Sufficient Conditions for Monotonicity in Stochastic Chemical Reaction Networks

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Abstract. Chemical reactions are best expressed as a system of differential equations. Here, we explore the ways we can model chemical reaction networks through these systems. These systems can then be abstracted as a dynamical system, which raises questions about monotonicity and emergent behavior. In this paper we lay the ground work for stochastic chemical reaction networks and explore the emergent behavior. We create software that helps in determining the monotonicity of a chemical reaction network and use that to conjecture about stochastic chemical reaction networks. We start being doing an in depth review of chemical reaction networks and monotone dynamical systems. We review them each in isolation before going over their connections. We then come up with a weaker definition than monotonicity for stochastic chemical reaction networks and outline the steps we take to try and solve our own conjecture.

INTRODUCTION

Chemical reactions network theory is a field of applied mathematics that attempts to model chemical systems. Chemical reactions can be represented using differential equations. Thus, a network of reactions induces a system of differential equations, which describe the change in the concentrations of each species in the network. There has been much work done in defining systems of chemical reactions that are monotone. In our research, we explore the ways to determine monotonicity in these systems. We will begin with a brief introduction to chemical reaction network theory, where we will use kinetics to write out our system. Afterwards, we will explore more general checks for monotonicity absent of any choice of kinetics. We will then pivot to studying monotonicity of stochastic chemical reaction networks and see what we can learn from the deterministic models. We are specifically interested in monotonicity because knowing that a system is monotone can help tell you if a system is globally convergent.

CHEMICAL REACTION NETWORKS

Recall that a chemical reaction networks is defined as a set

$$\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$$
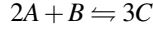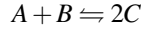
where...

- $\mathcal{S}$ is a finite set whose elements are the species of the network

- $\mathcal{C}$ is a finite set of vectors in $\overline{\mathbb{R}}_+^{\mathcal{S}}$ denoting the complexes of the network

- $\mathcal{R}$ is a set in $\mathcal{C} \times \mathcal{C}$ containing the reactions of the network

    For a reaction $y \to y'$, y is the reactant complex while y' is the product complex. For each complex $y \in \mathcal{C}$:
    - $(y, y) \notin \mathcal{R}$
    - There exists a $y' \in \mathcal{C}$ such that $(y, y') \in \mathcal{R}$ or $(y', y) \in \mathcal{R}$.

Since $\mathcal{S}$ denotes a finite set of species, $\mathbb{R}^{\mathcal{S}}$ represents the vector space of real-valued functions on $\mathcal{S}$. A vector $x \in \mathbb{R}^{\mathcal{S}}$ equates each entry $i \in \mathcal{S}$ with a real number, x_i. $\overline{\mathbb{R}}_+^{\mathcal{S}}$ represents the set of members of $\mathbb{R}^{\mathcal{S}}$ that take in non-negative values for each x_i.

Example: Given a system

$$A + B \rightleftharpoons 2C$$

$$2A + B \rightleftharpoons 3C$$

$\mathcal{S} = \{A, B, C\}$

$\mathcal{C} = \{A + B, 2C, 2A + B, 3C\} \subset \overline{\mathbb{R}}_+^{\mathcal{S}}$

$\mathcal{R} = \{A + B \rightarrow 2C, 2C \rightarrow A + B, 2A + B \rightarrow 3C, 3C \rightarrow 2A + B\}$

Kinetics

Endowing kinetics to a chemical reaction network is what allows us to consider the emergent properties of a system. In assigning each reaction a function that determines the rate at which is occurs, we are able to build systems of differential equations from our chemical reaction network. This in turn allows us to use the tools of dynamical systems to say meaningful things about our network. Naturally, we would like to assign each element of our set $\mathcal{R}$ a function that accounts for its occurrence rate.

