A bigraph-based framework for protein and cell interactions

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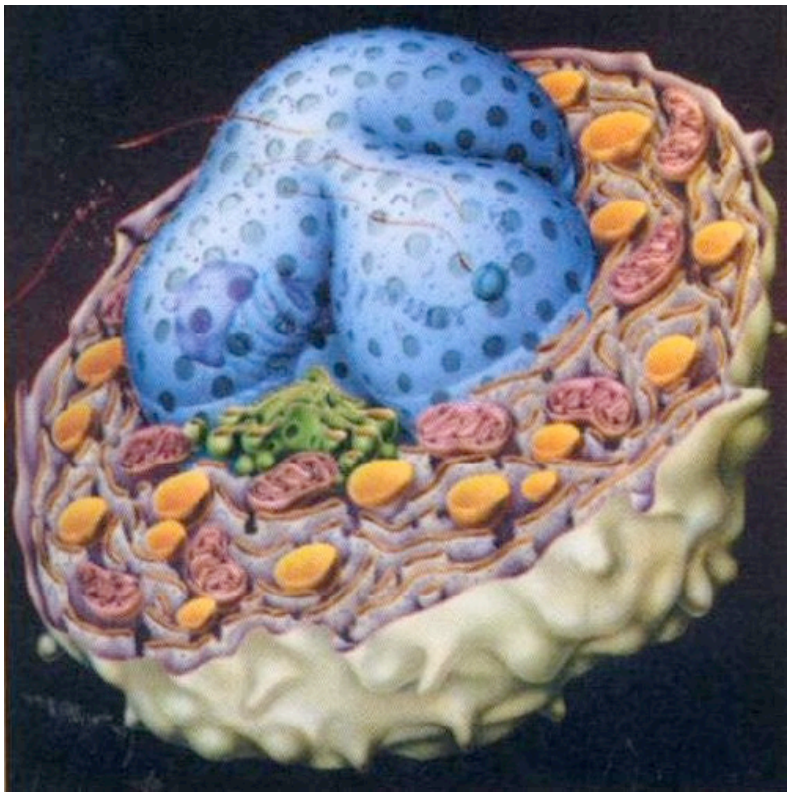
Introduction

In recent years, Formal Methods from CS have been (convincingly?) proposed for representing and understanding *biological systems*

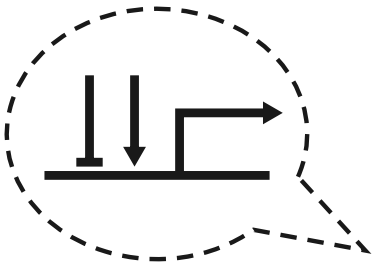
- \+ not as continuous (nonlinear) systems (e.g. by means of ODEs)
- \+ but as **discrete reactive systems**, with event-driven transitions

Aha! We know how to deal with discrete reactive systems! We have modelled concurrency!
But. . . how to deal with the overwhelming complexity?



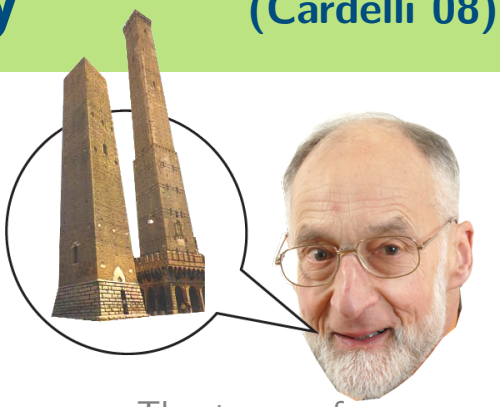
Abstract Machines of Systems Biology (Cardelli 08)

gene regulatory networks,
stochastic π-calculus,
Hybrid Systems, ...



regulation

Genes



The tower of informatic models (Milner 09)

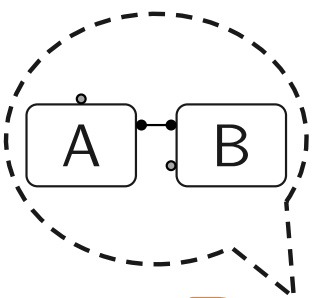
makes proteins
where/when/howmuch

signals and events

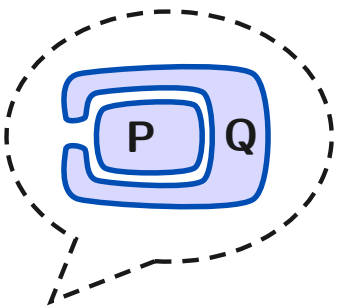
confines regulators

directs protein embedding,
membrane construction

κ-calculus,
β Binders,
π-calculus,
Bio-PEPA,
LCLS, ...



Brane Calculus,
BioAmbients,
CLS+, ...



implements fusion/fission

Proteins

Membranes

holds receptors/reactions

**signal processing,
metabolism regulation**

**confinements,
storage, transport**

Abstract Machines of Systems Biology (Cardelli 08)

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Hybrid Systems, ...

regulation

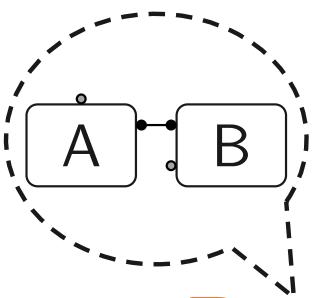
Genes

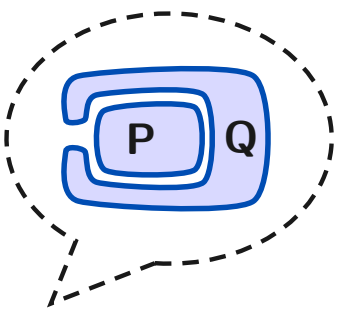
In this talk: **bigraphs**
as a formal framework theory for
integrating and comparing models

κ-calculus,
β Binders,
π-calculus,
Bio-PEPA,
LCLS, ...

Brane Calculus,
BioAmbients,
CLS+, ...

