BIOINFORMÁTICA

Asignatura 400CIS016
Doctorado en Ingeniería

Pontificia Universidad JAVERIANA Cali

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“Computer science is to biology what mathematics is to physics -Harold Morowitz”

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BIOCHAM: An Environment for Modeling Biological Systems and Formalizing Experimental Knowledge

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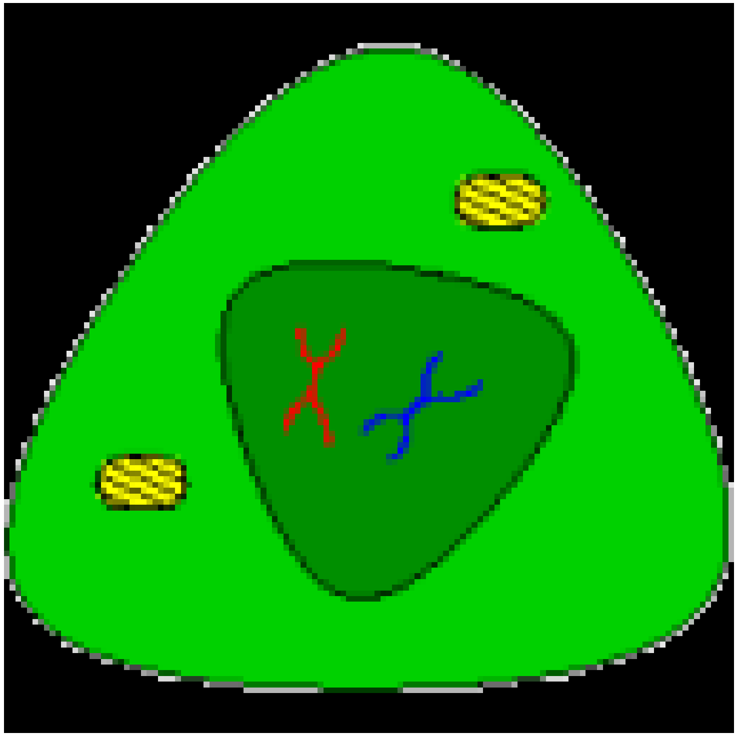
http://contraintes.inria.fr/

https://lifeware.inria.fr/biocham/

BIOCHAM - Tutorial



- Overview
- Create a model
- Start BIOCHAM GUI
  - Create a model
  - Run a model
    - Boolean Analysis
    - Numerical Analysis

Overview

Biocham stands for "Biochemical Abstract Machine". It is a free software environment for modeling and analyzing biochemical systems.

Biocham is mainly composed of :

- **a rule-based language** for modeling biochemical systems (compatible with SBML and SBGN),
- **different simulators** (Boolean, differential, stochastic),
- **a temporal logic based-language** to formalize the temporal properties of a biological system and validate models with respect to such specifications,
- unique features for **developing/correcting/completing/reducing/coupling** models, including the inference of kinetic parameters in high dimension from temporal logic constraints.

Boolean semantics of Biocham models

- One reasons on the presence and absence of molecules over time, both the multiplicity (stoichiometry) of molecules in a solution and the reaction kinetics are ignored.

- In such a Boolean abstraction, a reaction transforms one solution matching the left-hand side of the rule, in another solution in which the objects of the right-hand side have been added.

- The molecules in the left-hand side of the rule which do not appear in the right-hand side are non-deterministically present or consumed in the resulting solution. This convention reflects the capability of Biocham to reason about all possible behaviors of the system with unknown kinetic parameters.

Expresiones Booleanas

Son útiles para almacenar valores de verdad del tipo verdadero (True) o falso (False).

