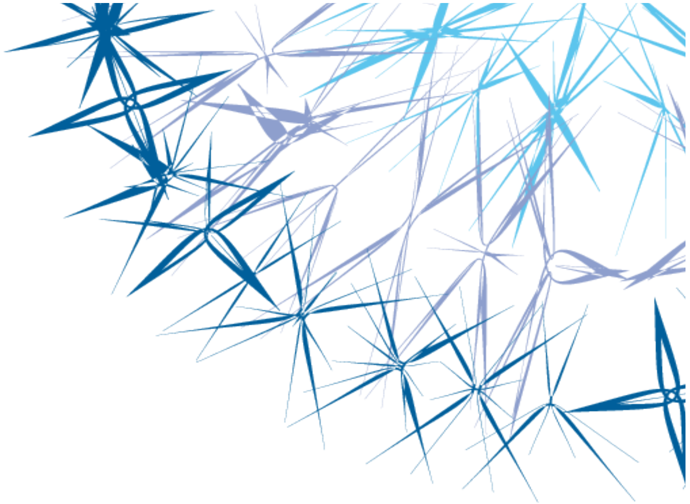
COSBI

Programming-based systems biology

Corrado Priami



outline

Biology needs a theory able to highlight causality and abstract data into knowledge to elucidate the architecture of biological complexity.

Sidney Brenner

The grand challenge for all scientific and engineering disciplines in the 21st century is complexity.

Lee Hood

IMPACT CORE COMPUTER SCIENCE AND SYSTEMS BIOLOGY

Quantitative operational descriptions of the mechanistic behavior of biological systems

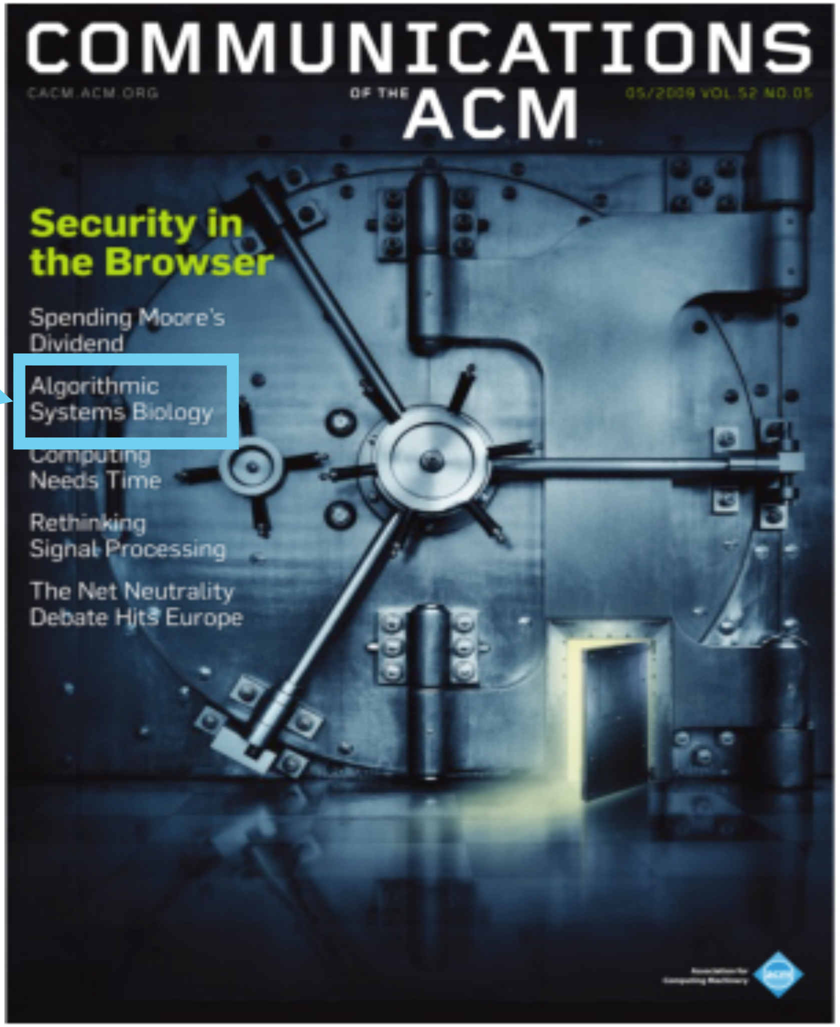
Computational thinking

Not ambiguous specifications for simulation and analysis tools

Coping with combinatorial explosion of systems description

MOVING BEYOND MATH MODELING:

ADDRESS CONCURRENCY AND COMPLEXITY



COMMUNICATIONS OF THE ACM

CACM.ACM.ORG

05/2009 VOL.52 NO.05

Security in the Browser

Spending Moore's Dividend

Algorithmic Systems Biology

Computing Needs Time

Rethinking Signal Processing

The Net Neutrality Debate Hits Europe

BIOINFORMATICS IS DIFFERENT

Comparison of strings

Storage of experiment results

Visualization of complex data

Search and analysis of data sets…

Mainly Structural/Static descriptions

MATHEMATICAL AND COMPUTATIONAL BIOLOGY ARE DIFFERENT

Static abstract relationships

Computer assisted solutions

Global pictures of dynamics

OUR DRIVING CHALLENGES

Interaction

Emergence

Partial knowledge

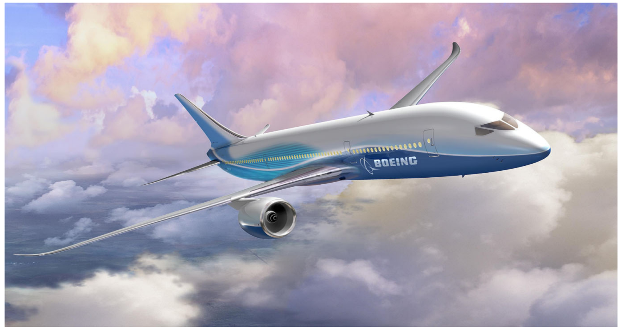
Ambiguous observations

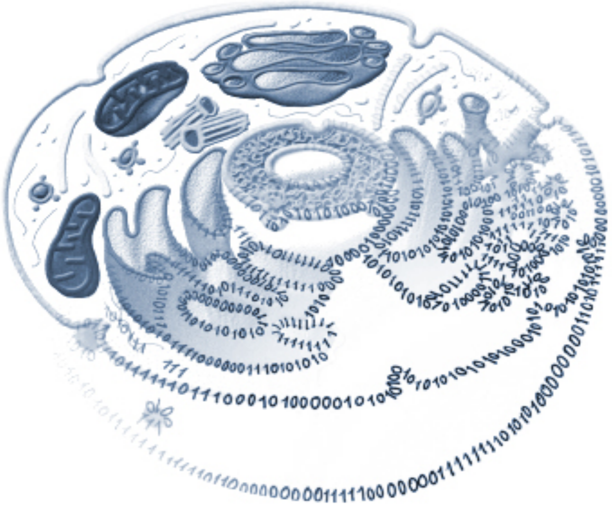
Multi-level, multi-scale in space and time

Causal relationships and context-awarness

LOW-LEVEL LOCAL MECHANISMS AFFECT HIGH-LEVEL GLOBAL BEHAVIOR

SIMULATION-BASED, DATA-DRIVEN SCIENCE

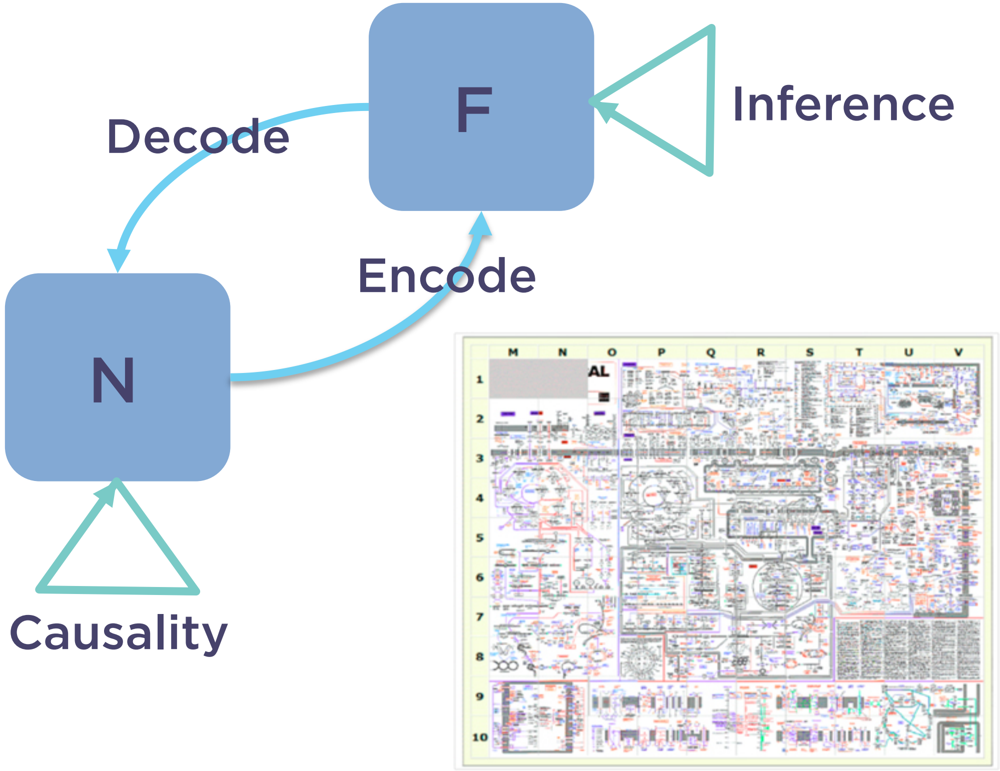




```
//
Tree.prog

[ steps = 10, delta = 10 ]

<< BASERATE:inf, HIDE:inf, UNHIDE:inf, CHANGE:inf >>

// Initiator Definition
let Initiator : bproc = #(out,l) [ out?().out!(root).nil ];

// Node Definition
let p1 : pproc = !out1?().out2?().out1!(node).out2!(node).nil;
let p2 : pproc = !out1?().out2?().inp!().inp?(m).out1!(m).out2!(m ).nil;
let nodeP : pproc =
  inp!().inp?(t).( t!() | (
    node?().unhide(out1).unhide(ou 2).p2 +
      root?().unhide(out1).unhide (out2).p)
    ) );
```

CoSBi LAB

A MODELING FORMALISM



F

Inference

Decode

Encode

N

Causality

Encode info manipulation by bio-systems

A formal framework to reason about bio-systems

Predict biological behavior and identify new hypotheses

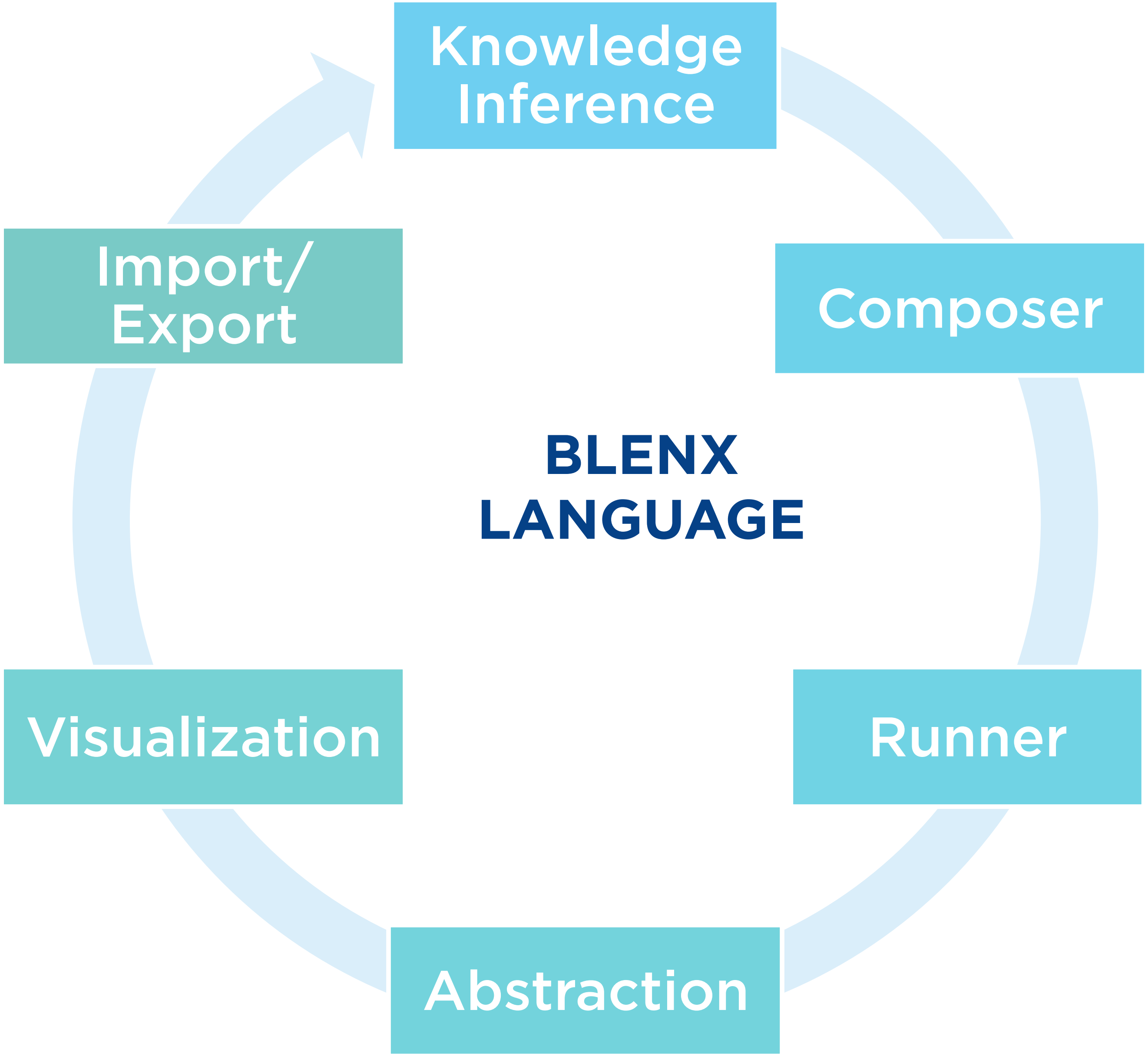
Unambiguous description to share knowledge the development of the appropriate languages to describe information processing in biological systems and the generation of more effective methods to translate biochemical descriptions into the functioning of the logic circuits that underpin biological phenomena

Paul Nurse

THE METAPHOR

biological entities	processes
interaction capabilities	interfaces
complex/decomplex	binding/unbinding
dynamics	state change

THE ENVIRONMENT



Knowledge Inference

Composer

Runner

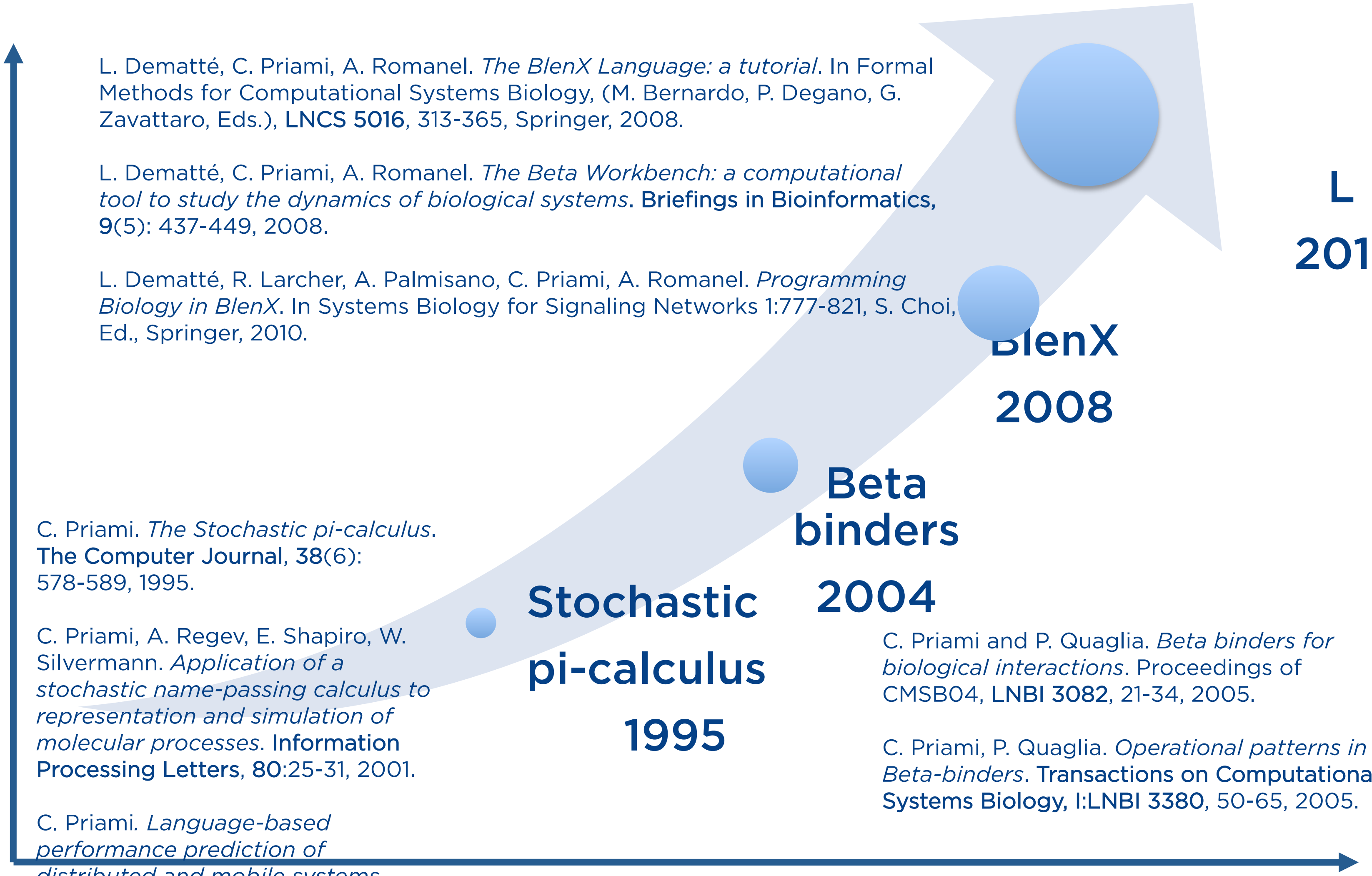
Abstraction

Visualization

Import/ Export

BLENX LANGUAGE

BLENX GENESIS



Case Studies

L. Dematté, C. Priami, A. Romanel. *The BlenX Language: a tutorial*. In Formal Methods for Computational Systems Biology, (M. Bernardo, P. Degano, G. Zavattaro, Eds.), **LNCS 5016**, 313-365, Springer, 2008.

L. Dematté, C. Priami, A. Romanel. *The Beta Workbench: a computational tool to study the dynamics of biological systems*. **Briefings in Bioinformatics, 9**(5): 437-449, 2008.

L. Dematté, R. Larcher, A. Palmisano, C. Priami, A. Romanel. *Programming Biology in BlenX*. In Systems Biology for Signaling Networks 1:777-821, S. Choi, Ed., Springer, 2010.

L

2011

BlenX

2008

Beta binders

2004

Stochastic pi-calculus

1995

C. Priami. *The Stochastic pi-calculus*. **The Computer Journal**, **38**(6): 578-589, 1995.

C. Priami, A. Regev, E. Shapiro, W. Silvermann. *Application of a stochastic name-passing calculus to representation and simulation of molecular processes*. **Information Processing Letters**, **80**:25-31, 2001.

C. Priami. *Language-based performance prediction of distributed and mobile systems*. **Information and Computation, 175**:119-145, 2002.

C. Priami and P. Quaglia. *Beta binders for biological interactions*. Proceedings of CMSB04, **LNBI 3082**, 21-34, 2005.

C. Priami, P. Quaglia. *Operational patterns in Beta-binders*. **Transactions on Computational Systems Biology, I:LNBI 3380**, 50-65, 2005.

Implementation

PI-CALCULUS

Processes	• Domains, Molecules/Proteins, Systems
Primitives	• Join/Split, Conditional Events • Restriction for Compartments, Membranes, Complexes
Complex/ Decomplex	• Not explicitly modeled • Interplay between private names and scope size
Low-level programming	• Reversibility of interactions
Modeling	• Emergent behavior must be programmed
Interaction	• Key-lock mechanism
Implementation	• General structural congruence

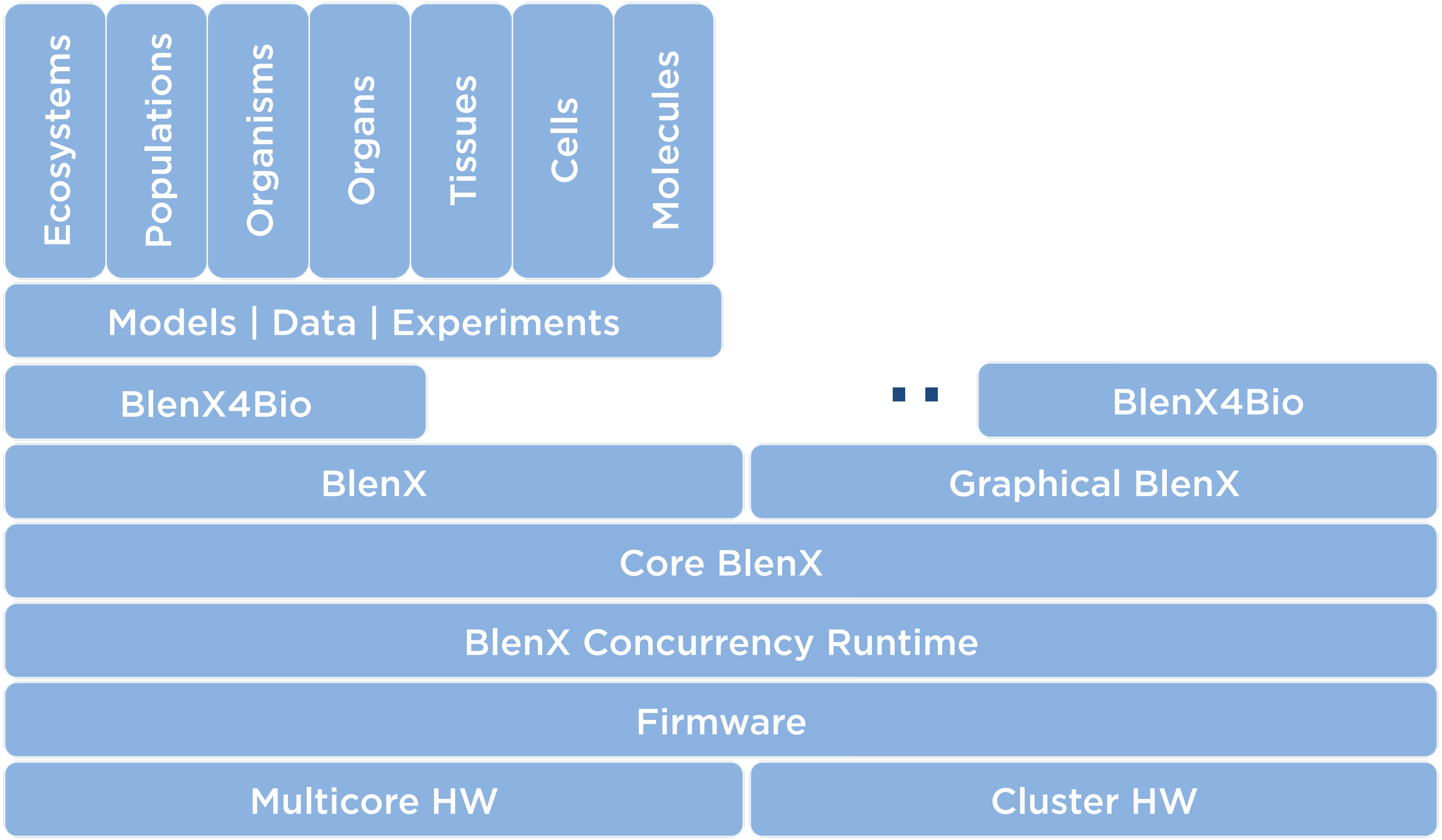
BETA-BINDERS

Processes	• Domains, Molecules/Proteins, Systems
Primitives	• Join/Split, Conditional Events • Restriction for Compartments, Membranes, Complexes
Complex/ Decomplex	• Not explicitly modeled • Interplay between private names and scope size
Low-level programming	• Reversibility of interactions
Modeling	• Emergent behavior must be programmed
Interaction	• Key-lock mechanism
Implementation	• General structural congruence

BLENX PRINCIPLES

- Set of interacting boxes with internal behavior
- Non key-lock interaction mechanism
- Complex description and their Dynamic generation
- Typed and dynamic varying interfaces
- 1-1 correspondence with Biological elements
- Events

BLENX TOWER



Ecosystems
Populations
Organisms
Organs
Tissues
Cells
Molecules

Models | Data | Experiments

BlenX4Bio .. BlenX4Bio

BlenX | Graphical BlenX

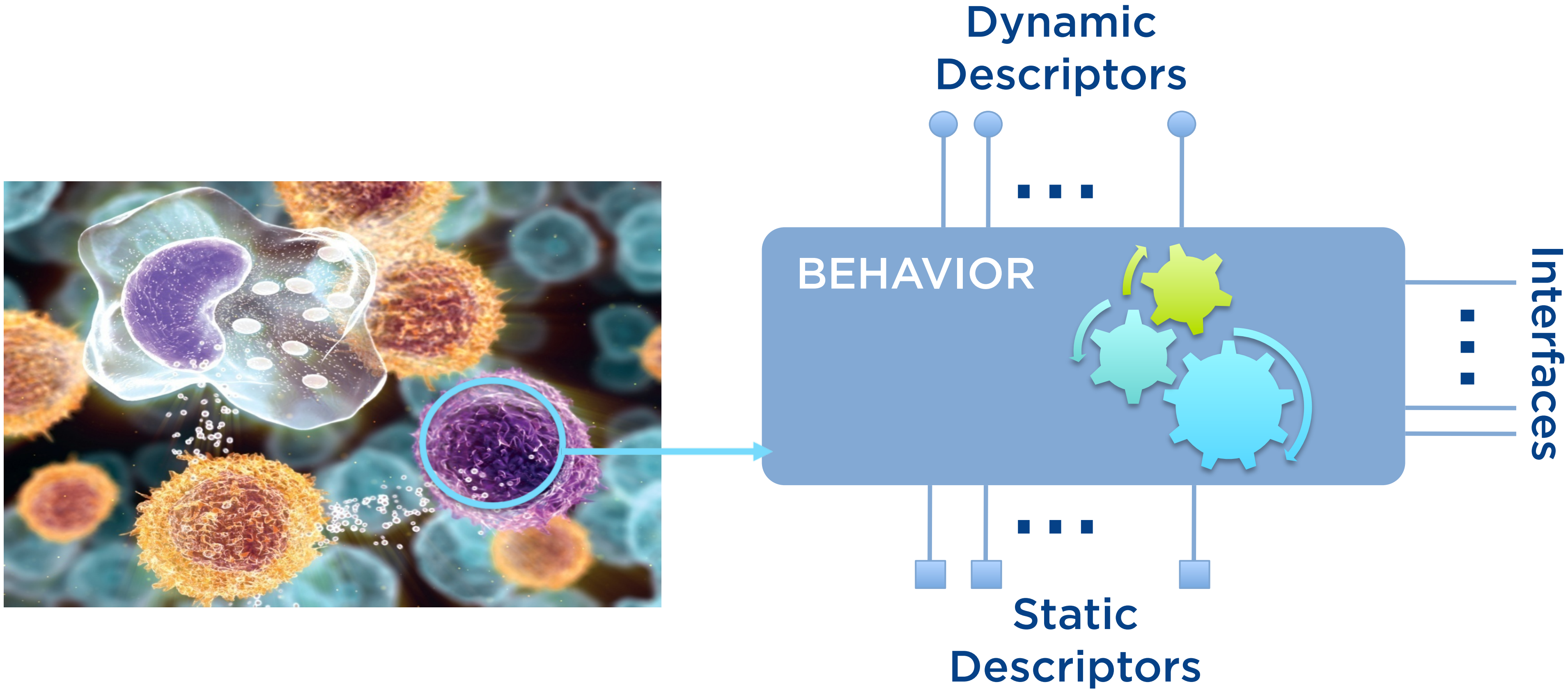
Core BlenX

BlenX Concurrency Runtime

Firmware

Multicore HW | Cluster HW

BLENX CORE ELEMENTS



Dynamic Descriptors

BEHAVIOR

Interfaces

Static Descriptors

C. Priami, P. Quaglia and A. Romanel. *BlenX - static and dynamic semantics*. Proceedings of CONCUR09, **LNCS 5710**, 37-52, Springer, 2009.

A. Romanel. Dynamic Biological Modelling: a language-based approach. PhD Thesis. COSBI TR PhD-1-2010.

BLENX PROGRAMMING LANGUAGE

```
// CDP
let CDP_ : bproc = #(y,CDP) [ rep start?().Prog_CDP | Prog_CDP ];
let dCDP_ : bproc = #(y,dCDP) [ rep start?().Prog_CDP | Prog_CDP ];
let dCTP_ : bproc = #(y,dCTP) [ rep start?().Prog_CDP | Prog_CDP ];
// RR
let RR_ : bproc = #(r,RR) [ rep start?().Prog_RR | Prog_RR ];
// CELL
// f1
let Cell : bproc = #(cell,Alive) [ nil ];
when ( Cell : : cell_death_function ) delete(1);
run  100 CDP_  || 100 dFdC_  || 1000 CDA_ || 1000 RR_  || 100 Cell || 100 DNA_healthy
```

LANGUAGE FLAVOR: BLENX

```
// Tree.prog

[ steps = 10, delta = 10 ]

<<  BASERATE:inf, HIDE:inf, UNHIDE:inf, CHANGE:inf >>

// Initiator Definition
let Initiator : bproc = #(out,I) [ out?().out!(root).nil ];

// Node Definition
let p1 : pproc = !out1?().out2?().out1!(node).out2!(node).nil ;
let p2 : pproc = !out1?().out2?().inp!().inp?(m).out1!(m).out!(m).nil ;
let nodeP : pproc =
   inp!().inp?(t).( t!() | (
         node?().unhide(out1).unhide(out2).p2 +
          root?().unhide(out1).unhide(out2).p1
     ) );

let Node : bproc = #(inp,IN),#h(out1,ONE),#h(out2,TWO)
            [ nodeP ];

// Init
run 2 Initiator  || 10 Node
```

```
// Tree.types

{ I, IN, ONE, TWO }
%%
{
 (I,IN,100,0,inf),
 (ONE,IN,1,0,inf),
 (TWO,IN,1,0,inf)
}
```

a static list of the entities of the initial configuration

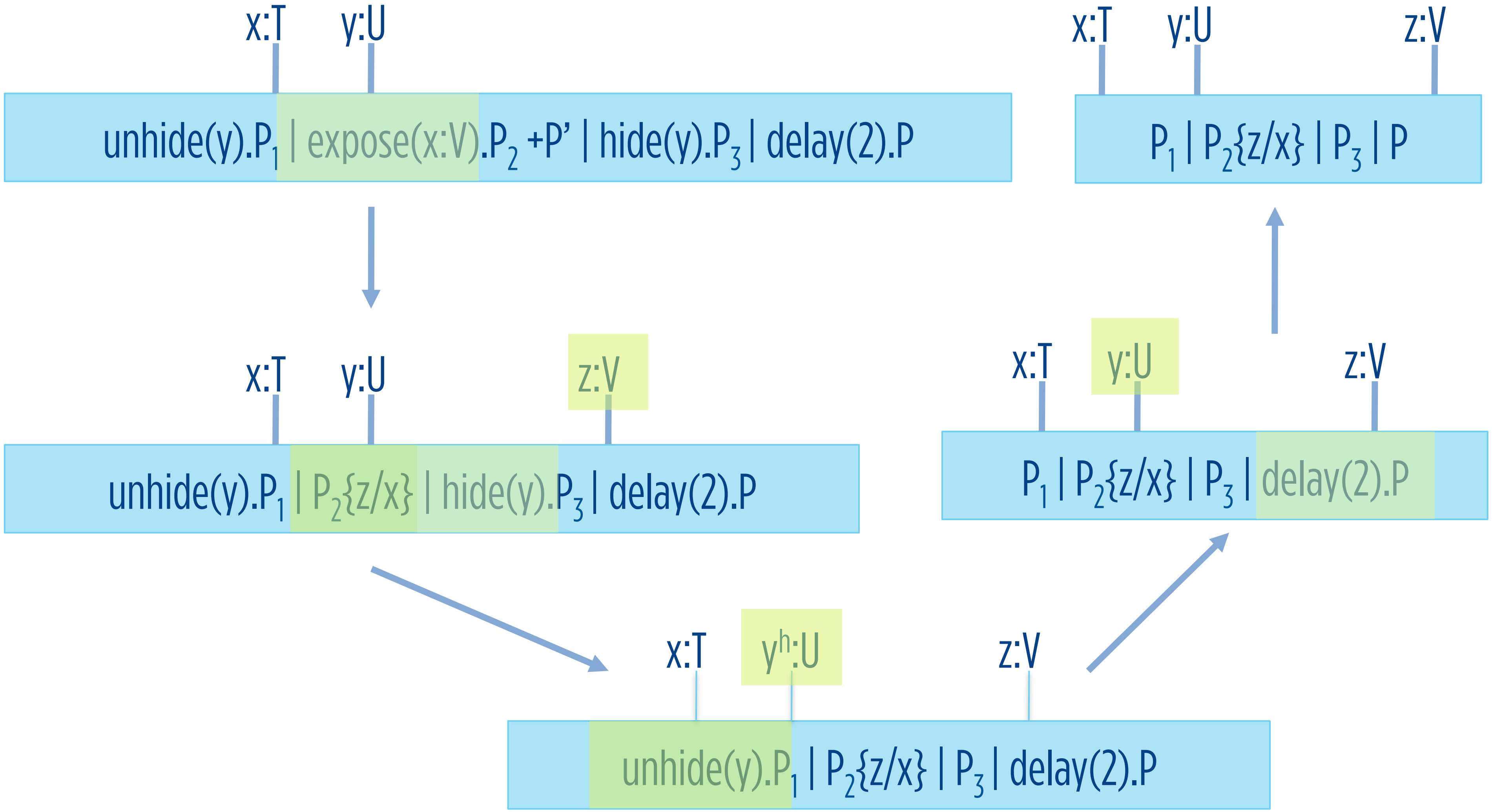
+

their amount and specificity for interaction.

ENABLING LIBRARY-BASED MODELING

Further examples and downloads: http://www.cosbi.eu/index.php/research/prototypes/beta-wb

BLENX: MONOMOLECULAR ACTIONS



x:T y:U

$\text{unhide}(y).P_1 \mid \text{expose}(x{:}V).P_2 + P' \mid \text{hide}(y).P_3 \mid \text{delay}(2).P$

x:T y:U z:V

$\text{unhide}(y).P_1 \mid P_2\{z/x\} \mid \text{hide}(y).P_3 \mid \text{delay}(2).P$

x:T y^h:U z:V

$\text{unhide}(y).P_1 \mid P_2\{z/x\} \mid P_3 \mid \text{delay}(2).P$

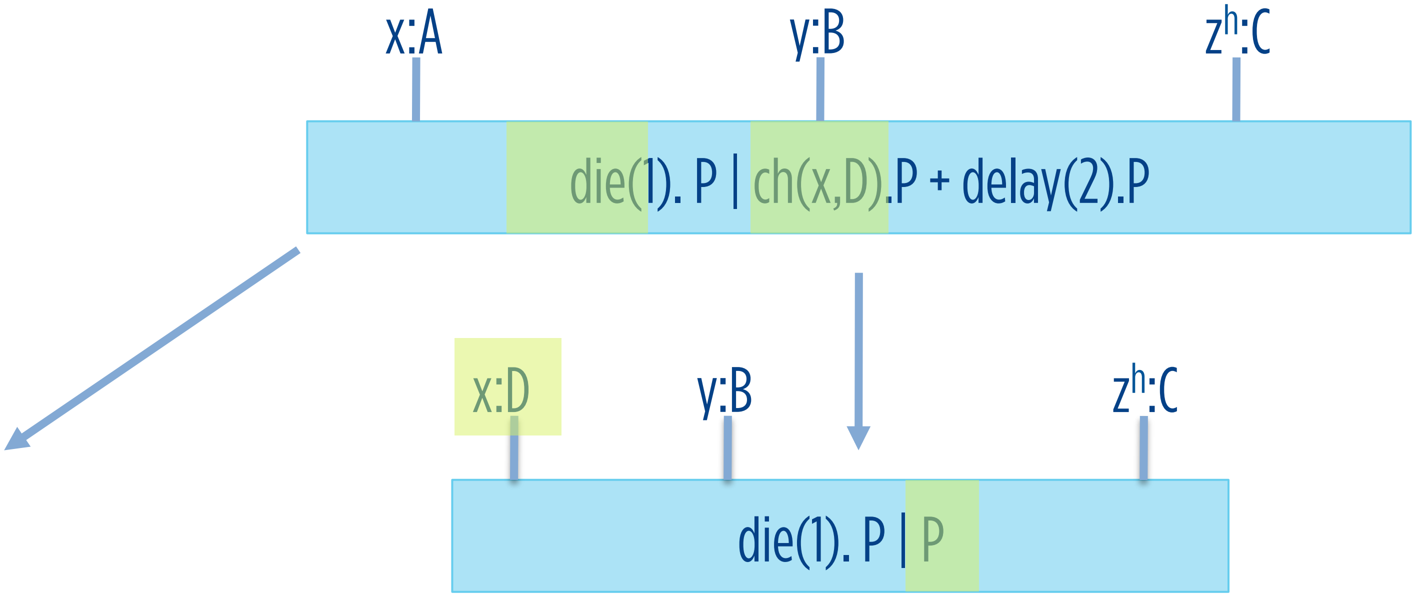
x:T y:U z:V

$P_1 \mid P_2\{z/x\} \mid P_3 \mid \text{delay}(2).P$

x:T y:U z:V

$P_1 \mid P_2\{z/x\} \mid P_3 \mid P$

BLENX: MONOMOLECULAR ACTIONS



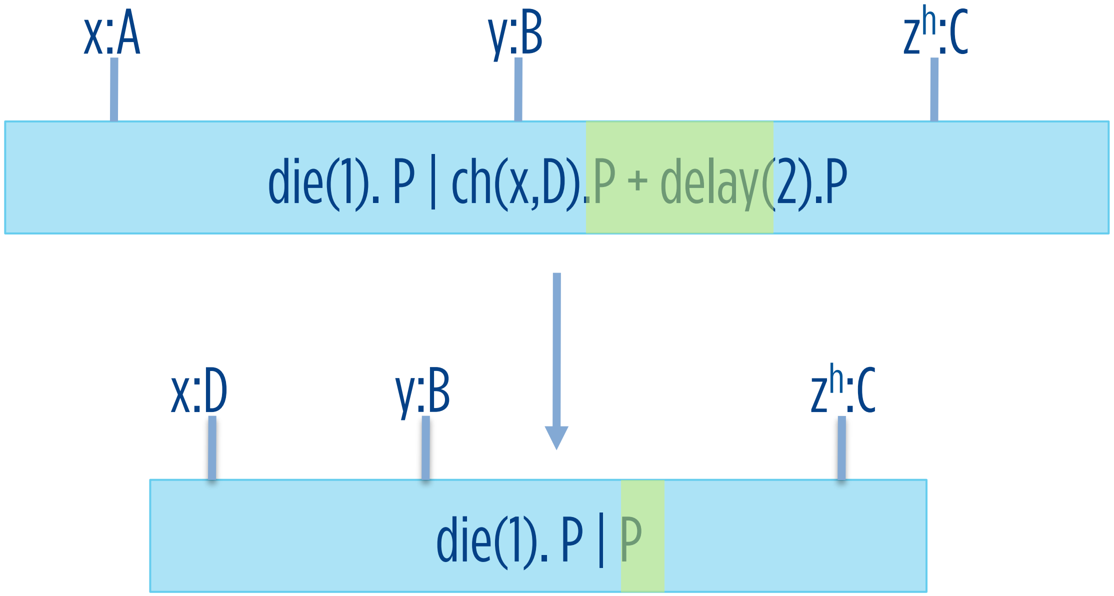
x:A y:B z^h:C

die(1). P | ch(x,D).P + delay(2).P

x:D y:B z^h:C

die(1). P | P

BLENX: MONOMOLECULAR ACTIONS



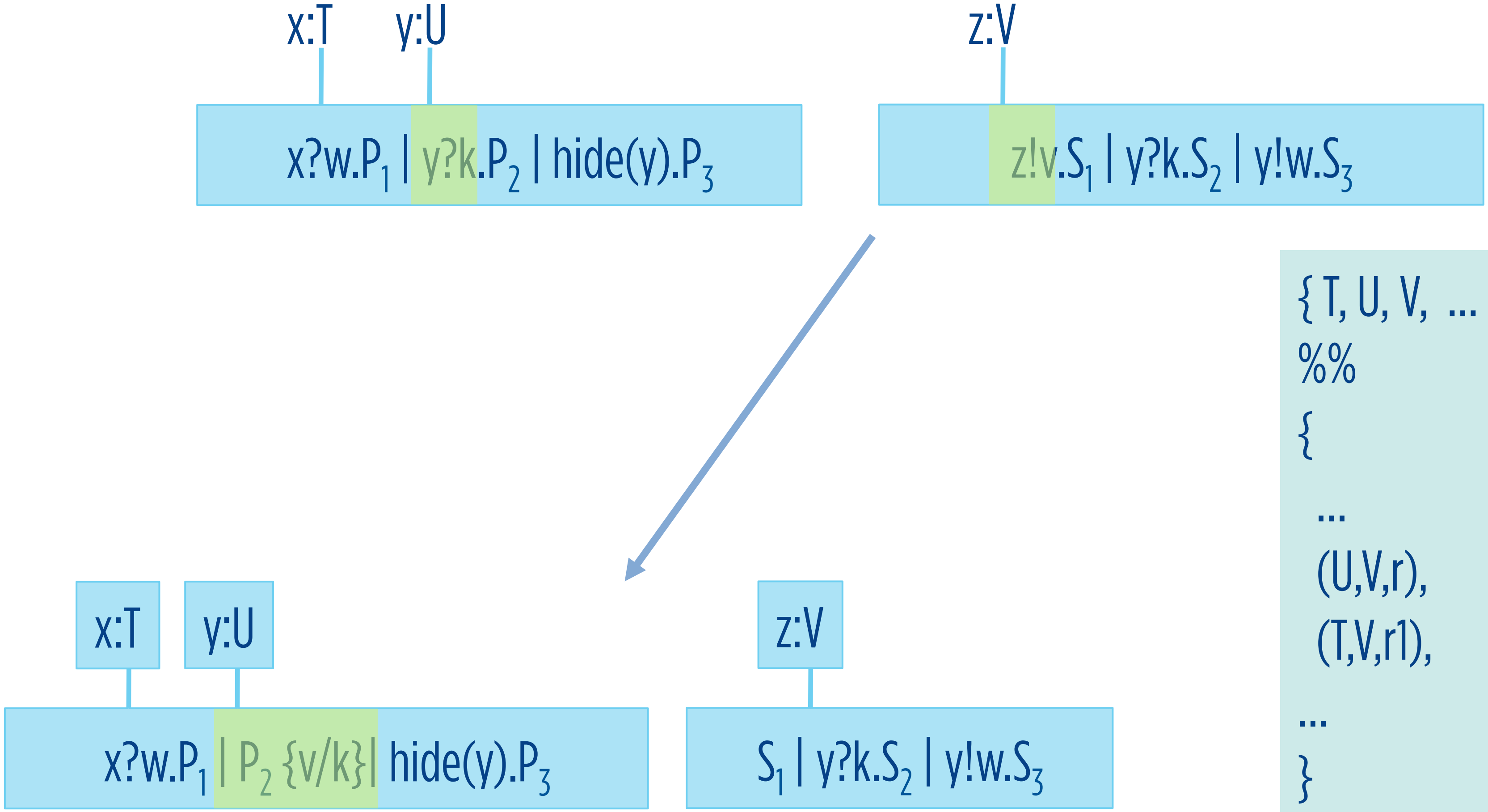
x:A y:B z^h:C

die(1). P | ch(x,D).P + delay(2).P

x:D y:B z^h:C

die(1). P | P

BLENX: BIMOLECULAR ACTIONS



$x?w.P_1 \mid y?k.P_2 \mid hide(y).P_3$

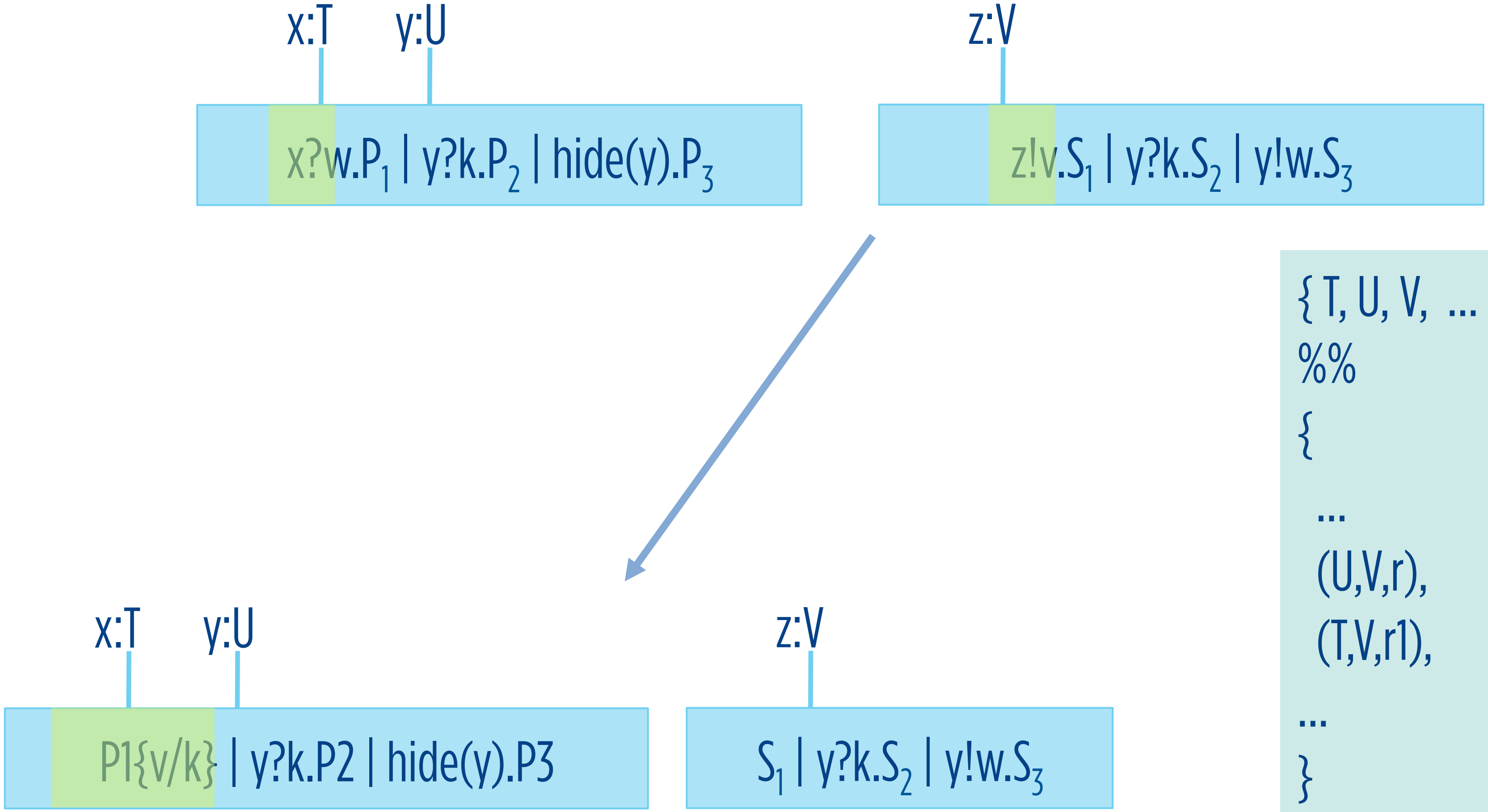
$z!v.S_1 \mid y?k.S_2 \mid y!w.S_3$

$x?w.P_1 \mid P_2\,\{v/k\} \mid hide(y).P_3$

$S_1 \mid y?k.S_2 \mid y!w.S_3$

```
{ T, U, V,  ... }
%%
{
  ...
  (U,V,r),
  (T,V,r1),
...
}
```

