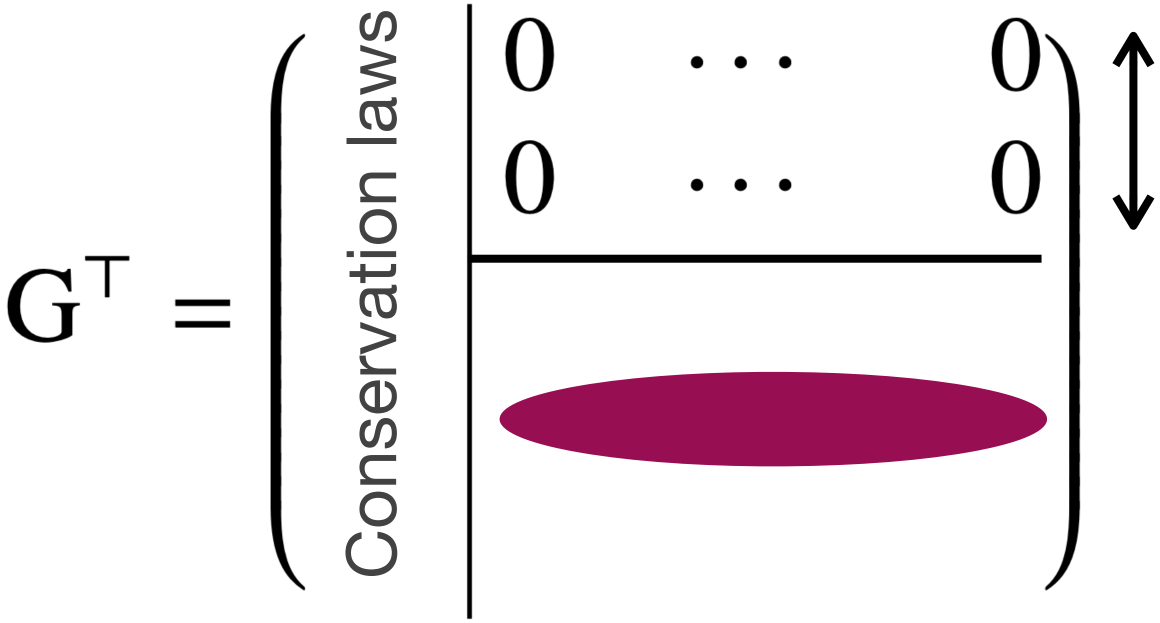
$|c^\alpha\rangle$ Still a basis for Ker $\mathbb{S}$

$|c^\gamma\rangle$ Still a basis for Im $\mathbb{S}^\top$

No need of graph theory to identify the cycles and cocycles!

Geometry of hypergraphs?

Integrator operator on the hypergraph:



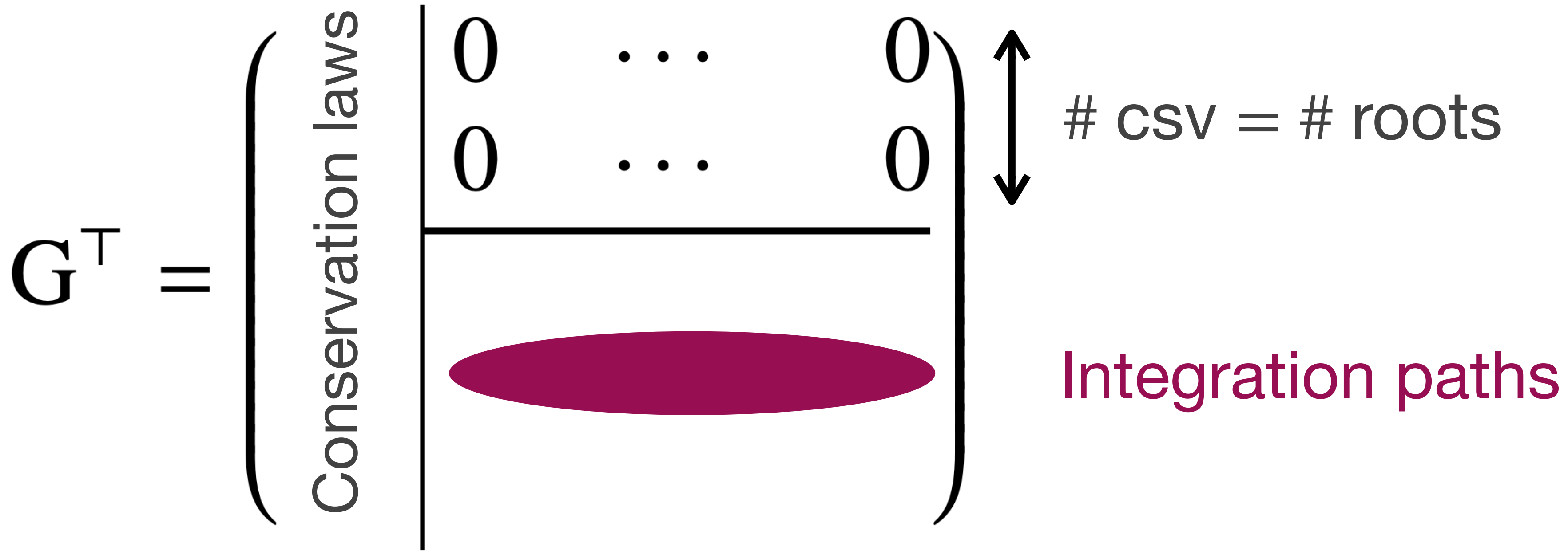
$$G^\top = \left(\begin{array}{c|ccc} \text{Conservation laws} & 0 & \cdots & 0 \\ & 0 & \cdots & 0 \\ \hline & & & \end{array}\right)$$

csv = # roots

Integration paths

Geometry of hypergraphs?

Integrator operator on the hypergraph:

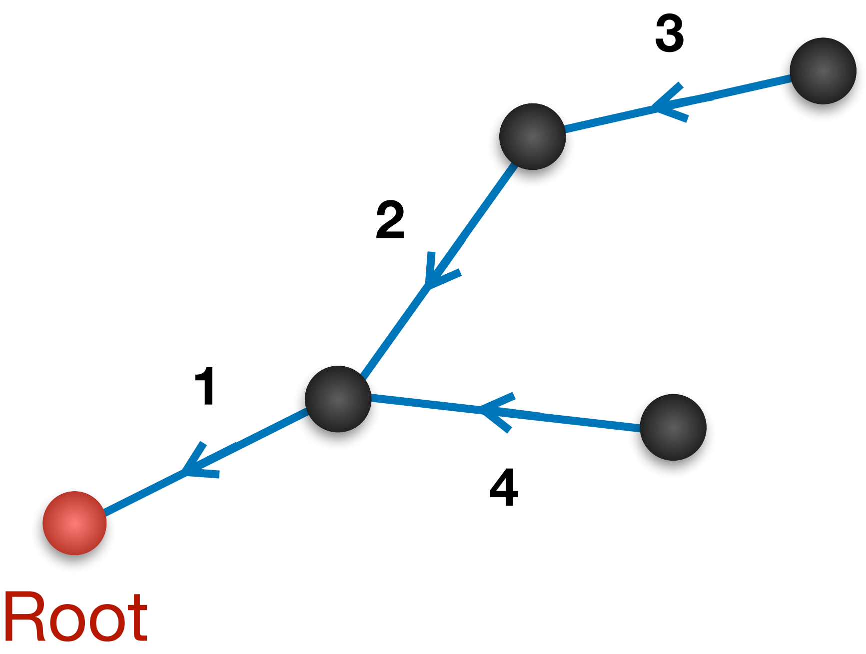


For the simple graph:

$$G^\top = \left(\begin{array}{c|cccc} 1 & 0 & 0 & 0 & 0 \\ \cline{2-5} 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 \end{array}\right)$$