Se denomina bool por el matemático británico George Bool. El operador == compara dos valores y produce una expresión Booleana.

```
>>> 5 == 5
True
>>> 5 == 6
False
```

Operadores Relacionales

Operador	Descripción	Ejemplo
==	¿son iguales a y b?	r = 5 == 3 # r es False
!=	¿son distintos a y b?	r = 5 != 3 # r es True
<	¿es a menor que b?	r = 5 < 3 # r es False
>	¿es a mayor que b?	r = 5 > 3 # r es True
<=	¿es a menor o igual que b?	r = 5 <= 5 # r es True
>=	¿es a mayor o igual que b?	r = 5 >= 3 # r es True

Operadores lógicos

p	q	p ∧ q
V	V	V
V	F	F
F	V	F
F	F	F

```
>>> (5>0) and (5<10)
True
```

x>0 **and** x<10 es cierto, **sólo si** x es mayor a cero **y** menor que 10.

p	q	p v q
V	V	V
V	F	V
F	V	V
F	F	F

```
>>> (10%2==0) or (10%3==0)
True
```

(n%2 == 0) **or** (n%3 == 0) es cierto, **si alguna** de las condiciones **es verdadera**, es decir, si el número es divisible por 2 **ó** por 3.

Operadores lógicos

```
>>> 13<11
False
not (13<11)
True
>>> 13>11
True
not (13>11)
False
```

p	~ p
V	F
V	F
F	V
F	V

el operador **not** niega una expresión Booleana, así que **not(x<y) es verdadera si (x<y) es falsa**.
En el segundo caso,
not(x>y) es falsa si (x>y) es verdadera.

Expresiones Booleanas

Son útiles para almacenar valores de verdad del tipo verdadero (True) o falso (False).

Se denomina bool por el matemático británico George Bool. El operador == compara dos valores y produce una expresión Booleana.

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Operadores Relacionales

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Operadores lógicos

CONJUNCIÓN

p	q	p ∧ q
V	V	**V**
V	F	**F**
F	V	**F**
F	F	**F**

```
>>> (5>0) and (5<10)
True
```

x>0 **and** x<10 es cierto, **sólo si** x es mayor a cero **y** menor que 10.

DISYUNCIÓN

p	q	p ∨ q
V	V	**V**
V	F	**V**
F	V	**V**
F	F	**F**

```
>>> (10%2==0) or (10%3==0)
True
```

(n%2 == 0) **or** (n%3 == 0) es cierto, **si alguna** de las condiciones **es verdadera**, es decir, si el número es divisible por 2 **ó** por 3.

Operadores lógicos

Variable Booleana		Variable binaria
Y = verdadero	$\longrightarrow$	y = 1
Y = Falso	$\longrightarrow$	y = 0
$\neg Y$	$\longrightarrow$	(1-y)

A + B => C

CONDICIONAL

p	q	p => q
V	V	V
V	F	F
F	V	V
F	F	V

Differential semantics of Biocham models

The kinetic expressions in the reaction rules are used to associate to a Biocham model an ordinary differential equation (ODE).

Biocham can handle three types of chemical kinetics:

- Mass Action law: the parameter given as argument will be multiplied by all reactants' concentrations to provide the kinetic law.
- Michaelis-Menten: two arguments represent the Vm and Km of the Michaelis-Menten kinetics; the law will have the form: $Vm*[S]/(Km+[S])$, where S is the single reactant.

Differential semantics of Biocham models

The kinetic expressions in the reaction rules are used to associate to a Biocham model an ordinary differential equation (ODE).