BLENX: BIMOLECULAR ACTIONS



x:T y:U

$x?w.P_1 \mid y?k.P_2 \mid hide(y).P_3$

z:V

$z!v.S_1 \mid y?k.S_2 \mid y!w.S_3$

x:T y:U

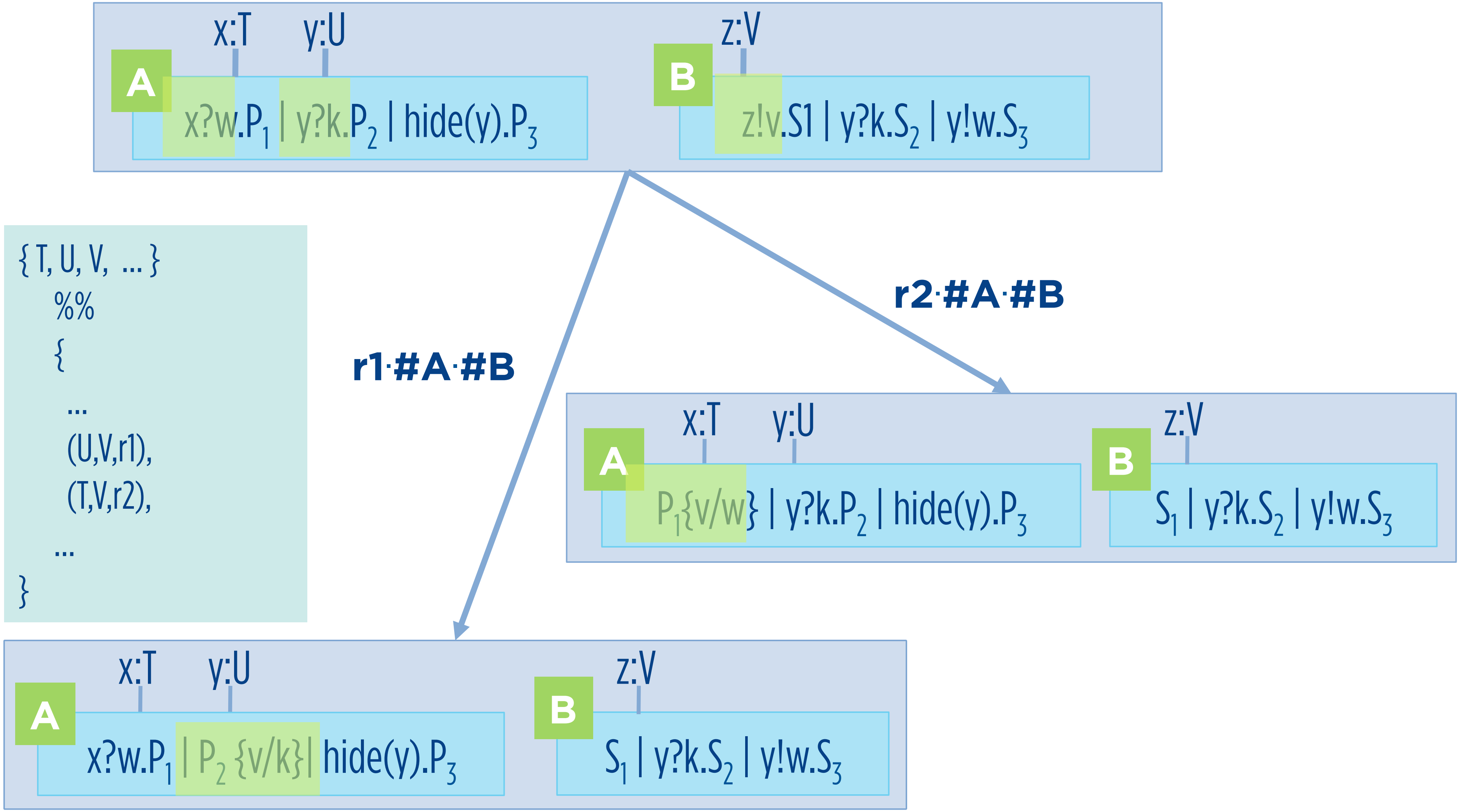
$P1\{v/k\} \mid y?k.P2 \mid hide(y).P3$

z:V

$S_1 \mid y?k.S_2 \mid y!w.S_3$

```
{ T, U, V,  ... }
%%
{
  ...
  (U,V,r),
  (T,V,r1),
...
}
```

BLENX: BIMOLECULAR ACTIONS



$x{:}T$ $y{:}U$

A $x?w.P_1 \mid y?k.P_2 \mid hide(y).P_3$

$z{:}V$

B $z!v.S1 \mid y?k.S_2 \mid y!w.S_3$

```
{ T, U, V,  ... }
   %%
   {
     ...
     (U,V,r1),
     (T,V,r2),
   ...
}
```

r1·#A·#B

$x{:}T$ $y{:}U$

A $x?w.P_1 \mid P_2\{v/k\} \mid hide(y).P_3$

$z{:}V$

B $S_1 \mid y?k.S_2 \mid y!w.S_3$

r2·#A·#B

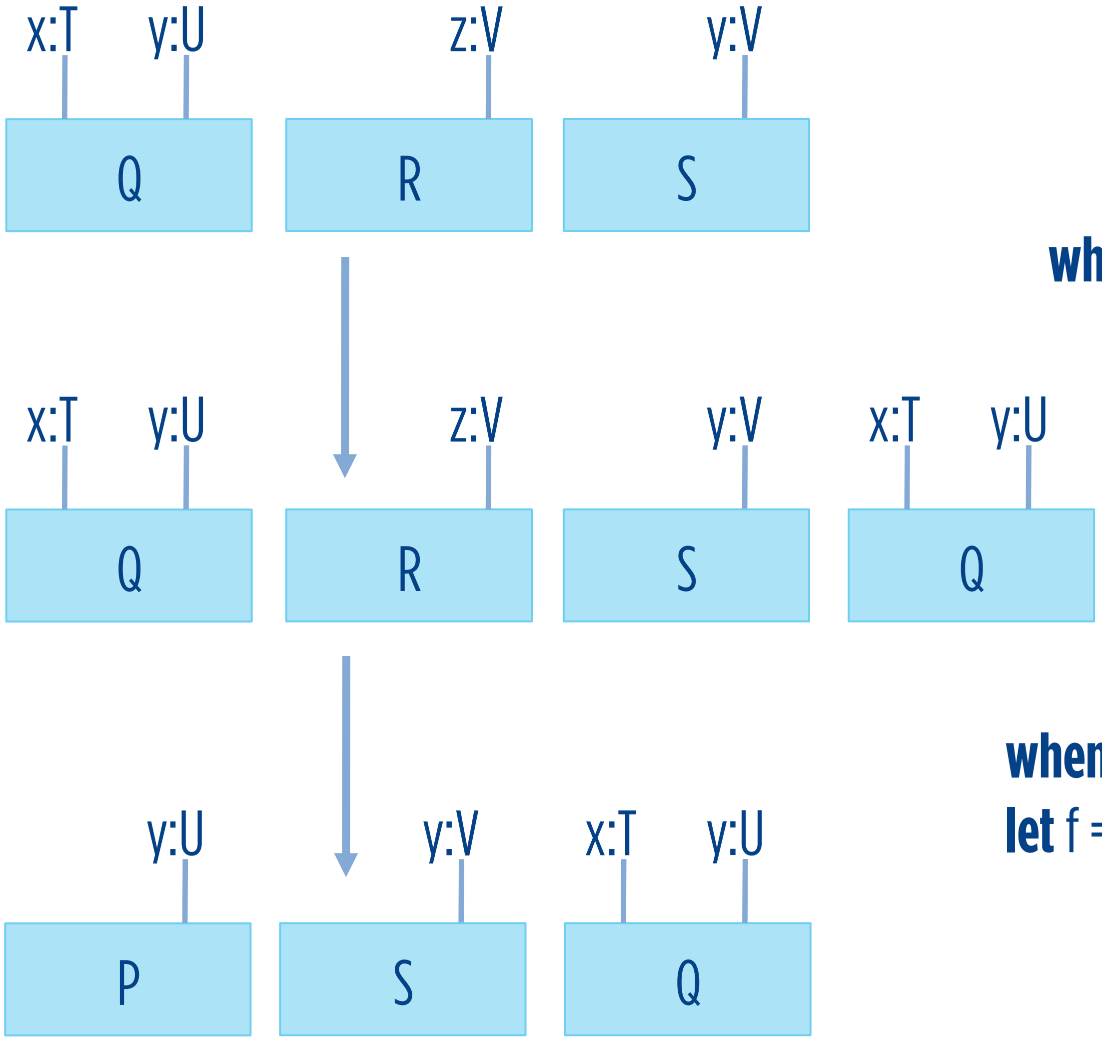
$x{:}T$ $y{:}U$

A $P_1\{v/w\} \mid y?k.P_2 \mid hide(y).P_3$

$z{:}V$

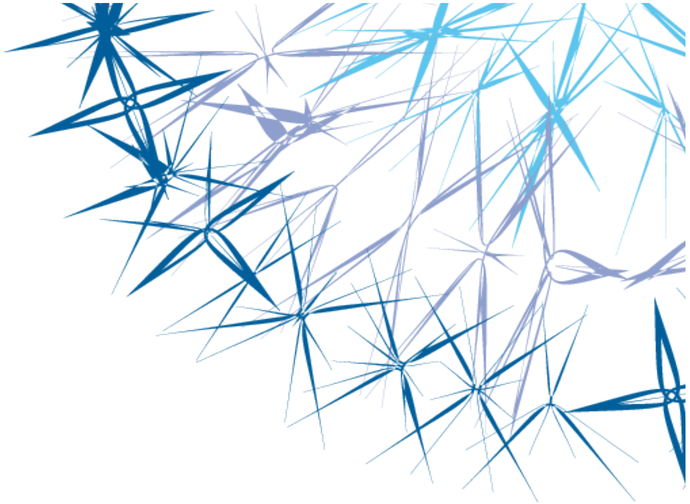
B $S_1 \mid y?k.S_2 \mid y!w.S_3$

BLENX: EVENTS



when (Q :: 10) **new** (1);

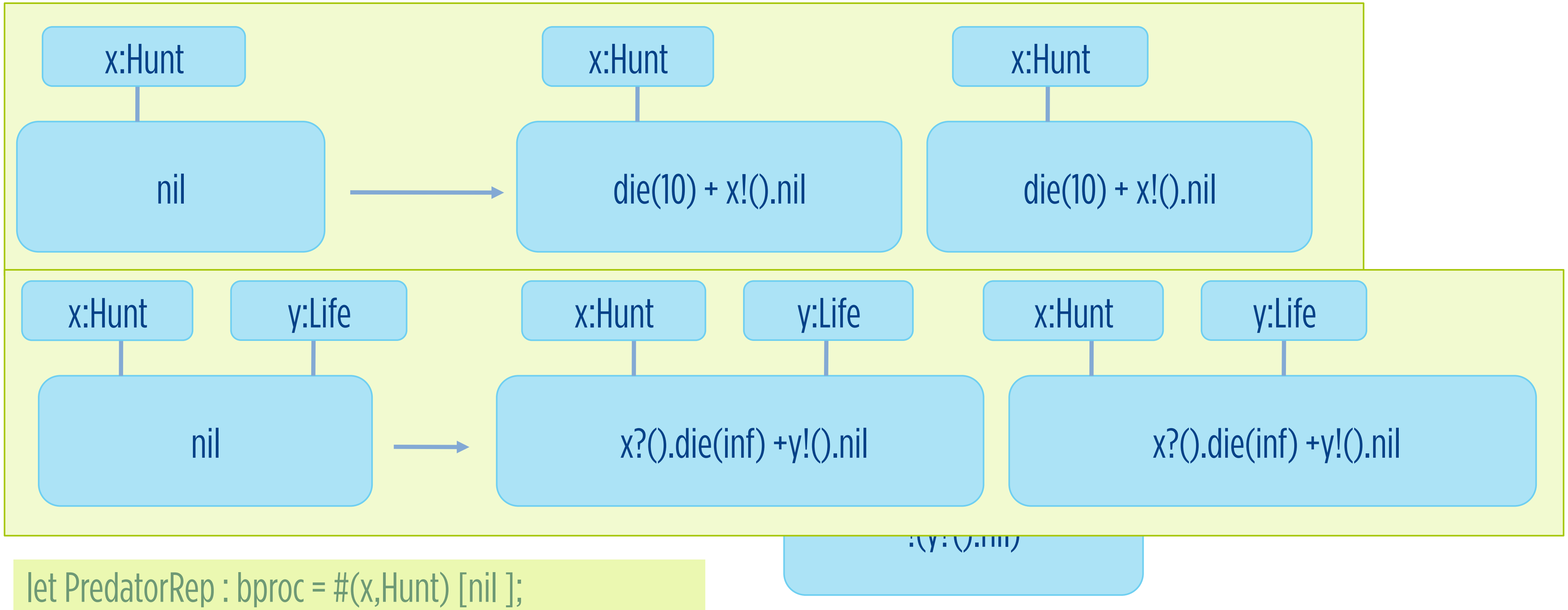
when (R , Q :: f) **join** (P);
let f = |S|*sqrt(|Q|)/k



Example

Predator - Prey

PREDATOR - PREY


x:Hunt

nil

x:Hunt

die(10) + x!().nil

x:Hunt

die(10) + x!().nil

x:Hunt

y:Life

nil

x:Hunt

y:Life

x?().die(inf) +y!().nil

x:Hunt

y:Life

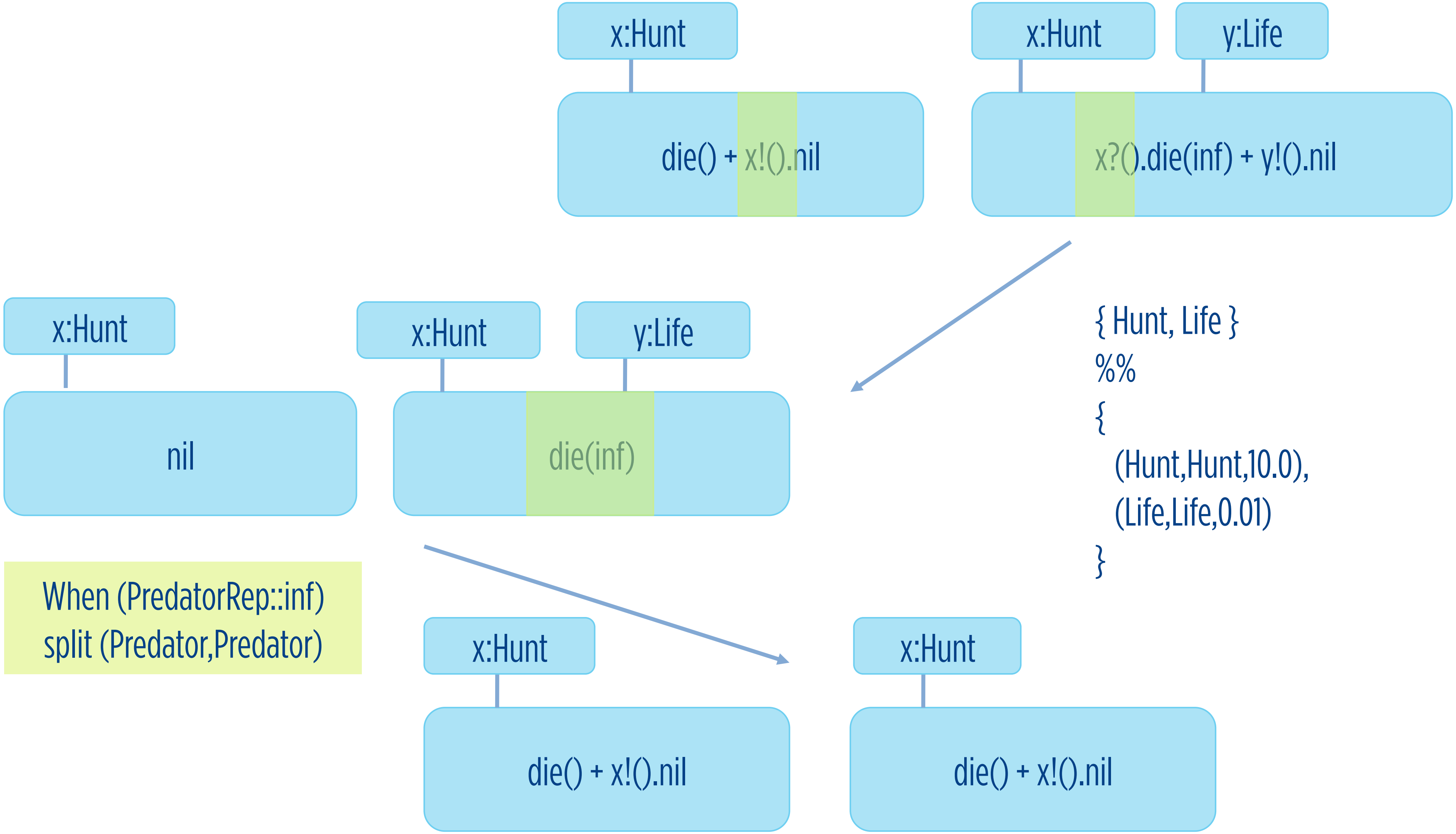
x?().die(inf) +y!().nil

```
let PredatorRep : bproc = #(x,Hunt) [nil ];
when (PredatorRep :: inf) split (Predator,Predator);
```

```
let PreyRep : bproc = #(x,Hunt),#(y,Life) [nil ];
when (PreyRep :: inf) split (Prey,Prey) ;
```

run 1000 Predator || 1000 Prey || 1 Nature

PREDATOR - PREY



x:Hunt

die() + x!().nil

x:Hunt y:Life

x?().die(inf) + y!().nil

{ Hunt, Life }
%%
{
  (Hunt,Hunt,10.0),
  (Life,Life,0.01)
}

x:Hunt

nil

x:Hunt y:Life

die(inf)

When (PredatorRep::inf)
split (Predator,Predator)

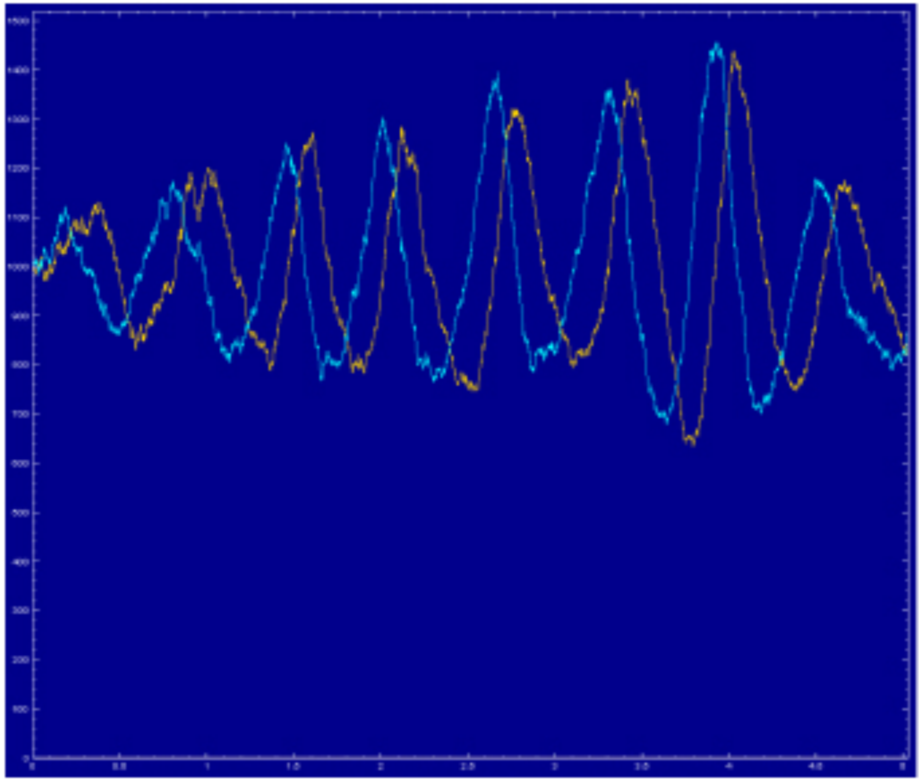
x:Hunt

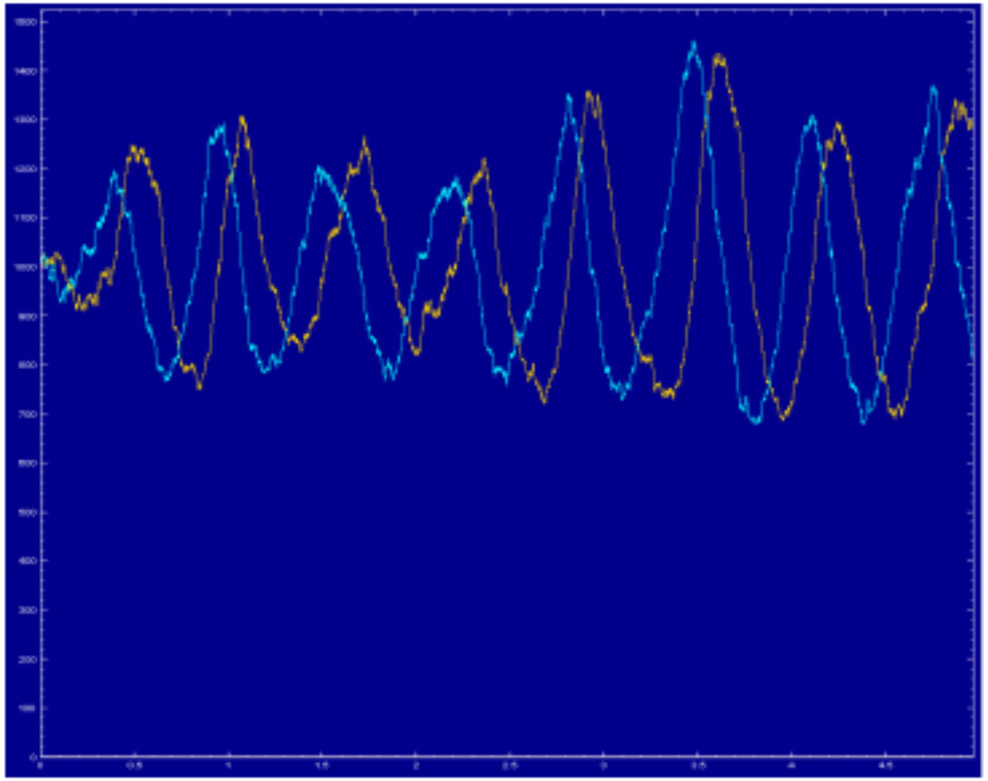
die() + x!().nil

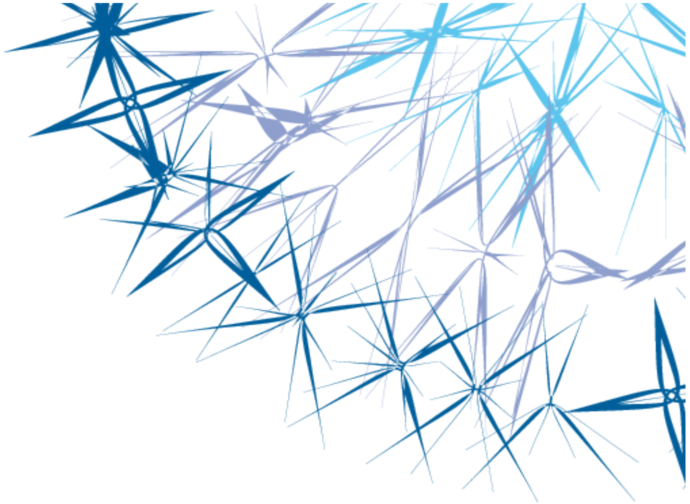
x:Hunt

die() + x!().nil

PREDATOR - PREY



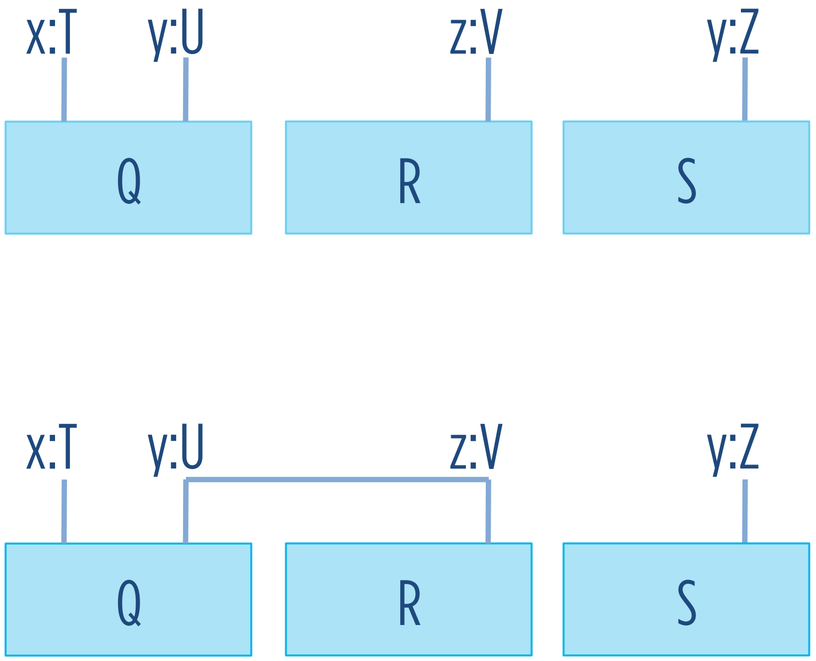




END Example

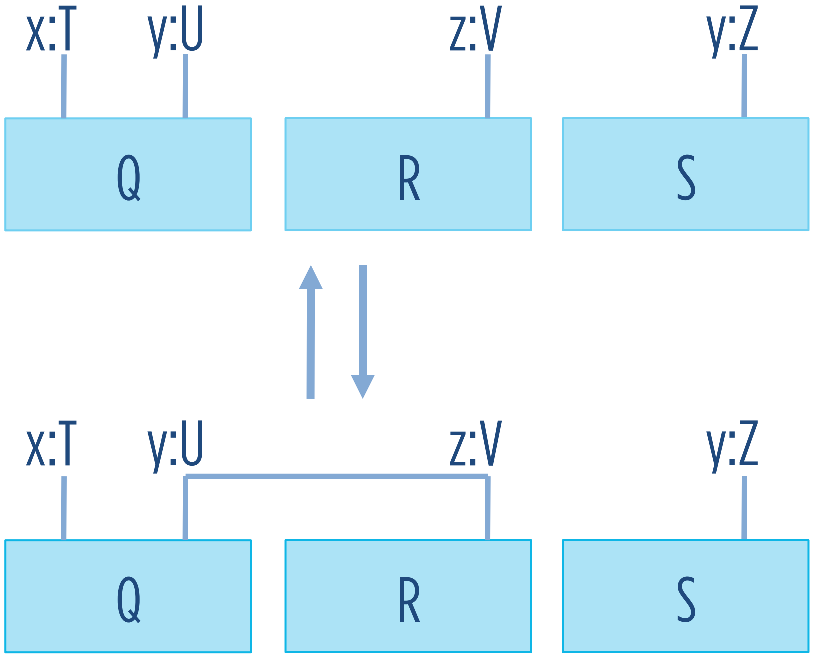
Predator - Prey

BLENX: COMPLEXES



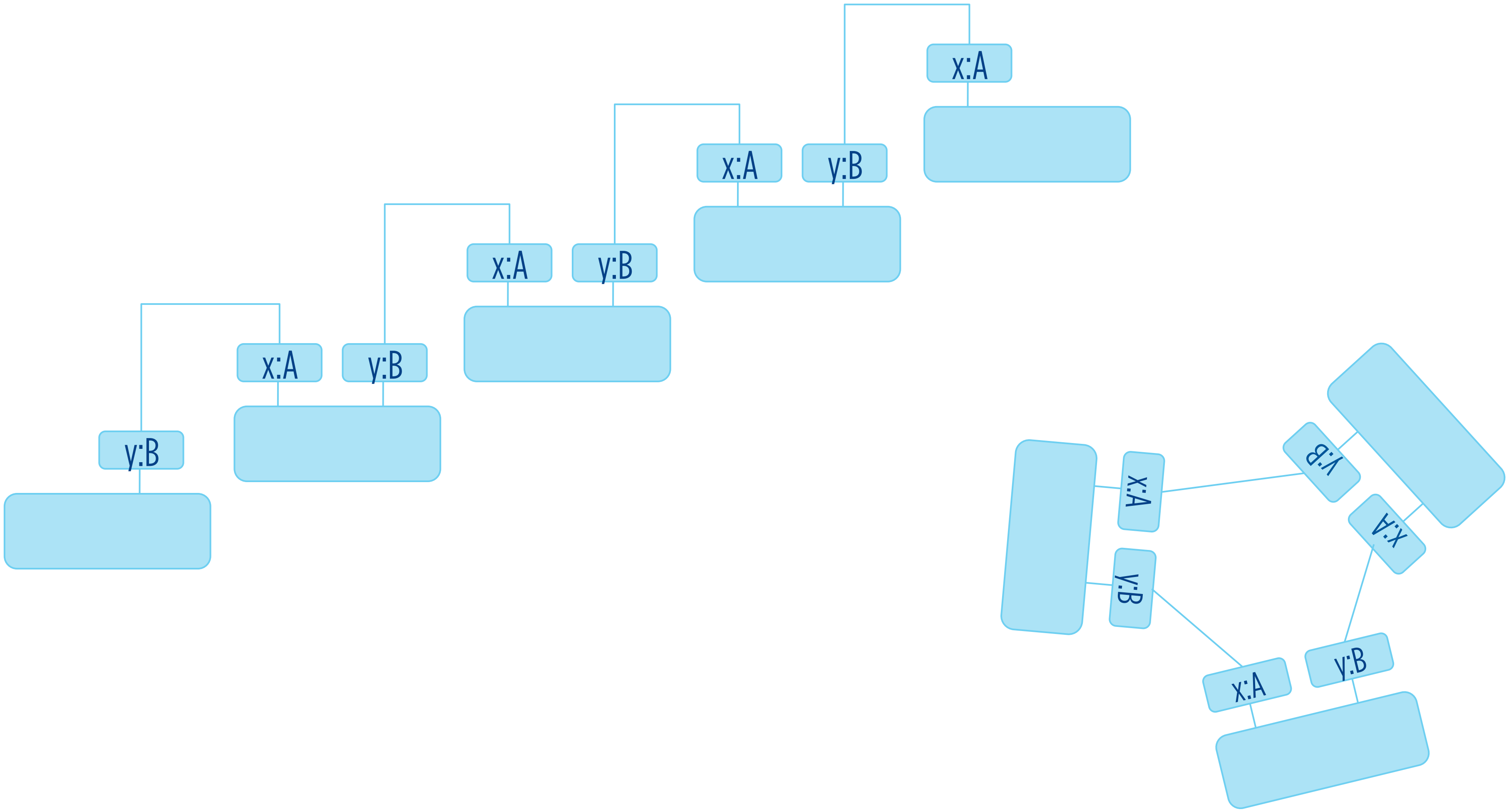
```
{ T, U, V, Z, ... }
%%
{
  (U, Z, 3.5),
  (U, V, 1.5)
}
```

BLENX: COMPLEXES



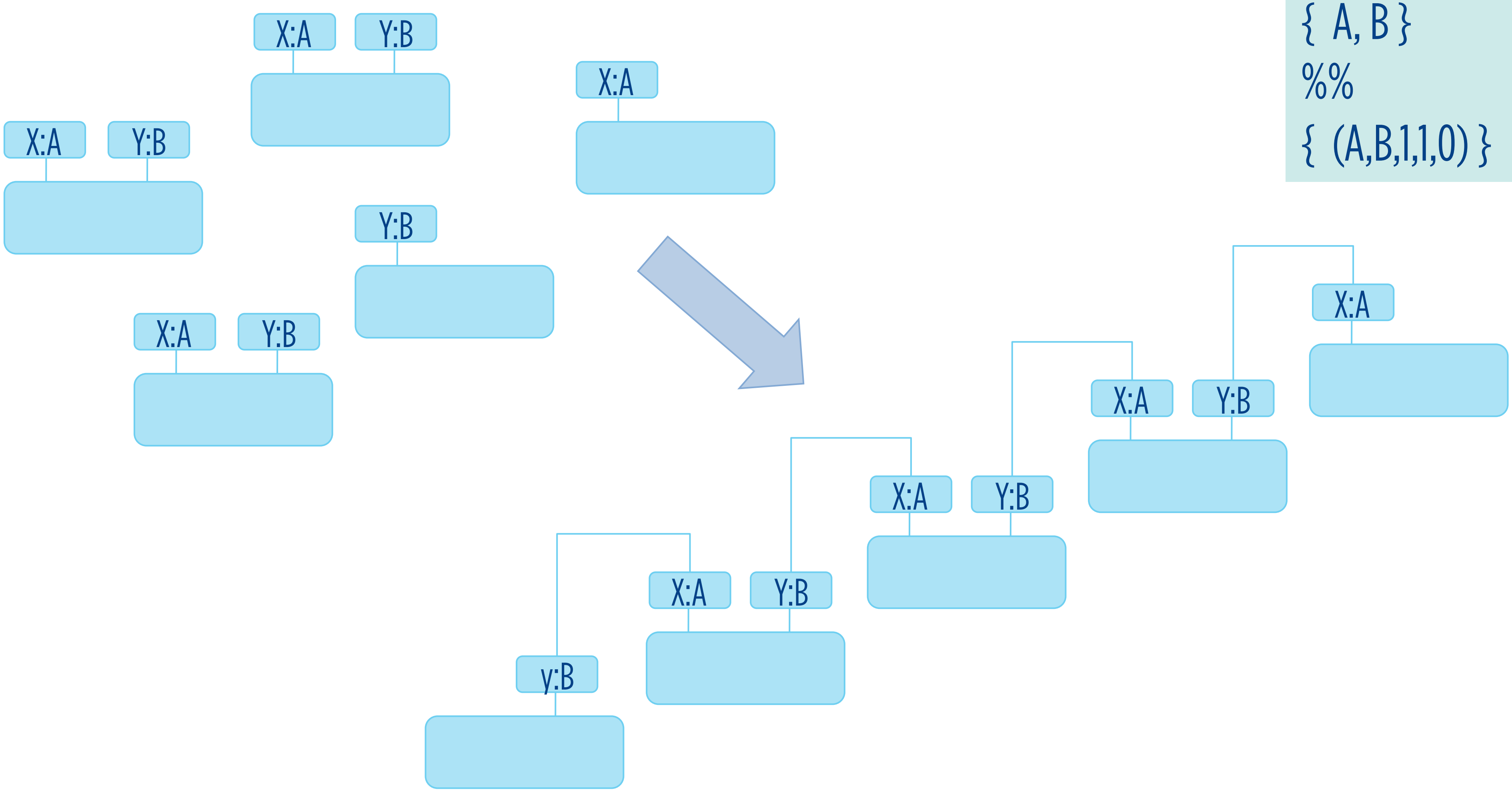
{ T, U, V, Z, ... }
%%
{
(U, Z, 3.5),
(U, V, 1.5, **2.5, 10**)
}

BLENX: STRUCTURES



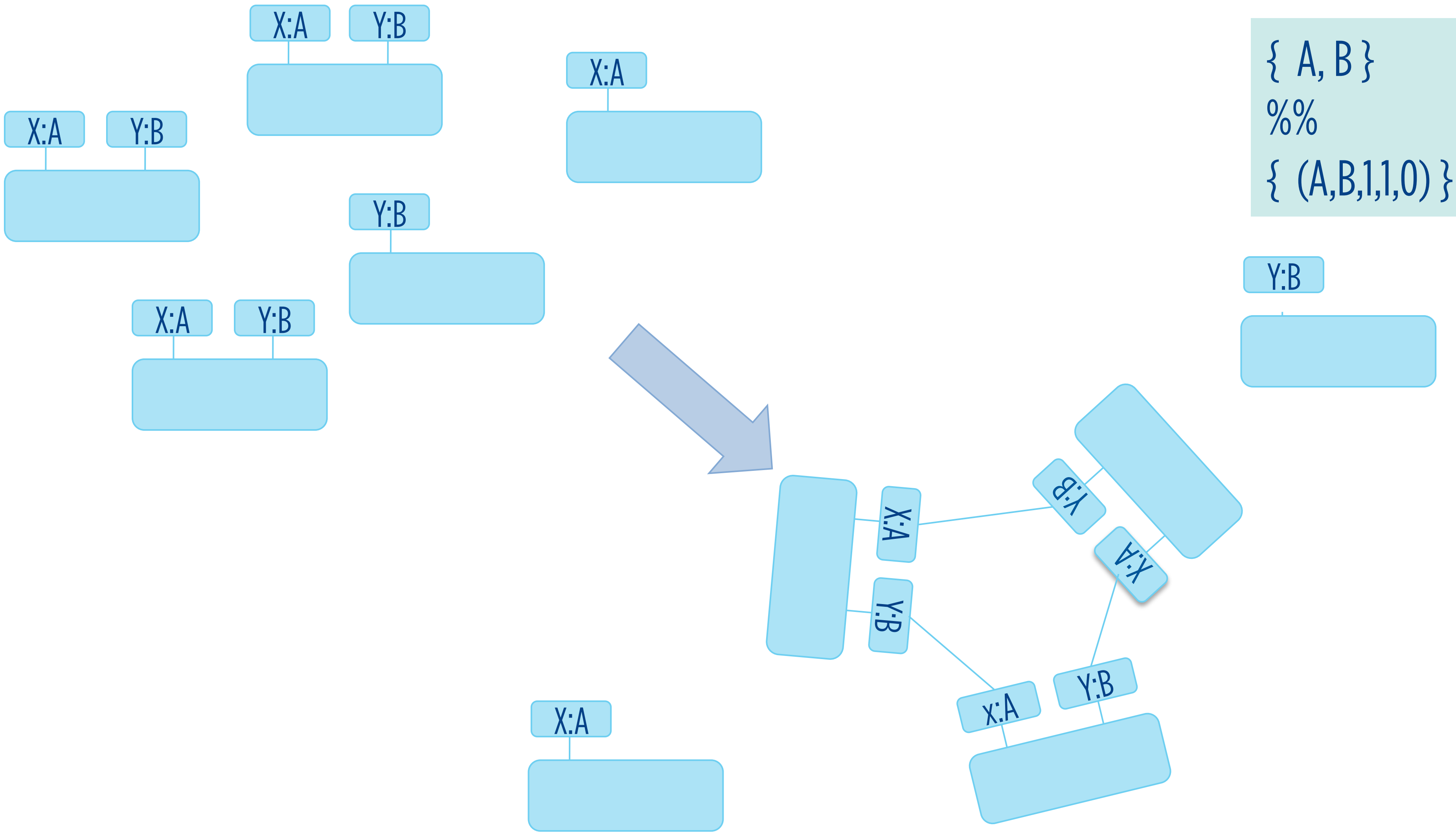
R. Larcher, C. Priami and A. Romanel. *Modelling self-assembly in BlenX*.
Transactions on Computational Systems Biology, XII:LNBI 5945, 163-198, 2010.