Definition: A kinetics for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is an assignment to each reaction $y \rightarrow y' \in \mathcal{R}$ of a continuously differentiable rate function $\mathcal{K}_{y \rightarrow y'} : \overline{\mathbb{R}}_+^{\mathcal{S}} \rightarrow \overline{\mathbb{R}}_+$ such that

$$\mathcal{K}_{y \rightarrow y'}(c) > 0 \text{ } \textit{if and only if } \text{supp } y \subset \text{supp } c$$

where the support of a vector $x \in \mathbb{R}^{\mathcal{S}}$ is the subset of $\mathcal{S}$ on which x takes non-zero values: $\text{supp } x := \{i \in \mathcal{S} : x_i \neq 0\}$

$\mathcal{K}_{y \rightarrow y'}(c)$ denotes the reaction rate of $y \rightarrow y'$ when the mixture has composition c. If we take c to be the instantaneous composition of the mixture, the support of c is the species present in the mixture. Furthermore, for the reaction, the support of y is the set of reactant species. The condition above thus means the rate function of a reaction is positive if and only if all the of reactants required for the reaction are present in the current mixture.

Definition: A kinetic system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ is a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ taken with a kinetics $\mathcal{K}$.

Mass Action Kinetics

There is no canonical way to assign kinetics to a chemical reaction network. However, one of the most simple and powerful ways to do this comes in the form of mass action kinetics. Mass action kinetics presumes the instantaneous occurrence rate of a reaction to be proportional to the instantaneous concentration of the reactants involved in the reaction.

Definition: A kinetics $\mathcal{K}$ for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is **mass action** if, for each reaction $y \rightarrow y' \in \mathcal{R}$, there is a positive number $k_{y \rightarrow y'}$ such that

$$\mathcal{K}_{y \rightarrow y'}(c) \equiv k_{y \rightarrow y'} \prod_{s \in \mathcal{S}} c_s^{y_s},$$

where $k_{y \rightarrow y'}$ is the rate constant for the reaction $y \rightarrow y'$ and y_s is the stoichiometric coefficient of species s in the reactant complex y of the reaction.

Definition: A **mass action system** $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ is a chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ taken with a **rate constant specification** $k \in \mathbb{R}_+^{\mathcal{R}}$.

Example: Given a mass-action system with $k = \begin{bmatrix} k_1 & k_2 & k_3 & k_4 \end{bmatrix}^T$,
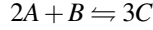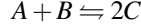
$$A + B \rightleftharpoons 2C$$

$$2A + B \rightleftharpoons 3C$$

$$\mathcal{K}_{\text{A + B} \rightarrow \text{2C}} \equiv k_1(c_A)^1(c_B)^1(c_C)^0(c_D)^0(c_E)^0 = k_1 c_A c_B$$

$$\mathcal{K}_{\text{2A + B} \rightarrow \text{3C}} \equiv k_3(c_A)^2(c_B)^1(c_C)^0(c_D)^0(c_E)^0 = k_3 c_A^2 c_B$$

$$\mathcal{K}_{\text{3C} \rightarrow \text{2A + B}} \equiv k_4(c_A)^0(c_B)^0(c_C)^3(c_D)^0(c_E)^0 = k_4 c_C^3$$

$$\mathcal{K}_{\text{2C} \rightarrow \text{A + B}} \equiv k_2(c_A)^0(c_B)^0(c_C)^2(c_D)^0(c_E)^0 = k_2 c_C^2$$

Induced Equations

Definition: The **species-formation-rate function** for a mass action kinetic system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ is defined by the condition: for all $c \in \overline{\mathbb{R}}_+^{\mathcal{S}}$

$$f(c) := \sum_{\mathcal{R}} k_{y \rightarrow y'} c^y (y' - y),$$

where $(y' - y)$ is the reaction vector corresponding to the reaction $y \rightarrow y'$ and $f_s(c)$ gives the instantaneous generation rate of species s as a result of all the reactions in the network occurring.

