Dynamics of Weakly Reversible Reaction Networks and the Global Attractor Conjecture

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My plan

1. This will be a technical talk.

2. Give details of proof of Global Attractor Conjecture in single linkage class case.

Notation

Definition

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Definition

The vectors

$$y_k' - y_k \in \mathbb{Z}^N,$$

will be called reaction vectors.

Notation

Definition

To each reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, there is a unique directed graph, called a reaction diagram, constructed in the following manner:

1. The nodes of the graph are the complexes, $\mathcal{C}$.
2. A directed edge from y to y' exists if and only if $y \to y' \in \mathcal{R}$.

Example.

$$S_1 + S_2 \leftrightarrows S_3 \to S_6 + S_2, \qquad S_2 \leftrightarrows S_5 + S_4, \qquad \emptyset \leftrightarrows S_4.$$

Definition

Each connected component of the reaction diagram is termed a linkage class of the graph.

Structure of a chemical reaction network

Definition

The chemical reaction network is said to be weakly reversible if each linkage class of the corresponding reaction diagram is strongly connected.

Mass-action kinetics

For a general reaction network, the rate of the kth reaction:

$$\kappa_k(t)x(t)^{y_k},$$

where the $\kappa_k(t)$ are bounded (above and below) functions of times.

And the ODE governing the system is

$$\dot{x}(t) = \sum_k \kappa_k(t)x(t)^{y_k}(y_k' - y_k).$$

ω-limit points, Persistence, and some Conjectures

Definition

Let $\phi(t, x_0)$ be a solution to a dynamical system in $\mathbb{R}^N$ with initial condition x_0. The set of *ω-limit points* for this trajectory is

$$\omega(x_0) \stackrel{\text{def}}{=} \{x \in \mathbb{R}^N \ : \ \phi(t_n, x_0) \to x \text{ for some sequence } t_n \to \infty\}.$$

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Definition

A bounded trajectory, $x(t)$, is called persistent if

$$\omega(x_0) \cap \partial \mathbb{R}^N_{\geq 0} \; = \; \emptyset.$$

A system for which each trajectory remains bounded is called persistent if each trajectory is persistent.

Idea: no species dies out.

Persistence conjecture

Persistence Conjecture (Feinberg - 1987): Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with mass action kinetics. Suppose:

1. The network is weakly reversible and
2. each trajectory remains bounded.

Then this system is persistent.

Complex-Balanced Systems

Definition

An equilibrium $c \in \mathbb{R}^N_{\geq 0}$ is said to be complex-balanced if the following equality holds for each $\eta \in \mathcal{C}$:

$$\sum_{\{k \mid y_k = \eta\}} \kappa_k c^{y_k} = \sum_{\{k \mid y'_k = \eta\}} \kappa_k c^{y_k}.$$

A complex-balanced system is a system that admits a complex-balancing equilibrium.

Behavior of Complex-Balanced Systems

Theorem (Horn, Jackson, Feinberg - 1972)

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be a complex-balanced system. Then, within the interior of each positive class, P, there is precisely one equilibrium value, c, and that equilibrium is:*

1. *Complex-balanced.*
2. *Locally asymptotically stable relative to its compatibility class.*

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Global Attractor Conjecture: For a complex-balanced system, each of the equilibria $c \in \mathbb{R}^N_{>0}$ is globally asymptotically stable relative to the interior of its compatibility class P.

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Persistence conjecture implies the global attractor conjecture!

Goal

- We now assume the system is weakly reversible and try to consider what can happen as $x(t_n) \to \partial \mathbb{R}^N$.

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- We now assume the system is weakly reversible and try to consider what can happen as $x(t_n) \to \partial\mathbb{R}^N$.
- Will prove this convergence can not happen in single linkage class case with bounded trajectories (+ technical condition).
- Conditions satisfied by complex balanced systems $\implies$ GAC holds in single linkage class case.

Four main ideas to the proof I will cover today:

1. Consider a reduced system.
2. Partitioning the complexes along a sequence of times.
3. Using partition to get a conservation relation.
4. Using Lyapunov functions to prove in single linkage class case.

