

HYPATIA GRADUATE SCHOOL 2024
BASICS ON CHEMICAL REACTION
NETWORKS

Alicia Dickenstein

Departamento de Matemática, FCEN,
Universidad de Buenos Aires,
and Instituto de Matemática Luis A. Santaló, UBA-CONICET

CRM, June 3, 2024

OUR GOAL FOR THIS CLASS:

Define the main characters of this course.

OUR SETTING

- (Bio)chemical reaction networks define systems of ordinary differential equations with (in general, unknown) parameters
- We will assume: Mass Action Kinetics (MAK).
- The basic mathematical theory was developed by chemical engineers: Horn, Jackson y Feinberg and independently Volpert, since 1972.
- Tools from (real and complex) algebraic geometry are more recent: [Gatermann '01-'04], [Craciun, D., Shiu, Sturfels '07], [Conradi et al. 2007-...], [Gunawardena et al, '08-...], [Shiu-Sturfels '10-...], [Feliu, Wiuf '10-...], [D., Pérez Millán '11-...], etc.

OUR SETTING

- (Bio)chemical reaction networks define systems of **ordinary differential equations** with (in general, unknown) **parameters**
- **We will assume: Mass Action Kinetics (MAK).**
- The basic mathematical theory was developed by chemical engineers: **Horn, Jackson y Feinberg** and independently **Volpert**, since 1972.
- Tools from (real and complex) algebraic geometry are more recent: [Gatermann '01-'04], [Craciun, D., Shiu, Sturfels '07], [Conradi et al. 2007-...], [Gunawardena et al, '08-...], [Shiu-Sturfels '10-...], [Feliu, Wiuf '10-...], [D., Pérez Millán '11-...], etc.

OUR SETTING

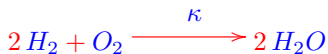
- (Bio)chemical reaction networks define systems of **ordinary differential equations** with (in general, unknown) **parameters**
- We will assume: **Mass Action Kinetics (MAK)**.
- **The basic mathematical theory was developed by chemical engineers: Horn, Jackson y Feinberg and independently Volpert, since 1972.**
- Tools from (real and complex) algebraic geometry are more recent: [Gatermann '01-'04], [Craciun, D., Shiu, Sturfels '07], [Conradi et al. 2007-...], [Gunawardena et al, '08-...], [Shiu-Sturfels '10-...], [Feliu, Wiuf '10-...], [D., Pérez Millán '11-...], etc.

OUR SETTING

- (Bio)chemical reaction networks define systems of **ordinary differential equations** with (in general, unknown) **parameters**
- We will assume: **Mass Action Kinetics (MAK)**.
- The basic mathematical theory was developed by chemical engineers: **Horn, Jackson y Feinberg** and independently **Volpert**, since 1972.
- **Tools from (real and complex) algebraic geometry are more recent:** [Gatermann '01-'04], [Craciun, D., Shiu, Sturfels '07], [Conradi et al. 2007- ...], [Gunawardena et al, '08 -...], [Shiu-Sturfels '10-...], [Feliu, Wiuf '10-...], [D., Pérez Millán '11-...], etc.

CHEMICAL REACTION NETWORKS (CRN)

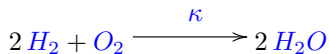
- Consider the following chemical reaction to produce water from H_2 and O_2 (diatomic hydrogen and oxygen):



- The positive number κ denotes a *reaction rate constant*.
- We order the *species* (H_2, O_2, H_2O) and the *complexes* $\{2H_2 + O_2, H_2O\}$ in the vertices of this small directed graph (*digraph*). We associate: $2 H_2 + O_2 \leftrightarrow (2, 1, 0)$, $2 H_2O \leftrightarrow (0, 0, 2)$ with nonnegative integer vectors.
- The *net production* of each species in this reaction is given by the difference $(0, 0, 2) - (2, 1, 0) = (-2, -1, 2) \in \mathbb{Z}^3$, which expresses the fact that 2 molecules of H_2 and one of O_2 are consumed and 2 molecules of water are created.

