

Lecture 17 — April 01

*Lecturer: Anne Shiu**Scribe/ Editor: Shaowei Lin/ Maria Cueto*

17.1 Toric Dynamical Systems I

Today's lecture is the first in a series of two lectures by Anne Shiu on Toric Dynamical Systems. It is joint work of G. Craciun, A. Dickenstein, A. Shiu and B. Sturmfels. See arXiv:0708.3431 and arXiv:0801.3689 for full reports.

17.2 Lecture Outline

Below is an outline of the topics in today's lecture:

1. Chemical reaction network theory
 - Polynomial ODEs model biochemical dynamics
2. Toric dynamical systems
 - The nicest chemical reaction networks
 - Those having a complex balancing steady state
3. Using algebra to study TDS's
 - Matrix-Tree Theorem
 - Birch's Theorem
 - Special case: deficiency zero

On Thursday, the lecture will cover:

1. Global attractor conjecture
 - Is convergence to the Birch point guaranteed?
2. Multiple steady states
 - What is the smallest instance of bistability?

17.3 Introduction to TDS's

Mass-action kinetics have been studied since the 1970s by researchers such as M. Feinberg, F. Horn and R. Jackson. One particular area of study was the deficiency theory of Feinberg, who discovered deficiency-zero and deficiency-one theorems. A more in-depth introduction to this topic can be found in:

- F. Horn and R. Jackson, *General mass action kinetics* (1972).
- M. Feinberg, “Lectures on chemical reaction networks” (1979).

The first connection between mass-action kinetics and computational algebra was introduced recently by K. Gatermann. References discussing this connection include:

- K. Gatermann and B. Huber, *A family of sparse polynomial systems arising in chemical reaction systems* (2002).
- J. Gunawardena, *Chemical reaction network theory for in-silico biologists* (2003).

In this lecture, we will explore some of these connections in greater detail.

17.4 First Example

To introduce the basic ideas of chemical reaction network theory and mass-action kinetics, let us study the example of the *ligand-reactor-antagonist-trap*. In the human body, a chemical reaction which occurs is that of the protein *interleukin-1*, denoted by (L) for “ligand,” binding with its receptor protein, which we denote by (R). This reaction leads to inflammation and occurs in individuals with rheumatoid arthritis.

Naturally, we are interested in inhibiting this binding. Methods for accomplishing this have been proposed by G. Gnacadja, et al. (2007)¹. The first uses drugs, known as antagonists and denoted by (A), which binds with the receptor (R), thus inhibiting the binding reaction between (L) and (R). A second method uses drugs known as decoy receptors. They bind with interleukin-1 (L), thus preventing the inflammatory binding reaction. We denote these drugs by (T) because they “trap” the interleukin-1 proteins. Unfortunately, these drugs (T) also bind with the antagonists (A). Therefore, if we want to use both drugs in conjunction with each other, we need a deeper analysis of the interactions among all these chemicals.

To model the L-R-A-T system, we first need to identify the chemical *species* involved. There are eight chemical species altogether, namely L,R,A,T, L&R, A&R, L&T and A&T, where L&T for instance represents the species coming from the binding of L and T. Each species has a concentration that varies with time and is denoted, say, by $c_{L\&T}(t)$ for L&T.

¹Gnacadja, G, Shoshitaishvili, A, Gresser, M, Varnum, B, Balaban, D, Dunst, M, Vezina, C, and Li, Y. Monotonicity of interleukin-1 receptor-ligand binding with respect to antagonist in the presence of decoy receptor. *J. Theor. Biol.*, 244:478-488, 2007.

Next, we identify the chemical reactions. We have four reversible reactions, for example $L + R \leftrightarrow L\&R$. Each reaction tells us the how the concentrations evolve with time, via differential equations. For instance, the above reaction gives us the equation:

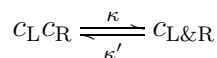
$$\frac{d}{dt}c_L = c_{L\&R}\kappa' - c_L c_R \kappa.$$

where $c_L c_R \kappa$ is the rate of the forward reaction and $c_{L\&R}\kappa'$ is that of the backward reaction. Here, κ and κ' are reaction rate constants. Finally, we may represent the state of the system by a vector of the eight concentrations of the different species:

$$c(t) = (c_L(t), c_R(t), \dots, c_{L\&R}(t)) \in \mathbb{R}^8.$$

Note that the differential equation consists of polynomials involving the variables $c(t)$ and also κ and κ' . Hence, we can use algebra and algebraic geometry to analyze these systems.

