QSSA and Solvability

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Chemical Reaction Networks

A *CRN* is described by three sets:

- species, $\mathcal{S}$
- complexes, $\mathcal{C} \subseteq \mathbb{R}_{\geq 0}^{\mathcal{S}}$ (or $\mathbb{Z}_{\geq 0}^{\mathcal{S}}$)
- reactions, $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$

From these, we get a system of (first order) differential equations

CRN Example

$$\mathsf{E} + \mathsf{S} \underset{\mathsf{k}_{-1}}{\overset{\mathsf{k}_1}{\rightleftharpoons}} \mathsf{E} \cdot \mathsf{S} \xrightarrow{\mathsf{k}_2} \mathsf{E} + \mathsf{P}$$

$$\begin{aligned} \mathcal{S} &= \{E,\ S,\ P,\ E \cdot S\} \\ \mathcal{C} &= \{E + S,\ E \cdot S,\ E + P\} \\ \mathcal{R} &= \{(c_1, c_2), (c_2, c_1), (c_2, c_3)\} \end{aligned}$$

CRN Example

$$\mathsf{E} + \mathsf{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathsf{E} \cdot \mathsf{S} \xrightarrow{k_2} \mathsf{E} + \mathsf{P}$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[E \cdot S] + k_2[E \cdot S]$$

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[E \cdot S]$$

$$\frac{d[E \cdot S]}{dt} = k_1[E][S] - k_{-1}[E \cdot S] - k_2[E \cdot S]$$

$$\frac{d[P]}{dt} = k_2[E \cdot S]$$

QSSA Method

- Reduce to a model with fewer ODEs
- Quasi-steady-state-assumption (QSSA) simplifies the system by assuming some components do not accumulate
- Eliminates some intermediates by replacing ODEs with algebraic constraints

QSSA Example

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{E} \cdot \mathrm{S} \xrightarrow{k_2} \mathrm{E} + \mathrm{P}$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[E \cdot S] + k_2[E \cdot S]$$

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[E \cdot S]$$

$$\frac{d[E \cdot S]}{dt} = k_1[E][S] - k_{-1}[E \cdot S] - k_2[E \cdot S] \quad = 0$$

$$\frac{d[P]}{dt} = k_2[E \cdot S]$$

QSSA Example

$$0 = k_1[E][S] - k_{-1}[E \cdot S] - k_2[E \cdot S]$$

$$(k_{-1} + k_2)[E \cdot S] = k_1[E][S]$$

$$[E \cdot S] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

Galois Theory

- If L/k is a normal, separable extension of fields, the automorphisms of L over k form a group G (the Galois group)
- G is solvable if (and only if) each $\alpha \in L$ can be expressed in terms of elements of k, roots of unity, radicals, and $+, -, \times, \div$
- Rules out a "quadratic formula" for polynomials with degree 5 or higher

Galois Theory Examples

solvable:

$$x^2 - 2 \longleftrightarrow \mathbb{Z}/2\mathbb{Z}$$
$$x^4 - 5 \longleftrightarrow D_8$$

insolvable:

$$x^5 - 3x^2 + 1 \longleftrightarrow S_5$$

$(k = \mathbb{Q})$

QSSA & Galois Theory

- Work over $\mathbb{k} = \mathbb{Q}(k_i, c_j, \ldots)$; adjoin all relevant constants

$$\begin{aligned} \text{QSSA} &\Leftrightarrow \text{systems of polynomials} \\ &\Leftrightarrow \text{ideals in } \mathbb{k}[x_1, \ldots, x_n] \end{aligned}$$

- Examples exist which reduce to insoluble univariate polynomials (over $\mathbb{k}$)

Main Questions

Under what circumstances will QSSA work?
When will it fail?

1. classes of networks
2. structural properties
3. small counterexamples
4. subnetworks/extensions

What does "possible" mean?

Many different ways of framing QSSA:

- Finitely many solutions
- Solutions expressible in radicals

What does "possible" mean?