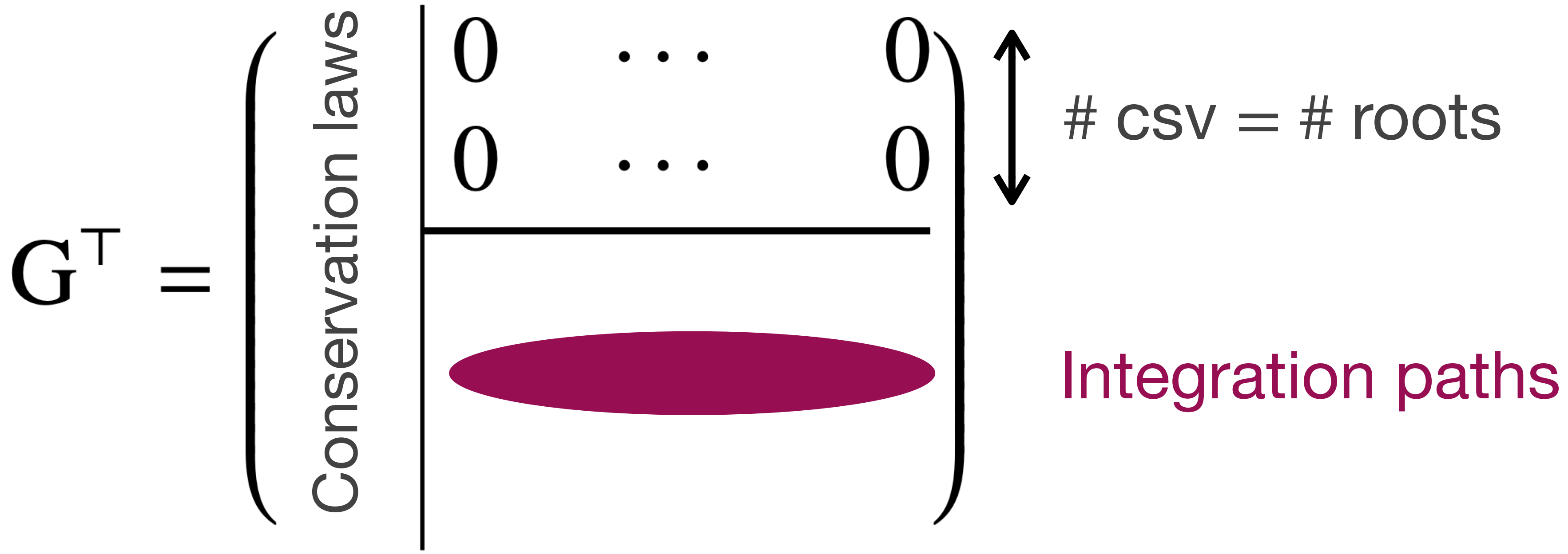
1 root

Mass conservation law



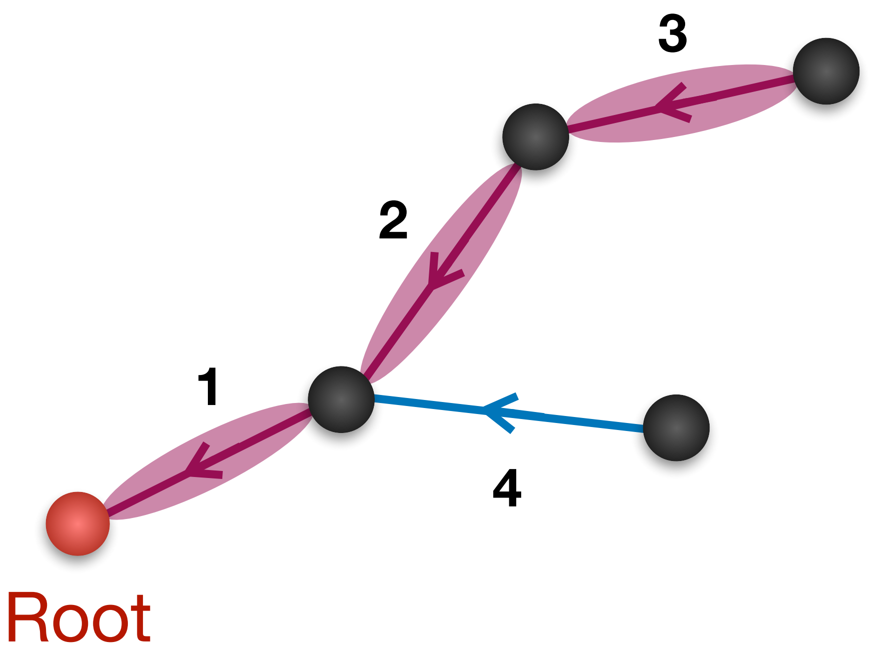
Geometry of hypergraphs?

Integrator operator on the hypergraph:



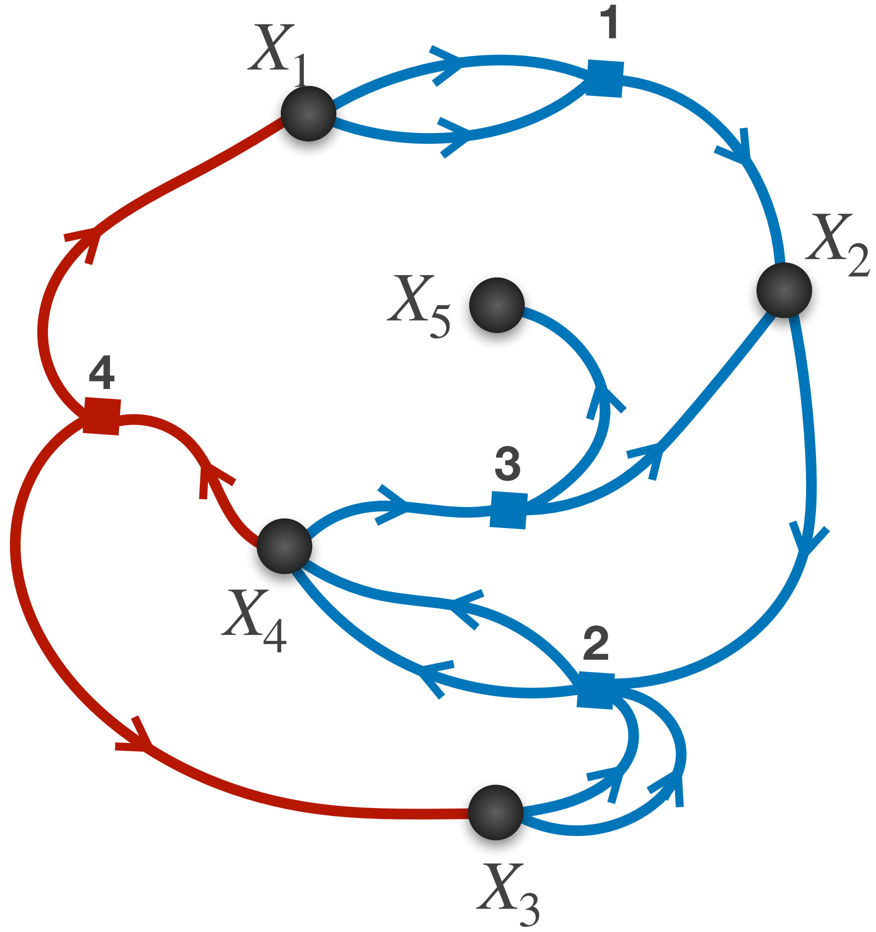
For the simple graph:

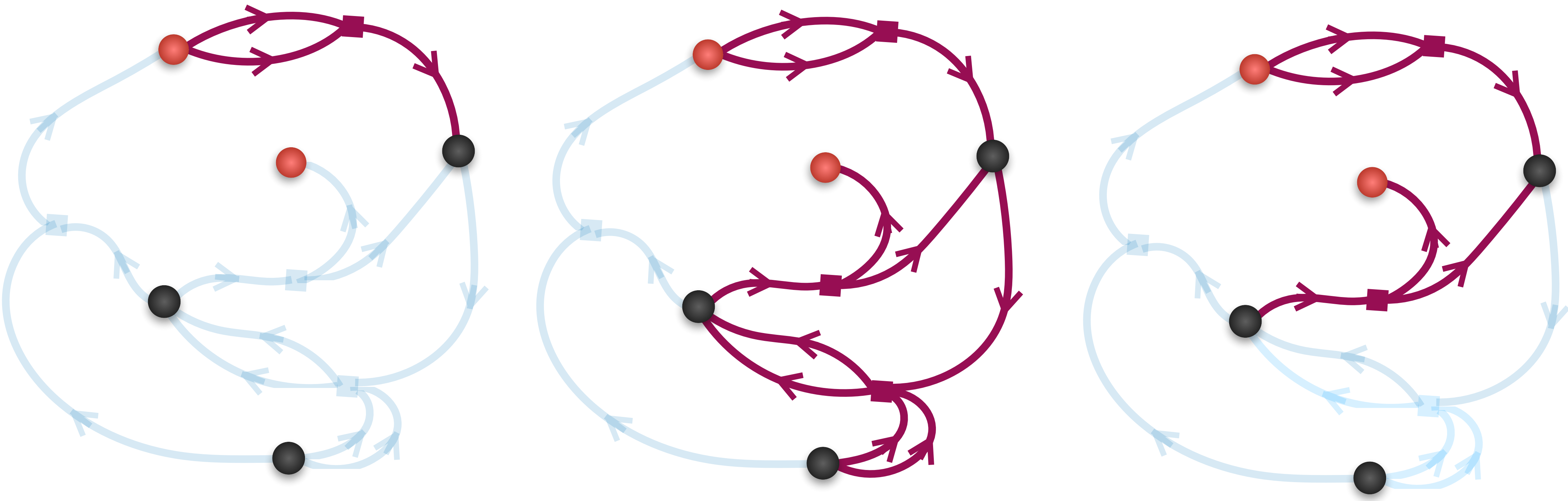
$$G^\top = \left(\begin{array}{c|cccc} 1 & 0 & 0 & 0 & 0 \\ \cline{2-5} 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 \end{array}\right) \quad \gamma = 3$$



Geometry of hypergraphs?

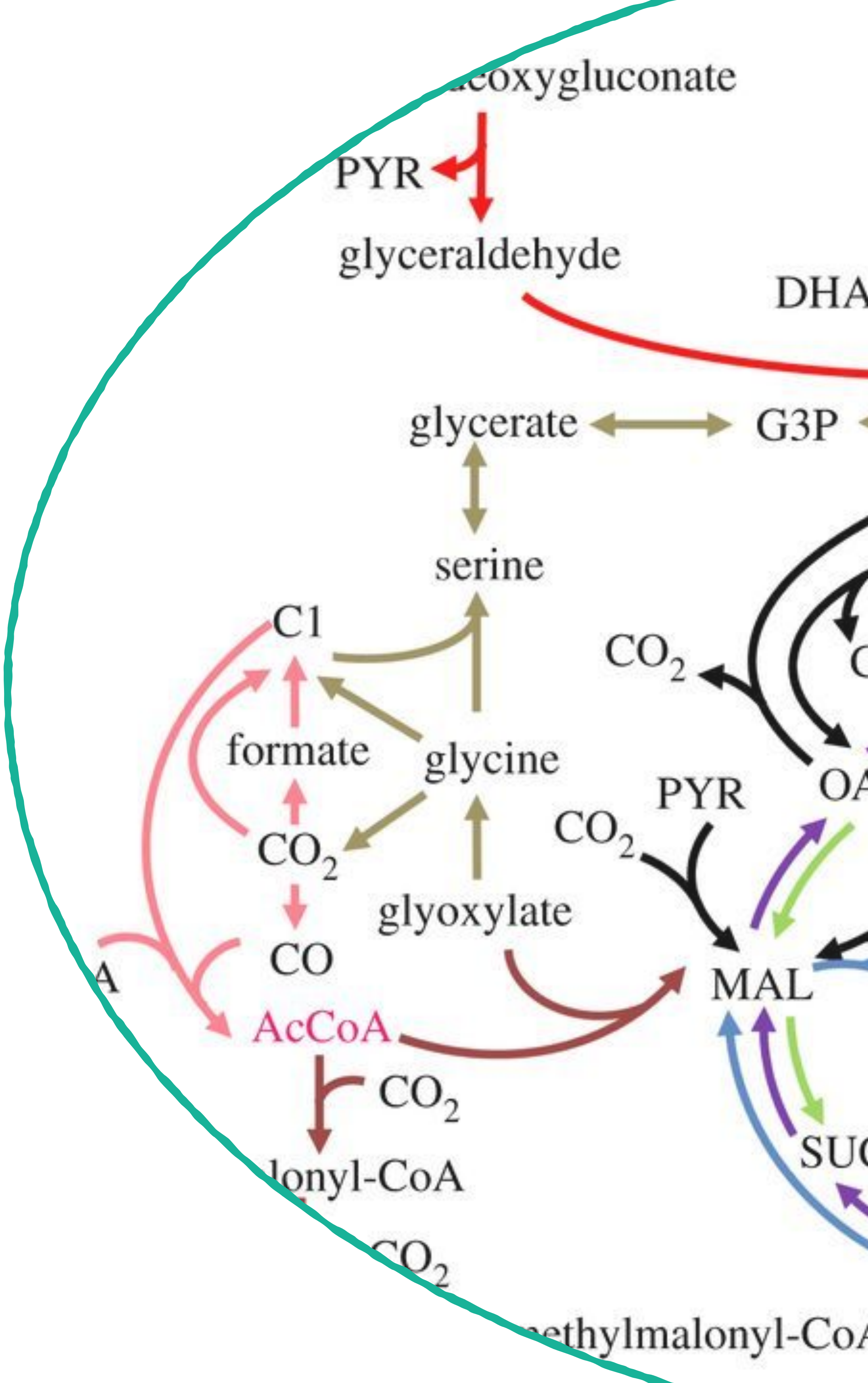
$$G^\top = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 2 & 0 & 1 & 0 & 0 \\ 1 & 1 & 1/2 & -1/2 & -1 \\ 2 & 1 & 1 & 0 & -1 \end{pmatrix}$$





Outline

4. An application: linear response(s)



Linear response(s)

Two ways to perturb equilibrium:

→ Finite-time relaxation due to initial condition $\neq x^{eq}$

→ Nonequilibrium steady-state due to external drive (chemostatting)

How are these two protocols related?

Linear response(s)

$$|A\rangle = A^c_\gamma |c^\gamma\rangle + A^e_\alpha |e^\alpha\rangle$$

$$|J\rangle = J^e_\gamma |e^\gamma\rangle + J^c_\alpha |c^\alpha\rangle$$

→ Finite-time relaxation due to initial condition $\neq x^{eq}$

$$\partial_t |x\rangle = \mathbb{S}|J\rangle = \mathbb{S}\, J^e_\gamma |e^\gamma\rangle \qquad \left(|c^\alpha\rangle \in \mathrm{Ker}\,\mathbb{S}\right)$$

M transient currents

M conservative affinities

$$J^e_\gamma \equiv \langle c^\gamma|J\rangle = \langle c^\gamma|\Lambda|A\rangle = \underbrace{\langle c^\gamma|\Lambda|c^{\gamma'}\rangle}_{\left(L^{\mathrm{rel}}\right)_{\gamma\gamma'}} A^c_{\gamma'}$$

Response matrix of relaxation

Linear response(s)

$$|A\rangle = A^c_\gamma |c^\gamma\rangle + A^e_\alpha |e^\alpha\rangle$$

$$|J\rangle = J^e_\gamma |e^\gamma\rangle + J^c_\alpha |c^\alpha\rangle$$

→ Nonequilibrium steady-state due to external drive (chemostatting)

$$\mathbb{S}|J^{ss}\rangle = 0 \implies |J^{ss}\rangle = J^{c,ss}_\alpha |c^\alpha\rangle$$

