From Computer Science to Systems Biology

and vice-versa

New modeling challenges, approaches and tools

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Outline

- Context
- Modeling for systems biology
  - objectives
  - approaches
  - tools
- Challenges
- Solutions devised in systems biology
  - hooks for computer sciences
- Summary

Context

Biological research

- The scientific community of biologists outnumbers by far all others
  - a hot research area
  - big private investments (in 2006, Pharma and BioTech, 100B$)
- Most of these resources are spent in experimental work in molecular biology studies
- Technological progress
  - increasing observability
  - speeding-up experiment execution
- A huge amount of experimental data is being generated
  - a fraction is available in various public repositories over the Internet

Systems Biology into play

- The complexity of biological systems soon called for mathematical tools
- Computers support to mathematical biology approaches has generated two main areas of activity
  - Bioinformatics
  - Computational Biology
- Recently, the aim to integrate knowledge coming from traditionally separate areas of biology (genetics, proteomics, metabolomics) has led to **Systems Biology**
- The fundamental paradigm of Systems Biology
  - behavior is emerging from the dynamical interaction of components
  - systems should be studied with tools able to represent this

…understand complex biological systems through the integration of experimental and computational research [H. Kitano, 02]

Research community size

A fast growing research area

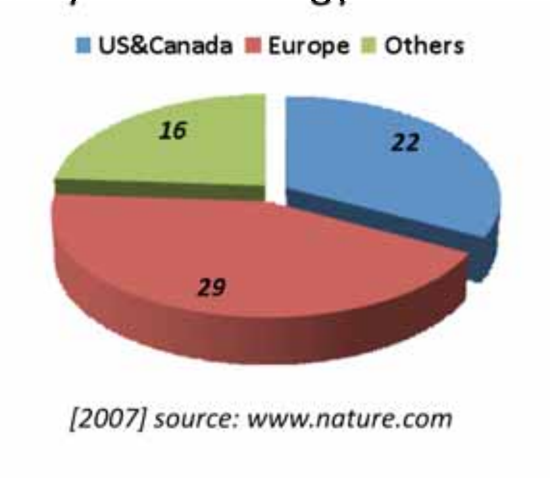
Around 70 international conferences and workshops in 2007 on related subjects

- 1100 attendants at the International Conference on Systems Biology 2008 in Gothenburg, Sweden

Standardization efforts

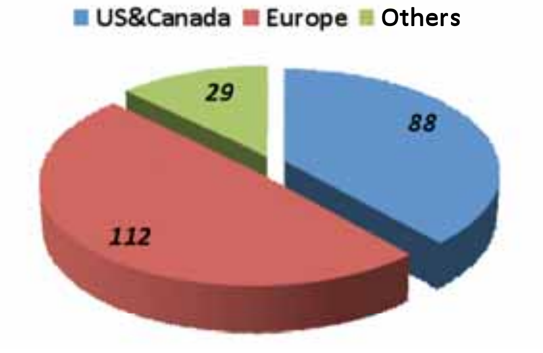
- SBML, CellML, BioPax
- SBGN
- SBO, SBRML
- 105 computational tools registered as SBML compliant

Systems Biology Institutes



[2007] source: www.nature.com

Systems Biology Departments



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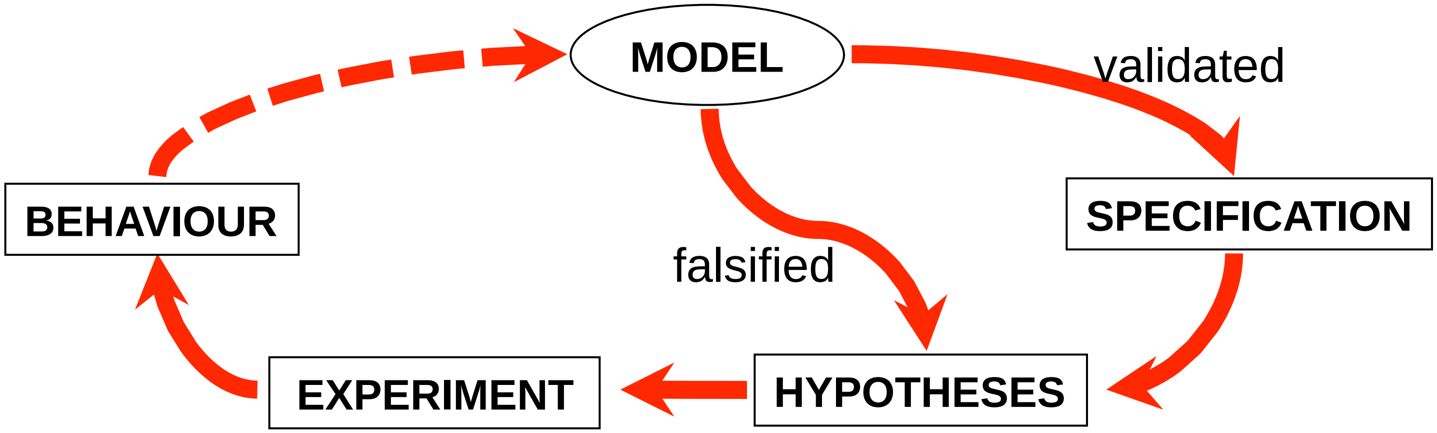
Objectives