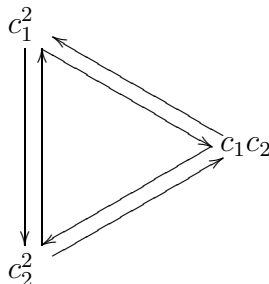
Now, instead of writing each reaction in the form $L + R \leftrightarrow L\&R$, we write it as



to reflect the algebraic structure of the differential equations. We call $c_L c_R$ a chemical *complex* because it consists of chemical species.

17.5 Preliminary Definitions

A *chemical reaction network* is a directed graph with vertices labeled by *monomials* and edges labeled by *parameters*. The figure below is an example of a *reaction diagram*



In the above diagram, we have $s = 2$ species c_1 and c_2 , and $n = 3$ complexes c_1^2 , c_1c_2 and c_2^2 . The diagram also reflects all six possible reactions. In general, we will use the following notations. We let the vertex i be labeled by the monomial

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

and collect all the exponents in an $n \times s$ matrix $Y = (y_{ij})$ of non-negative integers. The monomial labels are the entries in the row vector

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

For example, in the above 2-species example, we have

$$Y = \begin{pmatrix} 2 & 0 \\ 1 & 1 \\ 0 & 2 \end{pmatrix}, \quad \Psi(c) = (c_1^2, c_1 c_2, c_2^2).$$

Each directed edge $(i, j) \in E$ is labeled by a positive parameter κ_{ij} , the reaction rate constant. Now, view the concentrations of the s species c_1, c_2, \dots, c_s as functions $c_i(t)$ of time t . Then, the mass-action kinetics specified by the digraph G and the parameters κ_{ij} is the following dynamical system:

$$\frac{dc}{dt} = \Psi(c) \cdot A_\kappa \cdot Y \quad (17.1)$$

where A_κ is the Laplacian of G and we maps are composed in left-right direction (see (*) below). More precisely, for $i \neq j$, the (i, j) -th entry of A_κ is κ_{ij} if (i, j) is an edge in G , and 0 otherwise. The diagonal entries of A_κ are chosen so that the row sums are zero. For example, the Laplacian of the above digraph is

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

The differential equation (17.1) may be represented by the diagram

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

17.6 Two questions

For any chemical reaction network, one often asks the following two important types of questions:

1. Are there any steady states? When is $dc/dt = 0$?
2. For a given starting vector of concentrations $c^0 = (c_1^0, c_2^0, \dots, c_s^0)$, what happens to the concentrations as time $t \rightarrow \infty$?

For instance, for the L-R-A-T system, the questions come disguised in the following forms: is there any equilibrium concentration of interleukin-1-receptor binding? How much inflammation occurs at that concentration? For which reaction rate constants κ_{ij} will there be 0, 1, 2, ... steady states?

17.7 Steady States

We will distinguish between three different types of steady states. In general, *steady states* are equilibrium points at the level of species. They satisfy equations like

$$\frac{d}{dt}c_1 = \frac{d}{dt}c_2 = 0.$$

More specifically, we have *complex balancing* steady states which are equilibria at the level of complexes. The relevant equations in our example are

$$\frac{d}{dt}c_1^2 = \frac{d}{dt}c_1c_2 = \frac{d}{dt}c_2^2 = 0.$$

The most specialized steady states are called *detailed balancing* states which occur at the level of reactions. In our example, they are solutions of

$$\begin{aligned}\kappa_{12}c_1^2 &= \kappa_{21}c_1c_2 \\ \kappa_{23}c_1c_2 &= \kappa_{32}c_2^2 \\ \kappa_{31}c_2^2 &= \kappa_{13}c_1^2.\end{aligned}$$