CHEMICAL REACTION NETWORKS (CRN)

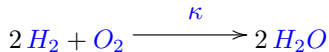
- Consider the following chemical reaction to produce water from H_2 and O_2 (diatomic hydrogen and oxygen):



- The positive number κ denotes a *reaction rate constant*.
- We order the species (H_2, O_2, H_2O) and the complexes $\{2H_2 + O_2, H_2O\}$ in the vertices of this small directed graph (digraph). We associate: $2 H_2 + O_2 \leftrightarrow (2, 1, 0)$, $2 H_2O \leftrightarrow (0, 0, 2)$ with nonnegative integer vectors.
- The net production of each species in this reaction is given by the difference $(0, 0, 2) - (2, 1, 0) = (-2, -1, 2) \in \mathbb{Z}^3$, which expresses the fact that 2 molecules of H_2 and one of O_2 are consumed and 2 molecules of water are created.

CHEMICAL REACTION NETWORKS (CRN)

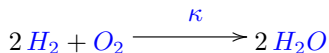
- Consider the following chemical reaction to produce water from H_2 and O_2 (diatomic hydrogen and oxygen):



- The positive number κ denotes a *reaction rate constant*.
- We order the species (H_2, O_2, H_2O) and the complexes $\{2H_2 + O_2, H_2O\}$ in the vertices of this small directed graph (digraph). We associate: $2 H_2 + O_2 \leftrightarrow (2, 1, 0)$, $2 H_2O \leftrightarrow (0, 0, 2)$ with nonnegative integer vectors.
- The net production of each species in this reaction is given by the difference $(0, 0, 2) - (2, 1, 0) = (-2, -1, 2) \in \mathbb{Z}^3$, which expresses the fact that 2 molecules of H_2 and one of O_2 are consumed and 2 molecules of water are created.

CHEMICAL REACTION NETWORKS (CRN)

- Consider the following chemical reaction to produce water from H_2 and O_2 (diatomic hydrogen and oxygen):

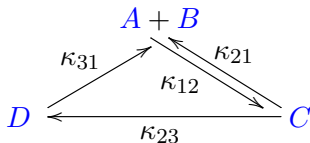


- The positive number κ denotes a *reaction rate constant*.
- We order the **species** (H_2, O_2, H_2O) and the **complexes** $\{2H_2 + O_2, H_2O\}$ in the vertices of this small directed graph (**digraph**). We associate: $2 H_2 + O_2 \leftrightarrow (2, 1, 0)$, $2 H_2O \leftrightarrow (0, 0, 2)$ with nonnegative integer vectors.
- The **net production** of each species in this reaction is given by the difference $(0, 0, 2) - (2, 1, 0) = (-2, -1, 2) \in \mathbb{Z}^3$, which expresses the fact that 2 molecules of H_2 and one of O_2 are consumed and 2 molecules of water are created.

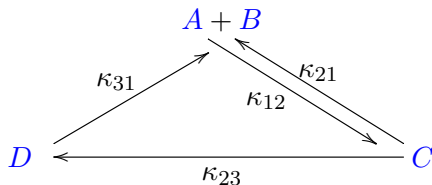
EXAMPLE: T-CELL SIGNAL TRANSDUCTION MODEL

T-cell receptors bind to both self-antigens and foreign antigens. *How can T-cells be sensitive and specific in recognizing self vs. foreign?*

Model due to [McKeithan '95], immunologist; [Sontag '01]:

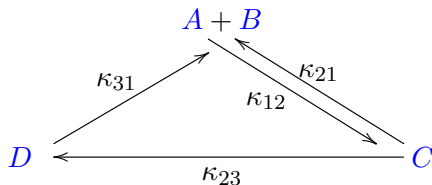


- A = T-cell receptor, B = MHC of antigen-presenting cell
- C = A bound to B , D = activated form of C



This *CRN* has:

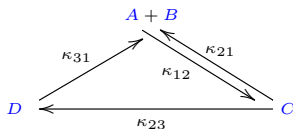
- 4 reactions among the...
- $m = 3$ complexes $A + B$, C , and D which are composed by...
- $s = 4$ species A , B , C , and D .



