

The Smallest Multistationary Mass-Preserving Chemical Reaction Network

ANNE SHIU

UNIVERSITY OF CALIFORNIA, BERKELEY

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Outline

Chemical reaction network theory

algebraic approach to mass-action kinetics

Moduli space of *toric dynamical systems*

the chemical reaction networks with a *complex balancing* steady state

Multiple steady states

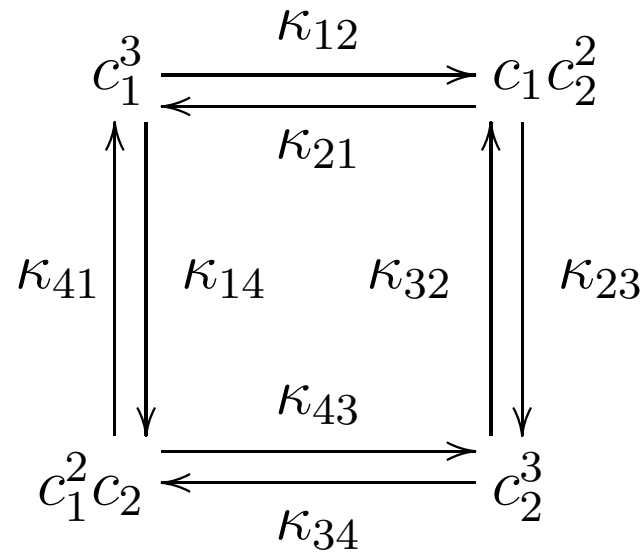
what is the smallest instance of bistability?
semi-algebraic decomp. of parameter space

Introduction to CRNT

- Chemical engineering (1970s+)
F. Horn and R. Jackson, *General mass action kinetics*.
M. Feinberg, “Lectures on chemical reaction networks.”
- K. Gatermann introduced connection between mass-action kinetics and computational algebra
K. Gatermann and B. Huber, *A family of sparse polynomial systems arising in chemical reaction systems* (2002).
- G. Craciun, A. Dickenstein, A. Shiu, B. Sturmfels, *Toric dynamical systems*, to appear.

Main result

The *Square* network is a “smallest” multistationary CRN:



$$\begin{aligned} \frac{dc_1}{dt} = & (-2\kappa_{12} - \kappa_{14})c_1^3 + (\kappa_{41} - 2\kappa_{43})c_1^2c_2 \\ & + (2\kappa_{21} - \kappa_{23})c_1c_2^2 + (\kappa_{32} + 2\kappa_{34})c_2^3 = -\frac{dc_2}{dt} \end{aligned}$$

Ligand-receptor-antagonist

In humans, **interleukin-1** (**L**) binds with its *receptor* (**R**). This leads to inflammation, and occurs in individuals with rheumatoid arthritis.

Goal: inhibit the binding (G. Gnacadja, *et al.* 2007).

Drug 1: *Antagonists* (**A**) bind with the receptors (**R**).

Drug 2: *Decoy receptors* ("traps" **T**) bind with interleukin-1 (**L**), but also with the antagonists (**A**).

Modeling the L-R-A-T system

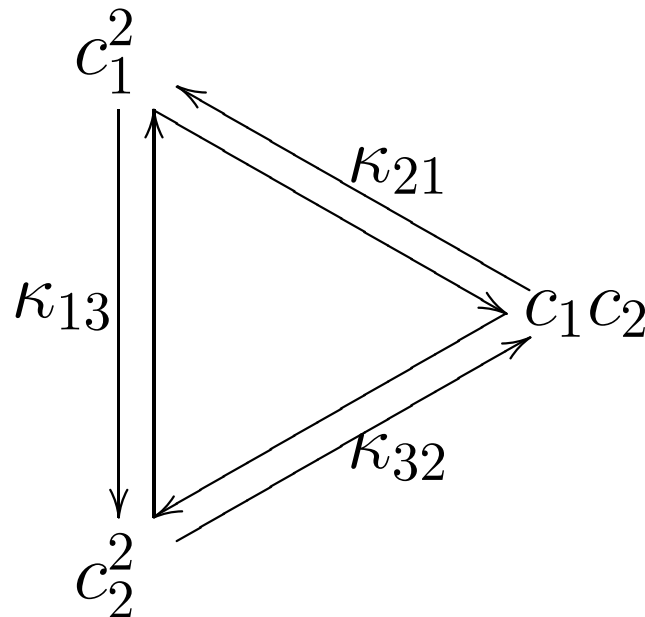
Eight (chemical) **species**: L, R, A, T, LR, AR, LT, AT.
Four reversible **reactions**, such as $L + R \leftrightarrow LR$.