DYNAMICALLY CREATING STRUCTURES



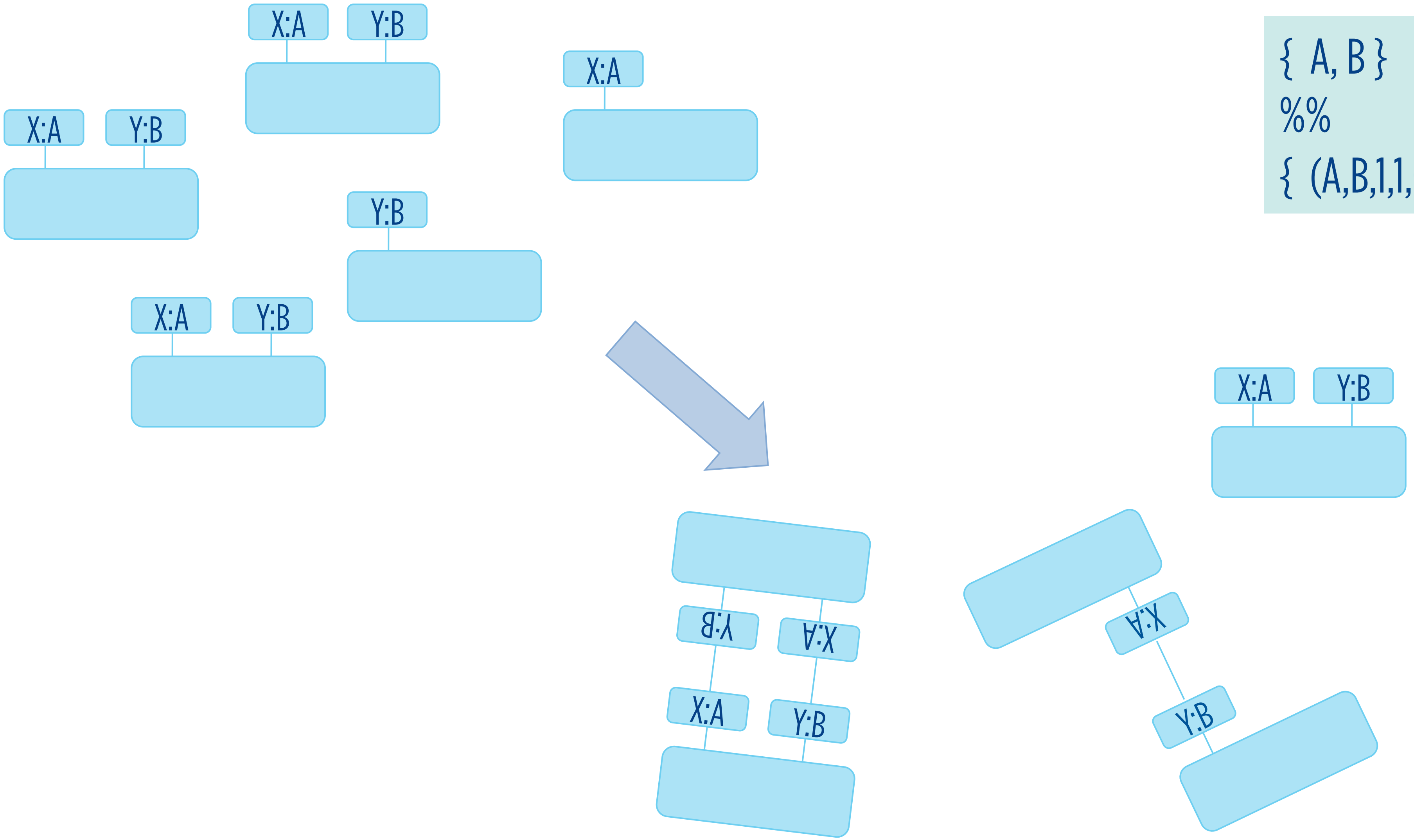
```
{ A, B }
%%
{ (A,B,1,1,0) }
```

DYNAMICALLY CREATING STRUCTURES

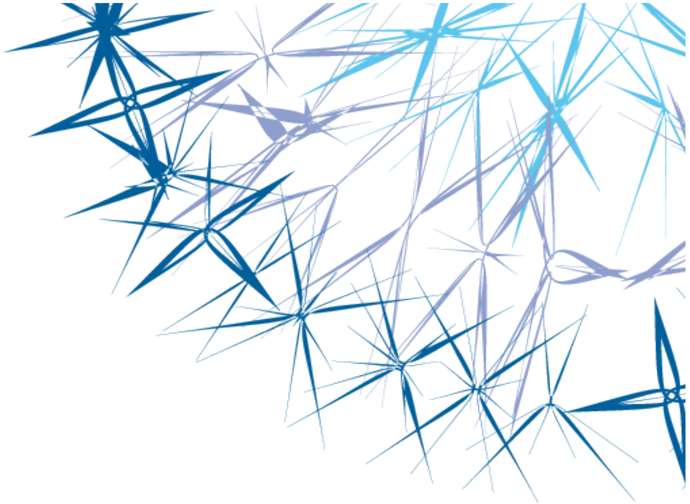


{ A, B }
%%
{ (A,B,1,1,0) }

DYNAMICALLY CREATING STRUCTURES



```
{ A, B }
%%
{ (A,B,1,1,0) }
```



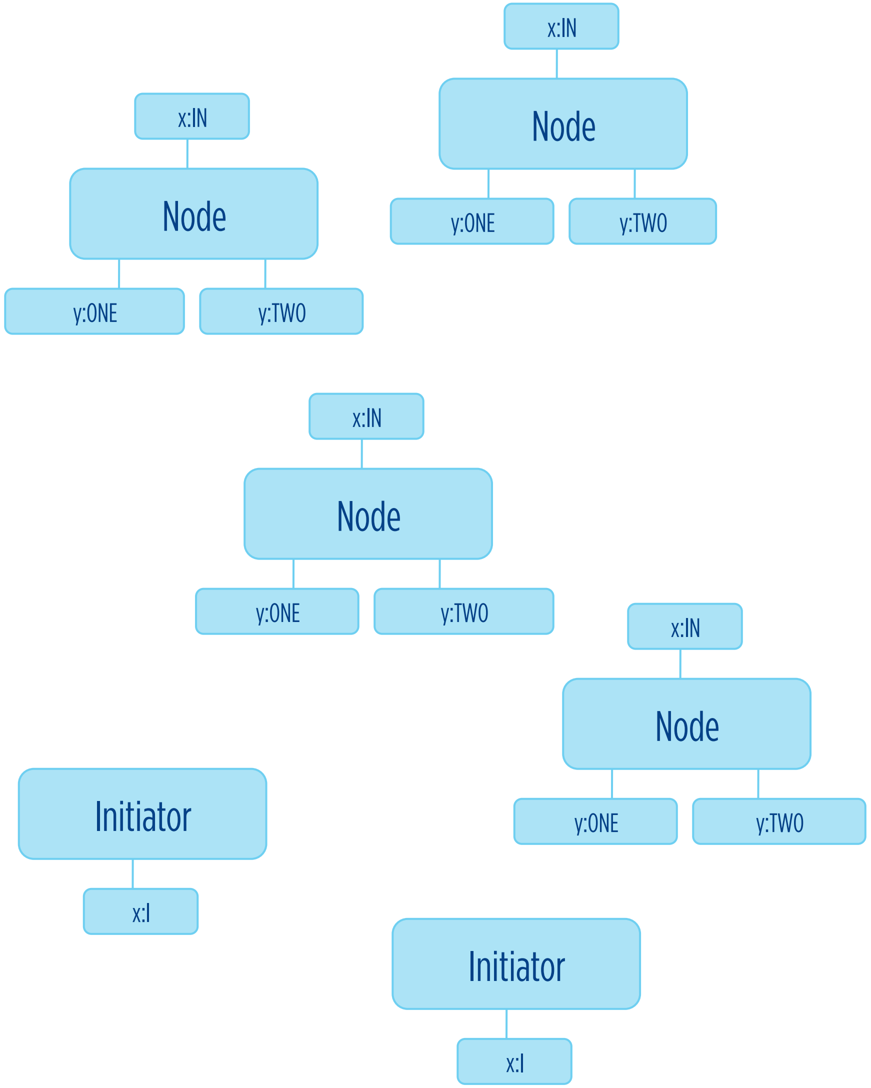
Example

SELF assembly of trees

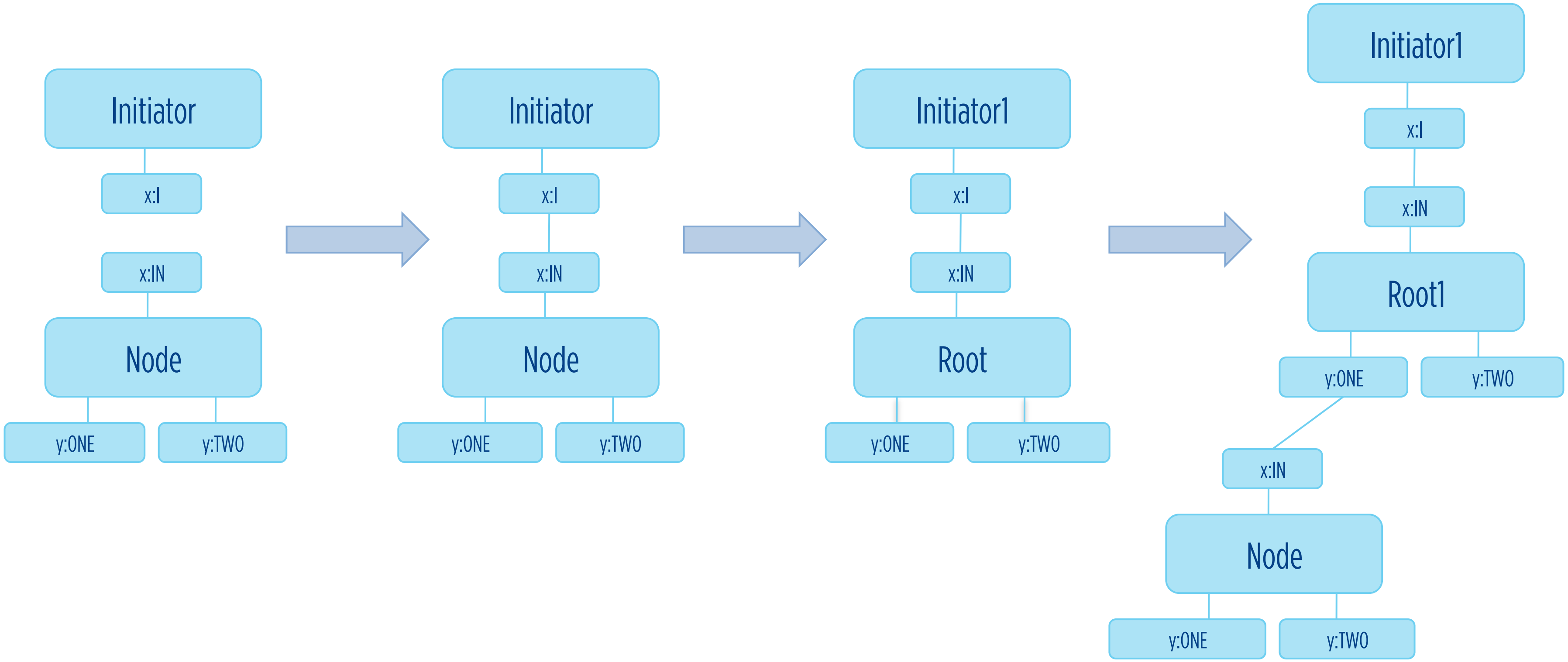
SELF ASSEMBLY OF TREES

```
// Tree.prog

[ steps = 10, delta = 10 ]

<<  BASERATE:inf, HIDE:inf, UNHIDE:inf >>

// Initiator Definition
let Initiator : bproc = #(out,I) [ out?().out!(root).nil ];

// Node Definition
let p1 : pproc = !(out1?().out2?().out1!(node).out2!(node).nil) ;
let p2 : pproc = !(out1?().out2?().inp!().inp?(m).out1!(m).out2!(m).nil) ;
let nodeP : pproc =
   inp!().inp?(t).( t!() | (
         node?().unhide(out1).unhide(out2).p2 +
          root?().unhide(out1).unhide(out2).p1
     ) );

let Node : bproc = #(inp,IN),#h(out1,ONE),#h(out2,TWO)
             [ nodeP ];

// Init
run 2 Initiator  || 10 Node
```

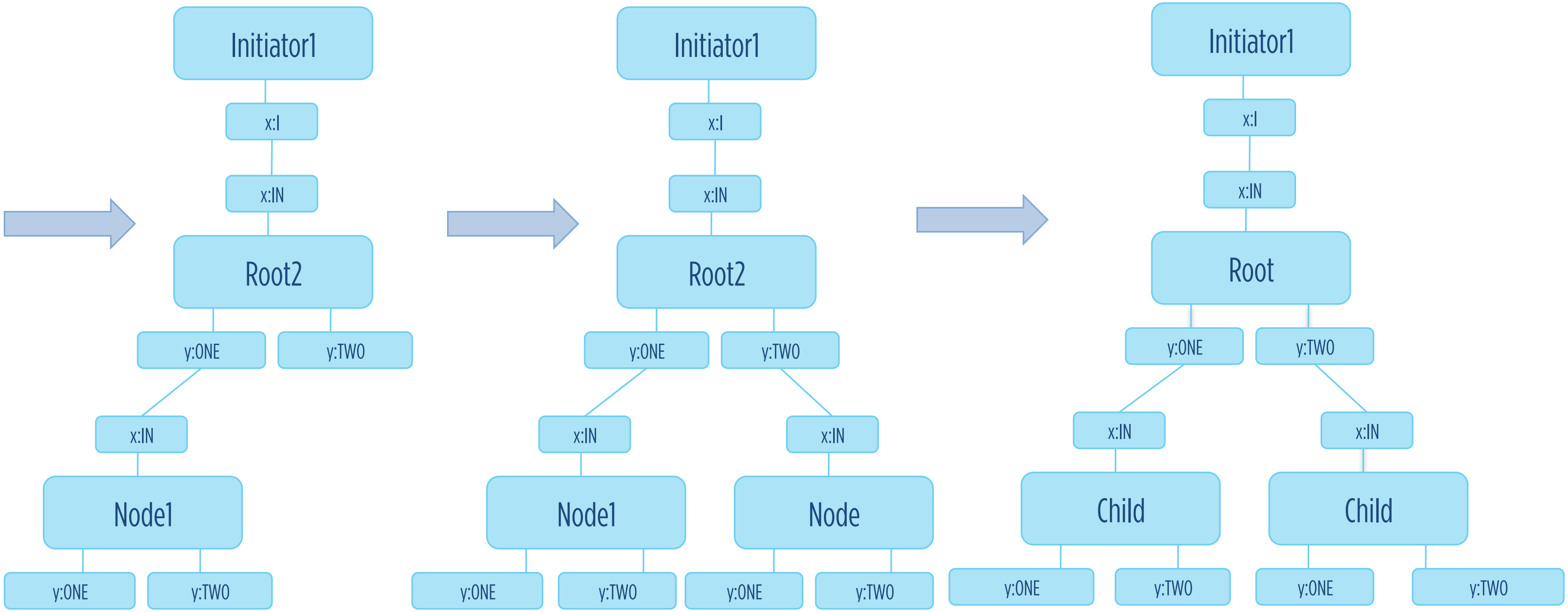
```
// Tree.types

{ I, IN, ONE, TWO }
%%
{
 (I,IN,100,0,inf),
 (ONE,IN,1,0,inf),
 (TWO,IN,1,0,inf)
}
```



SELF ASSEMBLY OF TREES



SELF ASSEMBLY OF TREES

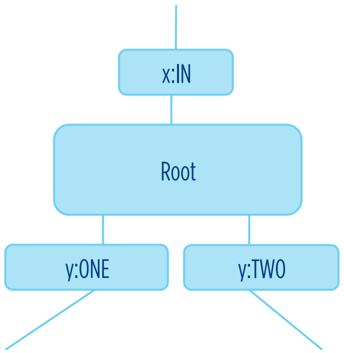


Initiator1
x:I
x:IN
Root2
y:ONE
y:TWO
x:IN
Node1
y:ONE
y:TWO

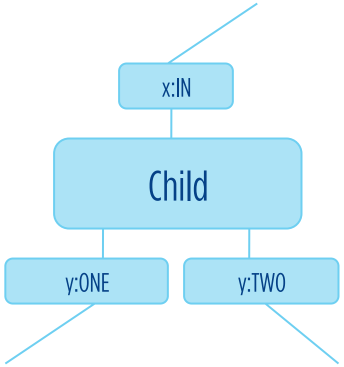
Initiator1
x:I
x:IN
Root2
y:ONE
y:TWO
x:IN
x:IN
Node1
Node
y:ONE
y:TWO
y:ONE
y:TWO

Initiator1
x:I
x:IN
Root
y:ONE
y:TWO
x:IN
x:IN
Child
Child
y:ONE
y:TWO
y:ONE
y:TWO

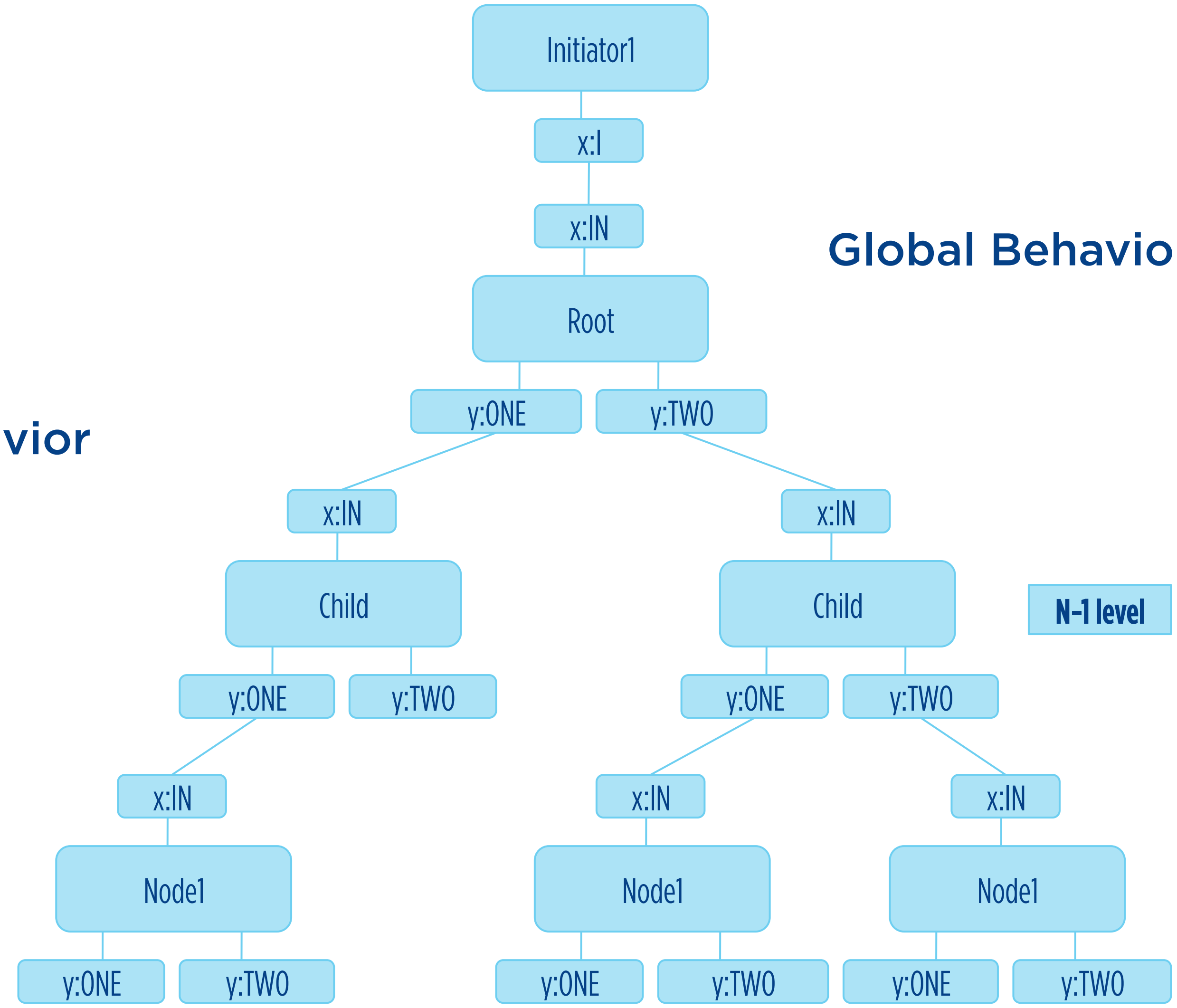
SELF ASSEMBLY OF TREES

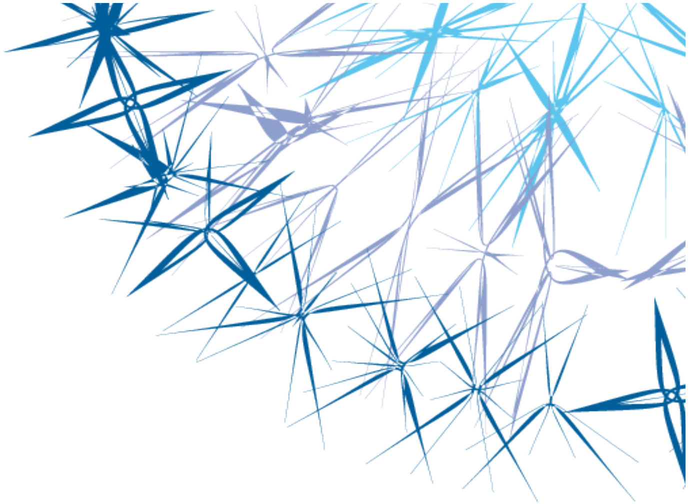


Local Behavior



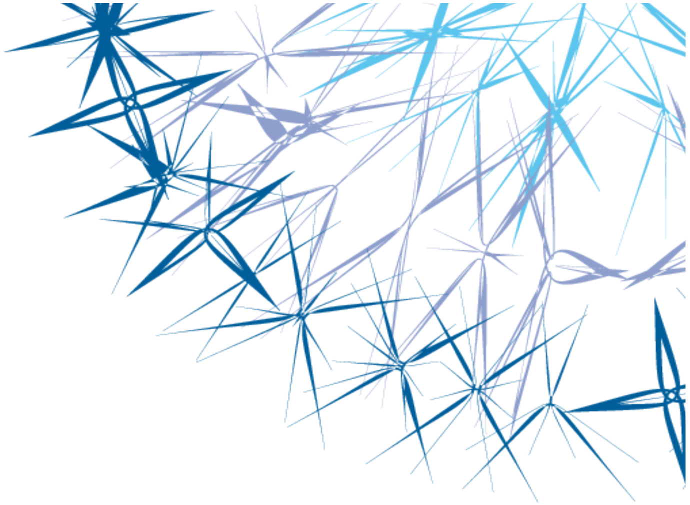
Global Behavior





END Example

SELF assembly of trees

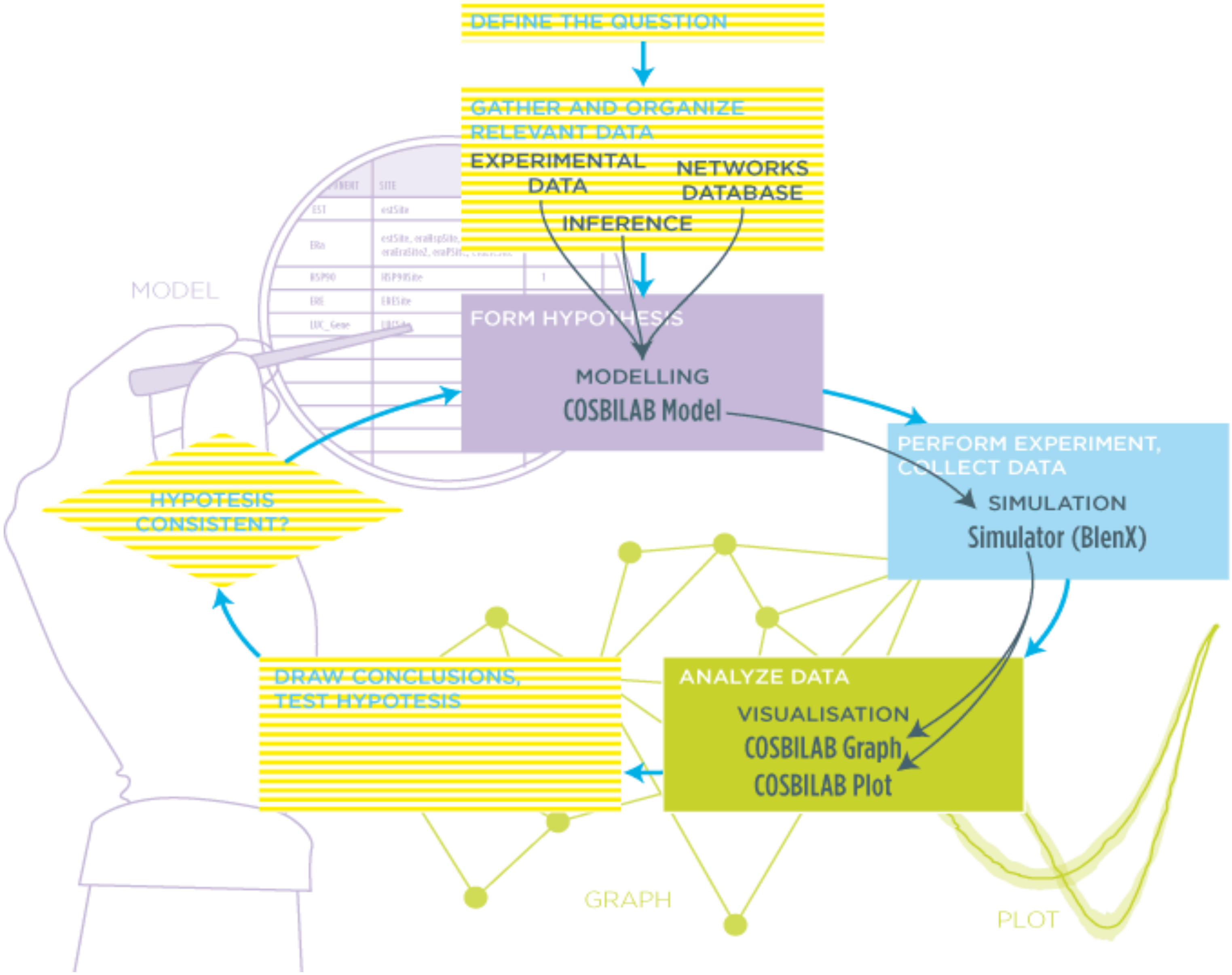


BLENX
RECAP MAIN CONCEPTS

RECAP BLENX

- Simulation and analysis (causality, logical properties)
- Scalability, modularity, compositionality
- Different levels of abstraction and refinement
- Easy models, easy libraries due to combinatorial effects ruled out at modeling level
- Executable vs. solvable specifications, modules vs. variables, dynamic relations vs. static relations

COSBI WORKING FLOW



DEFINE THE QUESTION

GATHER AND ORGANIZE RELEVANT DATA

EXPERIMENTAL DATA

NETWORKS DATABASE

INFERENCE

FORM HYPOTHESIS

MODELLING

COSBILAB Model

PERFORM EXPERIMENT, COLLECT DATA

SIMULATION

Simulator (BlenX)

ANALYZE DATA

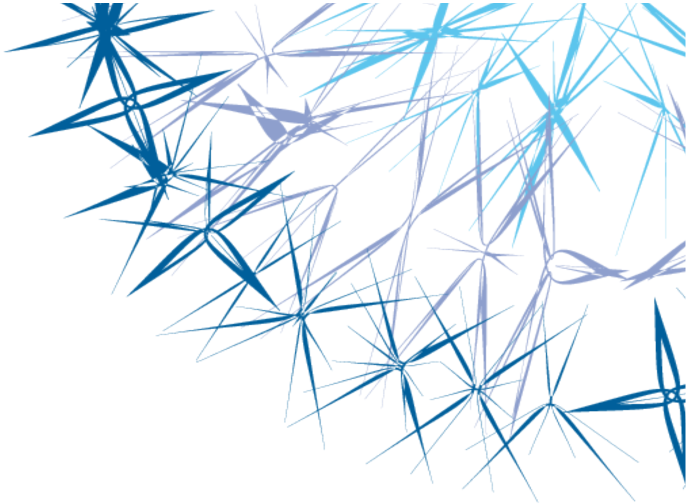
VISUALISATION

COSBILAB Graph

COSBILAB Plot

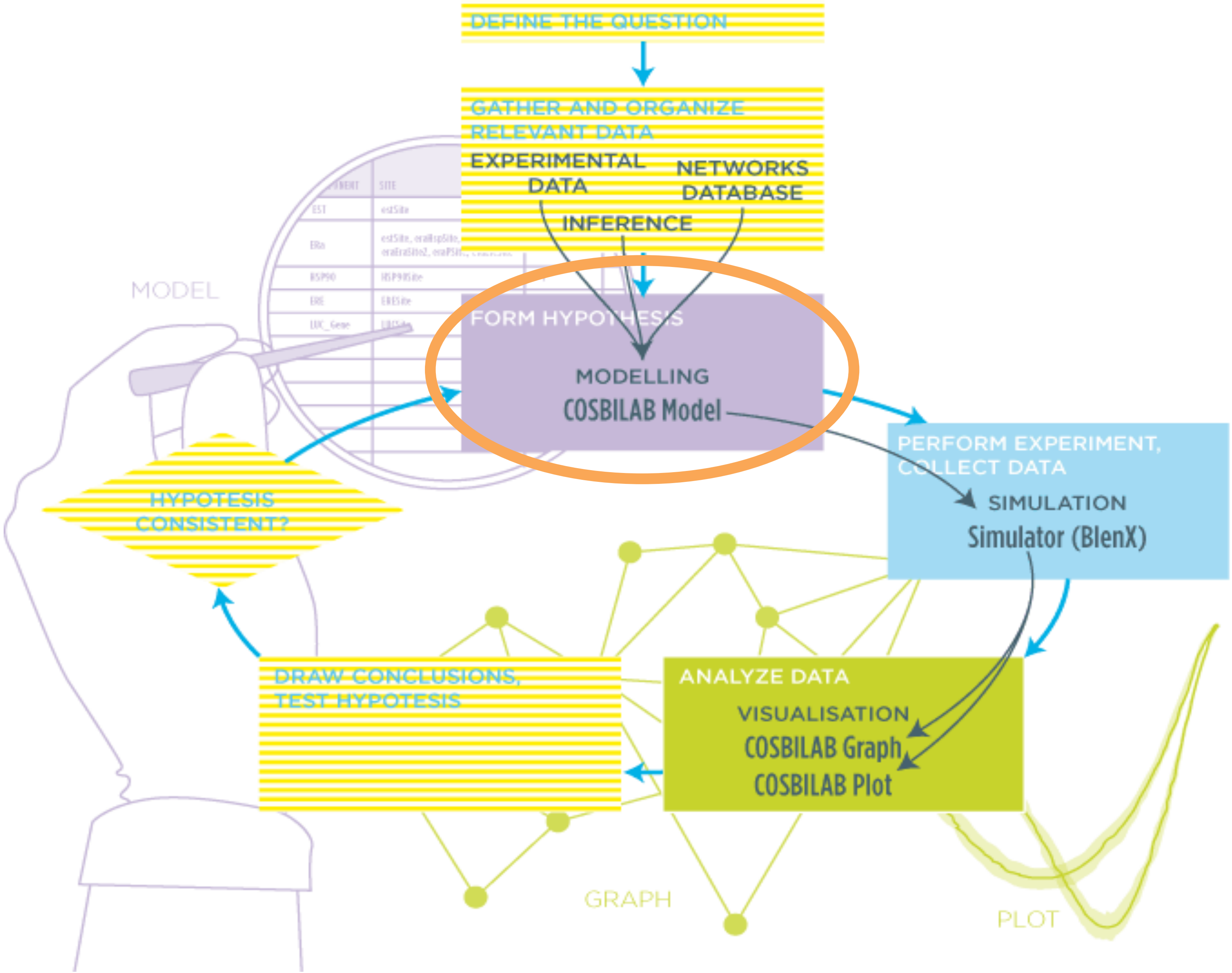
DRAW CONCLUSIONS, TEST HYPOTESIS

HYPOTESIS CONSISTENT?



Usability of the framework

COSBI WORKING FLOW



DEFINE THE QUESTION

GATHER AND ORGANIZE RELEVANT DATA

EXPERIMENTAL DATA

NETWORKS DATABASE

INFERENCE

FORM HYPOTHESIS

MODELLING

COSBILAB Model

PERFORM EXPERIMENT, COLLECT DATA

SIMULATION

Simulator (BlenX)

ANALYZE DATA

VISUALISATION

COSBILAB Graph

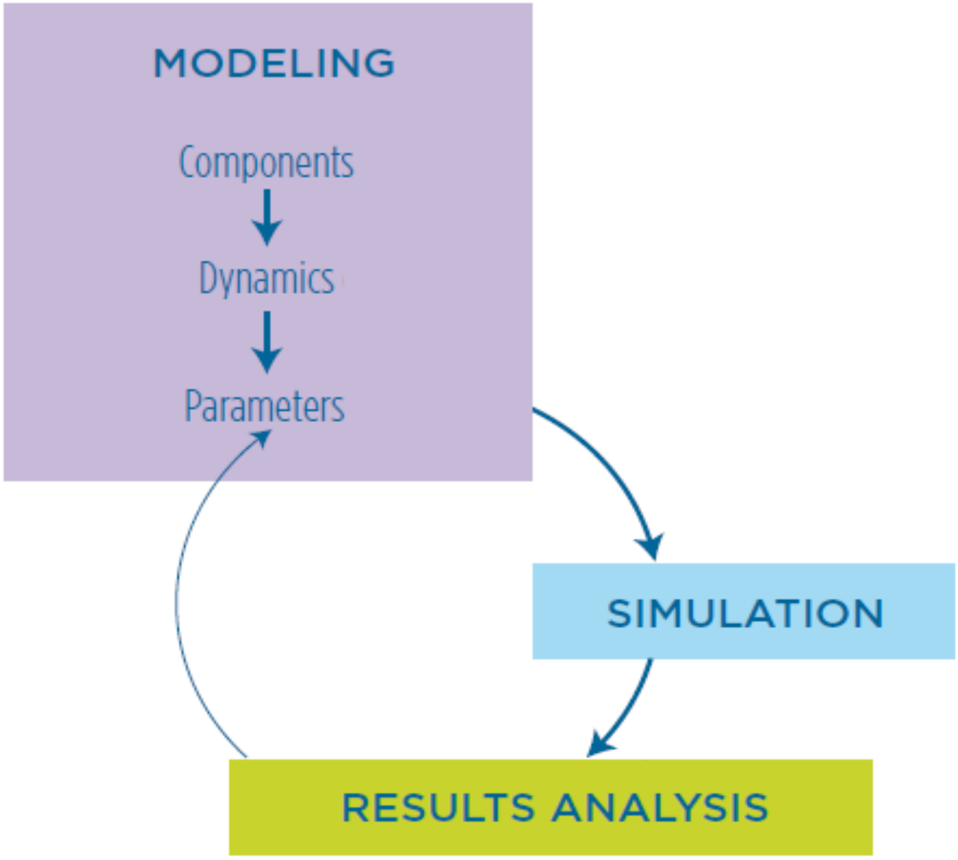
COSBILAB Plot

DRAW CONCLUSIONS, TEST HYPOTESIS

HYPOTESIS CONSISTENT?

MODELING WORKFLOW

- *Components* represent the biological entities acting in the scenario;
- Interaction rules are specified in an **intelligible, narrative language;**
- Kinetic *parameters* are summarized in a single page from where users can perform multiple **in silico experiments**;
- An integrated, stochastic simulation engine (based on the **Gillespie algorithm**) is included;
- Models are translated to BlenX, a lower level modeling language for biological systems.



MODELING

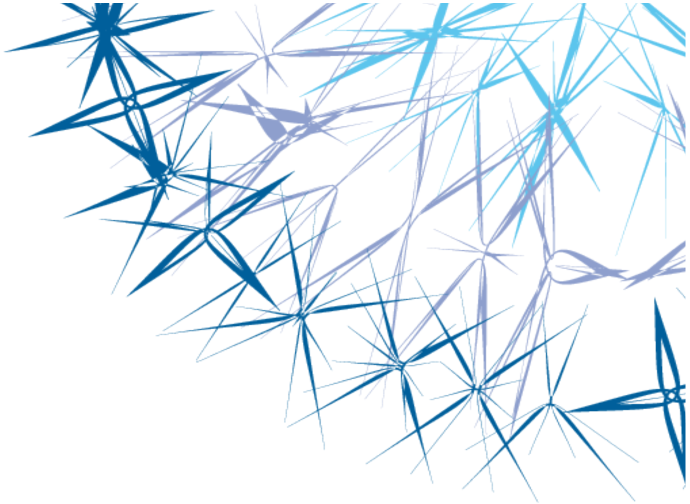
Components

Dynamics

Parameters

SIMULATION

RESULTS ANALYSIS



Programming without programming

COSBILAB MODEL

High-level, tabular interface for BlenX

Hiding programming details from BlenX users

Strongly inspired to a narrative language

M.L. Guerriero, J. Heath and C. Priami. *An automated translation from a narrative language for biological modelling into process algebra*. Proceedings of CMSB07, **LNBI 4695**, 136-151, Springer, 2007.

M.L. Guerriero, A. Dudka, N. Underhill-Day, J.K. Heath, C. Priami. *Narrative-based computational modelling of the Gp130/JAK/STAT signalling pathway*. **BMC Systems Biology, 3**:40, 2009.

C. Priami, P. Ballarini and P. Quaglia *BlenX4Bio: BlenX for Biologists*. Proceedings of CMSB09, **LNBI 5688**, Springer, 2009.

COSBI MODELING PHILOSOPHY

Intelligible models:

- Understandable to non-expert modelers
- Easy to write, modify and reuse
- Manage combinatorial complexity of dynamics