This *CRN* has:

- 4 *reactions* among the...
- $m = 3$ **complexes** $A + B$, C , and D which are composed by...
- $s = 4$ **species** A , B , C , and D .

EXPLICIT EQUATIONS



The differential equations that govern $x(t) = (x_A(t), x_B(t), x_C(t), x_D(t))$ are:

$$\frac{dx}{dt} = \kappa_{12} x_A x_B \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix} + \kappa_{21} x_C \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \end{pmatrix} + \kappa_{23} x_C \begin{pmatrix} 0 \\ 0 \\ -1 \\ 1 \end{pmatrix} + \kappa_{31} x_D \begin{pmatrix} 1 \\ 1 \\ 0 \\ -1 \end{pmatrix}$$

$$\frac{dx_A}{dt} = -\kappa_{12} x_A x_B + \kappa_{21} x_C + \kappa_{31} x_D = \frac{dx_B}{dt}$$

$$\frac{dx_C}{dt} = \kappa_{12} x_A x_B - \kappa_{21} x_C - \kappa_{23} x_C$$

$$\frac{dx_D}{dt} = \kappa_{23} x_C - \kappa_{31} x_D$$

TWO NORWEGIANS IN THE XIX-TH CENTURY

The **Law of Mass Action** was proposed by **Cato Guldberg** (1836–1902) and **Peter Waage** (1833-1900).



Waage was a **chemist** and Guldberg was a **mathematician**.

They were close friends and brothers in law.

Their work was published in **Norwegian** in 1862, then in **French** in 1867, and again in **German** around 1880, until it was recognized (in the meantime, it was rediscovered by the Dutch physicist **van't Hoff**.)

TWO NORWEGIANS IN THE XIX-TH CENTURY

The **Law of Mass Action** was proposed by **Cato Guldberg** (1836–1902) and **Peter Waage** (1833-1900).



Waage was a **chemist** and Guldberg was a **mathematician**. They were close friends and brothers in law.

Their work was published in **Norwegian** in 1862, then in **French** in 1867, and again in **German** around 1880, until it was recognized (in the meantime, it was rediscovered by the Dutch physicist **van't Hoff**.)

TWO NORWEGIANS IN THE XIX-TH CENTURY

The **Law of Mass Action** was proposed by **Cato Guldberg** (1836–1902) and **Peter Waage** (1833-1900).



Waage was a **chemist** and Guldberg was a **mathematician**. They were close friends and brothers in law.

Their work was published in **Norwegian** in 1862, then in **French** in 1867, and again in **German** around 1880, until it was recognized (in the meantime, it was rediscovered by the Dutch physicist **van't Hoff**.)

The **Law of Mass Action** was proposed by **Cato Guldberg** (1836–1902) and **Peter Waage** (1833-1900).

It is derived from the idea that the reaction **velocity** is **proportional** to the **probability** of collision of reactants (+ independence assumption). This kinetics assumes that all the species are **abundant** and that they are **well mixed**.



CRN WITH MAK

- **Starting data:** a set of n species + a directed graph whose arrows represent a set of r reactions (labeled edges $i \xrightarrow{\kappa_{ij}} j$, where $\kappa_{ij} \in \mathbb{R}_{>0}$ are the reaction rate constants) between m complexes in \mathbb{Z}^n . We also denote the reactions $y_i \xrightarrow{\kappa_{ij}} y_j$.
- View the concentrations x_1, x_2, \dots, x_n as *functions of time t* .
- *Mass-action kinetics* specified by the network G is the following autonomous system of ordinary differential equations:

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i), \quad (1)$$

with $x^{y_i} = x_1^{y_{i1}} x_2^{y_{i2}} \dots x_s^{y_{is}}$.

