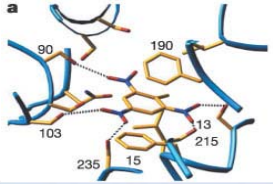
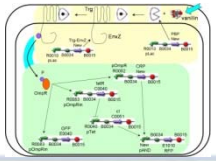
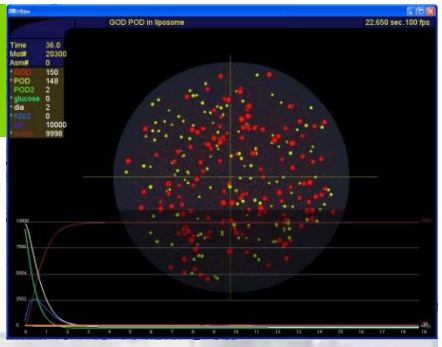
SysDiag
UMR3145



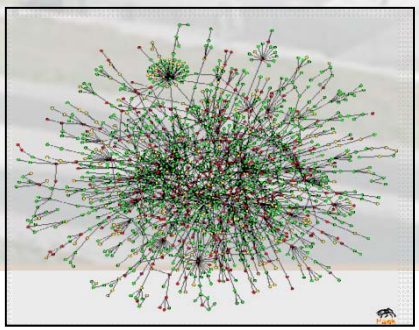
Colloquium Jacques Morgenstern

SysDiag, *Montpellier, France*

Biological Complex system modeling and engineering for diagnosis

Ingénierie des systèmes biologiques synthétiques : applications au diagnostic médical

Franck Molina, CNRS



franck.molina@sysdiag.cnrs.fr
http://sysdiag.cnrs.fr

BIO-RAD

SysDiag UMR3145

SysDiag's missions are :

• to understand the bases of chronic and multifactorial diseases (neurodegenerative and cardiovascular diseases, cancer, diabetes...)

• to identify new biomarkers associated with these pathological conditions

• to provide innovative solutions for clinicians that will contribute to improve the health and quality of life of their patients.

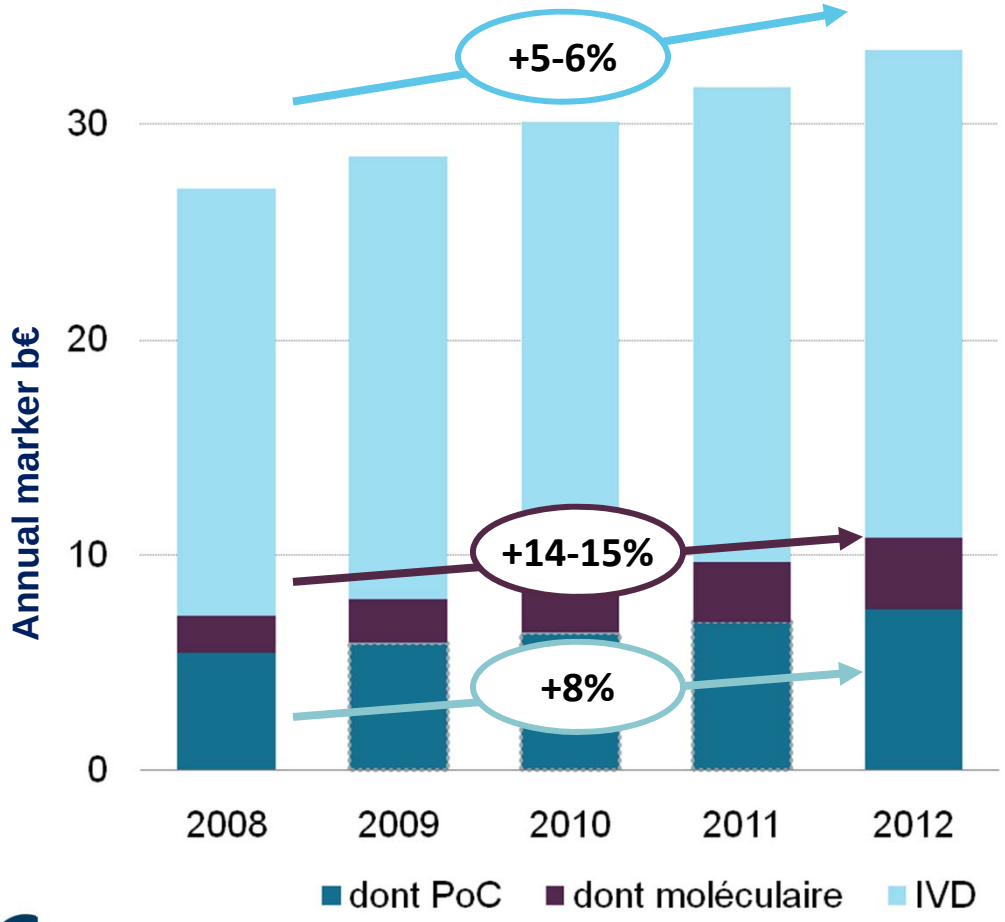
cnrs

BIO-RAD

SysDiag UMR3145

Diagnostic in mutation

Diagnostic tests represent ***less than 5%*** of hospital cost and about ***1.6 % of all*** health cost. Their results influence up to ***60-70% medical decision***"



- ➲ **Change of paradigm with the convergence of diagnosis and therapy, going to personalized medecine and theranostic**
- ➲ **New role of biomarker in biomedical and therapeutic, molecular assay development (nucleic acid, proteines, metabolites)**
- ➲ **explosion of POC Technologies and of home monitoring/testing)**
- ➲ **Integration with IT**
- ➲ **New interfaces electronic/biology (Biosensor)**

Source = **The Lewin Group, Inc.,** *The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care*,**July 2005**

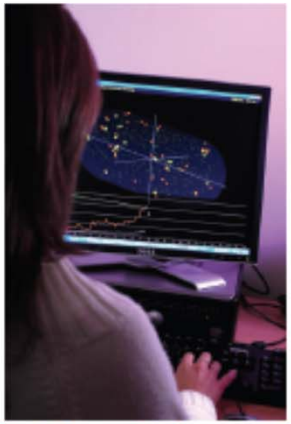
BIO-RAD

SysDiag UMR3145

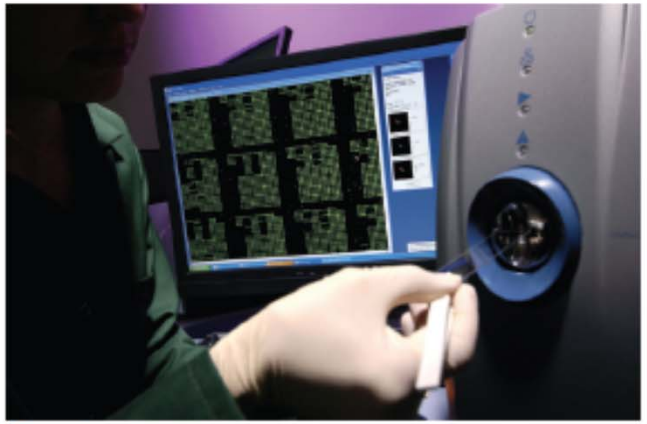
Interdisciplinarity : The SysDiag model

- Crossing disciplines for innovation in Diagnosis
- Combining experimental biology and complex systems modelling approaches
- 70% experimentalists and 30% theoreticians

Cell culture automation



Bioinformatic & modelling



Experimentation

cnrs

BIO-RAD

SysDiag UMR3145

Drug & Diag Discovery paths

2-4 years | 1-2 years | 1 year

4 – 7 years

Molina and Dupas, SysDiag

DIAG DISCOVERY

Diagnosis problem | Biomarker identification | Binding probes | Clinical studies | AMA

TEST DIAG

Diagnosis *Monitoring*

PRACTICIANS

Questions

Pathology characteristics
Therapeutic decision

THERANOSTIC

Patient

followup

treatment

DRUG DISCOVERY

Therapeutic problem | Target identification | Active compound | Clinical studies | AMA

DRUG

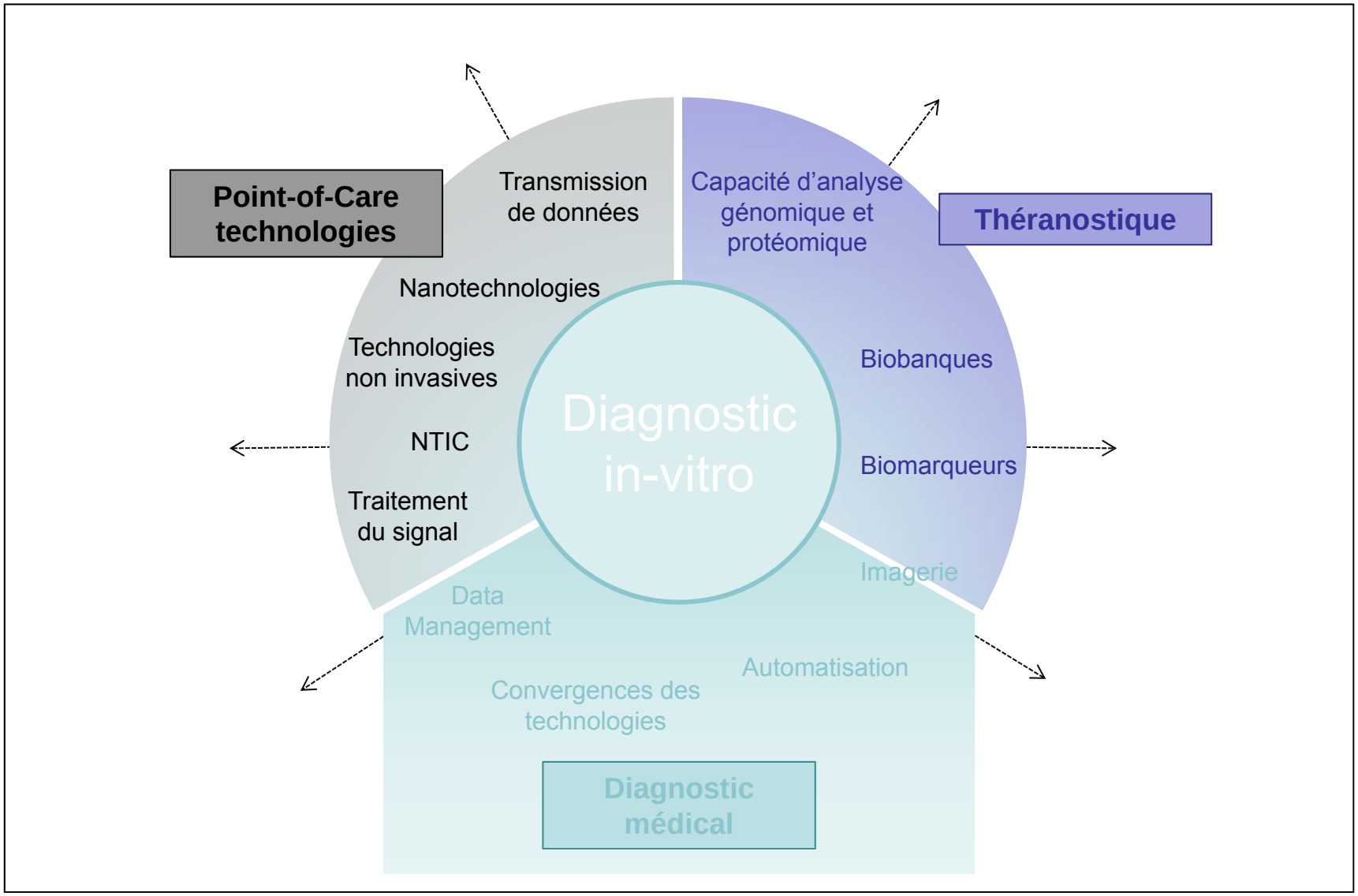
'Application for Market Authorization'

3-6 years | 6-8 years | 1 year

10 – 14 years

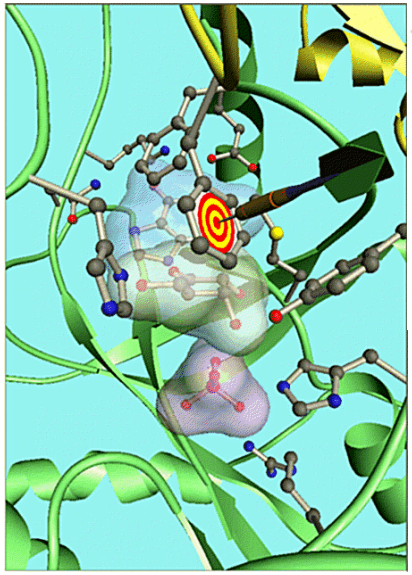
BIO-RAD

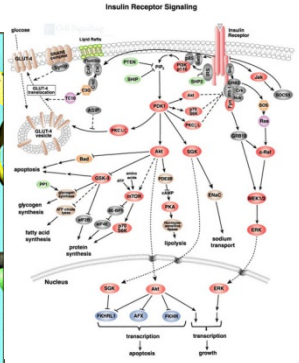
Various axes of development



Biomarkers

Parameters objectively measured (precise and reproductible), as an indicator of a biological process (physiological or pathological) or of a drug action.





Kinds of biomarkers :

Molecular (gene, RNA, Proteine, Chemical compound)