Models in a reverse engineering loop

- All in all, the main objective of modern biology is to solve a substantial problem of ***Reverse Engineering***



- Model: a formal representation, which when
  - validated confirms the validity of the inferred knowledge used to build it
  - invalidated allows postulating new hypotheses and driving definition of experiments

Predictive models

- Validated models are used for predictive purposes
  - refinement of available knowledge through deduction

- Many experimental scenarios hardly accessible in *wet-lab* experiments may be evaluated at low cost with the *in-silico* approach

- Example: gene silencing
  - in-silico: set one variable to FALSE
  - wet-lab: DNA engineering or RNA interference

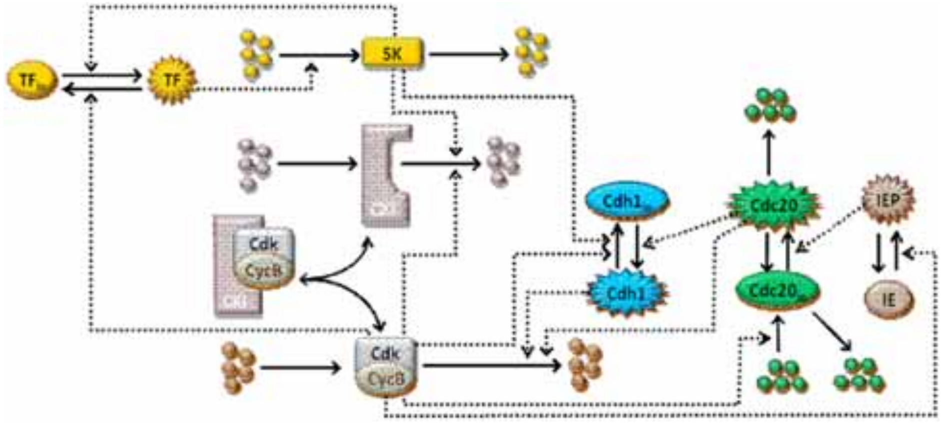
- Experiments run on a model can significantly reduce the effort required in the lab

Modeling approaches in SB

Classical approaches

Biologists mostly use unstructured graphical models for encoding knowledge about systems

- unclear semantics
- lack of quantitative information
- generalizations totally overlooked



A more expressive reaction based specification language has been borrowed from chemistry

- Ø →A, Ø →B
- A+B→C, C →A+B+C
- C → Ø

Models based on systems of ordinary differential equations

- quantitative information expressed in the form of kinetic rate constants

Intrinsic discreteness

- The truly molecular nature of biological interaction was considered hardly tractable
  - tracking single molecule state, location and movement is indeed quite heavy from a computational point of view

- This was considered to be true until 1976, when D. T. Gillespie
  - proved that the evolution of a well-stirred biochemical system can be accurately modeled by a continuous time discrete space Markov process
  - provided a very simple and extremely efficient simulation algorithm for computing realizations of such process

- Gillespie's algorithm (SSA) has paved the way for a number of discrete modeling approaches

Algorithmic approaches

- Algorithmic biology aims at representing causality in biological transformations
- Fueled by Gillespie result, new modeling tools have been proposed
  - discrete state-space
  - stochastic reaction times

Petri Nets

Modeling metaphor

- tokens count the number of molecules of species
- transition model reactions

Firing rates

- Transition rates always dependent on the marking of input places

Process Algebra

Modeling metaphor

- processes represent biological entities
- interactions are represented as communications on a channel

