

# The Chemical Reaction Metaphor

## Computational Models for Complex Systems

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# Introduction

We will see **how to model and simulate chemical reactions**.

## WHY?

For several reasons:

- chemical reactions are illustrative examples of complex systems:
  - ▶ they exhibit **complex dynamics** out of **very simple interactions**
- chemical reactions allow us to **interpret** some classes of ODEs (reverse engineering)
- chemical reactions allow us to introduce **stochastic modeling** and to relate it with ODEs
- chemical reactions are a **simple and effective metaphor** for many kinds of systems (populations, production systems, markets, ...)

# Molecules and chemical solutions

Chemical reactions describe **transformation of molecules**:

- A group of molecules (**reactants**) is transformed into another group of molecules (**products**)

**Molecules** are represented as symbols:

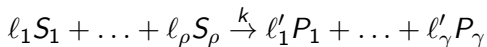
- $A, B, C, H_2, O_2, \dots$

Molecules are assumed to float in a fluid medium

- called **chemical solution**
- the quantity of molecules is usually expressed in terms of **concentrations** (density)
  - ▶  $[A]$  denotes the concentration of molecule  $A$
  - ▶ usually expressed in ***mol/L*** measure unit

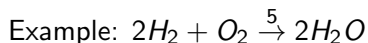
# Chemical reactions

Usual notation for chemical reactions:









where:

- $S_i, P_i$  are molecules (**reactants** and **products**, respectively)
- $l_i, l'_i \in \mathbb{N}$  are **stoichiometric coefficients**
- $k \in \mathbb{R}_{\geq 0}$  is the **kinetic constant**



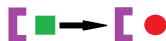
- **stoichiometric coefficients** express the **number of reactants/products** of each type that are consumed/produced by the reaction
- the **kinetic constant** is a coefficient used to compute the **rate** of occurrence of the reaction in a chemical solution

# Types of chemical reactions

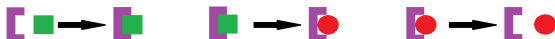
Type	Reaction	Illustration
Synthesis	$\xrightarrow{k} P$	
Degradation	$S \xrightarrow{k}$	
Transformation	$S \xrightarrow{k} P$	
Binding	$S_1 + S_2 \xrightarrow{k} P$	
Unbinding	$S \xrightarrow{k} P_1 + P_2$	
Catalysis	$E + S \xrightarrow{k} E + P$	
Other	$\vdots$	$\vdots$

# Types of chemical reactions

Catalysis (like other more complex types of reaction)



can be expressed in terms of binding, unbinding and transformation



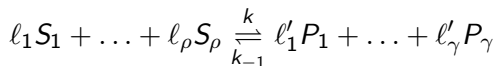
Synthesis, degradation, transformation, binding and unbinding are a quite “complete” set of reaction types

# Chemical reactions

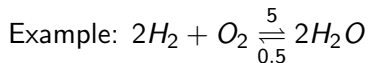
Chemical reactions are often **reversible**

- they can occur in both directions

The usual notation for reversible chemical reaction is:



where  $k_{-1} \in \mathbb{R}_{\geq 0}$  is the kinetic constant of the inverse reaction transforming products  $P_i$  into reactants  $S_i$

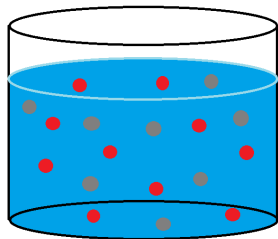


# The mass action kinetics of chemical reactions

The dynamics of chemical reactions is usually based on the following assumption:

molecules float in a (well-stirred) fluid medium (e.g. water)

Hence, they are free to move and randomly meet with each other

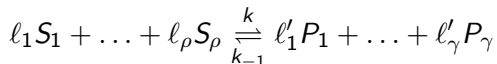


When a group of molecules meet, they **can** react

The dynamics (kinetics) of a chemical solution is modeled by the **law of mass action**



# The mass action kinetics of chemical reactions



The **rate** of a chemical reaction expresses the number of occurrences of such reaction in a given chemical solution in a time unit

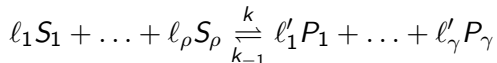
The **law of mass action** is an empirical law for the computation of the rate of a chemical reaction

## **Definition:** Law of mass action

The rate of a chemical reaction is proportional to the product of the concentrations of its reactants.

