# Steady-state invariants for complex-balanced networks

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# Motivation: model selection

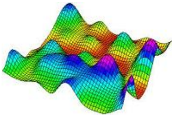
## Driving problem

Given observed data and multiple candidate models for the process generating that data, which is the most appropriate model for that process?

Standard approach: fit parameters, minimize error, assess

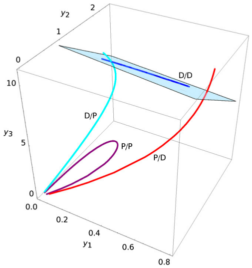
- Typically involves optimization over parameter space
- Can be hard due to nonlinearities and high dimensionality

Can we get by without parameter fitting?



# Summary of previous work

- Chemical reaction network: $$\sum_{j=1}^{N} r_{ij} X_j \xrightarrow{\kappa_i} \sum_{j=1}^{N} p_{ij} X_j, \quad i = 1, \ldots, R$$
- Mass-action dynamics: $$\dot{x}_j = \sum_{i=1}^{R} \kappa_i (p_{ij} - r_{ij}) \prod_{k=1}^{N} x_i^{r_{ik}}, \quad j = 1, \ldots, N$$
- Basic idea:
  - Assume steady state, fix $j$, define $\alpha_i = \kappa_i (p_{ij} - r_{ij})$ and $\xi_i = \prod_{k=1}^{N} x_i^{r_{ik}}$
  - Model compatibility implies $\sum_{i=1}^{R} \alpha_i \xi_i = 0$
  - 'Complex' concentrations $\xi \in \mathbb{R}^R$ are coplanar
  - Test coplanarity of data without regard to parameter values (SVD)
  - Can interpret coplanarity statistically




Manrai and Gunawardena (2008) *Biophys J*

Harrington, Ho, Thorne, and Stumpf (2012) *PNAS*, in press

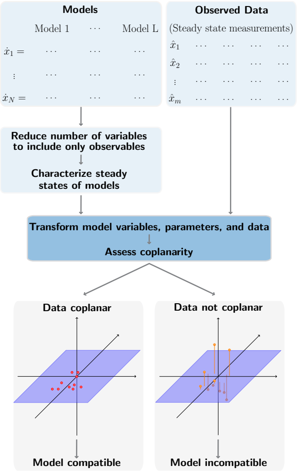
# Summary of previous work

Technical details:

- Can often measure only a subset of species
- Eliminate all others using Gröbner bases
  - Nonlinear, multivariate generalization of Gaussian elimination
  - Treat rate parameters symbolically
- Resulting invariants:

$$\sum_{i=1}^{n} \alpha_i \xi_i, \quad \alpha_i(\kappa) \text{ nonlinear}$$

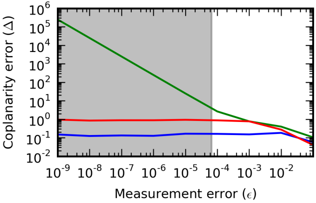
- 'Lifting' procedure linearizes in a higher-dimensional space
- Statistics via a chi distribution bound

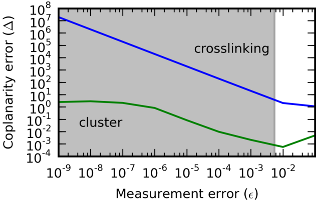


# Summary of previous work

Parameter-free statistical model discrimination

- Applied to models of multisite phosphorylation and cell death signaling
- Some success, reasonable rejection power




Complications:

- Choice of monomial ordering, convergence for Gröbner basis calculations
- Division by (symbolic) zero
- Existence of trivial invariants ($\alpha = 0$)

# Beyond Gröbner bases

- Use chemical reaction network theory to reveal linearity:

$$\dot{x}_j = \sum_{i=1}^{R} \kappa_i (p_{ij} - r_{ij}) \prod_{k=1}^{N} x_i^{r_{ik}}$$

$$\dot{x} = f(x) = YA_\kappa \Psi(x)$$

$$\begin{tikzcd} \mathbb{R}^{\mathcal{C}} \arrow[d, "Y"'] & \mathbb{R}^{\mathcal{C}} \arrow[l, "A_\kappa"'] \\ \mathbb{R}^{\mathcal{S}} & \mathbb{R}^{\mathcal{S}} \arrow[l, "f"] \arrow[u, "\Psi"'] \end{tikzcd}$$