We may rewrite the above equations in terms of our new notation. Firstly, steady states are concentrations $c \in (\mathbb{R}_{>0})^s$ satisfying

$$\Psi(c) \cdot A_\kappa \cdot Y = 0.$$

Meanwhile, complex balancing states satisfy

$$\Psi(c) \cdot A_\kappa = 0.$$

Finally, for detailed balancing steady states, we start by writing down A_κ as a sum of matrices $A_\kappa^{\{i,j\}}$ whose structure is seen most clearly in the example

$$\begin{aligned}A_\kappa &= A_\kappa^{\{1,2\}} + A_\kappa^{\{1,3\}} + A_\kappa^{\{2,3\}} \\ &= \begin{pmatrix} -\kappa_{12} & \kappa_{12} & 0 \\ \kappa_{21} & -\kappa_{21} & 0 \\ 0 & 0 & 0 \end{pmatrix} + \begin{pmatrix} -\kappa_{13} & 0 & \kappa_{13} \\ 0 & 0 & 0 \\ \kappa_{31} & 0 & -\kappa_{31} \end{pmatrix} + \begin{pmatrix} 0 & 0 & 0 \\ 0 & -\kappa_{23} & \kappa_{23} \\ 0 & \kappa_{32} & -\kappa_{32} \end{pmatrix}.\end{aligned}$$

Then, detailed balancing is described by equations

$$\Psi(c) \cdot A_\kappa^{\{i,j\}} = 0$$

for all edges (i, j) in G .

17.8 Toric Dynamical Systems

We are now ready to define a toric dynamical system.

Definition 17.1. *A toric dynamical system is a mass-action kinetics system with a complex balancing state.*

The most important property of such systems is given by the following:

Theorem 17.2. *(Birch) If one complex balancing steady state exists, then all steady states are complex balancing. Moreover, for each starting point, there is a unique steady state that the trajectory could reach.*

Later, we will show that a mass-action kinetics system is a toric dynamical system if and only if the parameters κ_{ij} lie in a certain toric variety. A toric variety is the set of points vanishing on polynomials in a toric ideal, and a toric ideal is an ideal generated by binomials, i.e. the difference of two monomials. Thus, equivalently, we may say that there exists certain binomials $B_k(\kappa_{ij})$, $k = 1, \dots, m$ such that a mass-action kinetics system is a toric dynamical system if and only if $B_k(\kappa_{ij}) = 0$ for all k . For instance, in the 2-species example above, the binomial defining toric dynamical systems is of the form $B(\kappa_{ij}) = K_1 K_3 - K_2^2$ where K_1 , K_2 and K_3 are polynomials in the κ_{ij} 's. We will discuss how to find these K_i 's in the next section on the Matrix-Tree Theorem.

In the meantime, let us consider the ideals representing the different steady states. The polynomial ring we are working over is the ring

$$\mathbb{Q}[c, \kappa] = \mathbb{Q}[\{c_1, c_2, \dots, c_s\} \cup \{\kappa_{ij} : (i, j) \in E\}].$$

Then, the *steady state ideal* is

$$\langle \Psi(c) \cdot A_\kappa \cdot Y \rangle$$

while the *complex balancing ideal* is

$$C_G := \langle \Psi(c) \cdot A_\kappa \rangle : \langle c_1 c_2 \cdots c_s \rangle^\infty.$$

Finally, the *detailed balancing ideal* is

$$\langle \Psi(c) \cdot A_\kappa^{\{i,j\}} \rangle : \langle c_1 c_2 \cdots c_s \rangle^\infty.$$

Here, the *ideal quotient* or *saturation* $I : J^\infty$ is defined to be the ideal

$$\{r \in \mathbb{Q}[c, \kappa] \mid r J^n \in I \text{ for some } n > 0\}.$$

Note that in the last two ideals, we saturate out by the ideal $\langle c_1 c_2 \cdots c_s \rangle$ because we want to ignore the boundary steady states, those where $c_i = 0$ for some i .