The differential equation for a kinetic system is simply $\dot{c} = f(c)$, with the dot signifying time differentiation. The differential equation for a chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ is then

$$\dot{c} := \sum_{\mathcal{R}} k_{y \rightarrow y'} c^y (y' - y)$$

Example: Given a system with $k = \begin{bmatrix} k_1 & k_2 & k_3 & k_4 \end{bmatrix}^T$,

$$\dot{c}_A = -k_1 c_A c_B + k_2 c_C^2 - 2k_3 c_A^2 c_B + k_4 c_C^3$$

$$\dot{c}_B = -k_1 c_A c_B + k_2 c_C^2 - k_3 c_A^2 c_B + k_4 c_C^3$$

$$\dot{c}_C = k_1 c_A c_B - 2k_2 c_C^2 + k_3 c_A^2 c_B - k_4 c_C^3$$

MONOTONE SYSTEMS

Monotone systems describe flows wherein relative starting positions between particles are enough to tell you something about the emergent behavior at time t. That is, if one particle is ahead of another, it remains ahead of it for the entire trajectory of the two particles. We make these ideas precise in the following subsections.

Dynamical Systems

Before developing the theory of monotone systems we must first define a more general mathematical structure. Dynamical systems are how a set of points X change in time.

Definition: A dynamical system is a tuple (T, X, Φ), where T is a monoid, X is a non-empty set, and Φ is a function $\Phi : U \subseteq X \times T \to X$. Additionally, a dynamical system must satisfty

1. $\Phi(0, x) = x$

2. $\Phi(t_2, \Phi(t_1, x)) = \Phi(t_2 + t_1, x)$

Systems of ordinary differential equations satisfy this definition and are our main object of study. Specifically, we would like to make meaningful statements about the trajectories and long term behavior of these systems. Dealing with systems of ordinary differential equations allows us to be more restrictive than the general machinery we just detailed for an arbitrary dynamical system.

Definition: A semi-flow on X is a continuous map $\Phi : X \times \mathbb{R}^+ \to X$ that satisfies the conditions of a dynamical system.

Definition: The orbit denoted $\mathcal{O}(x)$, is defined via $\mathcal{O}(x) \equiv \{\Phi_t(x) : t \geq 0\}$ The orbit outlines the trajectory that some element $x \in X$ in our phase space will undergo.

The orbit gives information about an entire trajectory, but we would also like to be able to formalize the end of the trajectory. This motivates the following definition.

Definition: For $x \in X$, the omega limit set $\omega(x) \equiv \cap_{t \geq 0} \overline{\cup_{s \geq t} \Phi_s(x)}$

The following definitions detail useful dynamical systems both in their ability to model biological processes and in how they lend themselves to monotonicity.

Definition: Given a C^1 system of differential equations in $\mathbb{R}^n$, $\frac{dx_i}{dt} = F_i(x_1, \ldots, x_n) = F_i(x)$, where $i = 1, \ldots, n$. We say that a system is cooperative if $\frac{\partial F_i}{\partial x_j} \geq 0 \ \forall i \neq j$

Example:

$$\begin{cases} \dot{x} = y - x \\ \dot{y} = x - y \end{cases}$$

Definition: Similarly, we say that a system is competitive if $\frac{\partial F_i}{x_j} \leq 0 \ \forall i \neq j$

Example:

$$\begin{cases} \dot{x} = x - y \\ \dot{y} = y - x \end{cases}$$

Stability Analysis

In the build up to studying monotonicity, we studied forms of convergence analysis common in dynamical systems. We examine fixed points that are attracting, Liupanov stable, and asymptotically stable.

Definition: Consider a system of differential equations of the form $\dot{x} = f(x)$. Points $x*$ where $f(x*) = 0$ are known as fixed points.

Fixed points are integral in studying the emergent or long term behavior of a dynamical system as they represent points where there is no flow. If the fixed points are stable, i.e, all points in a vector field point toward the fixed point

we can make claims about the convergence of a system to that fixed point. Otherwise, we may study the chaotic behavior that goes around that fixed point.

Definition: A fixed point $x*$ is attracting if there is a $\delta > 0$ such that $\lim\limits_{t \to \infty} x(t) = x*$ whenever $\|x(0) - x*\| < \delta$.

That is, a trajectory that starts sufficiently close to the fixed point will converge to the fixed point. In contrast, a fixed point is liupanov stable if trajectories remain close to the fixed point for all time $t \geq 0$.

Definition: A fixed point $x*$ is liupanov stable if for each $\varepsilon > 0$ there is a $\delta > 0$ such that $\|x(t) - x*\| < \varepsilon$ whenever $t \geq 0$ and $\|x(0) - x*\| < \delta$.

