18.1 Outline of Today’s Lecture

- Toric dynamical systems–systems with a complex balancing steady state
- Toric dynamical systems and binomials–the Matrix-Tree Theorem gives coordinates $K_i$ in which the toric dynamical system condition is binomial
- Steady states
  - Birch’s Theorem
  - Special case: deficiency zero
- Global attractor conjecture–Is convergence to the Birch point guaranteed?
- Multiple steady states–What is the smallest instance of bistability?

18.2 Examples

Recall that we are considering chemical reaction network theory, in which we start with a labeled graph $G$ and obtain from $G$ a dynamical system $\left( \frac{dc}{dt} \right)$. We now recall two examples from the last lecture.

Example 18.1 (L-R-A-T). Here we have two types of receptors ($R$ and $T$) and two types of ligands they might bind to ($L$ and $A$). Then for example $c_L$ is our concentration of unbound $L$ and $c_LT$ is our concentration of bound $L$ and $T$.

\[
\begin{align*}
  c_Lc_R &\longrightarrow c_{LR} \\
  c_Ac_R &\longrightarrow c_{AR} \\
  c_Lc_T &\longrightarrow c_{LT} \\
  c_Ac_T &\longrightarrow c_{AT}
\end{align*}
\]
Example 18.2 (Triangle). In the “triangle example,” $G$ is

There are parameters $\kappa$ for each of the reactions. We recall that the dynamical system is given by $\frac{dc}{dt} = \Psi(c)A_\kappa Y$, where here $\Psi(c) = (c^2_1 c_2, c_1^2 c_2, c_1 c_2)$,

$$A_\kappa = \begin{pmatrix} -\kappa_{12} - \kappa_{13} & \kappa_{12} & \kappa_{13} \\ \kappa_{21} & -\kappa_{21} - \kappa_{23} & \kappa_{23} \\ \kappa_{31} & \kappa_{32} & -\kappa_{31} - \kappa_{32} \end{pmatrix} \quad \text{and} \quad Y = \begin{pmatrix} 2 & 0 \\ 1 & 1 \\ 0 & 2 \end{pmatrix}$$

$A_\kappa$ is the Laplacian, so its row sums are 0. Recall that this is a toric dynamical system if there exists $c \in \mathbb{R}_{>0}^5$ such that $\Psi(c)A_\kappa = 0$, i.e. there is a complex balancing steady state. In this case, we have that this triangle example is a toric dynamical system if and only if $K_1 K_3 = K_2^2$, where the $K_i$ come from the Matrix-Tree Theorem.

Note that if we change $G$ to

by setting $\kappa_{12} = \kappa_{32} = 0$, the dynamical system is not toric for all positive rate constants.

18.3 Computing the Binomials

The Matrix-Tree Theorem gives us coordinates $K_i$. We define polynomials $K_i c^{y_i} - K_j c^{y_j} \in \mathbb{Q}[\kappa_{ij}, c_\ell]$, where the $c^{y_i}$ are the vertices of the graph. Then we let $I = \langle K_i c^{y_i} - K_j c^{y_j} \rangle$ and eliminate the $c$ coordinates by letting $J = I \cap \mathbb{Q}[\kappa_{ij}]$. We can compute $J$ via Gröbner basis techniques. Then $J$ is generated by binomials in the $K_i$ and is called the moduli ideal of $G$, written later as $M_G$.

Theorem 18.3. A system is a toric dynamical system if and only if there exists a complex balancing steady state if and only if the $\kappa_{ij}$ satisfy binomials.

18.4 Deficiency

Once we know that a toric dynamical system is defined by binomials, an obvious question arises: How many binomials do you need? The answer turns out to be (roughly) an integer called the deficiency.
Definition 18.4. For a reaction network $G$, define the subspace

$$S := \text{span}\{y_j - y_i | (i, j) \in E(G)\}.$$ 

$S$ is called the stoichiometric subspace.

Definition 18.5. The deficiency of $G$ is $\delta := n - \sigma - l$, where

- $n$ is the number of complexes (the number of vertices of $G$),
- $\sigma = \dim(S)$, and
- $l$ is the number of connected components of $G$.

Let’s find the deficiency of $G$ in our earlier examples. In the triangle example, $n = 3$, $l = 1$ and $\sigma = \dim \text{span}\{y_i - y_j\} = \dim \text{span}\{(1, -1), (2, -2)\} = 1$. So $\delta = 3 - 1 - 1 = 1$.

In the L-R-A-T example, $n = 8$ and $l = 4$. If $y_1$ is associated to $c_{LR}$, $y_2 = c_{LT}$ and so on, then each reaction gives us a linearly independent vector in $S$ so $\sigma = 4$. Thus $\delta = 0$. This means that there is always a steady state (see theorems below).

Theorem 18.6. The moduli ideal $M_G$ is toric (i.e. generated by binomials), and its codimension equals the deficiency of $G$, $\delta$.

This theorem tells us that the deficiency is essentially the number of binomials needed to define the ideal $M_G$.

Theorem 18.7 (Deficiency Zero Theorem). If $\delta = 0$, then $G$ has a unique complex balancing steady state.

Since $\frac{dc}{dt} = \Psi(c)A_nY \in S$, the trajectories $\{c(t) | t \geq 0\}$ always stay parallel to $S$, i.e. $c(t) \in c(0) + S$.

