SysDiag FRE3009

CompuBioTic, a methodology for *de novo* design of vesicles performing programmed tasks

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Complex System Modelling and Engineering for Diagnosis
Director : Franck MOLINA

Our goal

Design and build a **non-living** synthetic nanosystem,
« **programmed** » to perform *in vitro* or *in vivo*
diagnostic assays

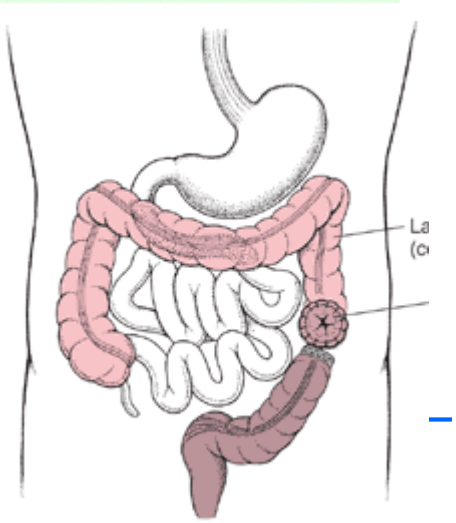
Colorectal cancer diagnosis and follow-up

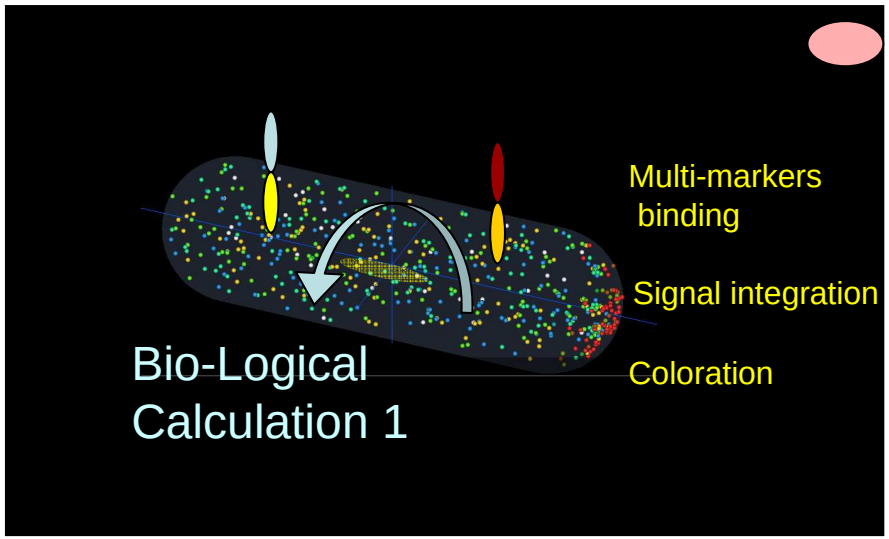
« Close to the patient » simple assay

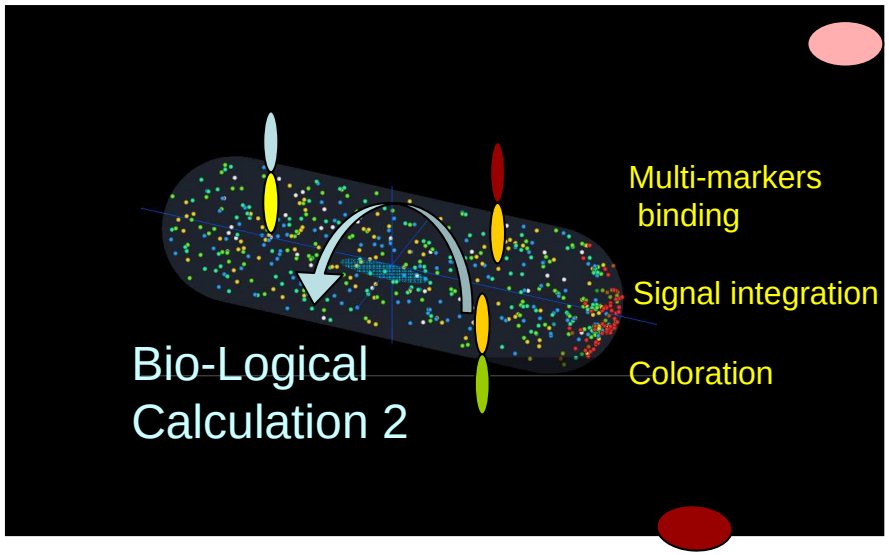
Multi-parametric measure

Sophisticated signal integration
(qualitative, quantitative, temporal, spatial etc.)