Claim: Two dimensional flows of the form $\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -k_1 & 0 \\ 0 & -k_2 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}$ have attracting fixed points at the origin. Constants k are assumed to be positive.

Proof: Consider the system

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -k_1 & 0 \\ 0 & -k_2 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} \tag{1}$$

Notice that $\begin{bmatrix} -k_1 & 0 \\ 0 & -k_2 \end{bmatrix}$ is diagonal, so we may easily solve this system row by row. We obtain

$$x(t) = c_1 e^{-k_1 t} \tag{2}$$

$$y(t) = c_2 e^{-k_2 t}. \tag{3}$$

In the limit as $t \to \infty$, we find $x(t) \to 0, y(t) \to 0$. Observe,

$$\left\| \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} x* \\ y* \end{bmatrix} \right\| = \left\| \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \end{bmatrix} \right\|$$

$$= \left\| \begin{bmatrix} c_1 e^{-k_1 t} \\ c_2 e^{-k_2 t} \end{bmatrix} \right\|$$

$$= \sqrt{e^{-k_1 t} + e^{-k_2 t}}.$$

For all $t \geq 0$, $\left\| \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} - \begin{bmatrix} x* \\ y* \end{bmatrix} \right\|$ is bounded between $\left(0, \sqrt{(c_1)^2 + (c_2)^2} \right)$ for any initial condition. If we choose $\delta > \sqrt{(c_1)^2 + (c_2)^2}$, then we have shown that the system (1) is attracting. $\square$

Lemma: This system is also Liapunov and therefore asymptotically stable.

Example:

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -1 & 0 \\ 0 & -5 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}$$

As we can see, all trajectories in this flow eventually convergence to the origin.
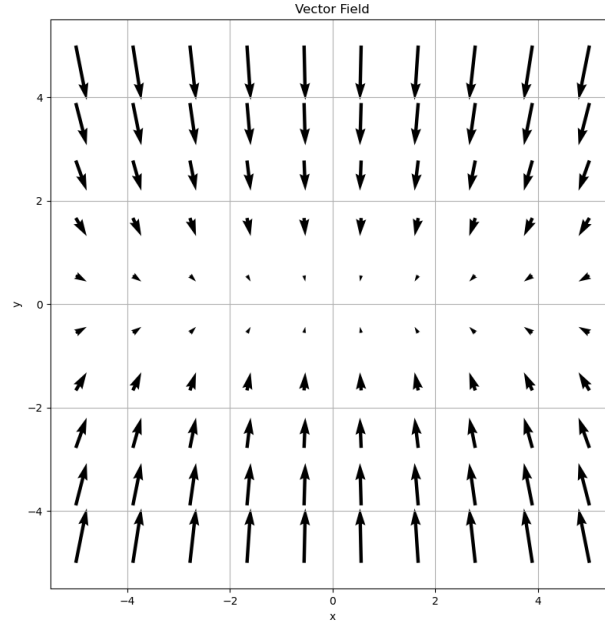
FIGURE 1. Vector Field for Example System

Monotone Dynamical Systems

Before we formally define monotonicity we should begin by defining a partial ordering. A partial ordering is a generalization of the standard $\leq$ operation.

<u>Definition</u>: If X is a metric space with metric d and partial order relation $\leq$, then $\leq$ must satisfy the following:

1. reflexive, $x \leq x \quad \forall x \in X$

2. transitive, $x \leq y \wedge y \leq z \implies x \leq z$

3. anti-symmetric, $x \leq y \wedge y \leq x \implies x = y$

<u>Definition</u>: We say that a system is monotonic if $\Phi_t(x) \leq \Phi_t(y)$ whenever $x \leq y$ and $t \geq 0$.
we can intuit this definition by considering the trajectories of two particles.

Monotonicity and Cones

<u>Definition</u>: A cone K is a subset of $\mathbb{R}^n$ satisfying $x \in K \Rightarrow \alpha x \in K$ for any positive scalar α

- K is pointed if $K \cap -K = 0$

- K is a proper cone if it is a closed and pointed convex cone in $\mathbb{R}^n$

A proper cone K, induces a partial ordering on $\mathbb{R}^n$ as follows:

$$x \leq_K y \iff y - x \in K$$

Using this machinery, we can come up with a more meaningful, equivalent, definition of cooperative.