Definition 18.8. The invariant polyhedron $P$ is $(c(0) + S) \cap \mathbb{R}_{\geq 0}$. (Chemists call this the stoichiometric compatibility class.

Theorem 18.9 (Birch’s Theorem). The set of detailed balancing solutions intersects $P$ at exactly on point $\tilde{p} := \tilde{p}(c, P)$. Further, this point $\tilde{p}$, which we call the Birch point, is in the interior of $P$ and is the unique entropy minimal point of $P$.

The book *Algebraic Statistics for Computational Biology* gives a different version of Birch’s Theorem. Recall that a toric model given by a $d \times n$ integer matrix $A = (a_{ij})$, whose columns $a_1, \ldots, a_n$ is the image of the map $f: \mathbb{R}_+^d \to \mathbb{R}^n$ given by

$$\theta \mapsto \frac{1}{\sum_{i=1}^{n} \theta^{a_i}}(\theta^{a_1}, \theta^{a_2}, \ldots, \theta^{a_n}).$$

The polytope $P_A(p(0))$ is defined by $P_A(p(0)) = \{q \in \mathbb{R}_{\geq 0}^n | A \cdot q = A \cdot p(0)\}$. Then Birch’s Theorem can be restated as follows.
Theorem 18.10. For the toric model given by the matrix $A$ and some initial point $p(0) \in \delta_{n-1}$ in the interior of the probability simplex, the intersection of the polytope $P_A(p(0))$ with the $c$-shifted toric model $f_c^d$ consists of exactly one point $\tilde{p}$. Further, this point $\tilde{p}$ is the unique entropy minimal point of $P$.

Theorem 18.11 (Detailed-Balancing). The intersection of the detailed balancing steady states with the polytope yields one Birch point. These two theorems are equivalent. To prove this, we let the correspondence between matrices $A$ and stoichiometric subspaces $S$ be defined by $\ker A = S$. We then need to check that

- The two polytopes are the same, i.e. $P = P_A(p(0))$.
- The toric model $f(\mathbb{R}^d_{\geq 0})$ equals the detailed balancing steady states.

We can use a Lyapunov function and a more general “entropy function”. Then

Theorem 18.12. The Birch point $c^*$ is the unique point in the invariant polyhedron $P$ for which the transformed entropy function

$$E(C) = \sum_{i=1}^{s} (c_i \log(c_i) - c_i \log(c_i^*) - c_i + c_i^*)$$

is a strict Lyapunov function of the toric dynamical system.

That $E(C)$ is a strict Lyapunov function of the toric dynamical system means

(a) For all $c \in P$ we have $E(c) \geq 0$ and equality holds if and only if $c = c^*$.

(b) We have $\frac{dE(c)}{dt} \leq 0$ along any trajectory $c(t)$ in $P$.

(c) Equality in (b) holds at a point $t$ of any trajectory $c(t)$ in $P^o$ if and only if $c(t) = c^*$.

18.5 Global Attractor Conjecture

Definition 18.13. A steady state $x$ in $P^o$ is called a global attractor if any trajectory that begins in $P^o$ converges to $x$.

Conjecture 18.14. For any toric dynamical system and any starting point $c^o$, the Birch point $c^*$ is a global attractor of the polytope $P = (c^o + S) \cap \mathbb{R}_{\geq 0}^s$.

For the L-R-A-T example, the global attractor conjecture holds since there are no boundary steady states, meaning that since $E(c)$ is a Lyapunov function, trajectories all converge to the Birch point.

This conjecture has been proven under some restrictions, including on the dimension of the polyhedron.

Theorem 18.15. Consider a detailed balancing system whose stoichiometric subspace $S = \{y_j - y_i \mid (i, j) \in E\}$ is two-dimensional and assume that the invariant polygon $P$ is bounded. Then the Birch point is a global attractor for $P$. 

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18.6 Multiple Steady States

We now turn our attention to systems having multiple steady states, in particular those that are not toric dynamical systems. We will focus on the Square network.

**Example 18.16.** The Square network shown below is a smallest reversible multistationary chemical reaction network.

![Square network diagram]

The number of complexes is $n = 4$, $G$ has $l = 1$ connected components, the number of species is $s = 2$ and the dimension of any invariant polyhedron $P$ is $\sigma = 1$.

**Theorem 18.17.** The square is a smallest multistationary, mass-preserving, reversible chemical reaction network with respect to each of the parameters $n, l, s,$ and $\sigma$.

Since $c_1(t) + c_2(t) = c_1(0) + c_2(0)$, we have $\frac{dc_1}{dt} = -\frac{dc_2}{dt}$. A steady state occurs when

$$0 = \frac{dc_1}{dt} = \alpha_1 c_1^3 + \alpha_2 c_1^2 c_2 + \alpha_3 c_1 c_2^2 + \alpha_4 c_2^3$$

for the appropriate $\alpha_i \in \mathbb{Q}[\kappa_{ij}]$. Then we can substitute $x = \frac{c_1}{c_2}$ to get

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

The steady states correspond to the positive roots of this polynomial. The binomials for determining when this is a toric dynamical system are the $2 \times 2$ minors of

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

namely $K_1K_3 - K_2K_4$, $K_2^2 - K_3K_4$ and $K_1K_2 - K_4^2$. When the roots are positive, the last binomial can be derived from the first two. These binomials define the twisted cubic curve.