INTELLIGIBILITY

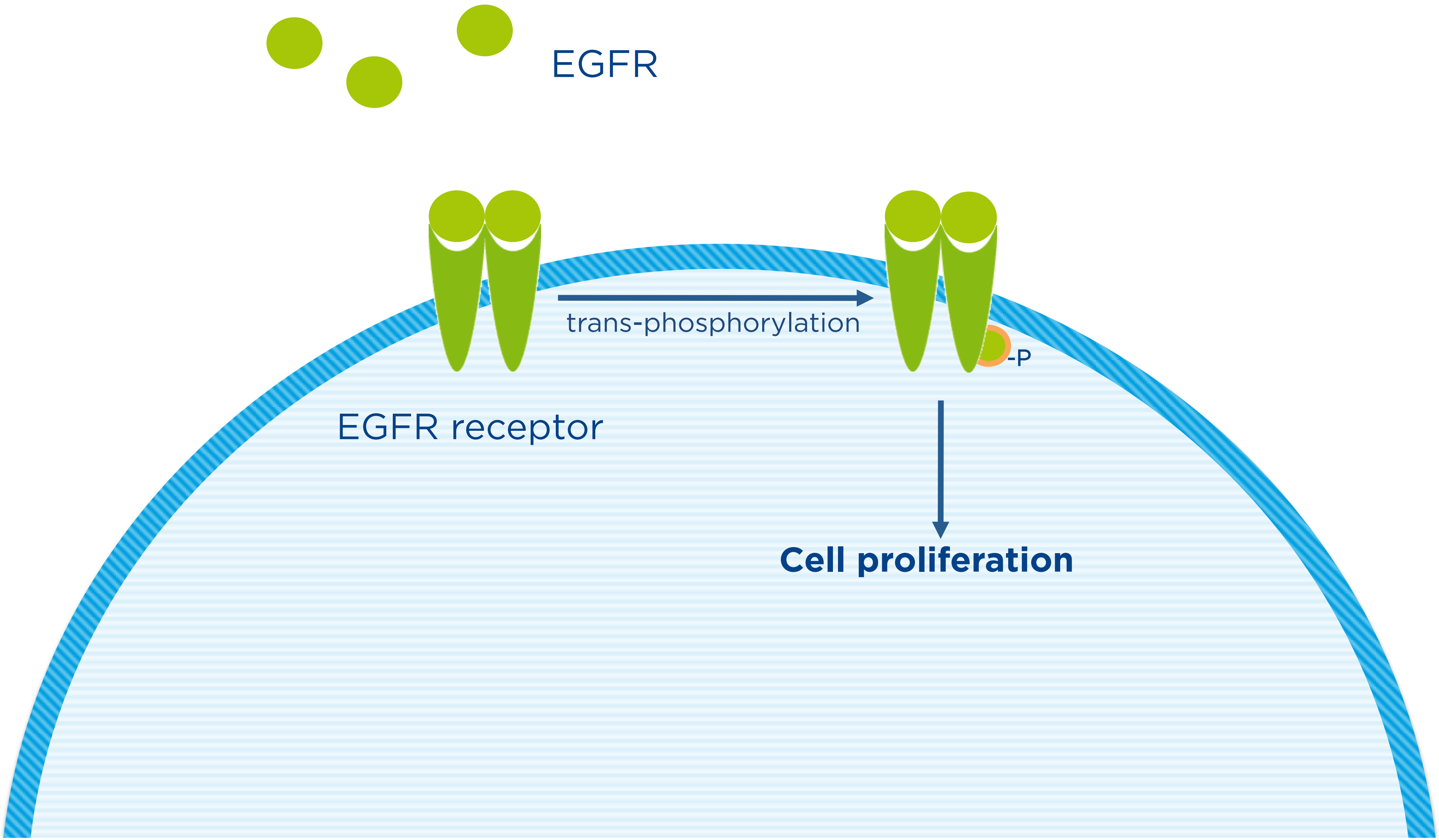
- Obscure syntax
- No bio keywords

Narrative Language

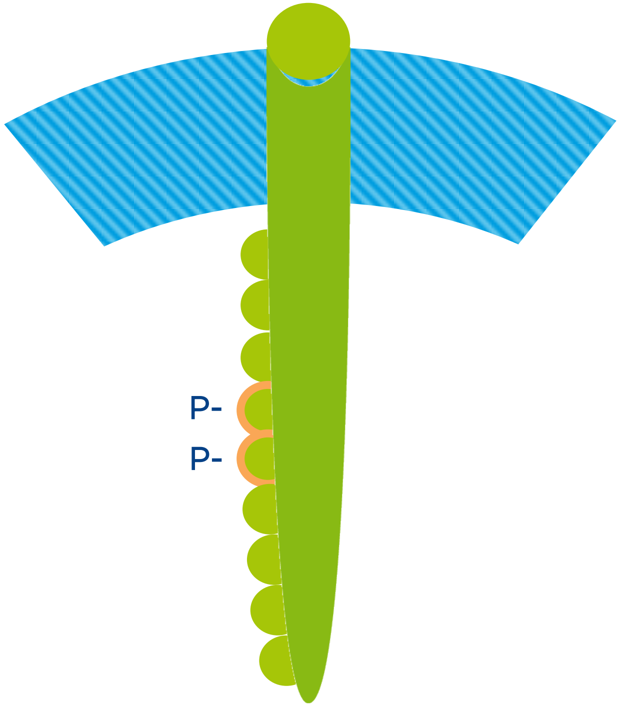
- Large size
- Complex mathematics

Minimize required modeling information

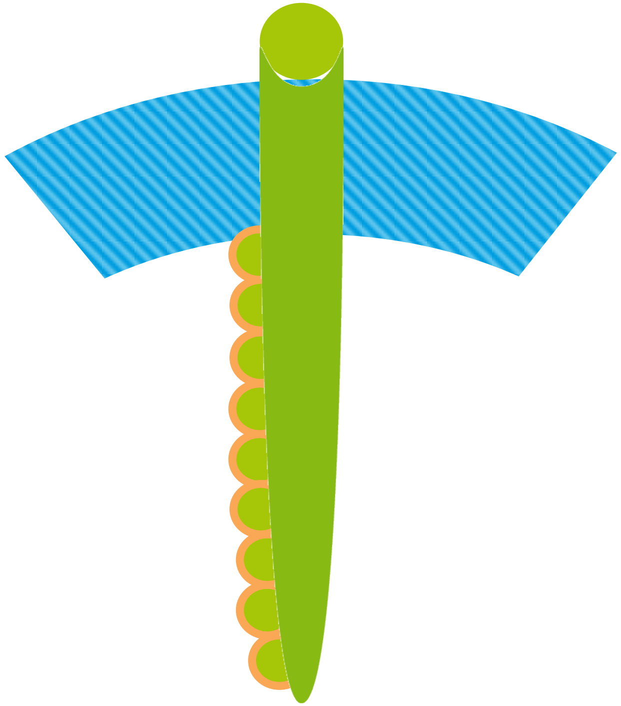
EPIDERMAL GROWTH FACTOR



EGFR MOLECULE



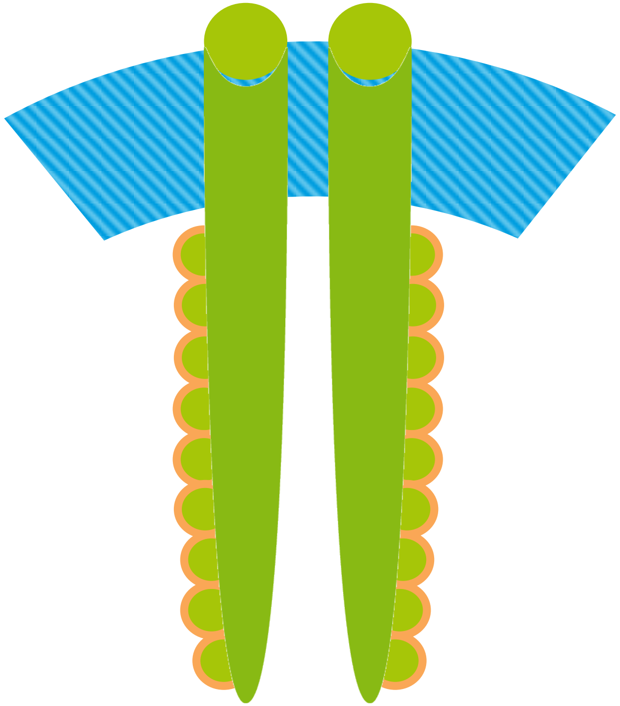
EGFR MOLECULE



2^9 configuration of EGFR

that is **512** different states

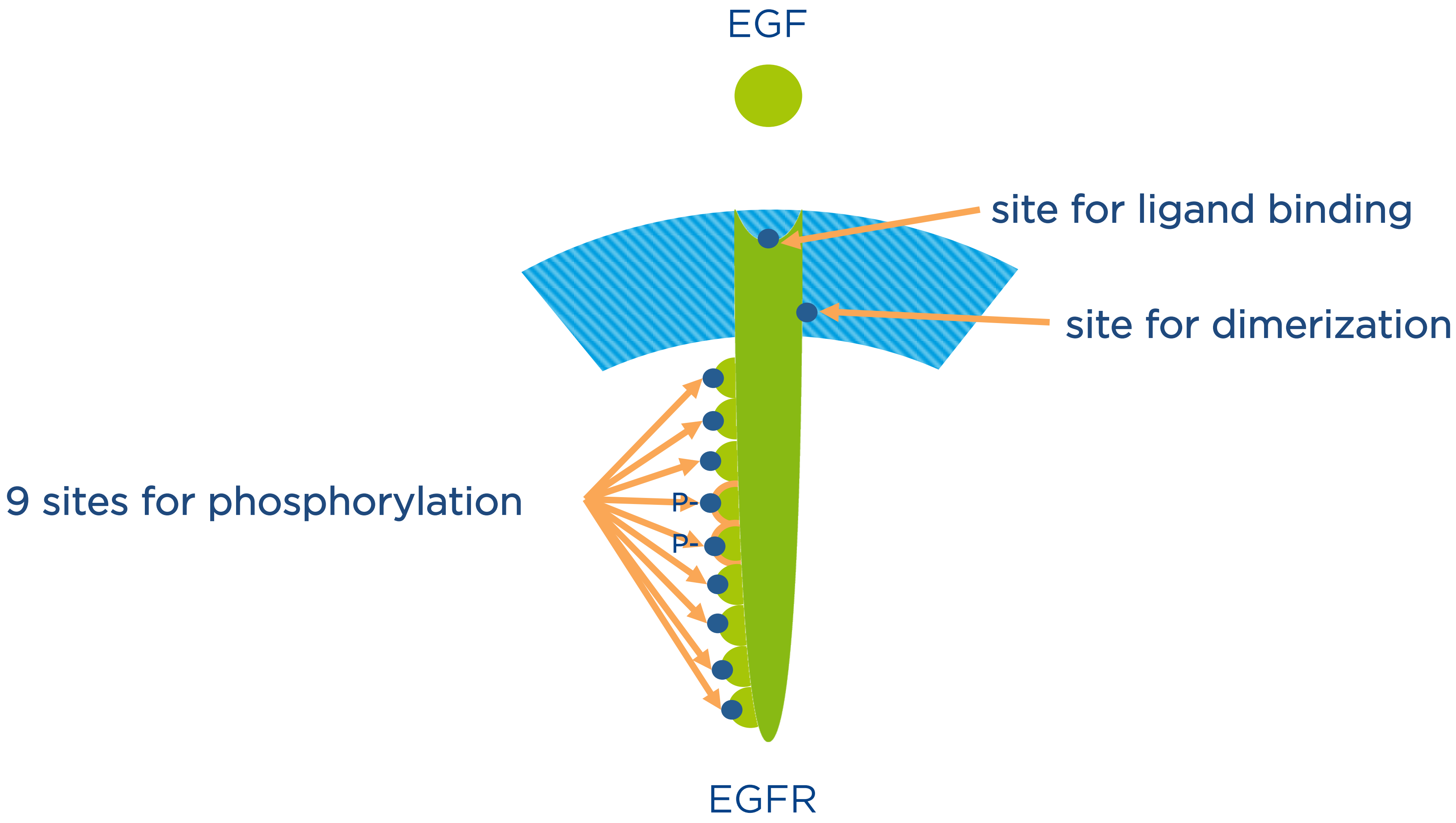
EGFR HOMODIMERS



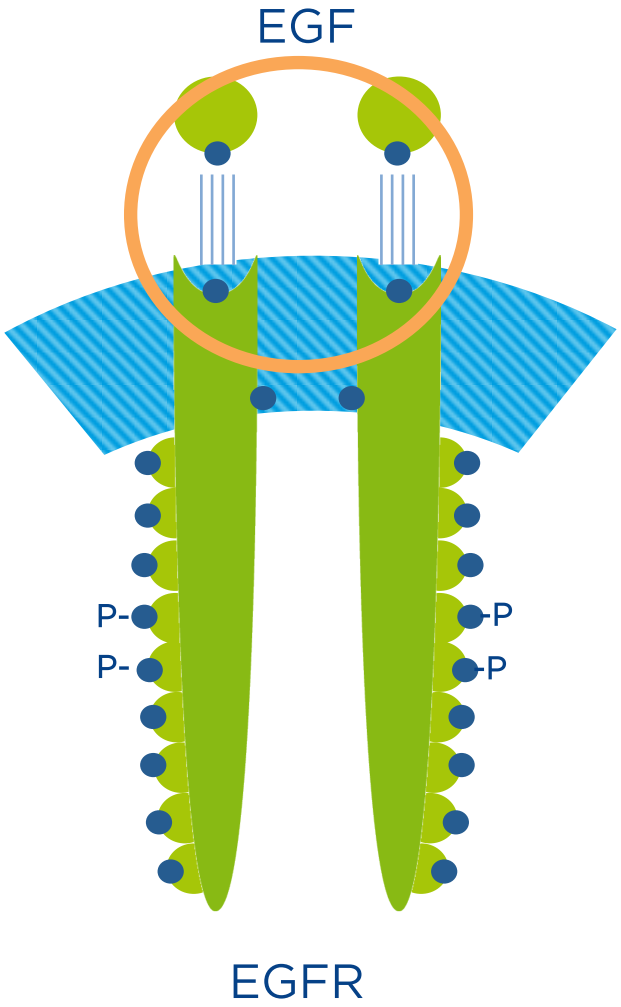
2^{18} configuration of EGFR Homodimers

that is more than **250 000** different states

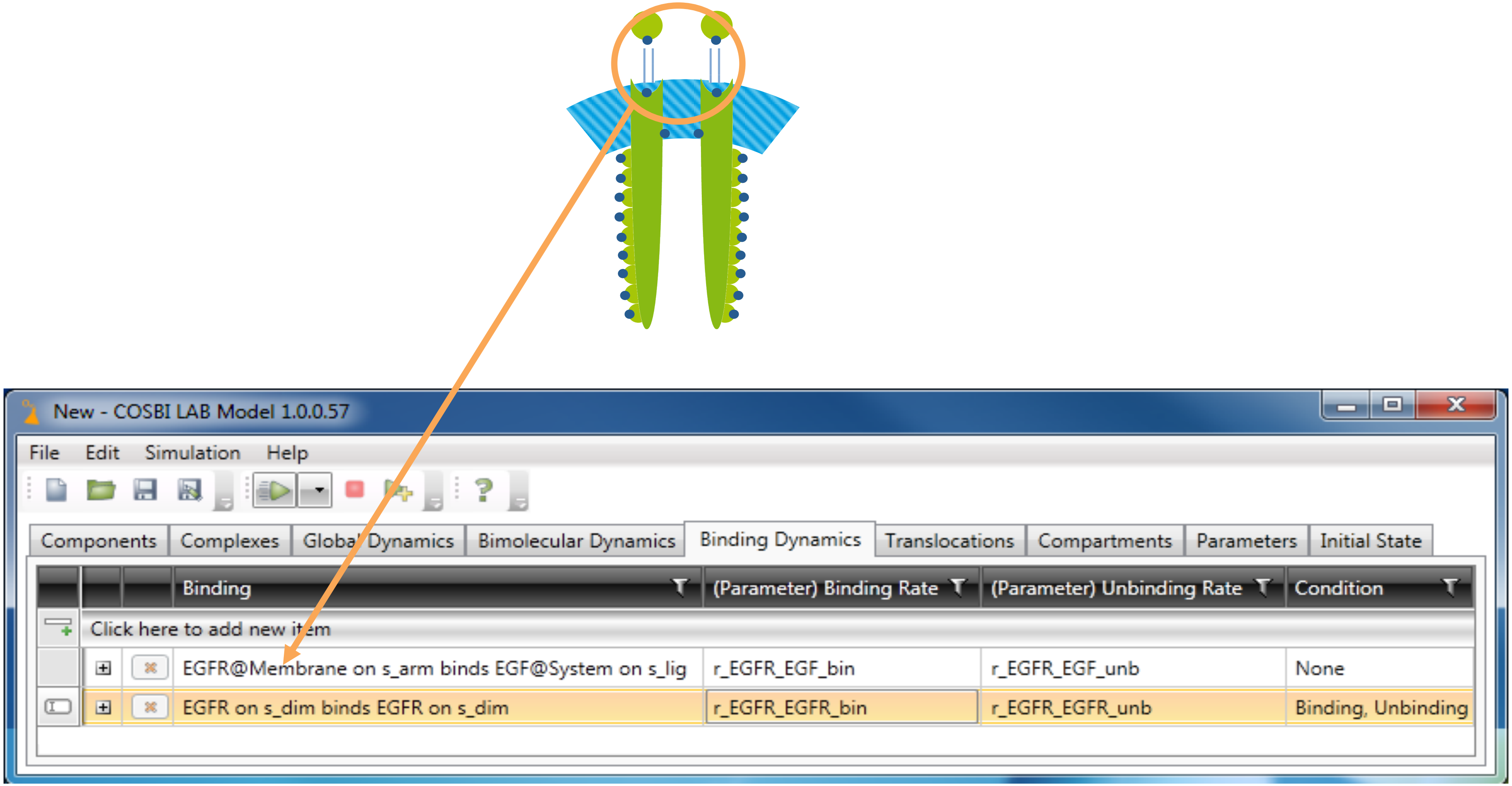
EGFR MOLECULE



INTERACTION BETWEEN EGFR AND EGF

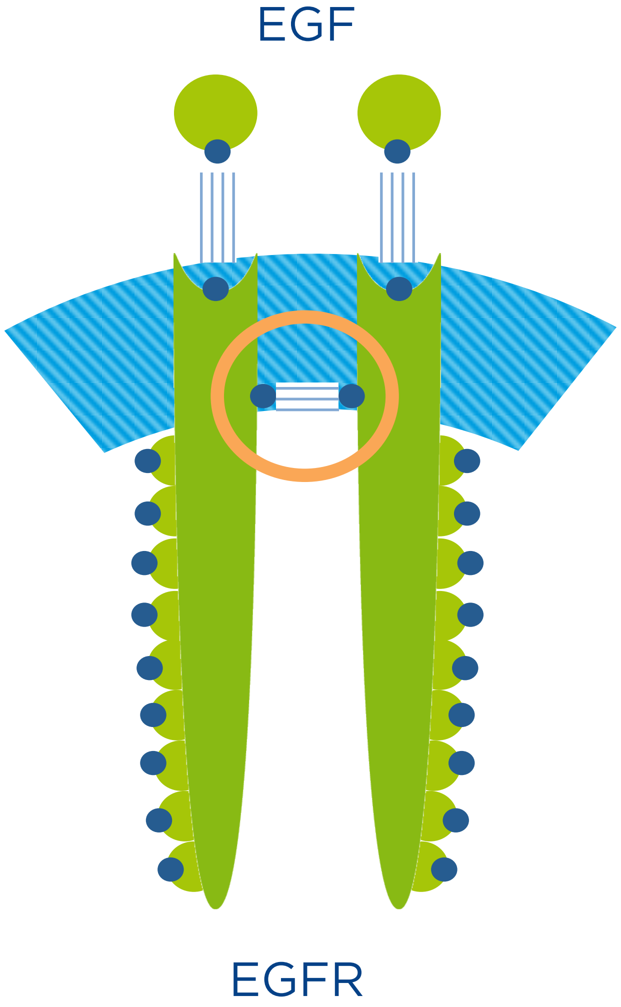


INTERACTION BETWEEN EGFR AND EGF

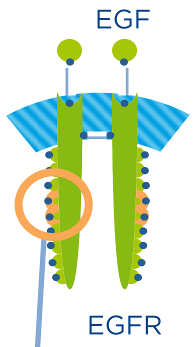


Binding	(Parameter) Binding Rate	(Parameter) Unbinding Rate	Condition
EGFR@Membrane on s_arm binds EGF@System on s_lig	r_EGFR_EGF_bin	r_EGFR_EGF_unb	None
EGFR on s_dim binds EGFR on s_dim	r_EGFR_EGFR_bin	r_EGFR_EGFR_unb	Binding, Unbinding

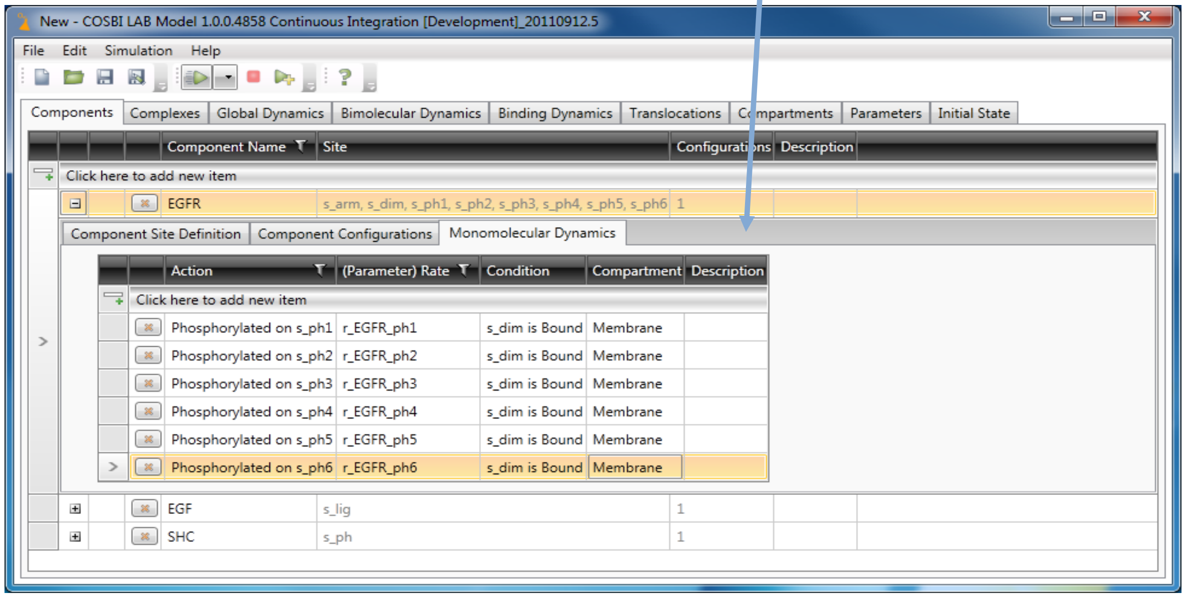
INTERACTION BETWEEN EGFR AND EGFR



SITE’S DYNAMIC FOR STATE CHANGE



Site’s Dynamic for state change

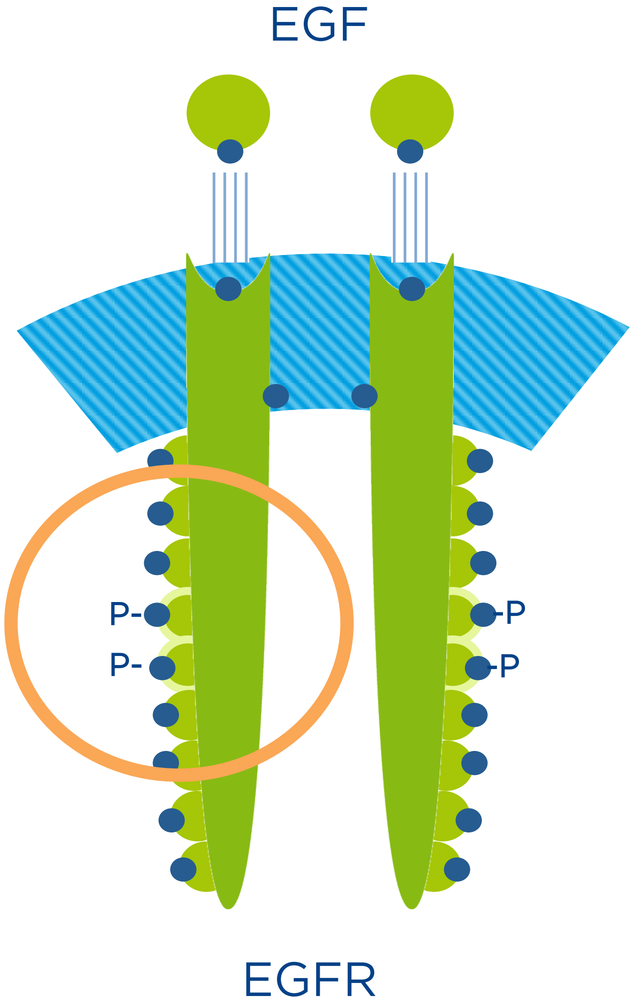


New - COSBI LAB Model 1.0.0.4858 Continuous Integration [Development]_20110912.5

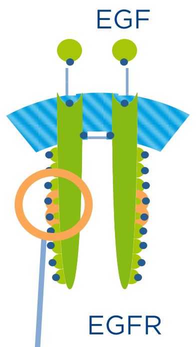
Component Name	Site	Configurations	Description
EGFR	s_arm, s_dim, s_ph1, s_ph2, s_ph3, s_ph4, s_ph5, s_ph6	1	
EGF	s_lig	1	
SHC	s_ph	1	

Action	(Parameter) Rate	Condition	Compartment	Description
Phosphorylated on s_ph1	r_EGFR_ph1	s_dim is Bound	Membrane	
Phosphorylated on s_ph2	r_EGFR_ph2	s_dim is Bound	Membrane	
Phosphorylated on s_ph3	r_EGFR_ph3	s_dim is Bound	Membrane	
Phosphorylated on s_ph4	r_EGFR_ph4	s_dim is Bound	Membrane	
Phosphorylated on s_ph5	r_EGFR_ph5	s_dim is Bound	Membrane	
Phosphorylated on s_ph6	r_EGFR_ph6	s_dim is Bound	Membrane	

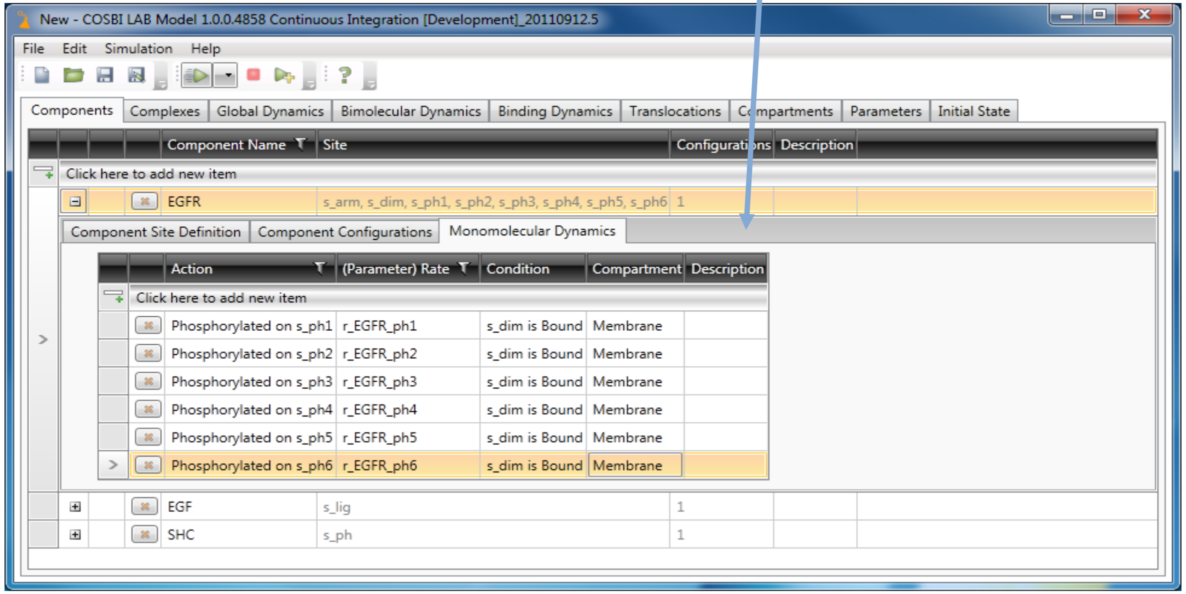
SITE'S DYNAMIC FOR STATE CHANGE



SITE’S DYNAMIC FOR STATE CHANGE



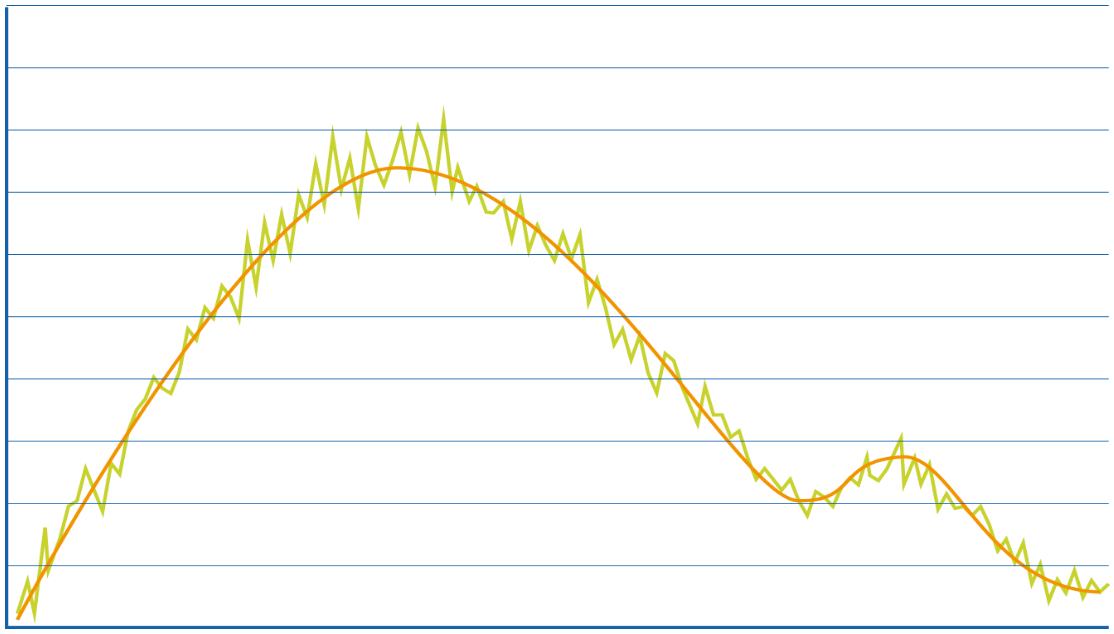
Site’s Dynamic for state change



Component Name	Site	Configurations	Description
EGFR	s_arm, s_dim, s_ph1, s_ph2, s_ph3, s_ph4, s_ph5, s_ph6	1	
EGF	s_lig	1	
SHC	s_ph	1	

Action	(Parameter) Rate	Condition	Compartment	Description
Phosphorylated on s_ph1	r_EGFR_ph1	s_dim is Bound	Membrane	
Phosphorylated on s_ph2	r_EGFR_ph2	s_dim is Bound	Membrane	
Phosphorylated on s_ph3	r_EGFR_ph3	s_dim is Bound	Membrane	
Phosphorylated on s_ph4	r_EGFR_ph4	s_dim is Bound	Membrane	
Phosphorylated on s_ph5	r_EGFR_ph5	s_dim is Bound	Membrane	
Phosphorylated on s_ph6	r_EGFR_ph6	s_dim is Bound	Membrane	

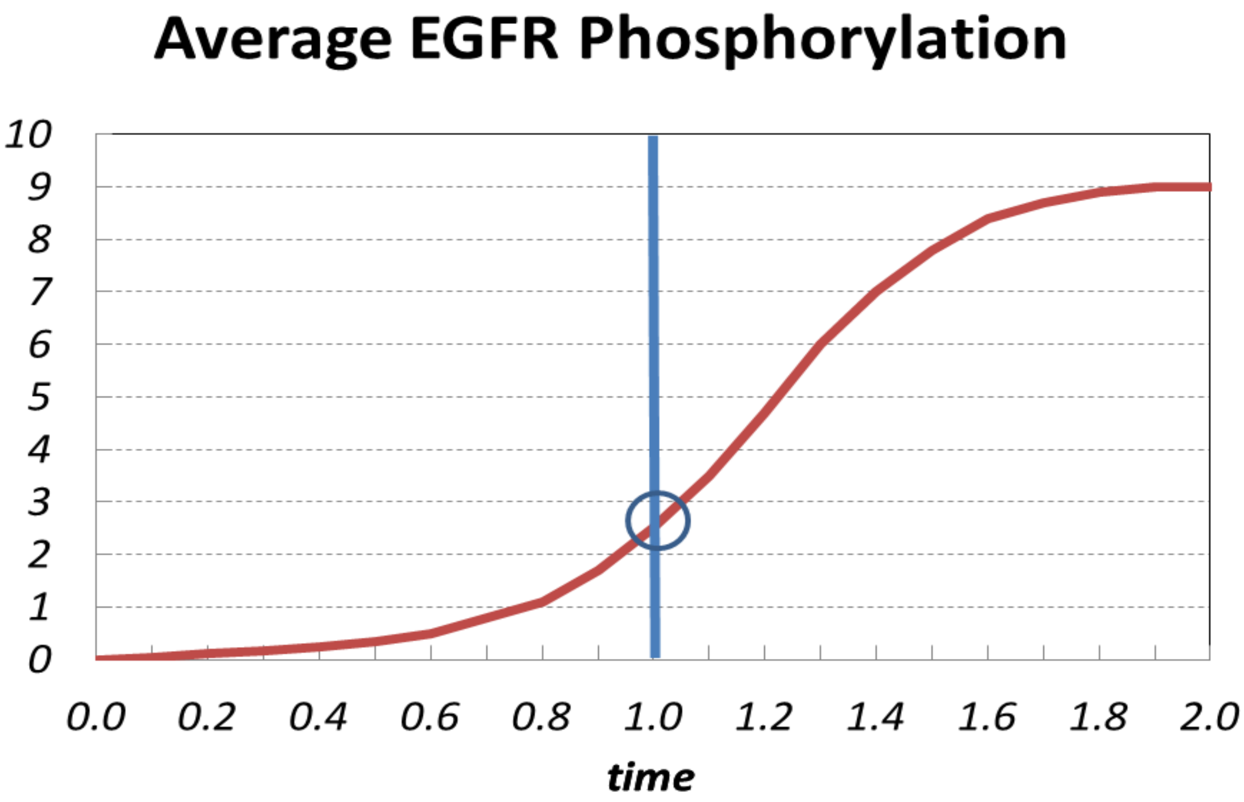
DISCRETE STOCHASTIC APPROACH



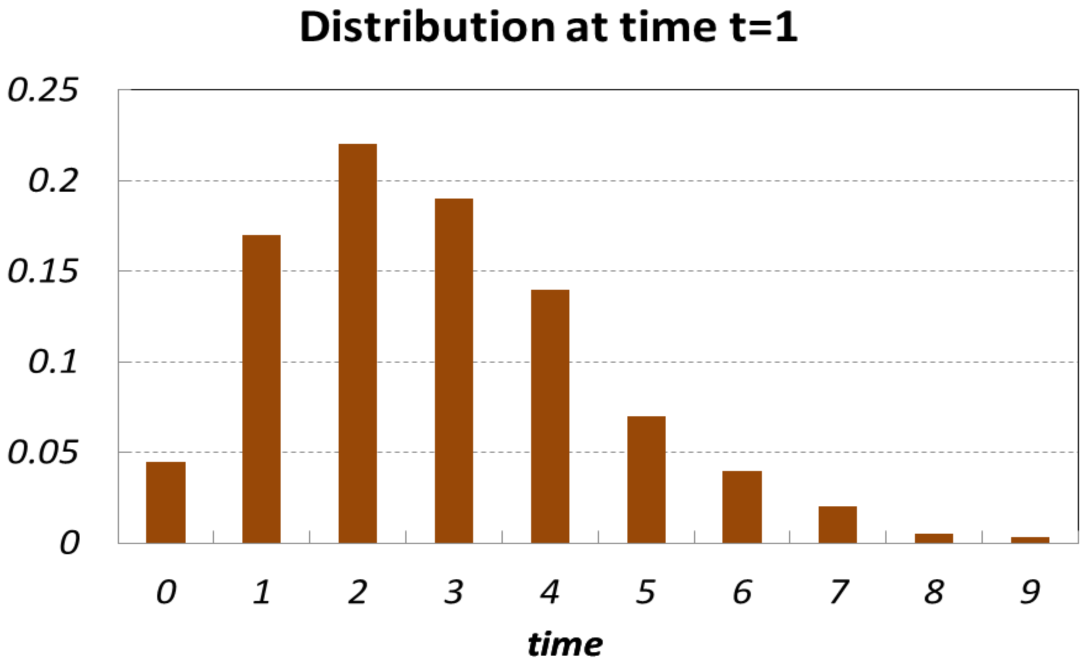
DISCRETE STOCHASTIC APPROACH

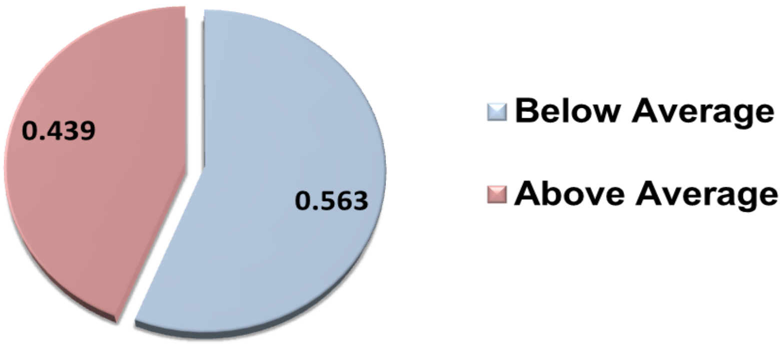
- Molecular interaction is discrete
- Receive more detailed information
- Able to produce more accurate predictions

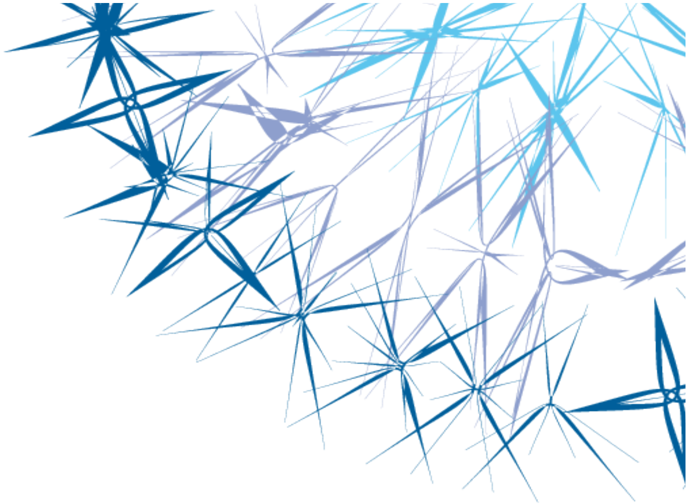
DISCRETE STOCHASTIC APPROACH EGFR EXAMPLE



DISCRETE STOCHASTIC APPROACH EGFR EXAMPLE







COSBILAB Model

The gemcitabine example

P. Lecca, O. Kahramanogullari, D. Morpurgo, C. Priami, R. Soo. Modelling the tumor shrinkage pharmacodynamics with BlenX, **1st IEEE International Conference on Computational Advances in Bio and medical Sciences (ICCABS)**, 2011

P. Lecca, O. Kahramanogullari, D. Morpurgo, C. Priami, R. Soo. Modelling and estimating dynamics of tumor shrinkage with BlenX and Kinfer, **UKSim 2001 - 13th International Conference on Modelling and Simulation.**, 2011

TUMOR SHRINKAGE BY GEMCITABINE

An algorithmic pharmacodynamics model for the time course of tumor shrinkage by gemcitabine in non small cell lung cancer patients with the following events:

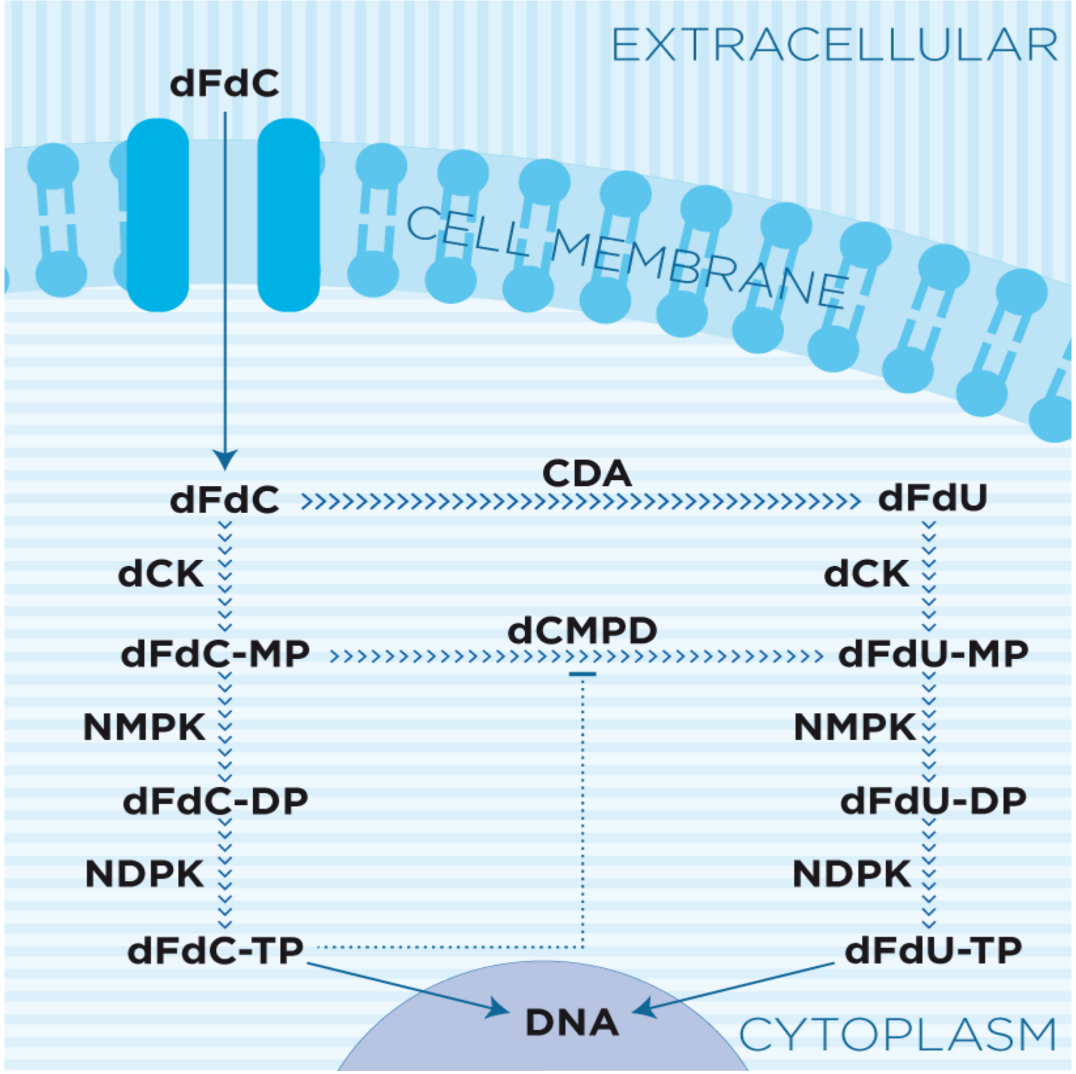
- part of the injected gemcitabine degrades;
- the gemcitabine interacts with the tumor without any effect;
- The gemcitabine interacts with the tumor, is consumed and the tumor cell is killed;
- tumor grows.
- new doses of drug are regularly injected

GEMCITABINE MECHANISM OF ACTION

- Gemcitabine (2’-2’-difluorodeoxycytidine, dFdC) is a nucleoside analog used in oncology to block DNA replication in tumor cells;

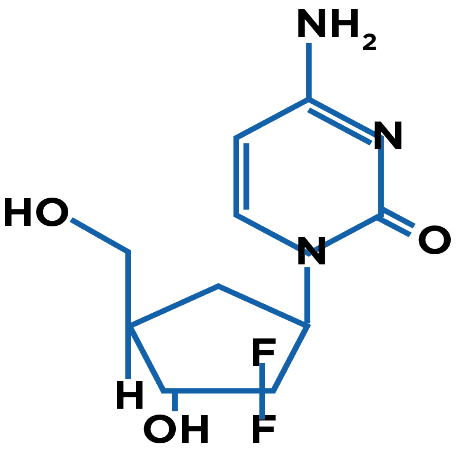
- Gemcitabine is transported from plasma into the cell and then it is subjected to deamination and/or multiple phosphorylation leading to its active triphosphate (dFdCTP and dFdUTP) metabolites;

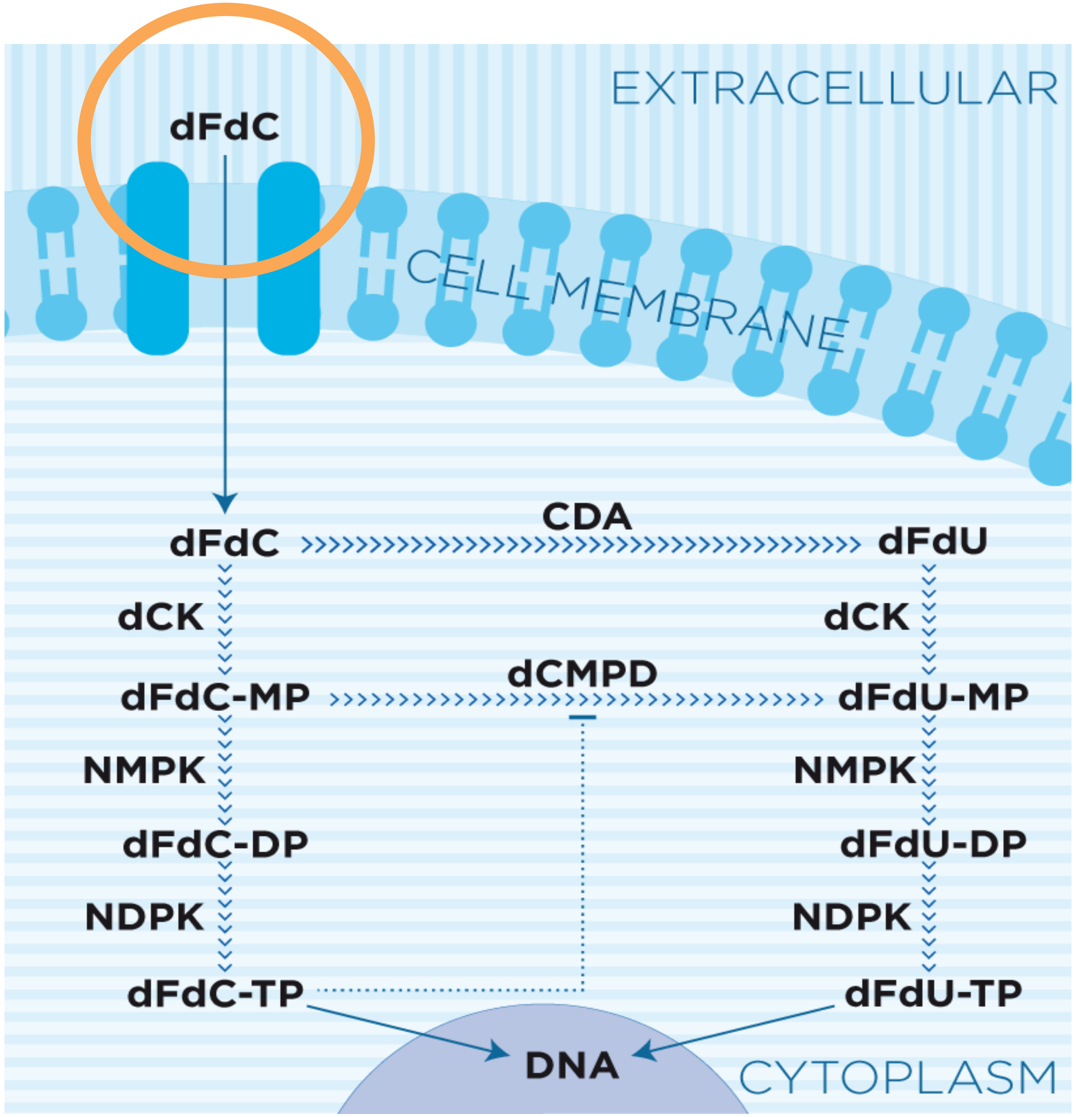
- As an example, a simplified version of gemcitabine metabolic network will be modeled.



COMPONENTS

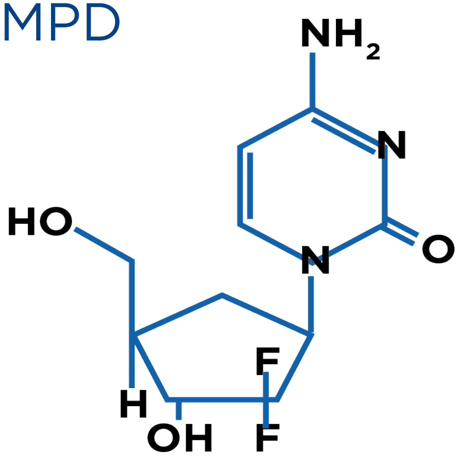
Gemcitabine (dFdC) has sites for deamination, phosphorylation, and inhibition of dCMPD enzyme.

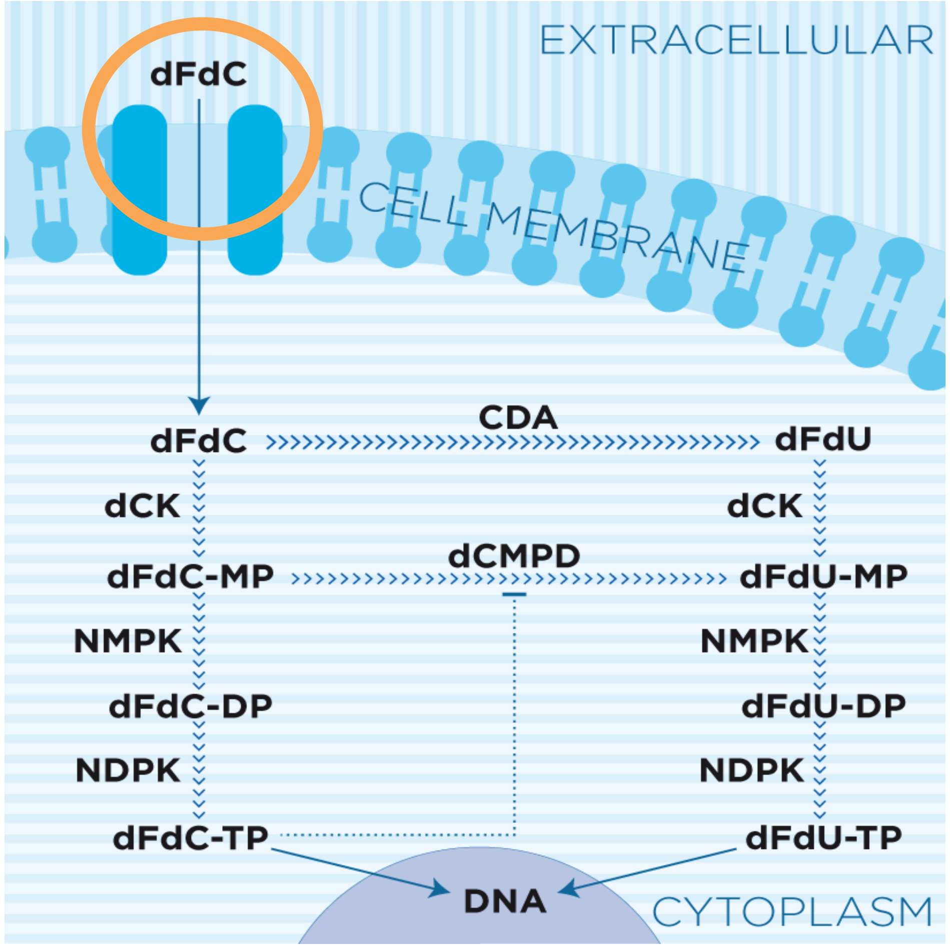




COMPONENTS

Gemcitabine (dFdC) has sites for deamination, phosphorylation, and inhibition of dCMPD enzyme.