<u>Definition</u>: Cooperative systems are monotone with respect to the partial ordering induced by the positive orthant, where the Positive orthant is the set of points in $\mathbb{R}^n$ such that each coordinate is non-negative.

HOW CHEMICAL REACTION NETWORKS RELATE TO MONOTONE SYSTEMS

There exist a number of different ways to check if a dynamical system is monotone. While many of these criterion aren't very strong, the following algebraic and graph theoretic conditions provide a starting point for deciding on the monotonicity of a chemical reaction network.

Qualitative Classes of Matrices

We begin our discussion by going over qualitative classes of matrices. Given an $n \times m$ matrix M, we are able to define classes of matrices of the same dimension based solely on the sign structure of M. The qualitative class of M $Q(M)$ consists of all $n \times m$ matrices with the same sign structure. The next class, $Q_0(M)$ is defined as the closure of $Q(M)$. It consists of all matrices X such that $M_{ij} > 0 \Rightarrow X_{ij} \geq 0$, $M_{ij} < 0 \Rightarrow X_{ij} \leq 0$, and $M_{ij} = 0 \Rightarrow X_{ij} = 0$. Subsequently, $Q_1(M)$ can be interpreted as the dual of $Q_0(M)$. It is defined as $Q_1(M) \subseteq Q_2(M)$. The last qualitative class we will introduce is $Q_2(M)$, defined $Q_2(M) \equiv Q_1(M) \cap Q_1(-M)$.

Algebraic Conditions

A chemical reaction with n reactants participating in m reactions is modeled by the following ordinary differential equation

$$\dot{c} = Sv(c),$$

where $c = [c_1, ..., c_n]^T$ is the non-negative vector of reactant concentrations, $v = [v_1, ..., v_n]^T$ is a vector of the reaction rates, and S is the constant $n \times m$ stoichiometric matrix.

To go over the algebraic conditions for monotonicity, we must make a weak yet important assumption about many reaction systems: the reaction rates are monotonic functions of its reactant concentrations.

<u>Definition</u>: The reaction system is **non-autocatalytic** if the stoichiometric matrix S and V^T have opposite sign structure such that $S_{ij}V_{ji} \leq 0$ for all i and j and $S_{ij} = 0 \implies V_{ij} = 0$.

More simply, this means if a reactant is used up in a reaction, increasing the reactant concentration whilst holding the other concentrations constant cannot cause the reaction rate to decrease. Additionally, if a species is not in the reactant complex of a reaction, its concentration does not affect the reaction rate. All reasonable kinetics produce non-autocatalytic systems as long as reactants do not occur in both the reactant and product complex of the reaction. This NAC condition means we do not consider irreversible systems in these algebraic methods of determining monotonicity.

<u>Definition</u>: A matrix J is **K-quasipositive** if there is a scalar α such that $J + \alpha I : K \mapsto K$. If such an α exists,

we choose it to be positive such that $\alpha > 0$.

We define $V_{ij}(c) \equiv \frac{\partial v_i}{\partial c_j}$ as it allows the Jacobian of our ODE to be $SV(c)$. This is useful because given a chemical reaction system, a cone K where the Jacobians of the system are K-quasipositive is preserved by all instances of the system with dynamics satisfying the NAC condition.

Another useful way to determine monotonicity is by considering each reaction within a system. The set of cones preserved by a reaction system is exactly the intersection of the cones preserved by the individual reactions of the system. As a result, we must identify cones that are preserved by a single chemical reaction.

Theorem: Take a system of m reactions where S_j is the stoichiometric vector for the j-th reaction and $S = [S_1|S_2|...|S_m]$. Let K be a cone with extremals $\{y_i\}$. The system preserves K if and only if each of its individual reactions do.