Communications based on affinity

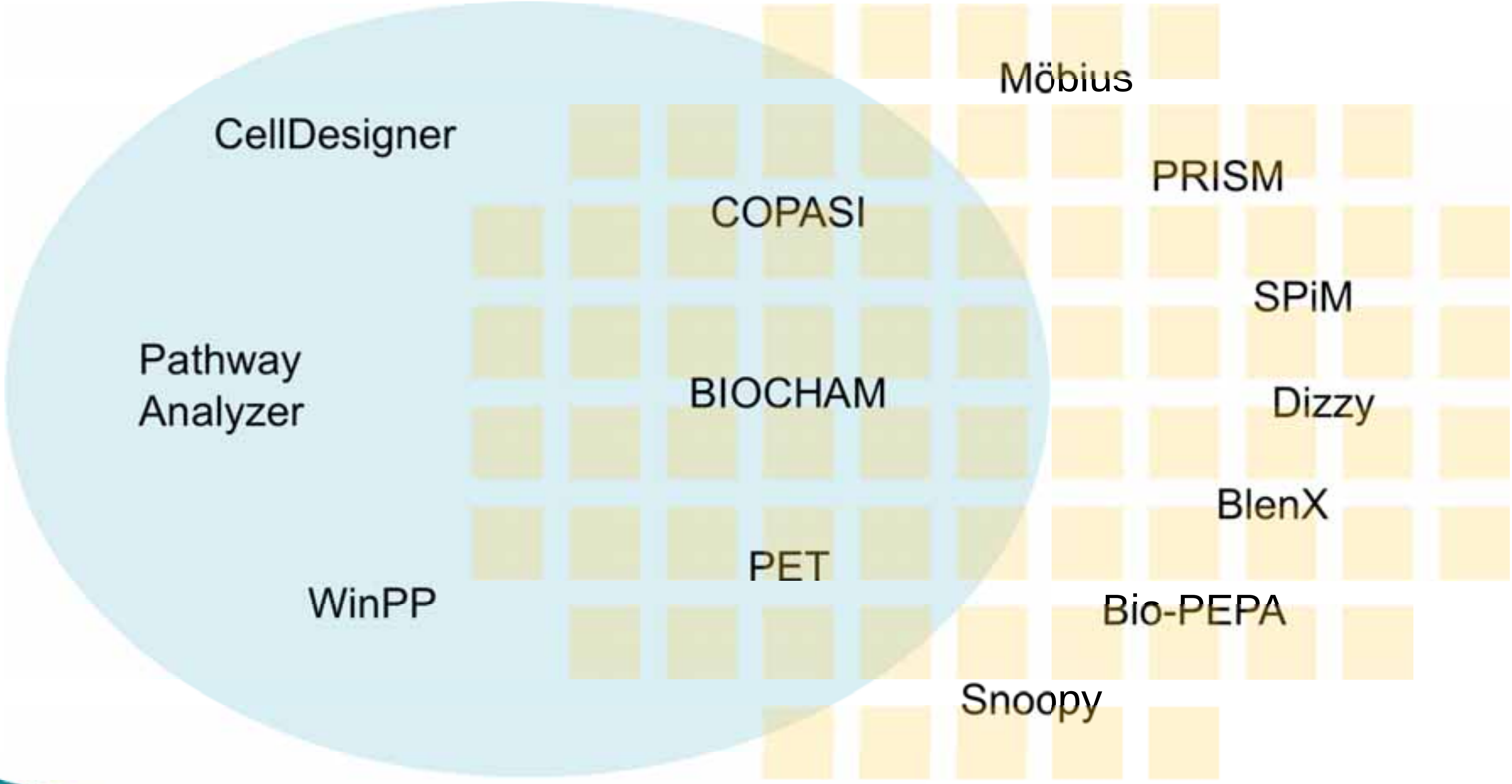
- interaction likelihood is defined through *affinities* of process

Tools in SB

An historical perspective

- Since the beginning of the Human Genome project, computational support to biology has come through *bioinformatics* tools
  - String manipulation
  - Databases
  - Data mining
  - Statistical applications (clustering)
- The 90's have seen a spread of tools for continuous modeling borrowed from physics approach to biology
  - ODEs and PDEs solvers
  - Metabolix flux analysis
- During the last decade, tools developed within the computer science community started to be used
  - Petri Nets (1998, Goss-Peccoud) and Process Calculi
  - P-systems
  - Model checking

The current situation



Measures of interest

- Typical quantitative aspects of interest on biological systems
- How resilient is a system to perturbations? If a gene is silenced, what will change in
  - the probability of entering deadly states
  - the speed of metabolism
  - the patterns of genes activation
- What are the likely causes of a wrong system response?
  - which kinetic rate determine the observed phenotype
- How can we interfere on a system that is wrongly responding to bring it back into operation?
  - which reactions should be targeted by a drug
  - which entities should be removed

