BIOINFORMÁTICA

Asignatura 400CIS016

Doctorado en Ingeniería

Pontificia Universidad JAVERIANA Cali

PROFESORA

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23-Ene-2017-03-Jun-2017 Miércoles 14:00-18:00 LG-0.5

Módulo Modelamiento Computacional y Simulación:6 Semanas; Semana Lun 23 Enero a la Semana Lunes 27 de Febrero

"Computer science is to biology what mathematics is to physics -Harold Morowitz"

Rule-Based Modeling of Biochemical Systems with BioNetGen

James R. Faeder, Michael L. Blinov, and William S. Hlavacek

Methods in Molecular Biology, Systems Biology, vol. 500, 2009, 113-167 pp.

http://bionetgen.org/index.php/Main_Page

Exercise: short oral presentation

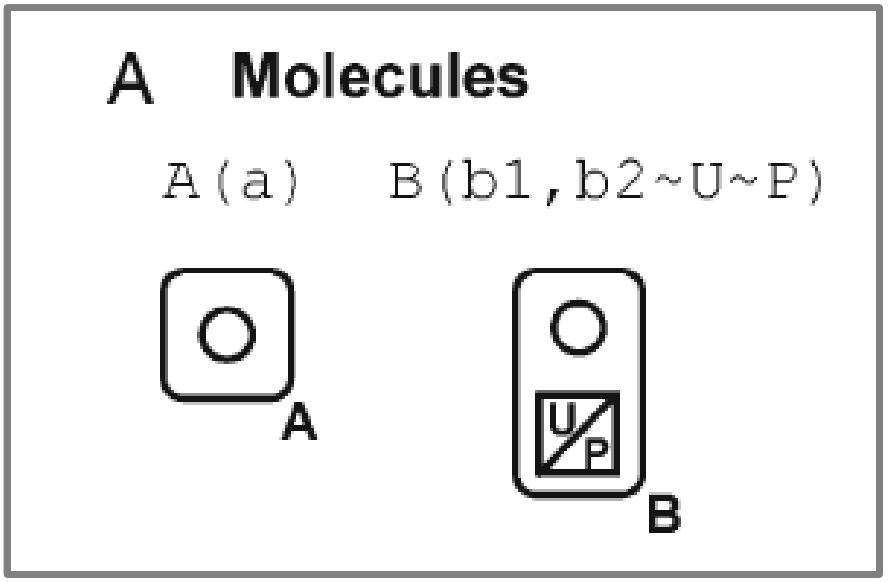
Please, elaborate a short ppt presentation based on the paper: Rules for Modeling Signal-Transduction Systems, Science's STKE, 2006: Vol. 2006, Issue 344, pp. Re6.

- 2:00-3:00 PM (Slide show design and group discussion)
- 3:00-3:15 PM (Oral presentation)