Result return in a simple way (local dying)

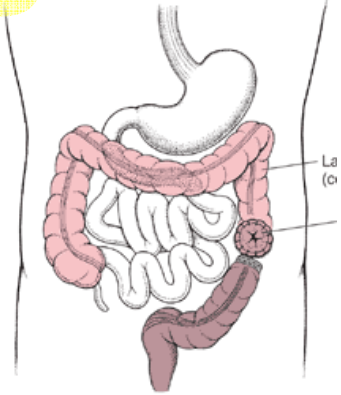






Local coloration depends on the response of multi-sensors to local biomarkers and the result of integrated « bio-logical calculation »

→ Low risk



→ High risk

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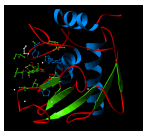
Our Strategy

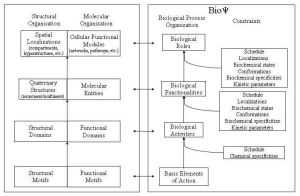
in vitro Proof of concept

Design - Simulation - Experimental validation

Identification and characterization of molecular compounds

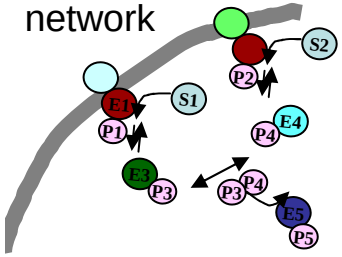


Functional bircks



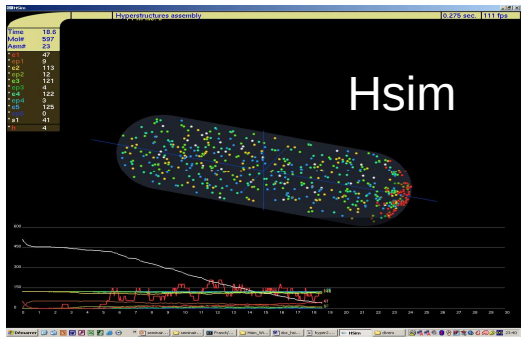
BioΨ Formalization

Design synthetic network

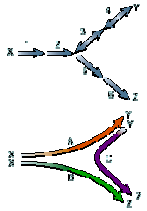


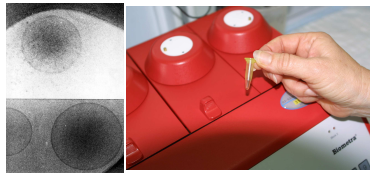
Simulation

Stochastic Cellular automaton, Multi-Agent



Modelling:
Control Th.
flux analyses
ODE
Elementary modes





Biotechnology

Auto-organisation/ Robustness

Validation *in vitro*

Design ⟺ Modelling/Simulation ⟺ Experimentation

cnrs dépasser les frontières

la Région Languedoc Roussillon

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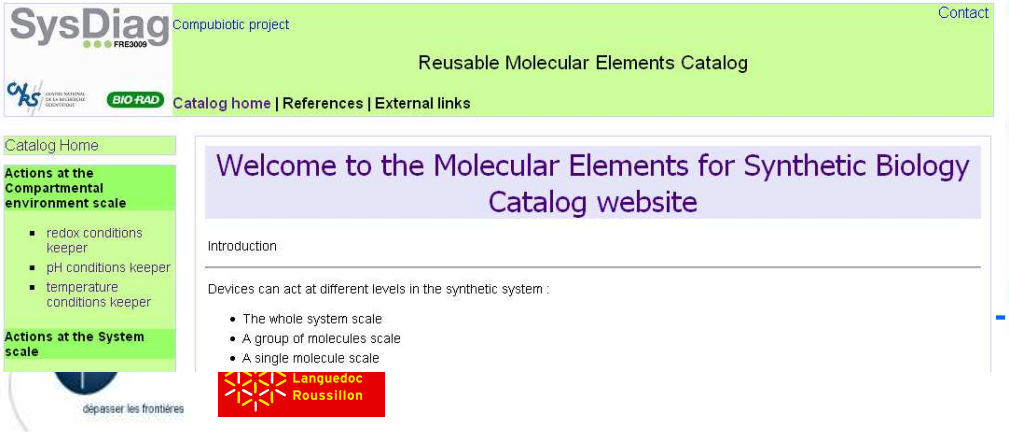
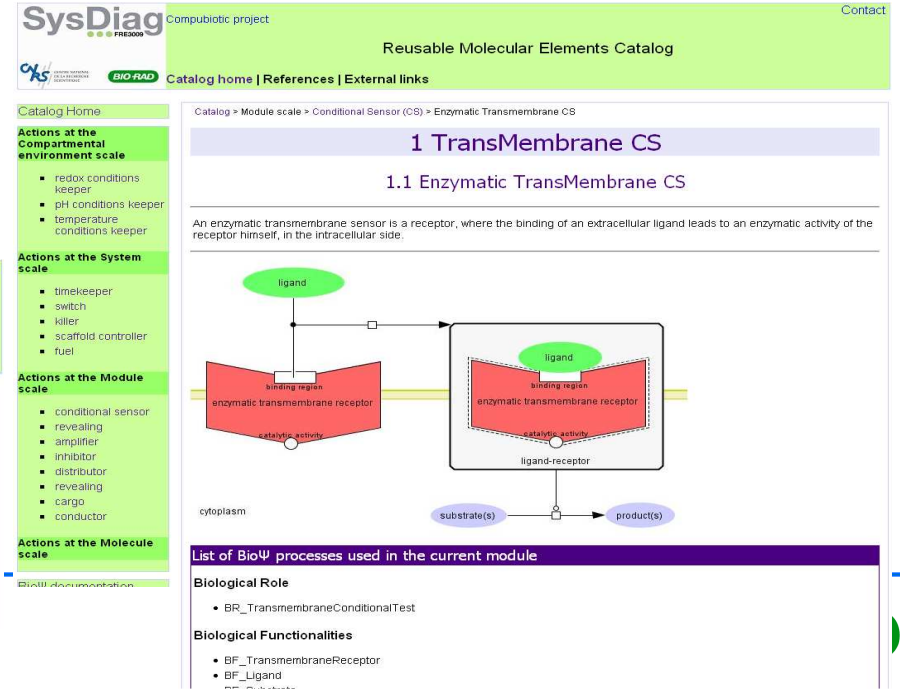
Design

Standardized catalog of proteic biological compounds:

↳ Processes are formalized (ready for modelling)
↳ Biological behavior characterized experimentaly (ready to use in a synthetic system)

- « compound » properties
- robustness
- stability
- functional diversity relative to context modifications





Molecular 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

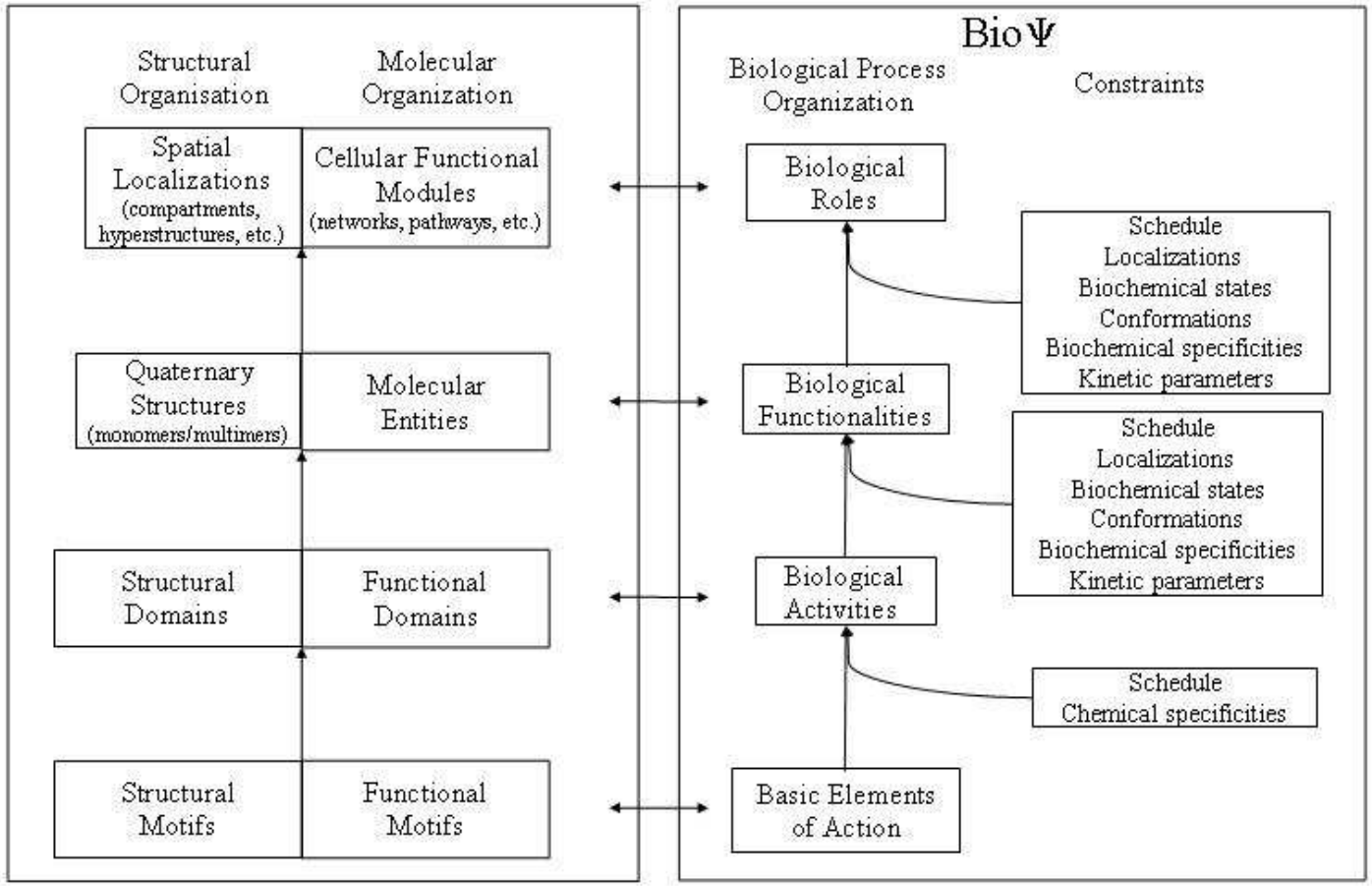
- Proteins and small molecules useful for synthetic biology