Physical

Imaging

others

Diagnostic biomarkers

Early detection biomarkers

Disease classification

Predictive biomarkers

Predict the response to a specific agent

Predict a particular adverse reaction

Metabolism biomarkers

Biomarkers that guide drug doses

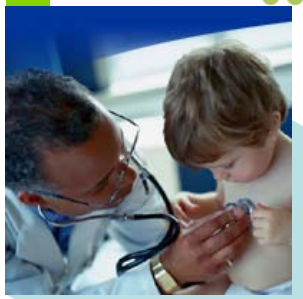
Outcome biomarkers

Those that predict response

Those that predict progression

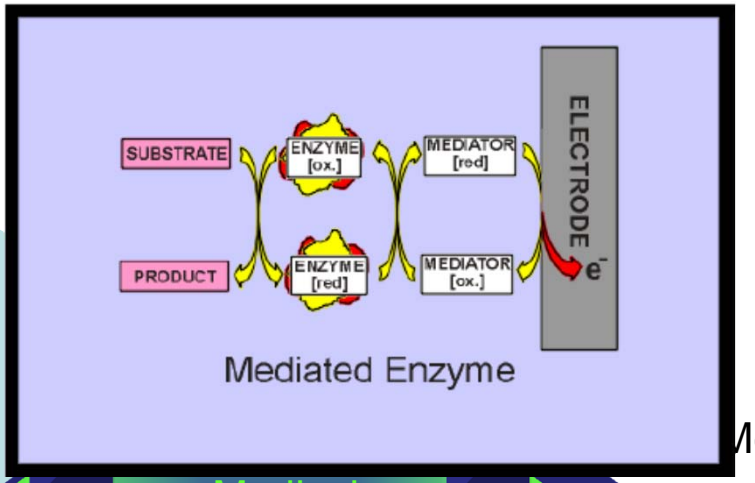
Those that forecast recurrence

SysDiag
UMR3145



Clinical question

Biomarkers



reliability

Mobility / miniaturization

Communication

ntrol

Undirect Cost

Direct

Medical

Coupling Biology with electronics Biosensors

Screening
Diagnosis
Monitoring

cnrs

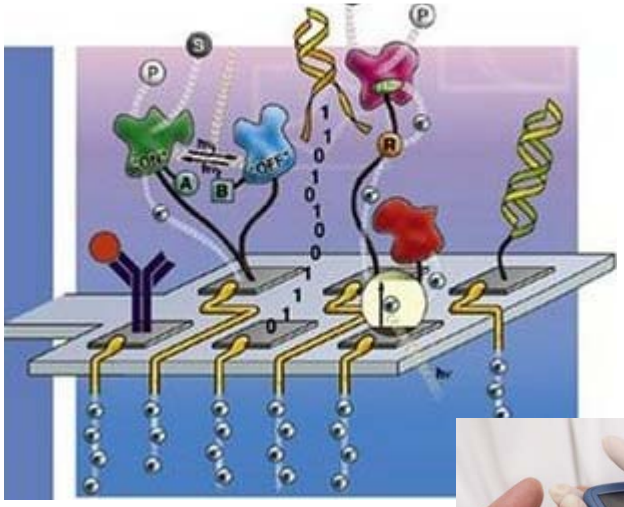
BIO-RAD

SysDiag UMR3145

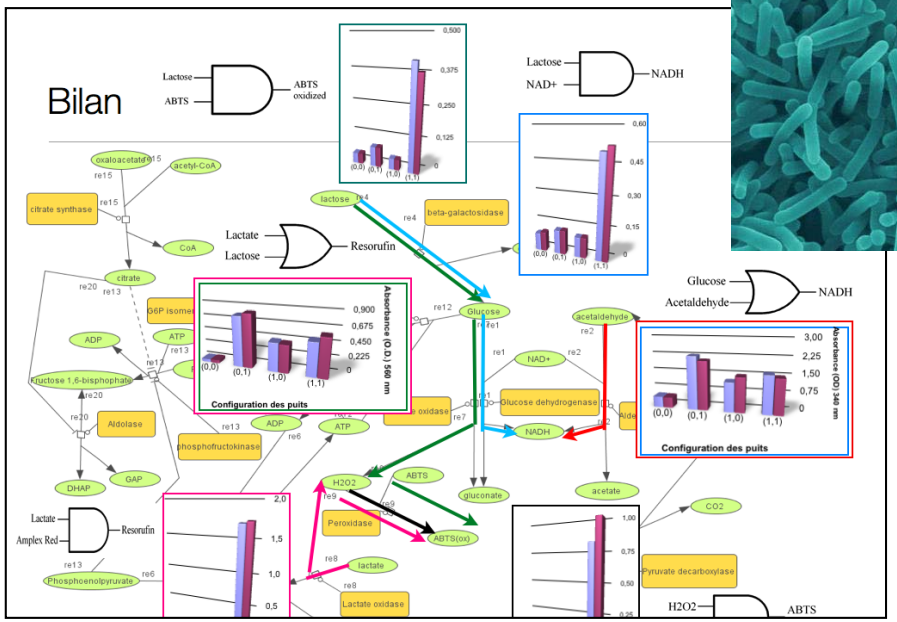
Synthetic biology

Engineered biology will transform diagnostic practices

From bioelectronics to artificial biological systems



Biosensor > Point of care and home testing



synthetic biology
Artificial biological systems

POC and futur patient wiring

Futur in vivo diagnostics

BIO-RAD

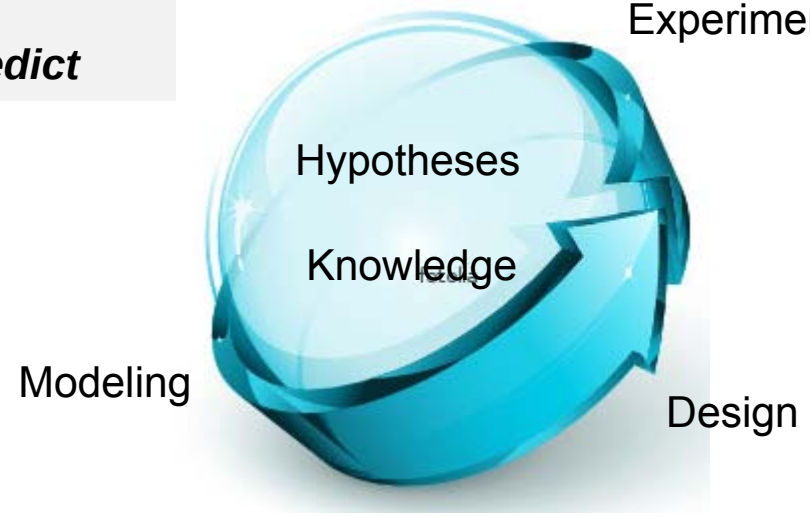
SysDiag UMR3145

cnrs BIO-RAD

Systems Biology and Synthetic Biology

to address complexity

Systems biology
Integrative biology and modeling
To
Understand and predict



Synthetic biology
Integrated prediction
To
Design

SysDiag UMR3145

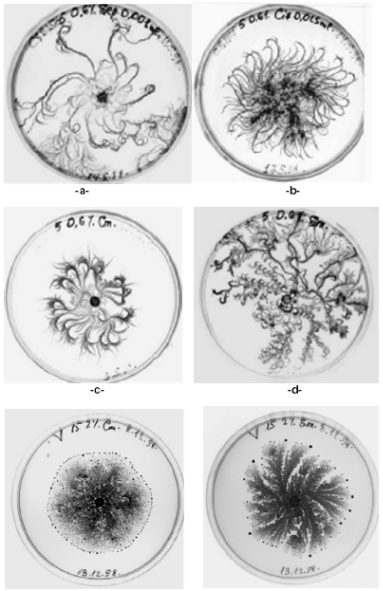
Synthetic Biology

A) the design and construction of new biological parts, devices, and systems

B) the re-design of existing, natural biological systems for useful purposes.

Zauner , 2006.

Biological molecules and biological systems are able of computer behavior in a robust and an auto-organized way



Bacteria Harnessing Complexity, E. Ben Jacob et al. 2002

Systems engineering

Specification → design → modeling → building → Quality assessment

Standardization

Abstraction

Decoupling and modularity

Gulati et al., 2009

Endy, 2005

cnrs

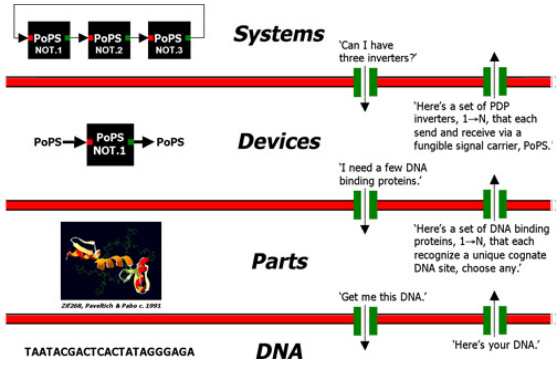
BIO-RAD

Synthetic Biology

Abstraction :

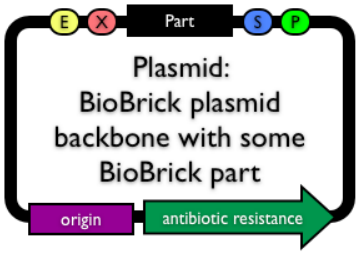
Different hierarchical levels to manage complexity

'**Parts**'=Basic Biological Functions
'**Devices**'= Combination of parts to perform a desired function
'**Systems**'= Combination of 'Devices'



Standardization :

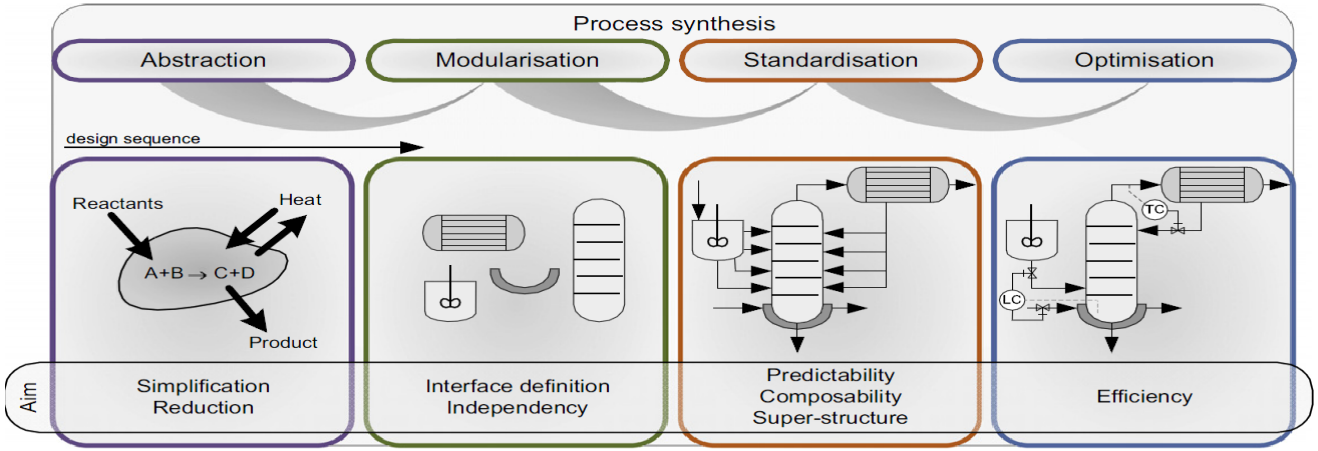
Concentrating information : description and characterization of components and conditions makes it easier for the user



Catalog of parts & devices
***partsregistry**.org/*

Decoupling and Modularity :

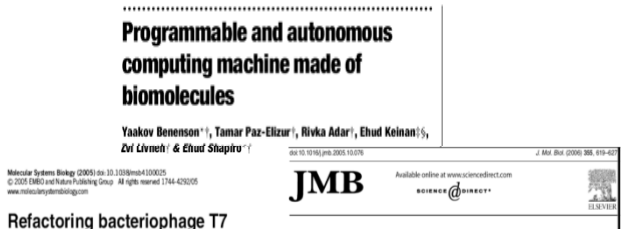
A complex problem is a set of tasks
A complex biological system is a set of separate devices



Designing biological systems: Systems Engineering meets Synthetic Biology, Sascha Rollie, Michael Mangold , Kai Sundmacher

SysDiag UMR3145

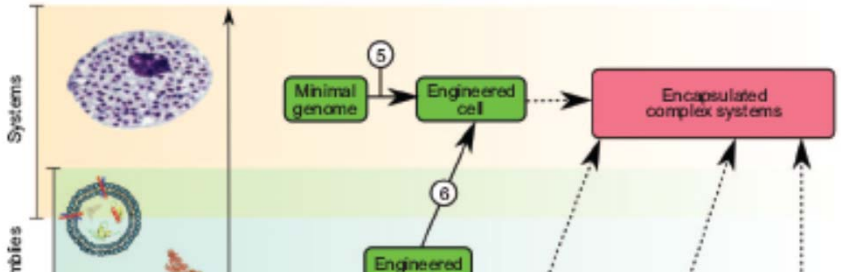
Various strategies in synthetic biology

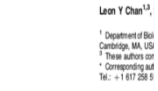

Programmable and autonomous computing machine made of biomolecules

Yaakov Benenson, Tamar Paz-Elizur, Rivka Adar, Ehud Keinan, Zvi Livneh & Ehud Shapiro

JMB

Refactoring bacteriophage T7





Ron Weiss, MIT, Harvard,

Design of a lentivirus able to target breast cancer intra-cellular biomarkers RNAi networks

Steem cell reprogramming by bact. for tissus reconstruction

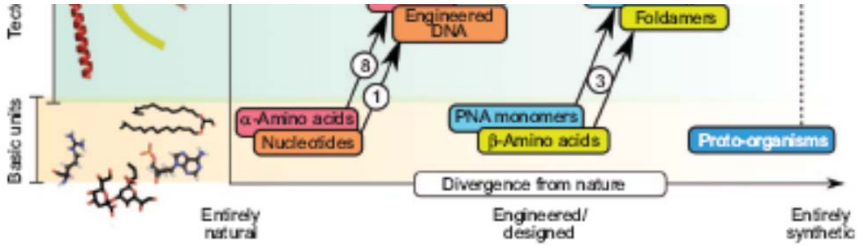
PL Luizi, Roma autocatalytic vesicules constructions, minimal cells.

J. Stelling ETHZ, Zurich Electronic-like circuit design with composable parts (Bact.)

V. Dos santos, Helmotz Inst. Germany reprogrammed bact. to target cancer cell

Pseudomonas putida.

Jim Haseloff, Univ Cambridge UK , Plant reprogramming



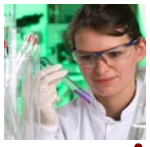
Bromley et al ACS Chem biol.2008

Adrianantoandro et al. EMBO 2006

cnrs

BIO-RAD

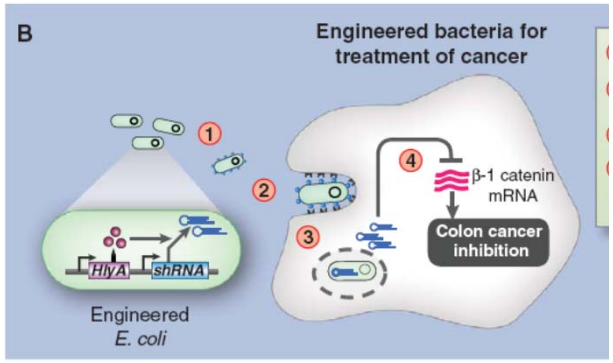
SysDiag UMR3145



Synthetic Biology and Health : Proof of concept and applications

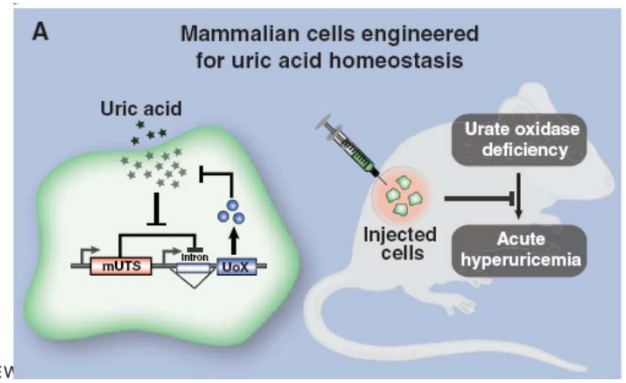
Drug production : metabolic engineering

Various "devices" have begun to emerge from Synthetic biology
-Orthogonal inducible promoters
-RBS libraries
-State sensors
-Spatiotemporal controllers…
Synthetic biology devices as tools for metabolic engineering Eric Shiue



Engineering of "smart" cell for therapeutic purpose

-Bacteria invading cancer cells in vitro
-Delivering a functional RNAi
-Control the virulence of pathogens
-Eliminate cancer cells based on their expression pattern of micro-RNAs



REVIEW

Synthetic Biology Moving into the Clinic

Warren C. Ruder,* Ting Lu,* James J. Collins†

Ruder et al Science 2011

Medical diagnostics :

Limited number of project

cnrs

No current clinical practice based on synthetic biology

BIO-RAD

SysDiag UMR3145

What synthetic biology can bring to clinical diagnostic ?

Possibility for local molecular measurments

high sensibility, Early diagnosis
Accessibility to difficult region, less invasive

Perturbations from local environment
Specificity, accessibility issues

Capabilities for integrated processing

Reduce need of heavy technology
low cost compatible to systematic screening, personnalized medicine etc.
Ability for sophisticated assays Supported by Modelling

Composability issues
Control and robustness problems
Complex experimental and Clinical validation

Biocompatibility

can be disposable
human compatible

Stability issues,
Human and environmental interaction issues

Can be interfaced with other supports

Electronics, physics, chemistry, automation, etc.

Linearity, Kinetics, normalization, etc.