Reduced system

Suppose that $x(t) \to \partial\mathbb{R}^N$. Let

$$U = \{i \in \mathcal{S} \mid x_i(t_n) \to 0 \text{ for some sequence } t_n\}.$$

Reduced system

Suppose that $x(t) \to \partial\mathbb{R}^N$. Let

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Now consider system only consisting of those species U.

More Notation

Definition

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ denote a chemical reaction network.

- Denote the complexes of the ith linkage class by $L_i \subset \mathcal{C}$.
- We say $T \subset \mathcal{C}$ consists of a union of linkage classes if

$$T = \bigcup_{i \in I} L_i$$

for some non-empty index set I.

Example.

$$S_1 + S_2 \leftrightarrows S_3 \to S_6 + S_2, \qquad S_2 \leftrightarrows S_5 + S_4, \qquad \emptyset \leftrightarrows S_4.$$

Partitioning vectors along a sequence

Definition

Let $\mathcal{C}$ denote a finite set of vectors in $\mathbb{R}^N$. Let $x_n \in \mathbb{R}^N_{>0}$ denote a sequence of points. We say that $\mathcal{C}$ is partitioned along the sequence $\{x_n\}$ if there exist

1. $T_i \subset \mathcal{C}$, $i = 1, \dots, P$, termed tiers, constituting a partition of $\mathcal{C}$, and
2. Constants $C_i > 1$, $i = 1, \dots, P$,

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(*i*) if $y_j, y_k \in T_i$ for some $i \in \{1, \ldots, P\}$, then for all n

$$\frac{1}{C_i} x_n^{y_j} \leq x_n^{y_k} \leq C_i x_n^{y_j},$$

which is equivalent to the conditions

$$\frac{1}{C_i} \leq \frac{x_n^{y_k}}{x_n^{y_j}} \leq C_i \quad \text{and} \quad \frac{1}{C_i} \leq x_n^{y_k - y_j} \leq C_i.$$

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(ii) if $y_j \in T_i$ and $y_k \in T_{i+m}$ for some $m \ge 1$, then

$$\frac{x_n^{y_j}}{x_n^{y_k}} \to \infty, \quad \text{as } n \to \infty.$$

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(ii) if $y_j \in T_i$ and $y_k \in T_{i+m}$ for some $m \geq 1$, then

$$\frac{x_n^{y_j}}{x_n^{y_k}} \to \infty, \quad \text{as } n \to \infty.$$

Therefore, we have a natural ordering of the tiers: $T_1 \succ T_2 \succ T_3 \succ \cdots \succ T_P$, and we say T_1 is the “highest” tier, whereas T_P is the “lowest” tier.

Partitioning vectors along a sequence

Lemma

Let $\mathcal{C}$ denote a finite set of vectors in $\mathbb{R}^N$. Let x_n be a sequence of points in $\mathbb{R}^N_{>0}$. Then, there exists a subsequence of $\{x_n\}$ along which $\mathcal{C}$ is partitioned.

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Idea of proof:

Proof.

1. Find $y_1 \in \mathcal{C}$ s.t. $x_n^{y_1}$ is largest an infinite number of times, $\{x_{n_k}\}$, restrict to this subsequence.

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Proof.

1. Find $y_1 \in \mathcal{C}$ s.t. $x_n^{y_1}$ is largest an infinite number of times, $\{x_{n_k}\}$, restrict to this subsequence.
2. Find $y_2 \in \mathcal{C}$ s.t. $x_n^{y_2}$ is largest (out of $y_i \in C \backslash \{y_1\}$) an infinite number of times and restrict. Etc.

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3. Hence, we've ordered the vectors. Now just ask if

$$\liminf_{n_k} \frac{y_i}{y_{i+1}} \to \infty.$$

   If no, then (after more restrictions) they can be put in the same tier.