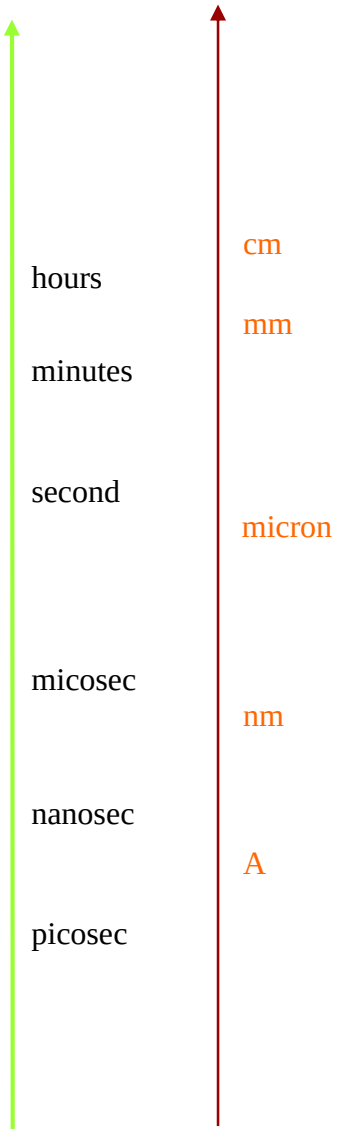
Ex : Peroxidase → **Revealing role**

The BioΨ language

Molecular description

Processes description





Maziere et al. (2004) J. Mol. Biol. (2004), J. BioScience 2007

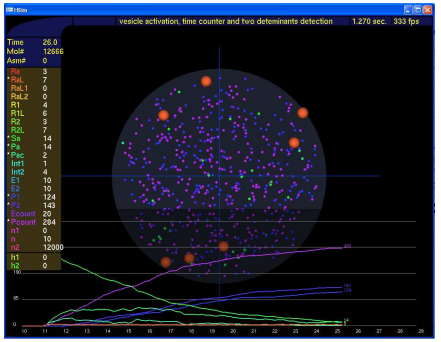
BioΨ what for ?

Modelling and simulation of biological processes

Elementary bricks of process at each level can be considered as primitives for formal langage construction.