  - Species: $\mathcal{S} = \{X_j \mid j = 1, \ldots, N\}$
  - Complexes: $\mathcal{C} = \left\{ \sum_{j=1}^{N} r_{ij} X_j ,\ \sum_{j=1}^{N} p_{ij} X_j \mid i = 1, \ldots, R \right\}$
  - $\Psi$ : nonlinear species-to-complex map
  - $A_\kappa$: complex-to-complex rate matrix
  - $Y$ : complex-to-species stoichiometric matrix
- Eliminate in complex space using linear methods
  - Related: Karp et al. (2012) *J Theor Biol*, in press
- Result: complex-linear invariants

# Main results

## Definition

A chemical reaction network is complex-balanced if $A_\kappa \Psi(x) = 0$ at any steady state $x \in \mathbb{R}^{\mathcal{S}}$. A network is unconditionally complex-balanced if it is complex-balanced for all rates $\kappa$.

For complex-balanced networks:

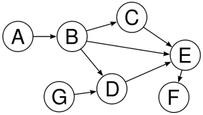
- Complex-linear invariants in any subset $\mathcal{C}^* \subseteq \mathcal{C}$ can be computed
- Unconditionally nontrivial iff certain graph-theoretic conditions hold

Operationally:

- Can tell if the complexes $\mathcal{C}^*$ are coplanar "without any work"
- Measure data, check complex balancing, test coplanarity
  - Graph conditions for complex balancing (deficiency zero by Feinberg)
- No ordering, convergence, division issues; correctness guaranteed

# General approach

- For complex-balanced networks, can eliminate only on $A_\kappa$
- $A_\kappa$ is highly structured (Laplacian)
  - Non-positive diagonal entries
  - Non-negative off-diagonal entries
  - Non-positive column sums
- Use structure to understand elimination procedure




Elimination on Laplacian graphs: a well-studied problem?

- May exist shorter, simpler proofs
- Any advice/perspective very much appreciated

# Preliminaries

- Pick a subset $\mathcal{C}^* \subseteq \mathcal{C}$ and let $p = |\mathcal{C}^*|$, $q = n - p$
- Assume first that the network is closed (no synthesis or degradation)
- Block partition of $A_\kappa \in \mathbb{R}^{n \times n}$:

$$A_\kappa = \begin{array}{cc} \begin{bmatrix} A & B \\ C & D \end{bmatrix} & \begin{array}{c} p \\ q \end{array} \\ \begin{array}{cc} \;p\; & \;\;q\;\; \end{array} & \end{array}$$

- Write in reduced form
  - Drop all complexes for which the corresponding column of $B$ vanishes
  - Redefine all entities as appropriate
  - Reorder $\mathcal{C} \setminus \mathcal{C}^*$ into irreducible components, $D$ becomes block triangular
- If $q = 0$ (nothing left), then done ($A$ provides invariant coefficients)
- Otherwise, coefficients given by Schur complement $A_\kappa / D = A - BD^{-1}C$

# Elimination of complexes

## Lemma

*$D$ is nonsingular (furthermore, a minus M-matrix).*

## Proof (nonsingularity).

If $D$ is irreducible, then it is irreducibly diagonally dominant (since $B \neq 0$), hence nonsingular. Otherwise, induct on irreducible components by writing

$$D = \begin{bmatrix} D_{11} & \\ D_{21} & D_{22} \end{bmatrix},$$

where $D_{11}$ is irreducible and $D_{22}$ is nonsingular by hypothesis. Then $D_{11}$ is irreducibly diagonally dominant and nonsingular, so $D$ is nonsingular. □

## Theorem

*The complexes $\mathcal{C} \setminus \mathcal{C}^*$ can always be eliminated.*

# Nontrivial invariants

- $A_\kappa / D$ always exists but can vanish (trivial invariants)
- When is $A_\kappa / D \neq 0$ unconditionally?
  - Has a strictly positive entry unconditionally
  - Has a strictly negative entry unconditionally

**Definition**

Write $c \rightsquigarrow c'$ if there exists a path from $c$ to $c'$ ($c \to \cdots \to c'$).