CRN WITH MAK

- Starting data:** a set of n species + a directed graph whose arrows represent a set of r reactions (labeled edges $i \xrightarrow{\kappa_{ij}} j$, where $\kappa_{ij} \in \mathbb{R}_{>0}$ are the reaction rate constants) between m complexes in \mathbb{Z}^n . We also denote the reactions $y_i \xrightarrow{\kappa_{ij}} y_j$.
- View the concentrations x_1, x_2, \dots, x_n as functions of time t .
- Mass-action kinetics specified by the network G is the following autonomous system of ordinary differential equations:

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i), \quad (1)$$

with $x^{y_i} = x_1^{y_{i1}} x_2^{y_{i2}} \dots x_s^{y_{is}}$.

CRN WITH MAK

- Starting data:** a set of n species + a directed graph whose arrows represent a set of r reactions (labeled edges $i \xrightarrow{\kappa_{ij}} j$, where $\kappa_{ij} \in \mathbb{R}_{>0}$ are the reaction rate constants) between m complexes in \mathbb{Z}^n . We also denote the reactions $y_i \xrightarrow{\kappa_{ij}} y_j$.
- View the concentrations x_1, x_2, \dots, x_n as *functions of time t* .
- Mass-action kinetics* specified by the network G is the following autonomous system of ordinary differential equations:

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} \mathbf{x}^{y_i} (y_j - y_i), \quad (1)$$

with $x^{y_i} = x_1^{y_{i1}} x_2^{y_{i2}} \dots x_s^{y_{is}}$.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are C^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are C^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are C^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are \mathcal{C}^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are \mathcal{C}^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are \mathcal{C}^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

$$\frac{dx}{dt} = \sum_{(i,j) \in E} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

$$\frac{dx_k}{dt} = f_k(x), \quad k = 1, \dots, s, \quad (2)$$

where f_1, \dots, f_s are **polynomials** in $\mathbb{R}[x_1, \dots, x_s]$. The **steady states** of the kinetic system (2) are the **(nonnegative real) zeros** of f_1, \dots, f_n .

BASIC IMPORTANT INFORMATION

As polynomials are \mathcal{C}^1 -functions, for each initial condition $x_0 \in \mathbb{R}^n$ there is a **unique solution curve (trajectory)** $x(t) : I \rightarrow \mathbb{R}^n$ defined in an interval around 0 with $x(0) = x_0$. A trajectory need not converge, but if it does, its limit is a **steady state** (and in general, the ss drive the dynamics). If a solution is bounded, then x is defined over all $\mathbb{R}_{>0}$. In most cases, the rate constants are **unknown (difficult or impossible to be determined)**, so we would like to infer dynamical properties of the system from the **structure** of the reaction network.

HOW GENERAL ARE THESE POLYNOMIAL SYSTEMS?

$$\frac{dx_k}{dt} = \sum \kappa_{i,j} x^{y_i} (y_{jk} - y_{ik}),$$

$$f_k(x) = \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{jk} \right)}_{p_k(x)} - \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{ik} \right)}_{x_k q_k(x)},$$

where p_k, q_k have non negative coefficients.

HUNGARIAN LEMMA - V. HÁRS, J. TÓTH, 1979

A polynomial system of n real polynomials f_1, \dots, f_n in n variables arises from a mass-action kinetics dynamical system if and only if there exists real polynomials $p_k, q_k, k = 1, \dots, n$ with **non negative** coefficients such that $f_k = p_k - x_k q_k$ for all k .

HOW GENERAL ARE THESE POLYNOMIAL SYSTEMS?

$$\frac{dx_k}{dt} = \sum \kappa_{i,j} x^{y_i} (y_{jk} - y_{ik}),$$

$$f_k(x) = \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{jk} \right)}_{p_k(x)} - \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{ik} \right)}_{x_k q_k(x)},$$

where p_k, q_k have non negative coefficients.

HUNGARIAN LEMMA - V. HÁRS, J. TÓTH, 1979

A polynomial system of n real polynomials f_1, \dots, f_n in n variables arises from a mass-action kinetics dynamical system if and only if there exists real polynomials $p_k, q_k, k = 1, \dots, n$ with **non negative** coefficients such that $f_k = p_k - x_k q_k$ for all k .