The kinetic constant is the proportionality ratio of the reaction

# The mass action kinetics of chemical reactions



The rate of a reaction (the left-to-right direction of the reversible reaction above) is defined as follows:

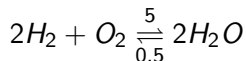
$$k[S_1]^{\ell_1} \dots [S_\rho]^{\ell_\rho}$$

similarly, the rate of the inverse reaction (the right-to-left direction) is

$$k_{-1}[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}$$

# The mass action kinetics of chemical reactions

For example, the rates of



are

- $5[H_2]^2[O_2]$  for the left-to-right direction
- $0.5[H_2O]^2$  for the right-to-left direction

In a solution with the following concentrations:

- 10 mol/L of  $H_2$
- 16 mol/L of  $O_2$
- 30 mol/L of  $H_2O$

rates take the following values:

- $5 \cdot 10^2 \cdot 16 = 8000$
- $0.5 \cdot 30^2 = 45$

(namely, the production of water is much faster than its decomposition)

## A small comment about kinetic constants

What is the **measure unit** of a kinetic constant  $k$ ?

It **depends** on the number of reactants!

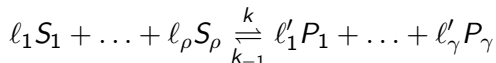
- The measure unit of **concentrations** is  $mol/L$
- The measure unit of the **reaction rate** is  $mol/(L \cdot sec)$  (it is the concentration of each product produced in one unit of time)

Examples:

- $A \xrightarrow{k} B$ : the rate is  $r = k[A]$ , that is  $k = r/[A]$ . So the measure unit of  $k$  is  $(mol/(L \cdot sec))/(mol/L) = 1/sec$
- $A + B \xrightarrow{k} C$ : the rate is  $r = k[A][B]$ , that is  $k = r/[A][B]$ . So the measure unit of  $k$  is  $(mol/(L \cdot sec))/(mol/L)^2 = L/(sec * mol)$
- $2A + B \xrightarrow{k} C$ : the rate is  $r = k[A]^2[B]$ , that is  $k = r/[A]^2[B]$ . So the measure unit of  $k$  is  $(mol/(L \cdot sec))/(mol/L)^3 = L^2/(sec * mol^2)$

**Some** kinetic constants have to be changed if you change the measure unit of concentrations (e.g.  $\mu mol$ ) or the time unit (e.g. hours)

## Dynamic equilibrium



A reversible reaction is said to be in **dynamic equilibrium** when the rates of its two directions are the same, namely:

$$k[S_1]^{\ell_1} \dots [S_\rho]^{\ell_\rho} = k_{-1}[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}$$

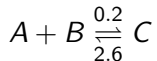
When the dynamic equilibrium is reached, often the chemical solution seems stable (it seems that nothing is happening inside it). Instead, reactions happen continuously, compensating each other.

It is easy to see that at the equilibrium we have:

$$\frac{k}{k_{-1}} = \frac{[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}}{[S_1]^{\ell_1} \dots [S_\rho]^{\ell_\rho}}$$

## Dynamic equilibrium: simple example

As an example, let's consider:



with the following initial concentrations:

- $[A]_0 = 10 \text{ mol/L}$
- $[B]_0 = 15 \text{ mol/L}$
- $[C]_0 = 2 \text{ mol/L}$

the forward rate is  $0.2 \cdot 10 \cdot 15 = 30$  and the backward rate is  $2.6 \cdot 2 = 5.2$ , hence the production of  $C$  is faster than the production of  $A$  and  $B$ .

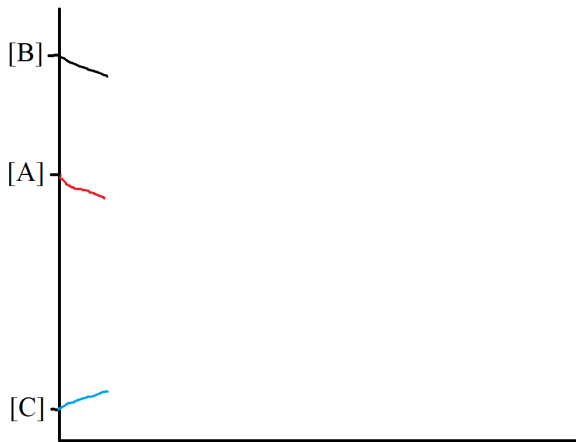
So, at the beginning the concentrations of  $A$  and  $B$  decrease, and the concentration of  $C$  increases

