bioκ: a simple calculus for proteins and cells

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Some features

- Several agents may interact at the same time by means of several domains (sites)
  - parallelism
  - competition
  - nondeterminism
- The overall behaviour is **deterministic**.
- Interactions may involve simple agents – proteins – or complex ones – cells – and may cause small local changes or huge structural changes.

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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, . . .

À la π-calcul

We intend to pursue an algebraic approach à la pi-calculus

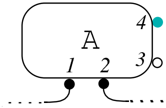
- few (biological) constructs
- a “faithful” rendering of biological interactions – not *via* an encoding
- a compositional semantics based on the notion of interaction

But simplicity has a cost ! we are loosing :

- expressiveness
- stochastic behaviours

A calculus for proteins . . .

Proteins



- ○ *visible site*
- ● *hidden site*
- ● *bound site*

is described in bioκ by $\mathrm{A}(1^x + 2^z + 3^v + 4^h)$ – actually we write $\mathrm{A}(1^x + 2^z + 3 + \overline{4})$

syntactically, a protein is $\mathrm{A}(\sigma)$:

- A belongs to a countable set of *protein names*
- for every A, $\mathfrak{s}(a)$ gives an integer – the number of *sites*
- there is a set $\mathcal{E}$ of *edge names* that are ranged over by x, y, z, etc. – $v, h \notin \mathcal{E}$
- σ is a total function from $1..\mathfrak{s}(a)$ to $\{v, h\} \cup \mathcal{E}$ such that σ is injective on $\mathcal{E}$

A calculus for proteins . . .

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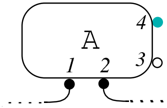

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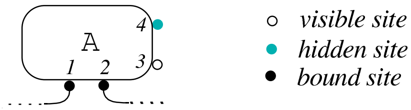

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. . . and cells

cells $m(\!|\,\mathsf{M}\,|\!)[\mathsf{S}]$

- m belongs to a countable set of *membrane types*
- M is the *membrane*
- S is a biological solution (that may contain cells)

- **well-formedness constraints** :
  - (*edge-condition*) every solution is such that edge names occur at most twice ;
  - (*membrane-condition*) every membrane is a multiset of proteins, that is cells do not occur in membranes – *we are abstracting out the bilipidic layer*
  - (*nucleus-condition*) the dangling edges of nuclei of cells are connected to the corresponding membrane

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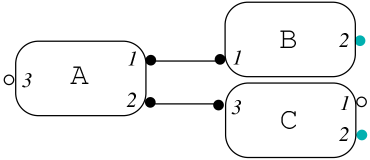
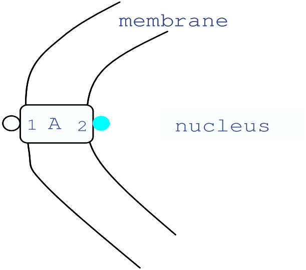
Examples en bioκ

Complexe of proteins :



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

Cell with a transmembrane protein :



$m\llparenthesis\, \mathrm{A}(1 + \overline{2}) \,\rrparenthesis[\mathrm{S}]$

remark : we do not specify whether a site of a protein is outside or inside a membrane

bioκ : The syntaxe

Solutions S :

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

Some notations

- v-h-maps, ranged over by $\phi, \psi, \cdots$, are partial maps from naturals to $\{v, h\}$
  - $\overline{\phi}$ is the v-h-map : $\overline{\phi}(i) = \begin{cases} h & \text{if } \phi(i) = v \\ v & \text{if } \phi(i) = h \\ \text{undefined} & \text{otherwise} \end{cases}$
- α, β, etc. range over (A, a, ϕ), such that $\{a\} \uplus \mathrm{dom}(\phi) \subseteq 1..\mathfrak{s}(\mathrm{A})$
- complexations $\mathcal{C}$ and decomplexations $\mathcal{D}$ are functions from rule names $\mathtt{r}$ to tupples (α, β) with disjoint domain.