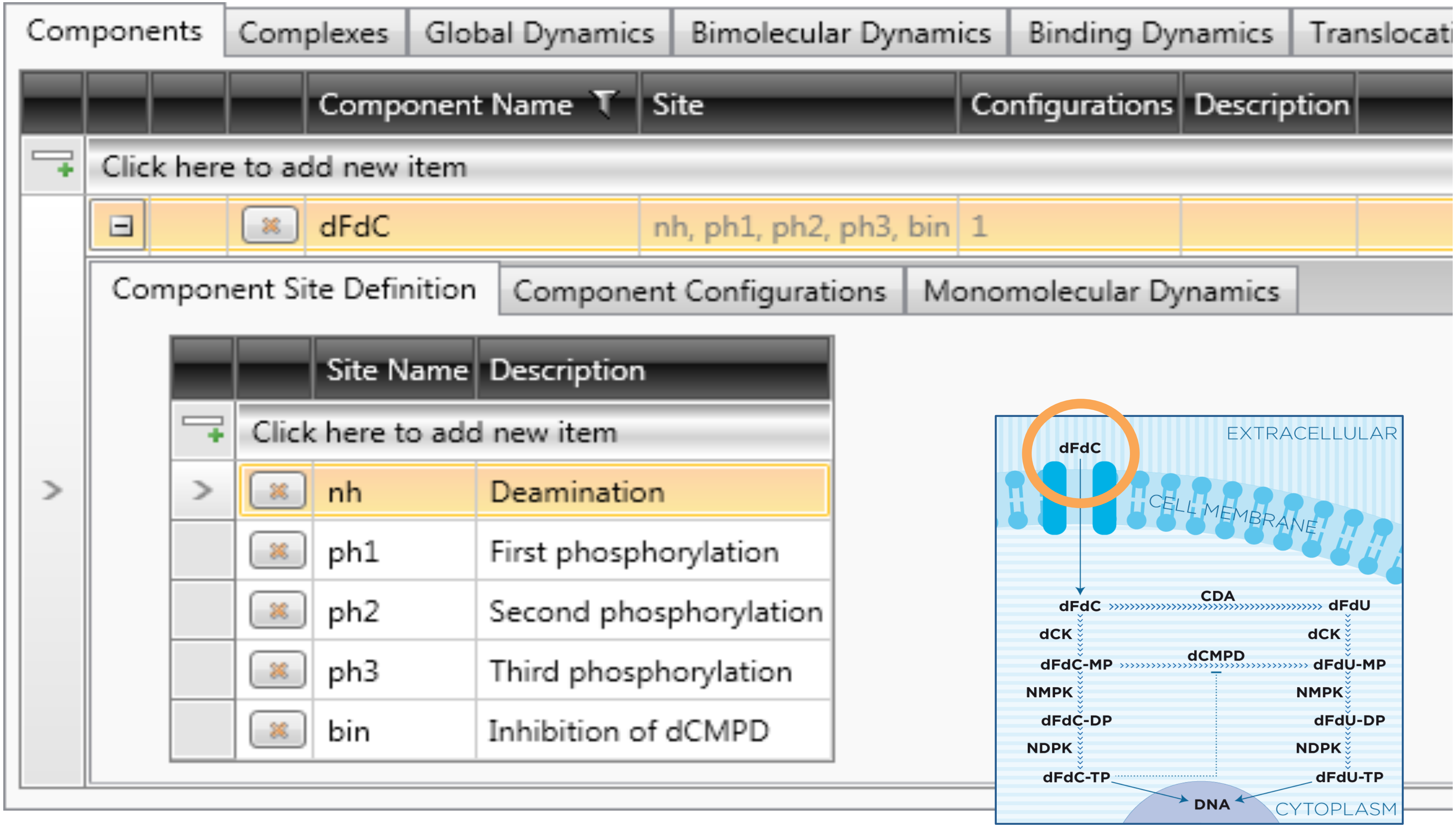




***BlenX* code:**

```
let dFdCout: bproc = #(s1, c_dFdCout1), #(s2, c_dFdCout2) [ p_main | rep start_p_main?().p_main ];
```

COMPONENTS

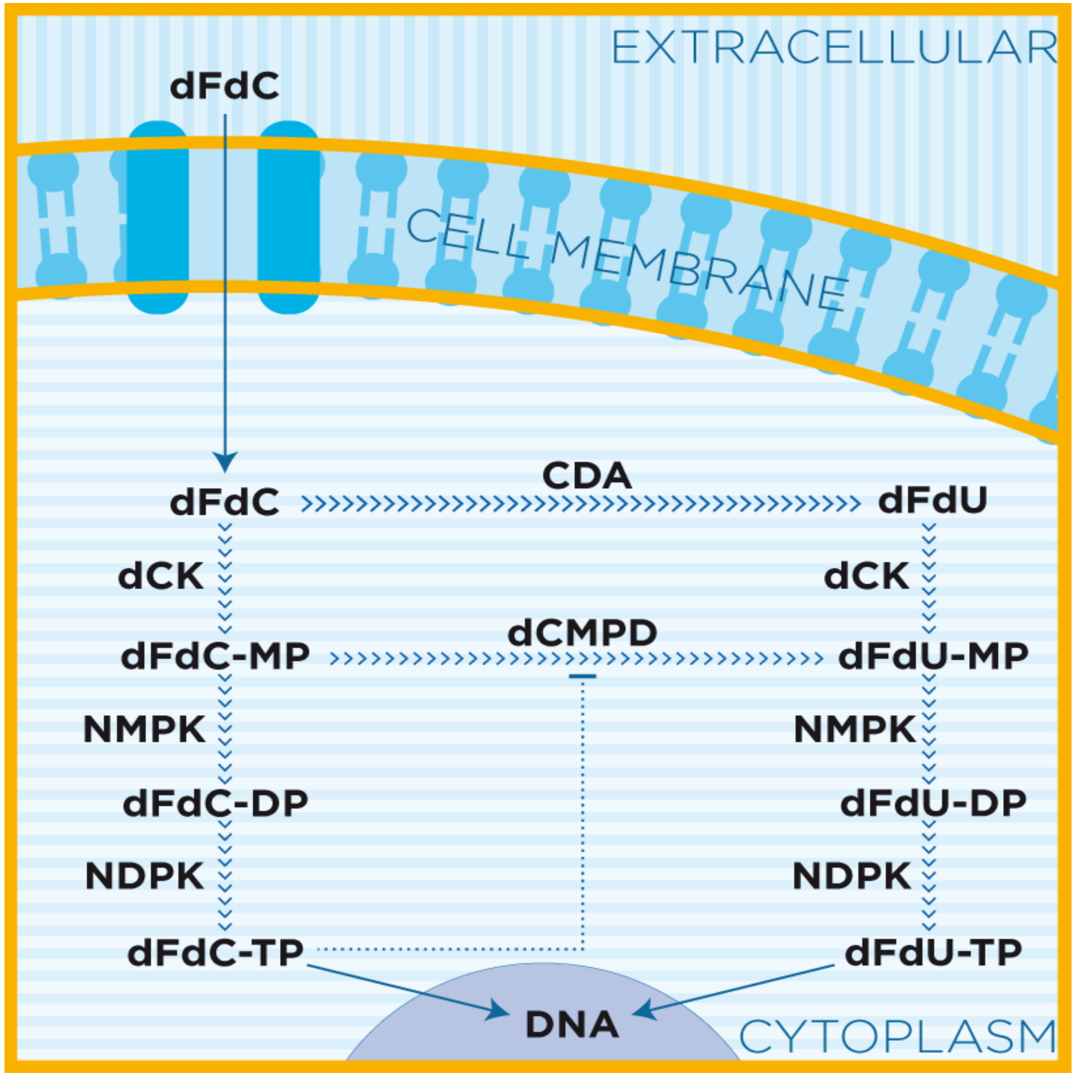


Component Name	Site	Configurations	Description
dFdC	nh, ph1, ph2, ph3, bin	1	

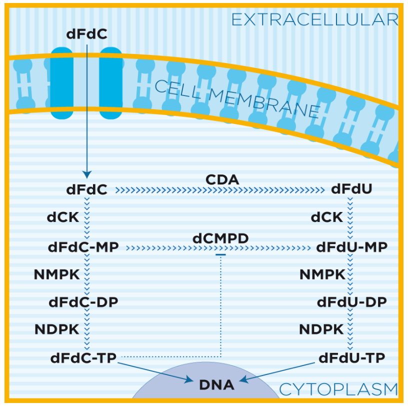
Site Name	Description
nh	Deamination
ph1	First phosphorylation
ph2	Second phosphorylation
ph3	Third phosphorylation
bin	Inhibition of dCMPD

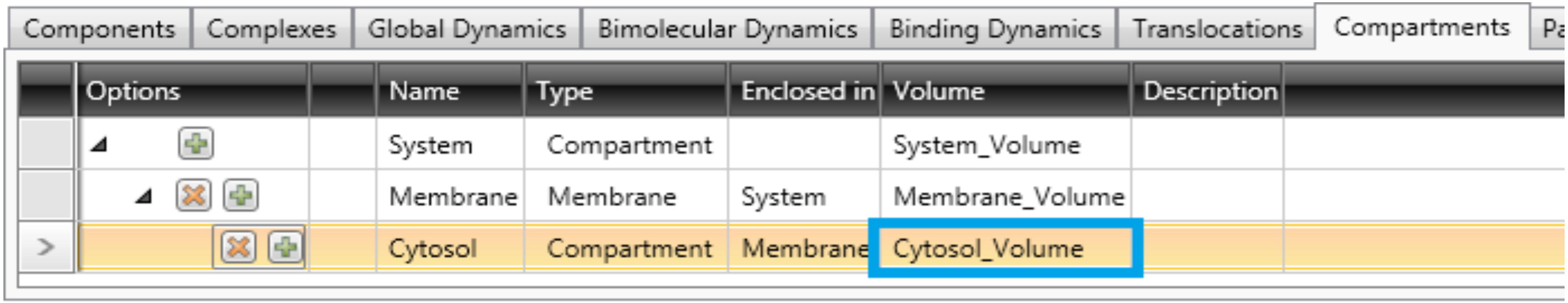
COMPARTMENTS

The extracellular medium, the cellular membrane, and the intracellular medium (cytosol) are considered;

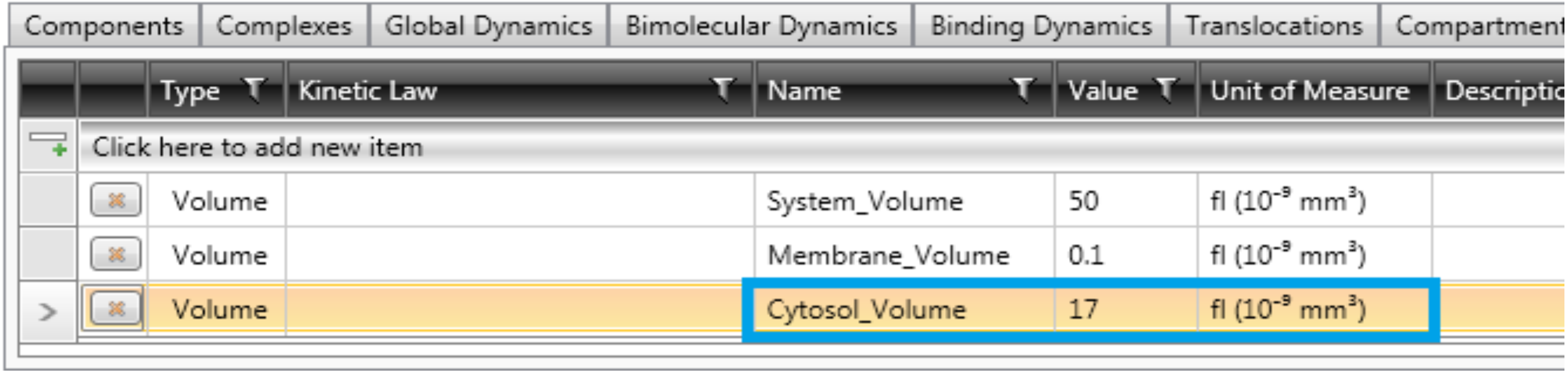


COMPARTMENTS





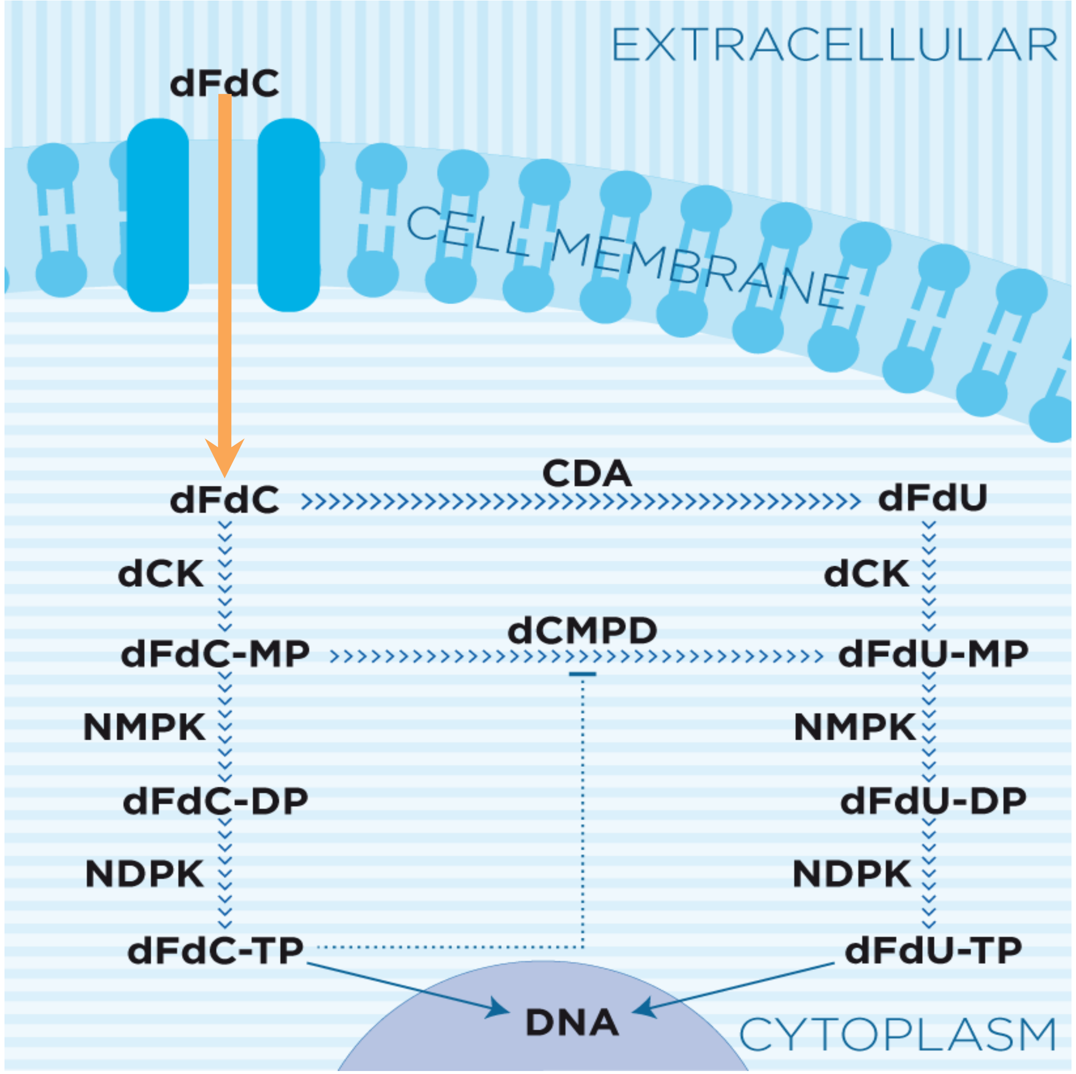
Options		Name	Type	Enclosed in	Volume	Description
◢ ✚		System	Compartment		System_Volume	
◢ ☒ ✚		Membrane	Membrane	System	Membrane_Volume	
☒ ✚		Cytosol	Compartment	Membrane	Cytosol_Volume	



	Type	Kinetic Law	Name	Value	Unit of Measure	Descriptio
Click here to add new item						
☒	Volume		System_Volume	50	fl (10^{-9} mm^3)	
☒	Volume		Membrane_Volume	0.1	fl (10^{-9} mm^3)	
☒	Volume		Cytosol_Volume	17	fl (10^{-9} mm^3)	

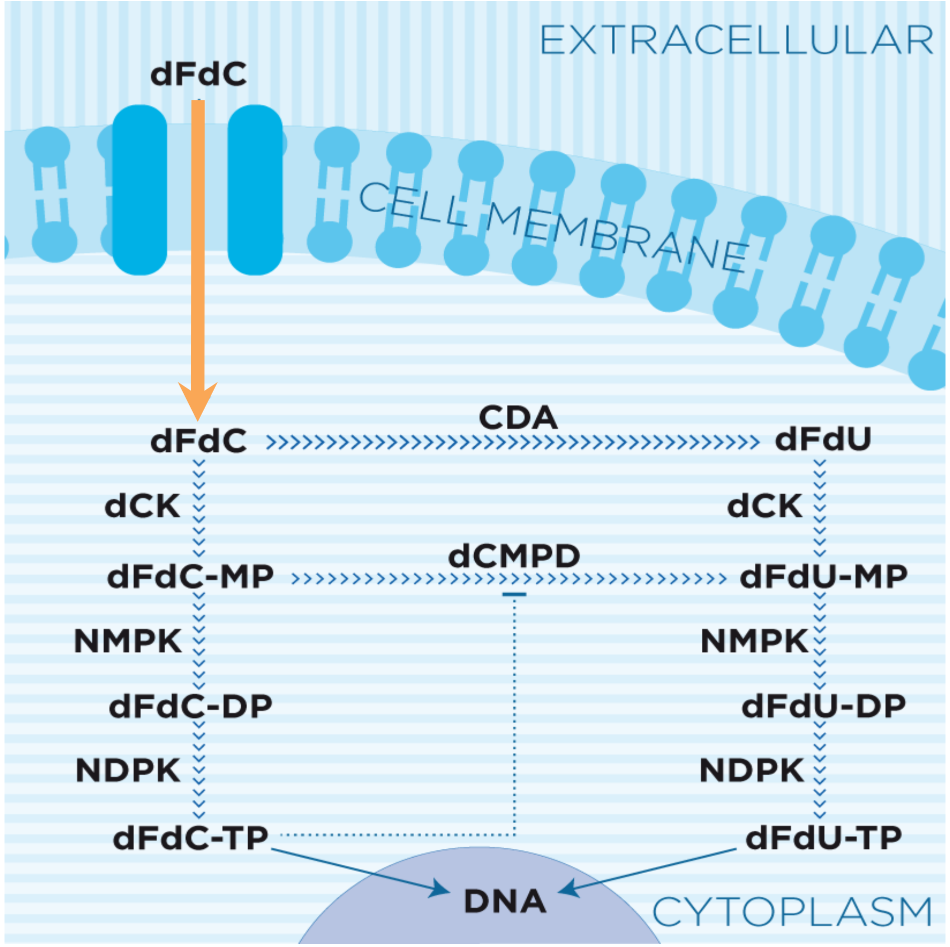
TRANSLOCATIONS

Gemcitabine moves from plasma into the cell passing through the cellular membrane;



TRANSLOCATIONS

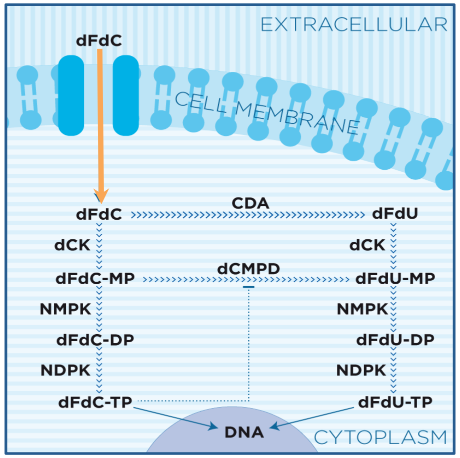
Gemcitabine moves from plasma into the cell passing through the cellular membrane;

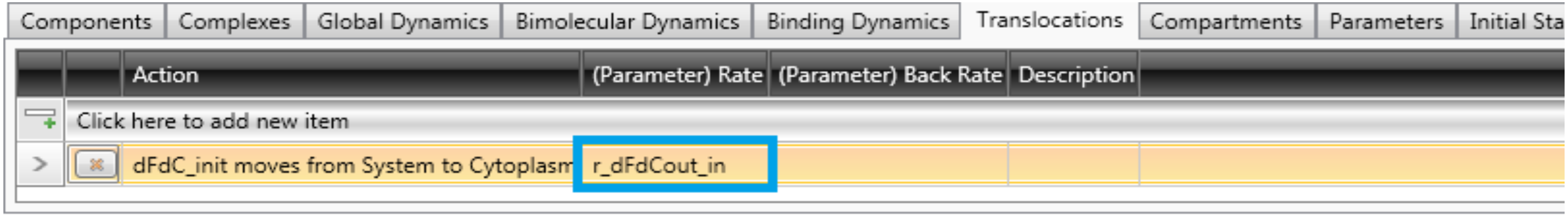


BlenX code:

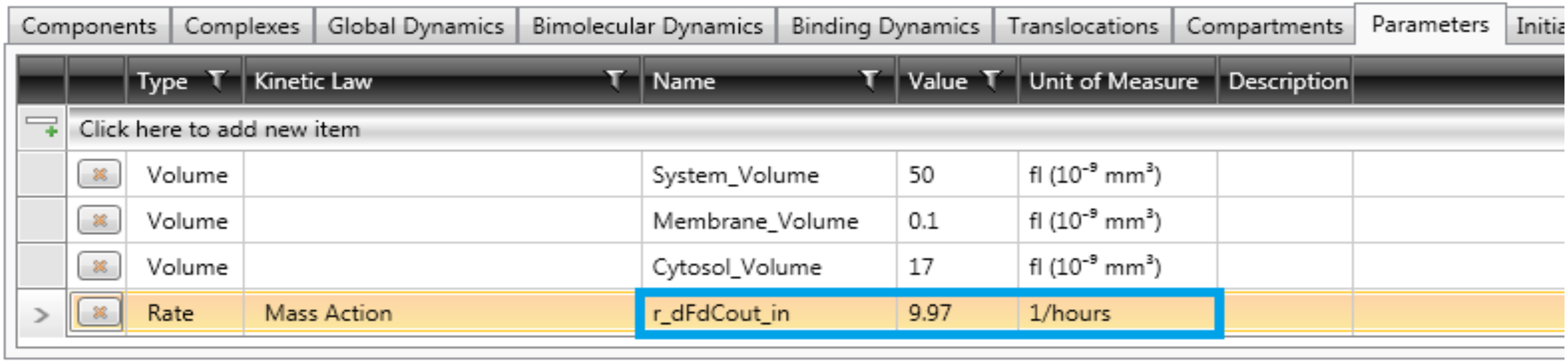
```
let p_main : pproc =
        if (s1, c_dFdCout1) then ch(rate(r_dFdCout_in), s1, c_dFdC1).ch(s2, c_dFdC2).start_p_main!()
        endif + ...

let dFdCout: bproc = #(s1, c_dFdCout1), #(s2, c_dFdCout2) [ p_main | rep start_p_main?().p_main ];
```

TRANSLOCATIONS





		Action	(Parameter) Rate	(Parameter) Back Rate	Description
		Click here to add new item			
>		dFdC_init moves from System to Cytoplasm	r_dFdCout_in		

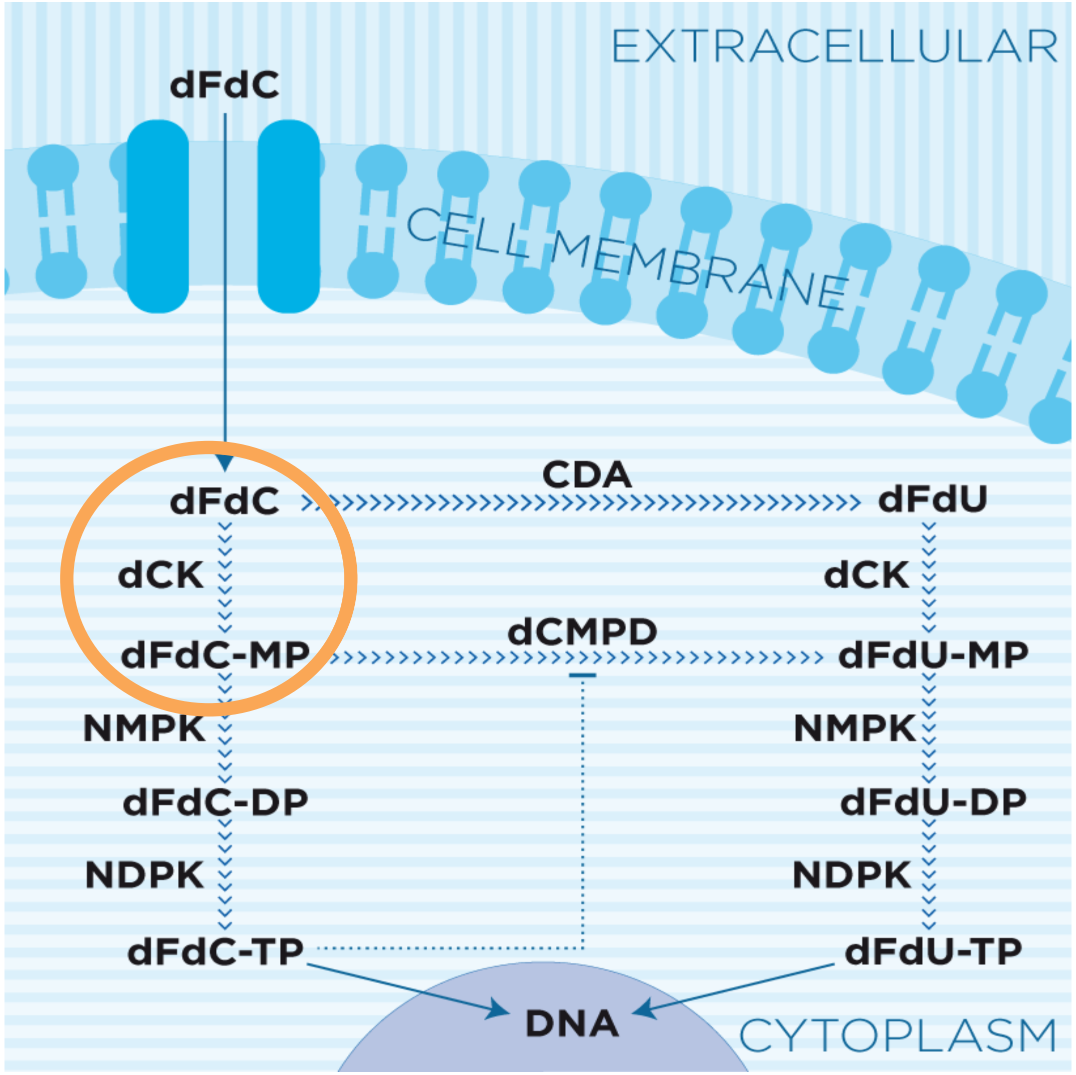


		Type	Kinetic Law	Name	Value	Unit of Measure	Description
		Click here to add new item					
		Volume		System_Volume	50	fl (10^{-9} mm^3)	
		Volume		Membrane_Volume	0.1	fl (10^{-9} mm^3)	
		Volume		Cytosol_Volume	17	fl (10^{-9} mm^3)	
>		Rate	Mass Action	r_dFdCout_in	9.97	1/hours	

BIMOLECULAR DYNAMICS

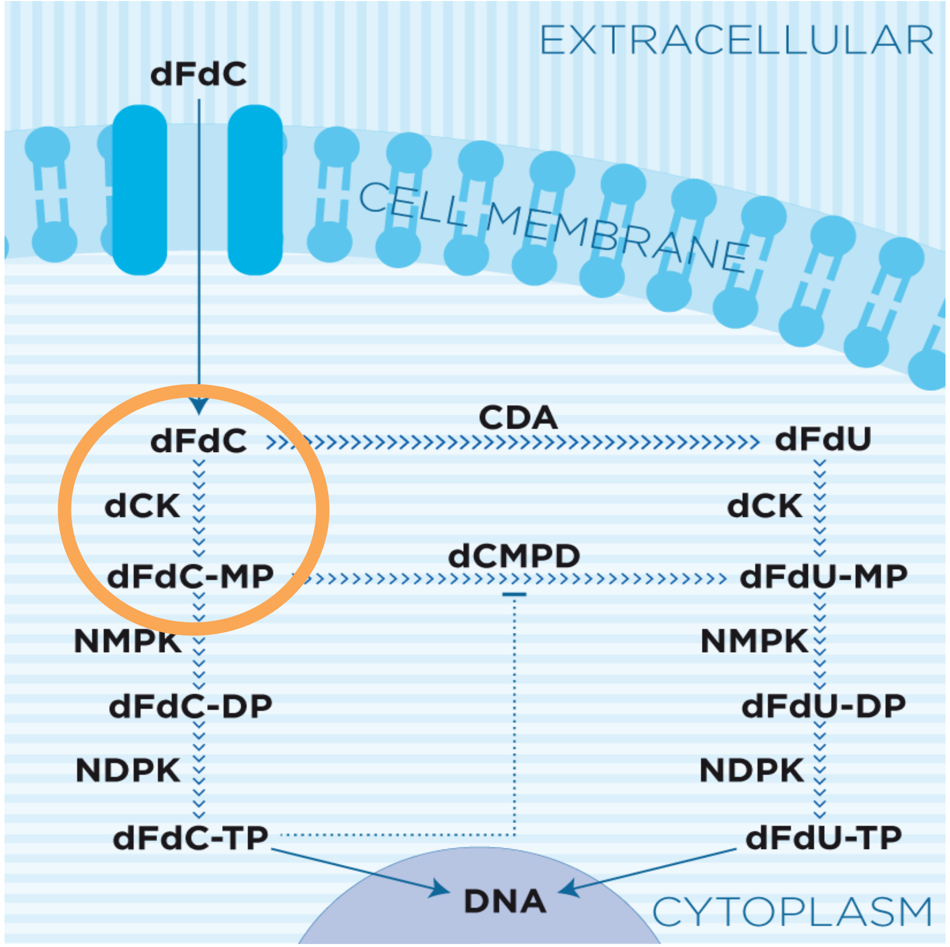
- Once inside the cytoplasm, dFdC is phosphorylated by deoxycytidine kinase (dCK);

- Built-in kinetic laws are available (Mass-Action, Michaelis-Menten, Hill) as well as User Defined;



BIMOLECULAR DYNAMICS

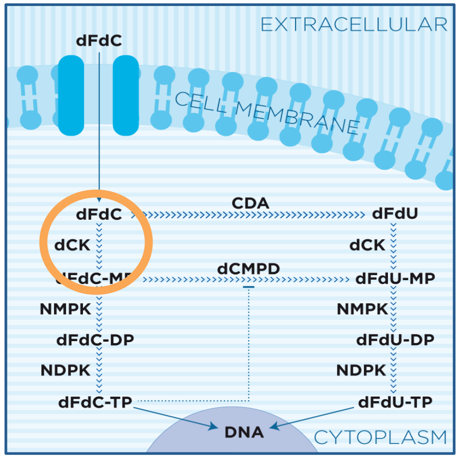
- Once inside the cytoplasm, dFdC is phosphorylated by deoxycytidine kinase (dCK);
- Built-in kinetic laws are available (Mass-Action, Michaelis-Menten, Hill) as well as User Defined;

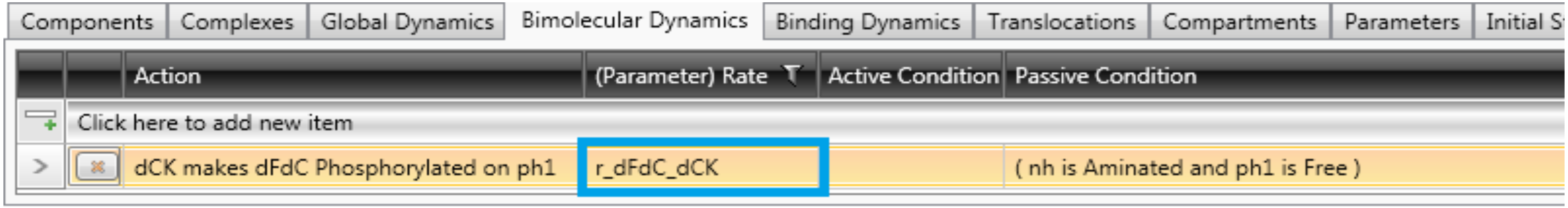


BlenX code:

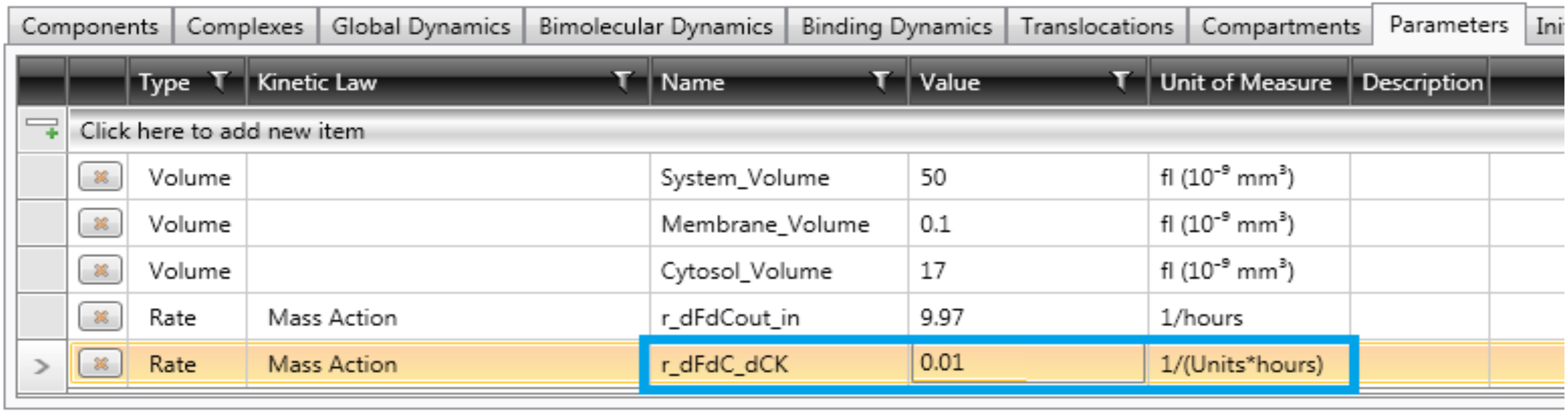
```
let p_main : pproc =...+if (s1, c_dFdC1) then s1?().ch(s1, c_dFdCMP1).ch(s2, c_dFdCMP2).start_p_main!() +
                        endif + ...
let dFdC : bproc = #(s1, c_dFdC1), #(s2, c_dFdC2) [ p_main | rep start_p_main?().p_main ];
let dCK : bproc = #(s, c_dCK) [ s!().startdCK!() | rep startdCK?().s!().startdCK!() ];

Affinity: (c_dCK, c_dFdC1, rate(r_dFdC_dCK))
```

BIMOLECULAR DYNAMICS





Action	(Parameter) Rate	Active Condition	Passive Condition
Click here to add new item			
dCK makes dFdC Phosphorylated on ph1	r_dFdC_dCK		(nh is Aminated and ph1 is Free)

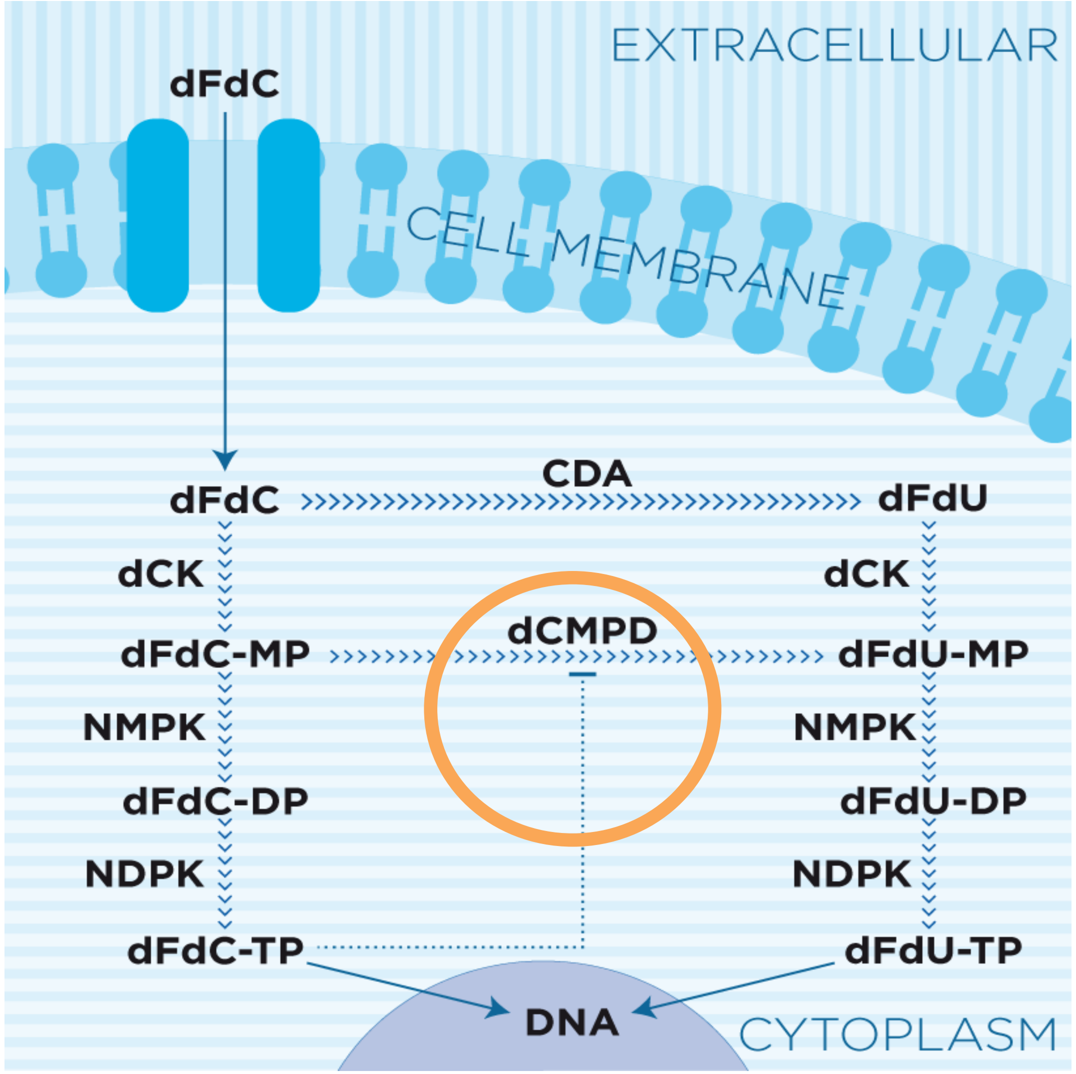


Type	Kinetic Law	Name	Value	Unit of Measure	Description
Click here to add new item					
Volume		System_Volume	50	fl (10^{-9} mm^3)	
Volume		Membrane_Volume	0.1	fl (10^{-9} mm^3)	
Volume		Cytosol_Volume	17	fl (10^{-9} mm^3)	
Rate	Mass Action	r_dFdCout_in	9.97	1/hours	
Rate	Mass Action	r_dFdC_dCK	0.01	1/(Units*hours)	

BINDING DYNAMICS

- Inhibition mechanisms can be modeled in different ways, in this case we considered an inhibitory complexation between dFdCTP and dCMPD;

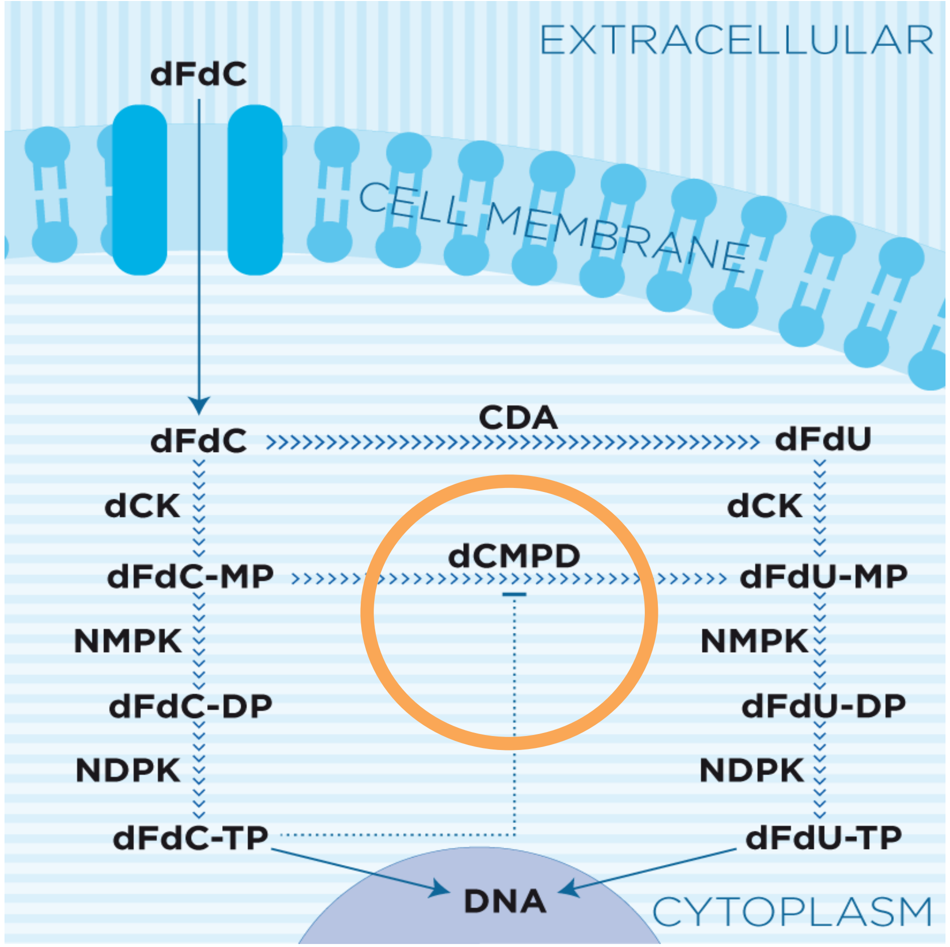
- Binding conditions are specified to identify the target configuration.



BINDING DYNAMICS

- Inhibition mechanisms can be modeled in different ways, in this case we considered an inhibitory complexation between dFdCTP and dCMPD;

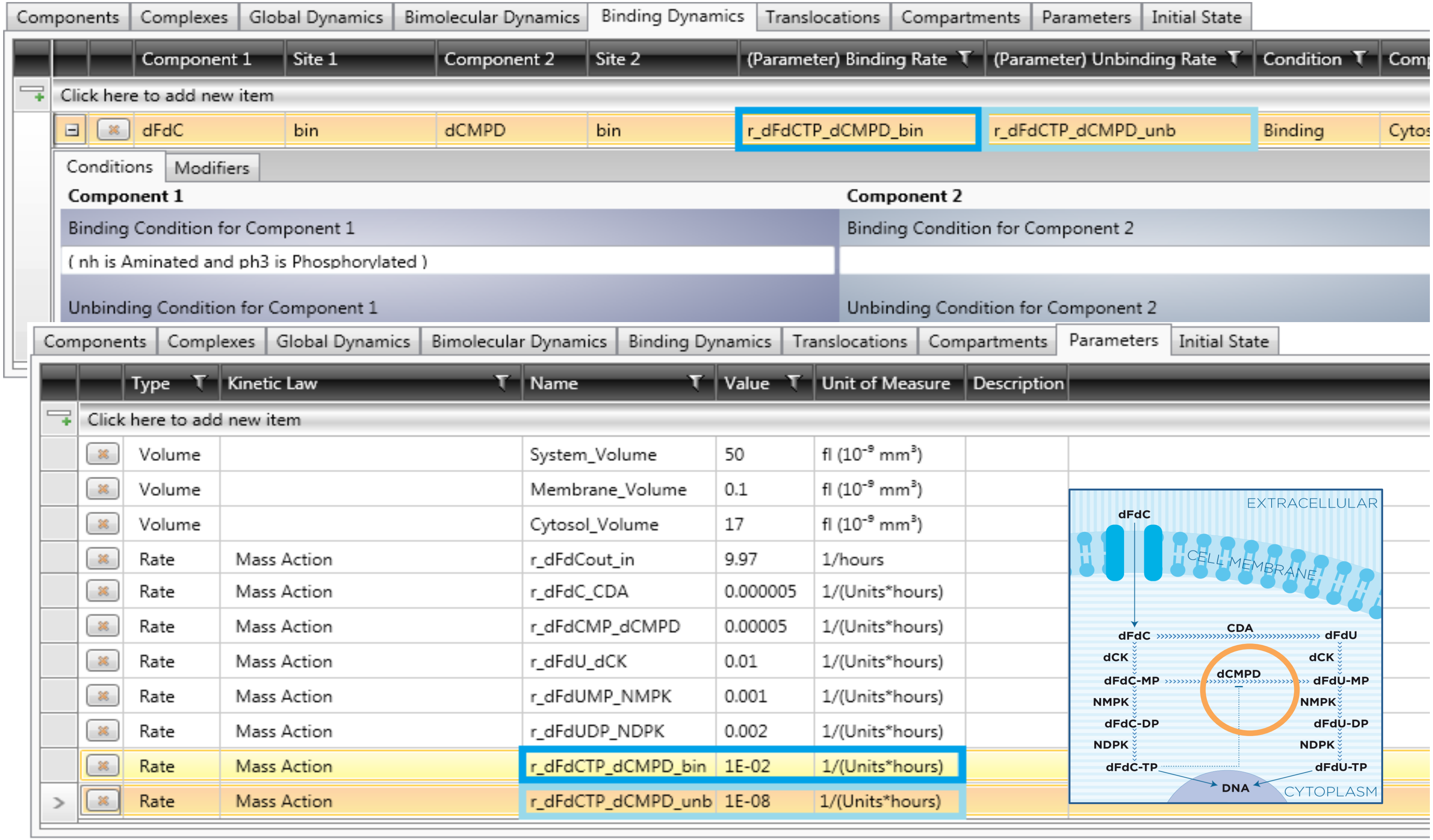
- Binding conditions are specified to identify the target configuration.