Genericity of processes description is an advantage for a non deterministic modelling

Easy to use with multi-agents approaches

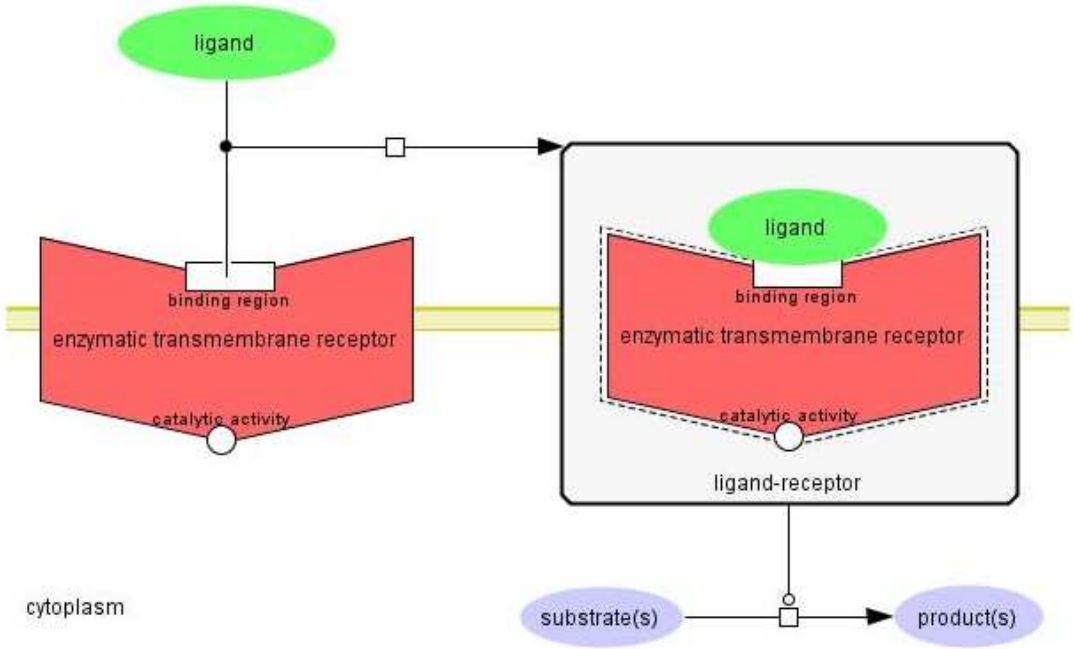


Conditional sensor

1 TransMembrane CS

1.1 Enzymatic TransMembrane CS

An enzymatic transmembrane sensor is a receptor, where the binding of an extracellular ligand leads to an enzymatic activity of the receptor himself, in the intracellular side.



List of BioΨ processes used in the current module

Biological Role

- BR_TransmembraneConditionalTest

Biological Functionalities

- BF_TransmembraneReceptor
- BF_Ligand

Generic BioΨ description

Biological Roles description

```
BREnzyme-linkedTransmembraneConditionalTest :=
        BFTransmembraneReceptor(Ligand) IN transmembrane |
        BFLigand(TransmembraneReceptor) IN extracell,
        BFTransmembraneReceptor/Ligand(Substrate) IN transmembrane |
        BFSubstrate(TransmembraneReceptor/Ligand) IN cytosol,
        BFProduct IN cytosol
```