Cones Preserved by a Single Reaction

Take a proper cone K with extremals $\{y_i\}$, and a reaction with stoichiometric vector $S \in \mathbb{R}^n$. Let's define the following two conditions:

1. There exists an index k and $r \neq 0$ where $S = ry_k$ and

    (a) If $r > 0$, then $y_j \in Q_1(-S)$ for all $j \neq k$.
    (b) If $r, 0$, then $y_j \in Q_1(S)$ for all $j \neq k$.

2. There exist indices i_1 and i_2 and $r_1, r_2 > 0$ such that $S = r_1 y_{i1} - r_2 y_{i2}$. Furthermore, $y_{i1} \in Q_1(S)_1(-S)$, $y_{i2} \in Q_1(-S)_1(S)$ and $y_j \in Q_2(S)$ for all $j \neq \{i_1, i_2\}$.

Theorem:

- If $\mathcal{S}$ and K fulfill condition 1 or 2 above, then the cone K is preserved by the system.

- If $\mathcal{S} \in K \cup -K$ and K is preserved by the system, then S and K must meet condition 1.

- If $\mathcal{S} \notin K \cup -K$ and K is a simplicial cone preserved by the system, then S and K must meet condition 2. [M. Banaji]

Graph Theoretic Conditions

Definition: Let $f(x)$ be a C^1 vector field on the domain $x \in X$. The $J-$Graph is an undirected signed graph determined by the jacobian $Df(x)$. If $[Df(x)]_{ji} \geq 0 \ \forall x \in X$ and $\exists x^* \in X$ s.t. $[Df(x^*)]_{ji} > 0$ then we say that the edge from node i to node j is positive. Likewise, If $[Df(x)]_{ji} \leq 0 \ \forall x \in X$ and $\exists x^* \in X$ s.t. $[Df(x^*)]_{ji} < 0$ then we say that the edge from node i to node j is negative. In the case that $[Df(x)]_{ji} = 0 \forall x \in X$, we don't draw an edge.

Definition: An undirected bipartite $\{+,-\}$-labeled graph, i.e. a graph having two types of nodes and two types of edges, called the species-reaction graph of a chemical reaction network, or $SR-$graph for short. Mathematically, such a graph is specified by a quadruple $(VS, VR, E+, E-)$ Positive edges represent species going into a reaction and negative edges represent a species going out of a reaction. $R-$ and $S-$ graphs correspond to $SR-$Graphs where only the VS and VR nodes are present.

Definition: The positive loop property for an arbitrary $J-$, $SR-$, $R-$ or $S-$graph, a simple loop is a path connecting nodes via edges, whose first and last node coincide and with the property that no nodes or edges are repeated twice, with the exception of the first and last node. The length of a simple loop is defined as its total number of edges.

Theorem: The R-graph (respectively the S-Graph) have the positive loop property if and only if the following two conditions are met:

1. all simple loops in the $SR-$graph are $e-$loops

2. in the $SR-$graph, each node in VR(respectively VR) is linked to at most two nodes

Consider the system defined as follows:

$$\dot{x}(t) = R(S_0 + \Gamma x(t)), x \in X_0 := \{x \in \mathbb{R}^{n_r} | S_0 + \Gamma x \geq 0\}$$

Theorem Pick any $S_0 \in \mathbb{R}^{n_s}$. Then system above is monotone with respect to an order induced by some orthant cone if and only if the $R-$ graph has the positive loop property (D. Angeli, et al.).

STOCHASTIC MONOTONE SYSTEMS

Recall the definition of monotonicity: $\Phi_t(x) \leq \Phi_t(y)$ whenever $x \leq y$ and $t \geq 0$.

Definition: We say that a system is monotone stochastic if it satisfies

$$\lim_{t \to \infty} P[\Phi_t(x) \leq \Phi_t(y)] = 1 \text{ for } x \leq y$$

NB: This is a weaker definition than monotonicity, it preserves the partial ordering only in the limit as $t \to \infty$. In the following subsections we will define stochastic chemical reaction networks before exploring if any of them are monotone stochastic but not monotone.

The Chemical Master Equation

A stochastic process is a collection of jointly distributed random variables indexed by time. The inherent randomness of chemical reactions means it is appropriate to model reaction networks as a stochastic process.