This causes the forward rate to decrease and the backward rate to increase, until they become equal (dynamic equilibrium), that is when

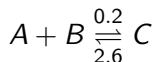
- $0.2[A][B] = 2.6[C]$

# Dynamic equilibrium: simple example

We have more or less this initial dynamics:



## Dynamic equilibrium: simple example



In order to determine the concentrations at the steady state, we can exploit the following **conservation properties**:

- $[A] + [C]$  is always constant (equal to  $[A]_0 + [C]_0 = 12$ )
- $[B] + [C]$  is always constant (equal to  $[B]_0 + [C]_0 = 17$ )

since each  $A$  and each  $B$  are transformed into a  $C$ , and viceversa)

So, from the formula of dynamic equilibrium, we can derive:

$$\frac{0.2}{2.6} = \frac{[C]}{[A][B]} \implies \frac{1}{13} = \frac{[C]}{(12 - [C])(17 - [C])} \implies$$

$$\implies [C]^2 - 42[C] + 204 = 0 \implies [C] \simeq 36.395 \text{ or } [C] \simeq 5.605$$



## Dynamic equilibrium

Since  $[A] = 12 - [C]$  and  $[B] = 17 - [C]$ , the two obtained values for  $[C]$  give the following two candidate solutions:

- $[A] \simeq -24.395$ ,  $[B] \simeq -7.395$  and  $[C] \simeq 36.395$
- $[A] \simeq 6.395$ ,  $[B] \simeq 11.395$  and  $[C] \simeq 5.605$

The first one is not acceptable (negative), so the second one is the steady state.

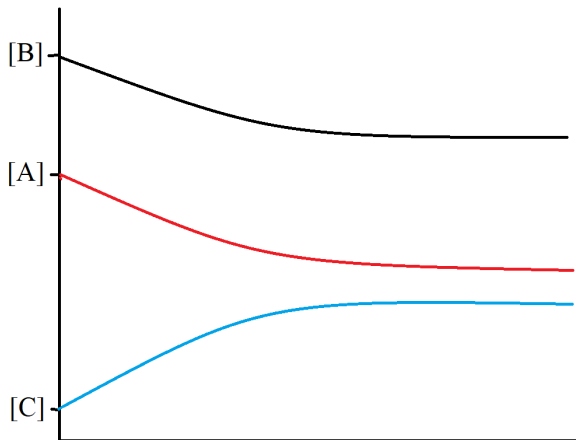
Indeed, those value make the rates of the two reactions equal:

$$0.2[A][B] = 0.2 \cdot 6.395 \cdot 11.395 \simeq 14.574$$

$$2.6[C] = 2.6 \cdot 5.605 \simeq 14.574$$

## Dynamic equilibrium: simple example

We have more or less this dynamics:



## From reactions to ODEs

Reaction rates can be used to construct a ODE model of the dynamics of a set of chemical reactions

The ODE model of a set of chemical reactions contains one differential equation for each molecular species

For each molecule  $S$ , an ODE is constructed by applying these two rules:

- for every reaction  $R$  in which  $S$  occurs as a reactant, its ODE contains a negative term

$$-lr$$

where  $l$  is the stoichiometric coefficient of reactant  $S$  in  $R$  and  $r$  is the rate of  $R$

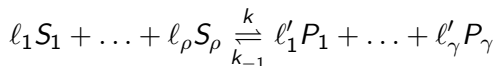
- for every reaction  $R$  in which  $S$  occurs as a product, its ODE contains a positive term

$$+lr$$

where  $l$  is the stoichiometric coefficient of product  $S$  in  $R$  and  $r$  is the rate of  $R$

# From reactions to ODEs

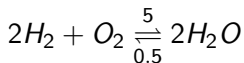
From these two generic reactions:



we obtain the following ODEs:

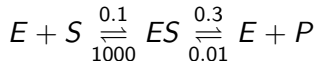
$$\left\{ \begin{array}{l} \frac{d[S_1]}{dt} = \ell_1 k_{-1} [P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma} - \ell_1 k [S_1]^{\ell_1} \dots [S_\rho]^{\ell_\rho} \\ \vdots \\ \frac{d[S_\rho]}{dt} = \dots \\ \frac{d[P_1]}{dt} = \ell'_1 k [S_1]^{\ell_1} \dots [S_\rho]^{\ell_\rho} - \ell'_1 k_{-1} [P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma} \\ \vdots \\ \frac{d[P_\gamma]}{dt} = \dots \end{array} \right.$$

## From reactions to ODEs



ODEs obtained from mass action kinetics:

$$\begin{cases} \frac{d[H_2]}{dt} = 2 \cdot 0.5[H_2O]^2 - 2 \cdot 5[H_2]^2[O_2] \\ \frac{d[O_2]}{dt} = 0.5[H_2O]^2 - 5[H_2]^2[O_2] \\ \frac{d[H_2O]}{dt} = 2 \cdot 5[H_2]^2[O_2] - 2 \cdot 0.5[H_2O]^2 \end{cases}$$

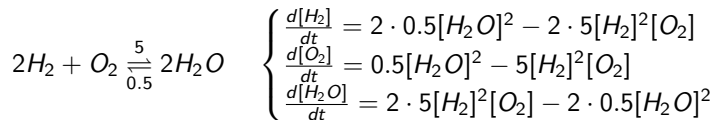


ODEs obtained from mass action kinetics:

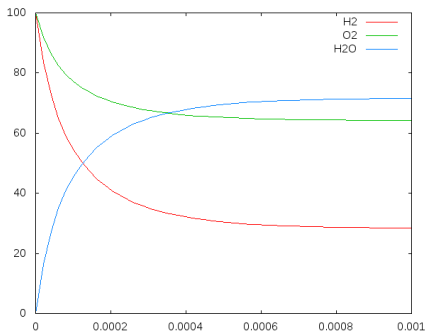
$$\begin{cases} \frac{d[E]}{dt} = 1000[ES] + 0.3[ES] - 0.1[E][S] \\ \frac{d[ES]}{dt} = 0.1[E][S] + 0.01[E][P] - 1000[ES] - 0.3[ES] \\ \frac{d[S]}{dt} = 1000[ES] - 0.1[E][S] \\ \frac{d[P]}{dt} = 0.3[ES] - 0.01[E][P] \end{cases}$$

## From reactions to ODEs

We can now simulate the dynamics of the reactions (from given initial concentrations) by using numerical integration



with initial concentrations  $[H_2]_0 = [O_2]_0 = 100$  and  $[H_2O]_0 = 0$ .



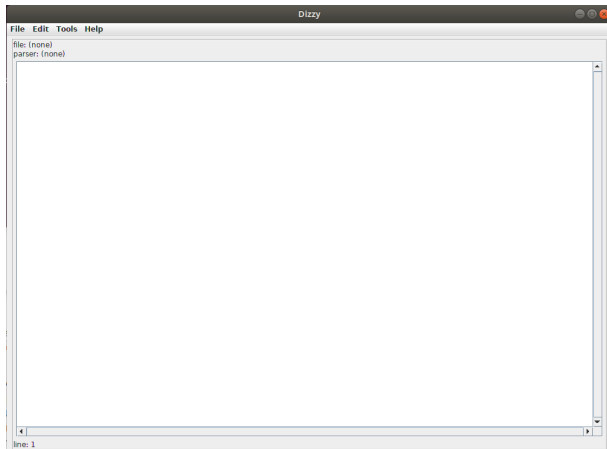
# Simulation tools of chemical reactions

Many tools and libraries are available for the numerical simulation of chemical reaction systems:

- COPASI (<http://copasi.org/>)  
Professional (free) tool
- libRoadRunner (<http://libroadrunner.org/>)  
Library for C++/Python
- Dizzy (available on the course web page)  
Multiplatform simulation tool. Unmantained, but very simple...
- Many other tools...  
See [sbml.org/SBML\\_Software\\_Guide/SBML\\_Software\\_Summary](http://sbml.org/SBML_Software_Guide/SBML_Software_Summary)  
for a list

# Simulating chemical reactions with Dizzy

Dizzy's input (the chemical reactions to be simulated) have to be inserted in **text format**





# Simulating chemical reactions with Dizzy

The input language requires:

- A sequence of **molecule declarations**  
(and initializations with concentration values)