Many different ways of framing QSSA:

- Finitely many solutions
- Solutions expressible in radicals
- Nondegenerate solutions
- Real solutions
- Positive solutions

Algebra Preliminaries

Fix ideals $I, J \subseteq k[x_1, ..., x_n]$

- the *variety*, $V(I) = \{\text{zeros of } I \text{ in } k^n\}$
- similarly, $V^a(I) = \{\text{zeros of } I \text{ in } (k^a)^n\}$
- a *Gröbner basis* of I: generalization of Gaussian Elimination
- the *ideal quotient*, $I : J$, which generalizes division

Reduction to Univariate Case

Lemma

Let I be an ideal in $k[x_1, ..., x_n]$. Then $V^a(I)$ is finite if and only if each intersection $I \cap k[x_i]$ is nonzero.

Almost always the case when using QSSA

Computing Intersections

Lemma

Let I be an ideal in $k[x_1, \ldots, x_n]$ with Gröbner basis G w.r.t.

$$x_1 > x_2 > \ldots > x_n$$

Then $G \cap k[x_n]$ generates $I \cap k[x_n]$.

For reduced GBs, there is a unique generator

Checking Solvability

- Together, these suggest an algorithm:
  1. Find the generators of $I \cap k[x_i]$
  2. Compute their Galois groups
  3. Check for solvability
- If all the generators are solvable, $V(I)$ has solvable entries in every coordinate

A Simple Case

Lemma

Fix $I \subseteq k[x,y]$, k algebraically closed. If there exist $f_1, f_2 \in I$ such that f_1 is irreducible and $f_2 \notin \langle f_1 \rangle$, then $V(I)$ is finite.

Lemma

Let $I = \langle f_1, ..., f_n \rangle$ and $\deg(f_i) = d_i$. If $V(I)$ is finite, then $\deg(g) \leq d_1 d_2 ... d_n$, where $I \cap k[x_i] = \langle g \rangle$.

A Simple Case

- S_4 is solvable
- if $\deg(f) = n$, Gal(f/k) embeds in S_n

Proposition (S.)

If a CRN has at-most-bimolecular kinetics and we choose two "chemically reasonable" intermediates, QSSA is always possible.

Example

$$A \xrightarrow{k_1} 2X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2Y$$

$$X + Y \xrightarrow{k_3} B$$

$$\frac{dx}{dt} = 0 = -2k_2x^2 - k_3xy + 2k_{-2}y + ak_1$$

$$\frac{dy}{dt} = 0 = -2k_{-2}y^2 - k_3xy + k_2x^2$$

Example

After computing a Gröbner basis, we get

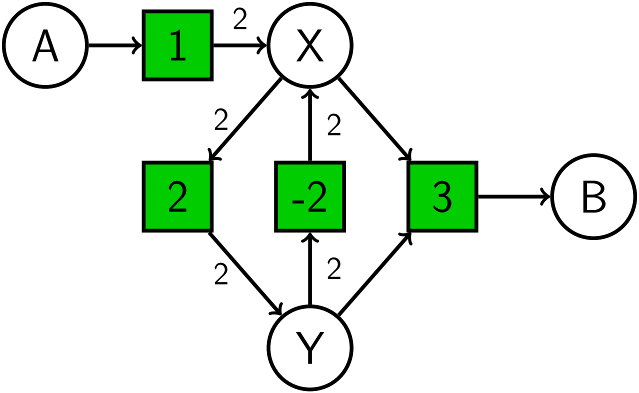
$$\begin{aligned} f(x) =&(8k_{-2}k_2^2 - 3k_2k_3^2)x^4 + (8k_{-2}k_2k_3)x^3 \\ &+ (-8ak_{-2}k_1k_2 + ak_1k_3^2 - 4k_{-2}^2k_2)x^2 \\ &- (2k_{-2}k_1ak_3)x + (2a^2k_{-2}k_1^2) \end{aligned}$$