□

Partitioning vectors along a sequence

So, if $x(t_n) \to \partial\mathbb{R}^N$, we can order the monomials:

$$x_n^{y_k}$$

at least along a subsequence of these times.

Recalling that

$$\dot{x}(t_n) = \sum_k x(t_n)^{y_k}(y_k' - y_k),$$

this seems like a really good thing as it tells us the "dominant directions" we are being pushed, but only at those times, t_n.

A conservation relation

Definition

Let

1. $\mathcal{C}$ denote a finite set of vectors in $\mathbb{R}^N$,
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3. $U \subset \{1, \ldots, N\}$ be non-empty.

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1. $\mathcal{C}$ denote a finite set of vectors in $\mathbb{R}^N$,
2. $\{T_i\}$ denote a partition of $\mathcal{C}$,
3. $U \subset \{1, \ldots, N\}$ be non-empty.

We say that the vector $w \in \mathbb{R}^N_{\geq 0}$ is a non-negative conservation relation that respects the pair $(U, \{T_i\})$ if the following two conditions hold:

1. $w_i > 0$ if and only if $i \in U$. That is, the support of w is U.
2. Whenever $y_j, y_\ell \in T_i$ for some i, we have that $w \cdot (y_j - y_\ell) = 0$.

A conservation relation

Theorem

Let

1. $\mathcal{C}$ *denote a finite set of vectors in* $\mathbb{R}^N$,
2. $x_n \in \mathbb{R}^N_{>0}$ *denote a sequence of points with* $x_n \to z \in \partial\mathbb{R}^N_{\geq 0}$, *as* $n \to \infty$,
3. *and*
$$U = U(z) = \{i \in \{1, \ldots, N\} \, : \, z_i = 0\}.$$
4. *Finally, suppose that* $\mathcal{C}$ *is partitioned along* $\{x_n\}$ *with tiers and constants* T_i, C_i, *for* $i = 1, \ldots, P$, *respectively.*

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4. *Finally, suppose that* $\mathcal{C}$ *is partitioned along* $\{x_n\}$ *with tiers and constants* T_i, C_i, *for* $i = 1, \dots, P$, *respectively.*

Then, there is a non-negative conservation relation $w \in \mathbb{R}^N_{\geq 0}$ *that respects the pair* $(U, \{T_i\})$.

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Theorem

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4. *Finally, suppose that* $\mathcal{C}$ *is partitioned along* $\{x_n\}$ *with tiers and constants* T_i, C_i*, for* $i = 1, \ldots, P$*, respectively.*

Then, there is a non-negative conservation relation $w \in \mathbb{R}^N_{\geq 0}$ *that respects the pair* $(U, \{T_i\})$*.*

Big point: Tier 1 can not be the entire set of complexes. Why?

1. In this case, w is a true conservation relation and
2. $\implies w \cdot x(t_n) \equiv w \cdot x(t_0) > 0$.

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1. In this case, w is a true conservation relation and
2. $\implies$ $w \cdot x(t_n) \equiv w \cdot x(t_0) > 0$.
3. But, $w \cdot x(t_n) \to 0$, since support of w is U.

$\implies$ We must have more than one tier.

Intuition

Suppose $A, C, D \to 0$ and all in same tier

$$2A + B \rightleftarrows C \implies A^2 \approx C$$

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$$A + C \rightleftarrows D + E \implies AC \approx D$$

$$2C \rightleftarrows D + F \implies C^2 \approx D$$

Second two imply $AC \approx C^2 \implies A \approx C$. nope.

Idea of proof

Proof.

- Define

$$W_i \stackrel{\text{def}}{=} \{y_j - y_k \mid y_j, y_k \in T_i\}, \qquad W \stackrel{\text{def}}{=} \bigcup_{i=1}^{P} W_i,$$

We need a conservation relation for W with support U.

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  We need a conservation relation for W with support U.

- Let $W|_U \subset \mathbb{R}^m$ be the restrictions of W_i and W to the components associated with the index set U.

Idea of proof

Proof.

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We need a conservation relation for W with support U.