we focus on these levels





implements fusion/fission

Proteins

Membranes

holds receptors/reactions

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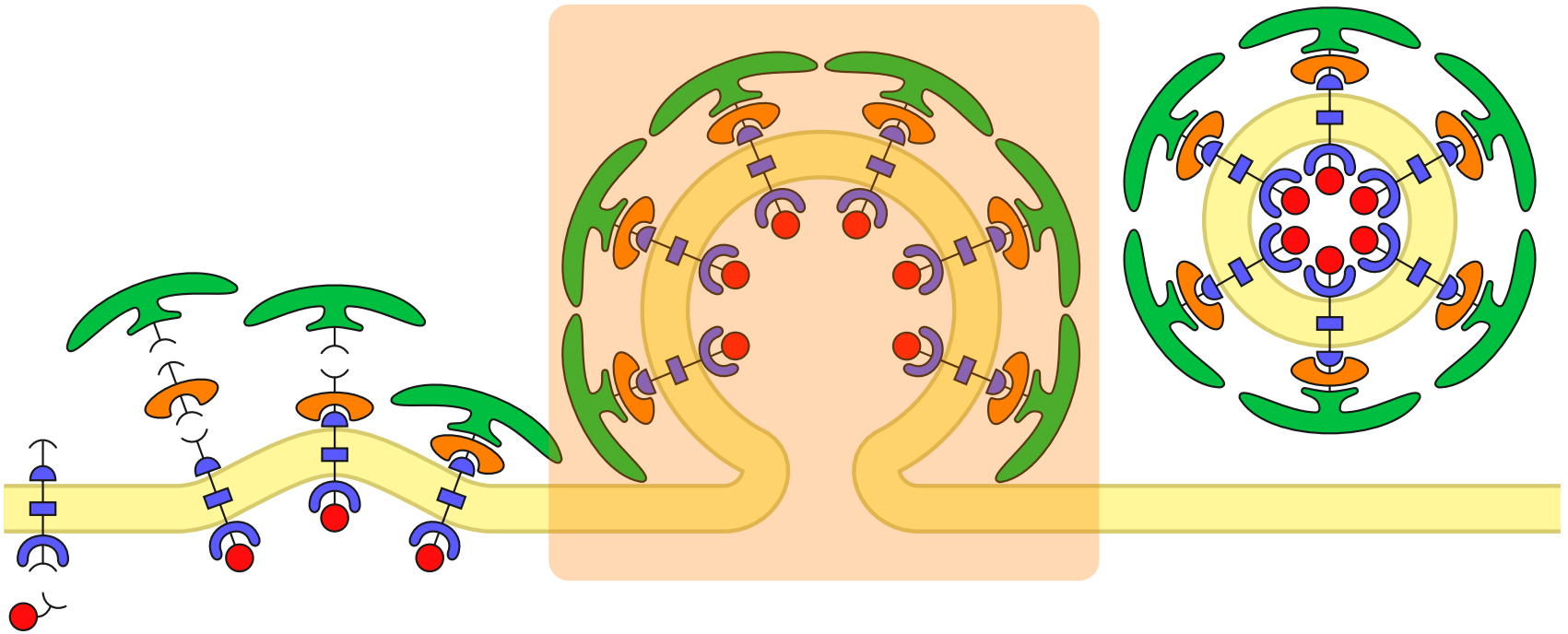
Interactions we want to model

Let take as example the vesicle formation process:



protein interactions
(complexations de-complexations)

protein-membrane interactions
(protein configurations that trigger a membrane reconfiguration)

membrane reconfigurations
(fissions and fusions)

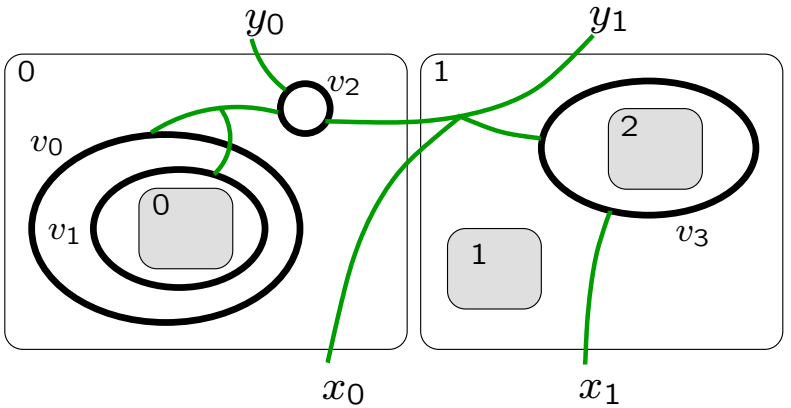
Talk outline

0. Introduction to Bigraphs
1. Biological Bigraphs and Bioβ framework
   - + syntax
   - + well-formedness
   - + semantics
2. Example: **vesicle formation**
3. Formal comparison results

A (very short) introduction to Bigraphs (Milner 01)

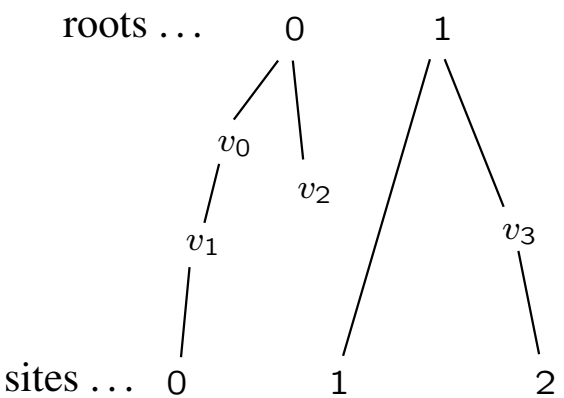
bigraph

$G : \langle m, X \rangle \to \langle n, Y \rangle$



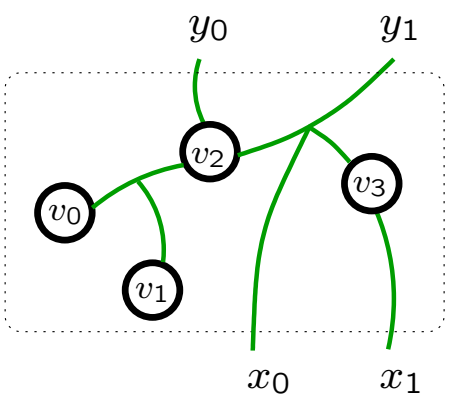
place graph

$G^{\mathrm{P}} : m \to n$



link graph

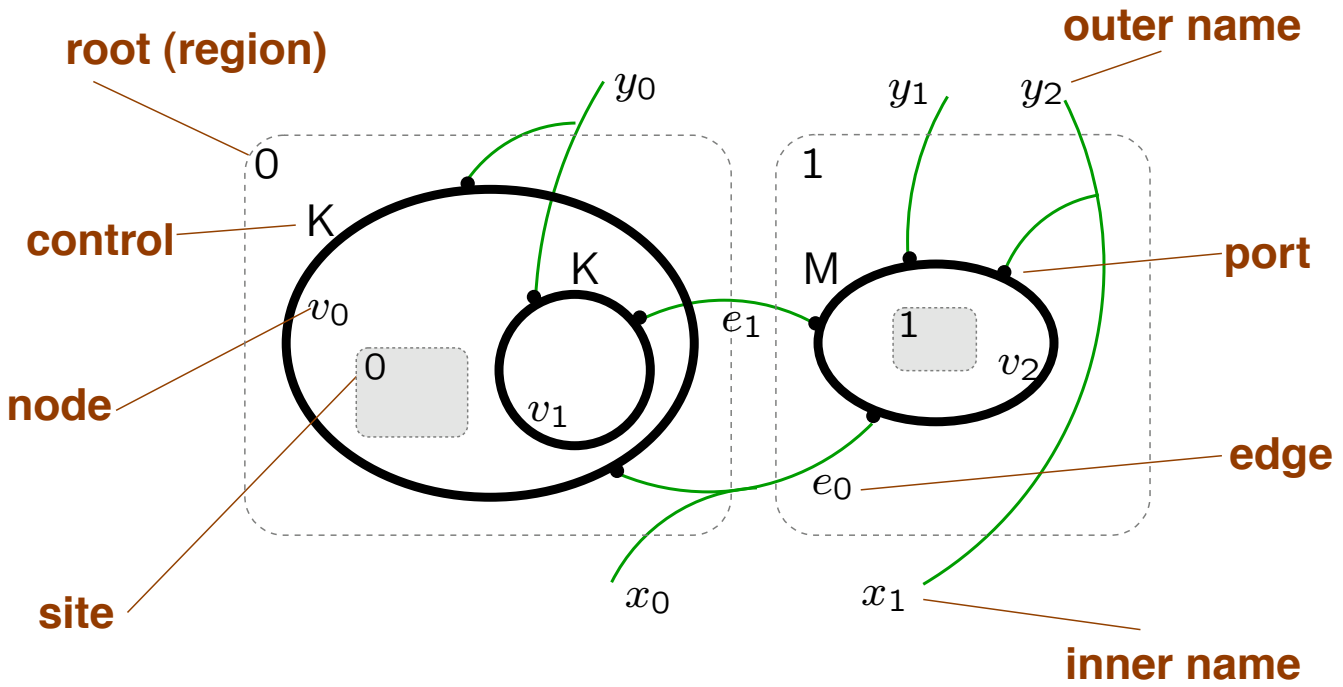
$G^{\mathrm{L}} : X \to Y$



... outer names

... inner names

. . . bigraphs continued (basic notation)



place = **root** or **node** or **site**

link = **edge** or **outer name**

point = **port** or **inner name**

. . . bigraphs continued (definition)

. . . we take advantage of the variant of (Bundgaard-Sassone 06) where edges have type.