HOW GENERAL ARE THESE POLYNOMIAL SYSTEMS?

$$\frac{dx_k}{dt} = \sum \kappa_{i,j} x^{y_i} (y_{jk} - y_{ik}),$$

$$f_k(x) = \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{jk} \right)}_{p_k(x)} - \underbrace{\left(\sum \kappa_{i,j} x^{y_i} y_{ik} \right)}_{x_k q_k(x)},$$

where p_k, q_k have non negative coefficients.

HUNGARIAN LEMMA - V. HÁRS, J. TÓTH, 1979

A polynomial system of n real polynomials f_1, \dots, f_n in n variables arises from a mass-action kinetics dynamical system if and only if there exists real polynomials $p_k, q_k, k = 1, \dots, n$ with **non negative** coefficients such that $f_k = p_k - x_k q_k$ for all k .

EXAMPLES AND NON-EXAMPLES

“Chaotic” Lorenz equations **cannot** come from a MAK modeling:

$$\frac{dx}{dt} = \alpha y - \alpha x$$

$$\frac{dy}{dt} = \gamma x - y - xz$$

$$\frac{dz}{dt} = xy - \beta z$$

Many models in **population dynamics**, as the **Lotka-Volterra** predator-prey model or the **standard epidemiological** models **are** of the MAK form:

$$\frac{dx}{dt} = ax - bxy,$$

$$\frac{dy}{dt} = cxy - dy, \quad a, b, c, d > 0.$$

CRN in **chemistry** might have complexes with **high** coordinates. Usual models in **systems biology**, in particular **enzymatic** pathways, are of this form, with **small** coordinates (exponents).

EXAMPLES AND NON-EXAMPLES

“Chaotic” Lorenz equations **cannot** come from a MAK modeling:

$$\frac{dx}{dt} = \alpha y - \alpha x$$

$$\frac{dy}{dt} = \gamma x - y - xz$$

$$\frac{dz}{dt} = xy - \beta z$$

Many models in **population dynamics**, as the **Lotka-Volterra** predator-prey model or the **standard epidemiological** models **are** of the MAK form:

$$\frac{dx}{dt} = ax - bxy,$$

$$\frac{dy}{dt} = cxy - dy, \quad a, b, c, d > 0.$$

CRN in **chemistry** might have complexes with **high** coordinates. Usual models in **systems biology**, in particular **enzymatic** pathways, are of this form, with **small** coordinates (exponents).

EXAMPLES AND NON-EXAMPLES

“Chaotic” Lorenz equations **cannot** come from a MAK modeling:

$$\begin{aligned}\frac{dx}{dt} &= \alpha y - \alpha x \\ \frac{dy}{dt} &= \gamma x - y - xz \\ \frac{dz}{dt} &= xy - \beta z\end{aligned}$$

Many models in **population dynamics**, as the **Lotka-Volterra** predator-prey model or the **standard epidemiological** models **are** of the MAK form:

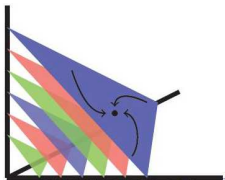
$$\begin{aligned}\frac{dx}{dt} &= ax - bxy, \\ \frac{dy}{dt} &= cxy - dy, \quad a, b, c, d > 0.\end{aligned}$$

CRN in **chemistry** might have complexes with **high** coordinates. Usual models in **systems biology**, in particular **enzymatic** pathways, are of this form, with **small** coordinates (exponents).

STOICHIOMETRIC SUBSPACE

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

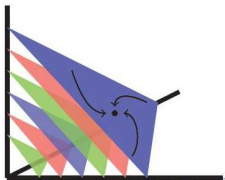
- The subspace $S \subset \mathbb{R}^n$ generated by the differences $\{y_j - y_i \mid y_i \rightarrow y_j\}$ is known as the **stoichiometric subspace**.
- Clearly, $\frac{dx}{dt}$ is in $S \forall t$.
- Thus, a trajectory $x(t)$ starting at a non-negative point $x(0)$ defined in an interval I containing 0 lies in an affine linear space parallel to S .
- The (linear) equations of $x(0) + S$ are **linear conservation relations**.