Rule-Based Modeling of Biochemical Systems with BioNetGen

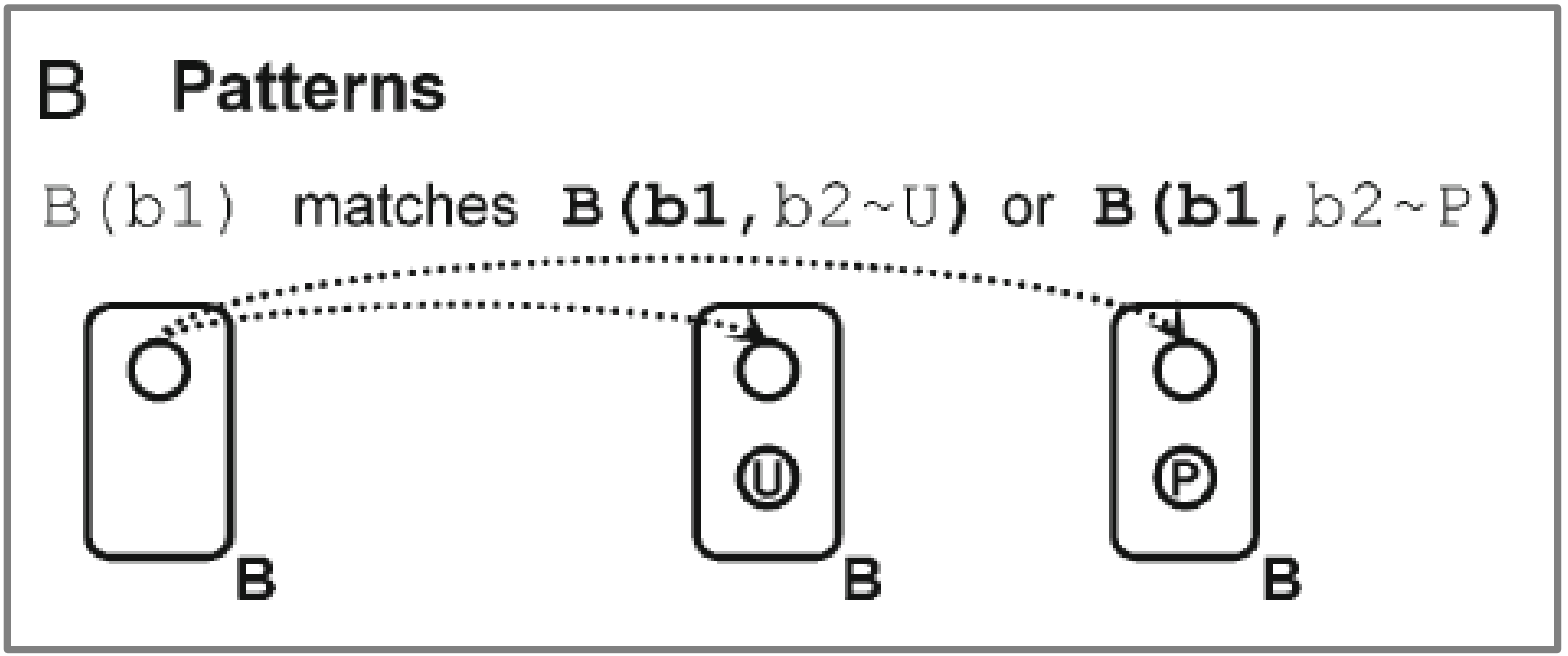
Rule-based modeling involves the representation of molecules as structured objects and molecular interactions as rules for transforming the attributes of these objects.