Signature: $\langle \mathcal{K}, ar, \mathcal{E} \rangle$

Bigraphs:

$G^P = (V, ctrl, prnt) \colon m \to n$ **(place graph)**

$G^L = (V, E, ctrl, edge, link) \colon X \to Y$ **(link graph)**

$G = (V, E, ctrl, edge, prnt, link) \colon \langle m, X \rangle \to \langle n, Y \rangle$ **(bigraph)**

$= (G^P, G^L)$

Why using bigraphical theory

Using bigraphs is convenient for many reasons:

+ connectivity together with locality
+ lots of successful encodings
  (CCS, π-calculus, Ambient Calculus, Petri nets, ...)
+ local reaction rules
+ construction of compositional bisimilarities for **observational equivalences**
+ general tools (see BPL project)

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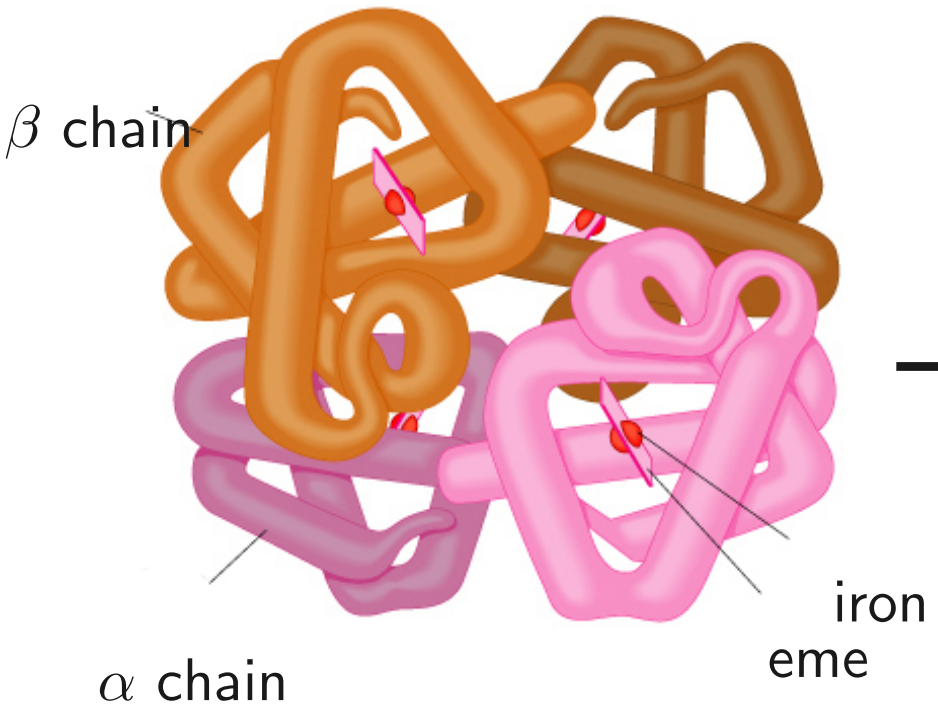
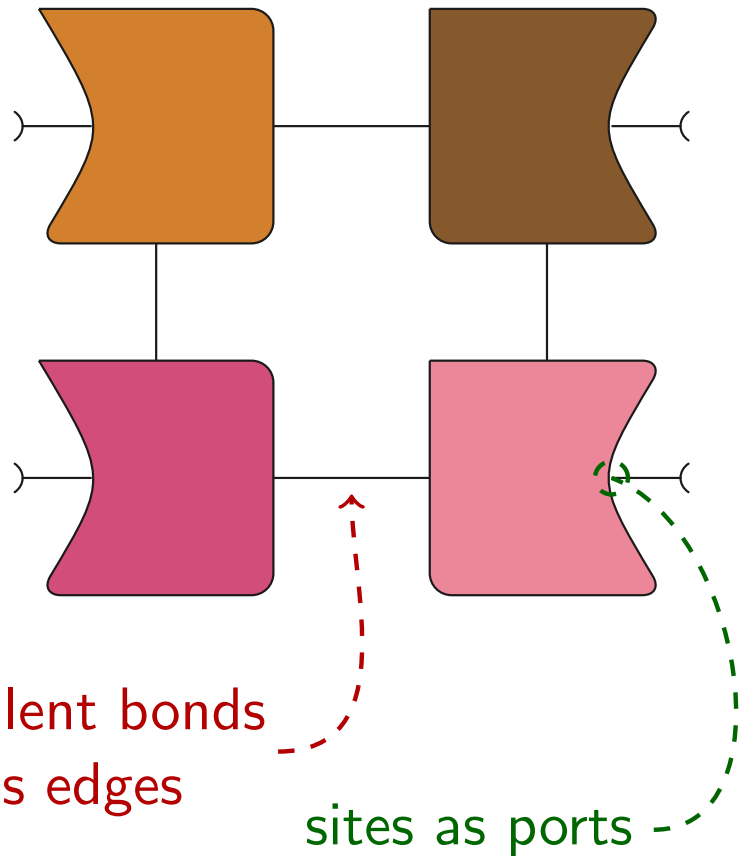
Abstraction on protein structure



(Hemoglobin A)

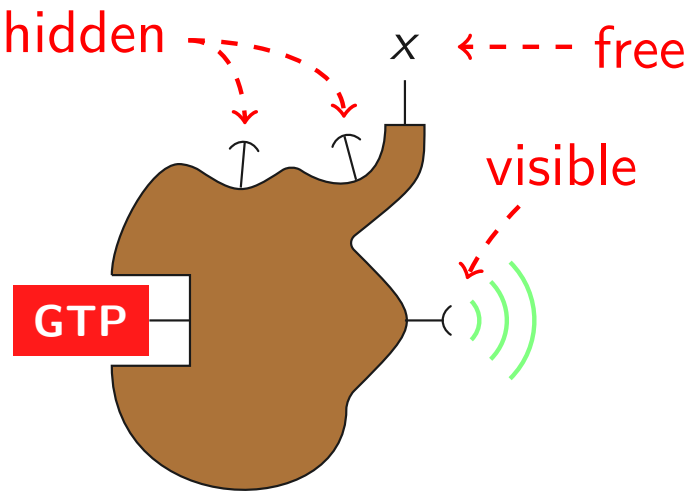
How we represent it. . .