STOICHIOMETRIC SUBSPACE

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

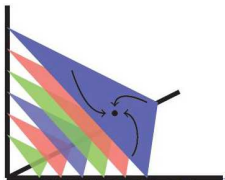
- The subspace $S \subset \mathbb{R}^n$ generated by the differences $\{y_j - y_i \mid y_i \rightarrow y_j\}$ is known as the **stoichiometric subspace**.
- Clearly, $\frac{dx}{dt}$ is in $S \forall t$.
- Thus, a trajectory $x(t)$ starting at a non-negative point $x(0)$ defined in an interval I containing 0 lies in an affine linear space parallel to S .
- The (linear) equations of $x(0) + S$ are **linear conservation relations**.



STOICHIOMETRIC SUBSPACE

$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

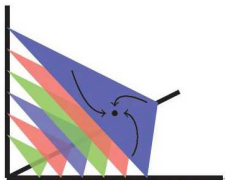
- The subspace $S \subset \mathbb{R}^n$ generated by the differences $\{y_j - y_i \mid y_i \rightarrow y_j\}$ is known as the **stoichiometric subspace**.
- Clearly, $\frac{dx}{dt}$ is in $S \forall t$.
- Thus, a trajectory $x(t)$ starting at a non-negative point $x(0)$ defined in an interval I containing 0 lies in an affine linear space parallel to S .
- The (linear) equations of $x(0) + S$ are **linear conservation relations**.



STOICHIOMETRIC SUBSPACE

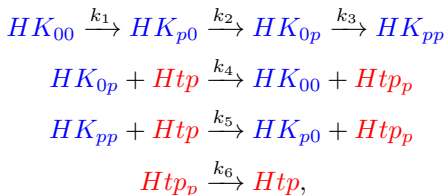
$$\frac{dx}{dt} = \sum_{y_i \rightarrow y_j} \kappa_{i,j} x^{y_i} (y_j - y_i).$$

- The subspace $S \subset \mathbb{R}^n$ generated by the differences $\{y_j - y_i \mid y_i \rightarrow y_j\}$ is known as the **stoichiometric subspace**.
- Clearly, $\frac{dx}{dt}$ is in $S \forall t$.
- Thus, a trajectory $x(t)$ starting at a non-negative point $x(0)$ defined in an interval I containing 0 lies in an affine linear space parallel to S .
- The (linear) equations of $x(0) + S$ are linear conservation relations.



A TWO-COMPONENT SYSTEM

Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. It relies on **phosphotransfer** reactions.



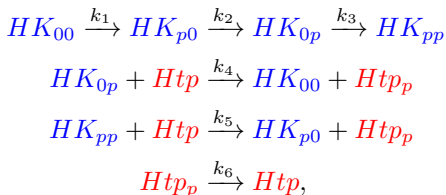
$k = (k_1, \dots, k_6)$ are positive rate constants.

The **hybrid histidine kinase** HK has two phosphorylatable domains: the four possible states of HK are HK_{00} , HK_{p0} , HK_{0p} , HK_{pp} .

Htp is the unphosphorylated **histidine phosphotransferase** protein, Htp_p the phosphorylated form.

A TWO-COMPONENT SYSTEM

Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. It relies on **phosphotransfer** reactions.



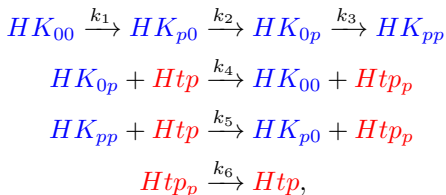
$k = (k_1, \dots, k_6)$ are positive rate constants.

The **hybrid histidine kinase** HK has two phosphorylatable domains: the four possible states of HK are HK_{00} , HK_{p0} , HK_{0p} , HK_{pp} .

Htp is the unphosphorylated **histidine phosphotransferase** protein, Htp_p the phosphorylated form.

A TWO-COMPONENT SYSTEM

Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. It relies on **phosphotransfer** reactions.



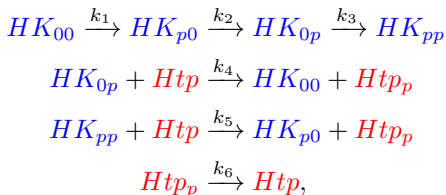
$k = (k_1, \dots, k_6)$ are positive rate constants.

