Dynamics of reaction systems

Anne Shiu
University of Chicago

Midwest Women in Mathematics Symposium
UIC
20 April 2013

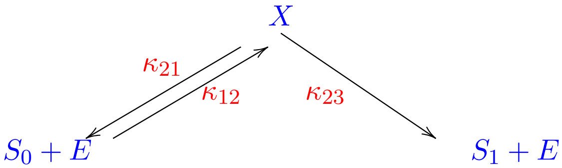
Outline of talk

- Chemical reaction systems
- Convergence properties
- Long-term dynamics (persistence)

Main message:

Algebraic and combinatorial techniques are complementary to existing dynamical systems approaches.

Chemical reaction networks



This *chemical reaction network* has:

- $r = 3$ **reactions** (with *reaction rate constants* κ_{ij}) among the ...
- $n = 3$ **complexes** $S_0 + E$, X, and $S_1 + E$ which are comprised of ...
- $s = 4$ **species** S_0, S_1, E, and X.

The multisite phosphorylation network

The n-**site (sequential and distributive) phosphorylation network** is:

$$S_0 + E \underset{k_{\text{off}_0}}{\overset{k_{\text{on}_0}}{\rightleftarrows}} ES_0 \overset{k_{\text{cat}_0}}{\to} S_1 + E \underset{k_{\text{off}_1}}{\overset{k_{\text{on}_1}}{\rightleftarrows}} \to \cdots \to S_{n-1} + E \underset{k_{\text{off}_{n-1}}}{\overset{k_{\text{on}_{n-1}}}{\rightleftarrows}} ES_{n-1} \to S_n + E$$

$$S_n + F \underset{l_{\text{off}_{n-1}}}{\overset{l_{\text{on}_{n-1}}}{\rightleftarrows}} FS_n \overset{l_{\text{cat}_{n-1}}}{\to} S_{n-1} + F \leftrightarrows \cdots \to S_1 + F \underset{l_{\text{off}_0}}{\overset{l_{\text{on}_0}}{\rightleftarrows}} FS_1 \overset{l_{\text{cat}_0}}{\to} S_0 + F$$

Given initial concentrations,
how do the concentrations of S_0, S_1, $\ldots$, E, F *evolve in time?*

$$c(t) = (c_{S_0}(t), c_{S_1}(t), \ \ldots, \ c_E(t), c_F(t))$$

2-SITE PHOSPHORYLATION IN AN OSCILLATOR

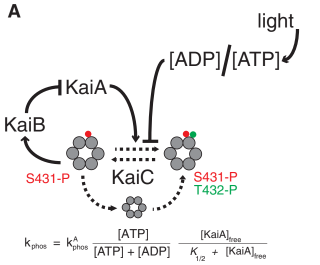


Fig. 4. A mathematical model of the KaiABC oscillator predicts entrainment by varying the ATP/ADP ratio. (**A**) Schematic of a mathematical model for nucleotide-driven entrainment of the KaiABC oscillator. Oscillations occur because the Ser^{431}-phosphorylated form of KaiC promotes its own production from KaiC phosphorylated at both Ser^{431} and Thr^{432} through a double-negative feedback loop involving sequestration of KaiA.

(Figure from Rust, Golden, and O'Shea, Light-Driven Changes in Energy Metabolism Directly Entrain the Cyanobacterial Circadian Oscillator, *Science* 2011).

Chemical reaction systems

Fix a chemical reaction network with s species.

- Each chemical complex defines a vector $y \in \mathbb{Z}^s_{\geq 0}$ (ex: $S_0 + E$ defines $y_1 = (1, 1, 0)$)
- (Guldberg and Waage 1864) According to **mass-action kinetics**, the concentration vector $\mathbf{c}(t) = (c_1(t), \ldots, c_s(t))$ evolves according to the following differential equations:

$$\frac{d\mathbf{c}}{dt} = \sum_{\substack{y_i \to y_j \\ \text{is a reaction}}} \kappa_{ij} \mathbf{c}^{y_i} (y_j - y_i)$$

Example: $S_0 + E \underset{\kappa_{21}}{\overset{\kappa_{12}}{\rightleftarrows}} X$

$$\frac{dc_{S_0}}{dt} = -\kappa_{12} c_{S_0} c_E + \kappa_{21} c_X$$

$$\frac{dc_E}{dt} = -\kappa_{12} c_{S_0} c_E + \kappa_{21} c_X$$

$$\frac{dc_X}{dt} = \kappa_{12} c_{S_0} c_E - \kappa_{21} c_X$$

Motivation

Question: Is the n-site phosphorylation network...

1. *bistable*?
   (Answer due to Wang and Sontag 2008: only for $n \geq 2$.)
2. *convergent to a unique steady state*? (Only for $n = 1$.)
3. *persistent*: does every species concentration $c_i(t)$ remain away from 0? (Yes.)

Rest of talk:
How can we answer questions 2 and 3 for arbitrary networks?