Rule-Based Modeling of Biochemical Systems with BioNetGen

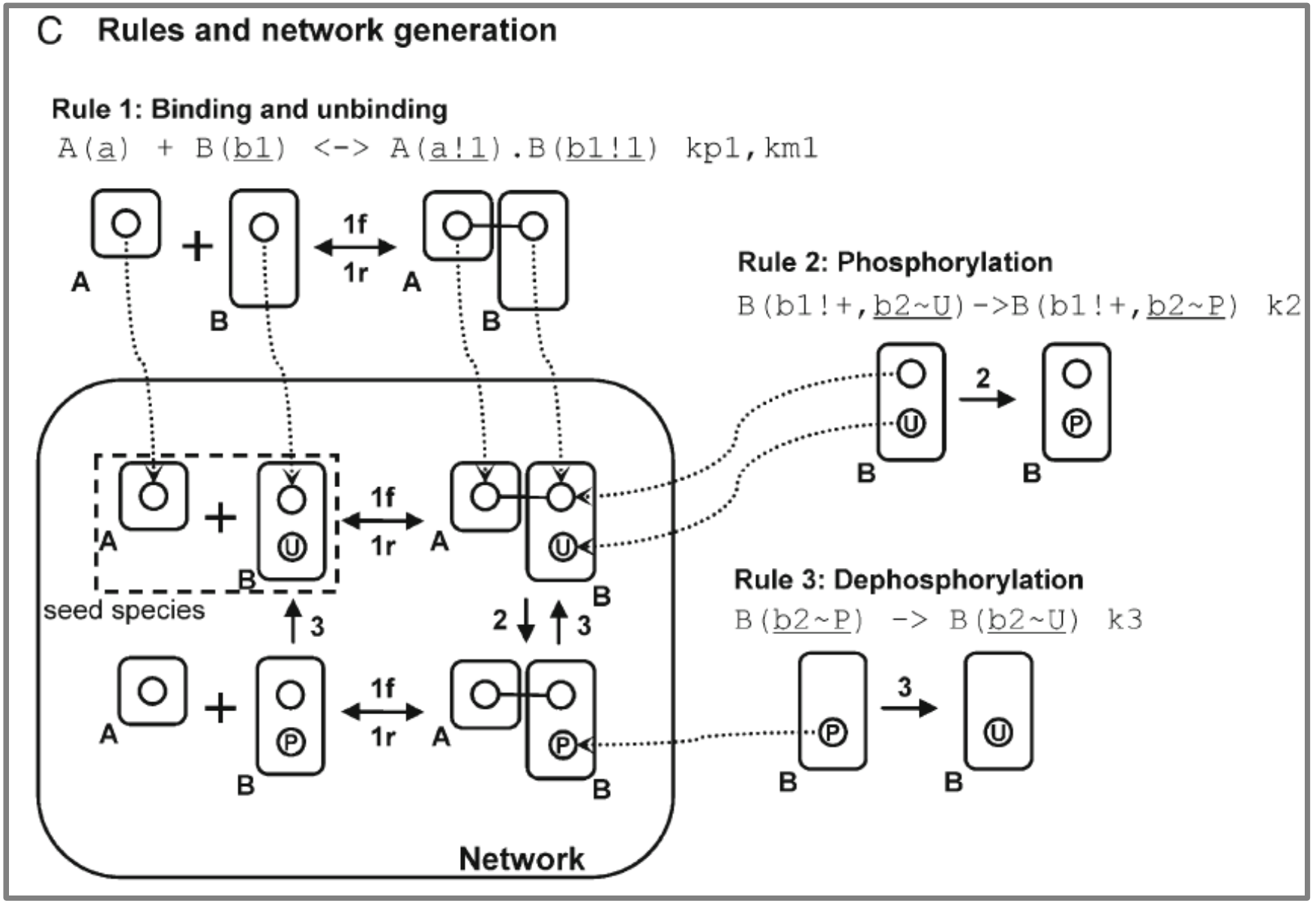


A. The basic building blocks are molecules, which are structured objects, composed of components that represent functional elements of proteins and may have associated states that represent covalent modifications or conformations. Molecules may be assembled into complexes through bonds that link components of different molecules.

Rule-Based Modeling of Biochemical Systems with BioNetGen



B. Patterns select particular attributes of molecules in species (shown in bold). The pattern shown here selects molecules of B with a free b1 binding site regardless of the phosphorylation or binding status of the b2 component.



C. Rules specify the biochemical transformations that can take place in the system and may be used to build up a network of species and reactions. Starting with the seed species, rules are applied to generate new reactions and species by mapping reactant patterns onto species and applying the specified transformation(s). Species generated by new reactions may be acted on by other rules to generate new reactions and species, and the process continues until no new reactions are found or some other stopping criteria are satisfied.

The following transformations are allowed:

- Forming a bond, e.g. `A(b) + B(a) -> A(b!0).B(a!0)`
- Breaking a bond, e.g. `A(b!0).B(a!0)-> A(b)+ B(a)`
- Changing of component state, e.g. `X(y~0) -> X(y~p)`
- Creating a molecule, e.g. `A(b) -> A(b) + C(d)`
- Destroying a molecule, e.g. `A(b) + B(a) -> A(b)`

A single reaction may involve any number of transformations.