- Concentrations of the eight species vary in time.
- Reactions describe how the concentrations evolve (according to *mass-action kinetics*).
- Ex: the reaction $L + R \leftrightarrow LR$ yields the polynomial differential equation:

$$\frac{d}{dt}c_L = \kappa_r c_{LR} - \kappa_f c_L c_R$$

Modeling chemical reactions

- In a chemical reaction network, chemical **complexes** are comprised of chemical **species**.
- Triangle Example: $s = 2$ species c_1 and c_2 , $n = 3$ complexes c_1^2 , c_1c_2 , c_2^2 , and all six possible *reactions*.
- *Reaction diagram* of the Triangle:



Mass-action kinetics

- The vertex i is labeled by the *monomial*

$$c^{y_i} = c_1^{y_{i1}} c_2^{y_{i2}} \cdots c_s^{y_{is}}.$$

- $Y = (y_{ij})$ is an $n \times s$ -matrix of non-negative integers.

- The monomial labels are the entries in the row vector

$$\Psi(c) = (c^{y_1}, c^{y_2}, \dots, c^{y_n}).$$

- View the concentrations of the s species c_1, c_2, \dots, c_s as functions $c_i(t)$ of time t .

- *Mass-action kinetics* specified by the digraph G and the parameters $\kappa_{i,j}$ is the following dynamical system:

$$\frac{dc}{dt} = \Psi(c) \cdot A_\kappa \cdot Y,$$

where A_κ is the Laplacian of G (see next slide).

The Laplacian

$$\frac{dc}{dt} = \Psi(c) \cdot A_{\kappa} \cdot Y,$$

$$\begin{array}{ccc} \mathbb{R}^n & \xrightarrow{A_{\kappa}} & \mathbb{R}^n & \text{complex space} \\ \psi \uparrow & & \downarrow Y & \\ \mathbb{R}^s & \xrightarrow{dc/dt} & \mathbb{R}^s & \text{species space} \end{array}$$

The **Laplacian** of the digraph G in the example is

$$A_{\kappa} := \begin{pmatrix} -\kappa_{12} - \kappa_{13} & \kappa_{12} & \kappa_{13} \\ \kappa_{21} & -\kappa_{21} - \kappa_{23} & \kappa_{23} \\ \kappa_{31} & \kappa_{32} & -\kappa_{31} - \kappa_{32} \end{pmatrix}.$$

Dynamics

- For $S := \text{span}\{y_j - y_i \mid (i, j) \in E(G)\}$, the *stoichiometric subspace*, we have

$$\frac{dc}{dt} = \Psi(c) \cdot A_\kappa \cdot Y \in S.$$

- Thus, a trajectory $c(t) = (c_1(t), c_2(t), \dots, c_s(t))$ remains in a polyhedron

$$P := (c(0) + S) \cap \mathbb{R}_{\geq 0}^s.$$

We call P the *invariant polyhedron*.

(Usually, it is called the *stoichiometric compatibility class*.)

Steady states

- What are the *steady states*? For which $c \in \mathbb{R}_{>0}^s$ is

$$\Psi(c) \cdot A_{\kappa} \cdot Y = 0?$$

- What about **complex balancing** steady states?

$$\Psi(c) \cdot A_{\kappa} = 0$$

- (def) A chemical reaction network is **multistationary** if there exists two concentration vectors $c, c' \in P$ that are both steady states.
- For which parameters κ_{ij} does a chemical reaction network have m steady states (in P)?

Toric Dynamical Systems

(def) A **toric dynamical system** is a mass-action kinetics system with a *complex balancing state*.

Properties: (**Birch's Theorem** - Horn, Jackson, Feinberg: **Deficiency Zero Theorem**)

If one complex balancing steady state exists, then all steady states are complex balancing.

Moreover, there is a *unique steady state* in P .

