Concurrency, self-organisation and molecular biology

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MOCA – June 25, 2007

Analysing the dynamic of netwoks

Some features of the networks:

- Concurrency : parallel composition
- Mobility : dynamics of the connections, migration

Suitable theoretical framework: Process algebras

- Computing unit $\longrightarrow$ process
- Emission/reception on channels
- Private name sharing

…π-calculus (Milner)

- Notion of compartment
- Locating the communications

…Mobile Ambient (Cardelli & Gordon)

An alternative

Applications:

- Self-organization phenomena
- Modeling of molecular biology

$\longrightarrow$ Symmetry of the interactions: collisions

Reformulation of previous framework: κ-calcul, Brane calculi

- Protein $\rightarrow$ process
- Bound between proteins $\rightarrow$ sharing of a common name

Contributions: extension, integration

Framework

Starting from κ-calculus (with Vincent Danos)

1. Top-down approach: Synthesizing distributed programs from a given specification:
   - for trees
   - for graphs
2. Exploring reversibility features:
   - in the langage itself
   - using reversible process algebra (with Jean Krivine)
3. Bottom-up approach: bioκ-calculus (with Cosimo Laneve)

Framework

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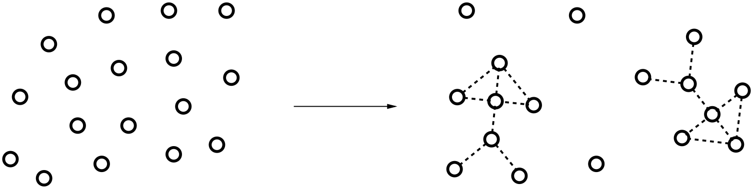
   - for graphs

3. Bottom-up approach: bioκ-calculus (with Cosimo Laneve)

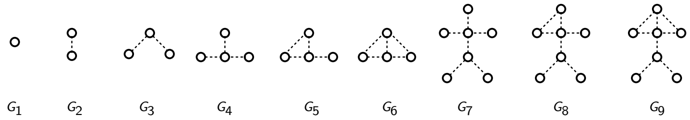
Collective behaviour



- Self-organizing: How a collective phenomenon may emerge from multiple interactions (analysis and synthesis)
- Recurrent problem:
  - Molecular biology (analysis)
  - Genetic engineering (synthesis)
  - Distributed robotics (synthesis)

Preliminary work

- $\mathcal{G}$: Set of explorative graphs :



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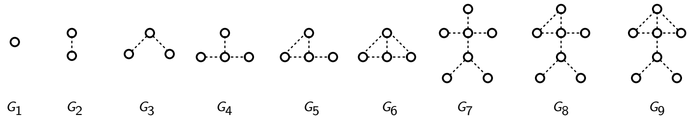
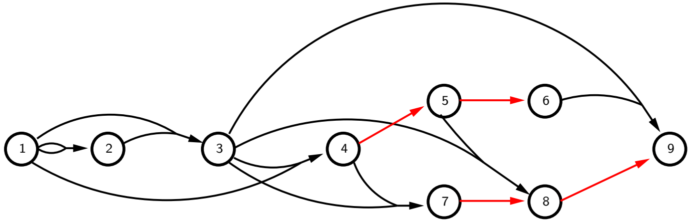


- Assembling graph of the final target:



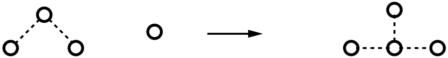
The syntax

Syntactic representation of graphs :

- Nodes = agents
- Edges = private names sharing

becomes $\langle x \rangle \ , \ \langle x, y \rangle \ , \ \langle y \rangle$

Construction rules :



becomes

$$\langle x \rangle \ , \ \langle x, y \rangle \ , \ \langle y \rangle \ , \ \langle \rangle \longrightarrow (\nu z)\,(\langle x \rangle \ , \ \langle x, y, z \rangle \ , \ \langle y \rangle \ , \ \langle z \rangle)$$

Formalisation of the problem

- Extraction of a core language:
  $\langle x \rangle \ , \ \langle x \rangle \ , \ \langle \rangle \ \not\rightarrow \ (\nu y)(\langle x \rangle \ , \ \langle x, y \rangle \ , \ \langle y \rangle)$
  $\Longrightarrow$ restriction on synchronisation ability
- Expected property: equivalent behaviour

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What does that mean ?