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bioκ : The labelled transition system

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

- **protein-protein reductions**

$$\frac{(\mathrm{A}, a, \phi) \in \mathcal{C}(\mathtt{r}) \quad x \notin \mathtt{en}(\sigma)}{\mathrm{A}(a + \phi + \sigma) \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} \mathrm{A}(a^{x} + \overline{\phi} + \sigma)} \qquad \frac{(\mathrm{A}, a, \phi) \in \mathcal{D}(\mathtt{r})}{\mathrm{A}(a^{x} + \phi + \sigma) \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} \mathrm{A}(a + \overline{\phi} + \sigma)}$$

$$\frac{\mathsf{S} \xrightarrow{\mathrm{A}_{\mathtt{r}}^{x}} \mathsf{S}' \quad \mathsf{T} \xrightarrow{\mathrm{B}_{\mathtt{r}}^{x}} \mathsf{T}' \quad \mathrm{A} \neq \mathrm{B}}{\mathsf{S}\ ,\ \mathsf{T} \xrightarrow{\tau} \mathsf{S}'\ ,\ \mathsf{T}'} \qquad \frac{\mathsf{S} \xrightarrow{\mu} \mathsf{S}' \quad \mathtt{diff}(\mathsf{S}, \mathsf{S}') \cap \mathtt{en}(\mathsf{T}) = \emptyset}{\mathsf{S}\ ,\ \mathsf{T} \xrightarrow{\mu} \mathsf{S}'\ ,\ \mathsf{T}}$$

plus the symmetric rule for groups

bioκ : The labelled transition system

- **protein-membrane reductions**

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- **cellular reductions**

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remarks 1. every edge name created in a complexation is fresh

2. the interaction between a protein outside a cell and the membrane of the cell is modelled by the last rule and the reaction rule

3. the nucleus of a cell cannot interact with agents external to the cell

4. the reductions do not change the cellular structure – core-bioκ

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bioκ : The RTK-MAPK pathway

1. a dimeric form of the epidermal growth factor EGF binds two receptors EGFR located on some plasmic membrane
2. the receptors EGFR cross-phosphorylate each other through their tyrosine kinase sites
3. then the EGFR activate another binding site that binds an adapter protein SHC and activate it
4. ... the signal goes further till reaching the nucleus

$$((\text{EGF}, 1, \overline{2}), (\text{EGF}, 1, \overline{2})) \in \mathcal{C} \quad (1)$$
$$((\text{EGF}, 2, \emptyset), (\text{EGFR}, 1, \overline{4})) \in \mathcal{C} \quad (2)$$
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& \big(\!\!\big|\, \mathrm{EGFR}(1^y+2+3+\bar{4}),\ \mathrm{EGFR}(1^u+2+3+\bar{4}),\ \mathsf{M} \,\big|\!\!\big) [\mathrm{SHC}(1+\bar{2}),\ \mathsf{S}] && (3') \\
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\end{aligned}
$$

bioκ : The RTK-MAPK pathway

$$\text{EGF}(1+\overline{2}),\ \text{EGF}(1+\overline{2})$$
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$$\xrightarrow{\tau}\ \text{EGF}(1^z+2),\ \text{EGF}(1^z+2)$$
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bioκ : The RTK-MAPK pathway

$$\begin{array}{ll}
\mathrm{EGF}(1+\overline{2}),\ \mathrm{EGF}(1+\overline{2}) & \\
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\end{array}$$

To compare the systems

Some notations :

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

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

1. if $\mathsf{S} \stackrel{\tau}{\longrightarrow} \mathsf{S}'$ then $\mathsf{T} \stackrel{\tau}{\Longrightarrow} \mathsf{T}'$ and $\mathsf{S}' \,\mathcal{R}\, \mathsf{T}'$
2. if $\mathsf{S} \stackrel{\mathrm{A}_{\mathrm{r}}^{x}}{\longrightarrow} \mathsf{S}'$ then $\mathsf{T} \stackrel{\mathrm{A}_{\mathrm{r}}^{x}}{\Longrightarrow} \mathsf{T}'$ and $\mathsf{S}' \,\mathcal{R}\, \mathsf{T}'$.

$\mathsf{S} \approx \mathsf{T}$ if $\mathsf{S} \,\mathcal{R}\, \mathsf{T}$ for some bisimulation $\mathcal{R}$.

Basic properties

- The transition system preserves the well-formedness constraints
- " , " is an abelian monoidal operator with identity $\mathbf{0}$:

$$\mathsf{S}\,,\,\mathsf{T} \approx \mathsf{T}\,,\,\mathsf{S} \qquad (\mathsf{S}\,,\,\mathsf{T})\,,\,\mathsf{R} \approx \mathsf{S}\,,\,(\mathsf{T}\,,\,\mathsf{R}) \qquad \mathsf{S}\,,\,\mathbf{0} \approx \mathsf{S}$$

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Merging membranes

- core-bioκ preserves the cellular structure of the solution
- it is not possible to describe phenomena such as *fusions* between endosomes :

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

question : how to define the semantics of an endosome, regardless of endosomes in the context ?