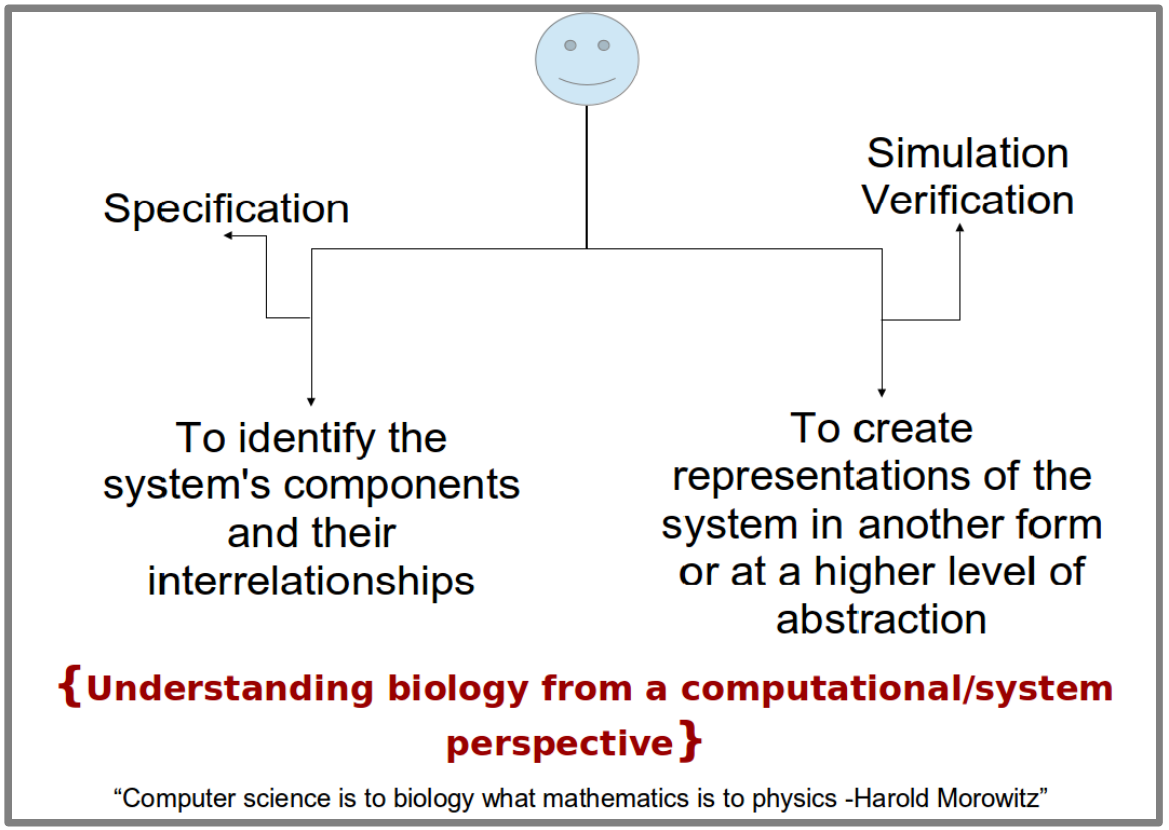
```
A(b) + B(a!0).C(d!0) -> A(b!0).B(a!0) + C(d)

A(b) + B(a!0).C(d!0) -> A(b!0).B(a!0)
```

Rule-Based Modeling of Biochemical Systems with BioNetGen

BioNetGen is a set of software tools for rule-based modeling.

How a model specification is analyzed using the BioNetGen software tool?



Modeling background

Law of Mass Action

Elementary Processes. An elementary process is an elementary reaction or an elementary step. It's a representation of how molecules interact with each other. Based on the number of molecular species involved, there are three kinds of elementary reactions: i) unimolecular, ii) bimolecular, and iii) trimolecular.