BlenX code:

```
let dFdCTP : bproc = #(s1, c_dFdCTP1), #(s2, c_dFdCTP2) [ p_main | rep start_p_main?().p_main ];
let dCMPD : bproc = #(s, c_dCMPD) [ s!().startdCMPD!() | rep startdCMPD?().s!().startdCMPD!() ];

Affinity: (c_dFdCTP1, c_dCMPD, rate(r_dFdCTP_dCMPD_bin), rate(r_dFdCTP_dCMPD_unb), 0)
```

BINDING DYNAMICS



Component 1	Site 1	Component 2	Site 2	(Parameter) Binding Rate	(Parameter) Unbinding Rate	Condition	Com
dFdC	bin	dCMPD	bin	r_dFdCTP_dCMPD_bin	r_dFdCTP_dCMPD_unb	Binding	Cytos

Component 1

Binding Condition for Component 1

(nh is Aminated and ph3 is Phosphorylated)

Unbinding Condition for Component 1

Component 2

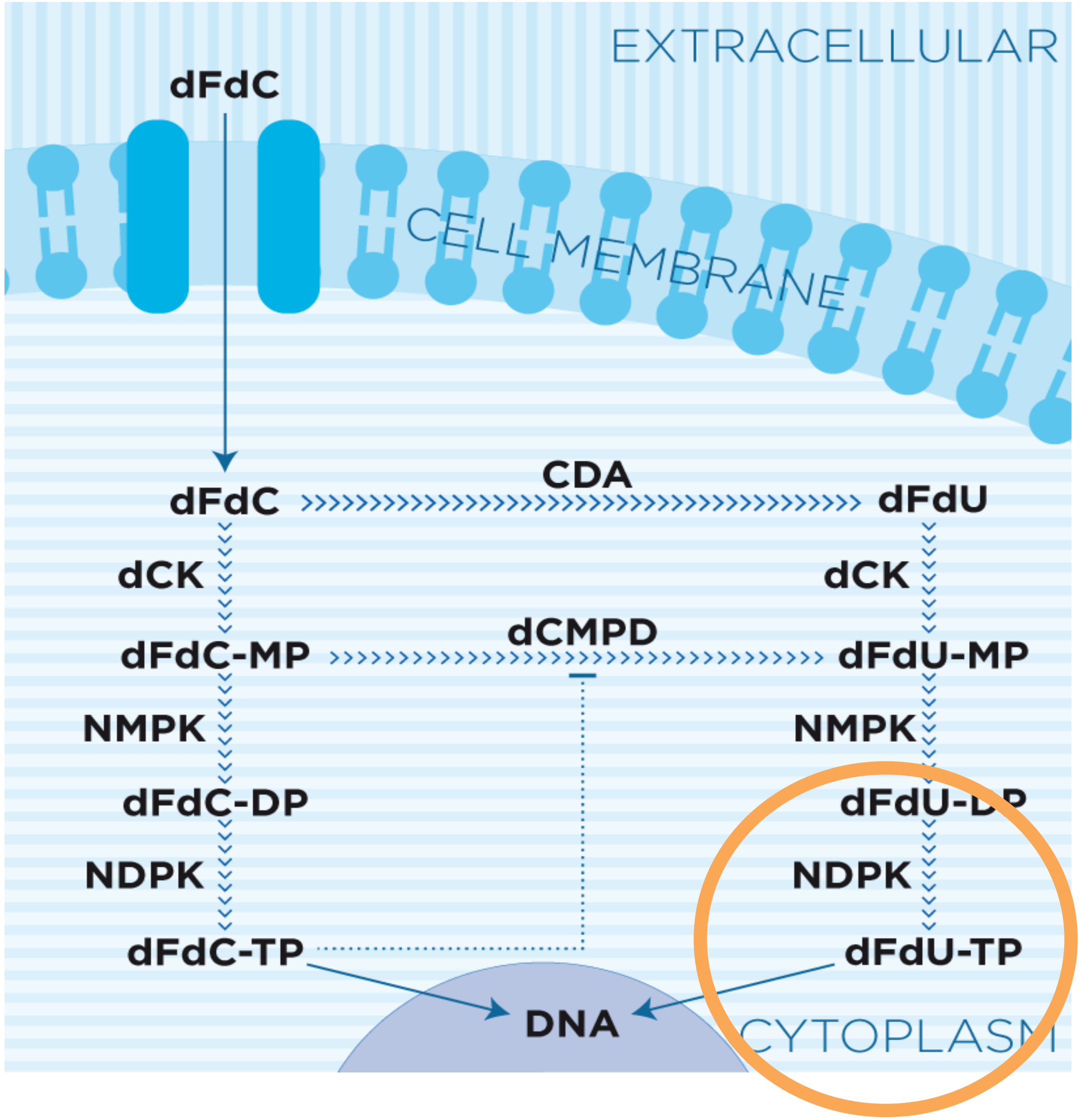
Binding Condition for Component 2

Unbinding Condition for Component 2

Type	Kinetic Law	Name	Value	Unit of Measure	Description
Volume		System_Volume	50	fl (10^{-9} mm^3)	
Volume		Membrane_Volume	0.1	fl (10^{-9} mm^3)	
Volume		Cytosol_Volume	17	fl (10^{-9} mm^3)	
Rate	Mass Action	r_dFdCout_in	9.97	1/hours	
Rate	Mass Action	r_dFdC_CDA	0.000005	1/(Units*hours)	
Rate	Mass Action	r_dFdCMP_dCMPD	0.00005	1/(Units*hours)	
Rate	Mass Action	r_dFdU_dCK	0.01	1/(Units*hours)	
Rate	Mass Action	r_dFdUMP_NMPK	0.001	1/(Units*hours)	
Rate	Mass Action	r_dFdUDP_NDPK	0.002	1/(Units*hours)	
Rate	Mass Action	r_dFdCTP_dCMPD_bin	1E-02	1/(Units*hours)	
Rate	Mass Action	r_dFdCTP_dCMPD_unb	1E-08	1/(Units*hours)	

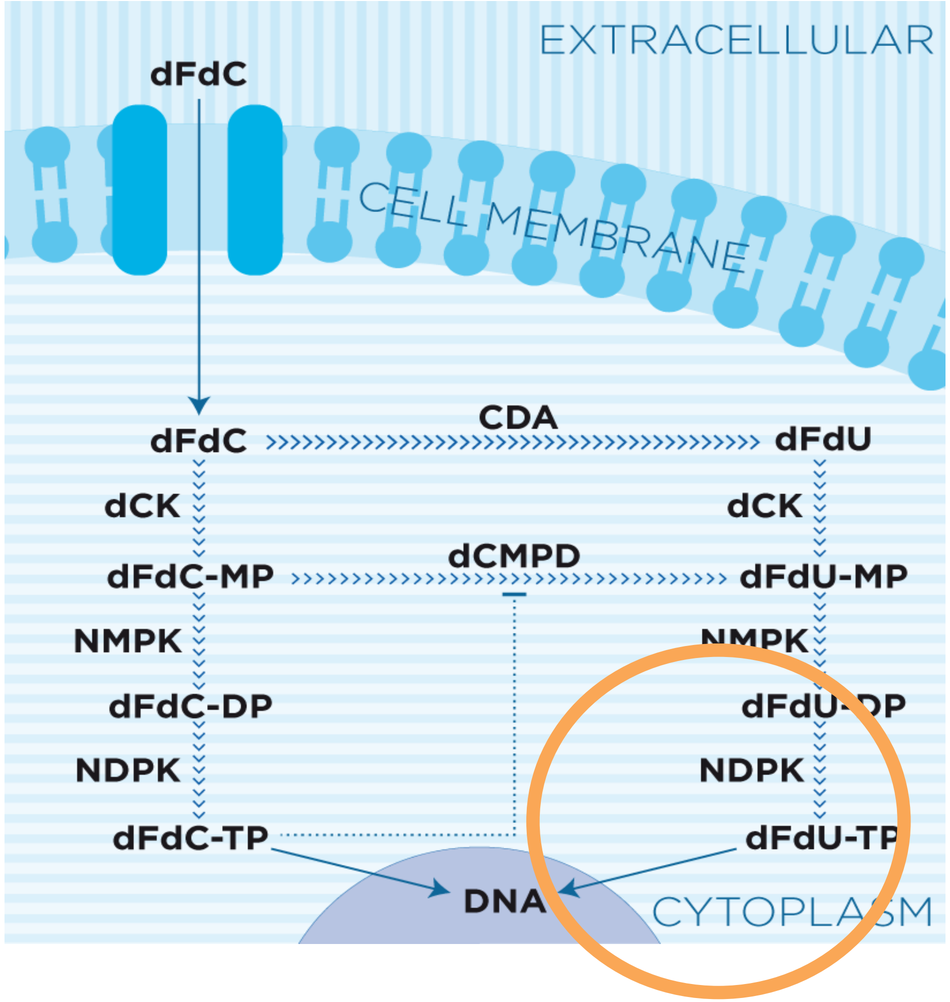
GLOBAL DYNAMICS

Gemcitabine triphosphate (dFdCTP and dFdUTP) is incorporated into DNA causing chain termination.



GLOBAL DYNAMICS

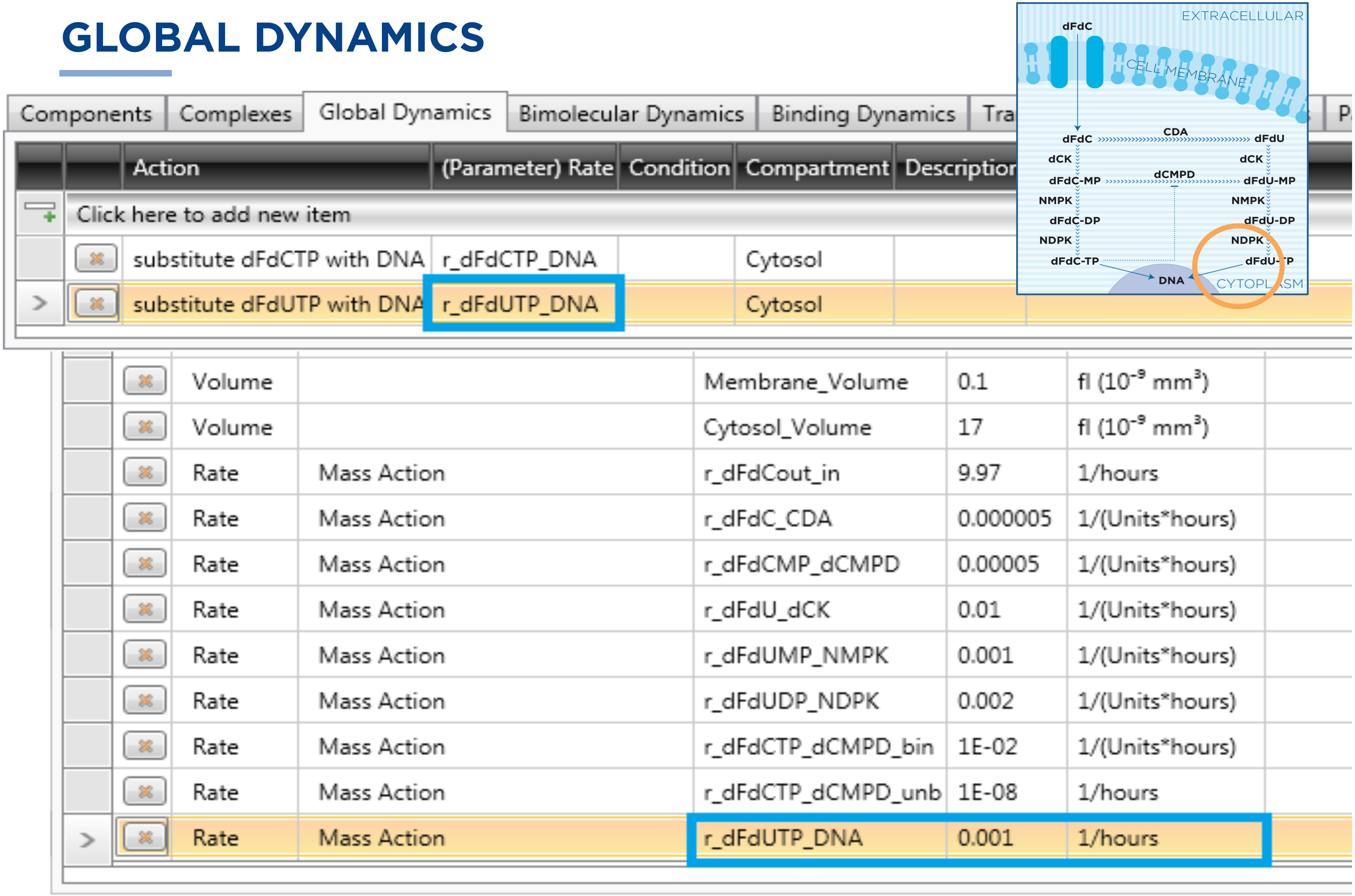
Gemcitabine triphosphate (dFdCTP and dFdUTP) is incorporated into DNA causing chain termination.



BlenX code:

```
let dFdUTP : bproc = #(s1, c_dFdUTP1), #(s2, c_dFdUTP2) [ p_main | rep start_p_main?().p_main ];
when (dFdUTP : : rate(r_dFdUTP_DNA)) split(DNA, Nil);
```

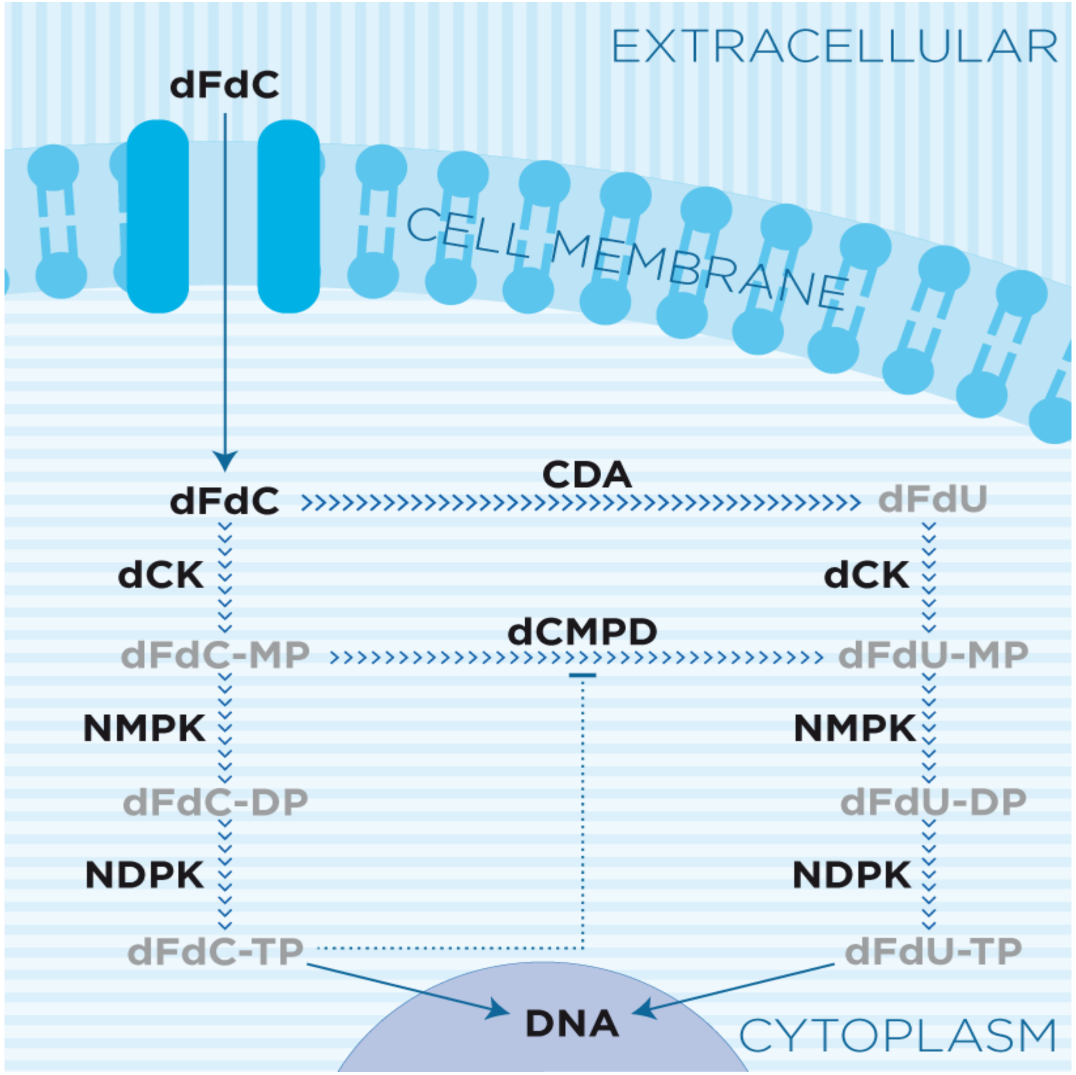
GLOBAL DYNAMICS



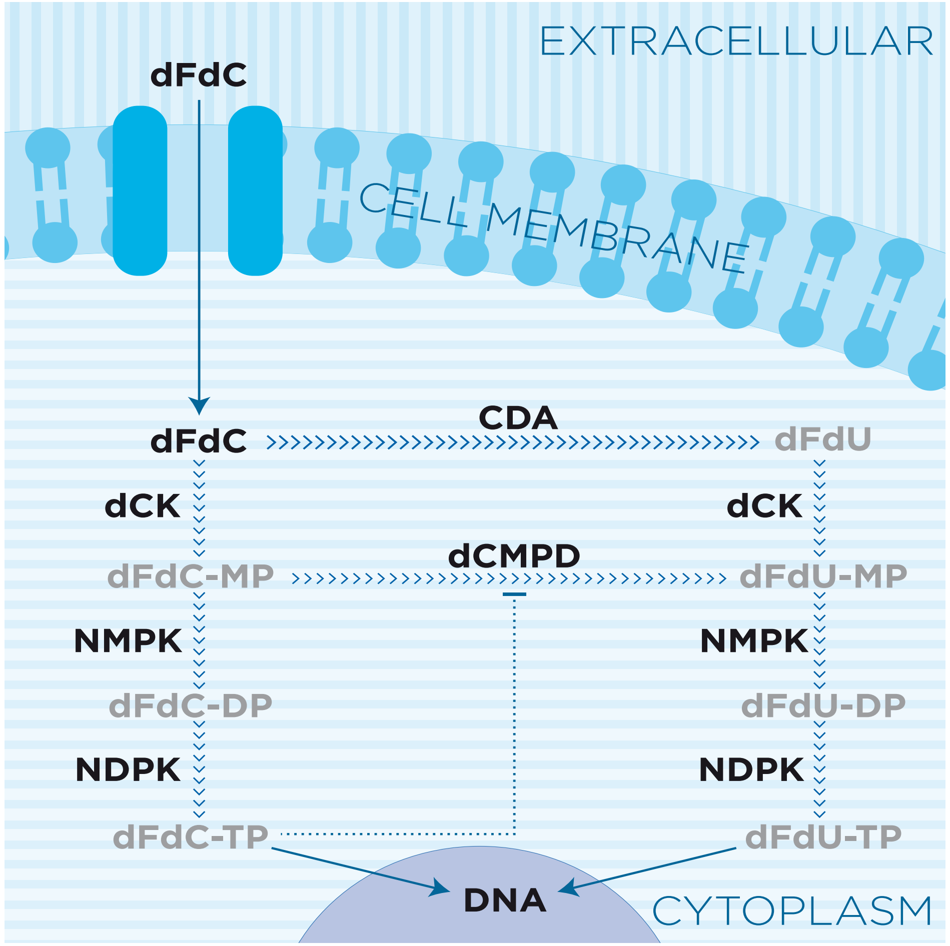
Action	(Parameter) Rate	Condition	Compartment	Description
Click here to add new item				
substitute dFdCTP with DNA	r_dFdCTP_DNA		Cytosol	
substitute dFdUTP with DNA	r_dFdUTP_DNA		Cytosol	

Volume		Membrane_Volume	0.1	fl (10^{-9} mm^3)
Volume		Cytosol_Volume	17	fl (10^{-9} mm^3)
Rate	Mass Action	r_dFdCout_in	9.97	1/hours
Rate	Mass Action	r_dFdC_CDA	0.000005	1/(Units*hours)
Rate	Mass Action	r_dFdCMP_dCMPD	0.00005	1/(Units*hours)
Rate	Mass Action	r_dFdU_dCK	0.01	1/(Units*hours)
Rate	Mass Action	r_dFdUMP_NMPK	0.001	1/(Units*hours)
Rate	Mass Action	r_dFdUDP_NDPK	0.002	1/(Units*hours)
Rate	Mass Action	r_dFdCTP_dCMPD_bin	1E-02	1/(Units*hours)
Rate	Mass Action	r_dFdCTP_dCMPD_unb	1E-08	1/hours
Rate	Mass Action	r_dFdUTP_DNA	0.001	1/hours

INITIAL STATE



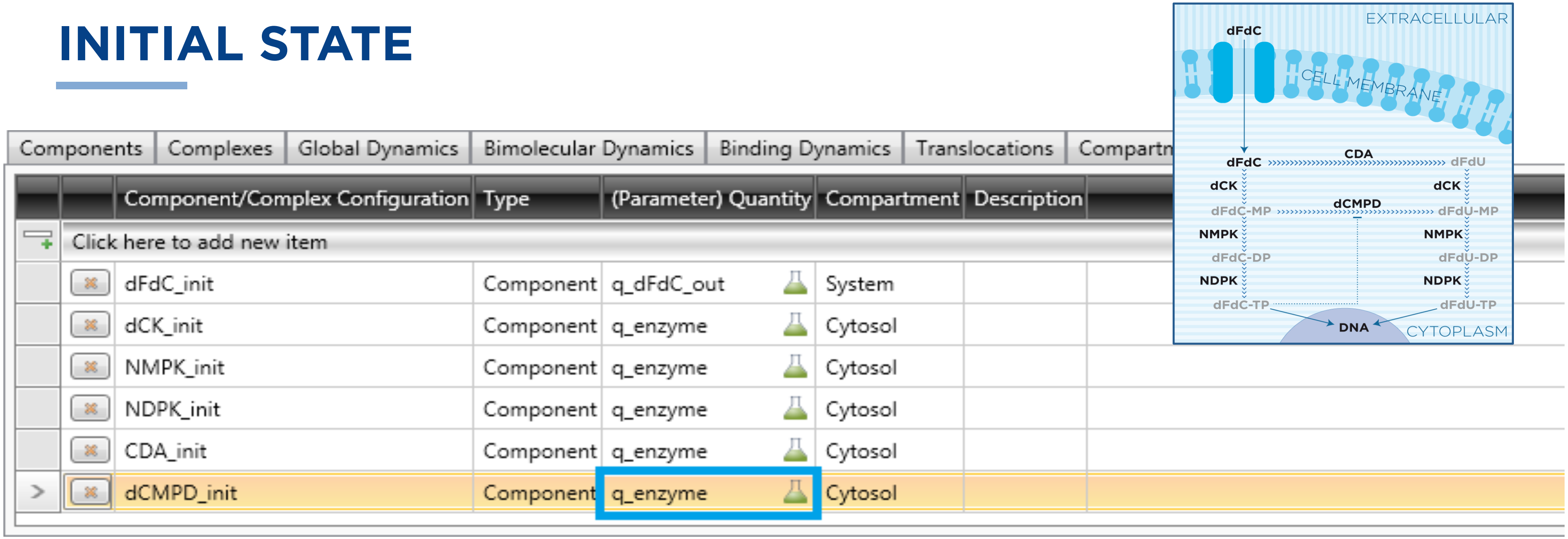
INITIAL STATE



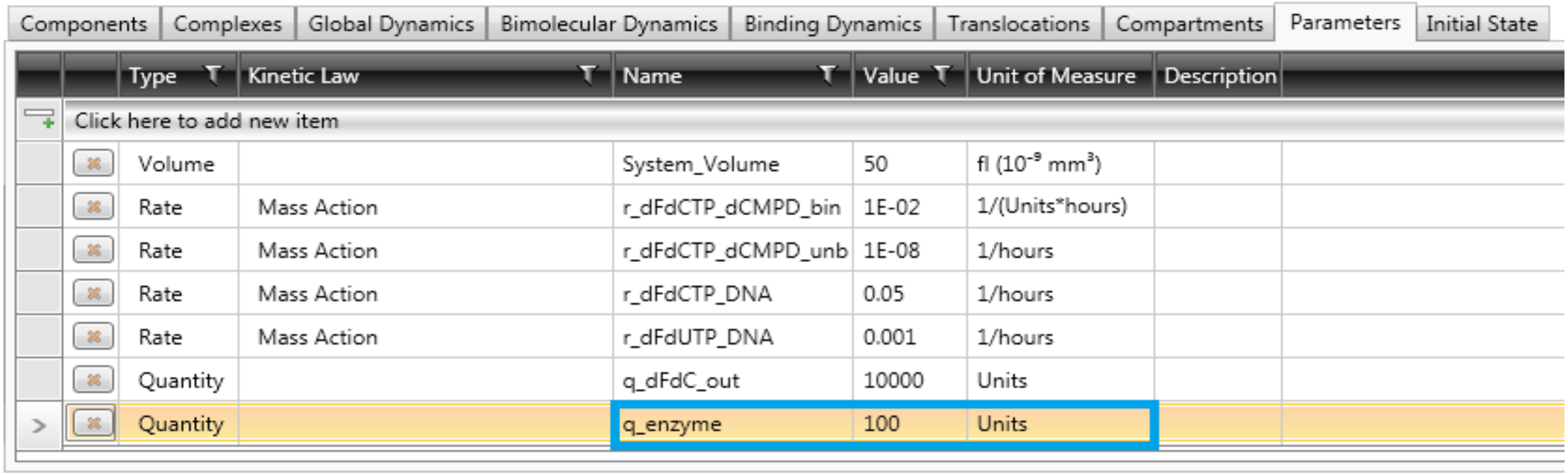
BlenX code:

```
run 10000 dFdCout || 100 dCK || 100 NMPK || 100 NDPK || 100 CDA || 100 dCMPD
```

INITIAL STATE

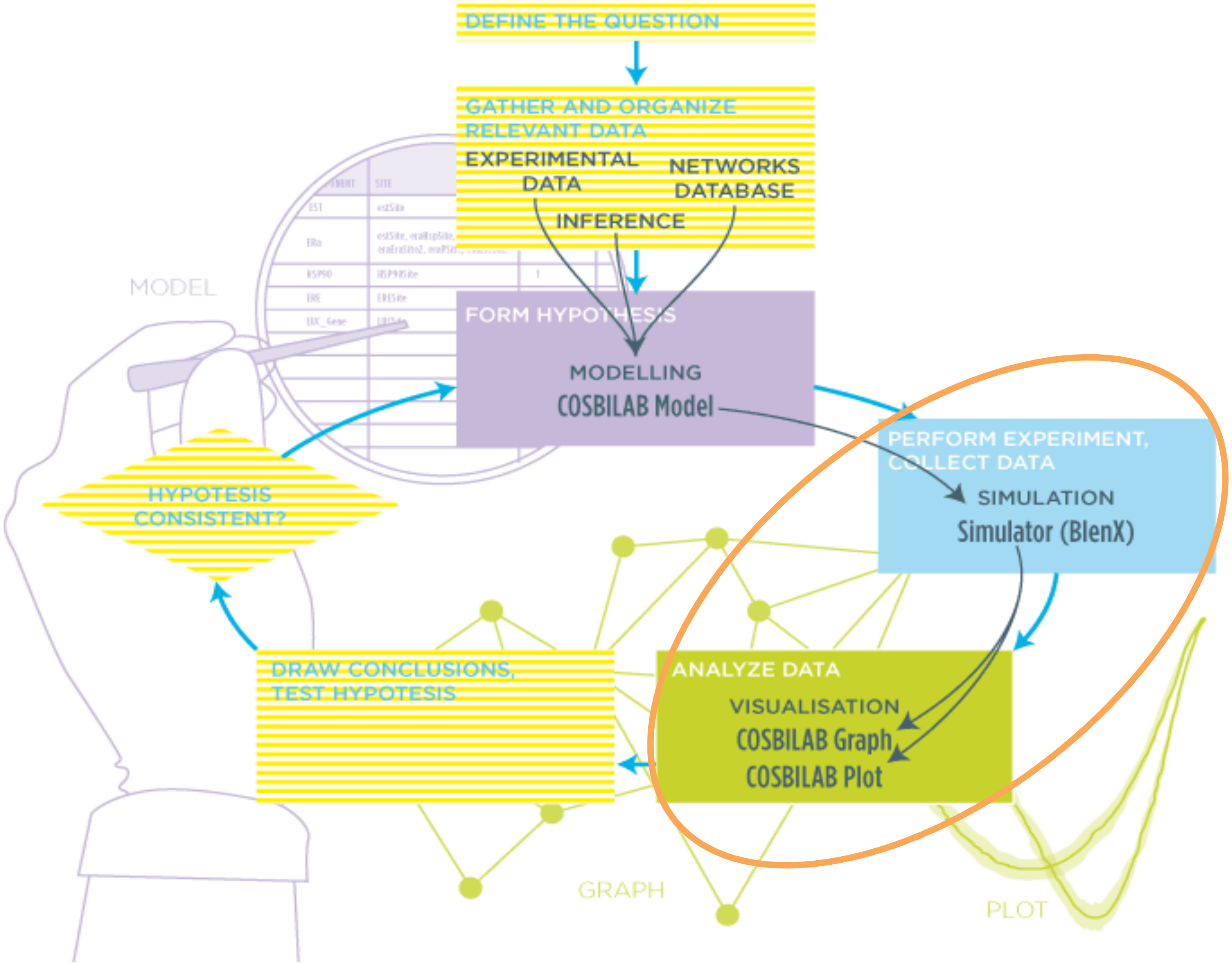


Component/Complex Configuration	Type	(Parameter) Quantity	Compartment	Description
dFdC_init	Component	q_dFdC_out	System	
dCK_init	Component	q_enzyme	Cytosol	
NMPK_init	Component	q_enzyme	Cytosol	
NDPK_init	Component	q_enzyme	Cytosol	
CDA_init	Component	q_enzyme	Cytosol	
dCMPD_init	Component	q_enzyme	Cytosol	



Type	Kinetic Law	Name	Value	Unit of Measure	Description
Volume		System_Volume	50	fl $(10^{-9}$ mm$^3)$	
Rate	Mass Action	r_dFdCTP_dCMPD_bin	1E-02	1/(Units*hours)	
Rate	Mass Action	r_dFdCTP_dCMPD_unb	1E-08	1/hours	
Rate	Mass Action	r_dFdCTP_DNA	0.05	1/hours	
Rate	Mass Action	r_dFdUTP_DNA	0.001	1/hours	
Quantity		q_dFdC_out	10000	Units	
Quantity		q_enzyme	100	Units	

COSBI WORKING FLOW



DEFINE THE QUESTION

GATHER AND ORGANIZE RELEVANT DATA

EXPERIMENTAL DATA

NETWORKS DATABASE

INFERENCE

FORM HYPOTHESIS

MODELLING

COSBILAB Model

PERFORM EXPERIMENT, COLLECT DATA

SIMULATION

Simulator (BlenX)

ANALYZE DATA

VISUALISATION

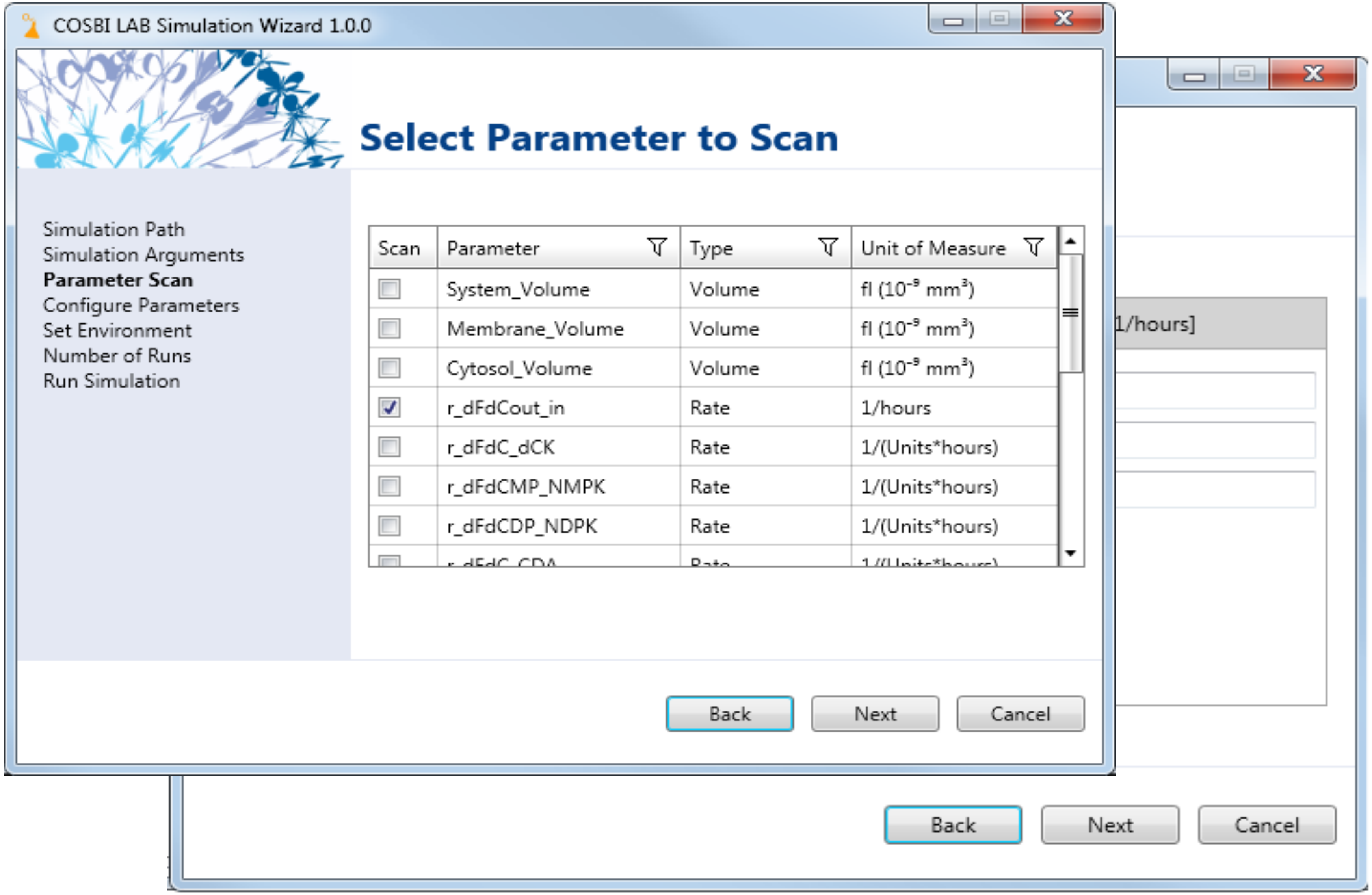
COSBILAB Graph

COSBILAB Plot

DRAW CONCLUSIONS, TEST HYPOTESIS

HYPOTESIS CONSISTENT?

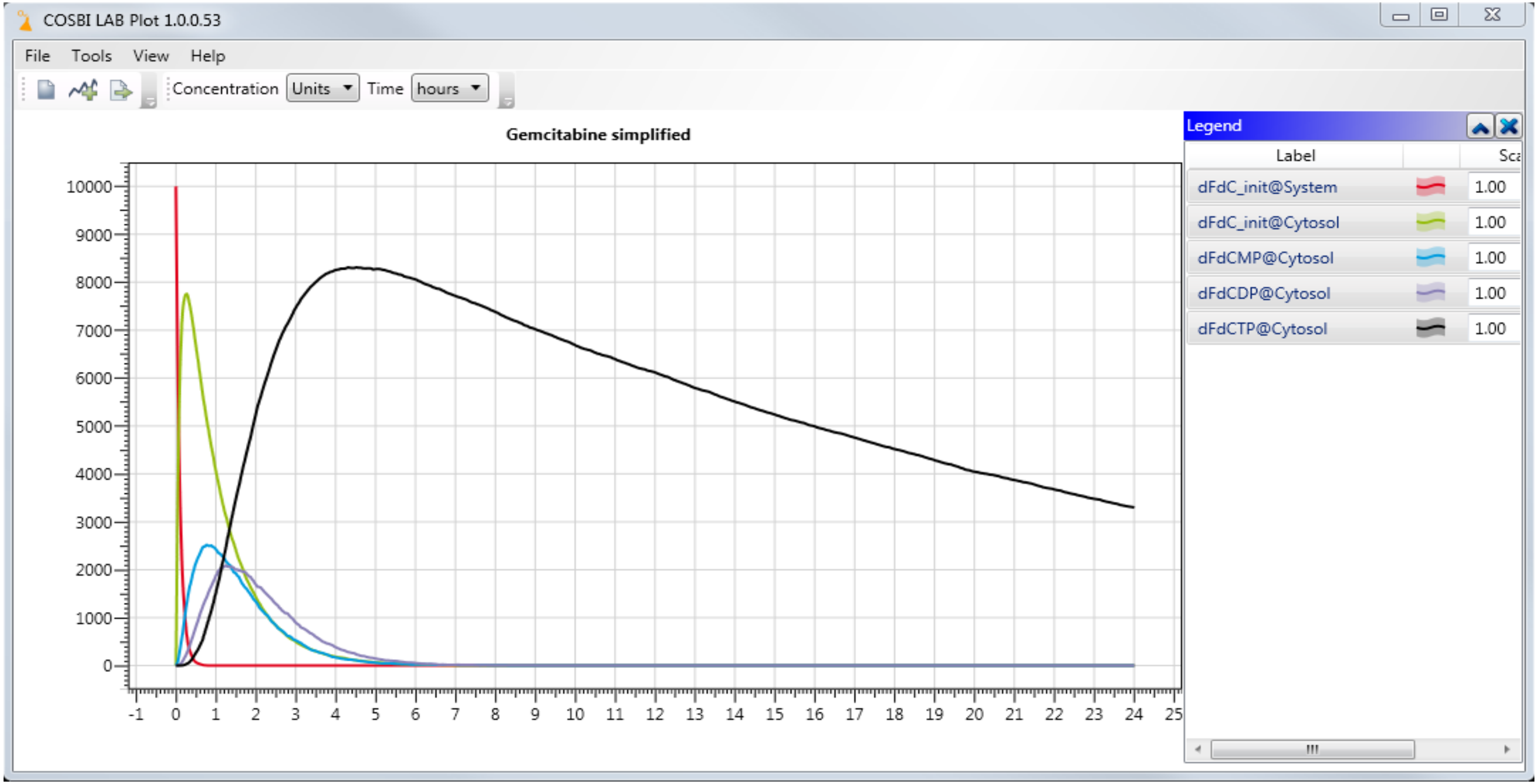
SIMULATION



Select Parameter to Scan

Scan	Parameter	Type	Unit of Measure
☐	System_Volume	Volume	fl (10^{-9} mm^3)
☐	Membrane_Volume	Volume	fl (10^{-9} mm^3)
☐	Cytosol_Volume	Volume	fl (10^{-9} mm^3)
☑	r_dFdCout_in	Rate	1/hours
☐	r_dFdC_dCK	Rate	1/(Units*hours)
☐	r_dFdCMP_NMPK	Rate	1/(Units*hours)
☐	r_dFdCDP_NDPK	Rate	1/(Units*hours)
☐	r_dFdC_CDA	Rate	1/(Units*hours)

VISUALIZE RESULTS

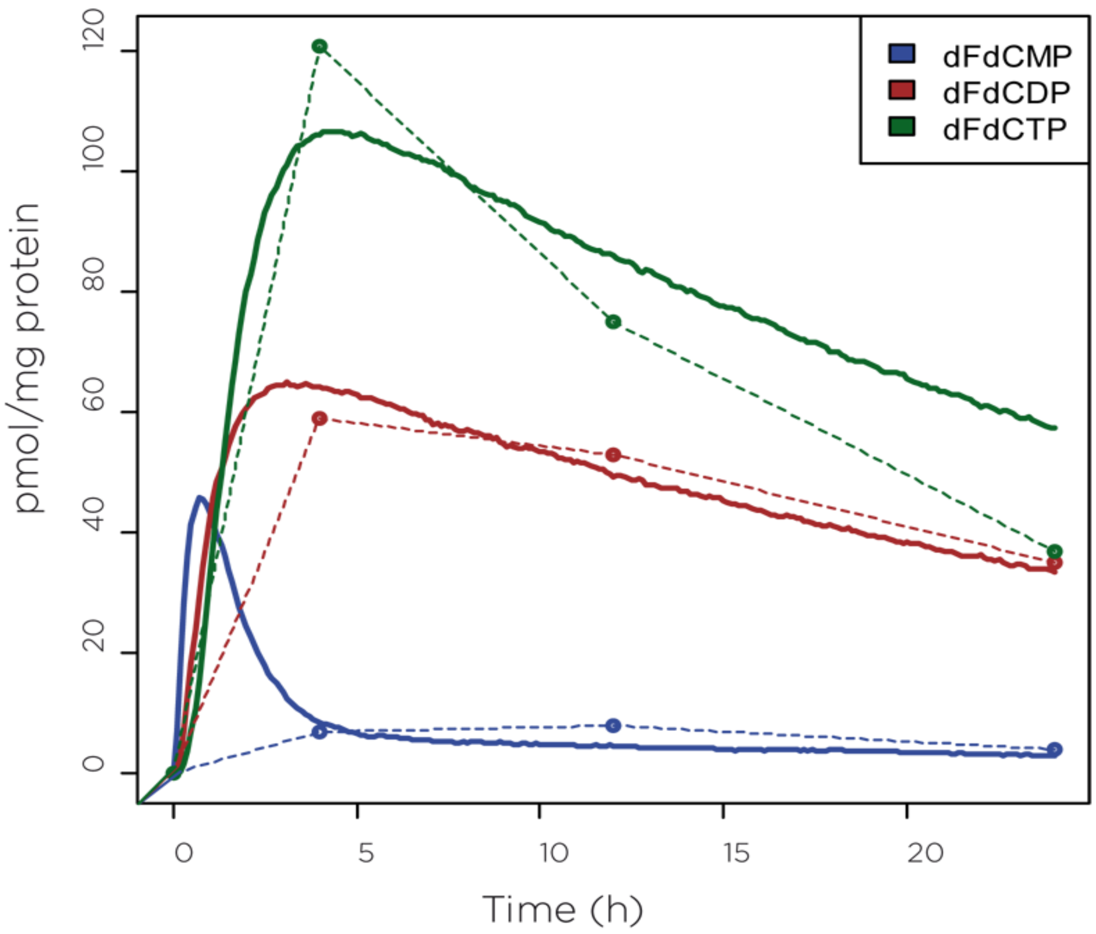


Concentration Units Time hours

Label		Sca
dFdC_init@System	🟥	1.00
dFdC_init@Cytosol	🟩	1.00
dFdCMP@Cytosol	🟦	1.00
dFdCDP@Cytosol	🟪	1.00
dFdCTP@Cytosol	⬛	1.00

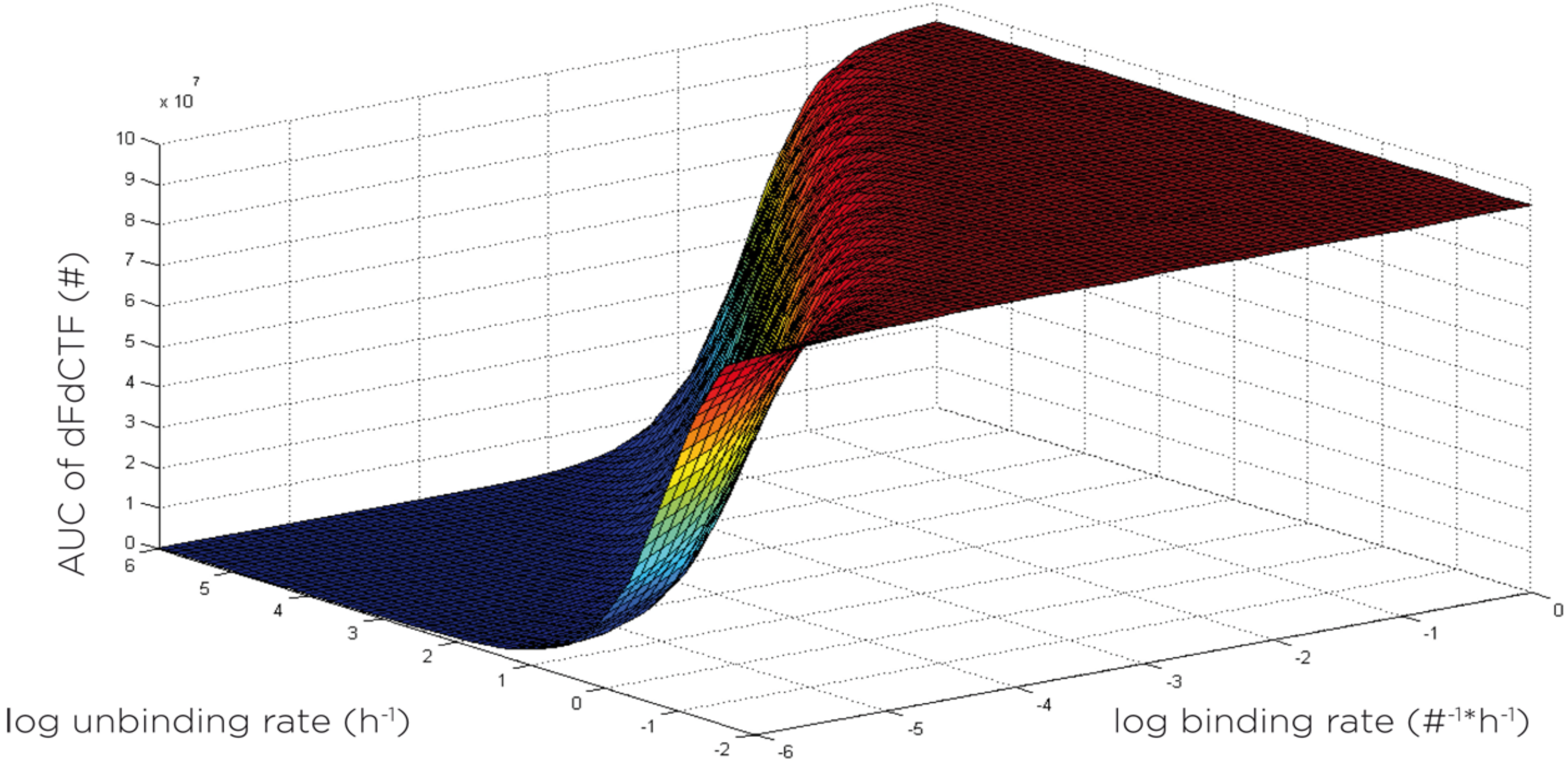
SIMULATION RESULTS PLOT

Intracellular concentration versus time



SENSITIVITY ANALYSIS

Accumulation of dFdCTP w.r.t. dCTP inhibition on dCK



COSBILAB MODEL:
MODELING & SIMULATING COMPLEX SYSTEMS

Create models via tabular interface.
No expertise in programming nor math needed

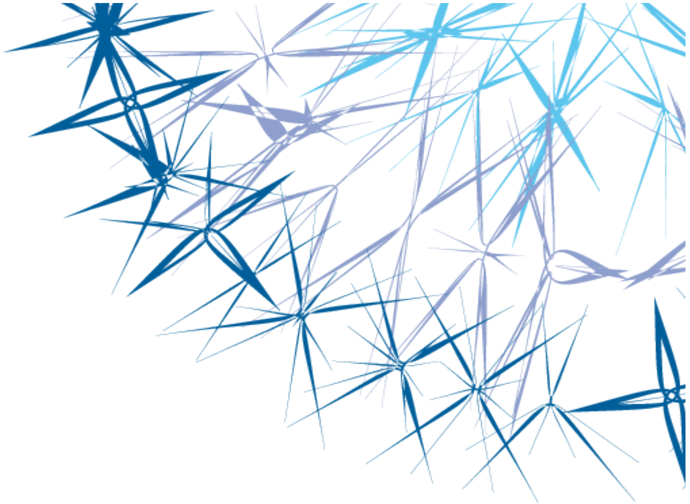
Allow life scientist analyze models

Easily manage experiments: knock-down genes, change rates, add a “virtual” drug.