#cy steady-state currents

Non-conservative forces

$$A^{e,ss}_\alpha \equiv \langle c^\alpha | A^{ss}\rangle = \langle c^\alpha | \Lambda^{-1} | J^{ss}\rangle = \underbrace{\langle c^\alpha | \Lambda^{-1} | c^{\alpha'}\rangle}_{\text{Response to external drive } \left(L^{\text{ext}}\right)_{\alpha\alpha'}} J^{c,ss}_{\alpha'}$$

Linear response(s)

The two response matrices, after a change of variables:

$$L^{\mathrm{rel}} = \left(\begin{array}{c|c} \mathbf{1}_M + \tilde{\mathbb{T}}\tilde{\mathbb{T}}^\top & (0) \\ \hline (0) & \mathbf{0}_{\mathrm{\#cy}} \end{array}\right) \qquad L^{\mathrm{ext}} = \left(\begin{array}{c|c} \mathbf{0}_M & (0) \\ \hline (0) & \mathbf{1}_{\mathrm{\#cy}} + \tilde{\mathbb{T}}^\top\tilde{\mathbb{T}} \end{array}\right)$$

Linear response(s)

The two response matrices, after a change of variables:

$$L^{\text{rel}} = \left(\begin{array}{c|c} \mathbf{1}_M + \tilde{\mathbb{T}}\tilde{\mathbb{T}}^\top & (0) \\ \hline (0) & \mathbf{0}_{\#\text{cy}} \end{array}\right) \qquad L^{\text{ext}} = \left(\begin{array}{c|c} \mathbf{0}_M & (0) \\ \hline (0) & \mathbf{1}_{\#\text{cy}} + \tilde{\mathbb{T}}^\top\tilde{\mathbb{T}} \end{array}\right)$$

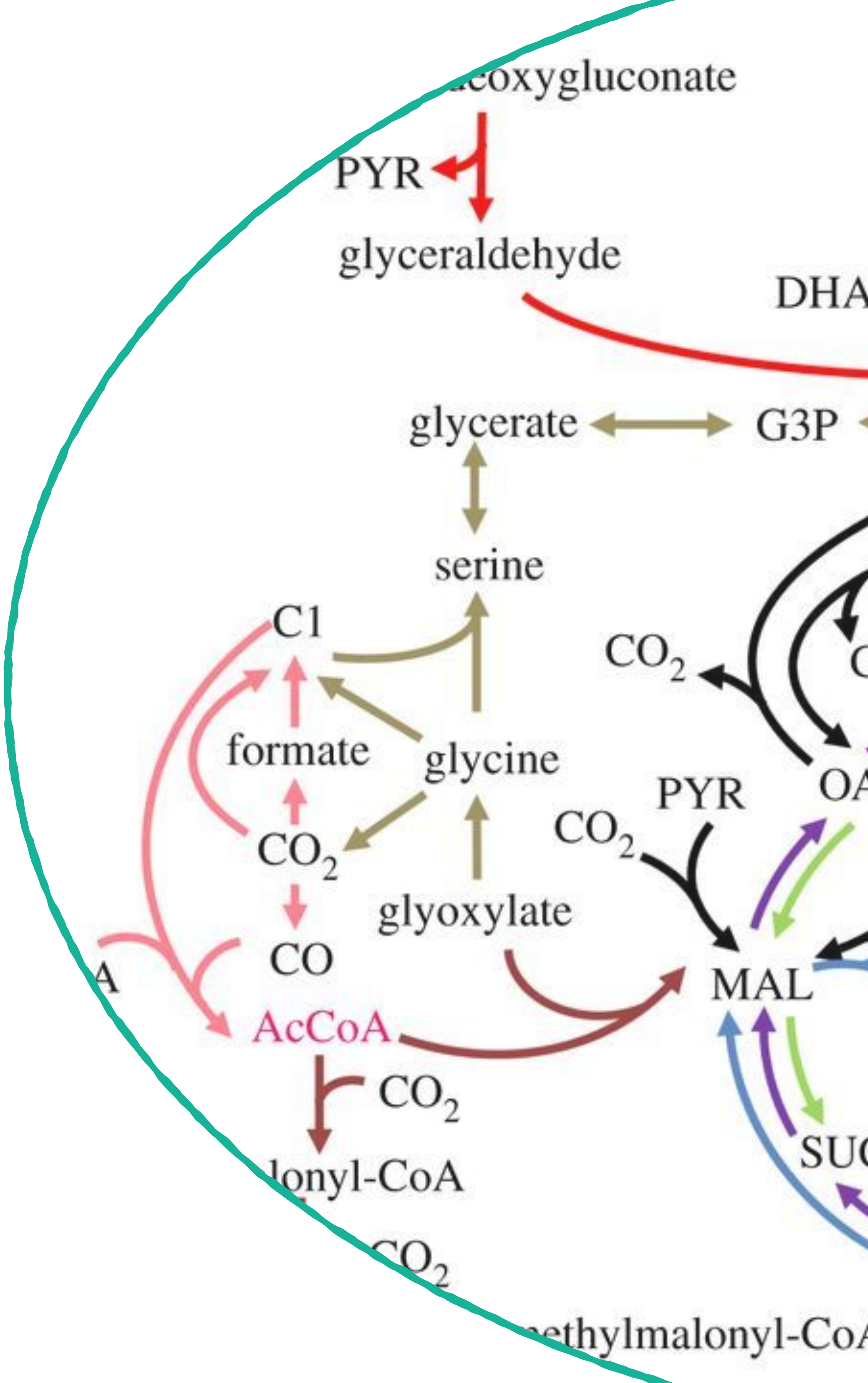
- Spectrum fully controls by the matrix $\mathbb{T}$
- They **share the same spectrum** up to the multiplicity of 0's and 1's eigenvalues
- Spectral Einstein relation ?

$L^{\text{rel}} \Longleftrightarrow$ Noise matrix

$L^{\text{ext}} \Longleftrightarrow$ Mobility

Outline

5. Perspectives and conclusions



Two physical decompositions:

$$|A\rangle = A^{c}_{\gamma}\,|\,c^{\gamma}\rangle + A^{e}_{\alpha}\,|\,e^{\alpha}\rangle$$

$$|J\rangle = J^{e}_{\gamma}\,|\,e^{\gamma}\rangle + J^{c}_{\alpha}\,|\,c^{\alpha}\rangle$$

Two physical decompositions:

$$|A\rangle = A^{c}_{\gamma}\,|\,c^{\gamma}\rangle + A^{e}_{\alpha}\,|\,e^{\alpha}\rangle$$

$$|J\rangle = J^{e}_{\gamma}\,|\,e^{\gamma}\rangle + J^{c}_{\alpha}\,|\,c^{\alpha}\rangle$$

For noninteracting CRNs
cycles and cocycles built
from graph theory

Two physical decompositions:

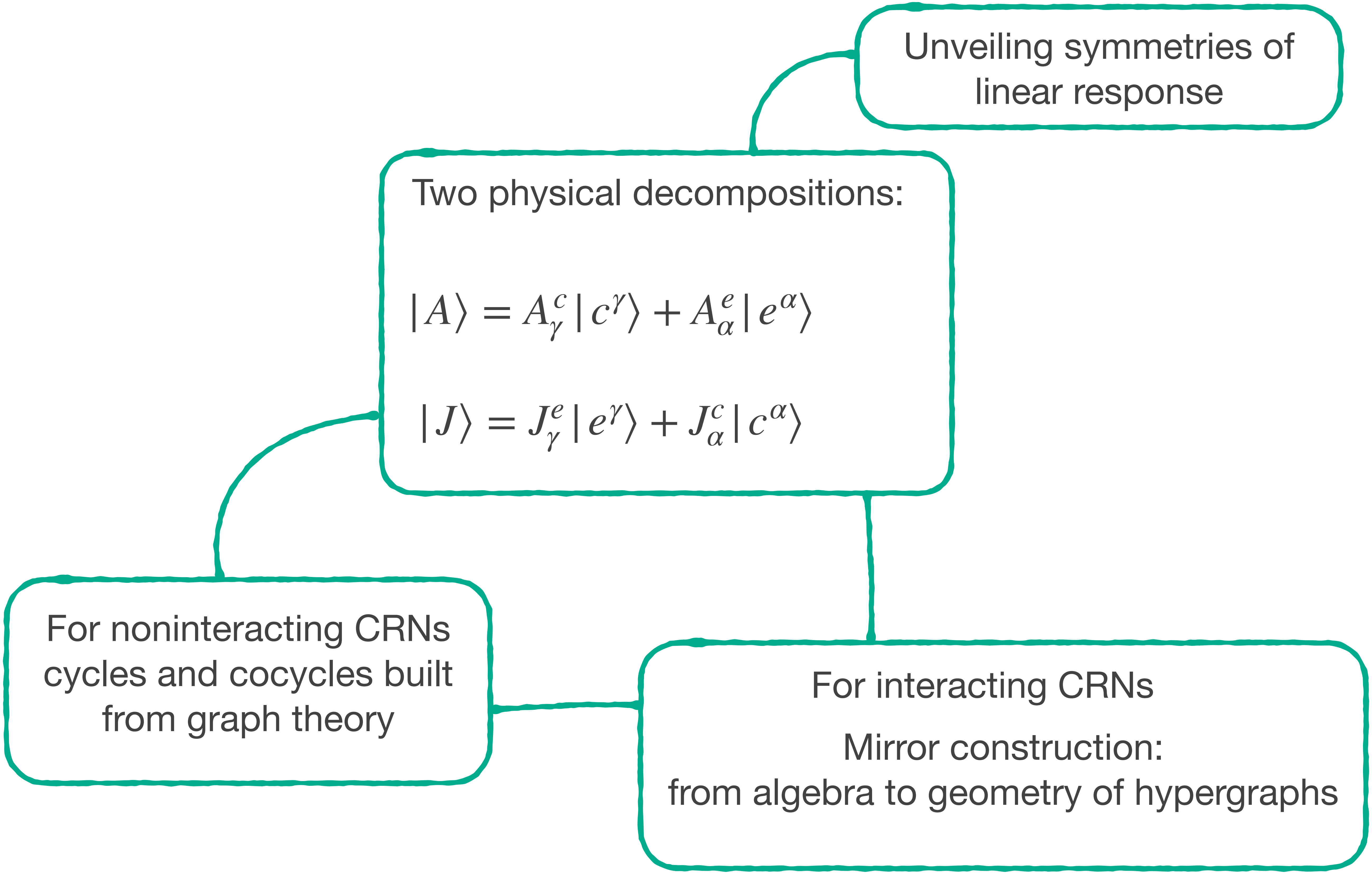
$$|A\rangle = A^c_\gamma \, | \, c^\gamma \rangle + A^e_\alpha \, | \, e^\alpha \rangle$$

$$|J\rangle = J^e_\gamma \, | \, e^\gamma \rangle + J^c_\alpha \, | \, c^\alpha \rangle$$

For noninteracting CRNs
cycles and cocycles built
from graph theory

For interacting CRNs

Mirror construction:
from algebra to geometry of hypergraphs



Unveiling symmetries of linear response

Two physical decompositions:

$$|A\rangle = A^c_\gamma \,|\, c^\gamma\rangle + A^e_\alpha \,|\, e^\alpha\rangle$$

$$|J\rangle = J^e_\gamma \,|\, e^\gamma\rangle + J^c_\alpha \,|\, c^\alpha\rangle$$

For noninteracting CRNs cycles and cocycles built from graph theory

For interacting CRNs

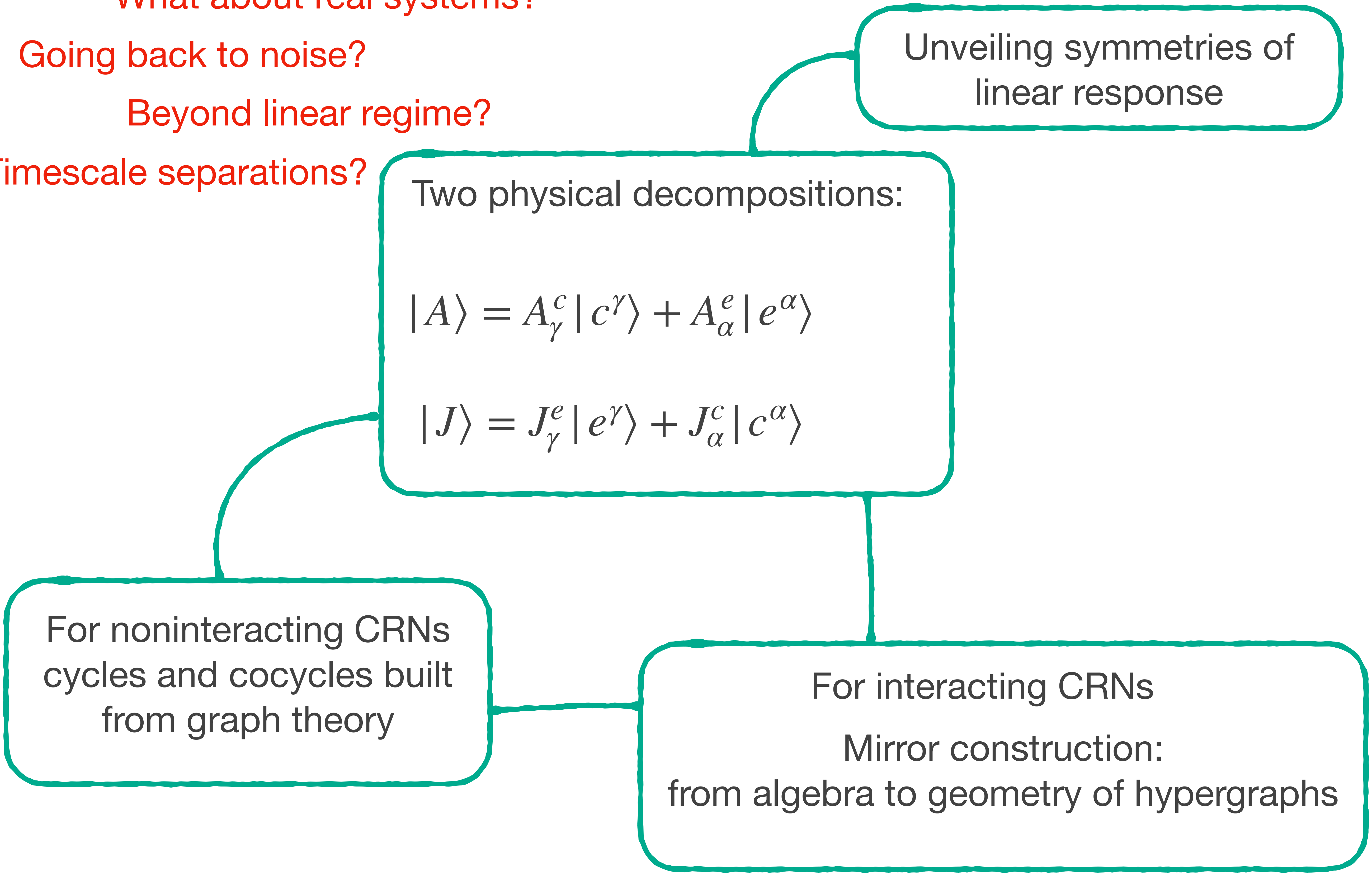
Mirror construction:
from algebra to geometry of hypergraphs

What about real systems?

Going back to noise?

Beyond linear regime?

Timescale separations?