Complex-balanced systems

Idea: amount produced of each complex at steady state = amount consumed; *a class of systems that converge to a unique steady state.*

- Rewrite the mass-action ODEs as:

$$\frac{dc}{dt} = \sum_{y_i \to y_j \text{ is a reaction}} \kappa_{ij} \left(y_j - y_i\right) c^{y_i}$$

$$= \left(c^{\widetilde{y_1}}, \ldots, c^{\widetilde{y_n}}\right) \cdot A_\kappa \cdot \left(\widetilde{y_{ij}}\right)_{i=1\ldots n, j=1\ldots s}$$

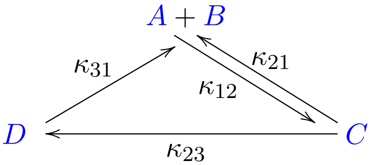
$$\mathbb{R}^{\#\text{species}} \longrightarrow \mathbb{R}^n \to \mathbb{R}^n \to \mathbb{R}^{\#\text{species}}$$

  where $\widetilde{y_1}, \ldots \widetilde{y_n}$ are the n complexes, s is the number of species, and A_κ is the *Laplacian matrix* of the network.

- (definition, Horn and Jackson 1972) A mass-action kinetics system is a **complex-balanced system** if there exists a steady state $c^* \in \mathbb{R}^s_{>0}$ with $\left((c^*)^{\widetilde{y_1}}, \ldots, (c^*)^{\widetilde{y_n}}\right) \cdot A_\kappa = 0$.

Laplacian matrix example

For the following *"kinetic proofreading" network*:



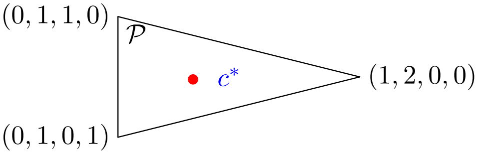
the Laplacian matrix is:

$$A_\kappa := \begin{pmatrix} -\kappa_{12} & \kappa_{12} & 0 \\ \kappa_{21} & -\kappa_{21} - \kappa_{23} & \kappa_{23} \\ \kappa_{31} & 0 & -\kappa_{31} \end{pmatrix}.$$

(McKeithan 1995, Sontag 2001)

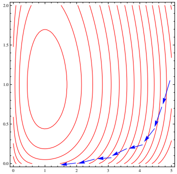
Complex-balanced systems, continued

- **Theorem** (Craciun, Dickenstein, AS, and Sturmfels 2009): A mass-action kinetics system is a **complex-balanced system** if and only if the parameters κ_{ij} lie in a certain *toric variety*.
- **Birch's Theorem** (1963), **Deficiency Zero Theorem** (Horn, Jackson, Feinberg 1970s): For complex-balanced systems, there is a *unique steady state* c^* in the relative interior of each forward-invariant polyhedron $\mathcal{P}$, called the **Birch point**, and it admits a strict Lyapunov function.
- Example: *"kinetic proofreading" model*



Complex-balanced systems: convergence?

- The Lyapunov function $\sum \left(x_i \log \frac{x_i}{c_i^*} - x_i \right)$ is not sufficient to prove global convergence to the Birch point:



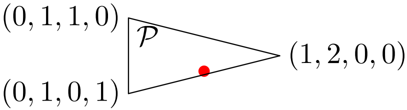
- **Global Attractor Conjecture** (Horn 1974): *For a complex-balanced system with positive initial condition,*

$$c(t) \to c^*,$$

for c^* *the Birch point of the forward-invariant set* $\mathcal{P}$*.*

Known convergence results

- A *boundary steady state* is a steady state with at least one zero coordinate:

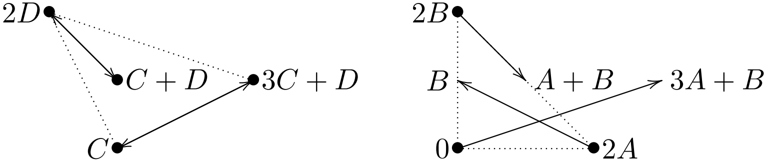


- **Theorem** (Anderson, Craciun, Dickenstein, Nazarov, Pantea, AS, Sturmfels 2007–2012): The Global Attractor Conjecture holds if *boundary steady states are confined to*:
  - vertices of $\mathcal{P}$,
  - relative interior points of facets (codim-1 faces) of $\mathcal{P}$, and
  - relative interior points of codim-2 faces of $\mathcal{P}$.
- **Corollary**: The Global Attractor Conjecture holds for when *the number of species is* ≤ 3.
- See also Johnston and Siegel 2011, *siphons* (Angeli, De Leenheer, Sontag,...), and *monotone systems* (Banaji, Hirsch, Smith,...).

New result on convergence and persistence

To prove the GAC, it suffices to prove that complex-balanced systems are **persistent**, that is, for all species i and trajectories $c(t)$ with positive initial condition, $\liminf_{t\to\infty} c_i(t) > 0$. (Smith, Theime)

- Thus, the GAC generalizes to:
  Conjecture (Craciun, Nazarov, Pantea): Every *endotactic* ("inward-pointing") network is persistent. Examples:



- **Theorem** (Gopalkrishnan, Miller, AS): Every *strongly endotactic* network is persistent. Example above on right.

Summary

Chemical reaction systems form a class of dynamical systems arising in systems biology for which methods from *computational algebra and polyhedral geometry* can be harnessed to prove results about the *existence, uniqueness, and stability of steady states.*

Thank you.