- Let $W|_U \subset \mathbb{R}^m$ be the restrictions of W_i and W to the components associated with the index set U.

- Stiemke's Lemma + no conservation implies $\exists\ c_k \in \mathbb{R}$ s.t.

$$\left(\sum_{v_k \in W|_U} c_k v_k \right)_j \leq 0,$$

for $j \in U$, with strict at least once.

- Define $M(x) \stackrel{\text{def}}{=} \prod_{u_k \in W} \left(x^{u_k}\right)^{c_k}.$

Idea of proof

Define $M(x) \stackrel{\text{def}}{=} \prod_{u_k \in W} \left(x^{u_k}\right)^{c_k}$.

Observation 1: $M(x_n)$ is bounded above and below by construction since each

$$x_n^{u_k} = \frac{x_n^{y_i}}{x_n^{y_\ell}},$$

and from same tier ($u_k \in W_i$ for some i).

Idea of proof

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and from same tier ($u_k \in W_i$ for some i).

Observation 2:

$$\ln(M(x_n)) = \left(\sum_{v_k \in W|_U} c_k v_k \right) \cdot \ln(x_n|_U) + \left(\sum_{u_k \in W} c_k u_k|_{U^c} \right) \cdot \ln(x_n|_{U^c}).$$

1. Second term is bounded above and below by construction (these are species not going to zero).
2. First term blows up to $+\infty$, as $n \to \infty$.

Collecting thoughts

1. We have, along a sequence, a conservation relation among the tiers.

2. Implies tier 1 can not be all complexes.

Collecting thoughts

1. We have, along a sequence, a conservation relation among the tiers.
2. Implies tier 1 can not be all complexes.
3. So?

Lyapunov functions

For any $\overline{x} \in \mathbb{R}^N_{>0}$, we define $V_{\overline{x}} : \mathbb{R}^N_{>0} \to \mathbb{R}_{\geq 0}$ by

$$V_{\overline{x}}(x) \overset{\text{def}}{=} \sum_{i=1}^{N} [x_i(\ln(x_i) - \ln(\overline{x}_i) - 1) + \overline{x}_i.]$$

Lyapunov functions

Lemma

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a weakly reversible, non-autonomous mass-action system with bounded kinetics. Suppose $x_0 \in \mathbb{R}^N_{>0}$ is such that $\phi(t, x_0)$ remains bounded and dist$(\phi(t, x_0), \partial\mathbb{R}^N_{\geq 0}) \to 0$ as $t \to \infty$. Then at least one of the following two conditions hold for this trajectory:

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C1: *For any $\overline{x} \in \mathbb{R}^N_{>0}$, there exists a $T = T_{\overline{x}} > 0$ such that $t > T$ implies*

$$\frac{d}{dt} V_{\overline{x}}(x(t)) = \sum_k \kappa_k(t) x(t)^{y_k} (y_k' - y_k) \cdot (\ln(x(t)) - \ln(\overline{x})) < 0,$$

where $x(t) = \phi(t, x_0)$ is the solution to the system with kinetics $K(t)$.

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where $x(t) = \phi(t, x_0)$ is the solution to the system with kinetics $K(t)$.

C2: *There exists a sequence of times, t_n, such that $x_n \stackrel{def}{=} \phi(t_n, x_0) \in \mathbb{R}^N_{>0}$ converges to a point $z \in \omega(\phi(t, x_0)) \cap \partial\mathbb{R}^N_{\geq 0}$, and*

- (*i*) *$\mathcal{C}$ is partitioned along x_n with tiers $\{T_i\}_{i=1}^P$, and constants $\{C_i\}_{i=1}^P$, and*
- (*ii*) *T_1 consists of a union of linkage classes.*

Lyapunov functions

Core idea of proof:

Suppose condition $C2$ (T_1 is union of linkage classes) does not hold

$$\sum_k \kappa_k(t_n) x_n^{y_k}(y_k' - y_k) \cdot \ln\left(\frac{x_n}{\overline{x}}\right) = \sum_{i=1}^{P}\Bigg[\sum_{\{i\to i\}} \kappa_k(t_n) x_n^{y_k}\left[\ln\left(\frac{x_n^{y_k'}}{x_n^{y_k}}\right) + c_k\right]$$

$$+ \sum_{m=1}^{P-i} \sum_{\{i\to i+m\}} \kappa_k(t_n) x_n^{y_k}\left[\ln\left(\frac{x_n^{y_k'}}{x_n^{y_k}}\right) + c_k\right]$$

$$+ \sum_{m=1}^{i-1} \sum_{\{i\to i-m\}} \kappa_k(t_n) x_n^{y_k}\left[\ln\left(\frac{x_n^{y_k'}}{x_n^{y_k}}\right) + c_k\right]\Bigg],$$

Second sum is negative and dominates. So condition one holds.

Start conclusions

Lemma

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a weakly reversible, single linkage class, non-autonomous mass-action system with bounded kinetics. Suppose $x_0 \in \mathbb{R}^N_{>0}$ is such that $\phi(t, x_0)$ remains bounded and dist($\phi(t, x_0), \partial\mathbb{R}^N_{\geq 0}$) $\to 0$ as $t \to \infty$. Then, there does not exists a subsequence of times $t_n \to \infty$ such that $\mathcal{C}$ is partitioned along $x_n \stackrel{def}{=} \phi(t_n, x_0)$ in which T_1 consists of a union of linkage classes.

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Proof: this would give us a conservation relation.

Thus, condition two holds.

Start conclusions

Lemma

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K(t)\}$*, with* $\mathcal{S} = \{S_1, \ldots, S_N\}$*, be a non-autonomous system with bounded mass-action kinetics. Suppose* $x_0 \in \mathbb{R}^N_{>0}$ *is such that for any* $\overline{x} \in \mathbb{R}^N_{>0}$*, there exists a* $T = T_{\overline{x}} > 0$ *such that* $t > T$ *implies*

$$\frac{d}{dt} V_{\overline{x}}(x(t)) < 0,$$

where $x(t) = \phi(t, x_0)$ *is the solution to the system with* $x(0) = x_0$ *and kinetics* $K(t)$*. Then* $\omega(\phi(\cdot, x_0)) = \{z\}$*, a single point.*

Start conclusions

Theorem

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K\}$*, with* $\mathcal{S} = \{S_1, \ldots, S_{|\mathcal{S}|}\}$*, be a weakly reversible, single linkage class chemical reaction network with mass-action kinetics. We assume that for* $x_0 \in \mathbb{R}^{|\mathcal{S}|}_{>0}$ *the trajectory* $\phi(t, x_0)$ *satisfies the following two conditions*

1. $\phi(t, x_0)$ *is bounded (in* t*), and*
2. $\omega(\phi(\cdot, x_0))$ *is either completely contained in* $\partial\mathbb{R}^{|\mathcal{S}|}_{\geq 0}$ *or completely contained within the interior of* $\mathbb{R}^{|\mathcal{S}|}_{>0}$*.*

Start conclusions

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Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K\}$, with $\mathcal{S} = \{S_1, \ldots, S_{|\mathcal{S}|}\}$, be a weakly reversible, single linkage class chemical reaction network with mass-action kinetics. We assume that for $x_0 \in \mathbb{R}^{|\mathcal{S}|}_{>0}$ the trajectory $\phi(t, x_0)$ satisfies the following two conditions

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1. Need technical condition to guarantee that either converge to boundary or never go to boundary.
2. From previous results, converge to single point. Lyapunov arguments ensure this can not happen.

Main result: GAC in one linkage class

Corollary

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, K\}$ denote a complex-balanced system with one linkage class. Then, any complex-balanced equilibrium contained in the interior of a positive compatibility class is a global attractor of the interior of that positive class.

Notes

Note, Persistence Conjecture is still open in this setting! Not clear that weakly reversible networks satisfy the “technical condition.”

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Single linkage class assumption was only used once!

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Thanks!

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