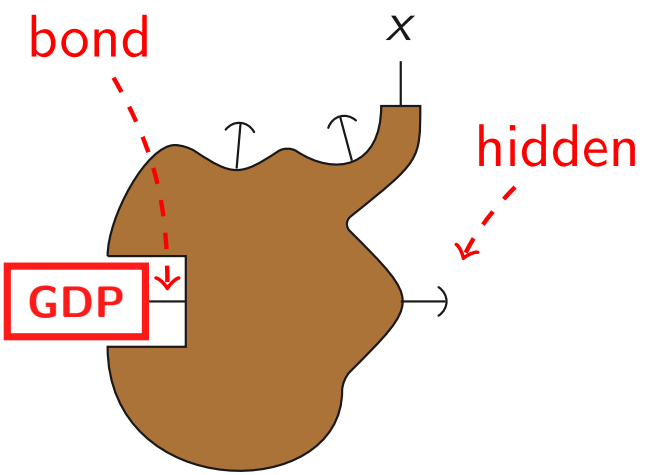


Proteins and bonds in bigraphs: intuition

Protein signature: $\langle \mathcal{P}, ar, \{\mathsf{v}, \mathsf{h}\} \rangle$

Sites can be visible, hidden, or free, determining the protein interface status





$\nu y.(G(1^y + \bar{2} + \bar{3} + 4^x + 5) \mid GTP(1^y))$

$\nu y.(G(1^y + \bar{2} + \bar{3} + 4^x + \bar{5}) \mid GDP(1^y))$

(*) Edge types could be extended to capture phosphorilated states (and more)

Bioβ syntax and bigraphical meaning

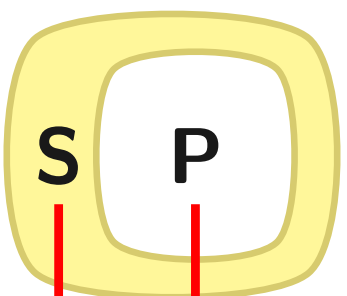
Systems $P, Q ::= \diamond \mid A_p(\rho) \mid (\!|S|\!)\, P \mid P * Q \mid \nu n.P$

$\mathsf{p}_n \fatsemi P \mid \mathsf{f}_n \fatsemi (\!|S|\!)\, P$ (pinch and fuse)

Membranes $S, T ::= \mathbf{0} \mid A_{ap}(\rho) \mid S \star T$

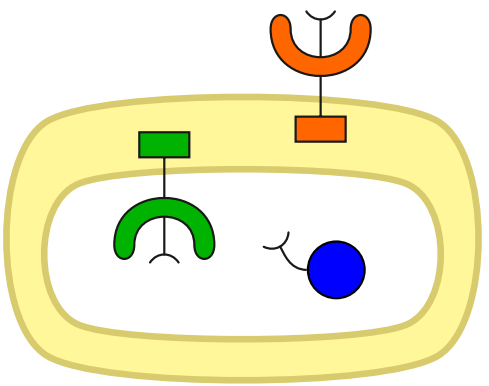
$\mathsf{p}_n^{\perp} \fatsemi S \mid \mathsf{f}_n^{\perp}$ (co-pinch and co-fuse)

$(\!|S|\!)\, P$



membrane

contents



$Ra(1 + 2^x) * (\!|Ma(1^x) \star Mb(1^y)|\!)\, Rb(1 + 2^y) * C(1)$

Well-formedness conditions

The syntax is too general: many syntactically correct terms do not have a clear biological meaning.

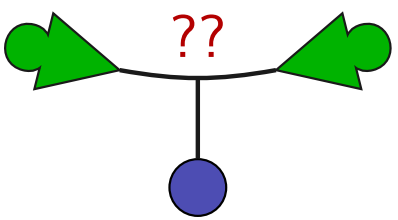
Definition (Well-formedness)

Graph-likeness: free names occurs at most twice + only binary bonds

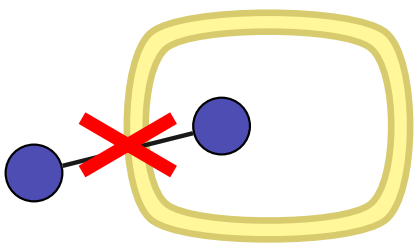
Impermebility: protein bonds cannot cross the double layer

Action pairing: actions and co-actions have to be well paired

Action prefix: no occurrences of action terms within an action prefix



hyper edges $\neq$ bonds



impermeability violated!

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Well-formedness is ensured by a

type system

Type system

$$\Gamma_1; \Gamma_2 \vdash K : \tau \qquad \textbf{(Judgement)}$$

(empty) $\dfrac{\epsilon \in \{\mathbf{0}, \diamond\}}{\emptyset; \emptyset \vdash \epsilon : \emptyset}$ $\qquad$ $\dfrac{A \in \mathcal{P} \quad \forall x \in fn(\rho).\ |\rho, x| \leq 2}{\{x \in fn(\rho) \mid |\rho, x| = 1\}; \{x \in fn(\rho) \mid |\rho, x| = 2\} \vdash A(\rho) : \emptyset}$ (prot)

(action) $\dfrac{t \in \{\mathsf{p}, \mathsf{p}^\perp, \mathsf{f}\} \quad \Gamma_1; \Gamma_2 \vdash K : \emptyset \quad act(K) = \emptyset}{\Gamma_1, x; \Gamma_2 \vdash t_x \fatsemi K : \{t_x\}}$ $\qquad$ $\dfrac{\Gamma_1; \Gamma_2 \vdash P : \tau \quad x \notin \Gamma_1 \quad \tau\restriction_{\{x\}} = \emptyset}{\Gamma_1; \Gamma_2 \setminus \{x\} \vdash \nu x.P : \tau}$ (ν-prot)

(co-f) $\dfrac{}{x; \emptyset \vdash \mathsf{f}_x^\perp : \{\mathsf{f}_x^\perp\}}$ $\qquad$ $\dfrac{t \in \{\mathsf{p}, \mathsf{f}\} \quad \Gamma_1; \Gamma_2, x \vdash P : \tau \cup \{t_x, t_x^\perp\} \quad \{t_x, t_x^\perp\} \cap \tau = \emptyset}{\Gamma_1; \Gamma_2 \vdash \nu x.P : \tau}$ (ν-action)

(par) $\dfrac{\begin{array}{c}\mathsf{op} \in \{*, \star\} \\ \Gamma_1, \Gamma; \Gamma_2 \vdash K : \tau \qquad \Delta_1, \Gamma; \Delta_2 \vdash L : \sigma \\ (\Gamma_1 \cup \Gamma_2) \cap (\Delta_1 \cup \Delta_2) \neq \emptyset \qquad (\tau\restriction_\Gamma)^\perp = \sigma\restriction_\Gamma\end{array}}{\Gamma_1, \Delta_1; \Gamma_2, \Delta_2, \Gamma \vdash K \ \mathsf{op}\ L : \tau \cup \sigma}$ $\qquad$ $\dfrac{\begin{array}{c}\Gamma_1, \Gamma; \Gamma_2 \vdash S : \tau \qquad \Gamma; \Delta_2 \vdash P : \sigma \\ (\Gamma_1 \cup \Gamma_2) \cap \Delta_2 \neq \emptyset \qquad (\tau\restriction_\Gamma)^\perp = \sigma\restriction_\Gamma\end{array}}{\Gamma_1; \Gamma_2, \Delta_2, \Gamma \vdash \wr S \wr P \int\!\!\int : \tau \cup \sigma}$ (cell)

Properties of the type system

Proposition (Unicity of type)

Let K a Bioβ term. If $\Gamma_1; \Gamma_2 \vdash K : \tau$ and $\Delta_1; \Delta_2 \vdash K : \sigma$, then $\Gamma_1 = \Delta_1$, $\Gamma_2 = \Delta_2$ and $\tau = \sigma$

Theorem (Well-formedness)

A Bioβ system P is well-formed if and only if $\Gamma_1; \Gamma_2 \vdash P : \tau$