Domain-specific challenges

Number of entities

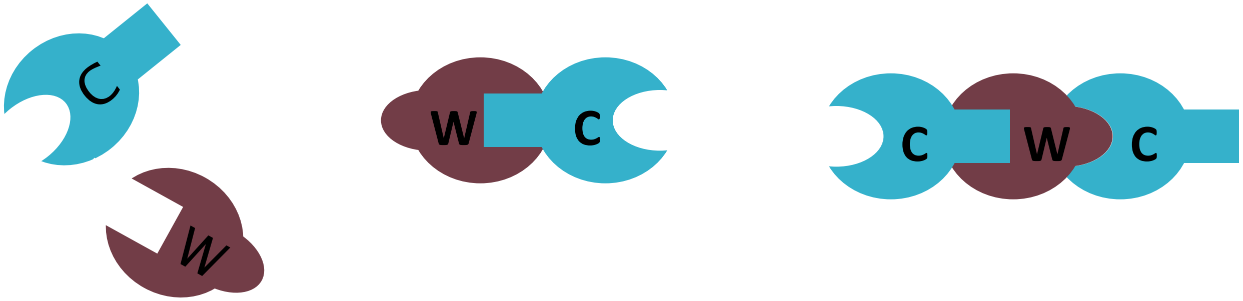
- Biological systems have to deal with molecular noise
  - predictable behaviors emerge from large numbers effect
  - in the small volume of a cell nucleus there can be thousands of copies of a molecule type

- Different scales of multiplicities within a single system
  - 1 copy of a gene
  - 10^9 molecules in one cell nucleus
  - 10^6 synapses for one neuron
  - 10^{14} cells in the human organism

- Immediate consequences on state spaces
  - 10^{24} states in a toy cell cycle model

Dynamic creation of entities

- Biological compounds have *sites* of interaction
  - multiple sites can be present in the same entity
  - bindings occur reversibly between **2** affine sites
  - complexes of biological components can assembly without a precise order and can result in different topological structures
  - example: protein C has 2 sites, both affine to 2 sites of protein W



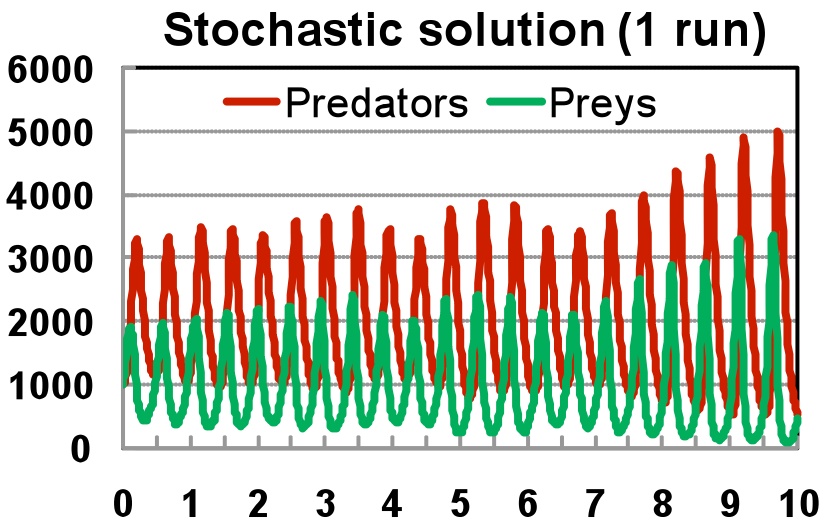
How many structures can form?

- It may be cumbersome or even impossible to specify such a behaviors in many formalisms

Oscillatory behaviors

- Many biological systems achieves equilibrium conditions that are not commonly found in artificial systems
  - living systems keep oscillating

- Many systems have transient oscillation that stop abruptly
  - dead



- This poses issues in
  - defining adequate measures that can characterize cyclic system behavior
  - comparing similar but different systems

Partial system knowledge

- Known unknowns
  - many biological entities are only partially characterized
  - interaction among entities are not always observable and thus values of many parameters to be used in models are unknown
- Unknown unknowns
  - not all the entities participating in an interaction network are known
  - we may not know which abstractions are actually used when defining models
- Modularity is only apparent
  - the number of roles and functions of entities keeps growing
  - one input rarely corresponds to a single response