Unveiling symmetries of linear response

Two physical decompositions:

$$|A\rangle = A^c_\gamma \,|\, c^\gamma\rangle + A^e_\alpha \,|\, e^\alpha\rangle$$

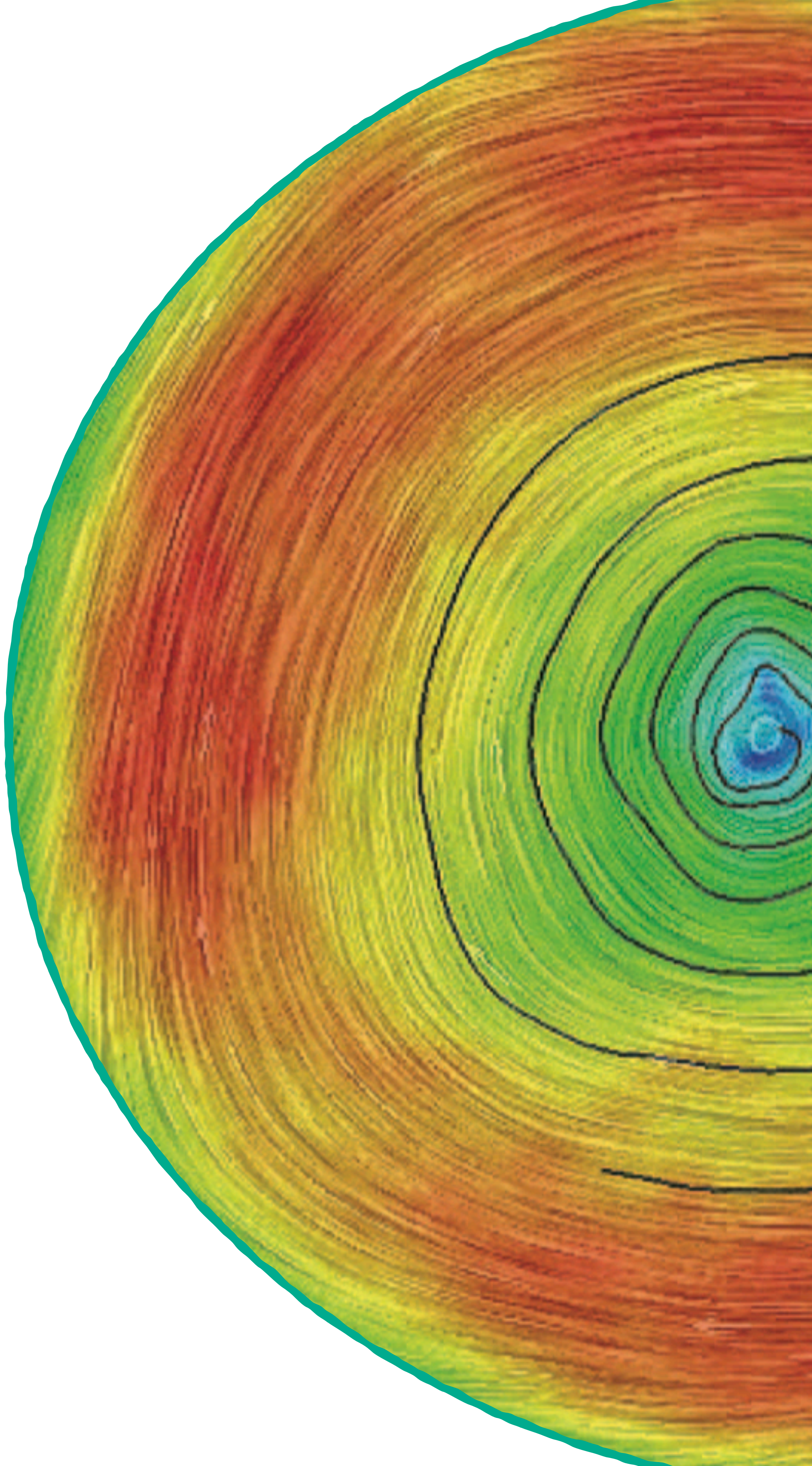
$$|J\rangle = J^e_\gamma \,|\, e^\gamma\rangle + J^c_\alpha \,|\, c^\alpha\rangle$$

For noninteracting CRNs cycles and cocycles built from graph theory

For interacting CRNs

Mirror construction:
from algebra to geometry of hypergraphs

Thank you!



A decomposition for the currents

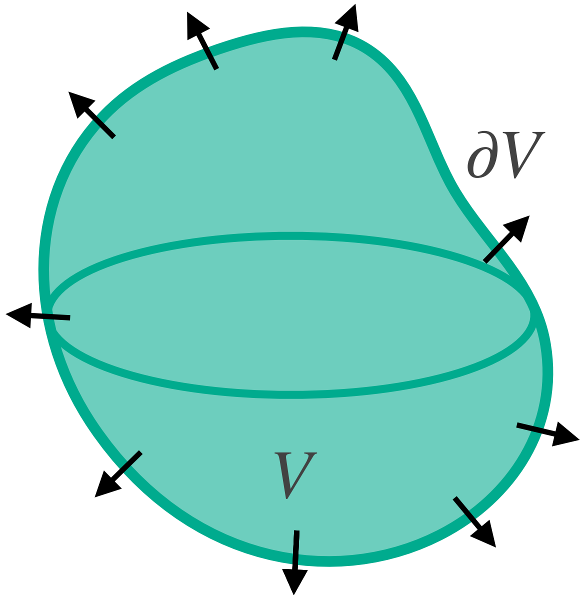
Decomposition of the currents $\in \mathbb{R}^R$ in terms of cochords and cycles

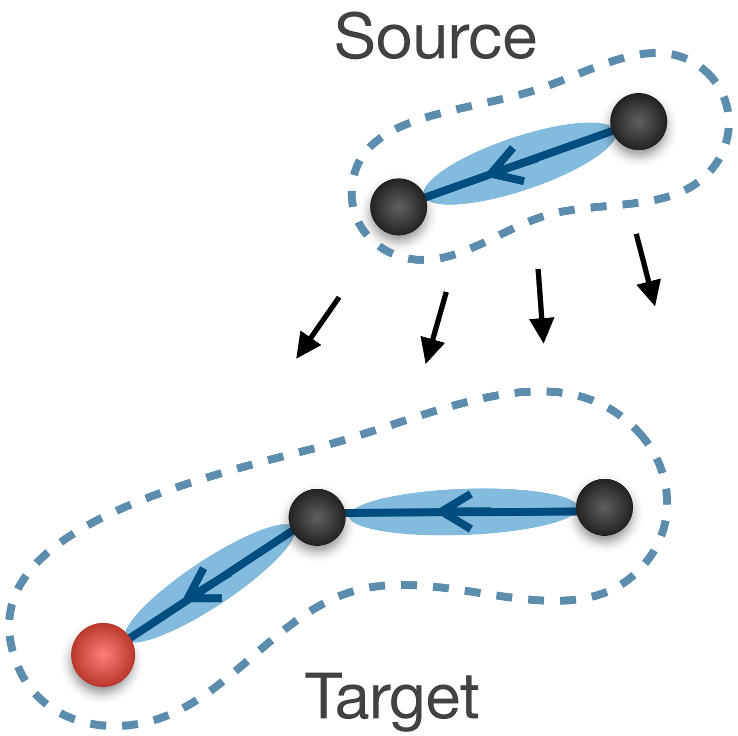
$$|J\rangle = J^e_\gamma\,|e^\gamma\rangle + J^c_\alpha\,|c^\alpha\rangle$$

Non-orthogonal decomposition

$$\langle e^\gamma | c^\alpha \rangle \neq 0$$

What is a cocycle?