- Comparison of transitions
- Comparison of states

$\Longrightarrow$ Mathematical tool: bisimulation

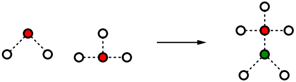
Intuitive features of the algorithm

- Only one active agent by component.
- Local knowledge of the component's structure.
- Each agent knows its role in the component.
- Propagation of the changes related to an interaction by the use of a spanning tree.

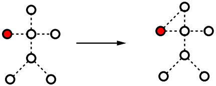
Traduction of the reactions

Set of reactions :

- Connection between 2 disjoint complexes

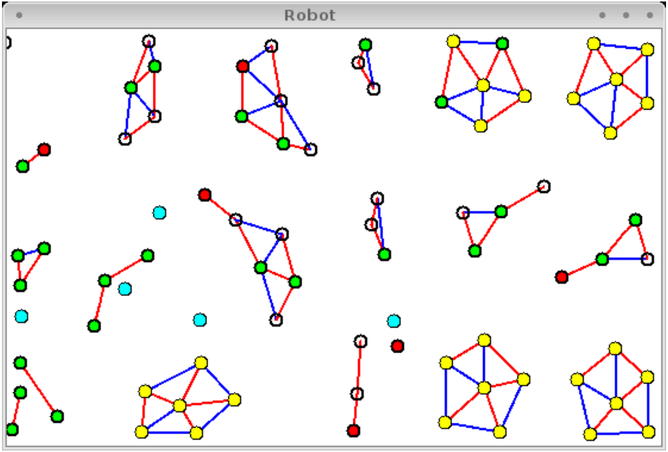


- Cyclic connection



- Propagation updates
- Activity switch
- Mechanism to handle the deadlocks

Demo



Bottom-up approach

Problem: Extracting a functional meaning of sub-networks

- Several agents may interact at the same time by means of several sites
  - competition for resources (sites)
  - concurrency of the interactions
  - nondeterminism
- Interactions may involve simple agents (proteins) or complex ones (compartments) and may cause small local changes or more structural ones.
- The overall behaviour is **deterministic** in general.

Two different directions

Two different approaches:

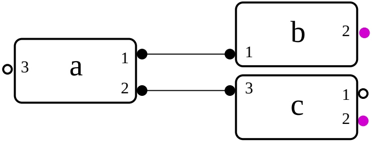
- Based on π-calculus (Regev-Shapiro, Danos-Laneve): κ-calcul
- Based on Ambients (Cardelli): Brane Calculi

For modelling different biological systems:

- Signal transduction pathways, gene regulatory networks, ...
- Molecular transport, virus infections, ...

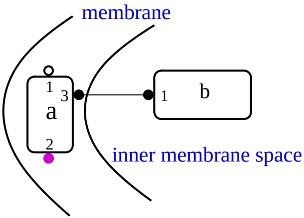
A language for proteins and membranes

Proteic complex:



$$\mathrm{A}(1^x + 2^y + 3)\ ,\ \mathrm{B}(1^x + \overline{2})\ ,$$
$$\mathrm{C}(1 + \overline{2} + 3^y)$$

Compartment with a transmembrane receptor:



$$(\!|\ \mathrm{A}(1 + \overline{2} + 3^x)\ |\!)[\mathrm{B}(1^x)]$$

BIOκ: THE SYNTAX

Solutions S:

S ::=		**solution**
	$\mathbf{0}$	(empty solution)
	$\mathrm{A}(\sigma)$	(protein)
	$m(\!| \mathrm{M} |\!)[\mathrm{S}]$	(compartment)
	S , S	(group)

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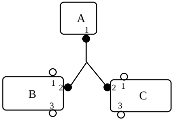
Well formedness constraints:

- *constraint on the connections*



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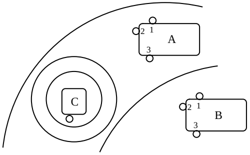
& \mathsf{S}\ ,\ \mathsf{S} & \text{(group)}
\end{array}
$$

Well formedness constraints:

- *constraint on the connections*
- *constraint on the membranes*



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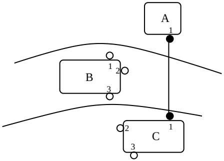
Well formedness constraints:

- *constraint on the connections*
- *constraint on the membranes*
- *constraint on the compartments*



Some notations

- We write $\phi, \psi, \cdots,$ for partial interfaces
- Simple interactions: complexations $\mathcal{C}$ and decomplexations $\mathcal{D}$ between proteins
- Based on a local knowledge of the proteins: $(\mathrm{A}, i, \phi, \phi')$

  Example: $((\mathrm{S}, 1, \_, \_)\ ,\ (\mathrm{R}, 1, \bar{2}, 2)) \in \mathcal{C}$

$$\mathrm{S}(1+2+\bar{3})\ ,\ \mathrm{R}(1+\bar{2}+3) \longrightarrow \mathrm{S}(1^x+2+\bar{3})\ ,\ \mathrm{R}(1^x+2+3)$$

BIOκ: The labelled transition system

The transition relation $\xrightarrow{\mu}$ is the least one satisfying the reductions:

- **semi-interactions**

$$\frac{(\mathrm{A}, i, \phi, \phi') \in \mathcal{C}(\mathtt{r})}{\mathrm{A}(i + \phi + \sigma) \xrightarrow{\mathrm{A}^x_{\mathrm{r}}} \mathrm{A}(i^x + \phi' + \sigma)} \qquad \frac{(\mathrm{A}, i, \phi, \phi') \in \mathcal{D}(\mathtt{r})}{\mathrm{A}(i^x + \phi + \sigma) \xrightarrow{\mathrm{A}^x_{\mathrm{r}}} \mathrm{A}(i + \phi' + \sigma)}$$

- **interactions proteins-proteins**

$$\frac{\mathsf{S} \xrightarrow{\mathrm{A}^x_{\mathrm{r}}} \mathsf{S}' \quad \mathsf{T} \xrightarrow{\mathrm{B}^x_{\mathrm{r}}} \mathsf{T}'}{\mathsf{S}\ ,\ \mathsf{T} \xrightarrow{\tau} \mathsf{S}'\ ,\ \mathsf{T}'} \qquad \frac{\mathsf{M} \xrightarrow{\mathrm{A}^x_{\mathrm{r}}} \mathsf{M}' \quad \mathsf{S} \xrightarrow{\mathrm{B}^x_{\mathrm{r}}} \mathsf{S}'}{m(\!|\,\mathsf{M}\,|\!)[\mathsf{S}] \xrightarrow{\tau} m(\!|\,\mathsf{M}'\,|\!)[\mathsf{S}']}$$

BIOκ: THE LABELLED TRANSITION SYSTEM

- **Lifting to the context**

$$\frac{\mathsf{S} \xrightarrow{\mu} \mathsf{S}'}{\mathsf{S}\ ,\ \mathsf{T} \xrightarrow{\mu} \mathsf{S}'\ ,\ \mathsf{T}} \qquad \frac{\mathsf{M} \xrightarrow{\mu} \mathsf{M}'}{m(\!|\ \mathsf{M}\ |\!)[\mathsf{S}] \xrightarrow{\mu} m(\!|\ \mathsf{M}'\ |\!)[\mathsf{S}]}$$

$$\frac{\mathsf{S} \xrightarrow{\tau} \mathsf{S}'}{m(\!|\ \mathsf{M}\ |\!)[\mathsf{S}] \xrightarrow{\tau} m(\!|\ \mathsf{M}\ |\!)[\mathsf{S}']}$$

A tool to compare the systems

Some notations:

- $S \stackrel{\tau}{\Longrightarrow} S'$ represents $S \stackrel{\tau}{\longrightarrow}^{*} S'$
- $S \stackrel{\mu}{\Longrightarrow} S'$, with $\mu \neq \tau$, represents $S \stackrel{\tau}{\longrightarrow}^{*} \stackrel{\mu}{\longrightarrow} \stackrel{\tau}{\longrightarrow}^{*} S'$