. . . later subject reduction

Semantics: Bioβ reactive system

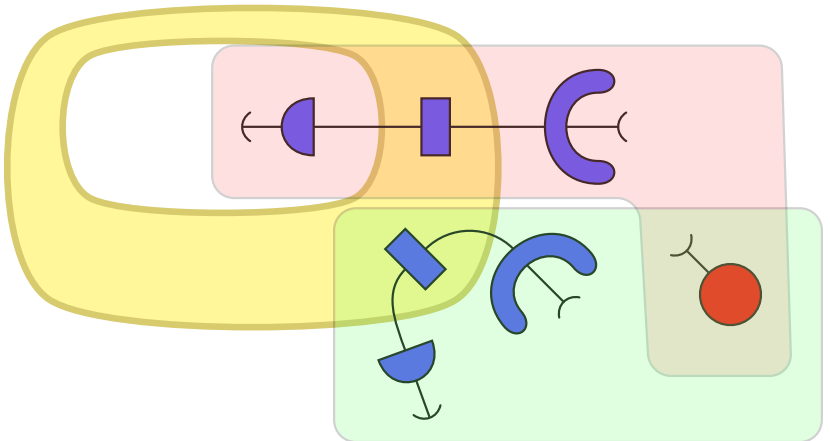
A Bioβ reactive system $(\Pi, \rightarrow)$ is parametrized over two reaction rule specifications:

+ **Protein reactions:** similar to chemical reaction rules, but **with (essential) spatial informations**

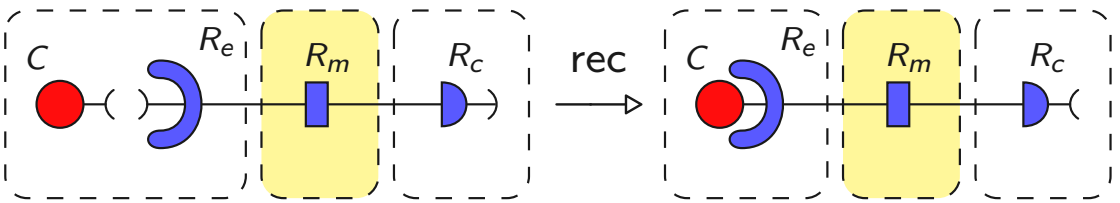
+ **Mobility configurations:** protein configurations that trigger membrane re-modeling

Reactions for **Membrane transport** are fixed
(indeed, biological membrane modifications are very limited: only pinching and fuse)

Protein reactions across multiple localities



Protein reactions are endowed with spatial information



$$\langle\, C(1) * R_e(1{+}2^x),\ R_c(1^y{+}\bar{2}) \mid R_m(1^x{+}2^y) \,\rangle \xrightarrow{\text{rec}}$$

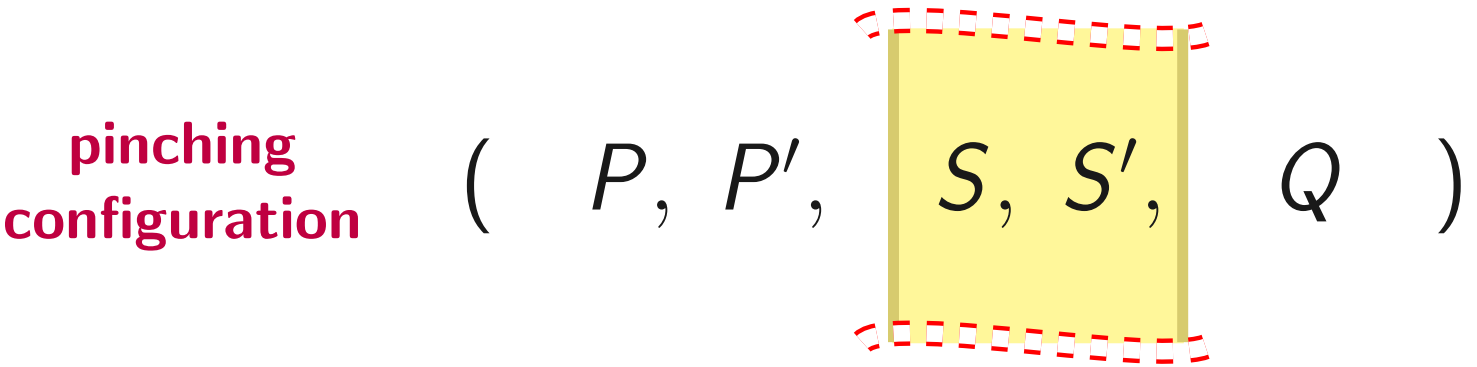
$$\nu z.\langle\, C(1^z) * R_e(1^z{+}2^x),\ R_c(1^y{+}2) \mid R_m(1^x{+}2^y) \,\rangle$$

Mobility configurations

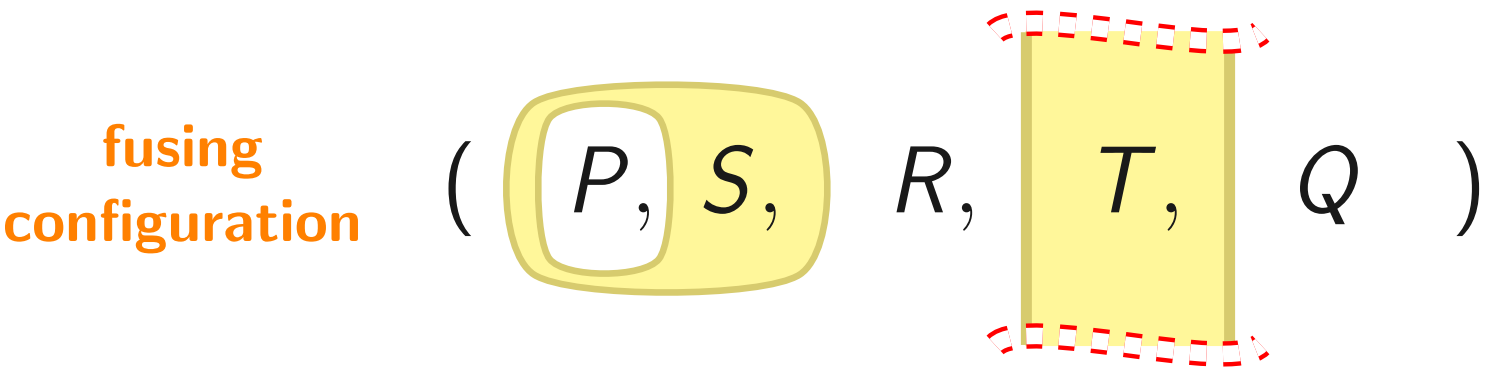
Membrane transport must be justified by protein interactions.