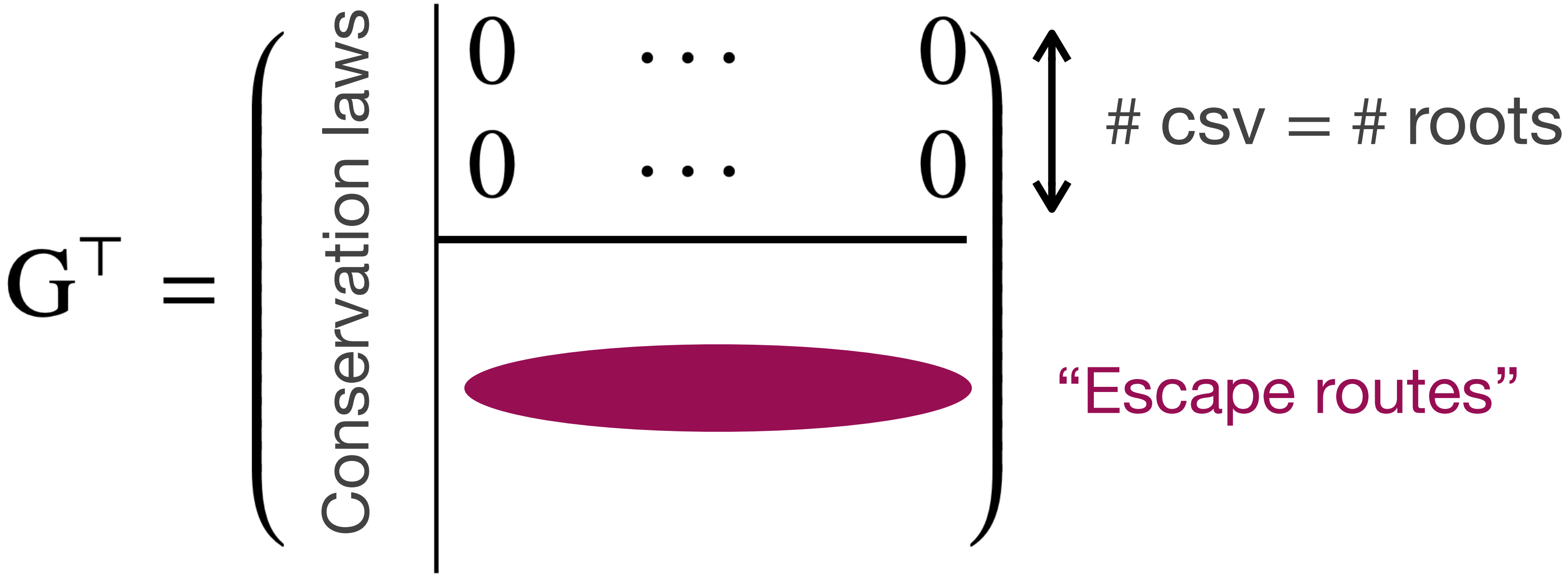




Effective
surface integral

$$\langle J | c^\gamma \rangle = J^e_\gamma$$

Non-local



$$G^{\top} = \left(\begin{array}{c|ccc} \text{Conservation laws} & 0 & \cdots & 0 \\ & 0 & \cdots & 0 \\ \hline & & & \\ & & & \end{array}\right)$$

csv = # roots

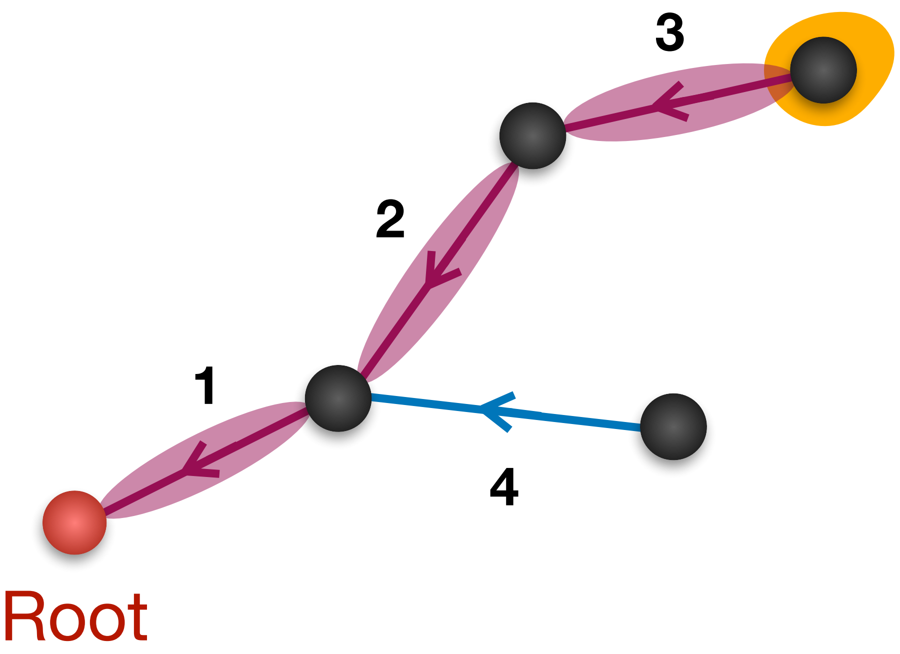
“Escape routes”

$$G^{\top} = \left(\begin{array}{c|cccc} 1 & 0 & 0 & 0 & 0 \\ \hline 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 \end{array}\right)$$

1 root

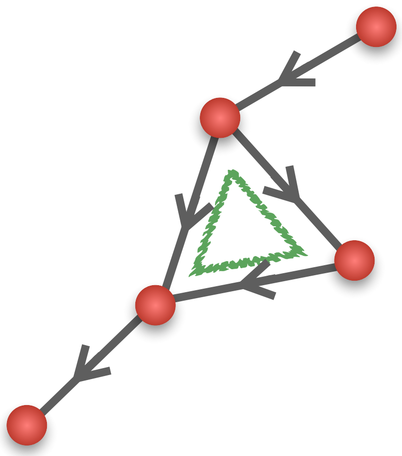
$\gamma = 3$

Mass conservation law



Connection to chemistry

How is WK violated?

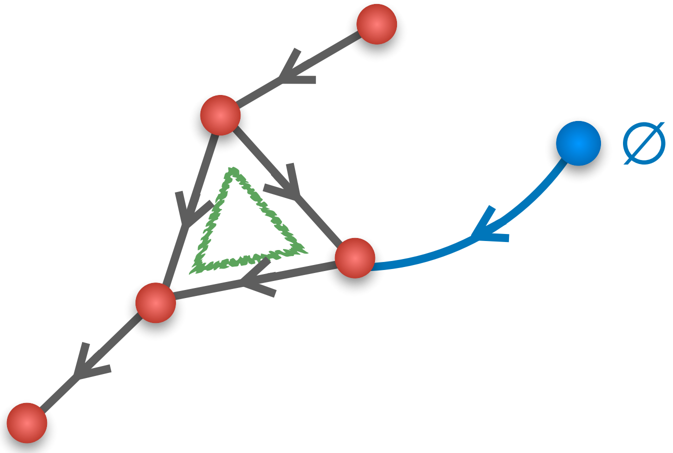


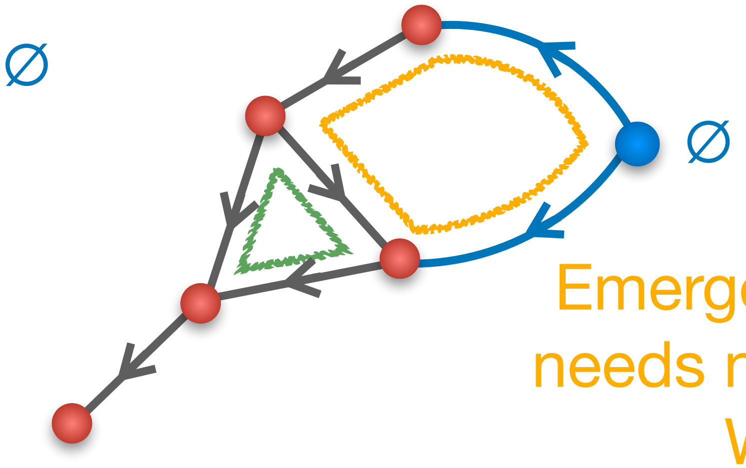
External reservoir

● $\varnothing$

$$\varnothing \underset{\gamma_i^-}{\overset{\gamma_i^+}{\rightleftharpoons}} Y_i$$

$$X_i \underset{k_\rho^-}{\overset{k_\rho^+}{\rightleftharpoons}} X_j$$





Emergent cycle
needs no to fulfill
WK

$$A = -\mathbb{S}^\top \mu + a$$

Local detailed balance (valid far from equilibrium)

To sum up

Complementary oblique decomposition for currents and affinities:

$$|A\rangle = \underbrace{A^c_\gamma\,|c^\gamma\rangle}_{\in\ \mathrm{Im}\ \mathbb{S}^\top} + A^e_\alpha\,|e^\alpha\rangle$$

$$\perp$$

$$|J\rangle = J^e_\gamma\,|e^\gamma\rangle + \underbrace{J^c_\alpha\,|c^\alpha\rangle}_{\in\ \mathrm{Ker}\,\mathbb{S}}$$

Linear response(s)

Two ways to perturb equilibrium:

→ Finite-time relaxation due to initial condition $\neq x^{eq}$

→ Nonequilibrium steady-state due to external drive (chemostatting)

How are these two protocols related?