**Syntax:**  $A = 10;$

- A sequence of **reactions**

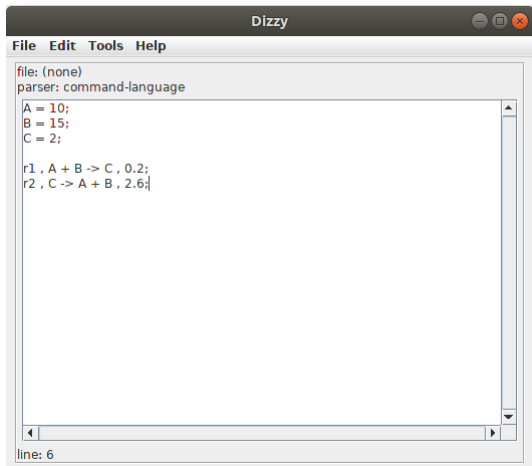
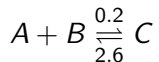
**Syntax:**  $r, A + B \rightarrow C, 0.1;$

where:

- ▶  $r$  is a reaction label
- ▶  $A + B \rightarrow C$  is the reaction
- ▶  $0.1$  is the kinetic constant (can be an expression)

# Simulating chemical reactions with Dizzy

Example:



The screenshot shows a window titled "Dizzy" with a menu bar containing "File", "Edit", "Tools", and "Help". The main text area contains the following text:

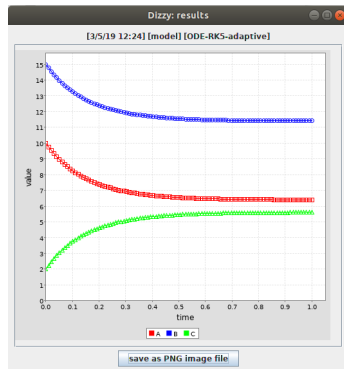
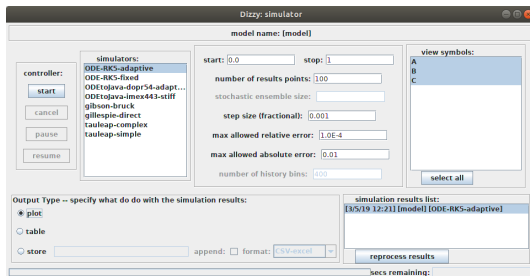
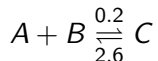
```
file: (none)
parser: command-language
A = 10;
B = 15;
C = 2;

r1 , A + B -> C , 0.2;
r2 , C -> A + B , 2.6;
```

The status bar at the bottom left of the window indicates "line: 6".

# Simulating chemical reactions with Dizzy

Example:



# Reverse engineering ODEs

The law of mass actions allows chemical reaction systems to be “translated” into ODEs

The obtained ODEs are polynomial

**Question:** can we perform the **inverse translation**?

- from polynomial ODEs to chemical reactions

**Answer:** **often!**

**Notation:** when we start from ODEs, we omit the  $[\cdot]$  brackets representing concentrations

- The idea is to start from **a generic system of ODEs**, possibly not describing chemical solutions

## Reverse engineering ODEs

Let us consider the following example:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

We can **translate it back** to a system of chemical reactions by constructing **one reaction for each term** of each equation

- we have to **match** each term with the pattern  $\ell_i k [S_1]^{\ell_1} \dots [S_1]^{\ell_r}$

For example,  $6X$  in the equation of  $X$  tells us that

- there is a reaction producing  $X$  (since the sign of the term is positive)
- the reaction has  $X$  as (its only) reactant
- $\ell_i k = 6$ , where  $\ell_i$  is the number of new  $X$  to be produced

Infinite solutions (all good and equivalent from the ODE viewpoint):



# Reverse engineering ODEs

Let's translate the whole system:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Reactions:

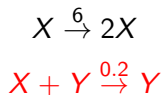


# Reverse engineering ODEs

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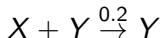
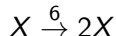


# Reverse engineering ODEs

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$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Reactions:



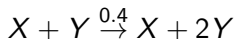
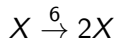


# Reverse engineering ODEs

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$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Reactions:

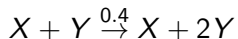
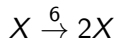


# Reverse engineering ODEs

Let's translate the whole system:

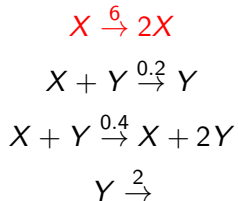
$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Reactions:



## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

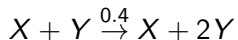
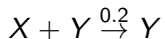
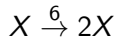


Reactions:

$$\begin{cases} \frac{dX}{dt} = -6X + 12X \\ \frac{dY}{dt} = \end{cases}$$

# Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

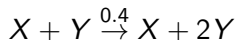
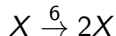


Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X \\ \frac{dY}{dt} = \end{cases}$$

# Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

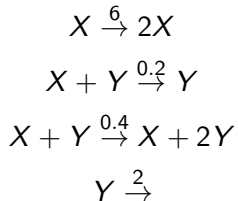


Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = -0.2XY + 0.2XY \end{cases}$$

## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

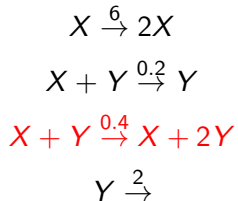


Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = \end{cases}$$

## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

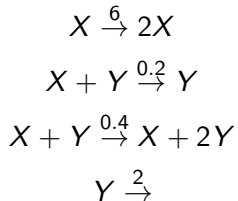


Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY - 0.4XY + 0.4XY \\ \frac{dY}{dt} = -0.4XY + 0.8XY \end{cases}$$

## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:



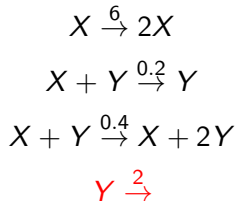
Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY \end{cases}$$



## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:

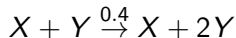
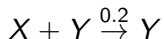
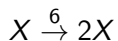


Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

## Reverse engineering ODEs

Let's re-translate to ODEs to check what we did:



Reactions:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

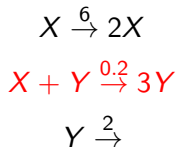
Which is exactly the system of ODEs we started from!

## Reverse engineering ODEs

Alternative translation. We can observe that two terms are very similar:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Since  $0.4XY = 2 \cdot 0.2XY$  we can assume that the two terms are obtained from the same reaction, hence:



This is another possible set of chemical reactions corresponding to the considered system of ODEs

# Reverse engineering ODEs

A system of ODEs may correspond to **infinite different sets of reactions**

- **infinite** in the number of possible parameters
- the number of possible combinations of reactants and products is **limited**

All these sets of reactions are equivalent under the point of view of the ODEs

- but they will be different under other viewpoints (we will see...)

The choice of the set of reactions should be guided by **knowledge** on the system

- E.g. is  $X + Y \xrightarrow{0.2} 3Y$  more realistic than  $X + Y \xrightarrow{0.2} Y$  and  $X + Y \xrightarrow{0.4} X + 2Y$ ?

# Reverse engineering ODEs

## Question:

Does the reverse translation work for all systems of polynomial ODEs?

Answer: No!

Let's see a counterexample:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY - Y \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

No reaction can reduce the concentration of  $X$   
without having  $X$  among its reactants!

**Conjecture:** The translation should work for all systems of polynomial ODEs in which each negative term contains the variable of its equation

## Reverse engineering the Lotka-Volterra model

$$\begin{cases} \dot{V} = rV - aVP \\ \dot{P} = -sP + abVP \end{cases}$$

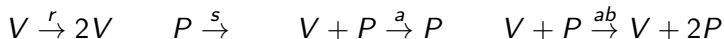
Where  $V$  are preys,  $P$  are predators and

- $a$  denote the portion of meetings resulting in a hunting
- $b$  denote the number of offsprings produced for each hunting

We obtain:



provided  $b \in \mathbb{N}$ , otherwise two separate reactions have to be considered for hunting and predator reproduction