cnrs

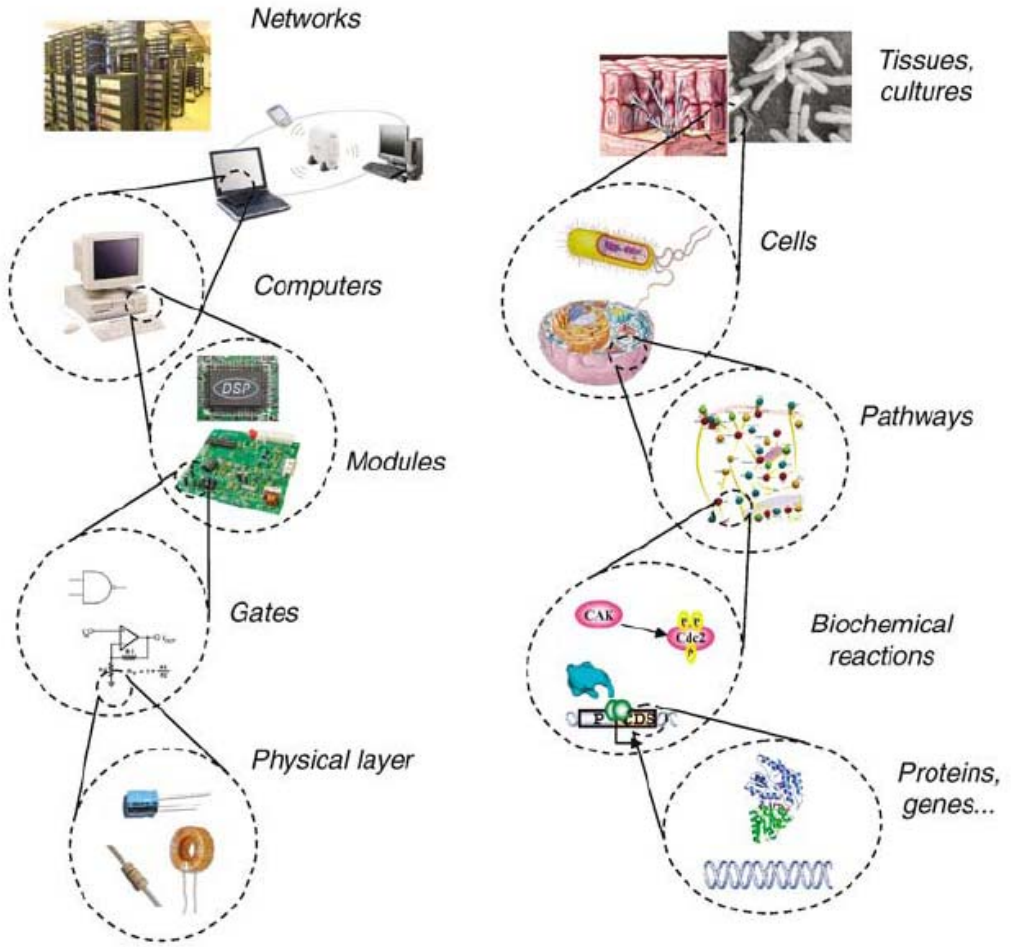
BIO-RAD

Adrianantoandro et al. EMBO 2006

SysDiag UMR3145

Design synthetic biological system based on functional parts

The modeling issue

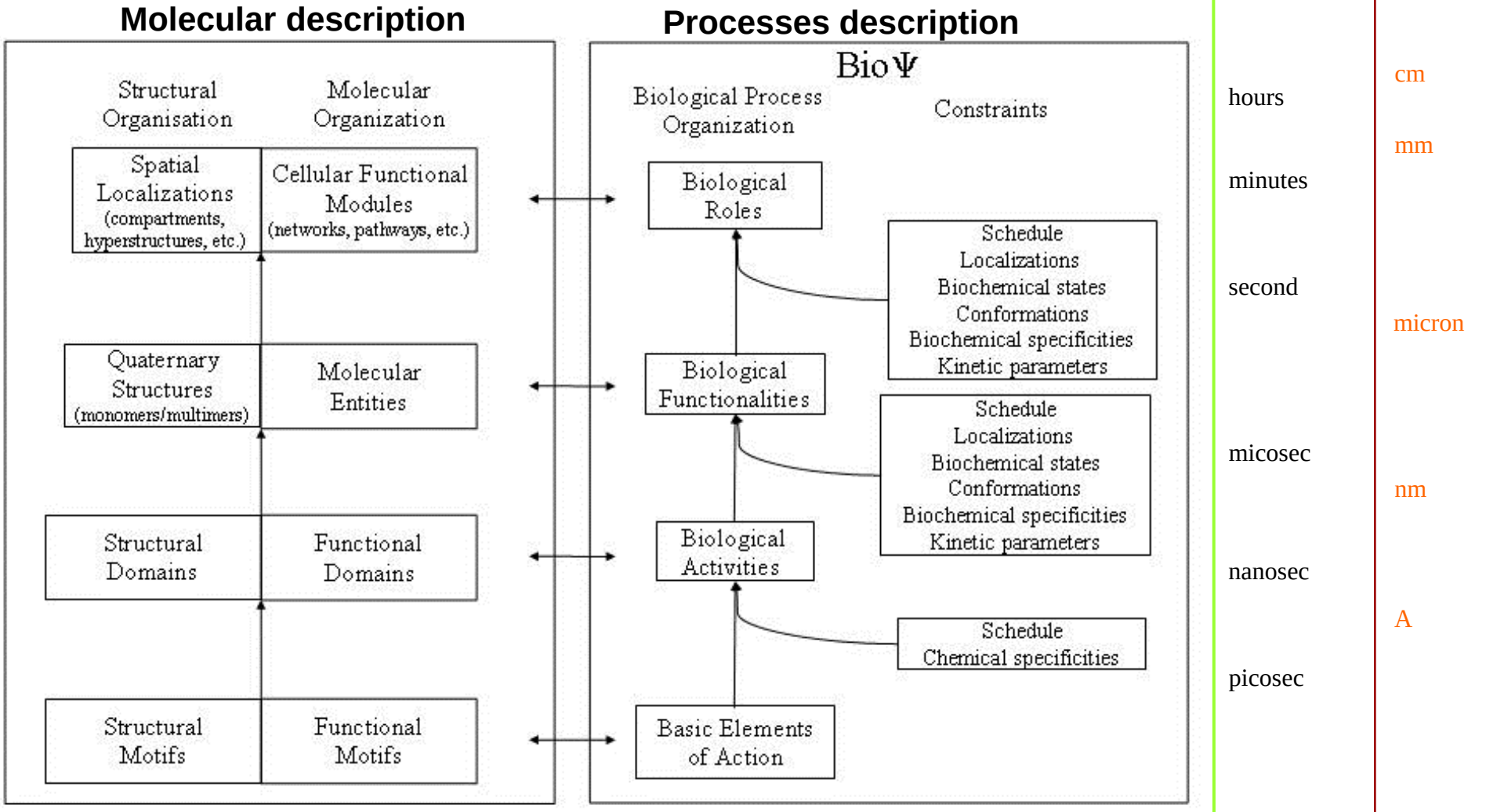


Adrianantoandro et al. EMBO 2006

cnrs

SysDiag UMR3145

Biological processes are made by combination of a limited number of elementary actions



Maziere, Granier and Molina J. Mol. Biol. 2004

Maziere, Granier and Molina J. BioScience 2007

A

Bond Modifiers

a split/link

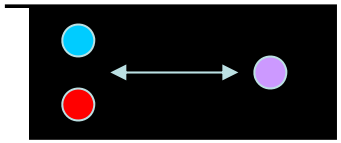
a *acting on C-C*

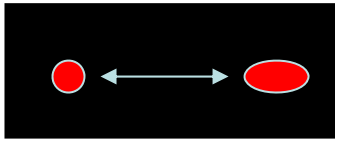
b *acting on C-O*

c *acting on C-N*

d *acting on C-S*

e *others*





C

Intramolecular modifications

a Isomerors

a *chirality*

b *cis/trans*

c *bond moves*

d *others*

B

Transferts

a Transferors

a *acting on C-C*

b *acting on C-O*

c *acting on C-N*

d *acting on C-S*

e *others*

b Oxidoreductors

a *acting on C-C*

b *acting on C-O*

c *acting on C-N*

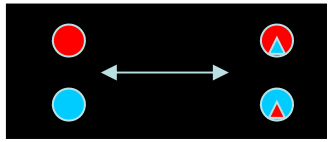
d *acting on C-S*

e *acting on S*

f *acting on N-O*

g *acting on S-O*

h *others*



Classification of 97 basic elements of actions BEA(for all known processes)

D

Non covalent interactions

a Binding:

a *Protein-Protein*

b *Protein-Nucleic Acid*

c *Protein-Other*

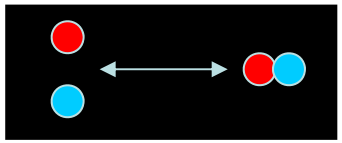
d *Nucleic Acids-Nucleic Acids*

e *Nucleic Acid-Others*

b Transport:

a *Tunnel*

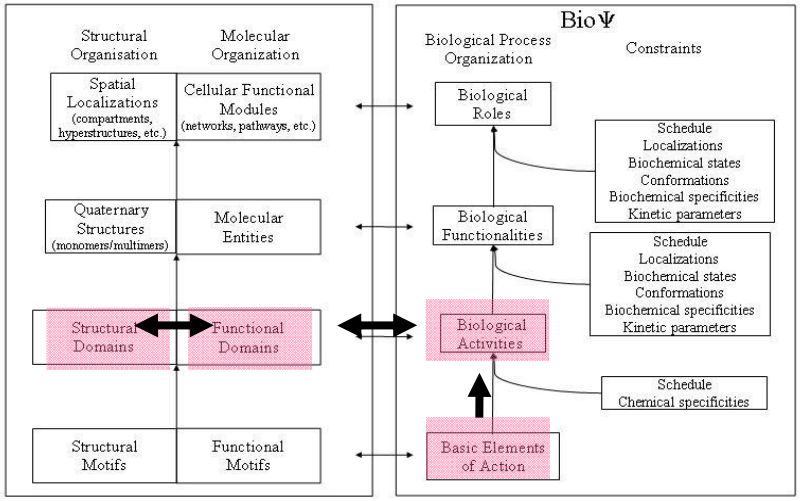
b *Cargo*

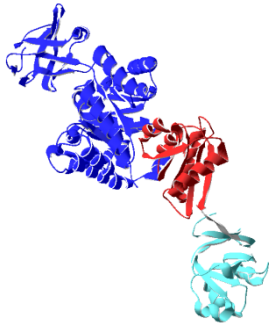


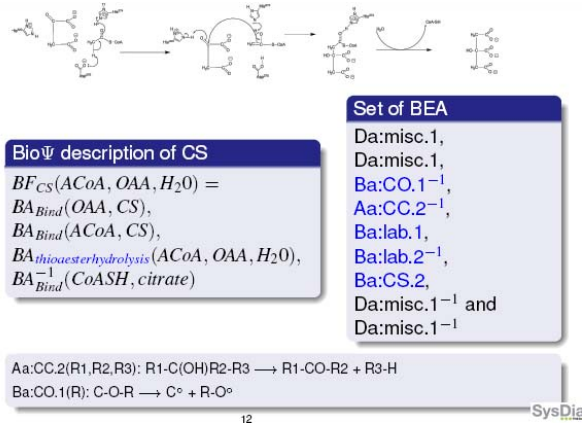
Maziere, Granier and Molina J. Mol. Biol. 2004

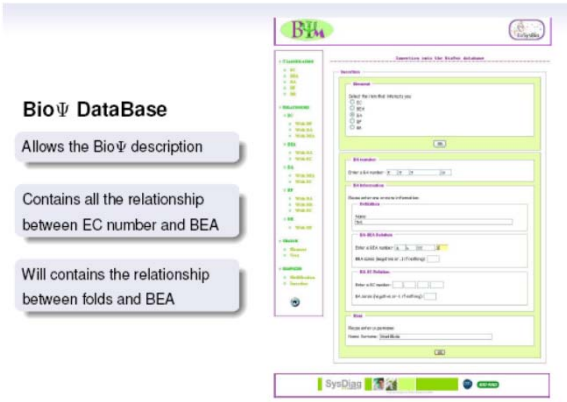
Formal structure-function description based on elementary actions

- Enzymatic activity on metabolites relies on chemical processes.
- **New** BioΨ formalism allows describing detailed elementary actions (BEA) at the chemical level









http://www.sysdiag.cnrs.fr/publications/supplementary-materials/BioPsi_Manager/

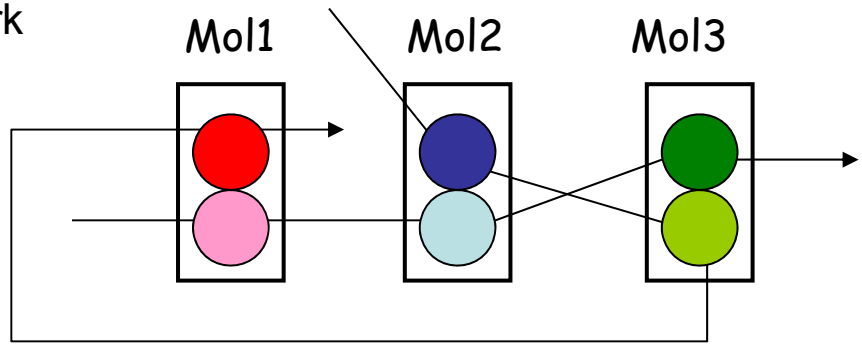
A functional unit has a sequence of BEA

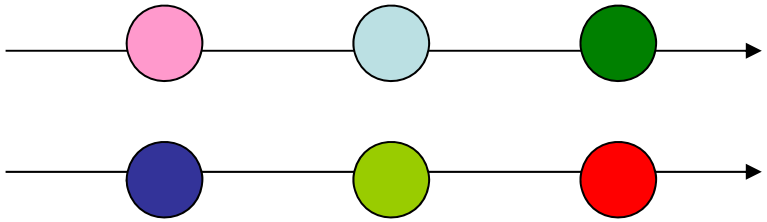
BioΨ better describes functions than GO, EC
BioΨ formalism allows calulating on functions

S. Pérès, F. Molina et al. Bioinformatics 2010

Paradigm shift for network modeling

Molecule based network





Functional unit based network

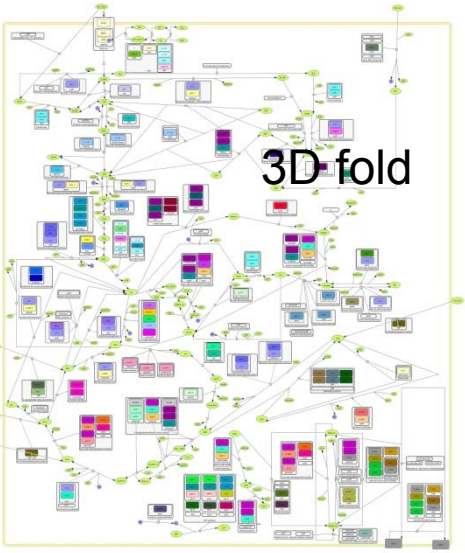
Functional units are defined by 3D fold and BEA sequences

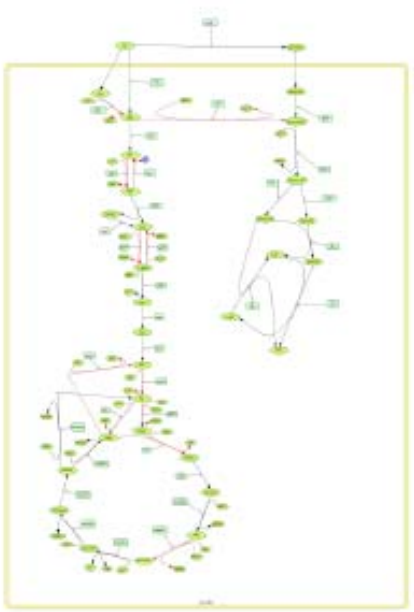
Pérès et al Bioinformatics 2010, Buesher, et al. Science 2012

SysDiag UMR3145

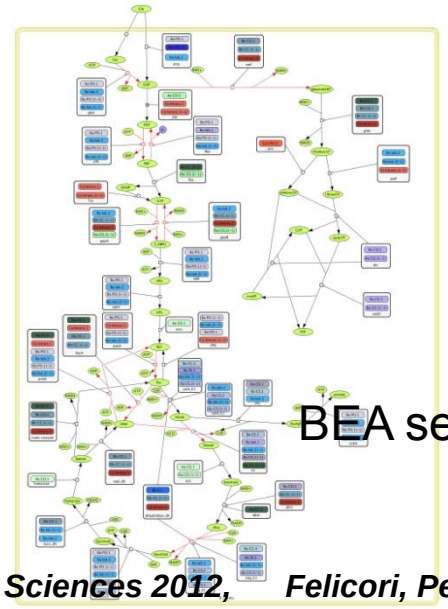
New paradigm for functional network representation

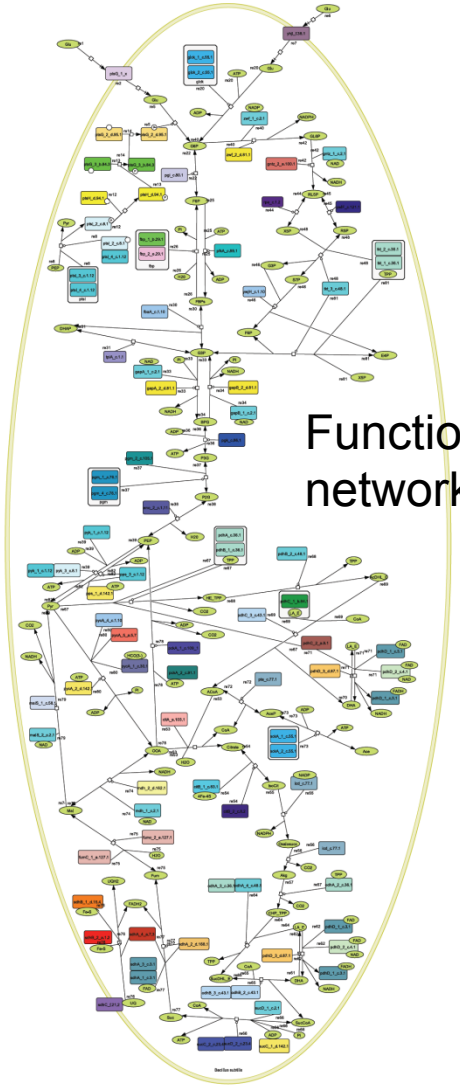
Consequences on :
Network topology analyzes
Dynamic network simulation
Functional interpretation





Molecular Network
CCM *B. subtilis*



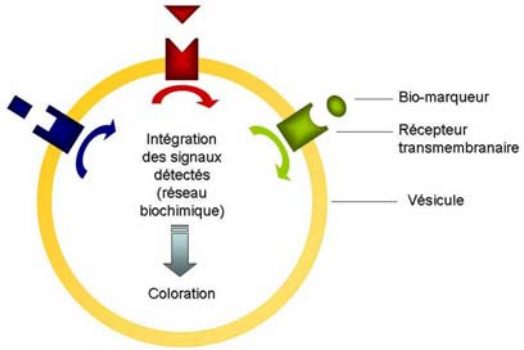


Buesher, Molina et al, Sciences 2012, *Felicori, Peres, Molina et al. in preparation*

SysDiag UMR3145

Design a cell-free synthetic biological system based on functional parts :

The composability issue



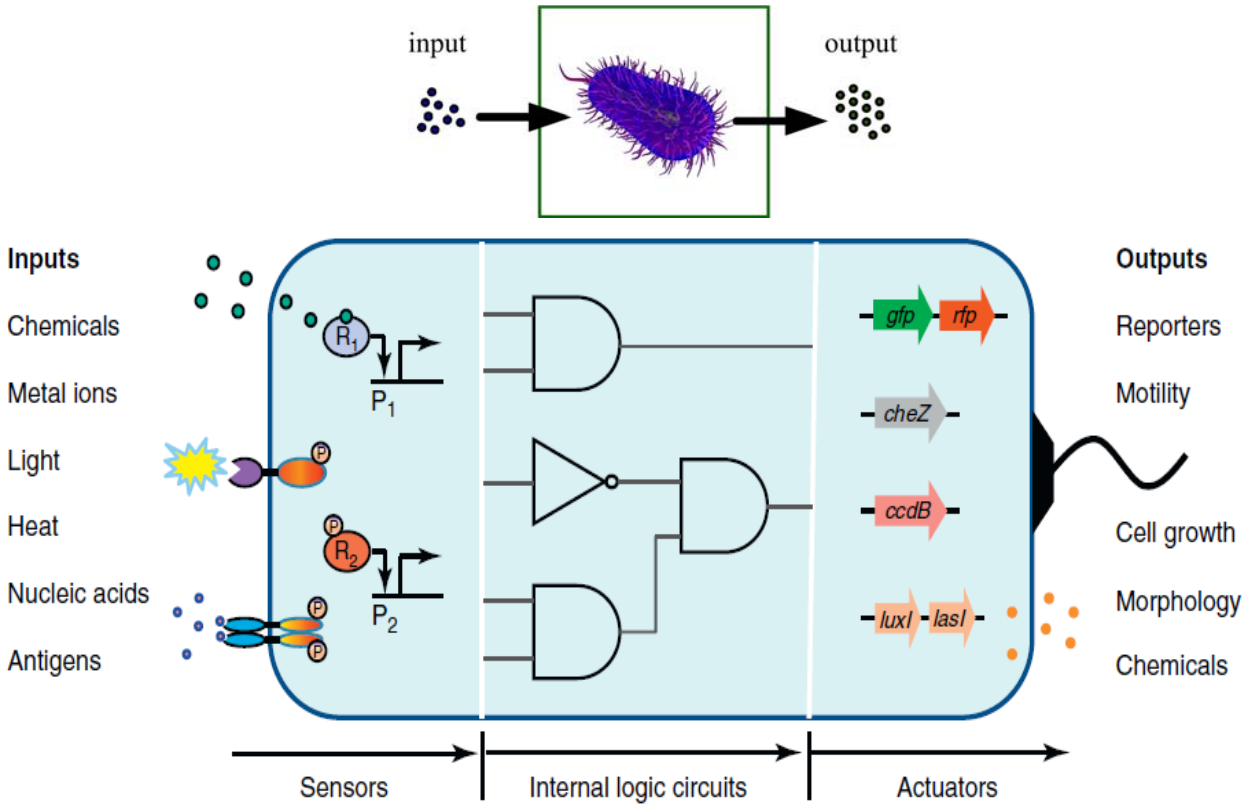
cnrs

BIO-RAD

SysDiag UMR3145

Synthetic Biology and Whole-Cell Biosensors

Whole-cell biosensors are intrinsically modular : consisting of a recognition element coupled to an arbitrarily chosen reporter