In silico science: adding knowledge, saving time.

Share models & results with colleagues, wherever they are.

Accelerate discovery process, add value to your work.



Spatial simulation

P. Lecca, L. Dematte', A. Ihekwaba, C. Priami. Redi: a simulator of stochastic biochemical reaction-diffusion systems, The Second International Conference on Advances in System Simulation (SIMUL 2010), 2010.

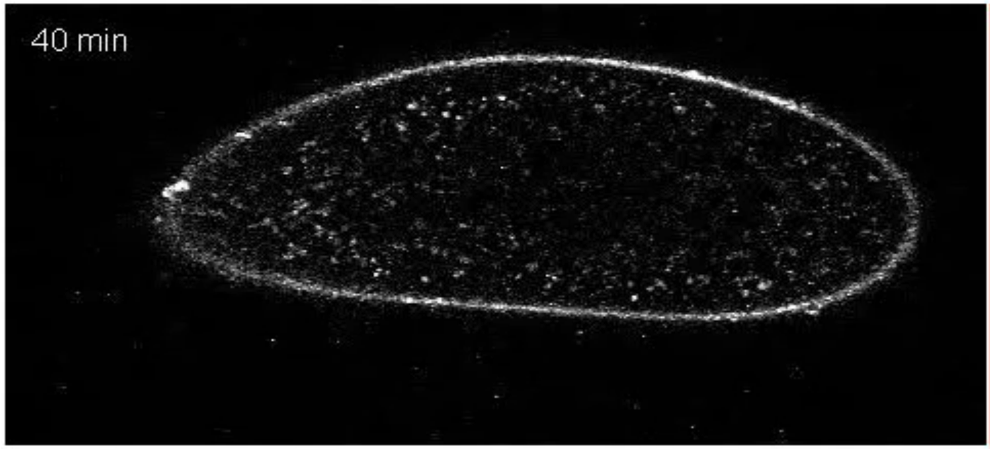
SPACE AND DIFFUSION

Reaction-diffusion simulator at the mesoscopic interaction scale.

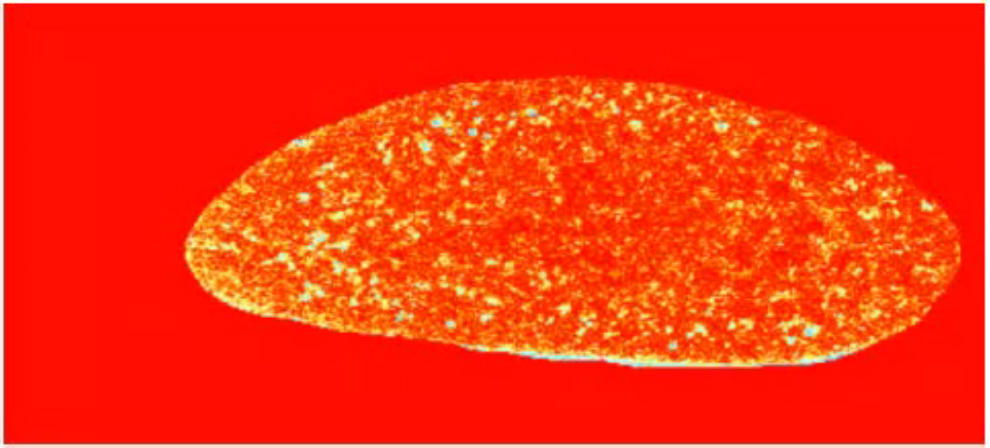
Space discretised variant of the Gillespie SSA.

Dynamically state-dependent diffusion coefficient.

BICOID SIMULATION

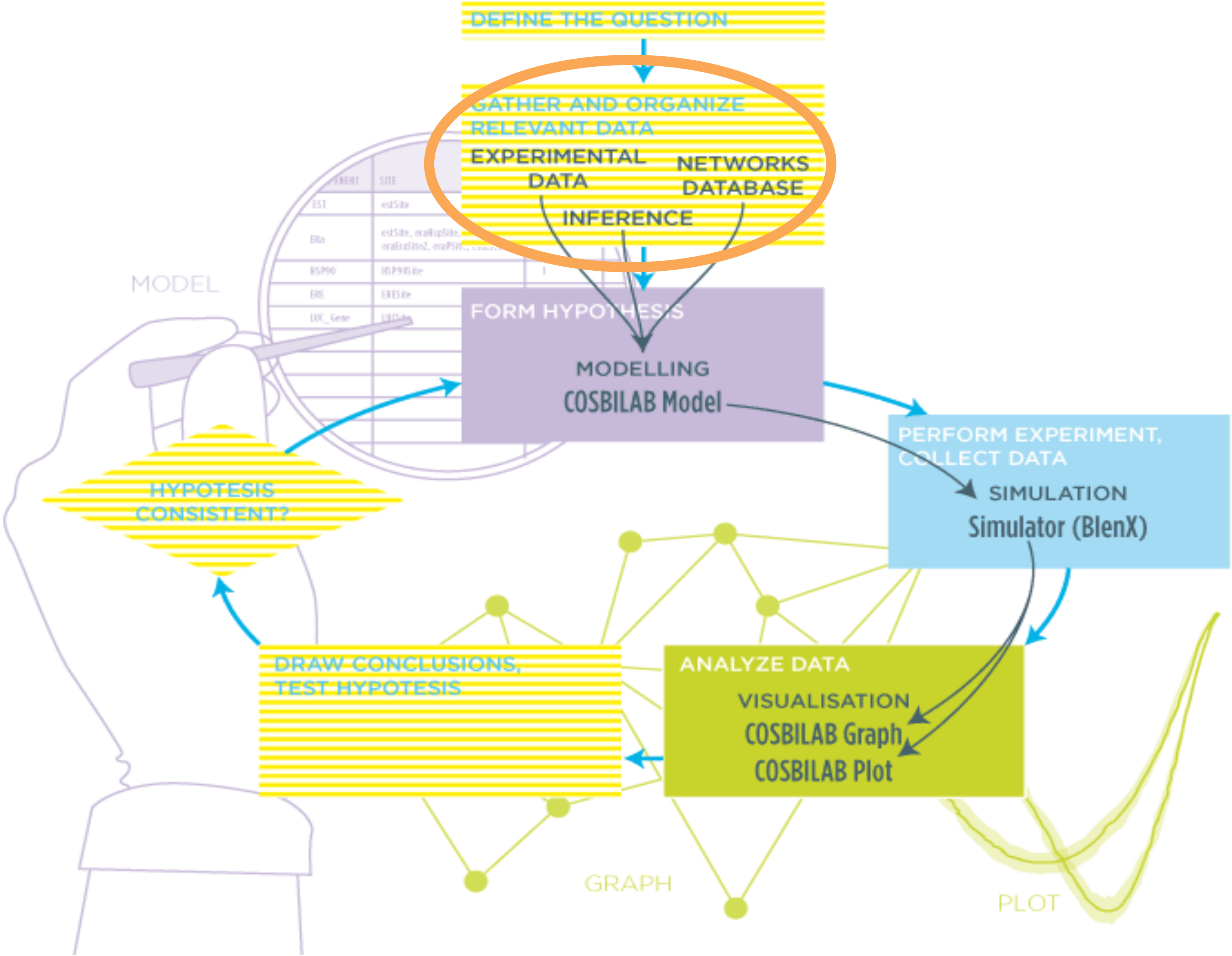


Experimental



Simulated

COSBI WORKING FLOW



DEFINE THE QUESTION

GATHER AND ORGANIZE RELEVANT DATA

EXPERIMENTAL DATA

NETWORKS DATABASE

INFERENCE

FORM HYPOTHESIS

MODELLING

COSBILAB Model

PERFORM EXPERIMENT, COLLECT DATA

SIMULATION

Simulator (BlenX)

ANALYZE DATA

VISUALISATION

COSBILAB Graph

COSBILAB Plot

DRAW CONCLUSIONS, TEST HYPOTESIS

HYPOTESIS CONSISTENT?

KNOWLEDGE EXTRACTION AND MODELING

Define the problem you want to address

SELECT DATABASES OF INTEREST

Clinical - *omics* experiments - Ontological

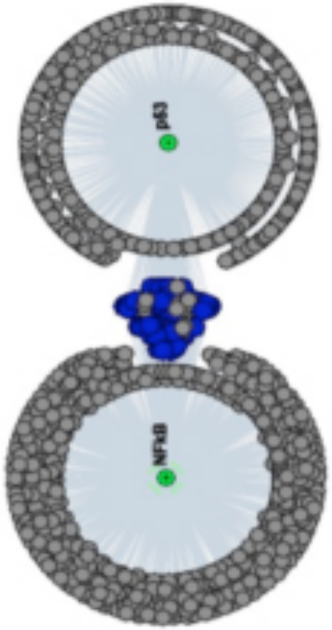
DATA MINING

Organize, integrate and analyze data

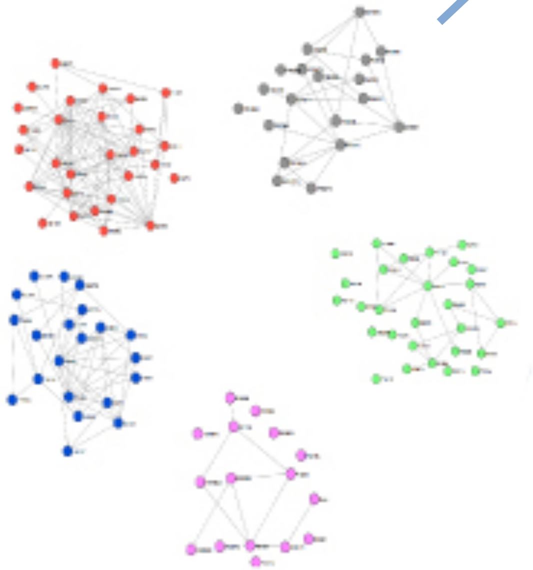
KNOWLEDGE EXTRACTION

KNOWLEDGE EXTRACTION AND MODELING

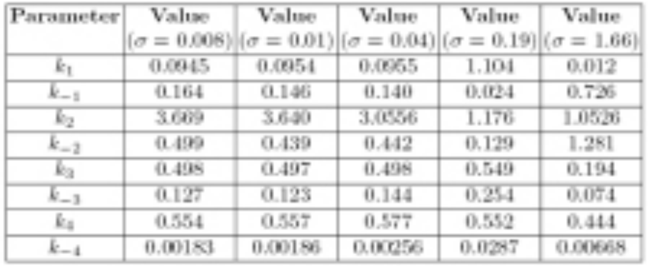
Model identification
Network inference



Model analysis
Network analysis

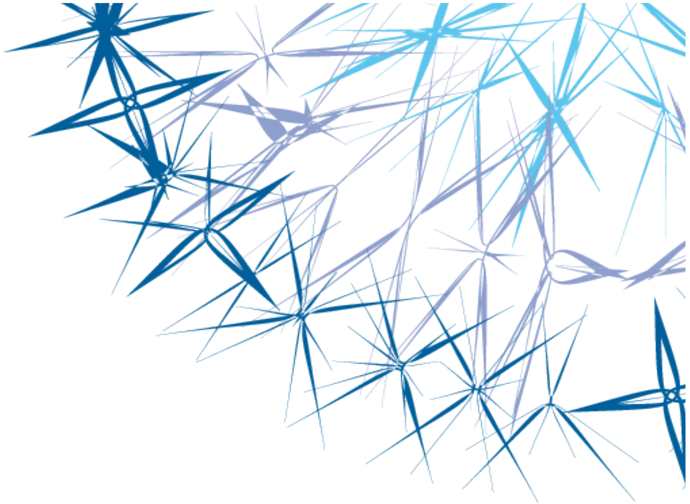


Model calibration
Parameter inference



Parameter	Value ($\sigma = 0.008$)	Value ($\sigma = 0.01$)	Value ($\sigma = 0.04$)	Value ($\sigma = 0.19$)	Value ($\sigma = 1.66$)
k_1	0.0945	0.0954	0.0955	1.104	0.012
k_{-1}	0.164	0.146	0.140	0.024	0.726
k_2	3.669	3.640	3.0556	1.176	1.0526
k_{-2}	0.499	0.439	0.442	0.129	1.281
k_3	0.498	0.497	0.498	0.549	0.194
k_{-3}	0.127	0.123	0.144	0.254	0.074
k_4	0.554	0.557	0.577	0.552	0.444
k_{-4}	0.00183	0.00186	0.00256	0.0287	0.00668

Algorithmic
modeling



Knowledge inference

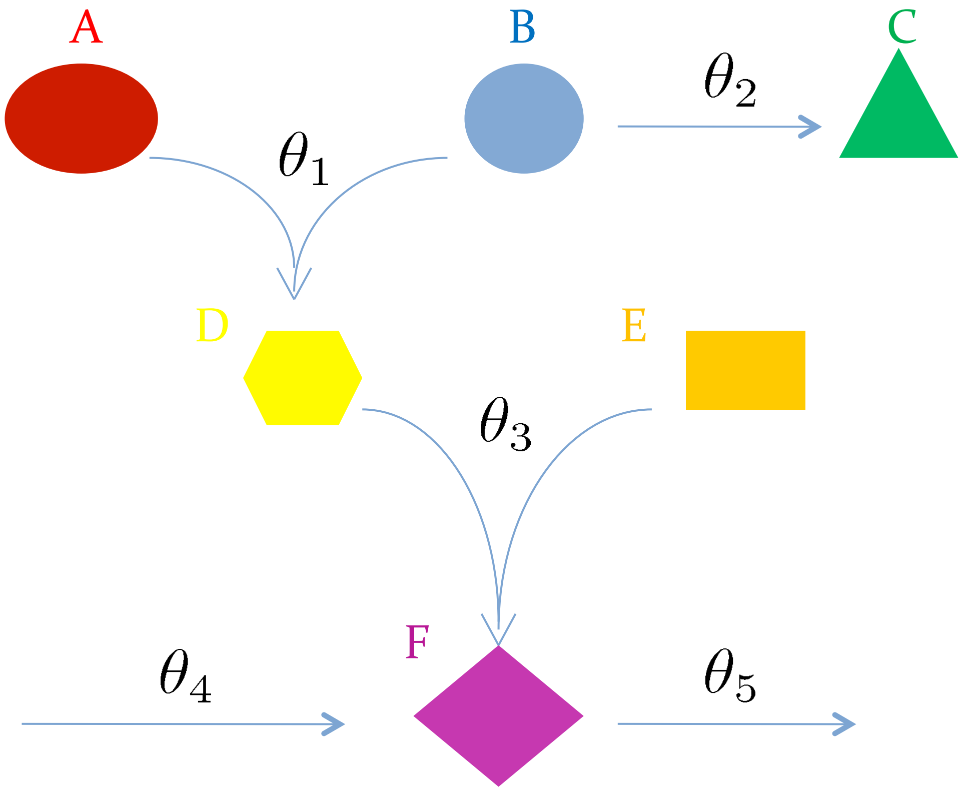
P. Lecca, A. Palmisano, C. Priami, G. Sanguinetti. *A new probabilistic generative model of parameter inference in biochemical networks*. Proceedings of the ACM Symposium on Applied Computing, 2009.

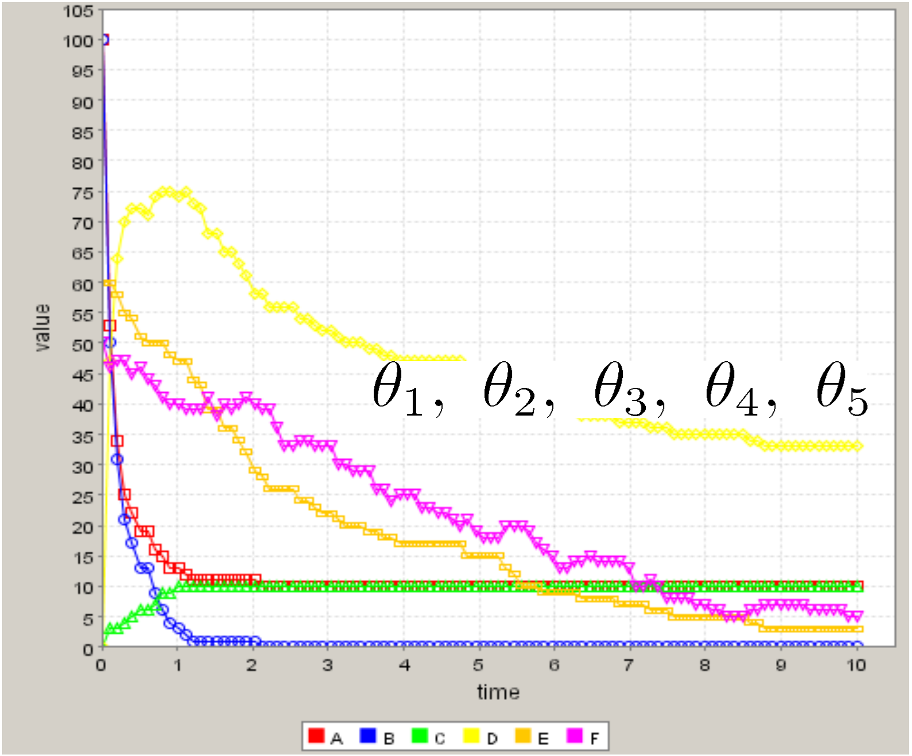
P. Lecca, A. Palmisano, A. Ihekwaba, C. Priami. *Calibration of dynamic models of biological systems with KInfer*. European Biophysics Journal, 39:1019-1039, 2010

THE SYSTEM AND THE DATA

Experimentally observed time course data of the reactants concentrations.

From these behaviors we want to estimate



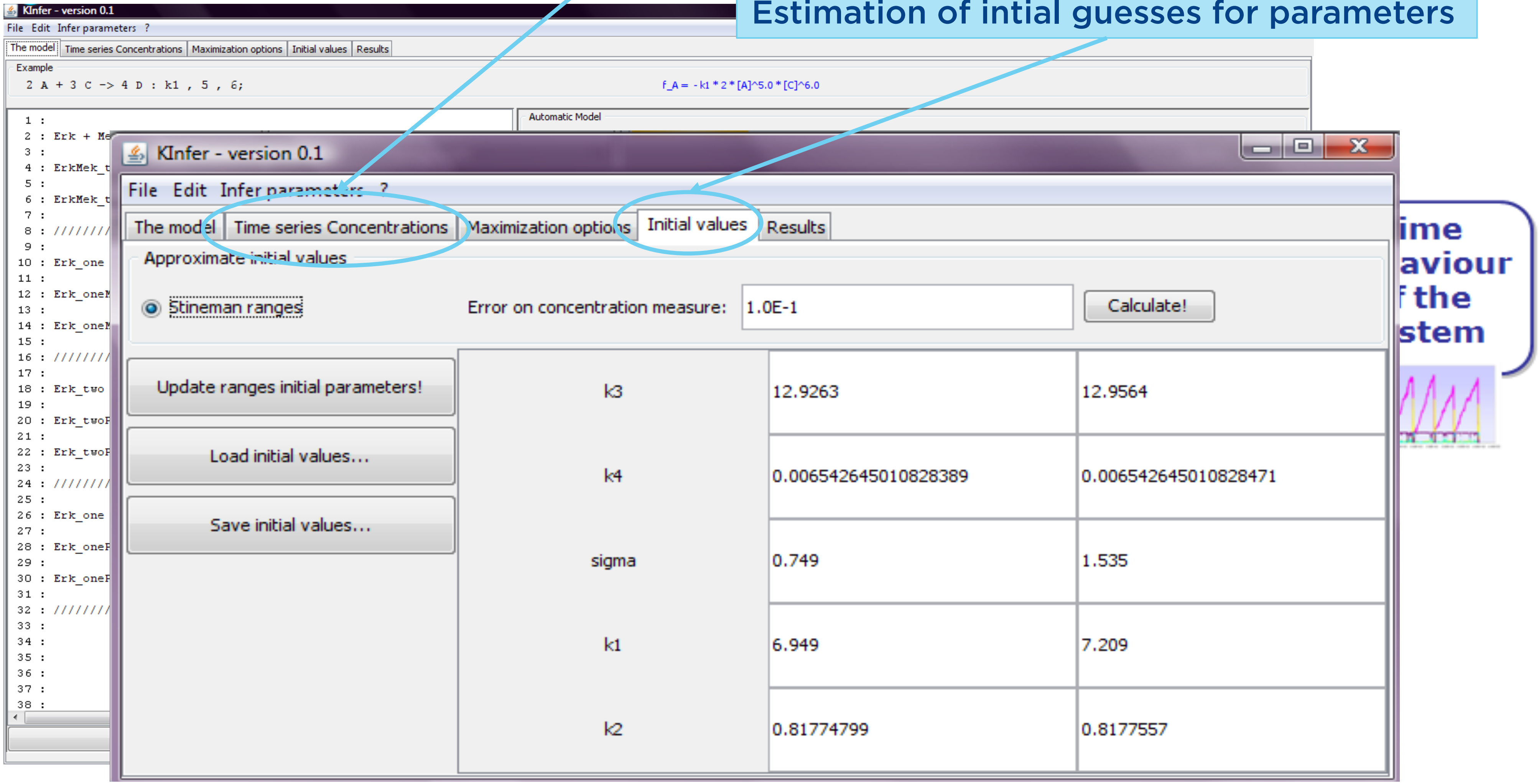


$\theta_1,\ \theta_2,\ \theta_3,\ \theta_4,\ \theta_5$

COMPUTATIONAL SUPPORT: KINFER

Loading time series of species concentrations

Estimation of intial guesses for parameters



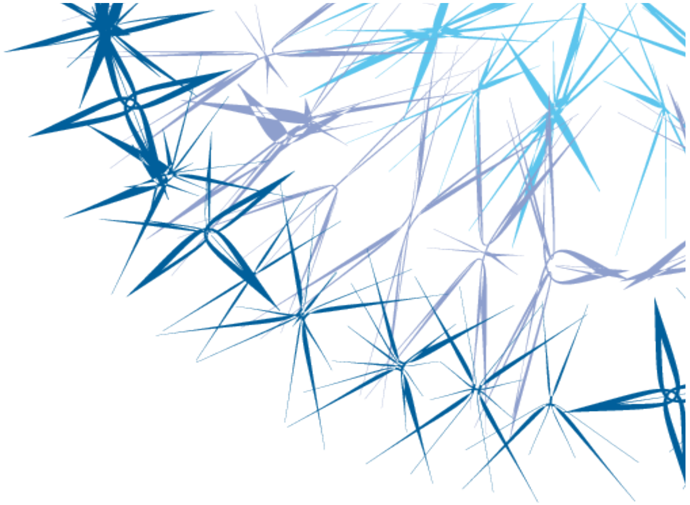
```
2 A + 3 C -> 4 D : k1 , 5 , 6;
```

f_A = - k1 * 2 * [A]^5.0 * [C]^6.0

● Stineman ranges

Error on concentration measure: 1.0E-1

k3	12.9263	12.9564
k4	0.006542645010828389	0.006542645010828471
sigma	0.749	1.535
k1	6.949	7.209
k2	0.81774799	0.8177557

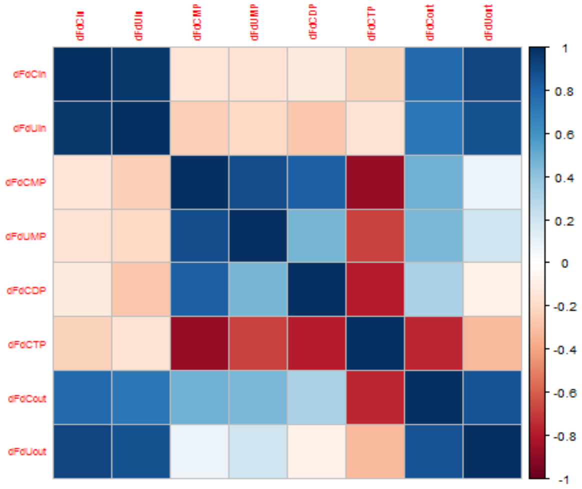


Network inference

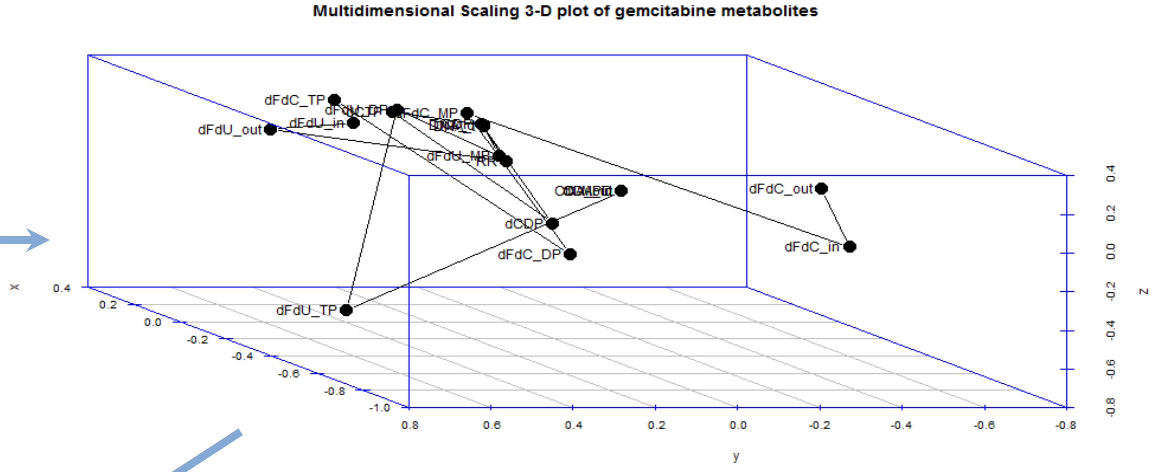
P. Lecca, P. Nguyen, C. Priami, P. Quaglia. Network inference from Time-Dependent Omics Data, Bioinformatics for Omics data: Methods and Protocols in Molecular Biology Springer Science+Business Media, LLC 2011, 2011

NETWORK INFERENCE

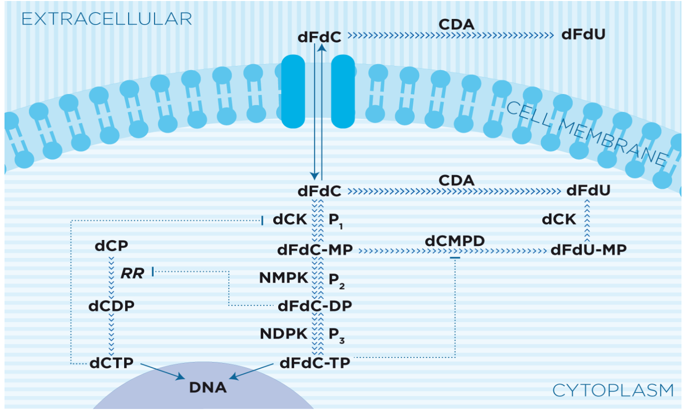
Lagged correlations



Distance clustering



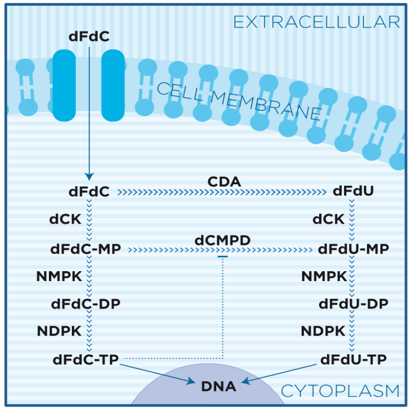
Network calibration

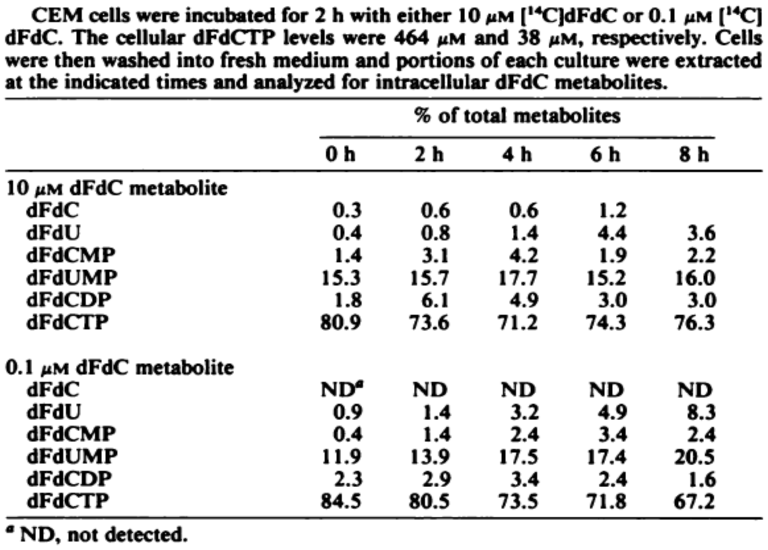


IDENTIFICATION OF METABOLIC NETWORKS

Gemcitabine metabolism: input data from

Volker Heinemann, Yi-Zheng Xu, Sherri Chubb, Alina Sen, Larry W. Hertel, Gerald B. Grindey, and William PlunkettCellular Elimination of 2′,2′-Difluorodeoxycytidine 5′-Triphosphate: A Mechanism of Self-PotentiationCANCER RESEARCH 52, 533-539, February 1, 1992



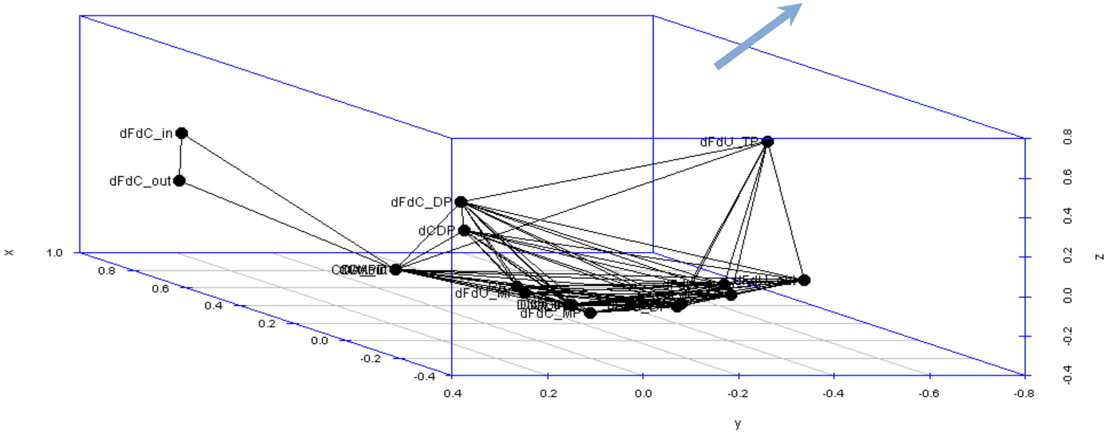


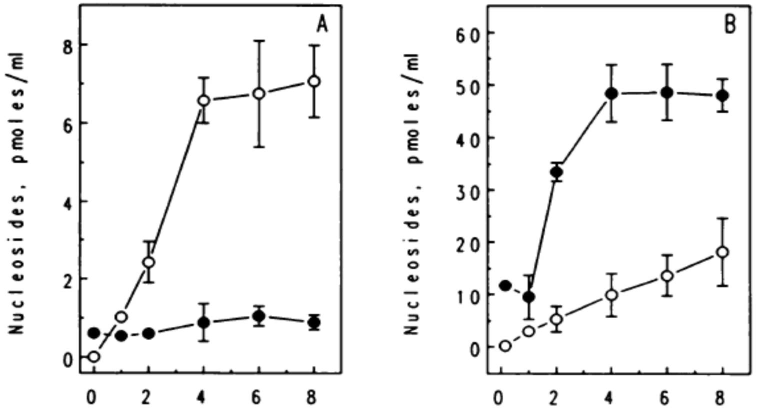
CEM cells were incubated for 2 h with either 10 μM [^{14}C]dFdC or 0.1 μM [^{14}C] dFdC. The cellular dFdCTP levels were 464 μM and 38 μM, respectively. Cells were then washed into fresh medium and portions of each culture were extracted at the indicated times and analyzed for intracellular dFdC metabolites.

	% of total metabolites				
	0 h	2 h	4 h	6 h	8 h
10 μM dFdC metabolite					
dFdC	0.3	0.6	0.6	1.2	
dFdU	0.4	0.8	1.4	4.4	3.6
dFdCMP	1.4	3.1	4.2	1.9	2.2
dFdUMP	15.3	15.7	17.7	15.2	16.0
dFdCDP	1.8	6.1	4.9	3.0	3.0
dFdCTP	80.9	73.6	71.2	74.3	76.3
0.1 μM dFdC metabolite					
dFdC	ND[a]	ND	ND	ND	ND
dFdU	0.9	1.4	3.2	4.9	8.3
dFdCMP	0.4	1.4	2.4	3.4	2.4
dFdUMP	11.9	13.9	17.5	17.4	20.5
dFdCDP	2.3	2.9	3.4	2.4	1.6
dFdCTP	84.5	80.5	73.5	71.8	67.2

[a] ND, not detected.

Multidimensional Scaling 3-D plot





MODEL PARAMETERS

The parameters are the specific speed of the following events:

- Degradation rate of gemcitabine (k1)
- Drug inefficiency rate (k2)
- Drug efficacy (i. e. constant-cell-kill rate) (k3)
- Tumor growth rate (k4)
- k5: injection is modeled as single instantaneous event having infinite rate constant

METHODS AND DATA

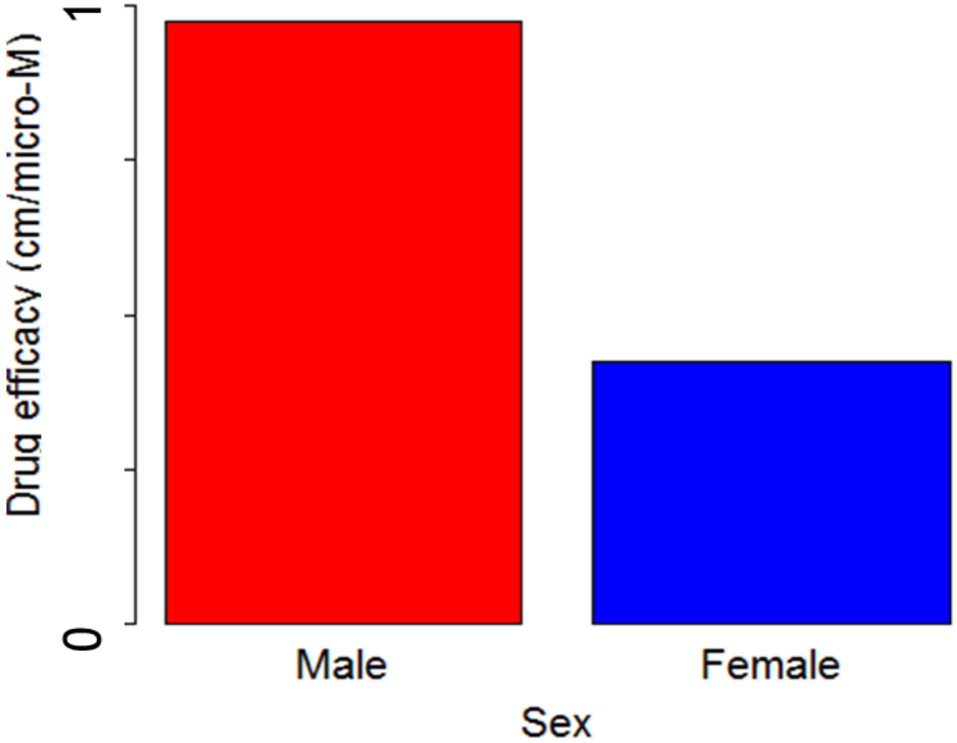
- We used KInfer on the time courses of tumor shrinkage and gemcitabine dosage on 56 patients to infer the parameters of the model.
- Patients have been divided with respect to sex, age and smoke history.
- The experimental curves of tumor shrinkage have been provided by R. A. Soo of the Department of Hematology-Oncology, National University Hospital, Singapore.

DRUG EFFICACY AND CLASSES OF PATIENTS

- We found that the drug efficacy (k3) is correlated to the patient sex, smoke history, and tumor stage.

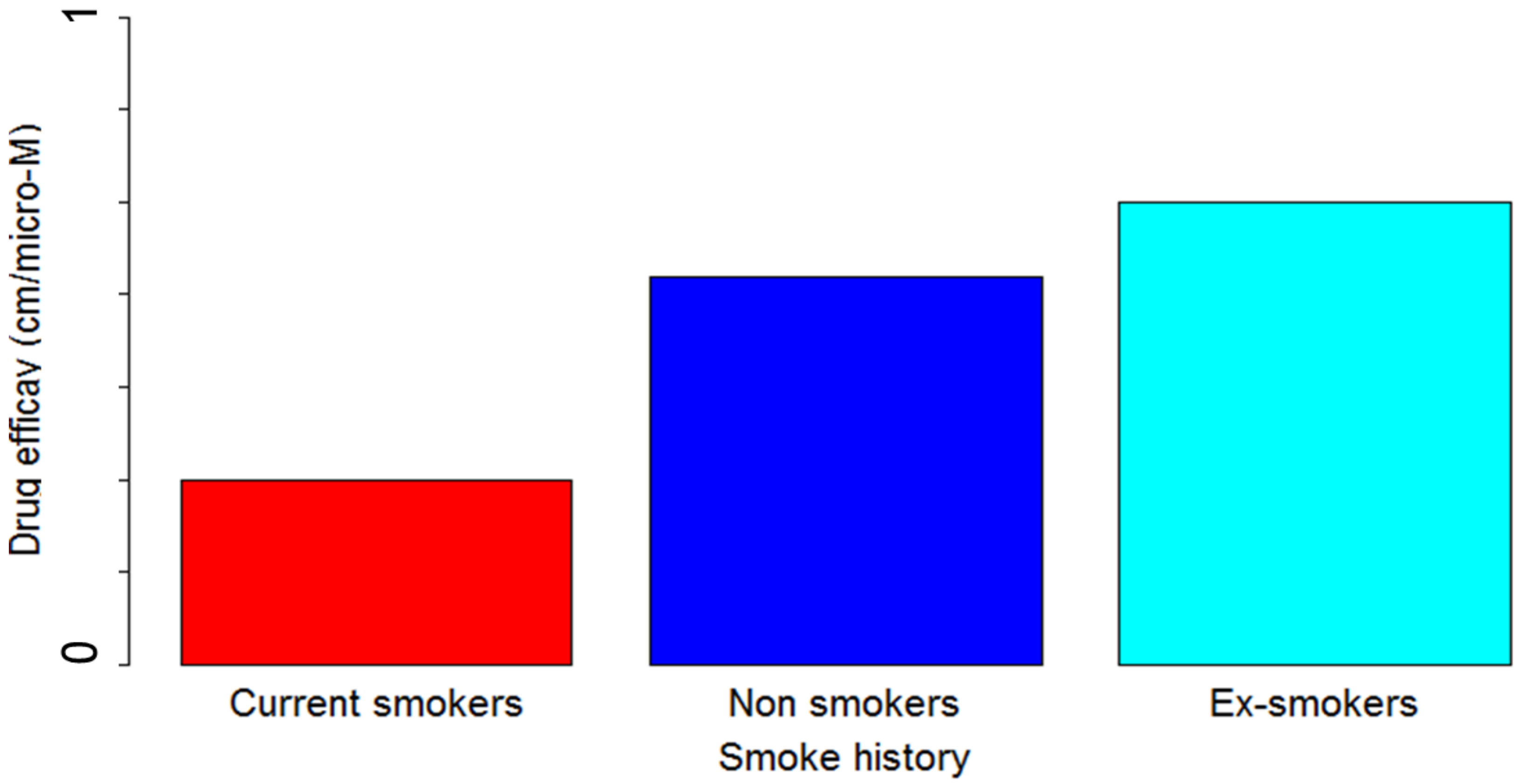
- No correlation seems to exist between drug efficacy and patient age.