The reaction rate is expressed in volumen-independent "macroscopic" terms, i.e., Molar/sec.

Unimolecular reaction

$A \rightarrow \text{Products} \qquad k_{uni}$

$$\text{Rate } r = -\frac{d[A]}{dt} = k_{uni}[A] \qquad \text{Molar/sec}$$

Bimolecular reaction

$A + B \rightarrow \text{Products} \qquad k_{bi}$

$$\text{Rate } r = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_{bi}[A][B] \qquad \text{Molar/sec}$$

Modeling background

Law of Mass Action

To aid modeling flexibility and simulation, it is preferable to specify rate constants such that the reaction rate is given in reaction-events/sec. This is known as the "microscopic" rate.

$$r = \frac{d[A]}{dt} = \frac{d\left(\frac{N_A}{VN_{Avo}}\right)}{dt} = \frac{1}{VN_{Avo}} \times \frac{dN_A}{dt} = \left(\frac{1}{VN_{Avo}}\right) r'$$

$$\Longrightarrow r' = r \times VN_{Avo}$$

where r = Macroscopic rate constant $(M^{-1}s^{-1})$

and r' = Microscopic rate constant (s^{-1})

Modeling background

Since BioNetGen treats the rate as microscopic, the modeler must convert the macroscopic rate constants to microscopic ones:

For unimolecular reactions, if N_A denotes the population number of the reactant molecules, then, the microscopic rate is:

$$r'(s^{-1}) = r \times VN_{Avo} = k_{uni}[A] \times VN_{Avo} = k_{uni}\left(\frac{N_A}{VN_{Avo}}\right) \times VN_{Avo}$$

$$r' = k_{uni}N_A$$

For bimolecular reactions, if NA and NB denote the population numbers of the two reactant molecules, then, the microscopic rate is:

$$r'(s^{-1}) = r \times VN_{Avo} = k_{bi}[A][B] \times VN_{Avo} = k_{bi}\left(\frac{N_A}{VN_{Avo}}\right)\left(\frac{N_B}{VN_{Avo}}\right) \times VN_{Avo}$$

$$r' = \left(\frac{k_{bi}}{VN_{Avo}}\right)N_A N_B$$

Modeling background

The following assumptions are made under this paradigm: the reaction occurs in a fixed volume reactor at constant temperature and pressure and the molecules are distributed uniformly through the volume, i.e., there are no spatial gradients. These assumptions are often reasonable for biological models of events on the plasma-membrane and in the cytosol.

Creating and simulating a model in BioNetGen

Case example: **Michaelis-Menten Kinetics**. The kinetic formulation of a catalytic process dates back to Michaelis and Menten and Briggs and Haldane. The ezyme/catalyst binds to the substrate in a reversible fashion. A fraction of the bound complex causes the substrate to be converted to the product and dissociate simultaneously in a unimolecular fashion. The canonical formulation is:

$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

Creating and simulating a model in BioNetGen

1. Open the folder RuleBender and execute the RB (RuleBender) application.

2. File → New

3. Select → New Project→ Project name: TutorialBioNetGen → Finish

4. File → New → File → Next → File name: MM.bngl

5. Open the url: http://bionetgen.org/index.php/MMexact.bngl and copy and paste the corresponding code.

6. Save the file and perform the simulation. Use the additional commands available on the website to perform a discrete-stochastic analysis.

Creating and simulating a model in BioNetGen

1. Compare the time course of the model MMexact.bngl with the results of the model MMapprox.bngl.

2. The model MMapprox.bngl can be found at:
http://bionetgen.org/index.php/MMapprox.bngl

3. In the model MMapprox.bngl to directly compare the rates of substrate conversion between this one and the exact model, try adding the following function:
ES_eff() E0*Su/(Km + Su) # effective amount of ES complex used to compute the rate of the MM reaction

4. Elaborate a report in format .doc regarding steps 1 to 3.

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.