Customizing cell signaling using engineered genetic logic circuits Baojun Wang

Advantages:

-Simple use
-Cost-effective
-Self-replication
-Fast, short analysis time
-Disposable
-High sensibility (signal amplification) and selectivity
-No need for sample preparation
-Multiplexing

Bacterial or artificial cell-free “computers” that can perform medical diagnostics

cnrs

BIO-RAD

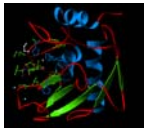
SysDiag UMR3145

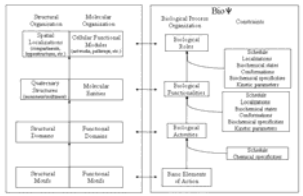
Our Strategy

Design - Simulation/modélisation - Experimental validation

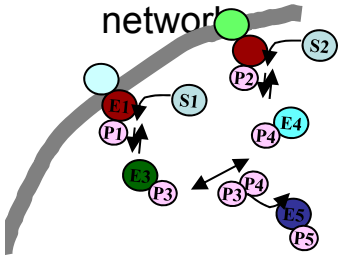
Identification and characterization of molecular compounds

Functional bircks





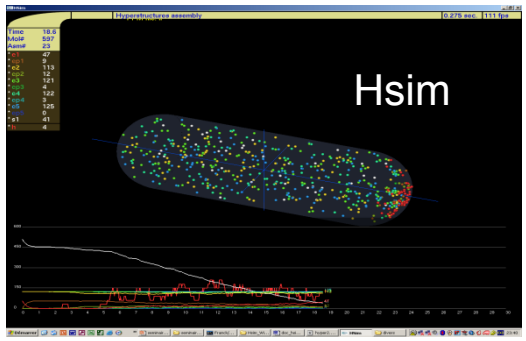
Design synthetic network



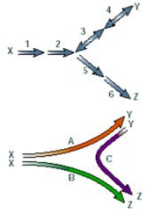
BioΨ Formalization

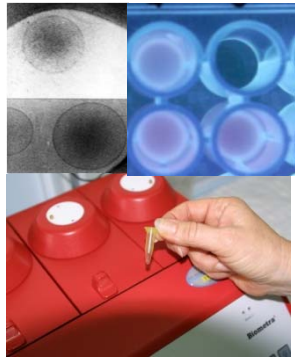
Simulation

Stochastic Cellular automaton, Multi-Agent



Modelling:
Control Th.
flux analyses
ODE
Elementary modes





Biotechnology

Auto-organisation/ Robustness

Validation *in vitro*

BioNetCAD network Computer Assisted Design

Rialle, S., Felicori, L., Dias-Lopes, C., Peres, S., El Atia, S., Thierry, A. R., Molina, F. (2010). BioNetCAD: Design, simulation and experimental validation of synthetic biochemical networks. *Bioinformatics,* 26(18):2298-304

cnrs

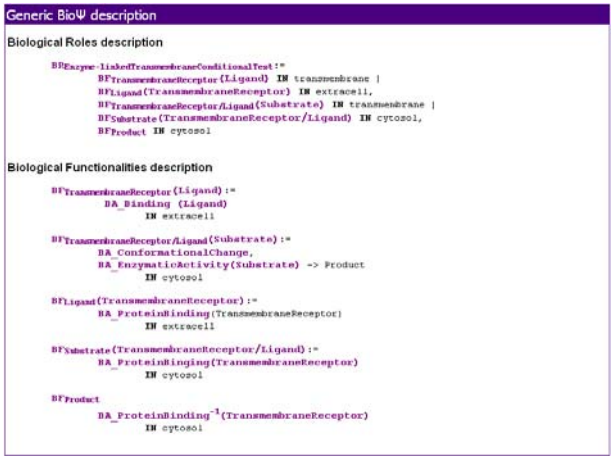
BIO-RAD

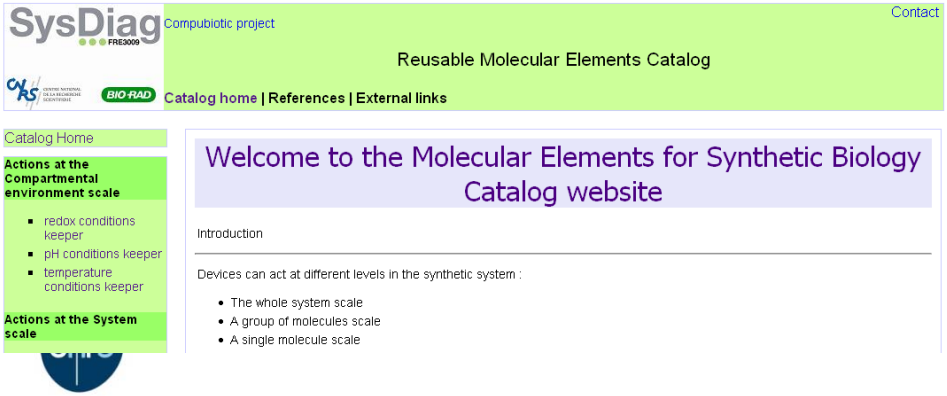
SysDiag UMR3145

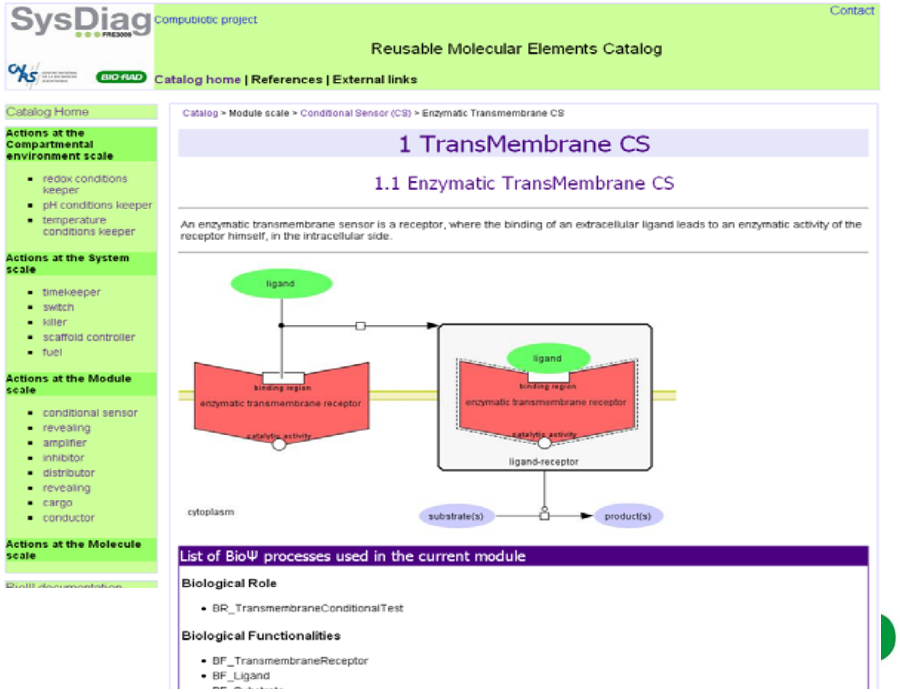
Standardized catalog of functional biological compounds:

Reusable, non toxic

- Processes are formalized (ready for modelling)
- Biological behavior characterized experimentaly (ready to use in a synthetic system)
  - « compound » properties
  - robustness
  - stability
  - « composability » score







SysDiag UMR3145

Molecular, modular compounds
Identification, characterization

- Modules with defined role

Redox conditions monitoring

pH conditions monitoring

Temperature conditions monitoring

Timekeeper (Time counter)

Switch On/Off

Killer (destruction component)

Scaffold controller

Fuel

Conditional Sensor

Amplifier

Inhibitor

Distributor

Revealing

Cargo

Conductor

- Proteins and small molecules useful for synthetic biology

Ex : Peroxidase + substrat → Revealing role

Ex : Glucose oxydase + glucose → Switch on role, Conditional sensor role

cnrs

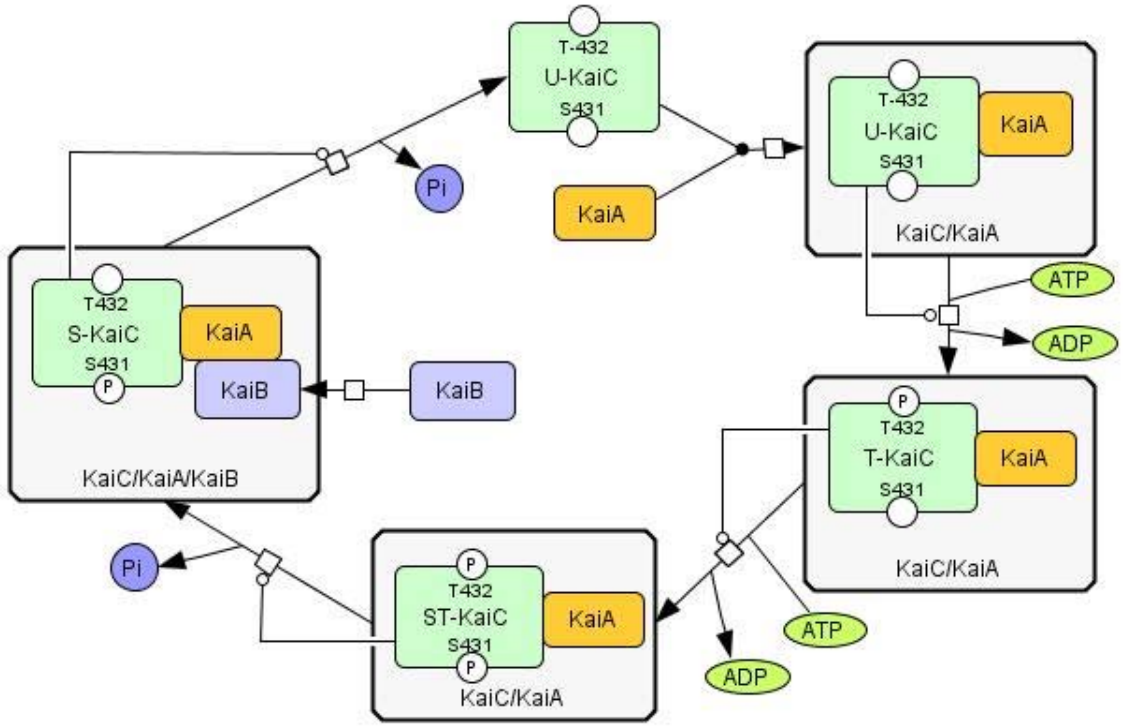
BIO-RAD

Oscillator

Type 1: Circadian oscillation

Implementation 1: Cyanobacterial KaiC phosphorylation

- *3 protéines : KaiA, KaiB, KaiC*
- *Phosphorylation de KaiC oscillante (période = 24h)*



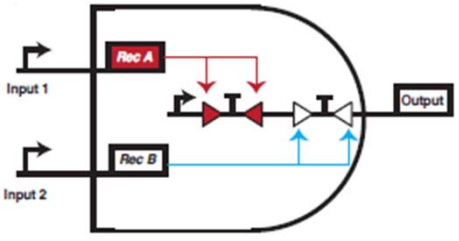
SysDiag UMR3145

Rewritable digital data storage in live cells via engineered control of recombination directionality

Jerome Bonnet, Pakpoom Subsoontorn, and Drew Endy[1]

Department of Bioengineering, Room 269B, Y2E2 Building, 473 Via Ortega, Stanford University, Stanford, CA 94305

First reliable and rewritable DNA inversion-based data storage system that works in vivo

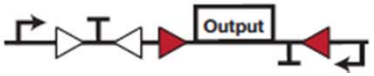


AND

Rec A	Rec B	Sortie
0	0	0
1	0	0
0	1	0
1	1	1

OR

Rec A	Rec B	Sortie
0	0	0
1	0	1
0	1	1
1	1	1



XOR

Rec A	Rec B	Sortie
0	0	0
1	0	1
0	1	1
1	1	0

Recombinase Logic gates memory offers multiples advantages :

i. Transient signals of low intensity can be stored
ii. Able to perfom sequential logic
iii. The result of the diagnostic test may be stored in ADN and read by different methods

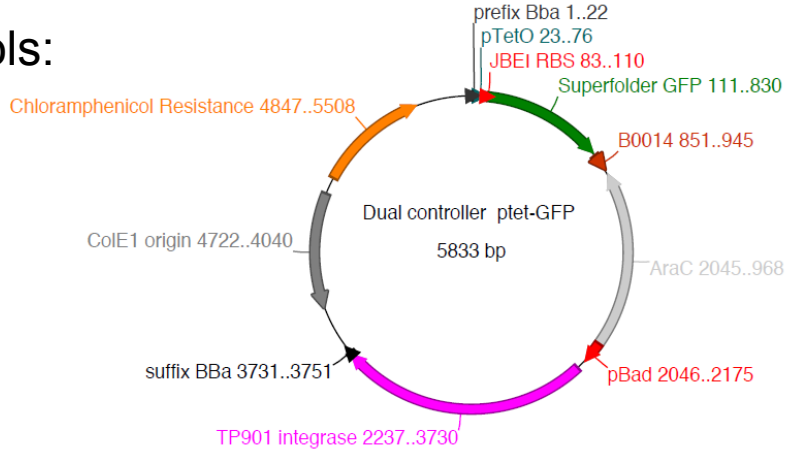
Control plasmids expressing two serine integrases adapted from bacteriophage TP901 and Bxb1 under the control of exogenous arabinose (ara) and anhydrotetracycline (aTc)

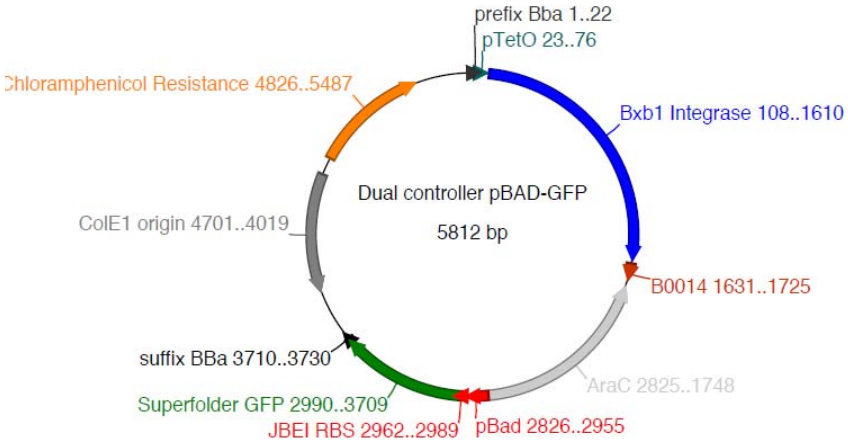
Plasmids encoding AND, OR, XOR, NAND, NOR, and XNOR logic elements placed between a standardized strong prokaryotic promoter and a GFP expression cassette

SysDiag UMR3145

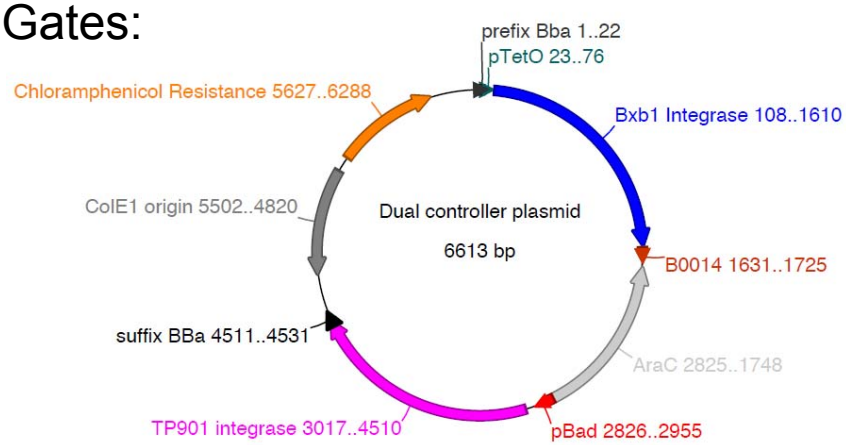
Biosensor in clinical context : testing function in samples

Controls:





Gates:



+

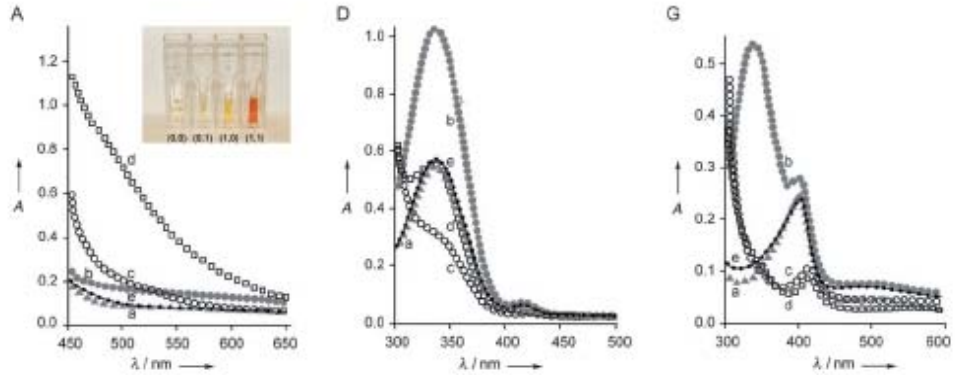
->Monitoring of logic through :

-Bulk GFP levels from bacterial cultures

-Single cell fluorescence distributions

Biological logic gates identification (AND, OR, XOR, etc.) In cell-free biological nextworks

It is possible, Willner et al. 2006, 2009



C

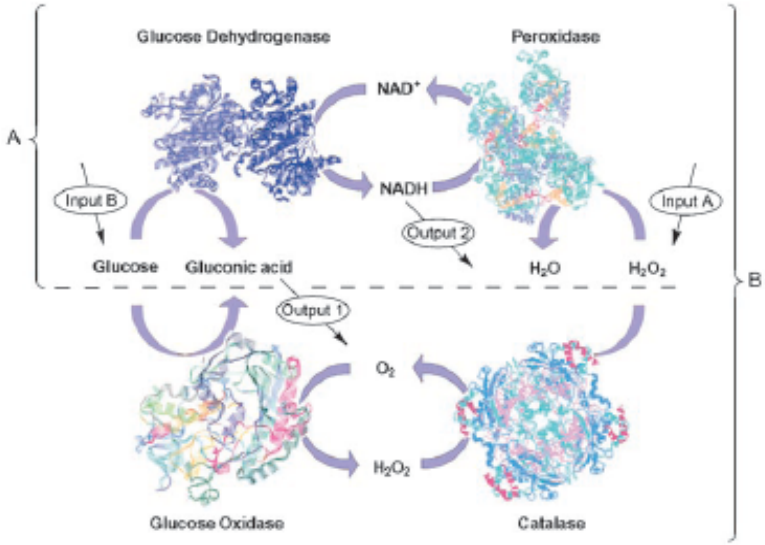
Input A	Input B	Output AND
0	0	0
0	1	0
1	0	0
1	1	1

F

Input A	Input B	Output XOR
0	0	0
0	1	1
1	0	1
1	1	0

I

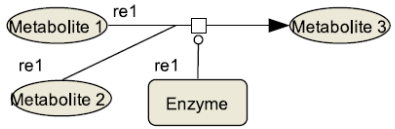
Input A	Input B	Output InhibAND
0	0	0
0	1	1
1	0	0
1	1	0

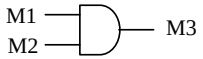


Scheme 1. A) Logic gates based on two coupled enzymes. B) Half-adder based on four coupled biocatalysts.

Rules for Bio-logic gates devoted to diagnosis use

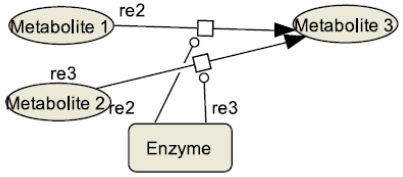
A

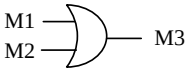




M1	M2	M3
0	0	0
1	0	0
0	1	0
1	1	1

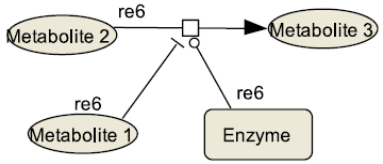
B

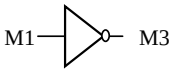




M1	M2	M3
0	0	0
1	0	1
0	1	1
1	1	1

C





M1	M3
0	1
1	0

Schematic representation corresponding to the different ways of obtaining each type of logic gate in a biochemical reaction.

(A) An enzymatic AND can be defined as two necessary and different metabolites (the inputs) lead to a product (the output) through one or several enzymatic reactions.

(B) An enzymatic OR gate could be defined by two different metabolites (inputs) that can individually produce (through one or several enzymatic reactions) the same metabolite (output) in identical external conditions.

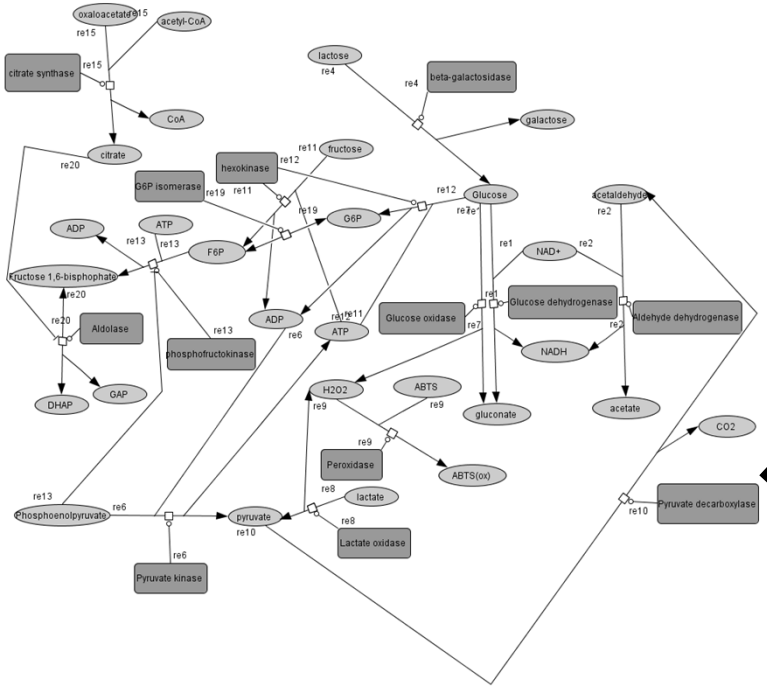
(C) An enzymatic NOT could be defined by a metabolite (input, an inhibitor typically) that prevents the production of another metabolite (the output).

SysDiag FRE3009

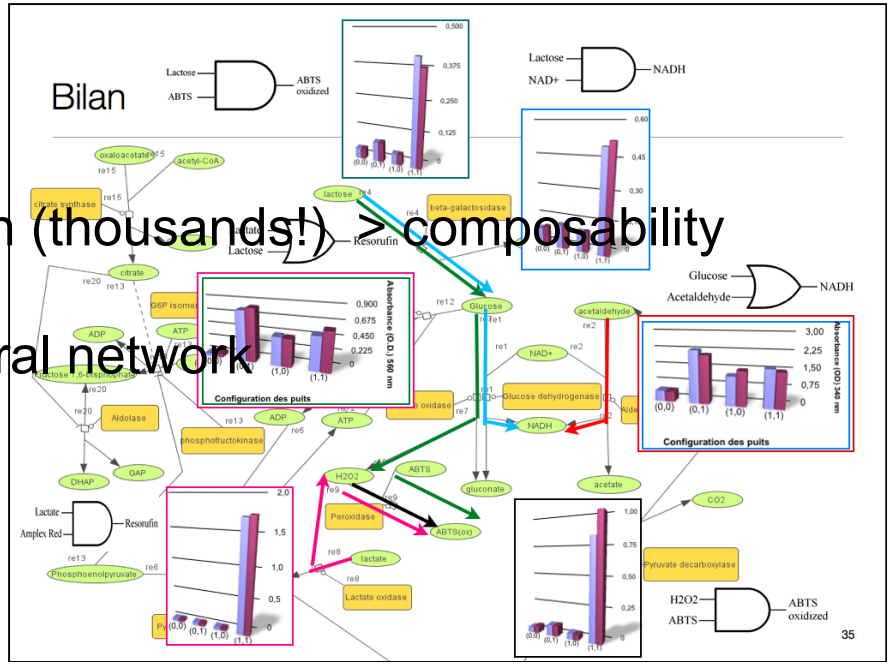
Large scale Bio-logic gate identification

Natural biological network

Felicori et al in preparation



-Network formal description
-EFM-like algorithm and Graph analyzes
-Selected set of pattern satisfying RULES

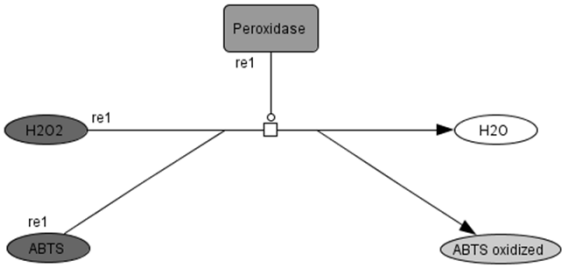


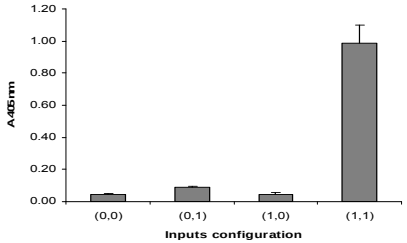
Method for large scale bio-logic gate design (thousands!) > composability
Compliant with Medical use (> safety)
Study of Bio-logic gates distribution in natural network

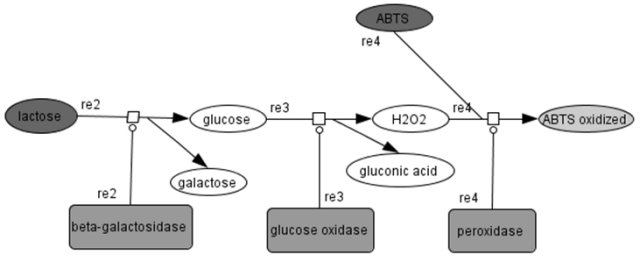
Set of validated bio-logic gates

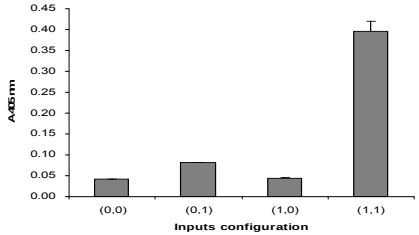
cnrs dépasser les frontières

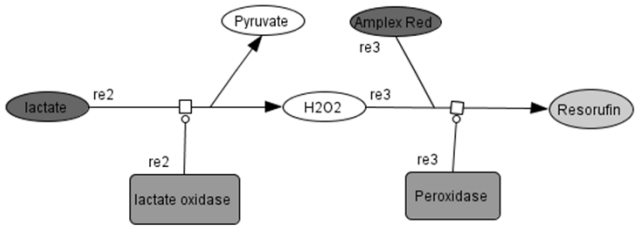
SysDiag FRE3009

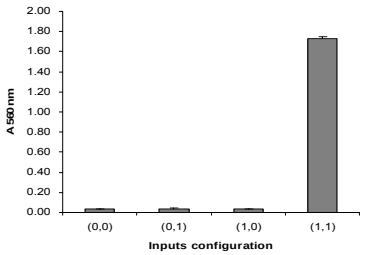


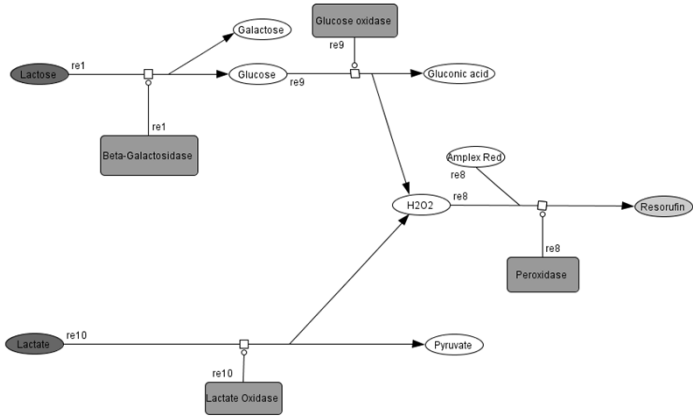


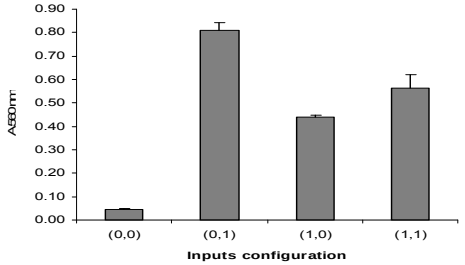






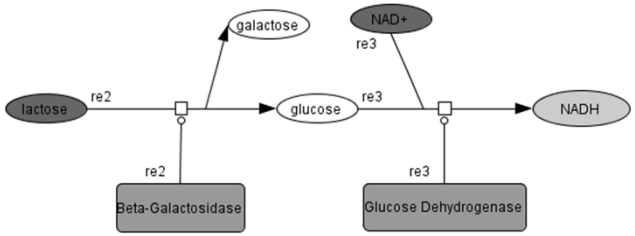


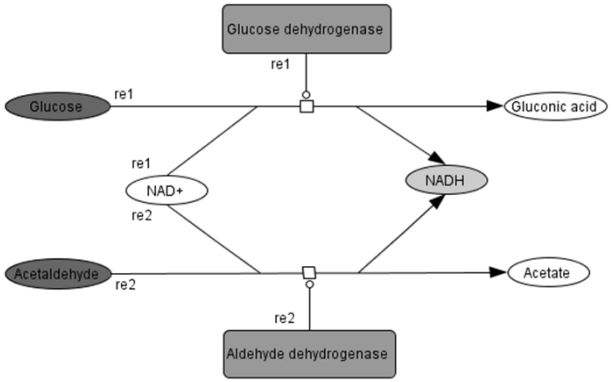


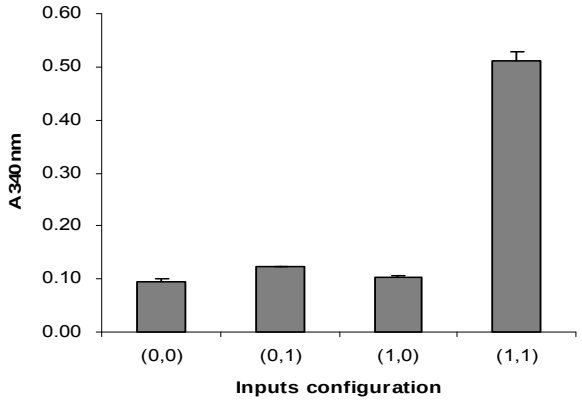


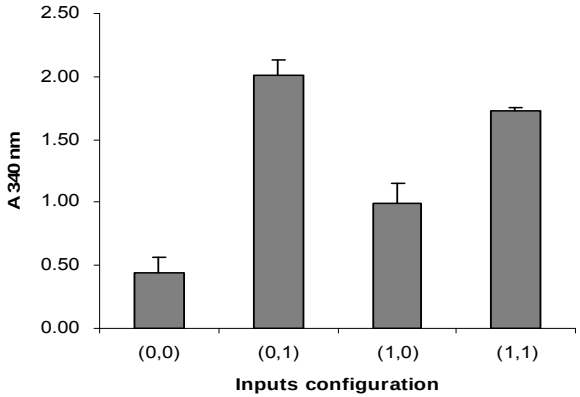
cnrs dépasser les frontières

BIO-RAD


galactose
NAD+
re3
lactose
re2
glucose
re3
NADH
re2
re3
Beta-Galactosidase
Glucose Dehydrogenase


Glucose dehydrogenase
re1
Glucose
re1
Gluconic acid
re1
NAD+
re2
NADH
Acetaldehyde
re2
Acetate
re2
Aldehyde dehydrogenase


0.60
0.50
0.40
0.30
0.20
0.10
0.00
A 340 nm
(0,0)
(0,1)
(1,0)
(1,1)
Inputs configuration

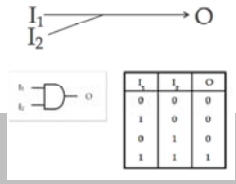

2.50
2.00
1.50
1.00
0.50
0.00
A 340 nm
(0,0)
(0,1)
(1,0)
(1,1)
Inputs configuration

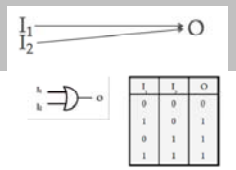
SysDiag UMR3145

Bio-Logic gates for diagnosis

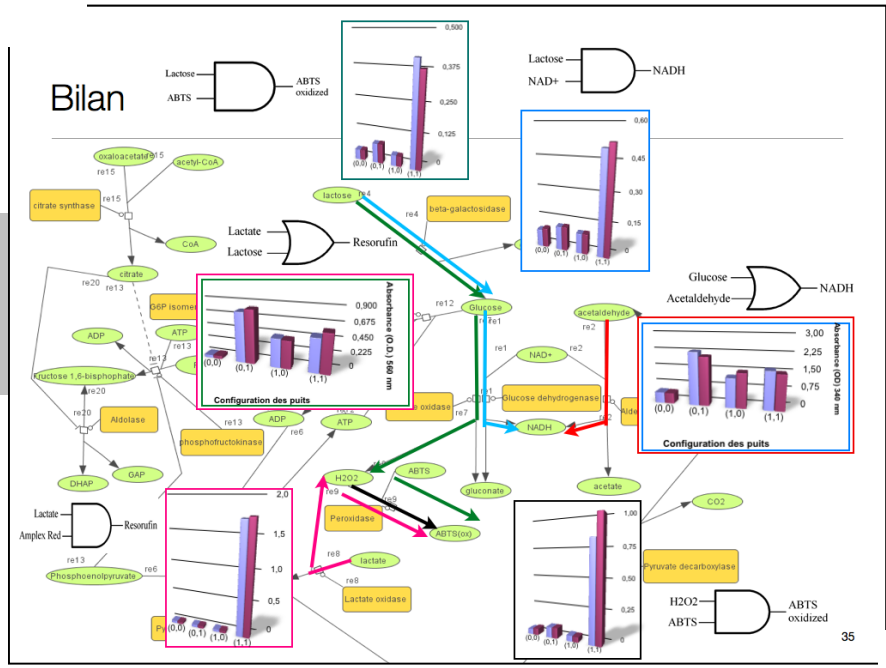
- Rules, method and tool to bio-logic gates identification in existing networks
- Study of logic properties of natural networks
- Experimental Validation

