Generalized Polynomial Models of Biochemical Systems

Gheorghe Craciun\(^1\), Stefan Müller\(^2\), Casian Pantea\(^3\), and Polly Yu\(^4\)

\(^1\) University of Wisconsin–Madison \(^2\) University of Vienna \(^3\) West Virginia University

### Biological Motivations

- Mass action systems model metabolite concentrations, but unrealistic assumptions for biological systems, e.g., well-mixed and homogeneous environment.
- Some other models are time-dependent parameters, power-law or generalized polynomials [4], and stochastic processes [1].
- Use generalized polynomial models as a tool to study dynamically equivalent mass action systems [3].

### Philosophical Objectives

- Avoid unwieldy computations: Infer dynamical properties based on network structure, independent of parameters.
- Beyond statistics: Insights into biological processes and mechanisms based on kinetics.

### Example: Futile Cycle

- Enzymes E, F catalyzing reactions on substrates S:\n  
  \[
  E + S \xrightleftharpoons{\kappa_{12}}{\kappa_{21}} S E \xrightleftharpoons{\kappa_{34}}{\kappa_{43}} E + S
  \]
  
  F + S \xrightleftharpoons{\kappa_{40}}{\kappa_{04}} S F \xrightleftharpoons{\kappa_{13}}{\kappa_{31}} F + S
  
  Let \( x^T = (x_E, x_S, x_{SE}, x_E, x_S, x_F, x_S) \) be a concentration vector.
  
  Represent the reaction complexes as:
  
  \( y_1 \sim E + S \), \( y_2 \sim ES \), \( y_3 \sim E + S \), \( y_4 \sim F + S \), \( y_5 \sim F + S \), \( y_6 \sim F + S \).
  
  Under mass action kinetics:
  
  \[
  \frac{dx}{dt} = \kappa_{12} x_E x_S \left[ y_2 - y_1 \right] + \kappa_{21} x_E x_S \left[ y_1 - y_2 \right] + \ldots
  \]
  
  Representation of the network as a directed graph:

  \[
  \begin{array}{ccc}
  \bullet & \xrightarrow{\kappa_{12}} & \bullet \\
  \bullet & \xrightarrow{\kappa_{21}} & \bullet \\
  \bullet & \xleftrightarrow{\kappa_{34}} & \bullet \\
  \bullet & \xleftrightarrow{\kappa_{43}} & \bullet \\
  \bullet & \xleftarrow{\kappa_{40}} & \bullet \\
  \end{array}
  \]

- **Weakly reversible** networks admit **complex-balanced equilibria**, positive steady states where the net flux across each vertex is 0.
- For mass action, complex-balanced implies uniqueness and stability of steady states.
- For stochastic mass action, complex-balanced system has a product of Poissons as its stationary distribution. [1]

### Generalized Mass Action Systems

- Reaction network: a weighted directed graph \( G_n = (V, E, \kappa) \)
- Assign a **reaction complex** \( y_i \in \mathbb{R}^n \) and a **kinetic complex** \( \tilde{y}_i \in \mathbb{R}^n \) to each vertex \( y_i \in V \).

```
  y_1 \sim E + S, \ y_2 \sim ES, \ y_3 \sim E + S, \ y_4 \sim F + S,
  y_5 \sim F + S, \ y_6 \sim E + S.
```

- The **sign vector** \( \sigma(x) \) of vector \( x \in \mathbb{R}^n \) is \( \sigma(x) = (\text{sign}(x_i))_{i=1}^n \).
- **Interpretations:**
  - the orthants that the vectors \( x \in S \) point in (geometry of \( S \)),
  - the face lattice of convex cone generated by basis elements of \( S^{\perp} \) (relative positions of vectors).
- **Closure** \( \overline{\sigma(S)} \) includes sign vectors in \( \sigma(S) \) and those with possibly more zero components, i.e., signs of vectors lying on the coordinate walls of orthants containing vectors of \( S \).

### Network Condition for Existence and Uniqueness of Steady State

- **Proposition: Uniqueness [4]**
  At most one vertex-balanced equilibrium exists within \( x_0 + S \) for any \( x_0 \in \mathbb{R}^n \) if and only if \( \sigma(S) \cap \overline{\sigma(S)} = \{0\} \).

- **Corollary:**
  A system is **multistationary** if \( \sigma(S) \cap \overline{\sigma(S)} \neq \{0\} \).

### Main Tool: Sign Vectors

- **Theorem: Uniqueness and Existence**
  Suppose \( Z_k \neq \emptyset \) if \( \dim S = \dim \overline{S} \) and \( \sigma(S) \subseteq \overline{\sigma(S)} \) then there is exactly one vertex-balanced equilibrium in \( x_0 + S \) for any \( x_0 \in \mathbb{R}^n \).

### Future Directions

- Characterize when a positive steady state of a mass action system is vertex-balanced for a dynamically equivalent generalized mass action system.
- Study the effects of perturbing \( S \mapsto \tilde{S} \) on the set of steady states of a mass action system.
- Find necessary and sufficient condition on the network, \( S \), and \( \tilde{S} \) for the existence of a vertex-balanced equilibrium.

### References