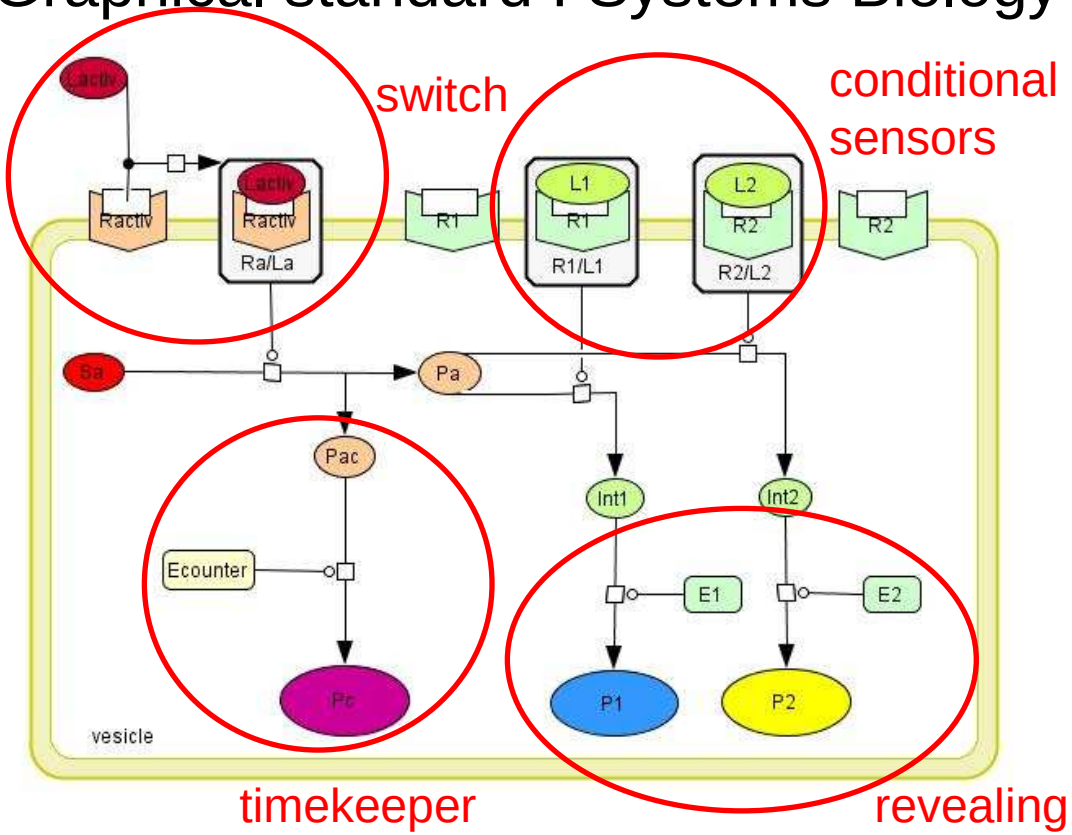
Biological Functionalities description

```
BFTransmembraneReceptor(Ligand) :=
         BA_Binding (Ligand)
                IN extracell

BFTransmembraneReceptor/Ligand(Substrate) :=
        BA_ConformationalChange,
        BA_EnzymaticActivity(Substrate) -> Product
                IN cytosol

BFLigand(TransmembraneReceptor) :=
        BA_ProteinBinding(TransmembraneReceptor)
                IN extracell

BFSubstrate(TransmembraneReceptor/Ligand) :=
        BA_ProteinBinging(TransmembraneReceptor)
                IN cytosol

BFProduct
        BA_ProteinBinding^-1(TransmembraneReceptor)
                IN cytosol
```

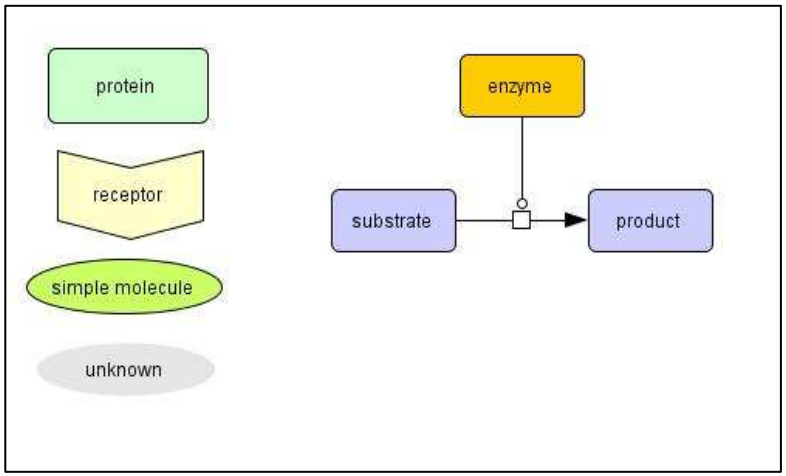
Nanobiosystem *in silico* design

Graphical representation tool : CellDesigner

Graphical standard : Systems Biology Graphical Notation (SBGN)