Felicori et al in preparation





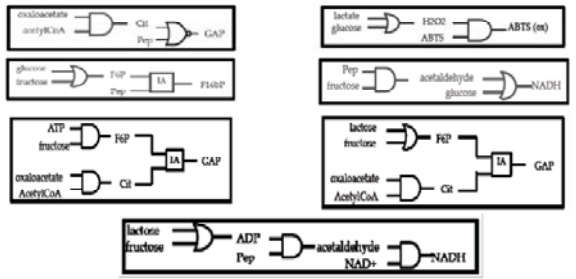
Set of rules for bio-logic gates suitable for diagnostic use



Systematic approach to identify Bio-logic gates in biological networks EFM, graph

Set of experimentaly validated Bio-logic gates. Robustness studies

Bio-logic gates Concatenation



SysDiag UMR3145

General principles for a simlpe biomarker sensing systems

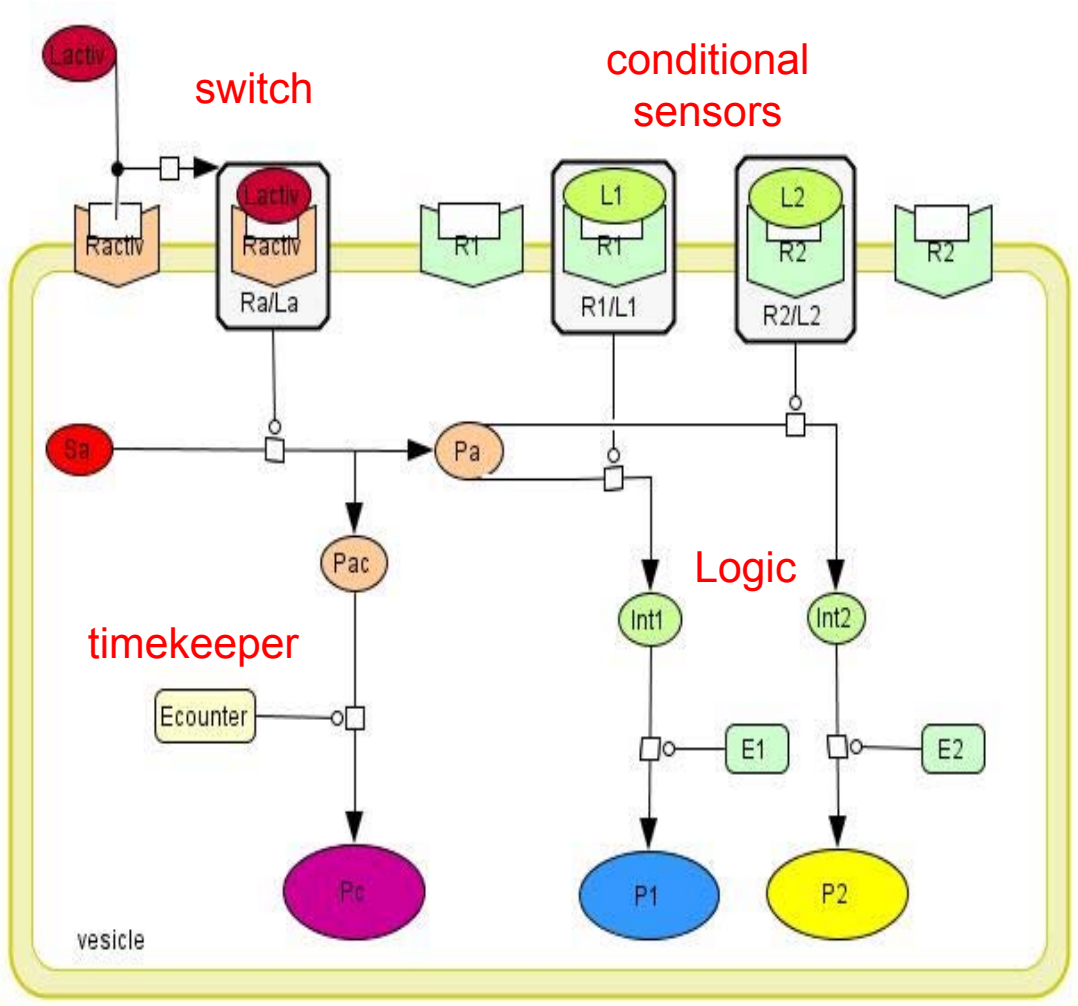
Conditional sensing
Receptors,
biosensors etc.

Signal transduction

Integration/Control
Logical processing
Algoritms
Amplification,
normalization,
etc.

Signal transduction

Revelation
Coloration,
fluorescence, contrast,
etc.



cnrs

BIO-RAD

SysDiag UMR3145

ab initio Artificial network design

from abstract network
to implemented network

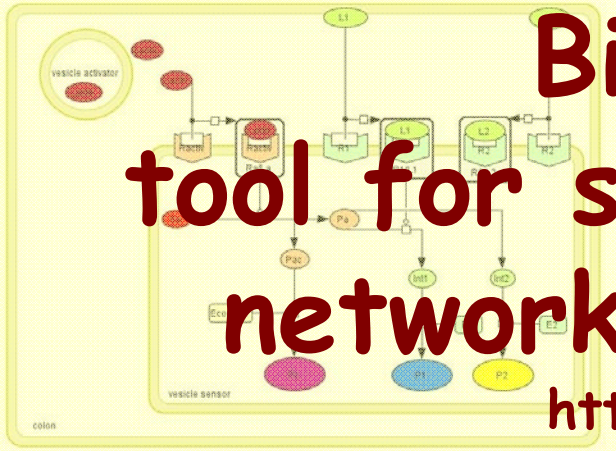
cnrs

BIO-RAD

SysDiag UMR3145

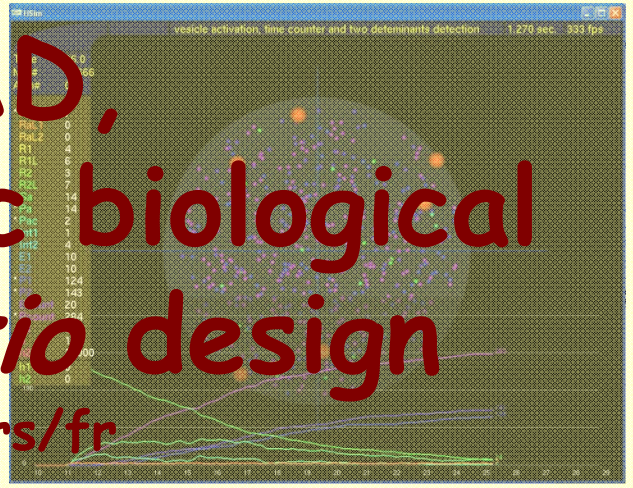
Design

Simulation



BioNetCAD, tool for synthetic biological network *ab initio* design

http://sysdiag/cnrs/fr



System design using our compound catalog SBGN and *Celldesigner*

BioΨ modelling
Formal description

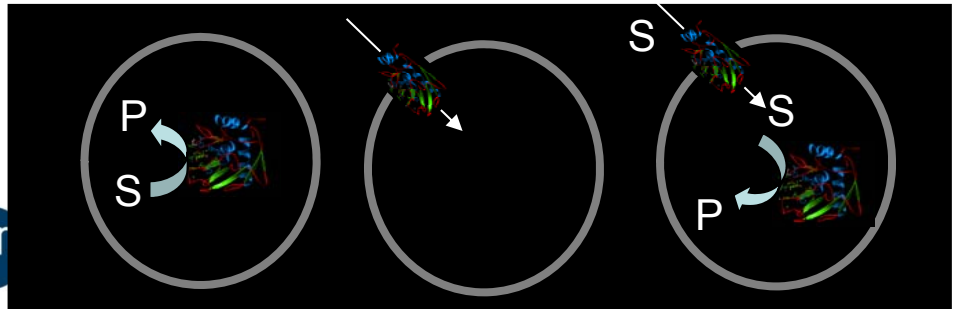
Simulation : Stochastic Cell automaton and multi-agent

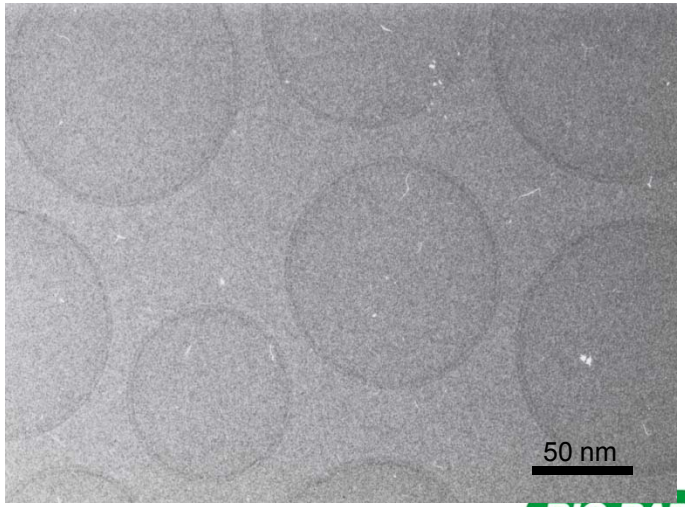
Experimental validation

☒ Stable Vesicules construction (liposomes) ~100nm

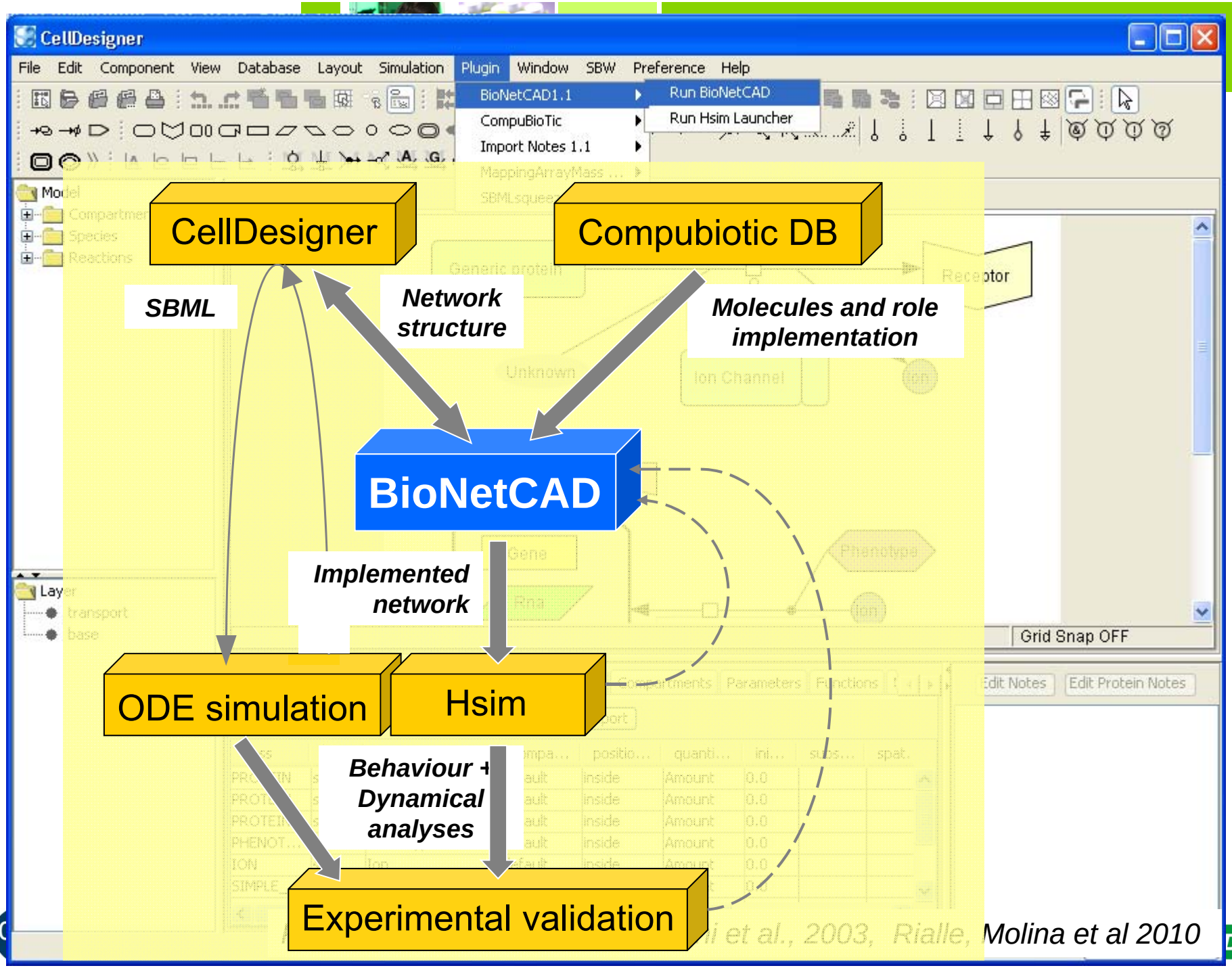
☑ Introduction of chosen functional compounds

☐ Opérational assays of full synthetic system (*in vitro*)