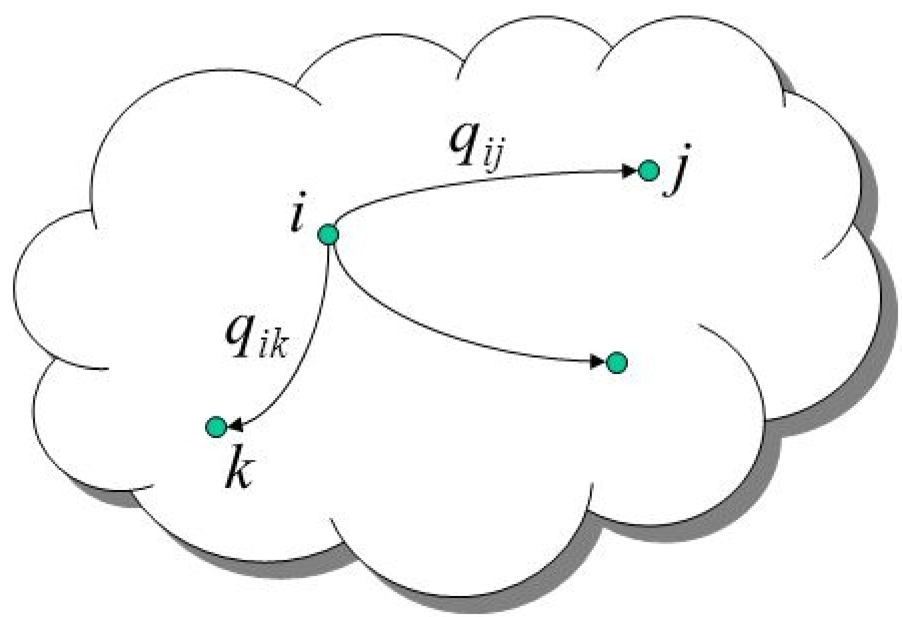
Biocham can handle three types of chemical kinetics:

- Hill kinetics: H(Vm,Km,n) = Vm*[S]\^n /(Km\^n+[S]\^n), the first argument Vm represents the maximum value, Km the threshold, n the order of Hill function and [S] is the concentration of the single reactant.

If a rule is provided without kinetic expression, a mass action law kinetic with reaction rate 1 is assumed, i.e., MA(1).

Stochastic semantics of Biocham models

The kinetic expressions in the reaction rules are used to associate to a Biocham model a continuous-time Markov Chain (CTMC).