A *(weak) bisimulation* is a symmetric binary relation $\mathfrak{R}$ between solutions such that $S \,\mathfrak{R}\, T$ implies:

1. if $S \stackrel{\tau}{\longrightarrow} S'$ then $T \stackrel{\tau}{\Longrightarrow} T'$ and $S' \,\mathfrak{R}\, T'$
2. if $S \stackrel{A_r^x}{\longrightarrow} S'$ then $T \stackrel{A_r^x}{\Longrightarrow} T'$ and $S' \,\mathfrak{R}\, T'$.

We write $S \approx T$ if $S \,\mathfrak{R}\, T$ for some bisimulation $\mathfrak{R}$.

The black box

Theorem : The bisimulation associated to the labelled transition system is a congruence.

Two solutions which are bisimilar can replace each other independently of the context in which they are.

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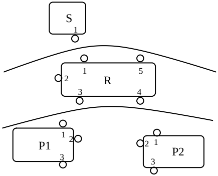

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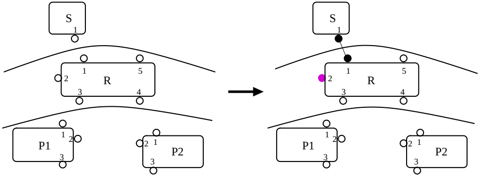

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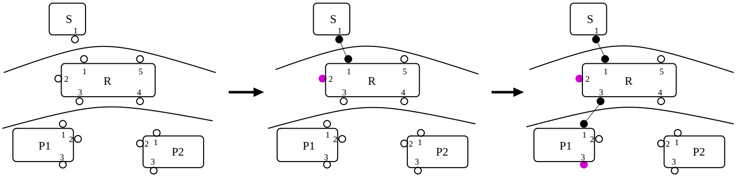

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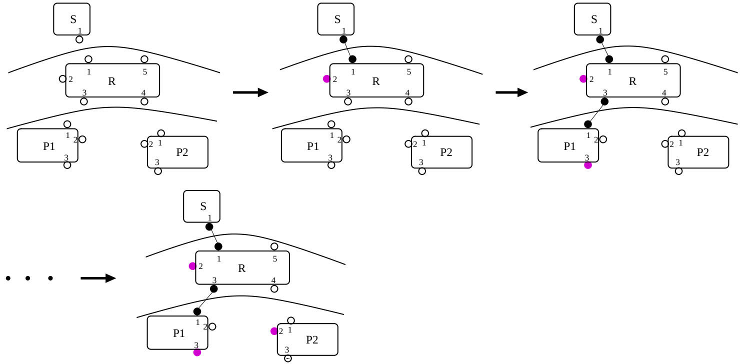

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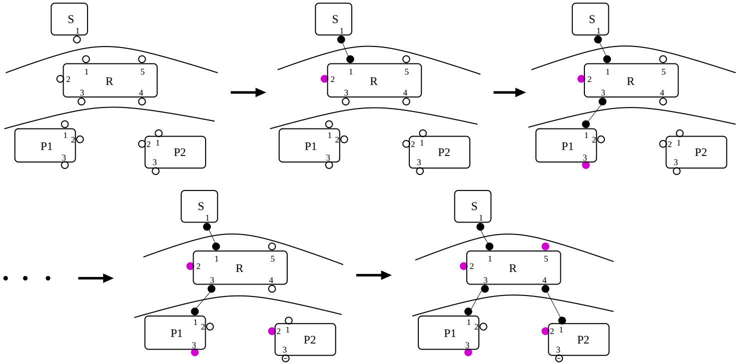