- $\mathrm{Gal}(f/\mathbb{k})$ is isomorphic to D_8
- For y, we obtain D_8 as well

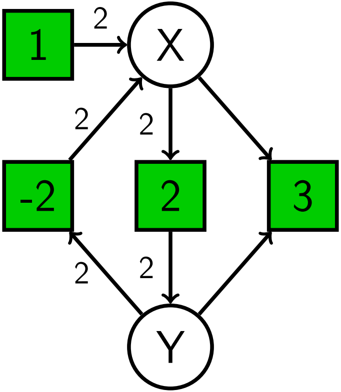
Extending Solvability

- The proposition describes some common systems, but is limited
- In some circumstances solvability can be extended:
  1. "treelike" mechanisms
  2. nondegenerate and/or physically achievable

Oriented Species-Reaction Graph



QSSA OSR Graph



Extending Solvability

Theorem (S.)

Given a QOSR graph H and intermediates $\mathcal{Q}$, QSSA is possible when there exists an equivalence relation $\sim$ on H such that $H/\!\sim$ has no directed cycles and QSSA is possible on each equivalence class in $\mathcal{Q}/\!\sim$ under particular kinds of substitution

Extending Solvability

Corollary (S.)

If we use Proposition 1 to prove solvability for the previous theorem, QSSA is possible for the nondegenerate achievable steady states.

Pantea et al.: "Counterexample"

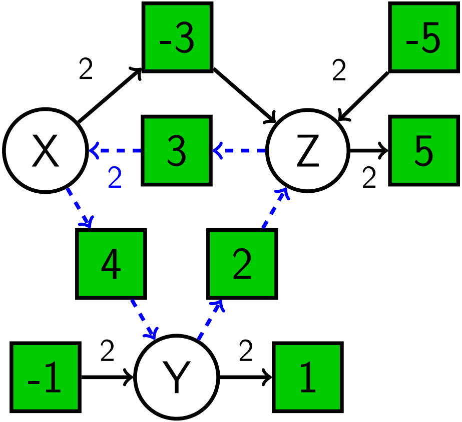
$$2\,Y \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2\,B$$

$$Y + B \xrightarrow{k_2} Z + A$$

$$Z + B \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} 2\,X$$

$$A + X \xrightarrow{k_4} Y + B$$

$$2\,Z \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} 2\,A$$



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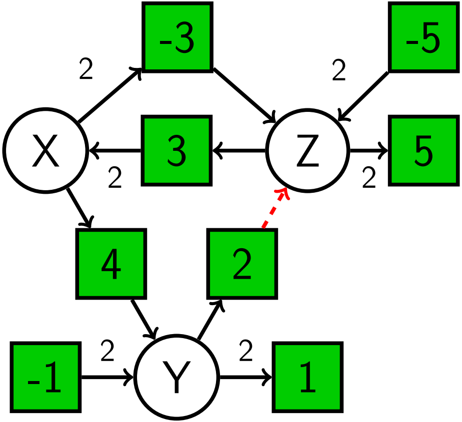
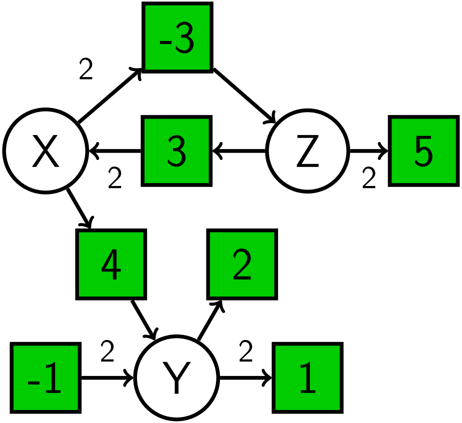