- answer : by means of higher-order mechanisms

The core bioκ with mreagents

The syntax of bioκ :

S ::=		**solution**
	$\mathbf{0}$	(empty solution)
	$\mathrm{A}(\sigma)$	(protein)
	$m(\!| \mathrm{M} |\!)[\mathrm{S}]$	(cell)
	S , S	(group)
	$\wr \mathrm{M} ; \mathrm{S} \int \cdot \mathrm{S}$	(mreagents)

constraint : in $\wr \mathrm{M} ; \mathrm{S} \int \cdot \mathrm{T}$

- S and T do not contain mreagents
- M is a multiset of proteins
- $\mathtt{de}(\mathrm{S}) \subseteq \mathtt{de}(\mathrm{M})$

Fusions and activations

- The fusion function $\mathcal{F}$ from rule name to pairs $(m \otimes m', n)$
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- We assume that $\mathcal{C}$, $\mathcal{D}$, $\mathcal{F}$, $\mathcal{A}$ have a disjoint domaine.

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

$$\frac{\mathsf{S} \xrightarrow{m_\mathrm{r}} \wr \mathsf{M} ; \mathsf{S}'' \wr \cdot \mathsf{S}' \quad \mathsf{T} \xrightarrow{n_\mathrm{r}} \wr \mathsf{N} ; \mathsf{T}'' \wr \cdot \mathsf{T}' \quad \mathcal{F}(\mathrm{r}) = (m \otimes n, m')}{\mathsf{S} , \mathsf{T} \xrightarrow{\tau} \mathsf{S}' , \mathsf{T}' , m'(\!| \mathsf{M} , \mathsf{N} |\!)[\mathsf{S}'' , \mathsf{T}'']} \qquad \frac{\mathsf{S} \xrightarrow{n_\mathrm{r}} \wr \mathsf{N} ; \mathsf{T} \wr \cdot \mathsf{S}' \quad \mathcal{F}(\mathrm{r}) = (m \otimes n, m')}{m(\!| \mathsf{M} |\!)[\mathsf{S}] \xrightarrow{\tau} \mathsf{T} , m'(\!| \mathsf{M} , \mathsf{N} |\!)[\mathsf{S}'}$$

$$\frac{\mathsf{M} \xrightarrow{\mathrm{A}^x_\mathrm{r}} \mathsf{M}' \quad \mathcal{A}(\mathrm{A_r}, m) = n \quad \mathtt{diff}(\mathsf{M}, \mathsf{M}') \cap \mathtt{en}(\mathsf{S}) = \emptyset}{m(\!| \mathsf{M} |\!)[\mathsf{S}] \xrightarrow{\mathrm{A}^x_\mathrm{r}} n(\!| \mathsf{M}' |\!)[\mathsf{S}]} \qquad \frac{\mathsf{M} \xrightarrow{\mathrm{A}^x_\mathrm{r}} \mathsf{M}' \quad \mathsf{S} \xrightarrow{\mathrm{B}^x_\mathrm{r}} \mathsf{S}' \quad \mathrm{A} \neq \mathrm{B} \quad \mathcal{A}(\mathrm{A_r}, m) = n}{m(\!| \mathsf{M} |\!)[\mathsf{S}] \xrightarrow{\tau} n(\!| \mathsf{M}' |\!)[\mathsf{S}']}$$

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$$\frac{\mathcal{A}(\mathtt{A}_\mathtt{r}, m) = n \quad \mathsf{M} \xrightarrow{\mathtt{A}^x_\mathtt{r}} \mathsf{M}' \quad \mathtt{diff}(\mathsf{M}, \mathsf{M}') \cap \mathtt{en}(\mathsf{S}) = \emptyset}{m\llparenthesis\, \mathsf{M} \,\rrparenthesis[\mathsf{S}] \xrightarrow{\mathtt{A}^x_\mathtt{r}} n\llparenthesis\, \mathsf{M}' \,\rrparenthesis[\mathsf{S}]} \qquad \frac{\mathsf{M} \xrightarrow{\mathtt{A}^x_\mathtt{r}} \mathsf{M}' \quad \mathsf{S} \xrightarrow{\mathtt{B}^x_\mathtt{r}} \mathsf{S}' \quad \mathtt{A} \neq \mathtt{B} \quad \mathcal{A}(\mathtt{A}_\mathtt{r}, m) = n}{m\llparenthesis\, \mathsf{M} \,\rrparenthesis[\mathsf{S}] \xrightarrow{\tau} n\llparenthesis\, \mathsf{M}' \,\rrparenthesis[\mathsf{S}']}$$

Fusions and activations

- The fusion function $\mathcal{F}$ from rule name to pairs $(m \otimes m', n)$
- The activation function $\mathcal{A}$ from pairs $(\mathrm{A}_{\mathtt{r}}, m)$ to membrane type.
- We assume that $\mathcal{C}$, $\mathcal{D}$, $\mathcal{F}$, $\mathcal{A}$ have a disjoint domaine.