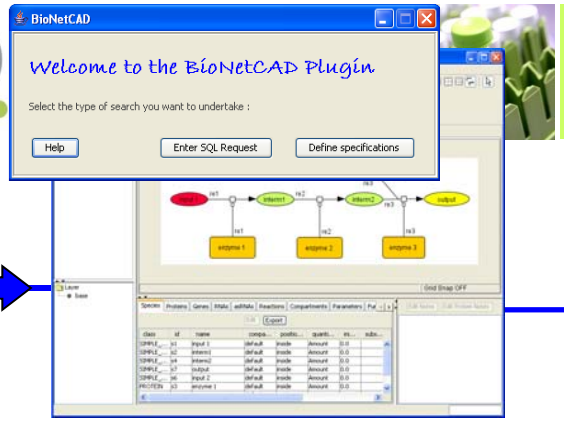
BIO-RAD



Molina et al 2010

SysD

User needs

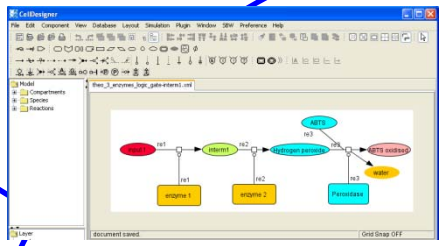


Abstract network

molecule Sélection

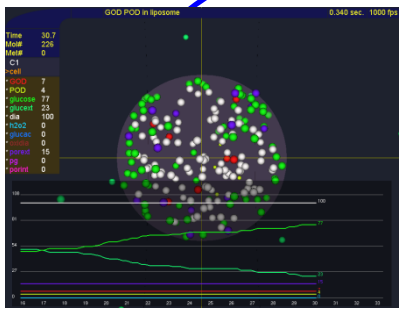
Molecular constraints

I. Selection molecule

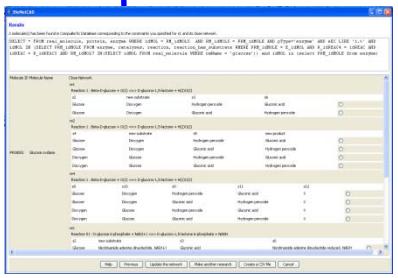


Intermediat implemented network

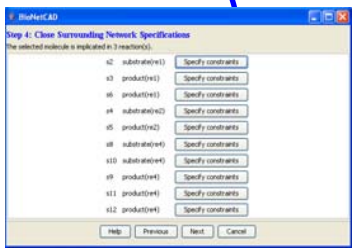
Implemented network



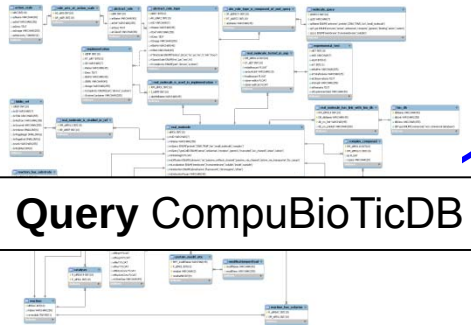
Simulation



Implementation checking and validation



Network constraints



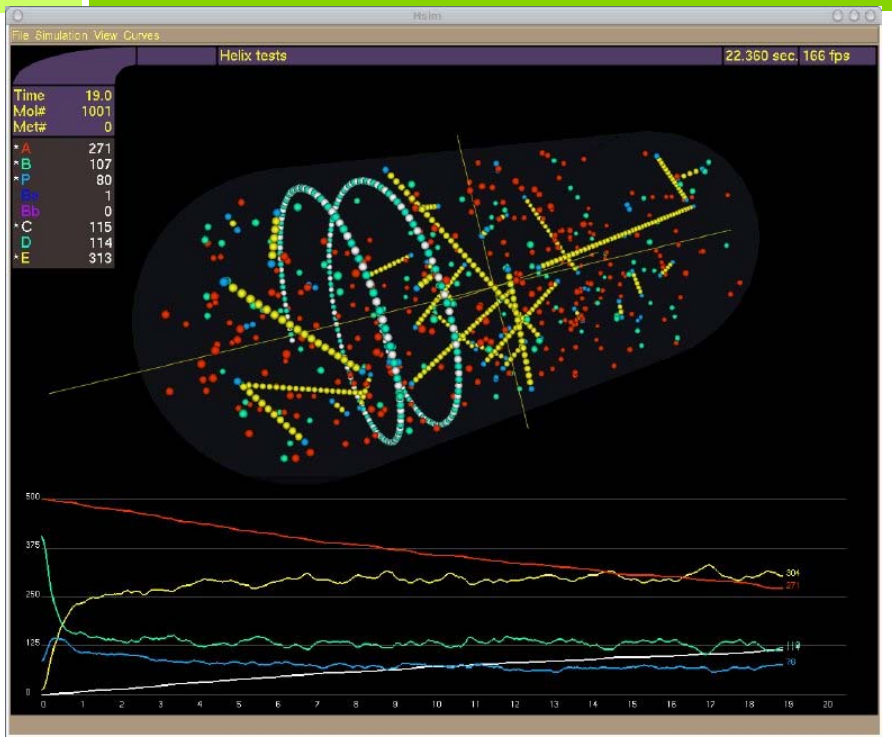
Query CompuBioTicDB

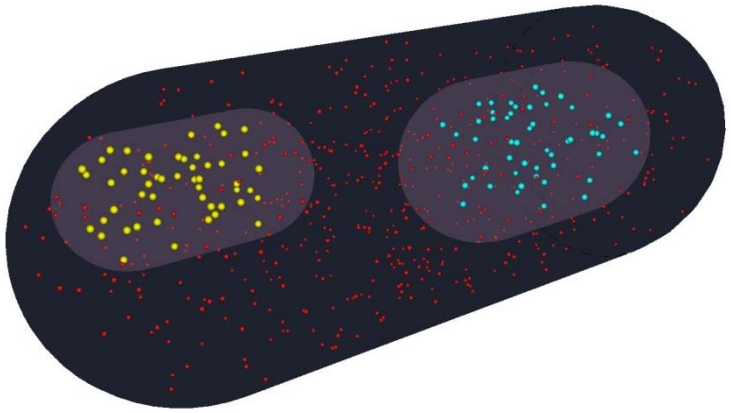
Rialle et al Bioinformatics 2010

SysDiag UMR3145

HSIM: Méthodes de calcul

1. Molécules individualisées
   - Localisation spatiale
   - Assemblages
   - Géométrie
2. Simulation Stochastique
   - Efficacité du calcul
3. Hybride: calcul individualisé/global
4. Equations différentielles ordinaires
   - Comportement moyen





Caractéristiques

1. Multi compartiments
   - Diffusion passive a travers la membrane
2. Interactif : affichage graphique temps réel
3. Batch : sortie dans un fichier CSV

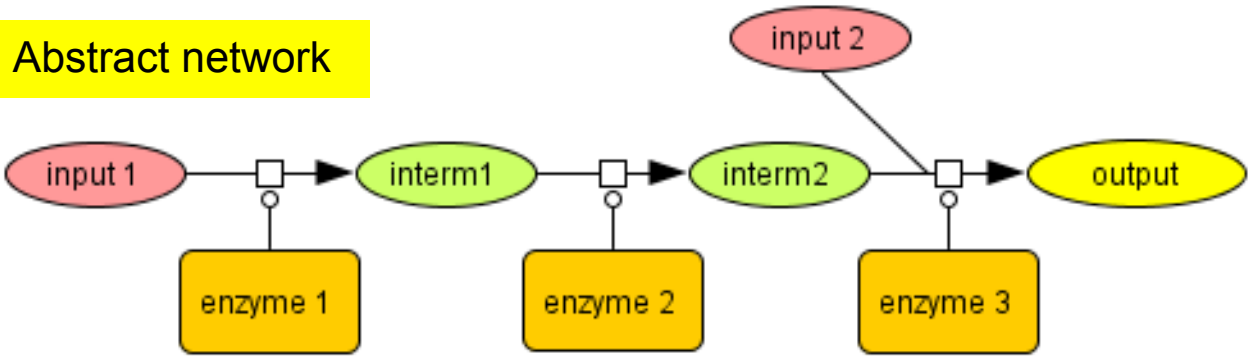
P. Amar et al. 2012 Hsim: an hybrid stochastic simulation system for systems biology, Third International Workshop on Static Analysis ans Systems Biology (SASB 2012)

BIO-RAD

SysDiag UMR3145

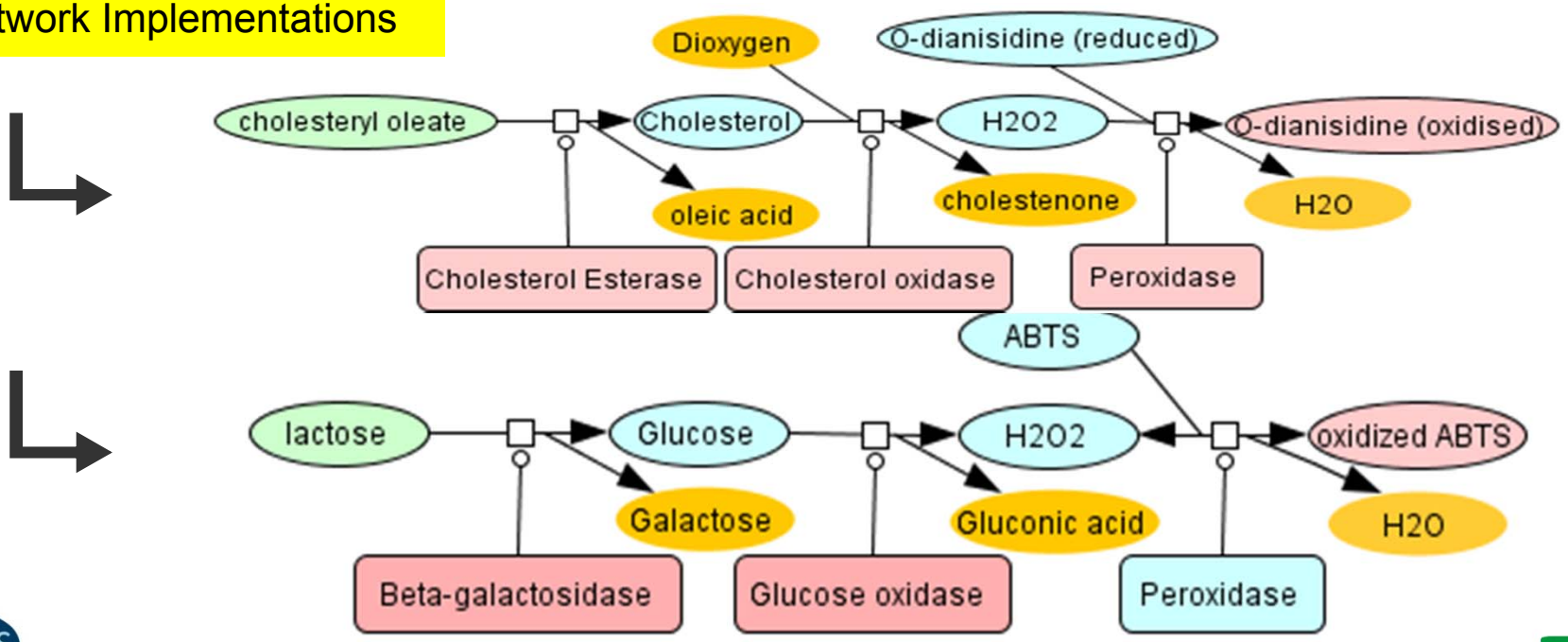
Bio-Logic gate design

Abstract network



input 1	input 2	output
0	0	0
0	1	0
1	0	0
1	1	1

Network Implementations



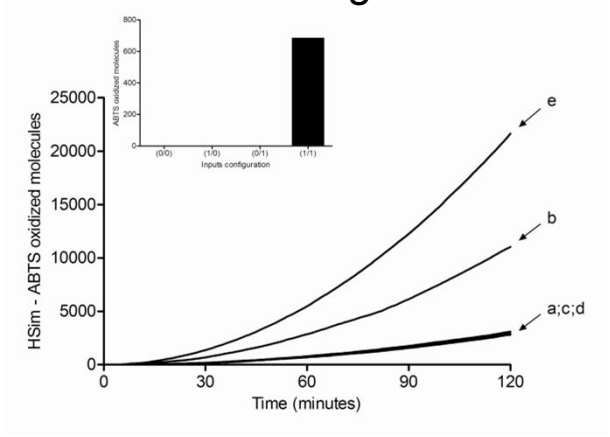
cnrs

BIO-RAD

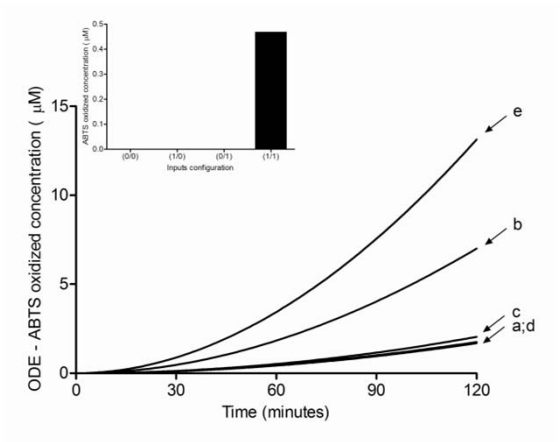
SysDiag UMR3145

Simulation vs experimentation

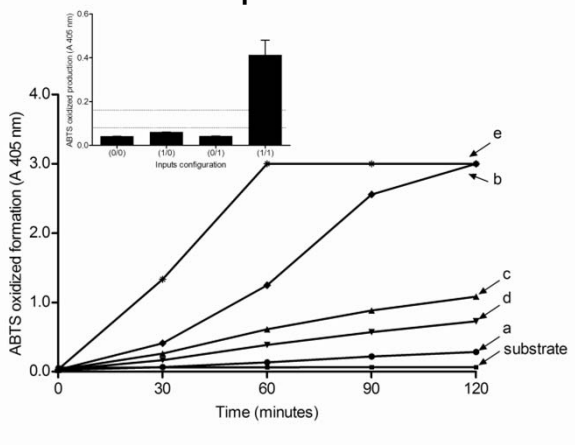
Multi-agent-like

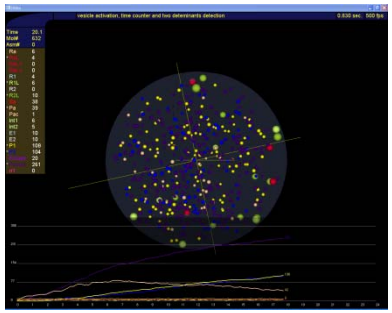


ODE



Experiment





$V_{\beta\text{-gal}} = kcat_{\beta\text{-gal}} . [\beta\text{-gal}]_0.[lactose] / (Km_{lactose} + [lactose])$

$V_{god} = kcat_{god}. [god]_0.[glucose] / (Km_{glucose} + [glucose])$

$V_{pod}=kcatp.[pod]_0.[H_2O_2].[ABTS]/(Km_{ABTS}[H_2O_2]+Km_{H2O2}.[ABTS]+[H_2O_2].[ABTS])$

Rialle, S., Felicori, L., Dias-Lopes, C., Peres, S., El Atia, S., Thierry, A. R., Molina F.(2010). BioNetCAD: Design, simulation and experimental validation of synthetic biochemical networks. *Bioinformatics,* 26(18):2298-304

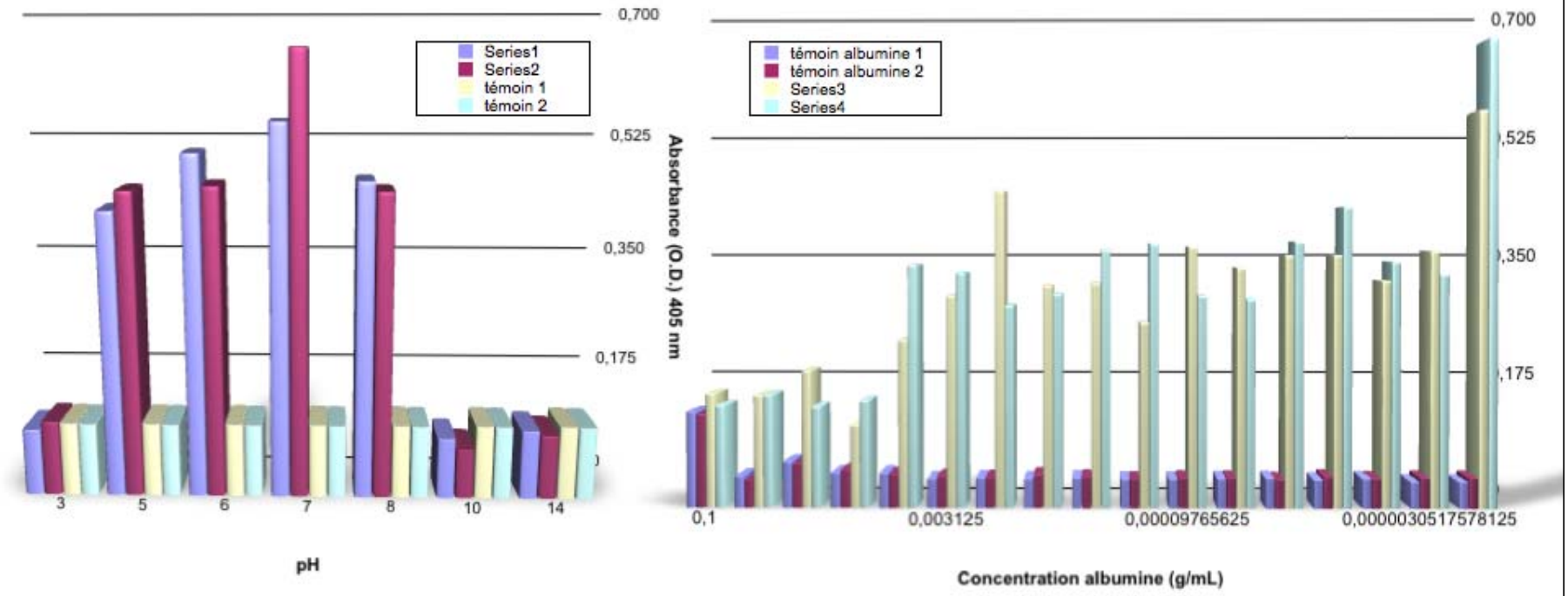
cnrs

BIO-RAD

Etude de la porte bGal-GOD-POD (2)
Robustesse

- Etude de la résistance de la porte face à la perturbation : ajout d'albumine et variation du pH

Après 1h de réaction



SysDiag UMR3145

New methods for biomarker detection
(Synthetic biology)

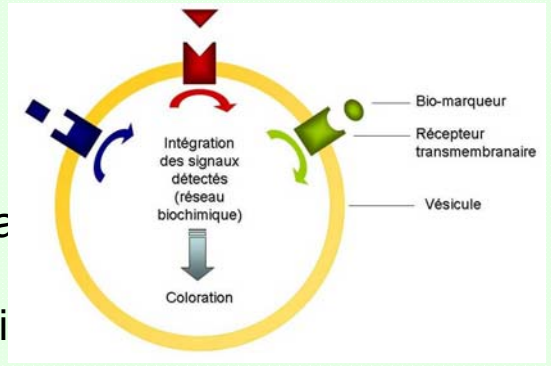
Implementation form ND/diabetis biomarker detection

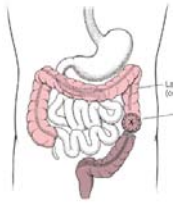
« Close to the patient » simple assay

Multi-parametric measure

Sophisticated signal integration
(qualitative, quantitative, temporal, spacia

Result return in a simple way (local dyi





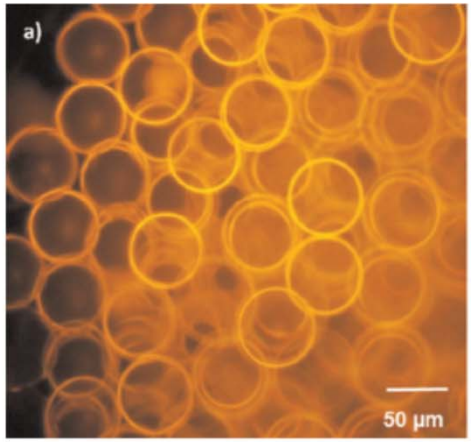
Application to diabetic nephropathy and colo-rectal cancer

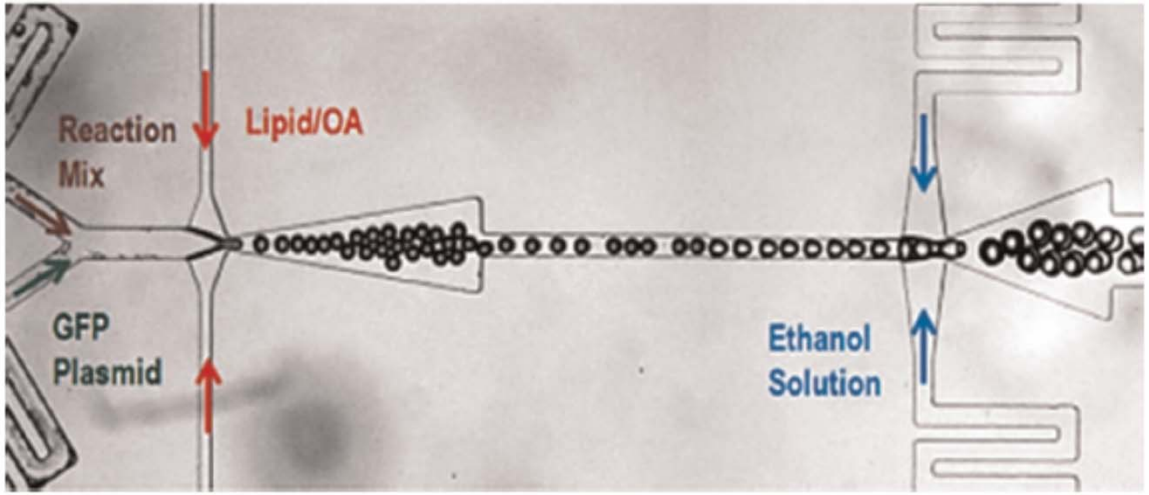
cnrs

BIO-RAD

SysDiag UMR3145

Vesicule building, film rehydratation, Microfluics etc.