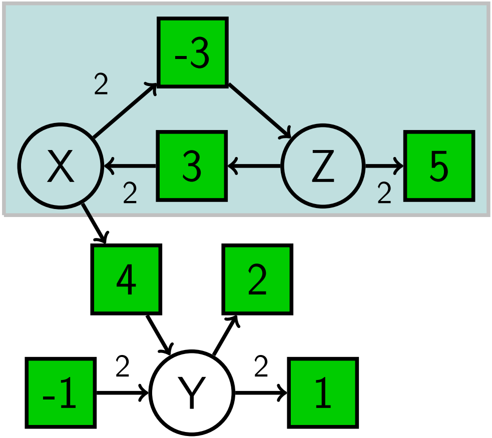
Remove reaction -5 as well

Modified Pantea Mechanism



Modified Pantea Mechanism

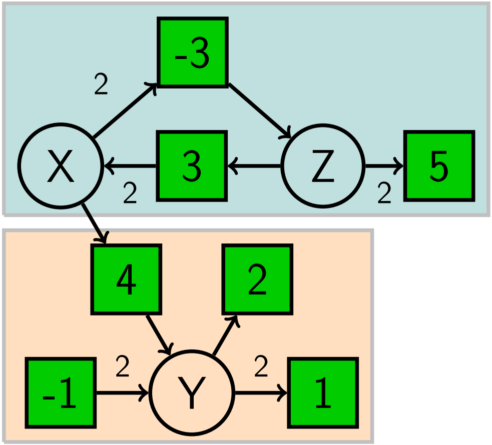
$Q_1 = \{X, Z\}$



Modified Pantea Mechanism

$$\mathcal{Q}_1 = \{X, Z\}$$

$$\mathcal{Q}_2 = \{Y\}$$



Modified Pantea Mechanism

$$\mathcal{Q}_1 = \{X, Z\} \text{ and } \mathcal{Q}_2 = \{Y\}$$

$$\Phi_x = -2k_{-3}x^2 - k_4 ax + 2k_3 bz$$
$$\Phi_y = -2k_1 y^2 - k_2 by + 2k_{-1} b^2 + k_4 ax$$
$$\Phi_z = -2k_5 z^2 - k_3 bz + k_{-3}x^2$$

$$x \longleftrightarrow S_3 \text{ or } \{e\}$$
$$y \longleftrightarrow S_4 \times \mathbb{Z}_2 \text{ or } \mathbb{Z}_2$$
$$z \longleftrightarrow S_3 \text{ or } \{e\}$$

Modified Pantea Mechanism

- Multiple Galois groups arise when a polynomial is reducible
- In this case, $\{e\}$ and $\mathbb{Z}_2$ correspond to *degenerate* solutions ($x = 0$ or $z = 0$)
- These are irrelevant for actual chemistry, so we would like to remove them

Modified Pantea Mechanism

- If we want to remove the zeros of an ideal J from another ideal I, we take their *saturation*:

$$I : J^{\infty} = \bigcup_{m=1}^{\infty} I : J^{m}$$

- Similar to performing division

Modified Pantea Mechanism

- To encode nondegeneracy we want to cut out

$$x = 0 \textit{ or } y = 0 \textit{ or } z = 0$$

- Which is summarized by $J = \langle xyz \rangle$
- The ideal we want:

$$I'_{\mathcal{Q}} = I_{\mathcal{Q}} : J^{\infty}$$

Modified Pantea Mechanism

- After performing the same steps to find the Galois groups:

$$x \longleftrightarrow S_3$$
$$y \longleftrightarrow S_4 \times \mathbb{Z}_2$$
$$z \longleftrightarrow S_3$$

Saturation

- Saturation is not immediately useful: it is easy to ignore a few solutions, but...

Conjecture

Corollary 1 only requires nondegeneracy (i.e. imaginary or negative concentrations are permissible)

Saturation

- Saturation removes the (infinitely many) degenerate solutions ahead of time
- This may (not) simplify computations
- Almost all "counterexamples" in CRNs lie at boundaries, so saturation may help generalize some of these results

Future Directions

- More (general) finiteness criteria
- More solvability criteria
- CRN structure $\Leftrightarrow$ Galois group
- Weakening QSSA to nondegenerate and/or achievable concentrations

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