Solutions devised in SB

To handle big size populations

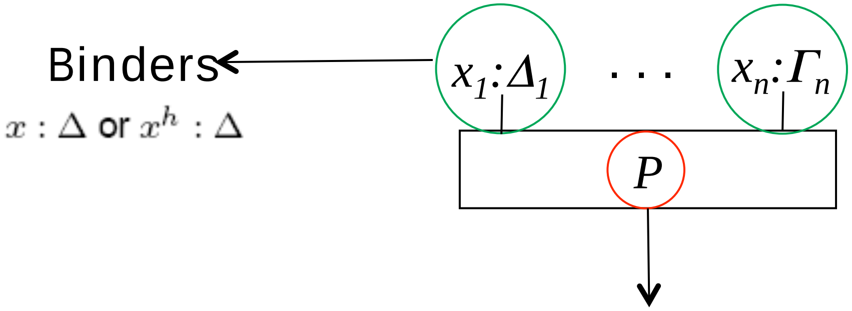
- Continuous approximation
  - the number of entities is approximated into a proportional concentration
  - variations of concentrations are modeled as changes in their first derivative
  - models are sets of non-linear ordinary differential equations, solved through numerical integration

- Many tools exist for continuous ODE modeling
  - reaction-based languages are commonly used for specification
  - ODEs are automatically obtained from reactions
  - efficient numerical solvers handle large/stiff models
  - time-dependent, equilibrium, vector fields and bifurcation analyses

- Work in progress…
  - some theoretical and experimental results show interesting relationship between results of discrete and continuous models

To handle dynamic creation of new entities

- Interaction-based modeling languages based on process algebra
- BlenX encapsulates π-calculus processes into boxes with interaction capabilities



Binders

$x : \Delta$ or $x^h : \Delta$

$x_1 : \Delta_1$ . . . $x_n : \Gamma_n$

P

π-Processes (a subset of syntax)

$$P ::= \mathsf{nil} \mid \pi.\,P \mid P \mid P \mid \nu y\, P \mid !\,\pi.\,P$$

$$\pi ::= x(y) \mid \overline{x}\langle z\rangle \mid \mathsf{hide}(\mathbf{x}) \mid \mathsf{unhide}(\mathbf{x}) \mid \mathsf{expose}(\mathbf{x},\, \boldsymbol{\Gamma})$$

- Evolutions of the internal process change the state of the box and of its interaction capabilities

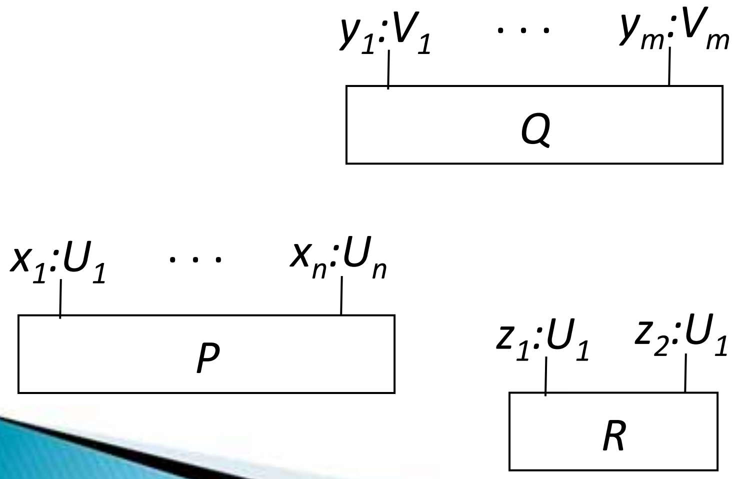
A separate specification

INTERFACES

- The set of interaction capabilities of entities are modeled by binders
- At any moment, interaction can only happen through visible binders
- Binders are typed

COMMUNICATION RATES

- The rate at which interaction happen through binders is specified by a type affinity table
- Multiple rates can be used to specify rate of start, failure, completion of the interaction



affinities

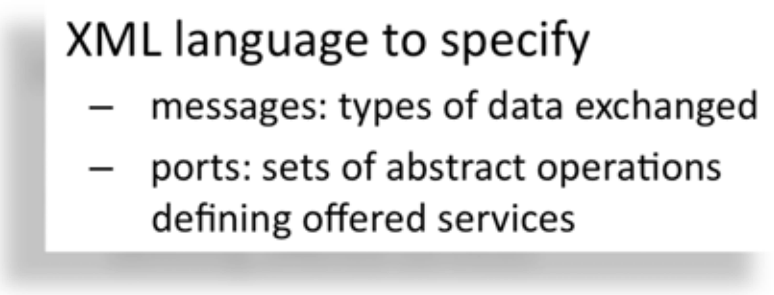
U_1,V_1	0	0	0
U_1,V_2	r_{12}	0	0
U_1,V_3	r_{13}	k_{13}	c_{13}

....