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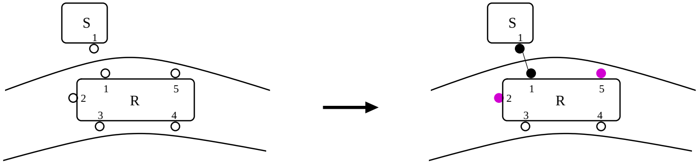
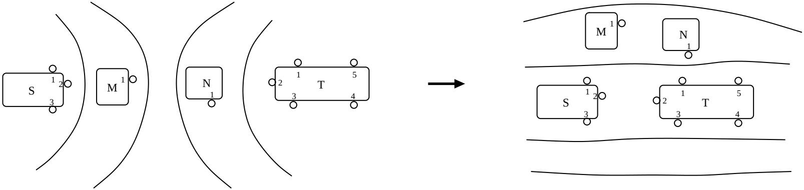


Fusions of membranes

- core-bioκ keeps the hierarchical structure of the solutions
- It is impossible to describe phenomena such as the *fusion* between two endosomes :

$$\mathit{esm}(\!| \mathsf{M} |\!)[\mathsf{S}]\ ,\ \mathit{esm}(\!| \mathsf{N} |\!)[\mathsf{T}] \longrightarrow \mathit{esm}(\!| \mathsf{M}\ ,\ \mathsf{N} |\!)[\mathsf{S}\ ,\ \mathsf{T}]$$



CORE BIOκ WITH MREAGENTS

The syntax of bioκ:

S ::=		**solution**
	0	(empty solution)
	$\mathrm{A}(\sigma)$	(protein)
	$m(\!\| \mathsf{M} \|\!)[\mathsf{S}]$	(compartment)
	S , S	(group)
	$m(\!\| \mathsf{M} \|\!)[\mathsf{S}] \parallel \mathsf{T}$	(mreagent)

Fusions

By the use of a fonction $\mathcal{F} : (m, m') = n$

$$\frac{m \in \mathcal{F}}{m(\!|\,\mathsf{M}\,|\!)[\![\mathsf{S}]\!] \xrightarrow{m} m(\!|\,\mathsf{M}\,|\!)[\![\mathsf{S}]\!] \;||\; \mathbf{0}} \qquad \frac{\mathsf{S} \xrightarrow{\mu} m(\!|\,\mathsf{M}\,|\!)[\![\mathsf{S}']\!] \;||\; \mathsf{S}''}{\mathsf{S}\,,\mathsf{T} \xrightarrow{\mu} m(\!|\,\mathsf{M}\,|\!)[\![\mathsf{S}']\!] \;||\; (\mathsf{S}''\,,\mathsf{T})}$$

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Horizontal fusion

$$\frac{\mathsf{S} \xrightarrow{m} m(\!| \mathsf{M} |\!)[\mathsf{T}] \ || \ \mathsf{U} \quad \mathsf{S}' \xrightarrow{m'} m'(\!| \mathsf{M}' |\!)[\mathsf{T}'] \ || \ \mathsf{U}'}{\mathsf{S}\ ,\ \mathsf{S}' \xrightarrow{\tau} \mathsf{U}\ ,\ \mathsf{U}'\ ,\ n(\!| \mathsf{M}\ ,\ \mathsf{M}' |\!)[\mathsf{T}\ ,\ \mathsf{T}']}$$

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Vertical fusion
$$\frac{\mathsf{S} \xrightarrow{m} m(\!|\,\mathsf{M}\,|\!)[\mathsf{T}] \;||\; \mathsf{U}}{m'(\!|\,\mathsf{M}'\,|\!)[\mathsf{S}] \xrightarrow{\tau} \mathsf{T}\,, n(\!|\,\mathsf{M}\,,\mathsf{M}'\,|\!)[\mathsf{U}]}$$