Theorem 1. *A mass-action kinetics system is a **toric dynamical system** if and only if the parameters k_{ij} lie in a certain toric variety $V(M_G)$.*

TDS examples

- For the **L-R-A-T** example, $M_G = (0)$, so there is always a *unique* (complex balancing) steady state.
- For the **Triangle** example, consider the following coordinates (coming from the Matrix-Tree Theorem):

$$K_1 = \kappa_{21}\kappa_{31} + \kappa_{23}\kappa_{31} + \kappa_{21}\kappa_{32}$$

$$K_2 = \kappa_{12}\kappa_{32} + \kappa_{13}\kappa_{32} + \kappa_{31}\kappa_{12}$$

$$K_3 = \kappa_{13}\kappa_{23} + \kappa_{21}\kappa_{13} + \kappa_{12}\kappa_{23}.$$

The Triangle defines a **toric dynamical system** if and only if the rate constants κ_{ij} satisfy $K_1 K_3 = K_2^2$. Further, we can show that in general there is a *unique* steady state.

Example

$$T_G = \langle K_1 c_1^2 - K_2 c_1 c_2, K_1 c_1^2 - K_3 c_2^2, K_2 c_1 c_2 - K_3 c_2^2 \rangle :$$

$$(c_1 c_2 \cdots c_s)^\infty \subset \mathbb{Q}[\kappa, c_i]$$

$$M_G := T_G \cap \mathbb{Q}[\kappa]$$

$$= \langle (\kappa_{21}\kappa_{31} + \kappa_{32}\kappa_{21} + \kappa_{23}\kappa_{31})(\kappa_{13}\kappa_{23} + \kappa_{21}\kappa_{13} + \kappa_{12}\kappa_{23}) \\ - (\kappa_{12}\kappa_{32} + \kappa_{13}\kappa_{32} + \kappa_{31}\kappa_{12})^2 \rangle$$

$$= \langle K_1 K_3 - K_2^2 \rangle.$$

The expression in the κ -coordinates appears in F. [Horn](#), *Necessary and sufficient conditions for complex balancing in chemical kinetics* (1973). See also M. [Feinberg](#), *Complex Balancing in General Kinetic Systems* (1973).

Connection to *deficiency*

For a reaction network G , the stoichiometric subspace is $S := \text{span}\{y_j - y_i \mid (i, j) \in E(G)\}$.

The **deficiency** δ is a non-negative integer associated to a reaction diagram.

(def) The **deficiency** of G is

$$\delta := n - \sigma - l,$$

where n =number of complexes (vertices of G),

$\sigma = \dim(S)$, and

l =number of connected components of G .

Deficiency examples

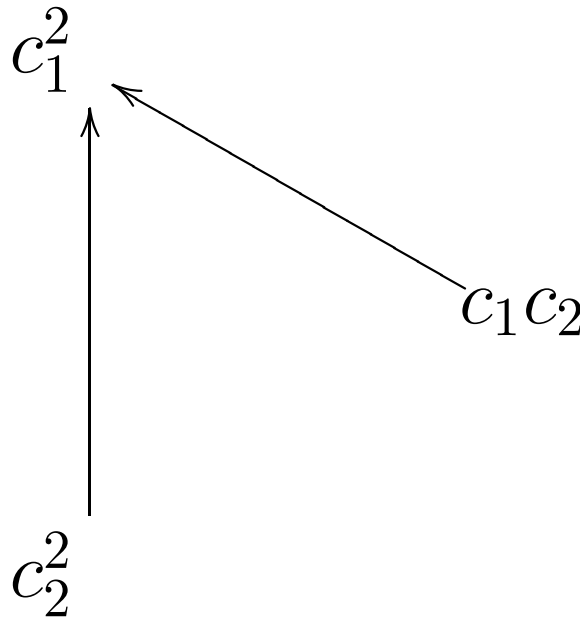
- Ex. 1: L-R-A-T
 $\delta = 0$
- Ex. 2: Triangle
 $\delta = 1$
- Ex. 3: Square
 $\delta = 2$
- Moduli ideal M_G and deficiency

Deficiency \approx number of binomials.