An example: Web services

- Web services use standardized XML messaging
- Allow for self-descriptive and discoverable services

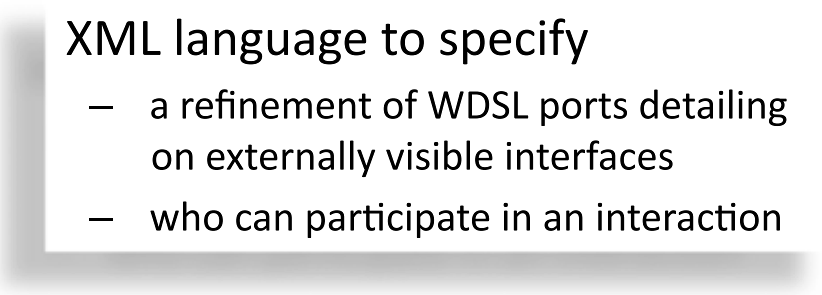
WDSL



XML language to specify

- messages: types of data exchanged
- ports: sets of abstract operations defining offered services

WSCI



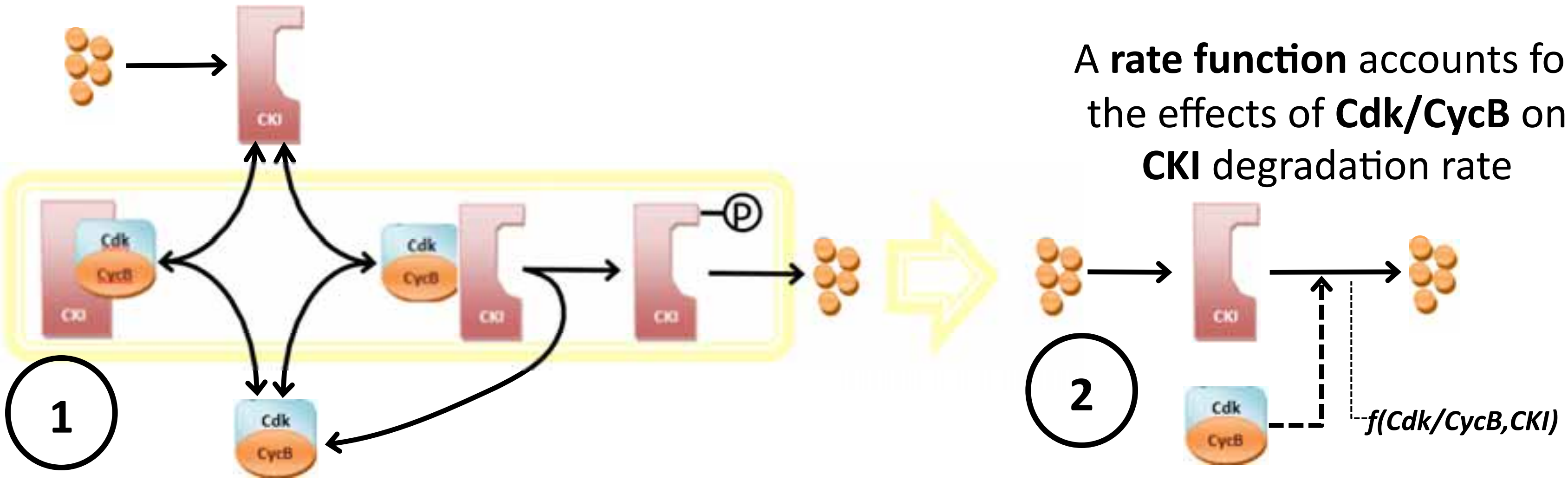
XML language to specify

- a refinement of WDSL ports detailing on externally visible interfaces
- who can participate in an interaction

- WDSL and WSCI specifications can be parsed to automatically obtain a BlenX model
- Quantitative information can be added to the model to conduct simulations

To manage unknowns

- An ideal abstraction usage: we want to simplify 1



A **rate function** accounts for the effects of **Cdk/CycB** on **CKI** degradation rate

- The real abstraction usage: current knowledge only allows building 2
- However, a good news is that we can obtain rate functions inferred from wet-lab experiments