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

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context bisimilarity

A context bisimulation is a symmetric binary relation $\mathcal{R}$ between solutions such that $\mathsf{S} \mathrel{\mathcal{R}} \mathsf{T}$ implies :

1. if $\mathsf{S} \xrightarrow{\tau} \mathsf{S}'$ then $\mathsf{T} \xRightarrow{\tau} \mathsf{T}'$ and $\mathsf{S}' \mathrel{\mathcal{R}} \mathsf{T}'$
2. if $\mathsf{S} \xrightarrow{\mathrm{A}^x_{\mathtt{r}}} \mathsf{S}'$ then $\mathsf{T} \xRightarrow{\mathrm{A}^x_{\mathtt{r}}} \mathsf{T}'$ and $\mathsf{S}' \mathrel{\mathcal{R}} \mathsf{T}'$.
3. if $\mathsf{S} \xrightarrow{m_{\mathtt{r}}} \wr \mathsf{M} \, ; \mathsf{S}'' \wr \cdot \mathsf{S}'$ then $\mathsf{T} \xRightarrow{m_{\mathtt{r}}} \wr \mathsf{M}' \, ; \mathsf{T}'' \wr \cdot \mathsf{T}'$ and for every N, R, and n such that $\mathcal{F}(\mathtt{r}) = (m \otimes n, n')$ both
   - $\left(\mathsf{S}'' , n'(\!|\mathsf{M} , \mathsf{N}|\!)[\mathsf{S}']\right) \mathrel{\mathcal{R}} \left(\mathsf{T}'' , n'(\!|\mathsf{M}' , \mathsf{N}|\!)[\mathsf{T}'']\right)$
   - $\left(\mathsf{S}' , n'(\!|\mathsf{M} , \mathsf{N}|\!)[\mathsf{S}'' , \mathsf{R}]\right) \mathrel{\mathcal{R}} \left(\mathsf{T}' , n'(\!|\mathsf{M}' , \mathsf{N}|\!)[\mathsf{T}'' , \mathsf{R}]\right)$.

$\mathsf{S} \approx_c \mathsf{T}$ if $\mathsf{S} \mathrel{\mathcal{R}} \mathsf{T}$ for some context bisimulation $\mathcal{R}$.

remark : activation is not mentioned !

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3. if $S \xrightarrow{m_r} \wr M ; S'' \int \cdot S'$ then $T \xRightarrow{m_r} \wr M' ; T'' \int \cdot T'$ and for every N, R, and n such that $\mathcal{F}(r) = (m \otimes n, n')$ both
   - $\left(S'' , n'(\!| M , N |\!)[S']\right) \mathcal{R} \left(T'' , n'(\!| M' , N |\!)[T'']\right)$
   - $\left(S' , n'(\!| M , N |\!)[S'' , R]\right) \mathcal{R} \left(T' , n'(\!| M' , N |\!)[T'' , R]\right)$.

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Properties of context bisimilarity

- $\approx_c$ have the same properties as $\approx$
- context bisimilarity retains a universal quantification that is hard to check

still to be done :

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  - instead of 4 we may use :
    if $m \in \mathcal{F}$ and $S \xrightarrow{m} \wr M ; S'' \wr \cdot S'$ then $T \xRightarrow{m} \wr N ; T'' \wr \cdot T'$
    and $M \mathfrak{r} N$, $S'' \mathfrak{r} T''$, $S' \mathfrak{r} T'$
    too much discriminating ?
  - constraining fusions when interacting cells have particular structures
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Conclusions

- Contribution :
  - one framework for two very different types of biological systems
  - sometimes with a finer description of the phenomena
  - reuse tools already developed for the pi-calculus
- Rules creating cells have been hidden
- The missing part :
  - comparisons with other models (Ambients)
  - more studies on the good notion of bisimulation
  - adding other significant primitives