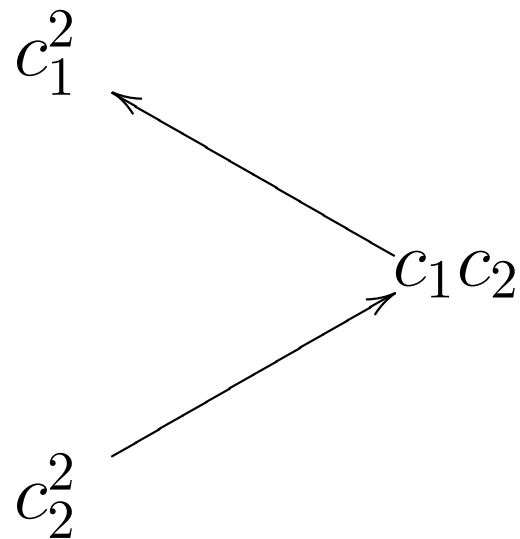
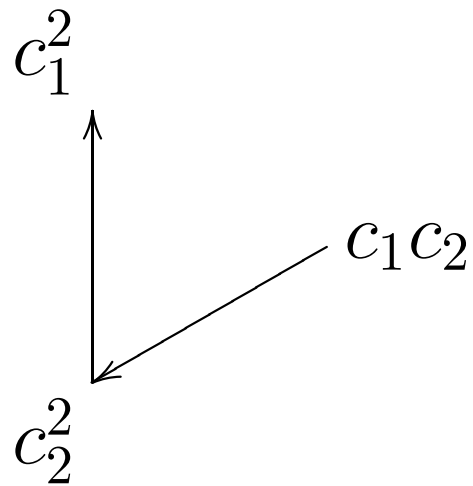
Theorem 2. *The moduli ideal M_G is toric, and its codimension equals the deficiency δ .*

Matrix-Tree Thm: i -trees

(Example for $i=1$) For the first vertex of G ($i = 1$), there are three i -trees T_1 , T_2 , and T_3 :



i-trees continued



Matrix-Tree Theorem (cont.)

- (Example) Each tree gives rise to a polynomial:

$$\kappa^{T_1} = \kappa_{21}\kappa_{31},$$

$$\kappa^{T_2} = \kappa_{23}\kappa_{31}, \text{ and}$$

$$\kappa^{T_3} = \kappa_{21}\kappa_{32}.$$

- (def) $K_i := \sum_{T \text{ an } i\text{-tree}} \kappa^T$

- In the example, we have

$$K_1 = \kappa_{21}\kappa_{31} + \kappa_{23}\kappa_{31} + \kappa_{21}\kappa_{32}.$$

Matrix-Tree Theorem

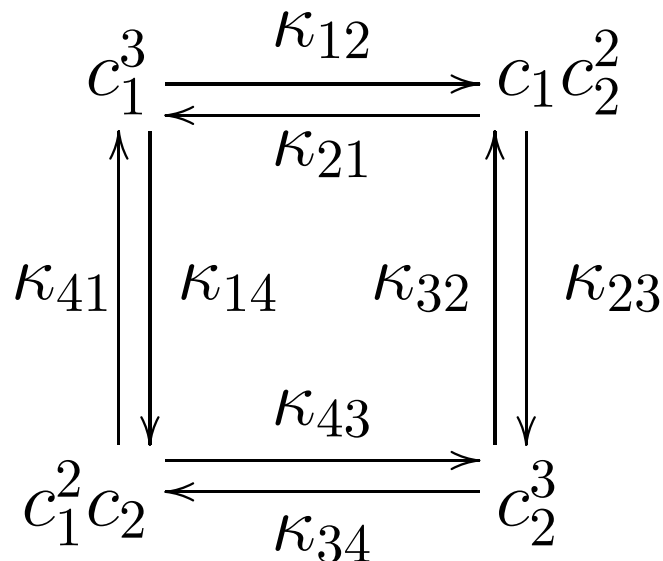
Assume that G is strongly connected.

Theorem 3 (Matrix-Tree Theorem). *Consider a submatrix of A_κ obtained by deleting the i^{th} row and any one of the columns. The signed determinant of this $(n-1) \times (n-1)$ -matrix equals $(-1)^{n-1} K_i$.*

Reference: R. Stanley, Enumerative Combinatorics, vol. 2 (1999).

Square network

Consider the *Square*:



$$\begin{aligned} \frac{dc_1}{dt} = & (-2\kappa_{12} - \kappa_{14})c_1^3 + (\kappa_{41} - 2\kappa_{43})c_1^2c_2 \\ & + (2\kappa_{21} - \kappa_{23})c_1c_2^2 + (\kappa_{32} + 2\kappa_{34})c_2^3 = -\frac{dc_2}{dt} \end{aligned}$$

When is the Square a TDS?