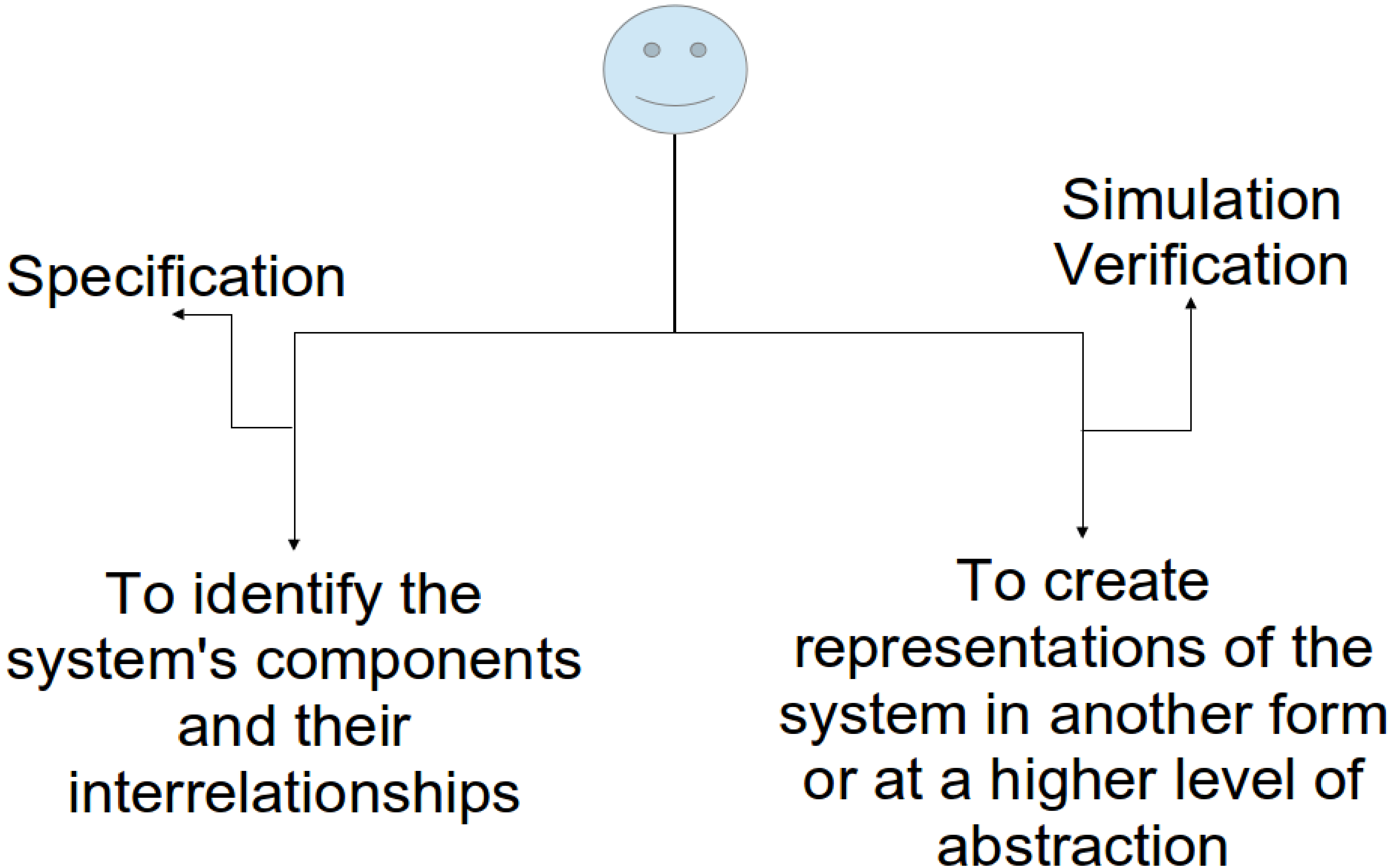


q_{ij} is the **transition rate** from state i to state j

Create a model

Step 1: Open a blank document in your favorite text editor

- **Step 2:** Define the chemical reactions
- **Step 3:** Assign kinetics to the rules
- **Step 4:** Define the parameter values
- **Step 5:** Define the initial conditions
- **Step 6:** Add a temporal logic specification to the model
- **Step 7:** Save the file



{Understanding biology from a computational/system perspective}

“Computer science is to biology what mathematics is to physics -Harold Morowitz”

Create a model

Identify a suitable biological model:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

MM.bc

```
MA(k1) for S + E => ES.
MA(k2) for ES => S + E.
MA(k3) for ES => P + E.
parameter(k1, 1).
parameter(k2, 1).
parameter(k3, 1).
present(S, 1).
present(E, 1).
```

Create a model

Repeat the **steps 2-7** by using the Biocham GUI.