This is formalized by means of
membrane reactions configurations

pinching configuration



fusing configuration



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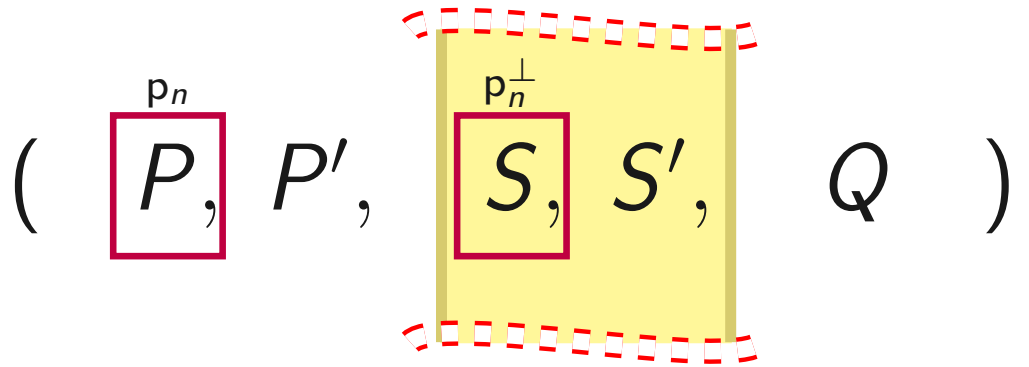
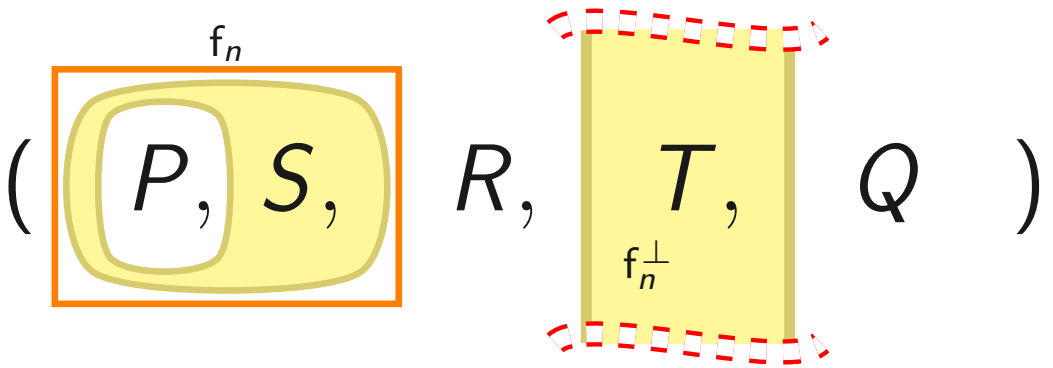
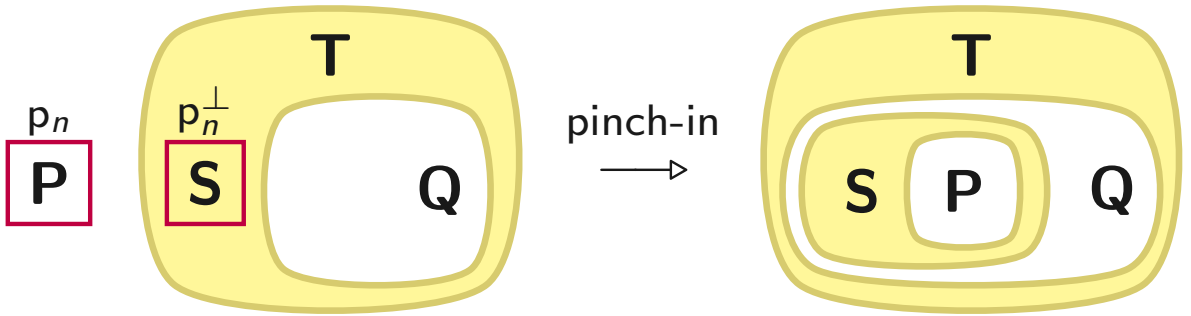


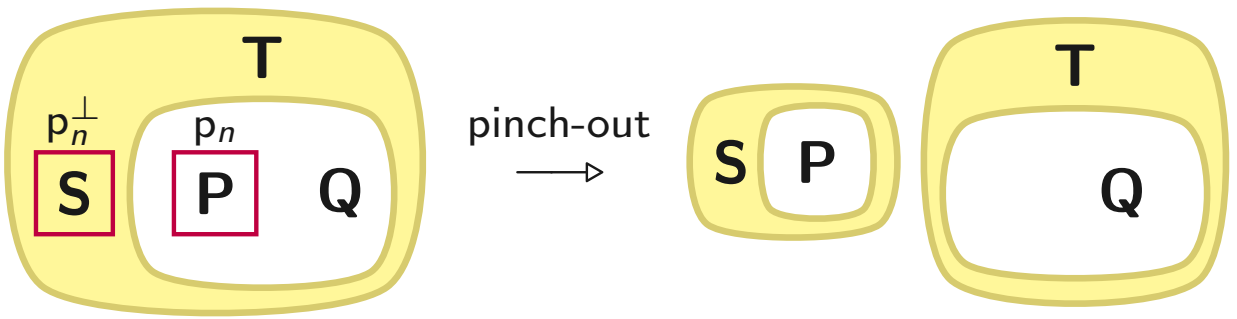
fusing configuration



Membrane transport: pinch

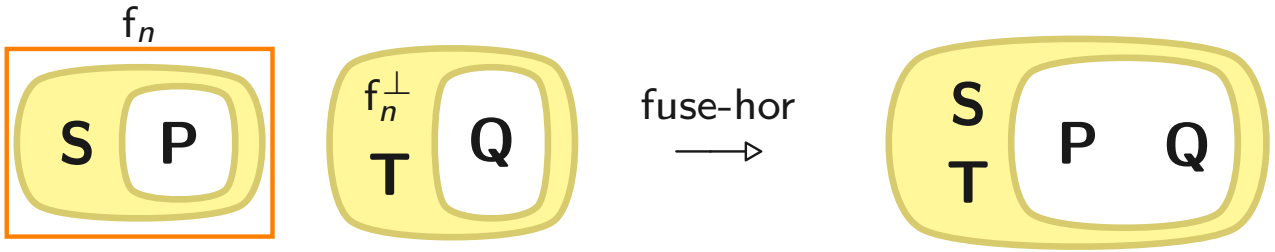


$$\mathsf{p}_n \wr P * \wr(\mathsf{p}_n^\perp \wr S \star T \wr Q\int\int \to \wr T \wr \wr S \wr P\int\int * Q\int\int$$

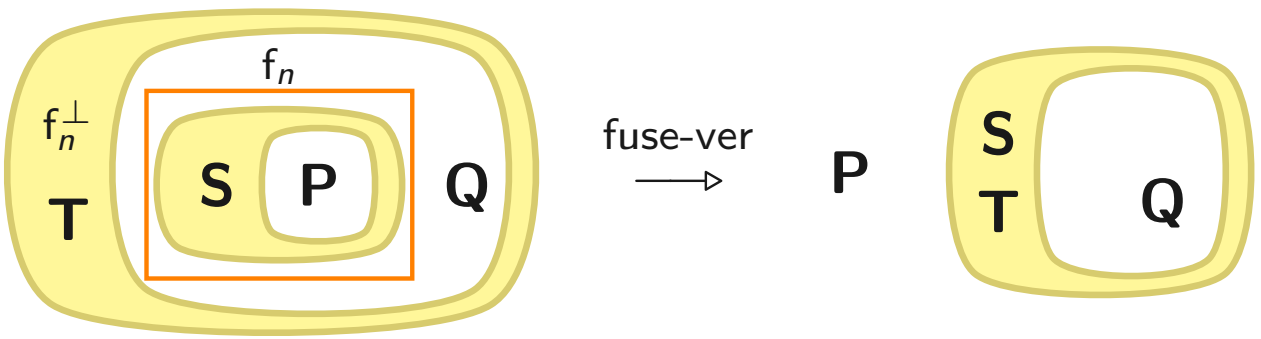


$$\wr(\mathsf{p}_n^\perp \wr S \star T \wr \mathsf{p}_n \wr P * Q\int\int \to \wr S \wr P\int\int * \wr T \wr Q\int\int$$

Membrane transport: fuse



$$\mathsf{f}_n \fatsemi (S \wand P) * (\mathsf{f}_n^\perp \star T \wand Q) \to (S \star T \wand P * Q)$$



$$(\mathsf{f}_n^\perp \star T) \wand \mathsf{f}_n \fatsemi (S \wand P) * Q \to P * (S \star T \wand Q)$$

Reactions preserve well-formedness

Theorem (Subject reduction)

Let P, Q be Bioβ systems.