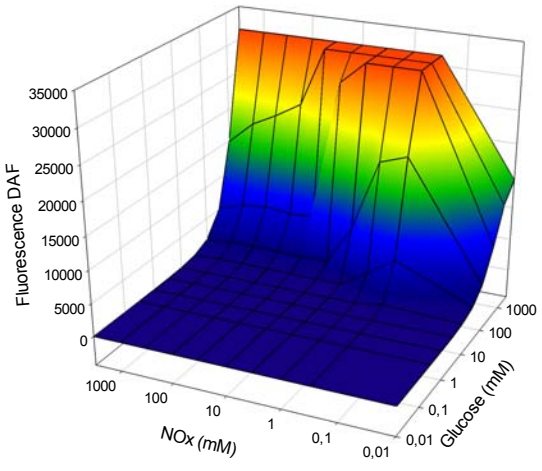
cnrs

BIO-RAD

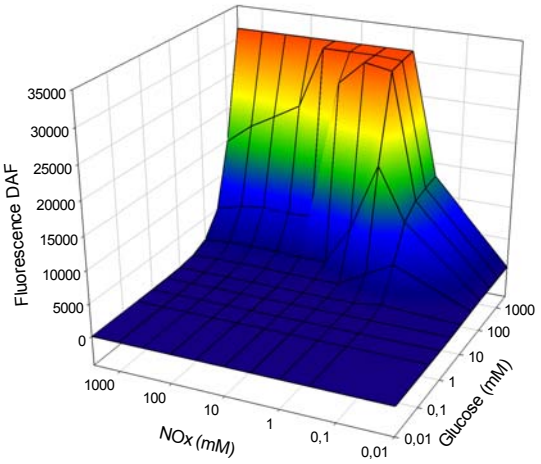
Ex Vivo synthetic biochemical Network : clinical relevant AND gate

Transfer functions
Sensitivity to enzyme (G1DH/NR) concentration ratio?

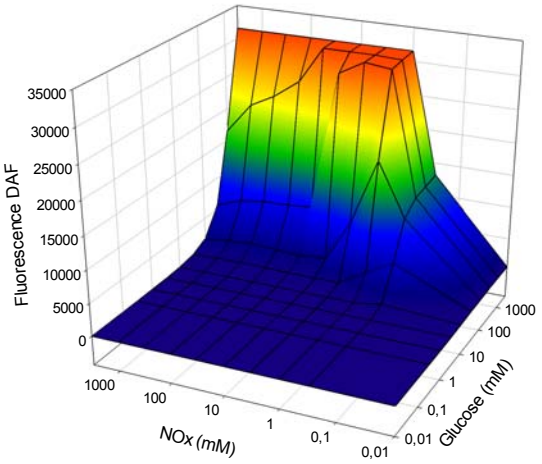
AND gate G1DH/NR=0.01



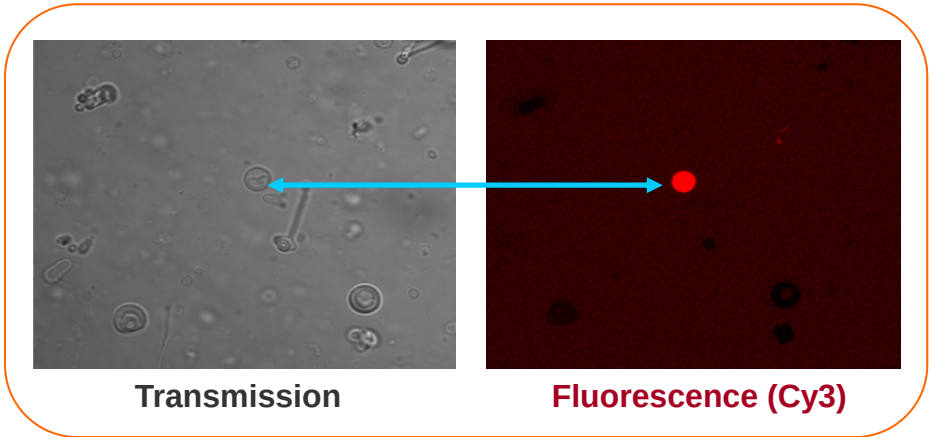
AND gate G1DH/NR=1



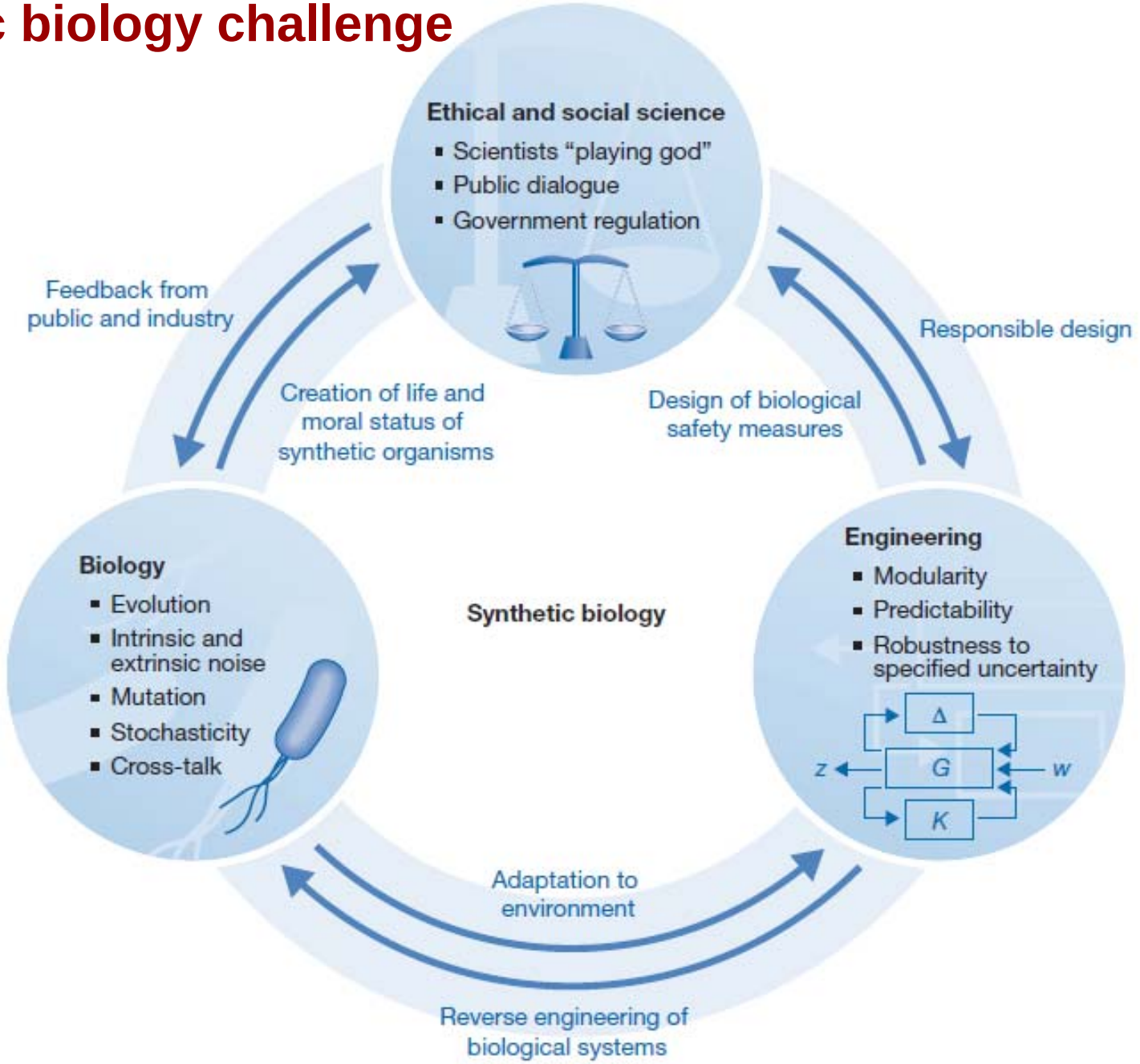
AND gate G1DH/NR=100



Simulation



The Synthetic biology challenge



SysDiag UMR3145

Challenges for Synthetic biology clinical applications

-Technical issues:
Robustness and reliability, comparison with current performances of clinical application

Table 1 | Engineering, natural and synthetic solutions for designing complex systems

Design challenge	Engineering solution	Natural organism	Synthetic biology solution
Scalability	Modularity	Motifs Modularity?	Modularity Well-characterized modules
Retroactivity/ cross-talk	Insulation and feedback	Feedback	Orthogonal design
Robustness	Feedback	Feedback	Feedback
Complexity	Hierarchical design	?	Hierarchical design
Evolution/ mutation	?	Efficiency/robustness trade-off	?

-Production and Cost issues

-Regulatory and Safety issues (Objective demonstration of composition, behavior, etc.)

-Ethics and social issues

-Misuse use (terrorism, etc.)

cnrs

BIO-RAD

SysDiag
UMR3145


Systems and synthetic biology team

Franck Molina
Alexis Courbet
Dung LeNguyen
Laurence Molina
Nicolas Salvetat
Patrick Amar (Visitor)
David Jean
Christophe Nguyen
Emmanuelle Sidot

Former members:
Claude Granier
Liza Felicori
Sabine Peres
Stéphanie Rialle
Randa Benhameur
Camila Lopes
Chams Kifagi
Francisco Schneider
Sylvaine Cordroch
Cécile Fleury
Sarah parisot

Collaborators:

Emilio Parisini, Havard Medical school, US
Alfonzo Jaramillo Univ Evry,
P. Amar, LRI, Orsay
Vic Norris, University lesceiter/Rouen
D. Boturyn, CNRS Grenoble
Luigi Luizi, Rome, Italy
J. Stelling, UTHZ, Swissland
European BaSysBio partners UE FP6
H. Mischak, Hanover, DE
H. Holtofer, Dublin, Irland
A Wlahou, Athens, Greece
A. Hamadi, Sfax, Tunisia
Sowdonamini and Srinivasan, Bangalore, NCBS, India.
C. Chavez, Belo Horizonte, Brazil
C. Godin INRIA, Montpellier
François Fages, INRIA Roquencourt
Tony Wilkinson, Univ. York, UK
Jerome Bonnet, Drew Endy, Univ Stanford, US

Clinicians

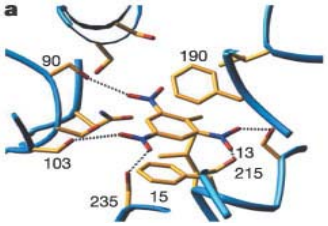
E. Renard, CHRU Montpellier
F. Jarraya Hopital de Sfax, Tunisie
A. Argiles, CHU Sète
M. Ychou, CRLC, Montpellier
Corinne Fayolle, CHU, Montpellier

Grants:
BaSysBio UE FP6, Eurokup UE FP7 ; LIA CNRS
ANR MSDmind ; PICS CNRS ; Région LR
France-Univ Stanford Grant

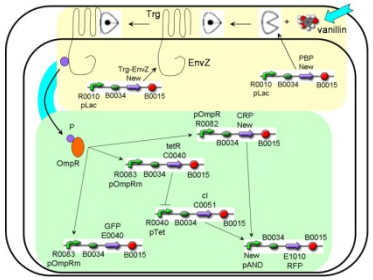
SysDiag FRE3009

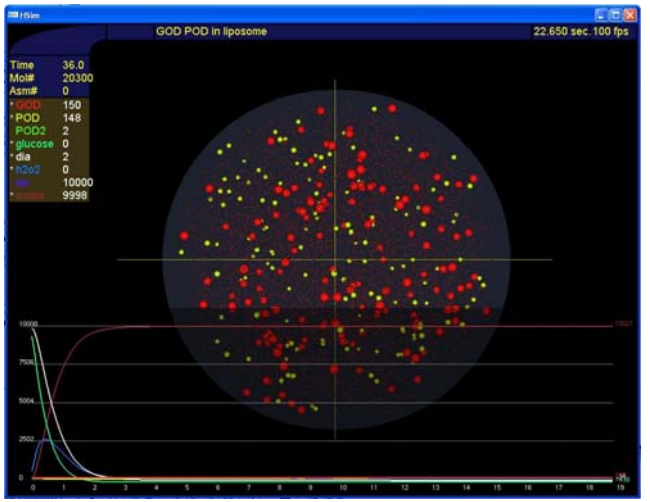
Complex System Modeling and Engineering for Diagnosis
UMR3145 CNRS/Bio-Rad , Montpellier

http://www.sysdiag.cnrs.fr



F. Molina, CNRS ,Montpellier





cnrs
dépasser les frontières

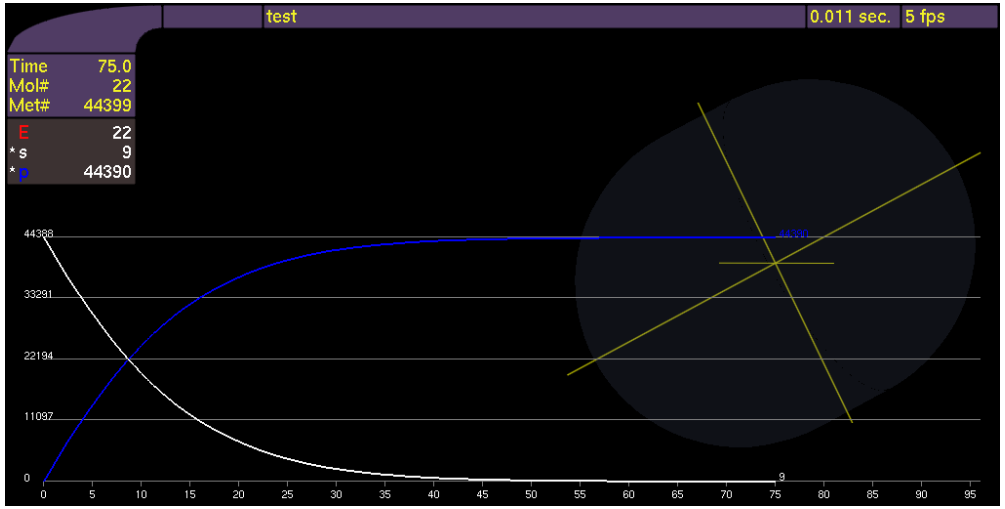
BIO-RAD

SysDiag UMR3145

Modèle HSIM

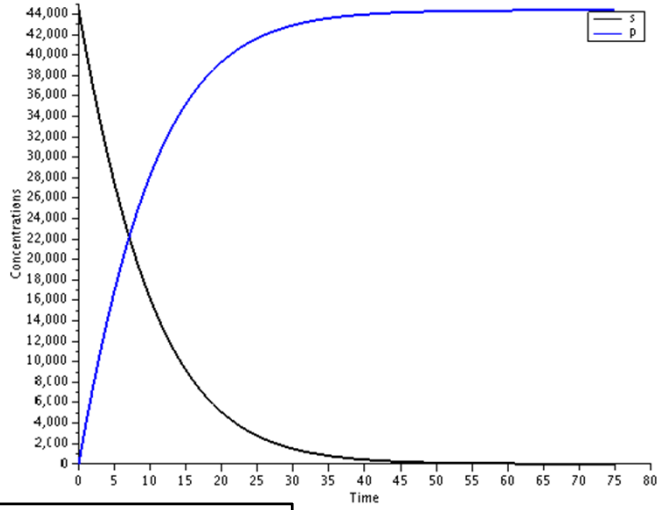
E (s -> p) Km = 0.25 mM; Kcat=337;

init (E, 0.1 uM);
init (s, 100 uM);



Réactions

E + s -> Es [0.5]
Es -> E + s [0.03125]
Es -> E + p [0.0337]



Export ODE

$$\frac{d[E]}{dt} = -k1 \cdot [E] \cdot [s] + k2 \cdot [Es] + k3 \cdot [Es]$$

$$\frac{d[s]}{dt} = -k1 \cdot [E] \cdot [s] + k2 \cdot [Es]$$

$$\frac{d[p]}{dt} = k3 \cdot [Es]$$

$$\frac{d[Es]}{dt} = k1 \cdot [E] \cdot [s] - k2 \cdot [Es] - k3 \cdot [Es]$$

Paramètres

$k_1 = 0.00847771$
$k_2 = 312.5$
$k_3 = 649.5.$