# Reverse engineering the Lotka-Volterra model

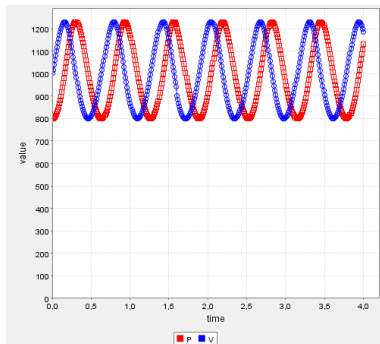
$V = 1000;$

$P = 800;$

$r1, V \rightarrow V + V, 10;$

$r2, P \rightarrow , 10;$

$r3, V + P \rightarrow P + P, 0.01;$



Dizzy source code

Numerical simulation

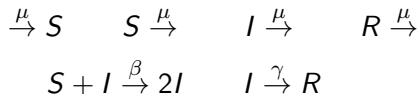
## Reverse engineering the SIR model

$$\begin{cases} \dot{S} = \mu - \beta SI - \mu S \\ \dot{I} = \beta SI - \gamma I - \mu I \\ \dot{R} = \gamma I - \mu R \end{cases}$$

Where  $S$  are susceptible,  $I$  are infected,  $R$  are recovered and:

- $\beta$  is the infection coefficient
- $\gamma$  is the recovery coefficient
- $\mu$  is the birth and death coefficient

We obtain:



that is a very natural (and elegant) description of the epidemic system



# Reverse engineering the SIR model

$S = 0.99;$

$I = 0.01;$

$R = 0;$

$r1, S + I \rightarrow I + I, 6;$

$r2, I \rightarrow R, 2;$

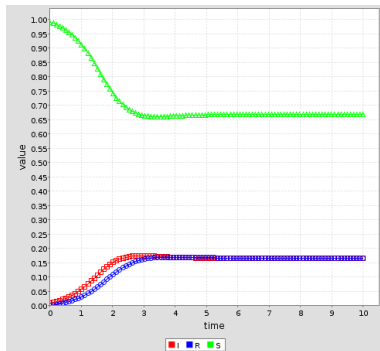
$r3, \rightarrow S, 2;$

$r4, S \rightarrow, 2;$

$r5, I \rightarrow, 2;$

$r6, R \rightarrow, 2;$

Dizzy source code



Numerical simulation

## Reverse engineering the logistic equation

$$\dot{N} = r_c N \left( 1 - \frac{N}{K} \right)$$

Where  $r_c$  is the birth rate and  $K$  is the carrying capacity of the environment.

The equation can be rewritten as:

$$\dot{N} = r_c N - \frac{r_c}{K} N^2$$

We obtain:



which is a reversible reaction! By the dynamic equilibrium we obtain

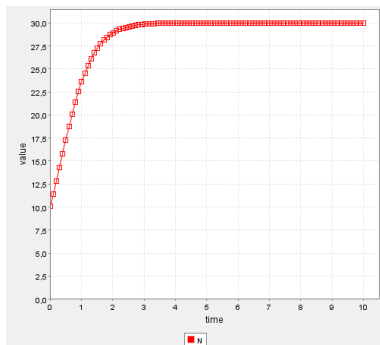
$$r_c N = \frac{r_c}{K} N^2 \quad \Rightarrow \quad r_c \frac{K}{r_c} = N^2 / N \quad \Rightarrow \quad K = N$$

# Reverse engineering the logistic equation

$N = 10;$

$r1, N \rightarrow N + N, 2;$

$r2, N + N \rightarrow N, 2/30;$



Dizzy source code

Numerical simulation

# Lessons learnt

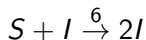
Summing up:

- **Chemical reactions** are a simple **language** for the modeling of interactions among individuals of a population (or components of a system)
- The **law of mass** action allows us to describe the dynamics of a set of chemical reactions in terms of (polynomial) ODEs
- In many cases polynomial ODEs (describing the dynamics of any kind of system) can be translated into a chemical reaction representation

# Lessons learnt

We are using **chemical reactions as a modeling language** and **ODEs as the semantics** of such language

- the **modeling language** focuses on the **description of the events** (e.g. infection)



- the **semantics** focuses on the **description of the behaviour** (e.g. the variation of infected in time)

$$\dot{I} = \beta SI - \gamma I - \mu I$$

## Next step

### Stochastic simulation of chemical reactions

- Chemistry provides us **algorithms** for the stochastic simulation of chemical reactions proved to be **consistent with the law of mass action**
- Such algorithms can be used also **outside of chemistry...**

# Exercises

- Have a look at the **Brussellator** system:  
<https://en.wikipedia.org/wiki/Brusselator>  
and try to implement and study it with Dizzy
- Consider the **males/females fish population model** we studied in the lesson on ODEs. Is it possible to translate it back into chemical reactions?