$$\textbf{If } \Gamma_1; \Gamma_2 \vdash P : \tau \textbf{ and } P \to Q\textbf{, then } \Gamma_1; \Delta_2 \vdash Q : \sigma$$

where *either* $\Gamma_2 = \Delta_2$ *and* $\tau = \sigma$,

or $\Gamma_2 = \Delta_2, n$ *and* $\tau = \sigma + \{t_n, t_n^{\perp}\}$ $(t \in \{\mathsf{p}, \mathsf{f}\})$

Note:

Free names of P and Q can differ
only for one occurrence of an action name

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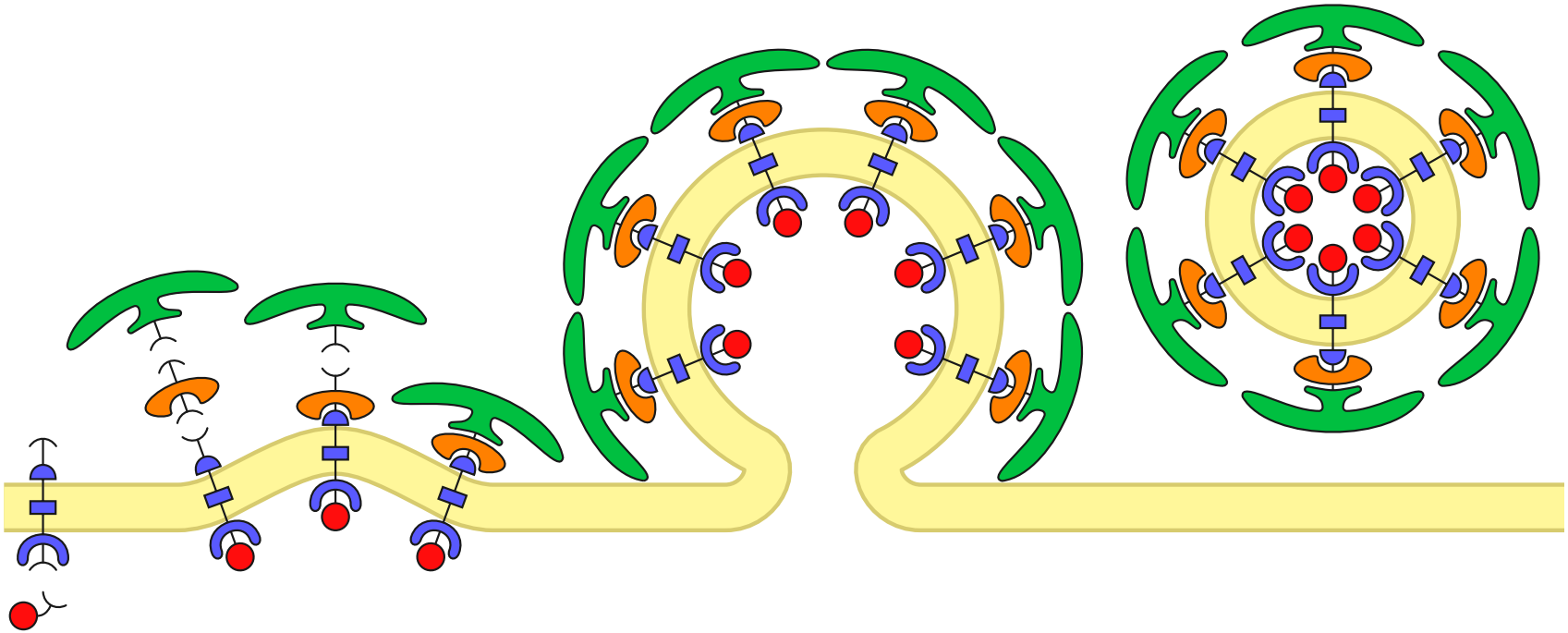
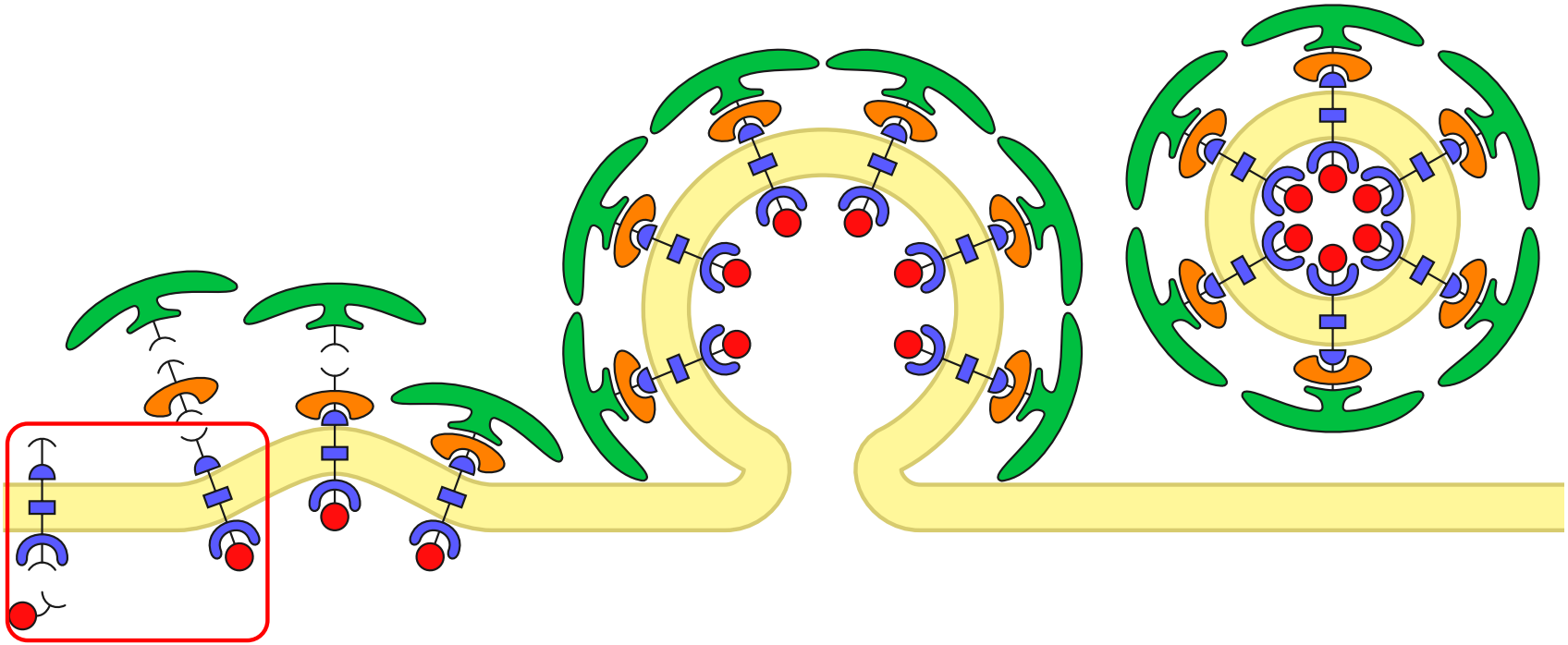
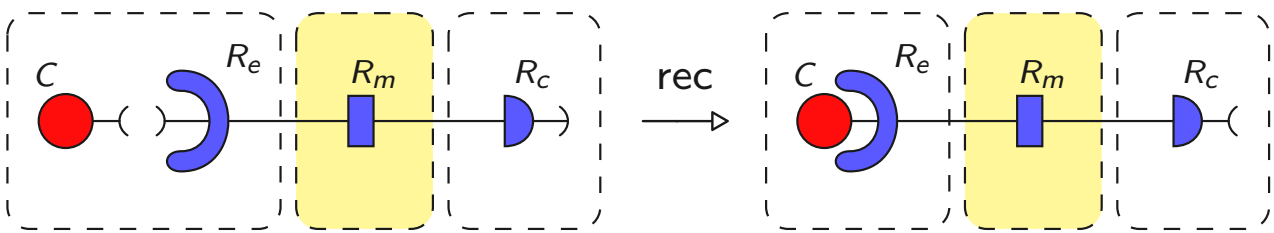
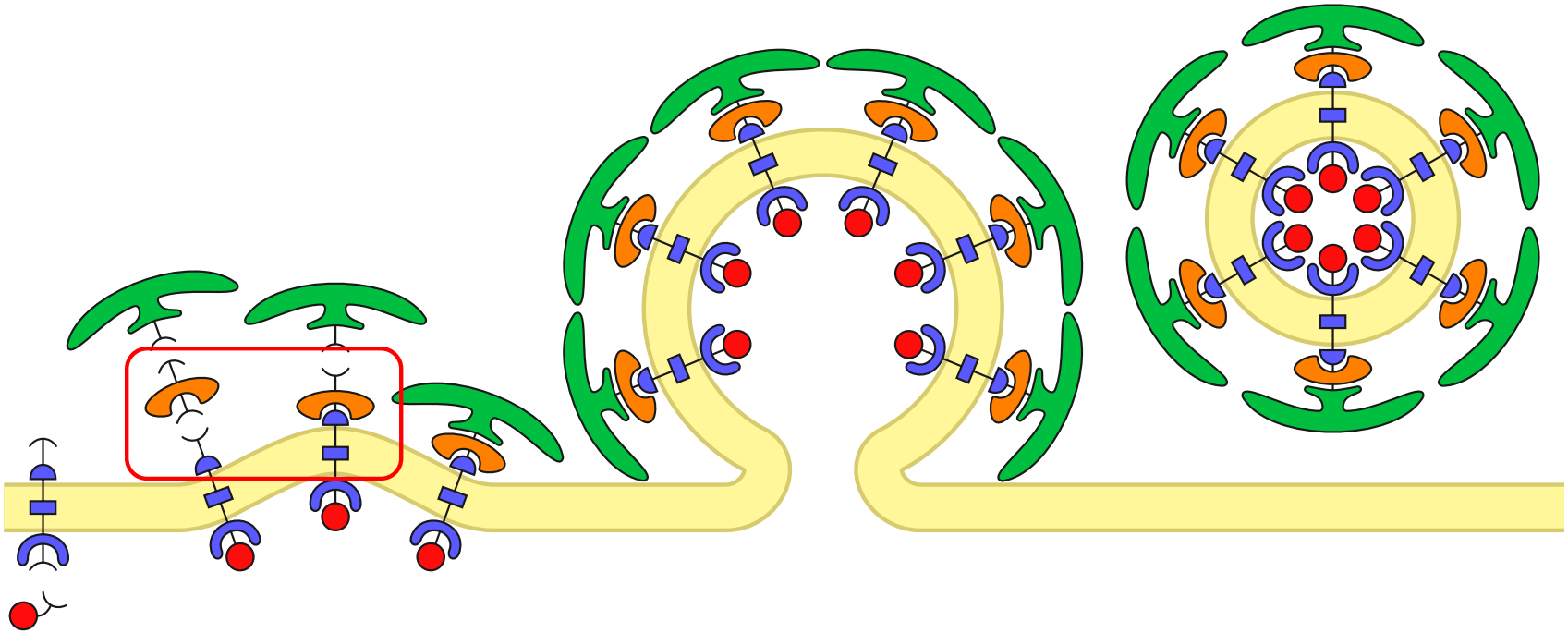