Consider a system of a homogeneous mixture with constant temperature and volume Ω. Again, suppose the system comprises n species $S_i, i \in \{1,..,n\}$, which participate in m reactions $R_j, j \in \{1,...,m\}$. Each reaction R_j is characterized by the combinations of its reactants and products:

$$R_j := \sum_{i=1}^{n} a_{ij} S_i \to \sum_{i=1}^{n} b_{ij} S_i,$$

where a_{ij} and b_{ij} are the non-negative stoichiometry coefficients.

The difference $\gamma_{ij} = b_{ij} - a_{ij}$ is the net change in units of species S_i each time reaction R_j happens. γ_{ij} are the entries of the $n \times m$ stoichiometry matrix Γ.

We use a column-vector state space $X = (X_1,...,X_n)'$ indexed by $t \geq 0$. $X(t)$ is a $\mathbb{Z}_{\geq 0}^n$ -valued random variable, where each entry $X_i(t) =$ the number of units of species i at time t. We are interested in the probability of the mixture composition being in a particular state, k, where there are k_1 units of species 1, k_2 units of species 2, and et cetera: $p_k(t) = \mathbb{P}[X(t) = k \in \mathbb{Z}_{\geq 0}^n]$. $p(t) = (p_k)_{k \in \mathbb{Z}_{\geq 0}^n}$ represents the probability mass function of $X(t)$.

A chemical master equation is a system of linear differential equations for the p_k's. We are given m functions

$$\rho_j^{\sigma} : \mathbb{Z}_{\geq 0}^n \to \mathbb{R}_{\geq 0}, \; j = 1,...,m, \text{ with } \rho_j^{\sigma}(0) = 0,$$

known as the propensity functions for each respective reaction R_j. We make note of these because $\rho_j^{\sigma}(k)dt$ represents the probability that reaction $\mathcal{R}_j$ occurs during a time jump, the short interval of length dt. The chemical master equation is then given by

$$\frac{dp_k}{dt} = \sum_{j=1}^{m} \rho_j^{\sigma}(k - \gamma_j)p_{k-\gamma_j} - \sum_{j=1}^{m} \rho_j^{\sigma}(k)p_k, \quad k \in \mathbb{Z}_{\geq 0}^n.$$

We may interpret this as the change in the probability of a species having k copies is equivalent to the probability that a species reacts to species k minus the probability that one of our species k reacts into something else. When $k < \gamma_j$ (coordinate wise), $\rho_j^\sigma(k - \gamma_j) = 0$

Propensities for Mass Action Systems

For each reaction R_j,

$$A_j = \sum_{i=1}^n a_{ij},$$

represents its order, or the total number of units of species participating in the reaction. For each state $k = (k_1, ..., k_m) \in \mathbb{Z}_{\geq 0}^n$, where $a_j = (a_{1j}, ..., a_{nj})'$:

$$\binom{k}{a_j} = \Pi_{i=1}^n \binom{k_i}{a_{ij}}$$

If $k_i < a_{ij}$, we choose $\binom{k_i}{a_{ij}}$ to be 0. Now we can define ideal mass action propensities as follow:

$$\rho_{j,\Omega}^\sigma(k) = \frac{c_j}{\Omega^{A_j-1}} \binom{k}{a_j}, \, j = 1, ..., m,$$

where c_j is an arbitrary non-negative constant dependent on properties of the reactant and physical and chemical contexts.

The Continuous Case

Thus far we have considered a stochastic process with discrete time jumps and a discrete state space. We now pivot our focus to continuous time, discrete state space Markov Chains. This means we assume our stochastic process $\{X(t)\}, t \in [0, \infty)$ to follow three conditions: the Markov property, stationarity, differentiability.

1. Markov: the evolution of the Markov Process only depends on the current state and not on past history. For any two non-negative real numbers t, h, function $x : [0, s] \to K$, and any $k \in K$,

$$\mathbb{P}[X(t+h) = k | X(s) = x(s), 0 \leq s \leq t] = \mathbb{P}[X(t+h) = k | X(t) = x(t)]$$

2. Stationarity: the transitional probabilities $\mathbb{P}[X(s) = \ell | X(t) = k]$ only depend on $t - s$ and do not change with time.