To speed-up stochastic simulation

- Gillespie's family of Stochastic Simulation Algorithms

- Fundamental hypothesis
  - times of occurrence of every reaction in the system follow a negative exponential distribution

- Let
  - $R_1, R_2, \ldots, R_m$ the reaction set
  - $X(t)=\mathbf{x}$ the state of the system
  - $a_1(\mathbf{x}), a_2(\mathbf{x}), \ldots, a_m(\mathbf{x})$ the reaction rates , also called *propensities*
  - $a_0(\mathbf{x})$ defined as $\Sigma_j a_j(\mathbf{x})$

Direct method (1976)

- Given X(t)=**x** , the probability that the next reaction happens in the infinitesimal time interval [t+τ ,t+τ+dt] and is a reaction of type j is

$$a_j(\mathbf{x}) \cdot exp(-a_0(\mathbf{x})\ \tau)$$

  - the time τ to the next reaction is an exponential random variable of mean 1/$a_0(\mathbf{x})$
  - the probability that next reaction is of type j is $a_j(\mathbf{x}) / a_0(\mathbf{x})$

- At each simulation step, 2 uniform r.n. u and v are drawn
  - τ is chosen to be ln(u^{-1})/$a_0(\mathbf{x})$
  - j is chosen as the smallest integer satisfying $\sum_{i=1}^{j} a_i(x) > v \cdot a_0(x)$

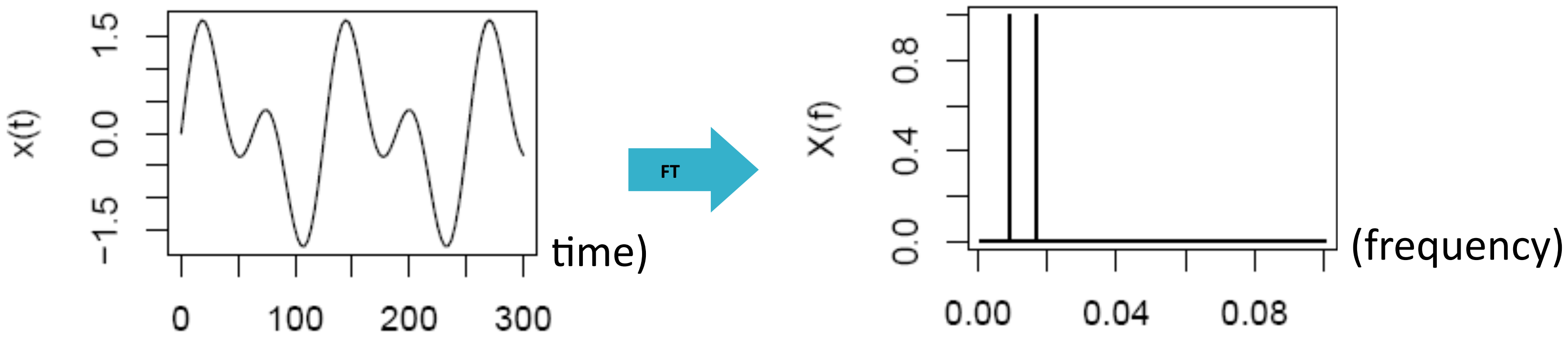
Reformulations of the method

- First reaction method (1976)
  - at each simulation step, draw m uniform r.n. and compute $\tau_{1}, \tau_{2},\ldots, \tau_{m}$, the putative time of all reactions
  - choose τ as the min($\tau_{1}, \tau_{2},\ldots, \tau_{m}$)
  - choose *j* as the index of the minimum above
- Next reaction (2000)
  - same as the above one, but the putative times are saved in an indexed binary tree so that the minimum is always at the top
  - a dependency graph is used to keep track of coupling among reactions to determine when putative times in the tree have to be resampled
- Modified direct method (2004)
  - a pre-run to determine a suitable order of reactions to minimize cost of step 2)
- Sorting direct method (2006)
  - self-adaptive version of the one above, no pre-run