The TDS ideal M_G is generated by the 2×2 -minors of the following matrix:

$$\begin{pmatrix} K_1 & K_2 & K_4 \\ K_4 & K_3 & K_2 \end{pmatrix}, \text{ where}$$

$$K_1 = \kappa_{23}\kappa_{34}\kappa_{41} + \kappa_{21}\kappa_{34}\kappa_{41} + \kappa_{21}\kappa_{32}\kappa_{41} + \kappa_{21}\kappa_{32}\kappa_{43},$$

$$K_2 = \kappa_{14}\kappa_{32}\kappa_{43} + \kappa_{12}\kappa_{34}\kappa_{41} + \kappa_{12}\kappa_{32}\kappa_{41} + \kappa_{12}\kappa_{32}\kappa_{43},$$

$$K_3 = \kappa_{14}\kappa_{23}\kappa_{43} + \kappa_{14}\kappa_{21}\kappa_{43} + \kappa_{12}\kappa_{23}\kappa_{41} + \kappa_{12}\kappa_{23}\kappa_{43},$$

$$K_4 = \kappa_{14}\kappa_{23}\kappa_{34} + \kappa_{14}\kappa_{21}\kappa_{34} + \kappa_{14}\kappa_{21}\kappa_{32} + \kappa_{12}\kappa_{23}\kappa_{34}.$$

The Square is a TDS if and only if its parameters lie in the variety of M_G , the *twisted cubic curve*!

Multiple steady states

How many steady states can a non-TDS Square network have?

Algebraic methods for studying multistationarity:

- C. Conradi, D. Flockerzi, J. Raisch, *Multistationarity in the activation of an MAPK: parametrizing the relevant region in parameter space* (2007).
- Wang, D. and Xia, B., *Stability analysis of biological systems with real solution classification*. (2005).

Multistationarity of Square

- Substitute $x := c_1/c_2$ into $dc_1/dt = -dc_2/dt$:

$$p_S(x) = (-2\kappa_{12} - \kappa_{14})x^3 + (\kappa_{41} - 2\kappa_{43})x^2 + (2\kappa_{21} - \kappa_{23})x + (\kappa_{32} + 2\kappa_{34}) .$$

Steady states correspond precisely to the *positive roots* of this cubic polynomial.

- Consider the following rate constants:

$$(\kappa_{12}, \kappa_{14}, \kappa_{21}, \kappa_{23}, \kappa_{32}, \kappa_{34}, \kappa_{41}, \kappa_{43}) = (1/4, 1/2, 1, 13, 1, 2, 8, 1) .$$

Then $p_S(x) = -x^3 + 6x^2 - 11x + 6$ has three positive roots: $x = 1, 2,$ and $3,$ in other words, *three steady states*.

Semi-algebraic decomposition

- For example, the Square has *three steady states* (two stable) if and only if p_S has positive discriminant and has all (signed) coefficients positive.
- Complete parametrization is based on the signs of the discriminant and coefficients of p_S .
- Horn and Jackson performed this analysis for the following special rate constants:

$$\begin{aligned} (\kappa_{12}, \kappa_{14}, \kappa_{21}, \kappa_{23}, \kappa_{32}, \kappa_{34}, \kappa_{41}, \kappa_{43}) &= \\ & (\epsilon, 0, 1, 0, \epsilon, 0, 1, 0), \end{aligned}$$

where $\epsilon > 0$. See also Feinberg (1980).

Square network

The Square has the following properties:

the number of complexes is $n = 4$,

the number of connected components of G is $l = 1$,

the number of species is $s = 2$, and

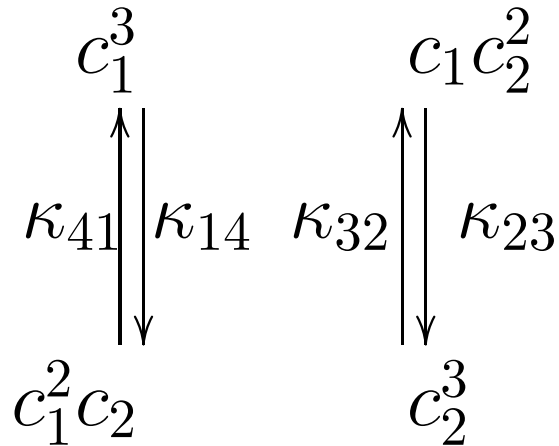
the dimension of any invariant polyhedron P is $\sigma = 1$.