Activations

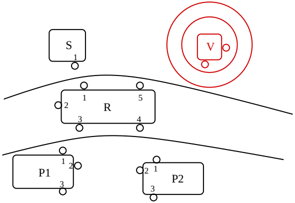
- Side effect of a complexation or a decomplexation
- By the use of a fonction $\mathcal{A} : (\mathrm{A}_{\mathtt{r}}, m) \mapsto n$

$$\frac{\mathsf{M} \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} \mathsf{M}' \qquad \mathcal{A}(\mathrm{A}_{\mathtt{r}}, m) = n}{m(\!|\, \mathsf{M} \,|\!)[\mathsf{S}] \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} n(\!|\, \mathsf{M}' \,|\!)[\mathsf{S}]}$$

$$\frac{\mathsf{M} \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} \mathsf{M}' \quad \mathsf{S} \xrightarrow{\mathrm{B}_{\mathtt{r}}^{x}} \mathsf{S}' \quad \mathcal{A}(\mathrm{A}_{\mathtt{r}}, m) = n}{m(\!|\, \mathsf{M} \,|\!)[\mathsf{S}] \xrightarrow{\tau} n(\!|\, \mathsf{M}' \,|\!)[\mathsf{S}']}$$

Impact on the bisimulation

Proving a bisimilarity has become harder.



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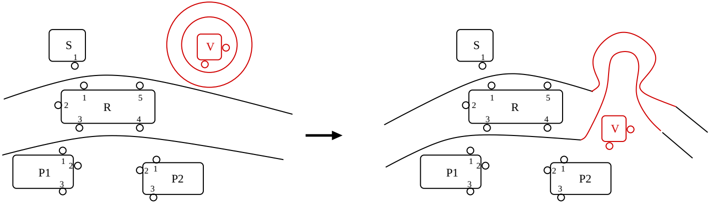

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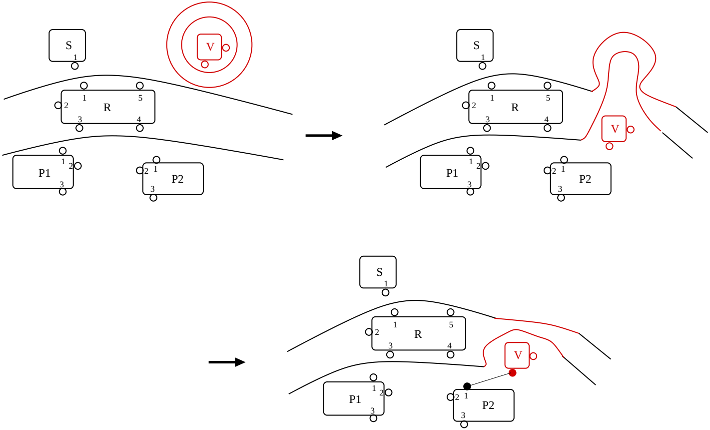

Contextual bisimulation

A contextual bisimulation is a symmetric relation $\mathfrak{R}$ between solutions such that $\mathsf{S}\,\mathfrak{R}\,\mathsf{T}$ implies:

1. if $\mathsf{S} \xrightarrow{\tau} \mathsf{S}'$ then $\mathsf{T} \stackrel{\tau}{\Longrightarrow} \mathsf{T}'$ and $\mathsf{S}'\,\mathfrak{R}\,\mathsf{T}'$
2. if $\mathsf{S} \xrightarrow{\mathrm{A}^x_\mathrm{r}} \mathsf{S}'$ then $\mathsf{T} \stackrel{\mathrm{A}^x_\mathrm{r}}{\Longrightarrow} \mathsf{T}'$ and $\mathsf{S}'\,\mathfrak{R}\,\mathsf{T}'$.

$\mathsf{S} \approx_c \mathsf{T}$ if $\mathsf{S}\,\mathfrak{R}\,\mathsf{T}$ for a contextual bisimulation $\mathfrak{R}$.

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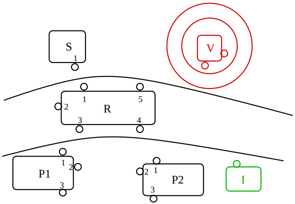
3. if $\mathsf{S} \xrightarrow{m} m(\!|\,\mathsf{M}\,|\!)[\mathsf{S}''] \parallel \mathsf{S}'$ then $\mathsf{T} \stackrel{m}{\Longrightarrow} m(\!|\,\mathsf{M}'\,|\!)[\mathsf{T}''] \parallel \mathsf{T}'$ and for every N, R, and n such that $\mathcal{F}(m,n) = p$ we have both
   - $\left(\mathsf{S}'' , p(\!|\,\mathsf{M} , \mathsf{N}\,|\!)[\mathsf{S}']\right) \mathfrak{R} \left(\mathsf{T}'' , p(\!|\,\mathsf{M}' , \mathsf{N}\,|\!)[\mathsf{T}'']\right)$
   - $\left(\mathsf{S}' , p(\!|\,\mathsf{M} , \mathsf{N}\,|\!)[\mathsf{S}'' , \mathsf{R}]\right) \mathfrak{R} \left(\mathsf{T}' , p(\!|\,\mathsf{M}' , \mathsf{N}\,|\!)[\mathsf{T}'' , \mathsf{R}]\right)$.