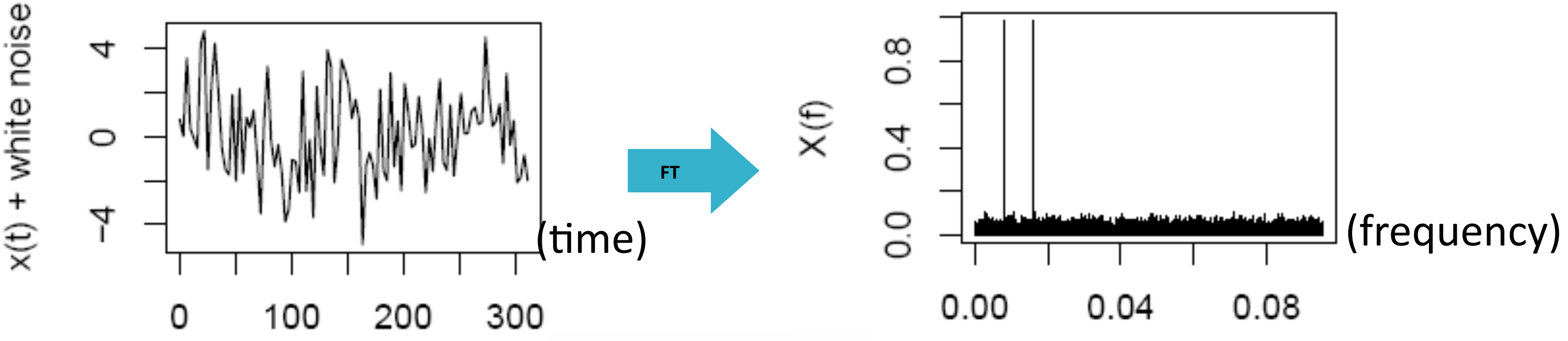
To analyze oscillatory regimes

- Convert time series to frequency spectra

x(t)=sin(t/10) + sin (t/20)

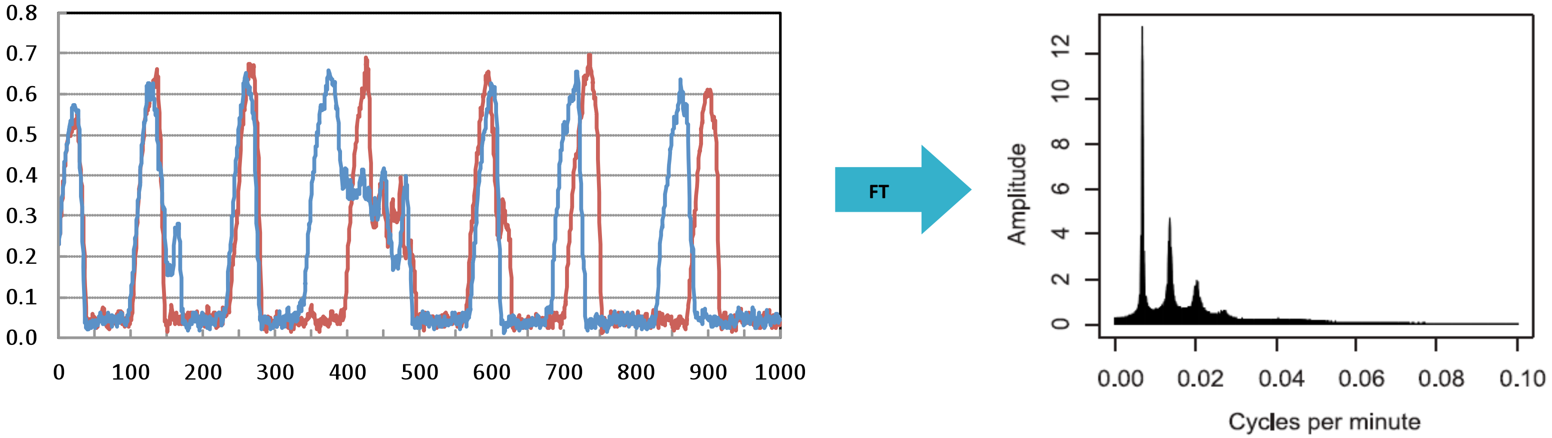


- Widely used in hardware



Statistical measures over FA

- Spectra of multiple stochastic runs are averaged



- Three measures

$\rho 1 = \log_2(\max(f_{1..N-1})/\langle f_{1..N-1}\rangle)$ log(peak/mean)

$\rho 2 = \sigma(f_{1..N-1})/\langle f_{1..N-1}\rangle$ coefficient of variance

$\rho 3 = \sup|F^1_{0..N-1} - F^2_{0..N-1}|$ Kolmogorov – Smirnov statistic

f_ω = ω^{th} complex frequency component, *F* = cumulative frequency distribution of f

Summary

- Models play a key role in Systems Biology
- Some modeling challenges are shared with computer science, some others are domain specific
- Approaches ant tools are in an explorative phase
- Some solutions independently devised may be useful/improve over current practice in computer science