**Lemma**

*$-D^{-1} \geq 0$ and has positive diagonal entries.*

# Unconditional positive entry

## Theorem

*$A_\kappa/D$ contains a positive entry iff there exist distinct $c, c' \in \mathcal{C}^*$ such that $c \rightsquigarrow c'$.*

## Proof ($\Leftarrow$).

Induct on path length. Base case: obvious. In general, let $c \rightsquigarrow c'' \longrightarrow c'$ and eliminate $c \rightsquigarrow c''$. This introduces a positive entry corresponding to $c \longrightarrow c''$ by hypothesis. Use $c'' \longrightarrow c'$ and diagonal positivity of $-D^{-1}$ to deduce $(A_\kappa/D)_{ij} > 0$, where $i, j$ are the indices of $c', c$. □

# Unconditional positive entry

## Theorem

*$A_\kappa/D$ contains a positive entry iff there exist distinct $c, c' \in \mathcal{C}^*$ such that $c \rightsquigarrow c'$.*

## Proof ($\Rightarrow$).

Induct on irreducible components. Base case: obvious. In general, write

$$B = \begin{bmatrix} B_1 & B_2 \end{bmatrix}, \quad C = \begin{bmatrix} C_1 \\ C_2 \end{bmatrix}, \quad D = \begin{bmatrix} D_{11} & \\ D_{21} & D_{22} \end{bmatrix}$$

with $D_{11}$ irreducible, and let $\mathcal{C} \setminus \mathcal{C}^* = \mathcal{C}_1 \cup \mathcal{C}_2$. If $B_2, C_2 \neq 0$, then $c \rightsquigarrow c'$ through $\mathcal{C}_2$ by induction; if $B_1, C_1 \neq 0$, through $\mathcal{C}_1$; if $B_2, C_1 \neq 0$, through $\mathcal{C}_1$ then $\mathcal{C}_2$. $\square$

# Unconditional negative entry

## Theorem

*$A_\kappa/D$ contains a negative entry unconditionally iff there exists $c \in \mathcal{C}^*$ and $c'$ outside the irreducible component containing $c$ in the subgraph on $\mathcal{C} \setminus \mathcal{C}^* \cup \{c\}$ such that $c \rightsquigarrow c'$.*

## Proof.

Take submatrix $A_\kappa(c)$ with the first block corresponding only to $c$. Clearly, $A_\kappa/D$ has no negative entry iff $A_\kappa(c)/D = 0$ for all $c$. If $A_\kappa(c)/D < 0$, then $A_\kappa(c)$ is nonsingular since $D$ is nonsingular. Reorder $A_\kappa(c)$ into irreducible components, and let $D_{ii}$ be the block of $D$ corresponding to the irreducible component containing $c$ in the subgraph. Then $A_\kappa(c)/D < 0$ unconditionally iff $D_{ii}$ is strictly diagonally dominant in at least one column. Thus, we require an outgoing edge. □

# Some comments

- Necessary and sufficient conditions for unconditionally nontrivial complex-linear invariants
- Intuition:
  - Positive entry ($c \rightsquigarrow c'$): think cascade, proportional by equilibrium constant
  - Negative entry ($c \rightsquigarrow$ out): has a sink, concentration goes to zero
- Extension to open systems: same conditions as above **or**
  - There exists $c \in \mathcal{C}^*$ such that $c \to \emptyset$ (strict diagonal dominance)
  - There exists $c \in \mathcal{C}^*$ such that $\emptyset \to c$ (if include constant term)
- Can generalize to other kinetics (e.g., Michaelis-Menten)

# Examples

$$\begin{tikzcd} A+B \arrow[r, shift left] & AB \arrow[l, shift left] \arrow[r] & A+C \arrow[r, shift left] & AC \arrow[l, shift left] \arrow[lll, bend left] \end{tikzcd}$$

$$A+B \rightleftarrows AB \qquad C+D \rightleftarrows CD$$

$$A \rightleftarrows B \longrightarrow C \rightleftarrows D$$

$$E+A \rightleftarrows EA \longrightarrow E+B \qquad F+B \rightleftarrows FB \longrightarrow F+A$$

# Conclusions

- Graph-theoretic conditions for unconditionally nontrivial invariants
- Only fast graph algorithms required; elimination comes for free
- Applications to parameter-free model discrimination
- Possible extensions beyond complex-balanced networks
  - In general, have to eliminate on $YA_\kappa$
  - Find $Z \in \mathbb{R}^{n \times N}$ such that $ZYA_\kappa$ is "as Laplacian as possible"
- Preliminary work, can possibly still go further

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