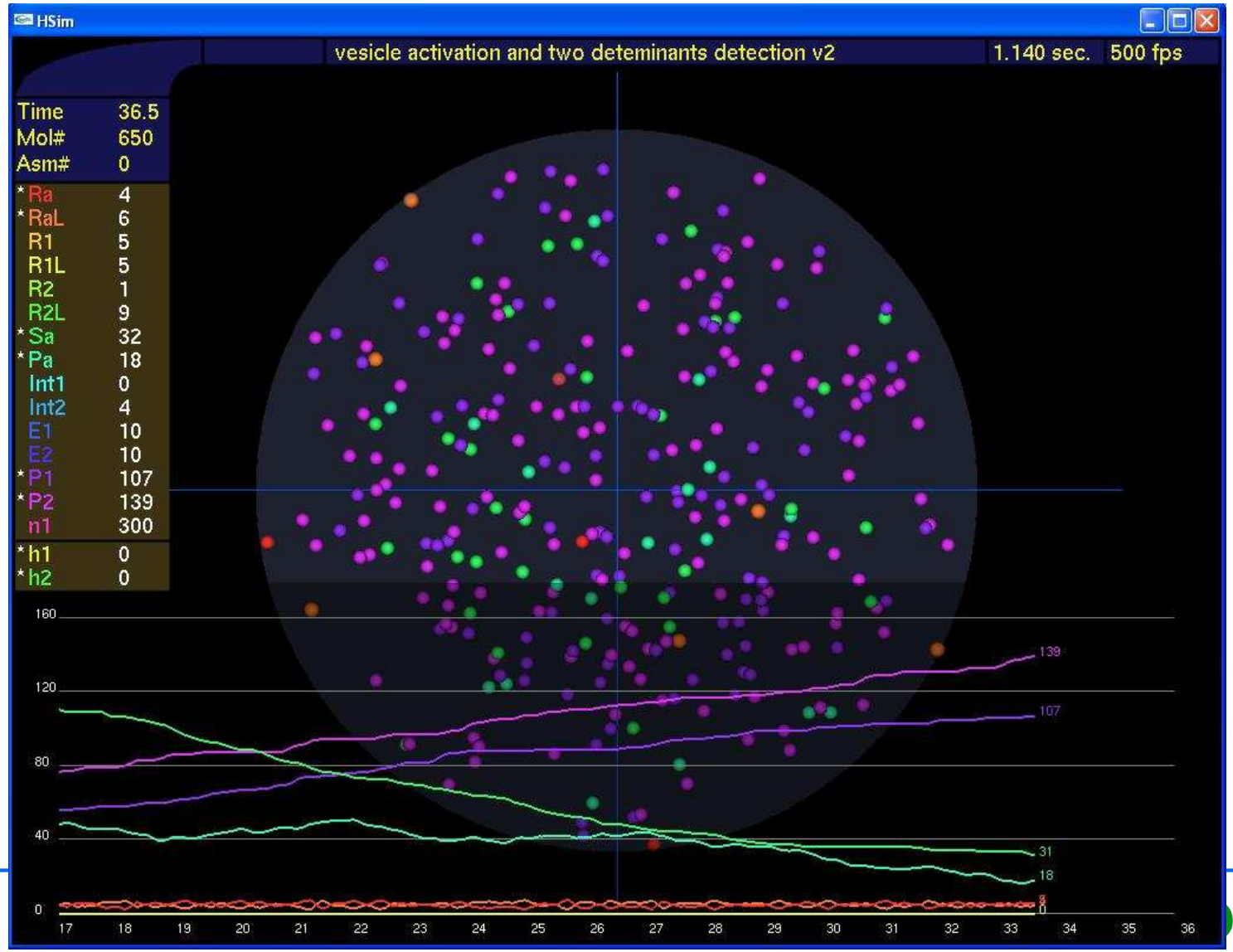


Légende



Modelling, simulations, analyses

HSIM
(Amar, 2004)



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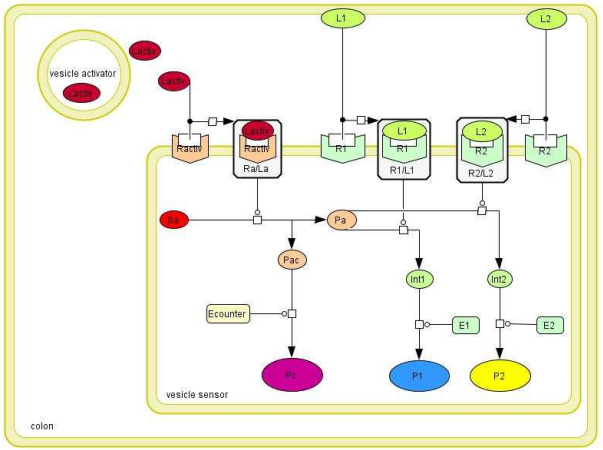
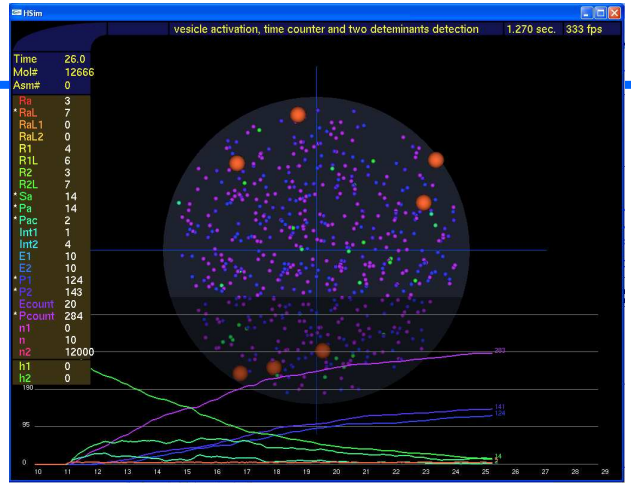
Simulation