In studying mass-action kinetics systems, we are most interested in points on the *positive* varieties of the above ideals, i.e. points $((c_i), (\kappa_{ij}))$ where $c_i > 0$ and $\kappa_{ij} > 0$ for all i and j . Since saturation only removes the boundary points, the following positive varieties coincide:

$$\begin{aligned} V_{>0}(C_G) &= V_{>0}(\langle \Psi(c) \cdot A_\kappa \rangle) \\ &= \{\text{complex balancing steady states}\} \end{aligned}$$

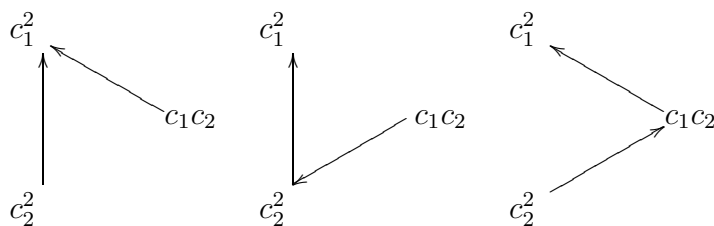
In fact, we are going to define a toric subideal $T_G \subset C_G$ such that

$$V_{>0}(T_G) = V_{>0}(C_G) = V_{>0}(\langle \Psi(c) \cdot A_\kappa \rangle).$$

The Matrix-Tree Theorem will provide the coordinates K_i alluded to earlier in which T_G is toric. For our 2-species example, we will see that $T_G \cap \mathbb{Q}[\kappa] = \langle K_1 K_3 - K_2^2 \rangle$.

17.9 Matrix-Tree Theorem

In this section, we will prove the Matrix-Tree Theorem. Before stating the theorem, let us start with some definitions. First, we say that a directed tree T is an i -tree if the node i is its unique sink, i.e., all edges are directed towards node i . For instance, in our 2-species example, for the first vertex of G (so $i = 1$), there are three i -trees T_1, T_2 and T_3 , as shown in the diagrams below:



Each tree gives rise to a monomial, which is the product of the parameters associated to the edges in the tree. Thus, for our example, we have

$$\begin{aligned} \kappa^{T_1} &= \kappa_{21} \kappa_{31}, \\ \kappa^{T_2} &= \kappa_{23} \kappa_{31}, \\ \kappa^{T_3} &= \kappa_{21} \kappa_{32}. \end{aligned}$$

Now, define

$$K_i := \sum_{T \text{ an } i\text{-tree}} \kappa^T. \quad (17.2)$$

In our example, we have just shown that $K_1 = \kappa_{21} \kappa_{31} + \kappa_{23} \kappa_{31} + \kappa_{21} \kappa_{32}$. Last but not least, we say that a digraph G is *strongly connected* if there is a directed path between any two vertices i and j in the graph. We are now ready for the Matrix-Tree Theorem, which may be found in R. Stanley's *Enumerative Combinatorics*, vol. 2 (1999).

Theorem 17.3. (*Matrix-Tree Theorem*) Let G be a strongly connected digraph with n vertices. Consider a submatrix $M(i, j)$ of A_κ obtained by deleting the i -th row and any one of the columns. The signed determinant $(-1)^{(i+j)} \det M(i, j)$ equals $(-1)^{n-1} K_i$.

Proof: This proof generalizes the one presented in Stanley's book. First, we claim that it suffices to assume that $j = 1$. To prove this claim, we need to show that

$$(-1)^{(i+j)} \det M(i, j) = (-1)^{(i+1)} \det M(i, 1). \quad (17.3)$$

We will prove this claim when A_κ is a 4×4 matrix, and $j = 3$. The general case follows by the same reasoning. Write

$$A_\kappa = \begin{pmatrix} | & | & | & | \\ a & b & c & d \\ | & | & | & | \end{pmatrix}.$$

Then, deleting the i -th row and $(j = 3)$ -th column gives

$$M(i, j) = \begin{pmatrix} | & | & | \\ a' & b' & d' \\ | & | & | \end{pmatrix}.$$

Note that because the rows of A_κ sum to zero, we have $a' = -d' - b' - c'$. Replacing the column a' with $-d' - b' - c'$ and performing the required column operations gives us

$$M(i, 1) = \begin{pmatrix} | & | & | \\ b' & c' & d' \\ | & | & | \end{pmatrix}.$$

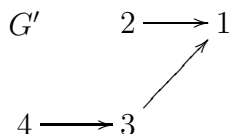
One can check that in this process, the determinant changes by $(-1)^{(j-1)}$. Hence, the equation (17.3) follows. Consequently, for the rest of the proof, we will assume that $j = 1$.