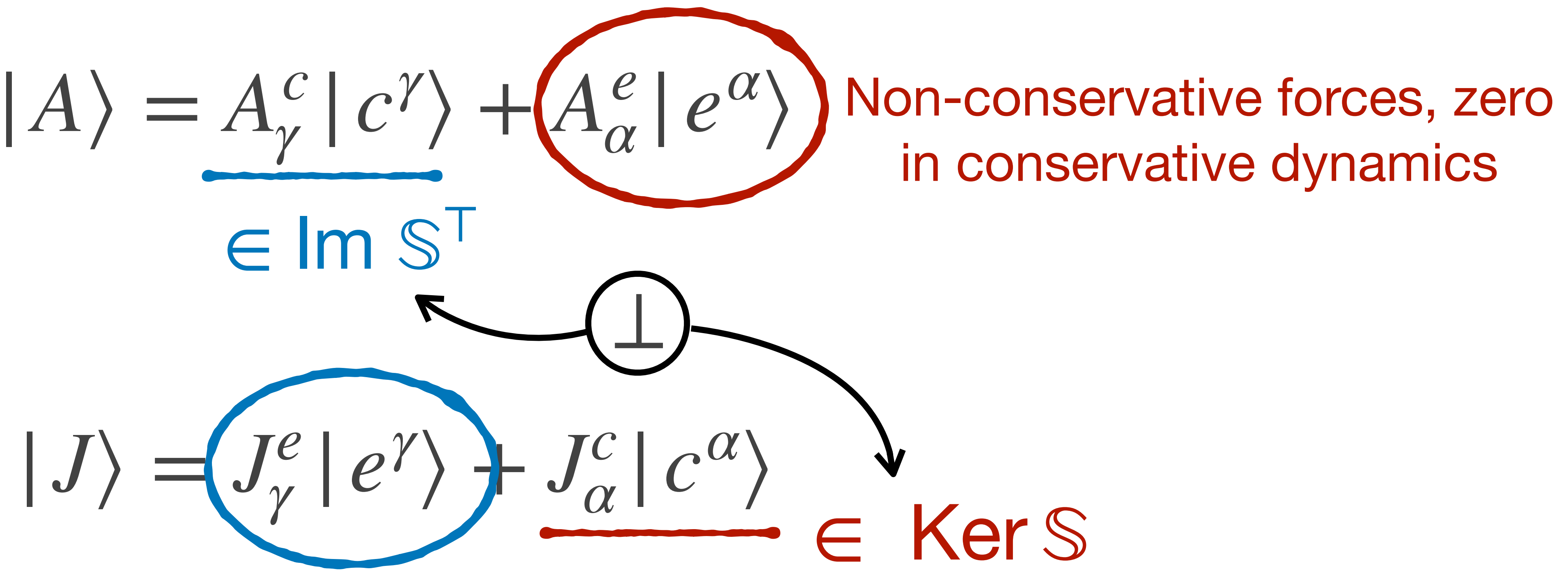
Linear regime:

$$J_\rho = \Lambda_\rho(x)\left(1 - e^{-A_\rho}\right) \xrightarrow{A_\rho \ll 1} |J\rangle = \Lambda\,|A\rangle$$

$(R \times R)$ Diagonal response matrix

To sum up

Complementary oblique decomposition for currents and affinities:



$$|A\rangle = \underline{A^c_\gamma\,|\,c^\gamma\rangle} + \boxed{A^e_\alpha\,|\,e^\alpha\rangle}$$

Non-conservative forces, zero
in conservative dynamics

$\in \mathrm{Im}\ \mathbb{S}^\mathsf{T}$

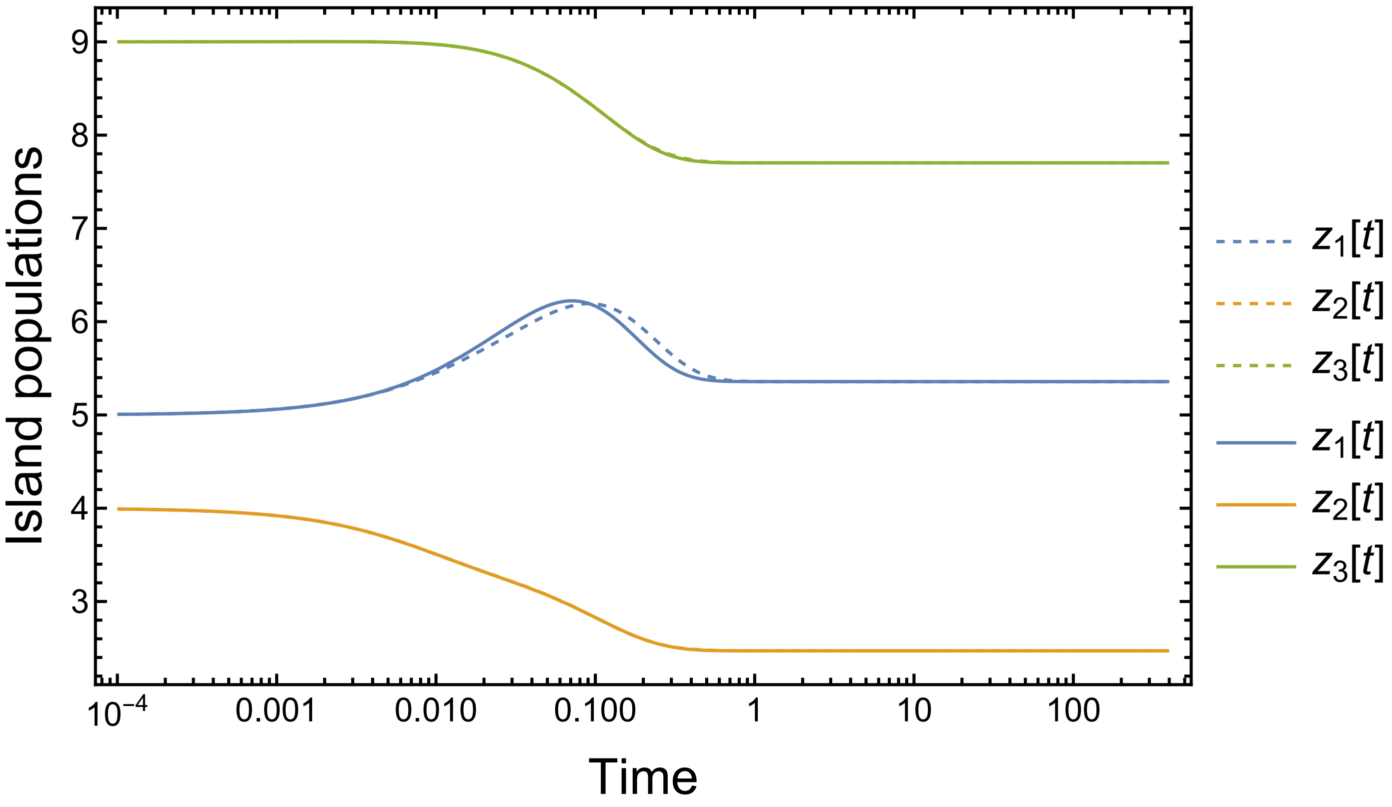
$\perp$

$$|J\rangle = \boxed{J^e_\gamma\,|\,e^\gamma\rangle} + \underline{J^c_\alpha\,|\,c^\alpha\rangle}$$

$\in$ Ker $\mathbb{S}$

Transient currents, zero
in the long time limit

Relaxation inhibiting a generic reaction



Relaxation inhibiting a cocycle

New timescale