System design using our compound catalog SBGN and *Celldesigner*

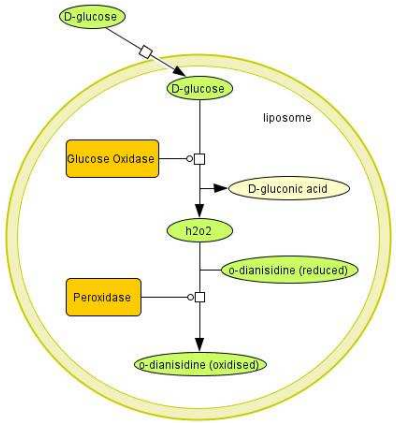
BioΨ modelling
Formal description

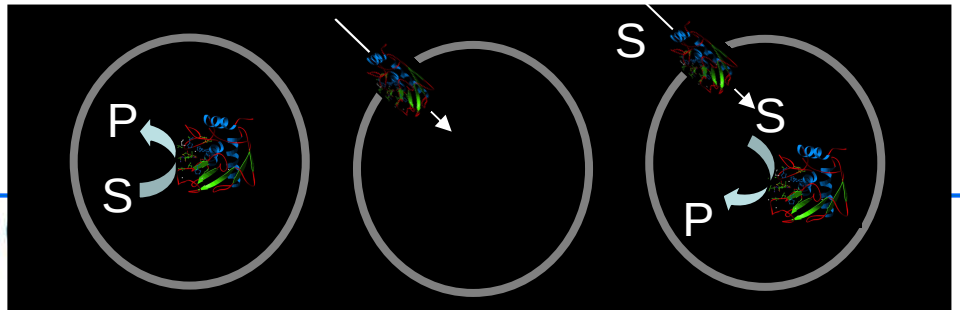


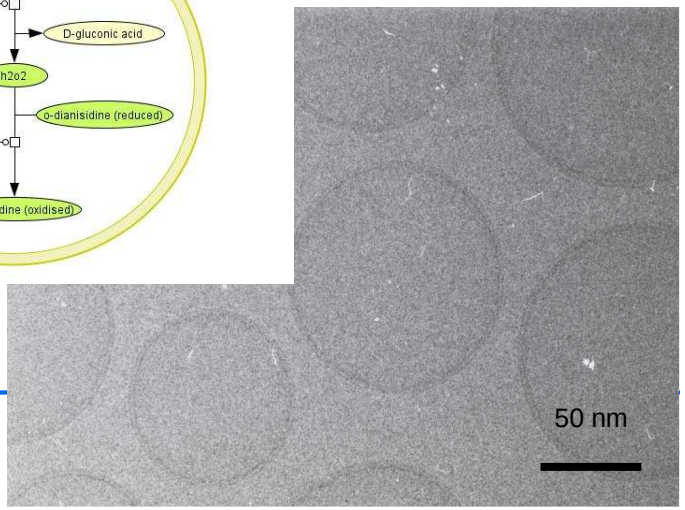
Simulation : Stochastic Cell automaton and multi-agent

Experimental validation

- ☒ Stable Vesicules construction (liposomes) ~100nm
- ☑ Introduction of chosen functional compounds
- ☐ Opérational assays of full synthetic system (*in vitro*)







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Expectations

- **Principles** and **method** for synthetic biological systems design from protein parts

- Set of **characterized "compounds"** re-usable in various synthetic systems

- **Formal description** of biological processes, including a description at the **protein domains level**

- A synthetic "bio-machine" dedicated to colorectal cancer **diagnosis**

CompuBioTic DB + CellDesigner + HSim
Integrated tools for Synthetic Biology

Project team:

Franck Molina, SysDiag director
Stéphanie Rialle Doctorante BDI
Sabine Peres Postdoc
Alain Thierry Inserm
Liza Felicori Postdoc

External collaborators :

Patrick Amar, LRI, Orsay, Simulation
Marc Ychou, CRLCC, Montpellier Oncology colo-rectale
Andrew Griffits, CNRS Strasbourg, nanodroplets
European BaSysBio parterns UE FP6 syst. modelling

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Thank you for your attention

SysDiag CNRS/ Bio-Rad UMR3145, Montpellier

Modélisation et Ingénierie des SyStèmes Complexes Biologiques pour le Diagnostic

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