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

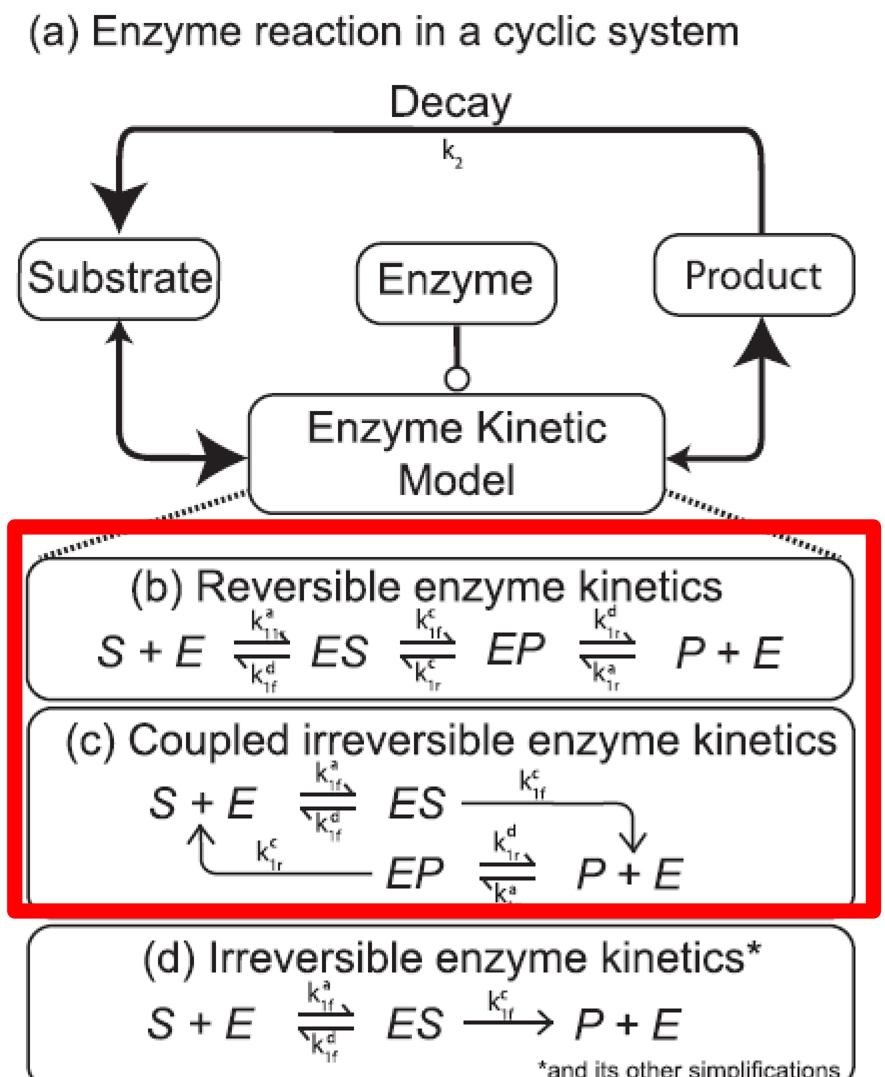
Start Biocham GUI

Biocham Models:

- Reaction Rule Model
- Simulation
- Boolean Temporal Properties
- Numerical Temporal Properties
- Abstractions

Exercise

Paper: "A generalised enzyme kinetic model for predicting the behaviour of complex biochemical systems". FEBS Open Bio 5 (2015) 226–239.



CONTENIDO-EVALUACIÓN

SEMANA	TEMA
1 Miércoles 25 Enero-17, 2-6PM, Lago 0.5	PRESENTACIÓN DEL MÓDULO INTRODUCTION TO COMPUTATIONAL BIOLOGY. Ejercicio en clase 10%
2 Miércoles 01 Febrero-17, 2-6PM, Lago 0.5	INTRODUCTION TO COMPUTATIONAL BIOLOGY: THE COMPLEXITY OF CELL-BIOLOGICAL SYSTEMS. Ensayo escrito 15%
3 Miércoles 08 Febrero-17, 2-6PM, Lago 0.5	INTRODUCTION TO COMPUTATIONAL BIOLOGY: COMPUTATIONAL APPROACHES TO BIOLOGICAL QUESTIONS. Ensayo escrito-Presentación oral 15%
4 Miércoles 15 Febrero-17, 2-6PM, Palmas 4.0	TUTORIAL 1: COMPUTATIONAL TOOLS AND APPLICATIONS: The Biochemical Abstract Machine (Biocham): a software and a modeling environment for computational and systems biology. Ejercicio en clase 15%
5 Miércoles 22 Febrero-17,2-6PM, Palmas Mac 4.5	TUTORIAL 2: COMPUTATIONAL TOOLS AND APPLICATIONS: BioNetGen: a multiscale software and a modeling environment for biological systems. Ejercicio en clase 15%
6 Miércoles 01 Marzo-17, 2-6PM, Lago 0.5	Proyecto 30%. Reporte de nota final del módulo.