Now, we may also assume that $i = 1$. Indeed, consider the graph G' which is the same as G except that with the labels of vertices 1 and i switched. Then,

$$\det M_G(i, 1) = \det M_{G'}(1, i) = (-1)^{(i+1)} \det M_{G'}(1, 1)$$

where the last equality follows from our first claim. From now on, assume that $i = j = 1$.

Let G' be the graph G with all directed edges from vertex 1 removed, and let q be the number of edges in G' . We will prove the theorem by induction on q . Because G is strongly connected, G' is connected so our base case is $q = n - 1$. In this case, G' is an i -tree with $i = 1$. We want to compute the determinant of the submatrix $M(1, 1)$ of A_κ . Consider the example depicted here:



$$A_\kappa := \begin{pmatrix} * & * & * & * \\ \kappa_{21} & -\kappa_{21} & 0 & 0 \\ \kappa_{31} & 0 & -\kappa_{31} & 0 \\ 0 & 0 & \kappa_{43} & -\kappa_{43} \end{pmatrix}.$$

Since relabeling the vertices corresponds to permuting the rows and columns simultaneously, it does not change the determinant of $M(1, 1)$. We relabel the vertices such that the edges point from vertices with larger labels to those with smaller ones. It is easy to see that $M(1, 1)$ will be lower triangular matrix with diagonal entries $-\kappa_{k, \text{out}(k)}$, for $k = 2, \dots, n$ where $\text{out}(k)$ is the vertex such that $(k, \text{out}(k))$ is an edge in G' ; for example, consider removing the first row and column in A_κ depicted above. Hence,

$$\det M_G(1, 1) = \det M_{G'}(1, 1) = \prod_{k=2}^n (-\kappa_{k, \text{out}(k)}) = (-1)^{n-1} K_1.$$

Now, suppose that $q > n - 1$ and that the theorem is true for all smaller q . There exists some vertex $u \neq 1$ such that u has out-degree at least 2 in G . Let S be the set of out-edges of u , and pick any edge $e \in S$. Define D_1 to be the graph G with e removed, and D_2 to be the graph G with $S \setminus \{e\}$ removed. Then,

$$K_1(G) = K_1(D_1) + K_2(D_2),$$

because $K_1(D_1)$ is the sum (17.2) over all 1-trees not containing e and $K_2(D_2)$ is the sum over those containing e . By the induction hypothesis,

$$\begin{aligned} (-1)^{n-1} K_1(D_1) &= \det M_{D_1}(1, 1), \\ (-1)^{n-1} K_1(D_2) &= \det M_{D_2}(1, 1). \end{aligned}$$

But the matrices at hand have the following structure

$$\begin{matrix} M_G(1, 1) & M_{D_1}(1, 1) & M_{D_2}(1, 1) \\ \left(\begin{array}{ccc|ccc} \cdots & a+b & \cdots & & & \\ & & & & & \\ & & & & & \end{array} \right) & \left(\begin{array}{ccc|ccc} \cdots & a & \cdots & & & \\ & & & & & \\ & & & & & \end{array} \right) & \left(\begin{array}{ccc|ccc} \cdots & b & \cdots & & & \\ & & & & & \\ & & & & & \end{array} \right) \end{matrix}$$

where the displayed column is the column corresponding to vertex u . Therefore, by the multilinearity of the determinant function, we have

$$\begin{aligned} M_G(1, 1) &= \det M_{D_1}(1, 1) + \det M_{D_2}(1, 1) \\ &= (-1)^{n-1} K_1(D_1) + (-1)^{n-1} K_1(D_2) \\ &= (-1)^{n-1} K_1(G). \end{aligned}$$

This completes our induction. □

Returning to our two-species example, recall that the system is toric if and only if the κ_{ij} satisfy $K_1 K_3 = K_2^2$. Using the Matrix-Tree Theorem, we may now compute K_1 , K_2 and K_3 without enumerating the i -trees of G . Hence, the equation $K_1 K_3 = K_2^2$ is equivalent to

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