3. Differentiability: with $p_{\ell k}(h) := \mathbb{P}[X(t+h) = \ell | X(t) = k]$ and $p_k(t) := \mathbb{P}[X(t) = k]$ for every $\ell, k \in K$ and all $t, h \geq 0$, the functions are differentiable in h, t.

The Stochastic Simulation Algorithm (SSA)

This algorithm is not deterministic due to the probability functions that appear in the solution, however, we may sample solutions of the chemical master equation using the Stochastic Simulation Algorithm (SSA).

```python
import math
import random

def simulate_SSA(k, Tmax):
    t = 0.0

    while True:
        rho = []
        for j in range(len(reactants)):
            rho_j = compute_rho_sigma_j(k, j)  # Step 1
            rho.append(rho_j)

        lamda = sum(rho)  # Step 2

        if lamda == 0:  # Step 3
            break

        r1 = random.uniform(0, 1)  # Step 4
        r2 = random.uniform(0, 1)

        T = -math.log(r1) / lamda  # Step 5

        if t + T > Tmax:  # Step 6
            break

        cumulative_prob = 0.0
        J = 0
        for j in range(len(reactants)):
            cumulative_prob += rho[j] / lamda
            if cumulative_prob <= r2 < (cumulative_prob + rho[j] / lamda):
                J = j
                break

        k += gamma[J]  # Step 8
        t += T  # Step 9

    return k, t
```

CONJECTURE

Earlier we saw that for a system $\dot{x}(t) = R(S_0 + \Gamma x(t)), x \in X_0 := \{x \in \mathbb{R}^{n_r} | S_0 + \Gamma x \geq 0\}$, the system is monotone with respect to an order induced by some orthant cone if and only if the $R-$ graph has the positive loop property.

Conjecture: A system that is monotone stochastic need not have the positive loop property, and so we can weaken the sufficient conditions for a network that is monotone stochastic as opposed to being just monotone.

ODE Solver

To explore this conjecture we started by writing an ODE Solver to gain a visual intuition for when chemical reaction networks are monotone. We know that a system is monotone if each of the solutions for the concentrations are monotone. See below a sample run through of the program, which assumes mass action kinetics.

FIGURE 2. Sample Run Through of Program

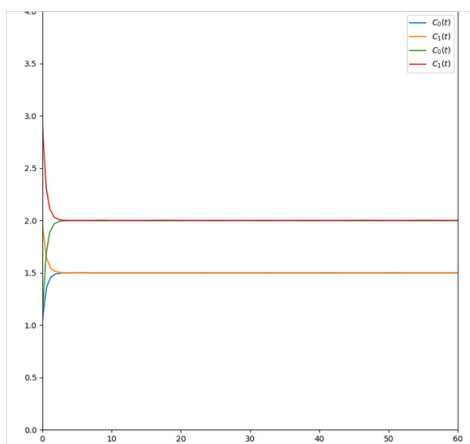Now, see a sample output plot from the program.

FIGURE 3. Output Plot

Monotonicity Checker

Using these plots to gain an intuition we then attempted to create a program that checks for monotonicity via the graph theoretic conditions.

This program is still in active development but the main loop checks if all loops are e-loops and if each species node is linked to at most two reaction nodes before returning true or false.

CONCLUSION

In this paper we developed the theory of chemical reaction networks and dynamical systems. We focus specifically on monotone dynamical systems and stochastic chemical reaction networks and attempt to bridge the gap between them mathematically. We created several algorithms to help us in this effort that simulate chemical reaction networks with mass action kinetics for deterministic and stochastic cases and started development on a graphical checker for monotonicity. In future work, we plan on connecting our definition of stochastic monotonicity with existent comparison methods for stochastic processes. One idea we will investigate is first-order stochastic dominance:

Definition: X is **stochastically dominated** by Y if $\mathbb{P}[X \in A] \leq \mathbb{P}[Y \in A]$ for all increasing events A.

ACKNOWLEDGMENTS

APPENDIX

Code for an Ordinary Differential Equation Solver to find conjectures: [Here]

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