The **hybrid histidine kinase** HK has two phosphorylatable domains: the four possible states of HK are HK_{00} , HK_{p0} , HK_{0p} , HK_{pp} .

Htp is the unphosphorylated **histidine phosphotransferase** protein, Htp_p the phosphorylated form.

A TWO-COMPONENT SYSTEM

Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. It relies on **phosphotransfer** reactions.



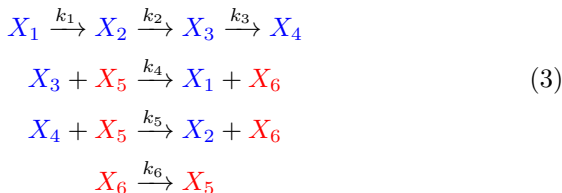
$k = (k_1, \dots, k_6)$ are positive rate constants.

The **hybrid histidine kinase** HK has two phosphorylatable domains: the four possible states of HK are HK_{00} , HK_{p0} , HK_{0p} , HK_{pp} .

Htp is the unphosphorylated **histidine phosphotransferase** protein, Htp_p the phosphorylated form.

A TWO-COMPONENT SYSTEM

Call x_1, \dots, x_6 the concentration of the species of the network:



Under **mass-action kinetics**, we get the following dynamical system

$$\begin{aligned}
 \frac{dx_1}{dt} &= -k_1x_1 + k_4x_3x_5, & \frac{dx_2}{dt} &= k_1x_1 - k_2x_2 + k_5x_4x_5, \\
 \frac{dx_3}{dt} &= k_2x_2 - k_3x_3 - k_4x_3x_5, & \frac{dx_4}{dt} &= k_3x_3 - k_5x_4x_5, \\
 \frac{dx_5}{dt} &= -k_4x_3x_5 - k_5x_4x_5 + k_6x_6, & \frac{dx_6}{dt} &= k_4x_3x_5 + k_5x_4x_5 - k_6x_6.
 \end{aligned}$$

LINEAR DEPENDENCIES GIVE CONSERVATION RELATIONS

From $f_1 + f_2 + f_3 + f_4 = f_5 + f_6 = 0$, we get two conservation relations:

$$\begin{aligned}x_1 + x_2 + x_3 + x_4 &= T_1, \\x_5 + x_6 &= T_2.\end{aligned}$$

Thus, trajectories lie in a 4d-plane in 6d-space. Total amounts T_1, T_2 are determined by the initial conditions $x(0)$.

Exercise: Is $S = \{x \in \mathbb{R}^6 : x_1 + x_2 + x_3 + x_4 = x_5 + x_6 = 0\}$?

LINEAR DEPENDENCIES GIVE CONSERVATION RELATIONS

From $f_1 + f_2 + f_3 + f_4 = f_5 + f_6 = 0$, we get two conservation relations:

$$\begin{aligned}x_1 + x_2 + x_3 + x_4 &= T_1, \\x_5 + x_6 &= T_2.\end{aligned}$$

Thus, trajectories lie in a 4d-plane in 6d-space. Total amounts T_1, T_2 are determined by the initial conditions $x(0)$.

Exercise: Is $S = \{x \in \mathbb{R}^6 : x_1 + x_2 + x_3 + x_4 = x_5 + x_6 = 0\}$?

LINEAR DEPENDENCIES GIVE CONSERVATION RELATIONS

From $f_1 + f_2 + f_3 + f_4 = f_5 + f_6 = 0$, we get two conservation relations:

$$\begin{aligned}x_1 + x_2 + x_3 + x_4 &= T_1, \\x_5 + x_6 &= T_2.\end{aligned}$$

Thus, trajectories lie in a 4d-plane in 6d-space. Total amounts T_1, T_2 are determined by the initial conditions $x(0)$.

Exercise: Is $S = \{x \in \mathbb{R}^6 : x_1 + x_2 + x_3 + x_4 = x_5 + x_6 = 0\}$?