Theorem 4. *The Square is a smallest multistationary, mass-preserving, reversible chemical reaction network with respect to each of the following parameters: n , l , s , and σ .*

Why small systems?

See *Subnetwork analysis reveals dynamic features of complex (bio)chemical networks*, C. Conradi, D. Flockerzi, J. Raisch, and J. Stelling (2007).

Special subnetwork of Square



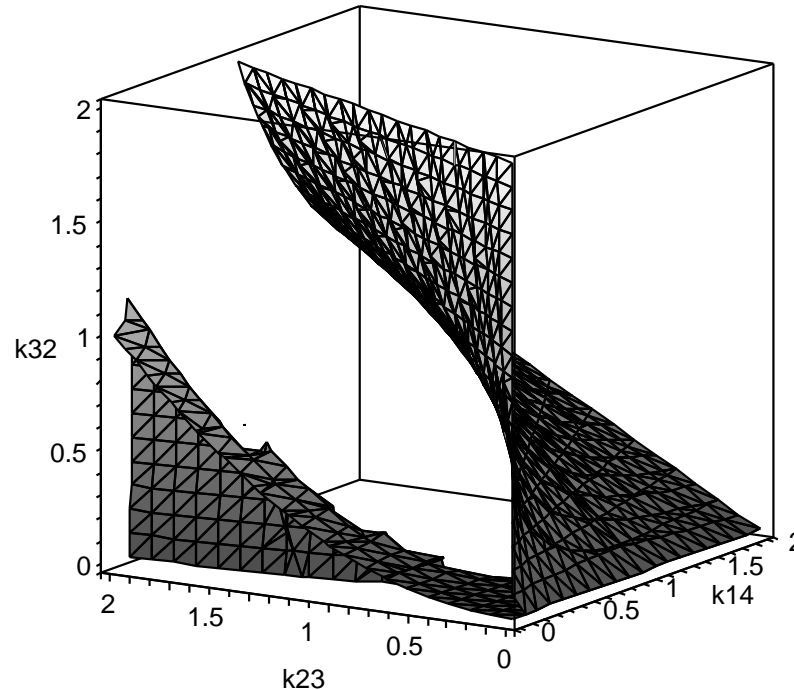
Multistationarity: when does p have 1, 2, or 3 positive roots?

$$p(x) = -\kappa_{14}x^3 + \kappa_{41}x^2 - \kappa_{23}x + \kappa_{32}$$

The **TDS condition** reduces to the single equation

$$\kappa_{23}\kappa_{41} = \kappa_{14}\kappa_{32} .$$

Semi-algebraic decomposition



Square subnetwork parameter space: at left is the **discriminant-zero locus**. At right, the Segre variety depicts the **TDS locus**.

Open problems

Posed during SAMSI Opening Workshop for 2008-09 Program on *Algebraic Methods in Systems Biology and Statistics*:

- (1b) [*M. Gopalkrishnan*, USC] Does there exist a reversible chemical reaction network that gives rise to oscillations?
- (3) [*A. Dickenstein*] Can we construct a counterexample to the **Global Attractor Conjecture** (i.e. complex balancing implies global attraction of the unique steady state, known as the Birch point) if each complex contains all species?
- (4) [*G. Gnacadja*] Given a (conservative if necessary) complex-balancing network, can we have a trajectory that is confined to the boundary and converges to a boundary steady state or oscillates around this state?

What is a (minimal) siphon?

Prop. Assume G is strongly connected. Then minimal siphons = minimal associated primes of ideal of complex monomials c^{y_i} .

```
> ideal I=a^2,a*b,b*c;
> LIB "primdec.lib";
> primdecGTZ(I);
[1]:
  [1]:
    _[1]=c,      _[2]=a
  [2]:
    _[1]=c
    _[2]=a
[2]:
  [1]:
    _[1]=b,      _[2]=a2
  [2]:
    _[1]=b
    _[2]=a
```

Future events

- Discrete Models in Systems Biology Workshop, SAMSI, December 3-5, 2008.
(One of the five topics is “[biochemical reaction networks](#).”)
- AMS Special Session on the [Mathematics of Biochemical Reaction Networks](#), Raleigh NC, April 4-5, 2009.

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