EFFICACY AND GENDER



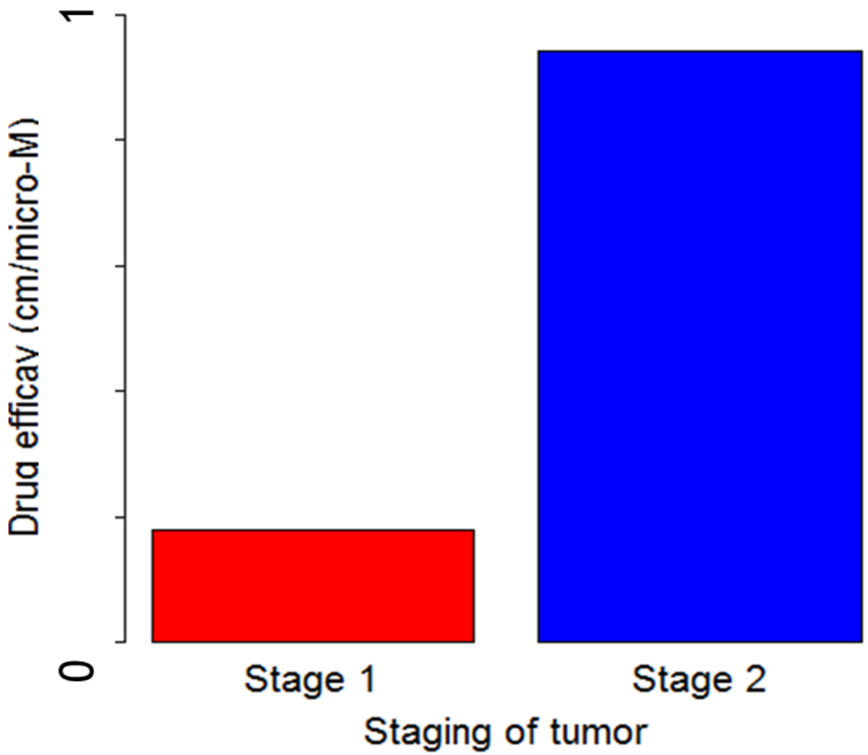
Normalized beween 0 and 1

EFFICACY AND SMOKE HISTORY

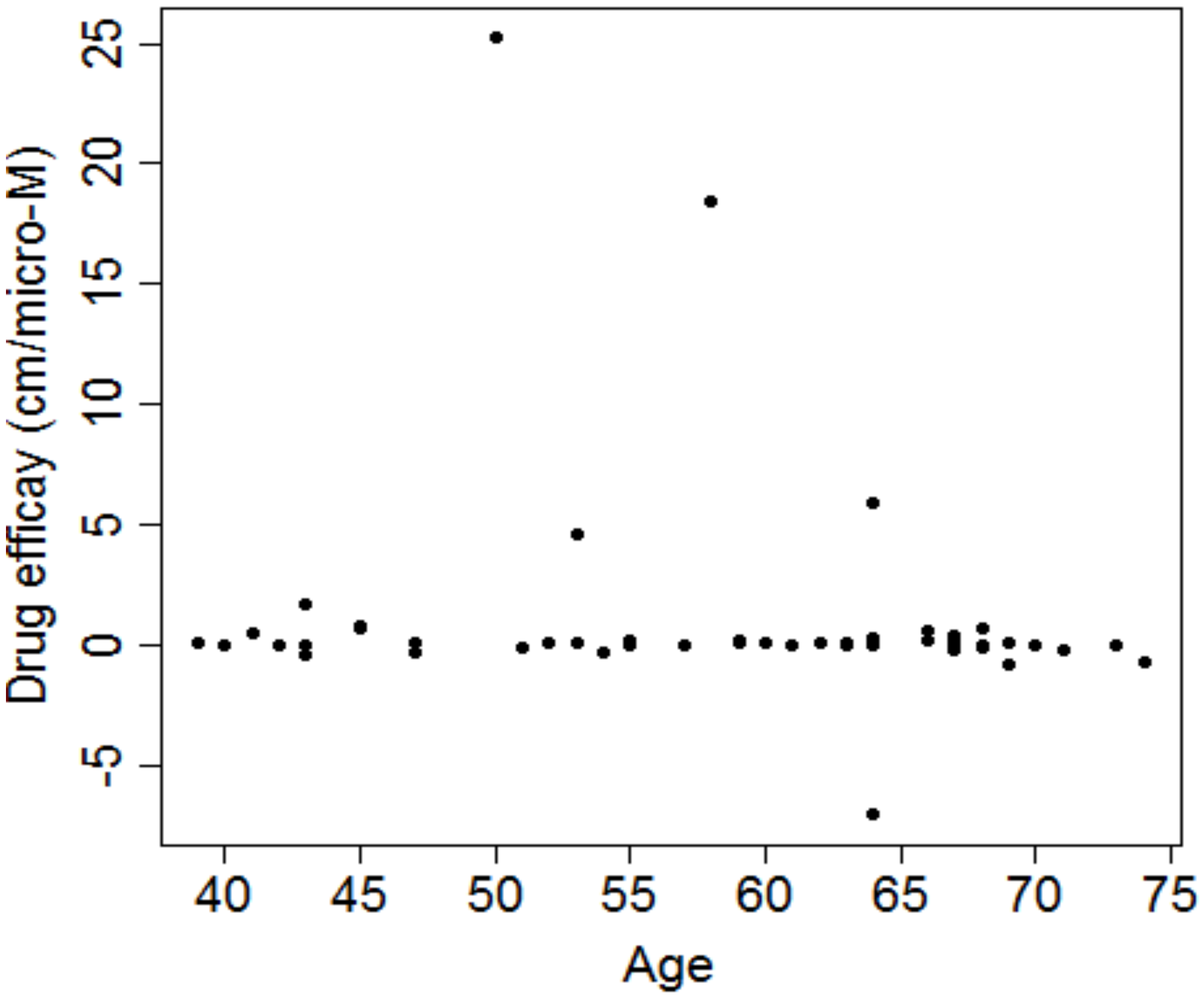


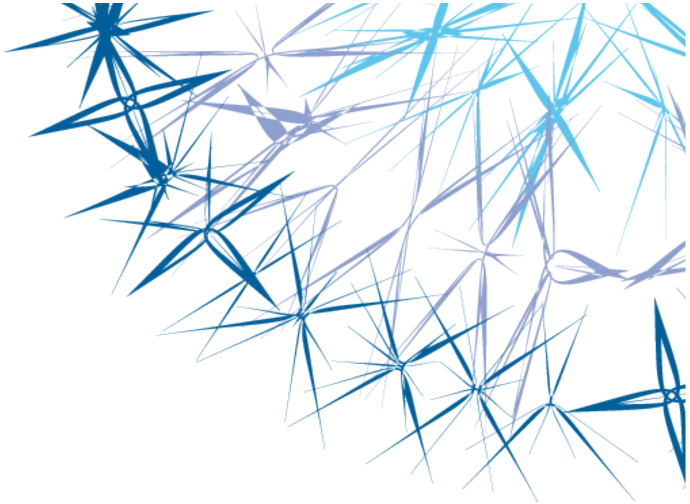
Normalized beween 0 and 1

EFFICACY AND TUMOR STAGE



DRUG EFFICAY VS PATIENT AGE





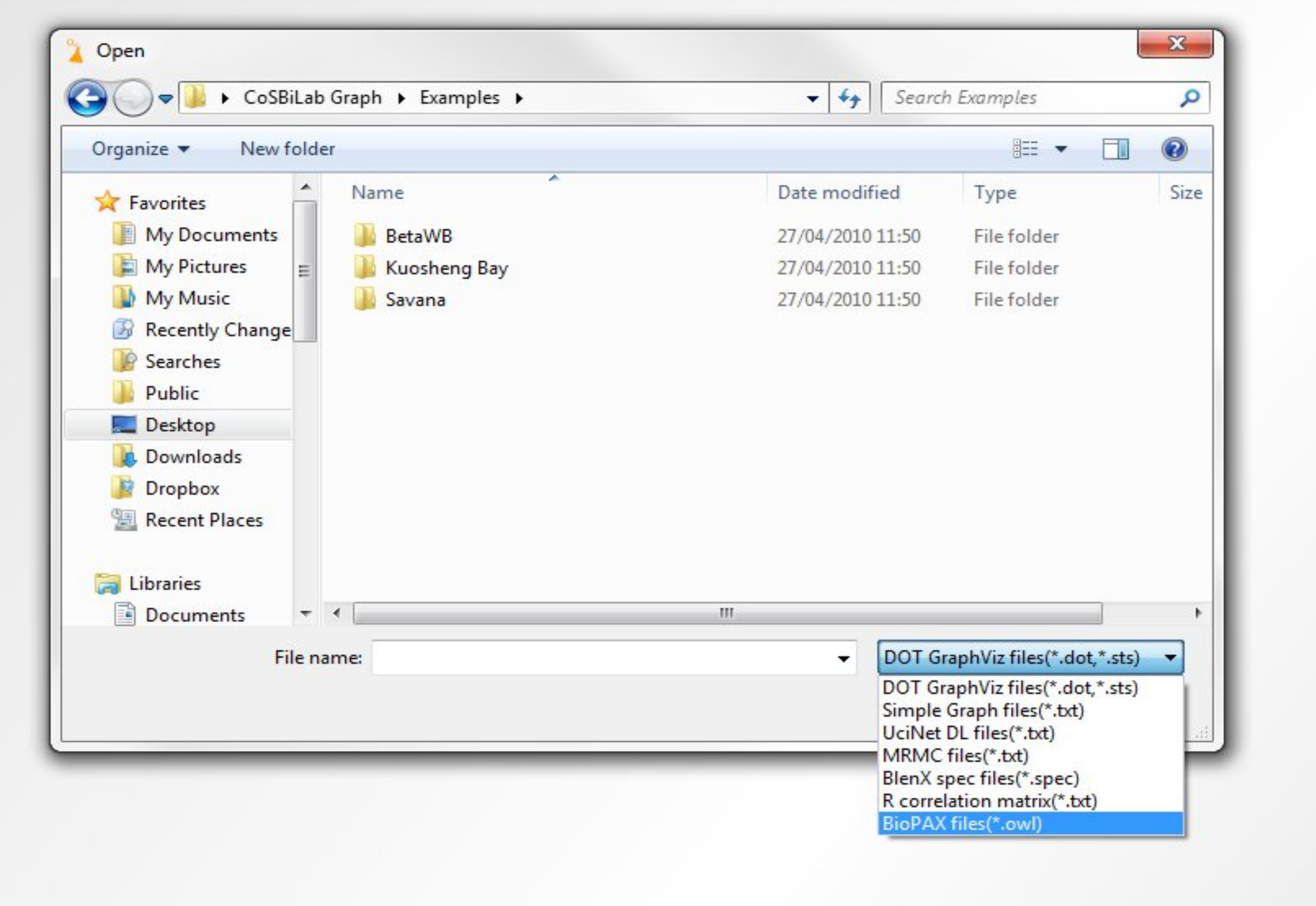
NETWORK Analysis and visualization

CoSBiLab Graph

R. Valentini, F. Jordan. *CoSBiLab Graph: the network analysis module of CoSBiLab.* **Environmental Modelling and Software, 25**:886-888, 2010.

Download:
http://www.cosbi.eu/index.php/research/prototypes/graph

INPUT FORMATS

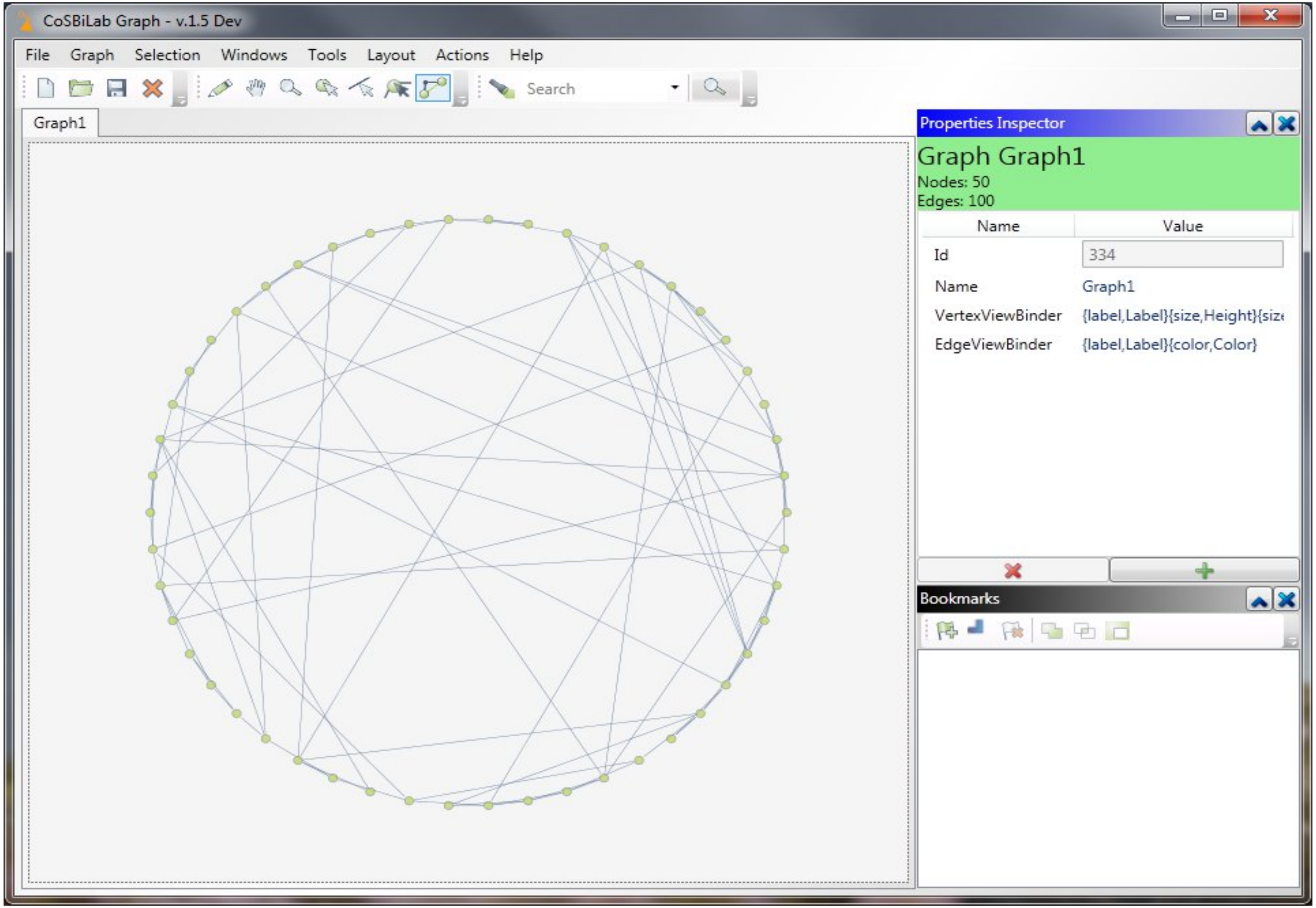


Name	Date modified	Type	Size
BetaWB	27/04/2010 11:50	File folder	
Kuosheng Bay	27/04/2010 11:50	File folder	
Savana	27/04/2010 11:50	File folder	

File name:

DOT GraphViz files(*.dot,*.sts)

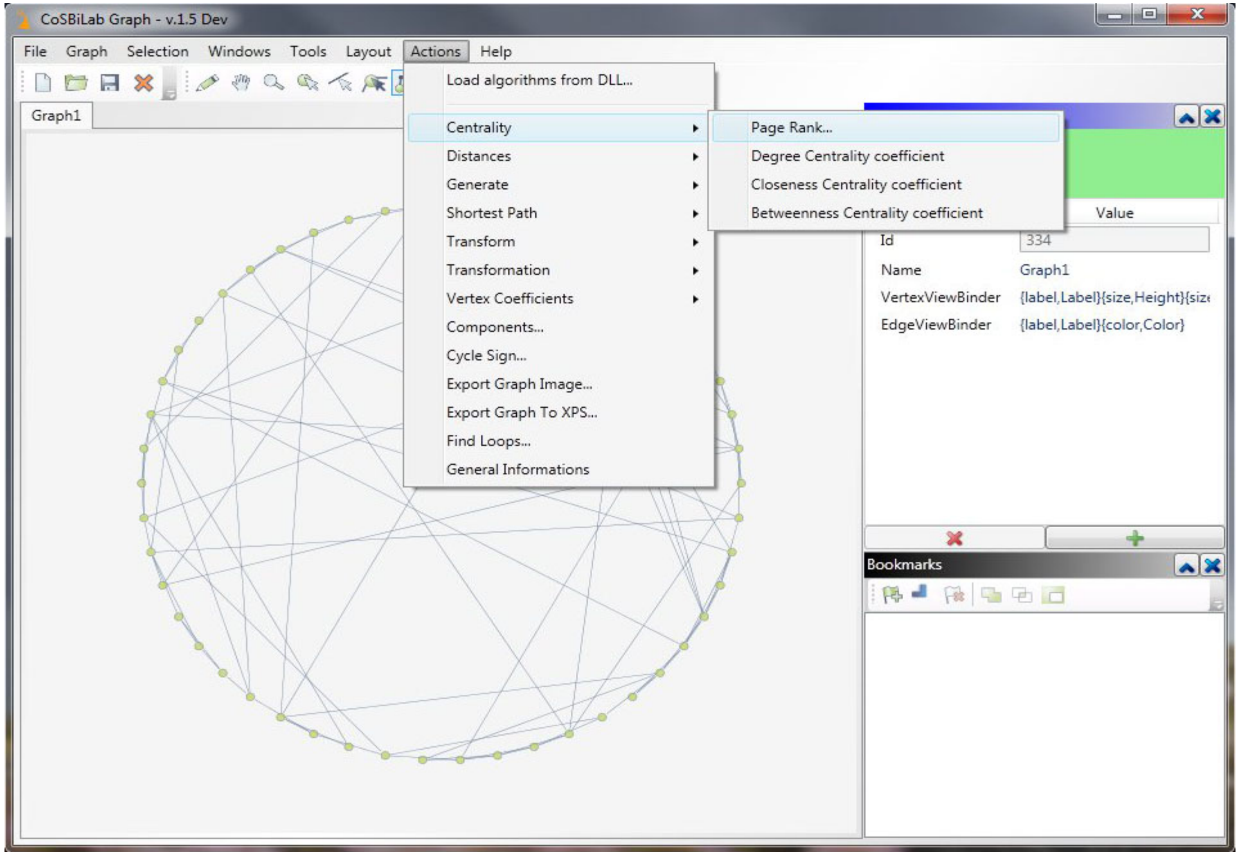
GRAPH IMPORTED



Graph Graph1
Nodes: 50
Edges: 100

Name	Value
Id	334
Name	Graph1
VertexViewBinder	{label,Label}{size,Height}{siz
EdgeViewBinder	{label,Label}{color,Color}

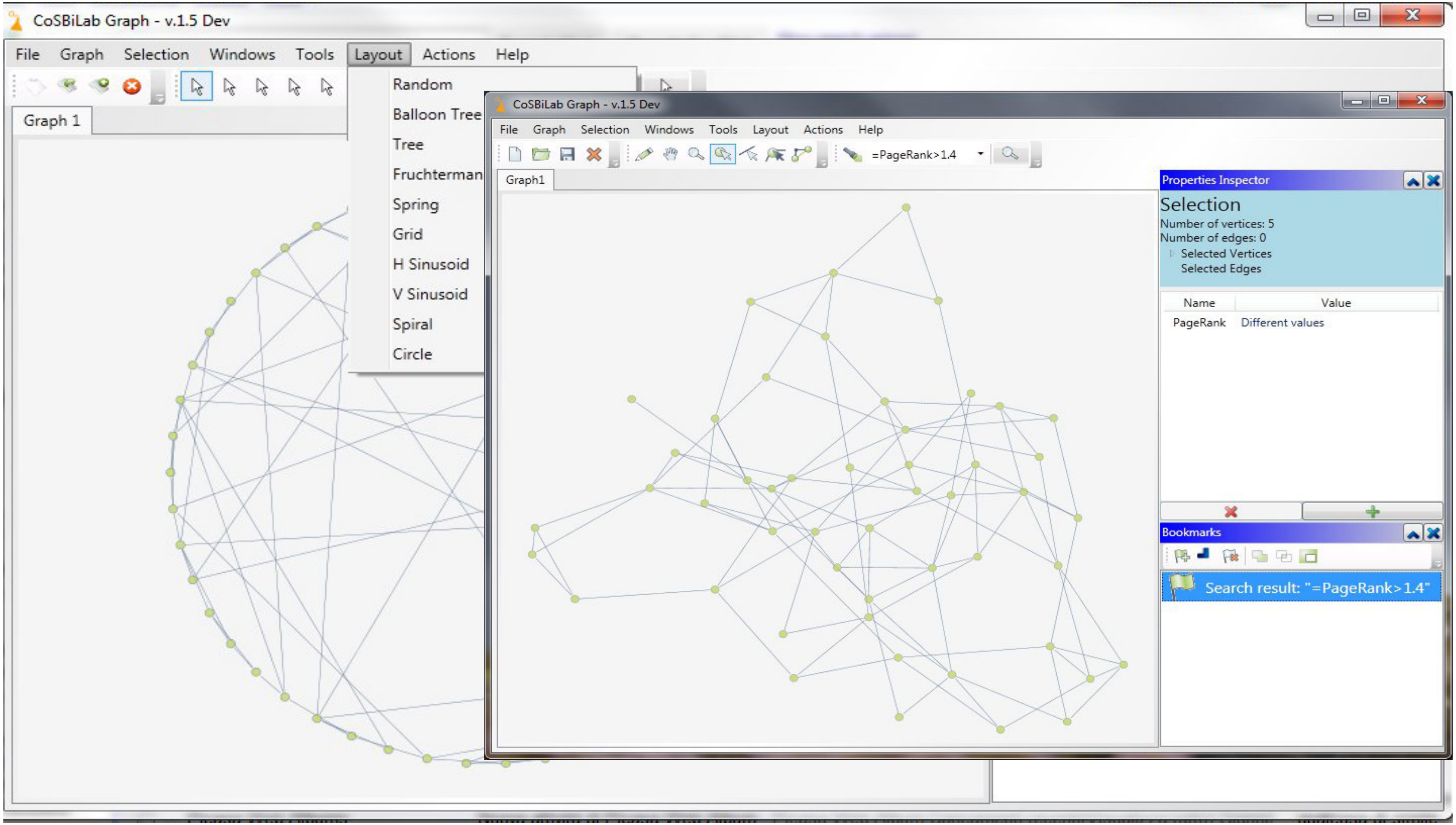
ALGORITHMS FOR NETWORK ANALYSIS



Id 334
Name Graph1
VertexViewBinder {label,Label}{size,Height}{size
EdgeViewBinder {label,Label}{color,Color}

Centrality:
Page Rank
Degree Centrality coefficient
Closeness Centrality coefficient
Distances:
Diameter
Compactness Index
Center of Gravity
Average Distance
Generate:
Watts-Strogatz Radom GraphErdos-Reyni Random Graph
Barabasi-Albert Random Graph
Shortest Path:
Shortest Path
Shortest Path Matrix
Dijkstra Shortest Path
BellmanFord Shortest Path
Vertex Coefficients:
Status, Contrastatus, Netstatus
K-Index
Degree
Clustering Coefficients

LAYOUTS: FRUCHTERMAN REINGOLD

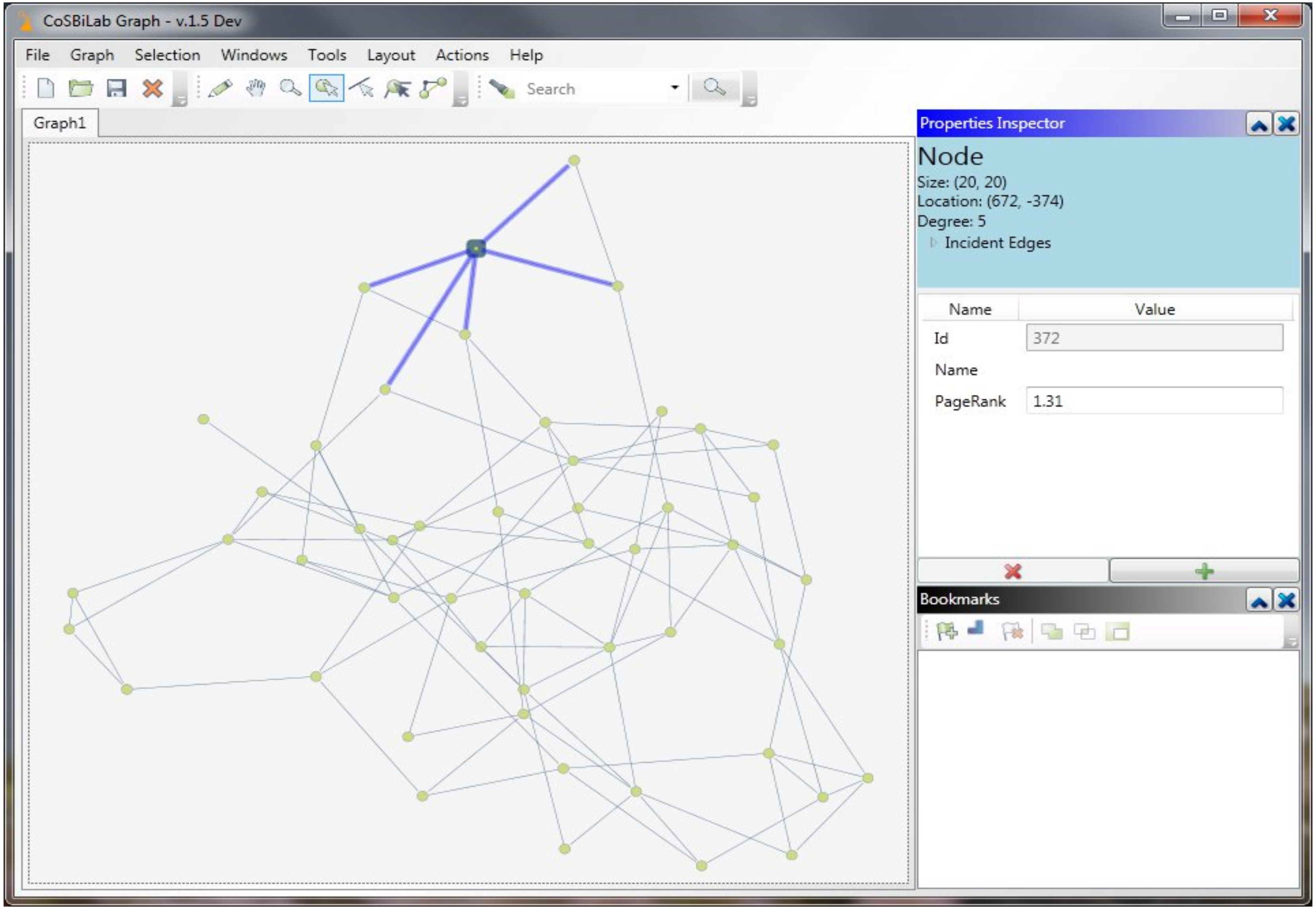


Selection
Number of vertices: 5
Number of edges: 0
Selected Vertices
Selected Edges

Name	Value
PageRank	Different values

Search result: "=PageRank>1.4"

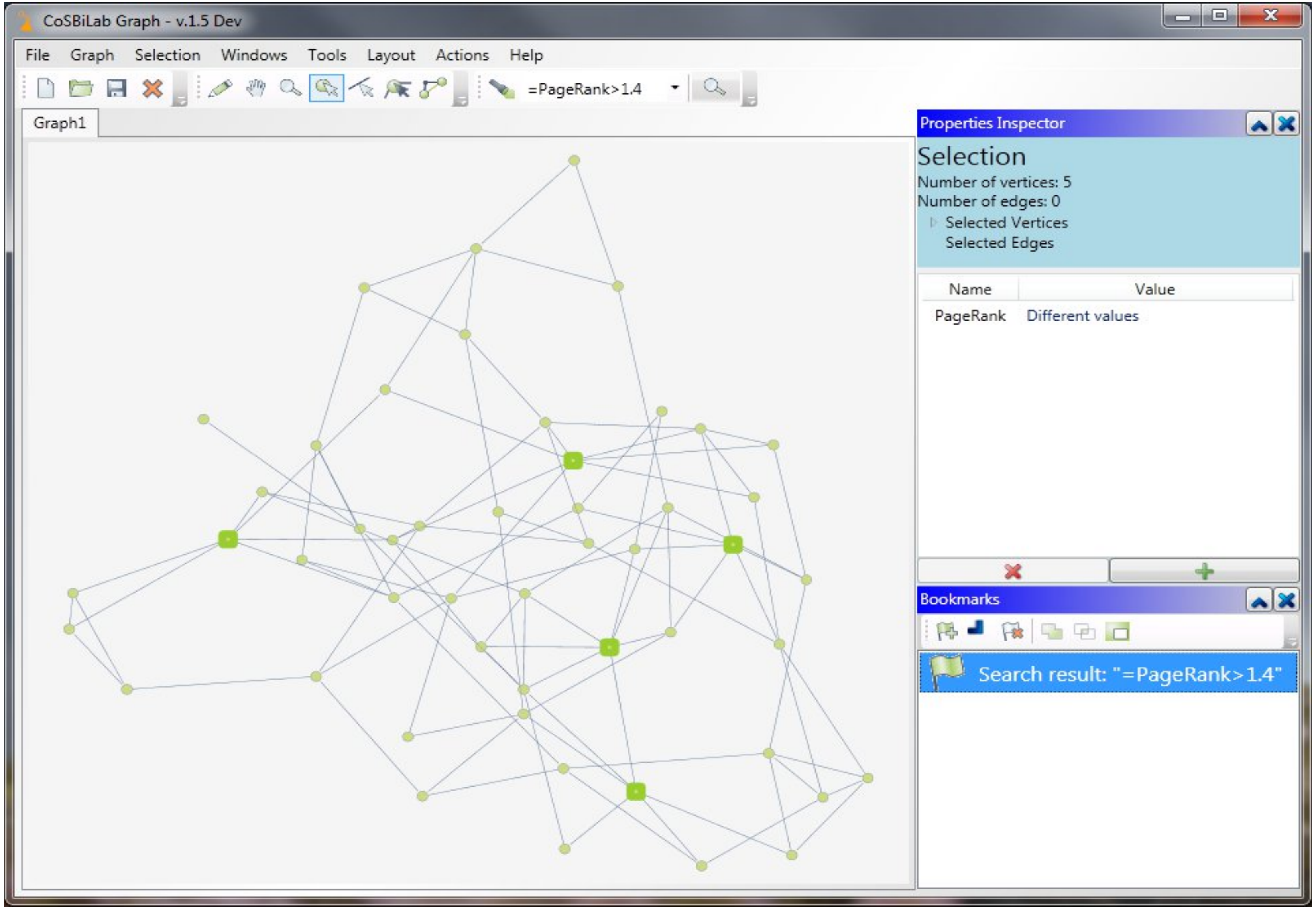
PROPERTY INSPECTOR



Node
Size: (20, 20)
Location: (672, -374)
Degree: 5
Incident Edges

Name	Value
Id	372
Name	
PageRank	1.31

SEARCH: PAGE RANK > 1.4



=PageRank>1.4

Selection

Number of vertices: 5

Number of edges: 0

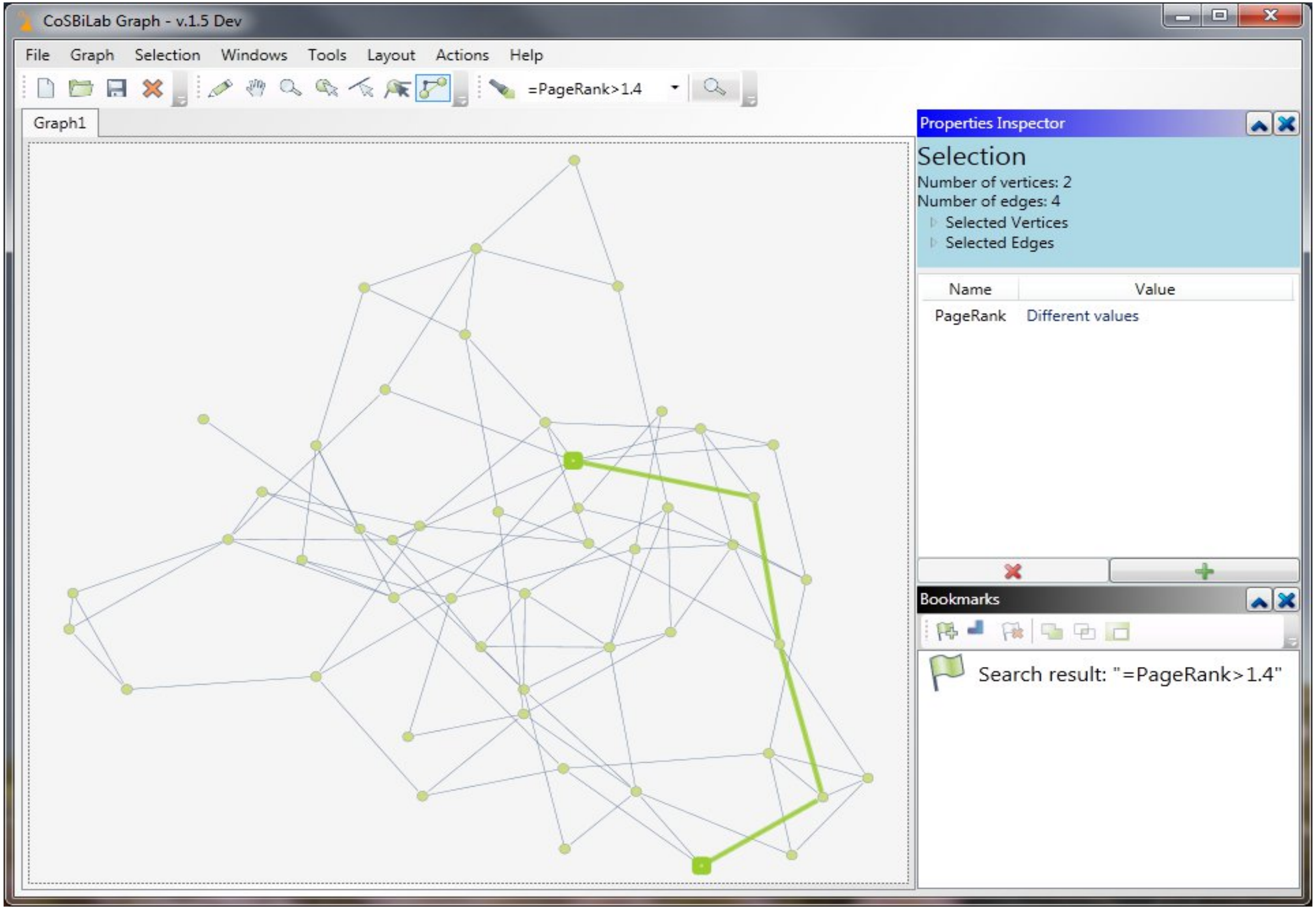
Selected Vertices

Selected Edges

Name	Value
PageRank	Different values

Search result: "=PageRank>1.4"

SHORTEST PATH TOOL



Selection

Number of vertices: 2

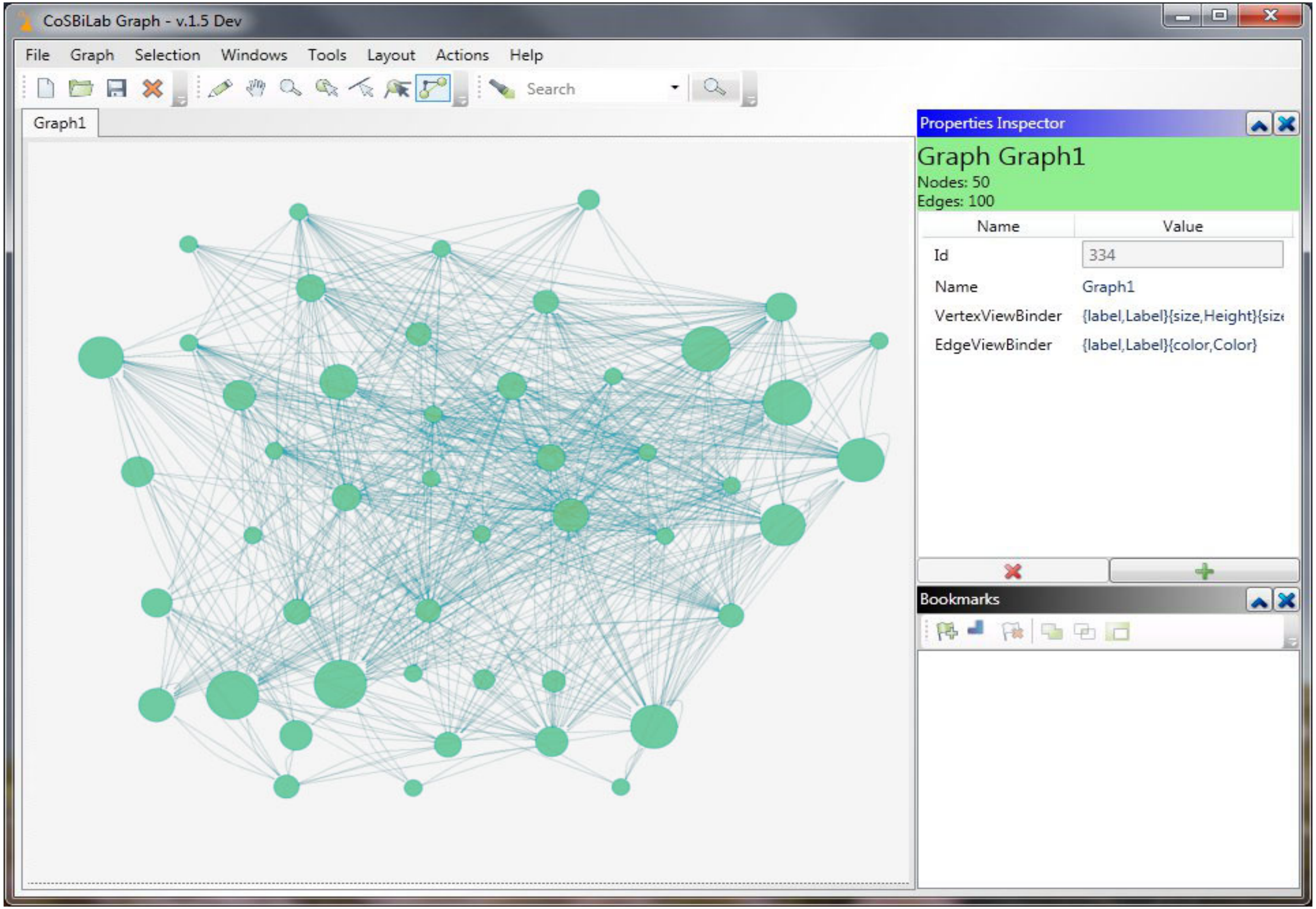
Number of edges: 4

- Selected Vertices
- Selected Edges

Name	Value
PageRank	Different values

Search result: "=PageRank>1.4"

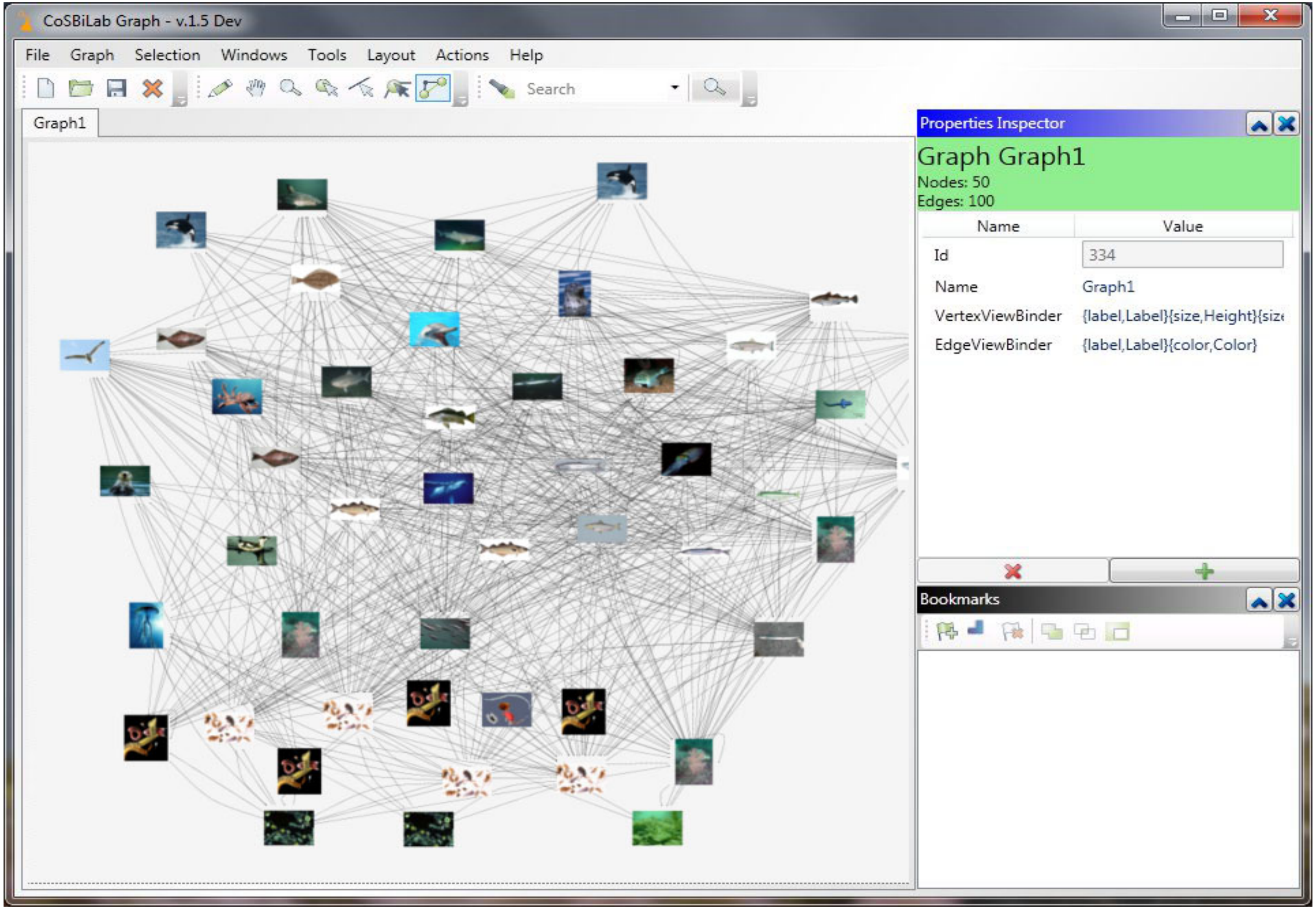
NODE SIZE REFLECTING A NODE PROPERTY



Graph Graph1
Nodes: 50
Edges: 100

Name	Value
Id	334
Name	Graph1
VertexViewBinder	{label,Label}{size,Height}{siz
EdgeViewBinder	{label,Label}{color,Color}

PICTURES AS NODE ATTRIBUTES



Graph Graph1

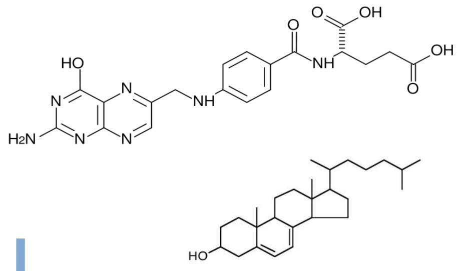
Nodes: 50

Edges: 100

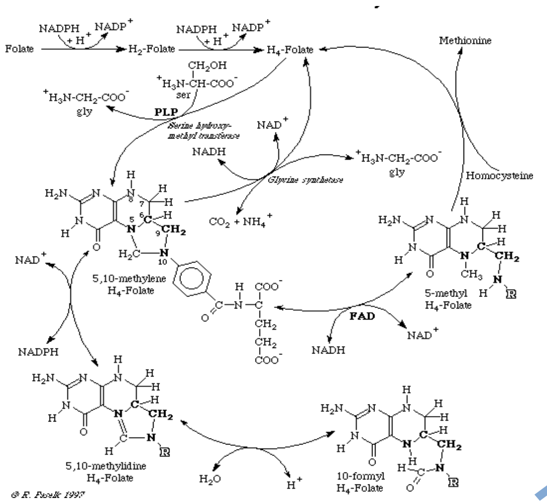
Name	Value
Id	334
Name	Graph1
VertexViewBinder	{label,Label}{size,Height}{siz
EdgeViewBinder	{label,Label}{color,Color}

VITAMINS AND OBESITY

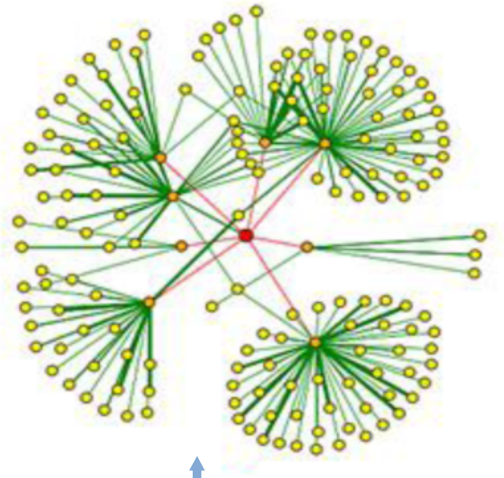
Select the micronutrients



Search Networks & Pathways



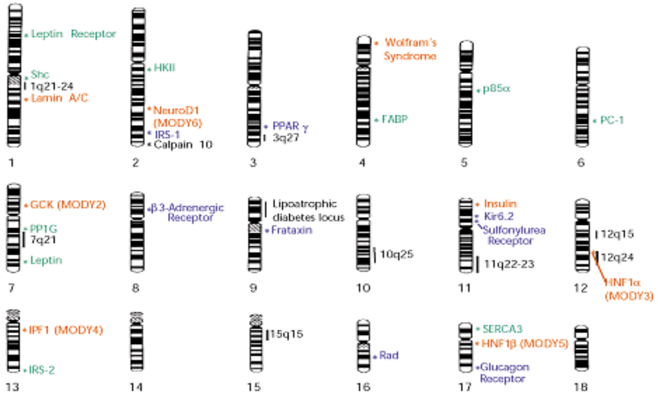
Search & Analyse Protein – Protein Interaction Database



Select genes involved and proteins codified

Select protein At Key Nodes

Map to QTL of Obesity/diabetes Phenotype



CANDIDATE GENES

VITAMINS AND OBESITY

Vitamins

Ascorbic acid
B12
Biotin
Folate
Niacin
Pantothenic
Pyridoxal
Pyridoxine
Retinol
Riboflavin
Thiamine
VitD2
VitD3
VitE
VitK

Metabolic & Network

200 proteins

Protein-Protein Interactions

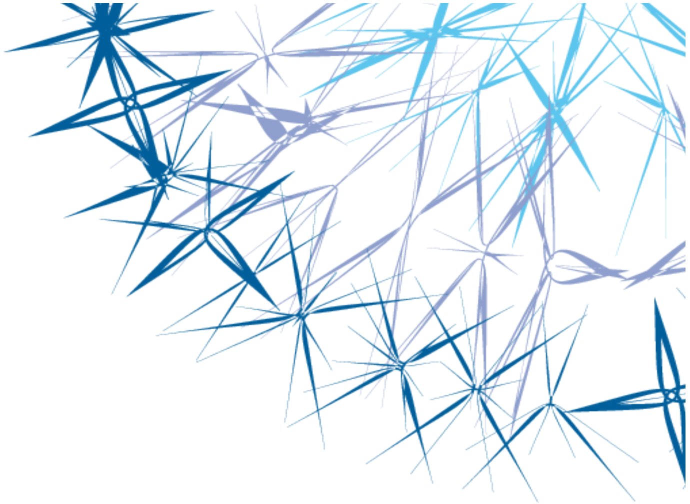
1647 proteins along 2672 edges

Candidates @ QTLs

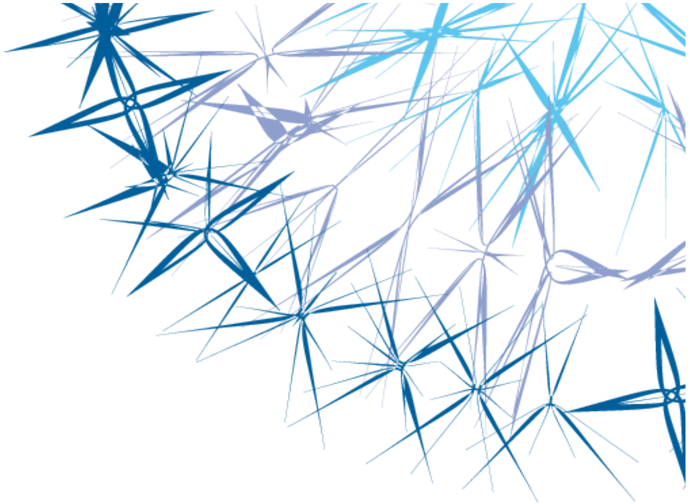
GFI1
NCOR1
NFKB1
PRKCA
PPP2CA
PPP2CB
VDR
RXRA
SHBG
SMAD3
SMARCA4

New Candidate

MED1



CONCLUSIONS



www.cosbi.eu

priami@cosbi.eu