$\mathsf{S} \approx_c \mathsf{T}$ if $\mathsf{S}\,\mathfrak{R}\,\mathsf{T}$ for a contextual bisimulation $\mathfrak{R}$.

Using the contextual bisimulation

Countering the former attack



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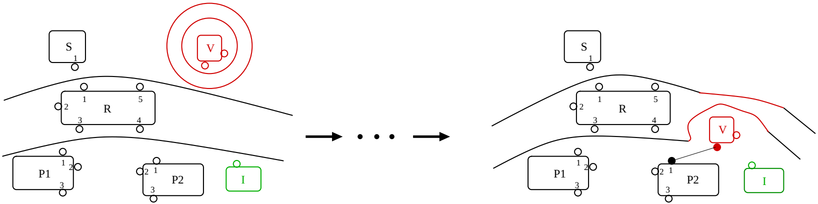

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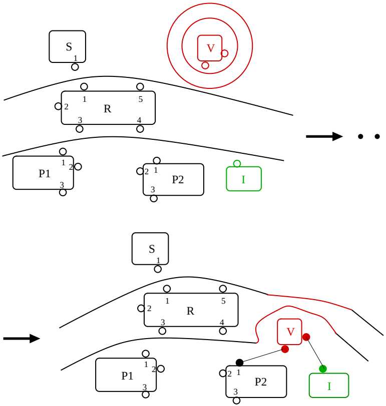

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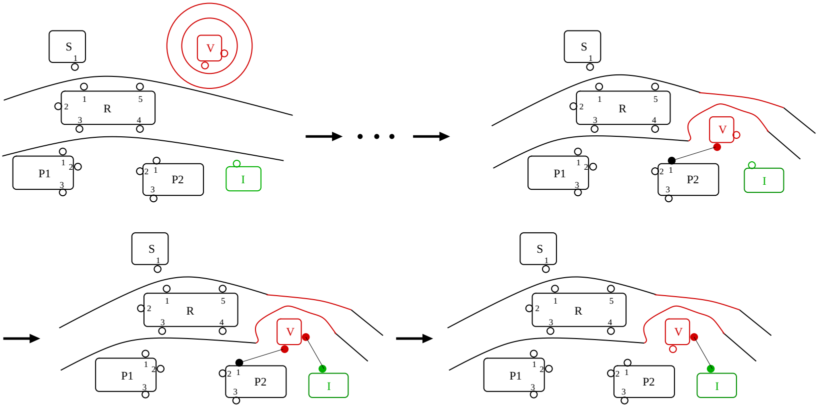


Perspective

Contribution :

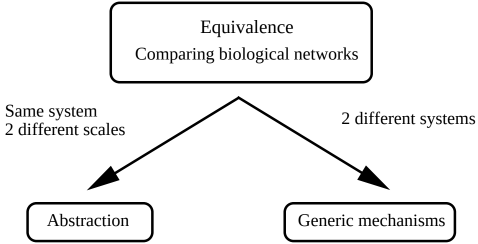
- Attempt for integrating proteins and membranes
- Aim of representing biological systems
- Direct link between interactions between proteins and membranes activities

Gives a tool for:

- Abstracting from the molecular details
- Giving a fonctionnal meaning
- Modularity

Perspective

- Molecular biology
  - automating the search for equivalences



  - extending the panel of technics for infering properties
  - diversifying the kind of biological systems modellised
- Self-organisation
  - Study of reversible behaviours
  - Optimization