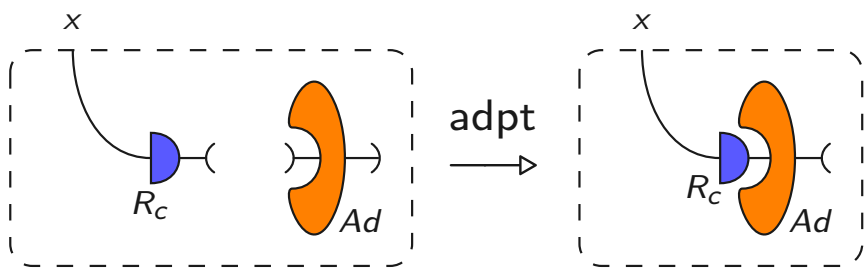
We formalize the above vesicle formation pathway showing the Bioβ specification needed to define the Bioβ reactive system



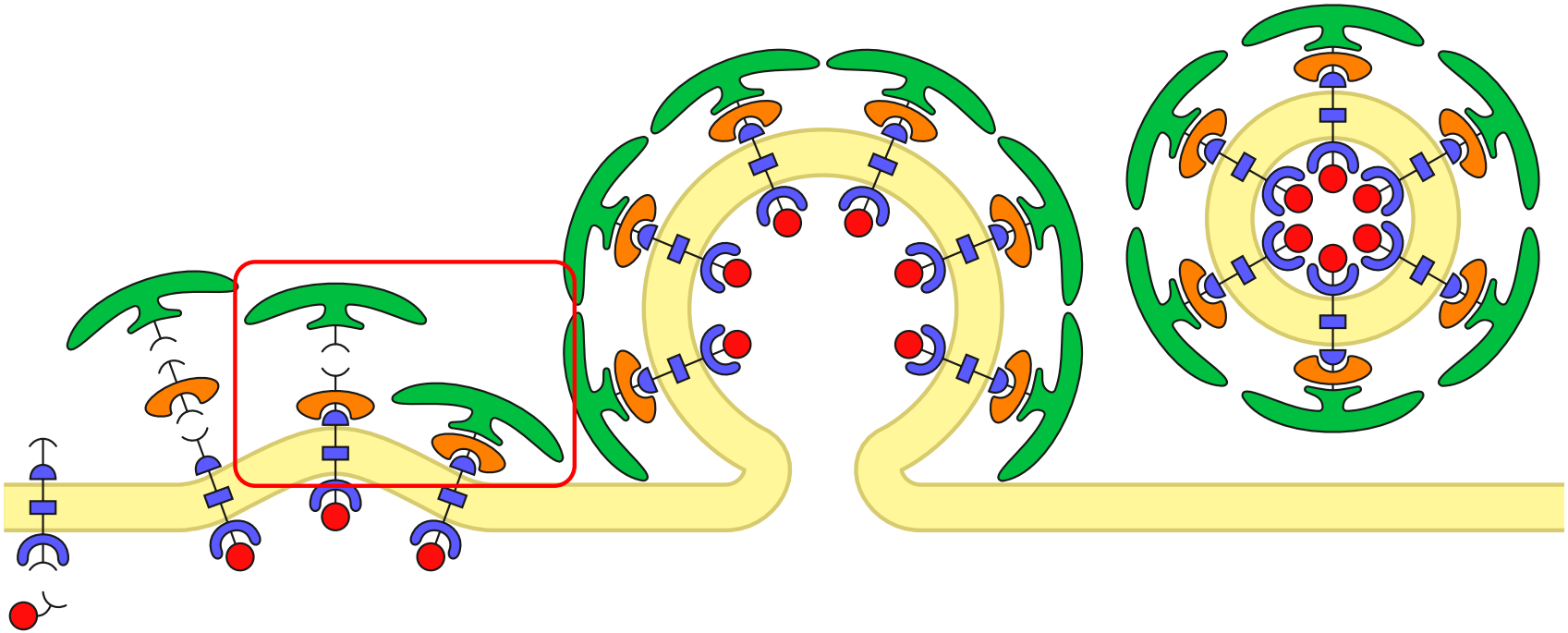


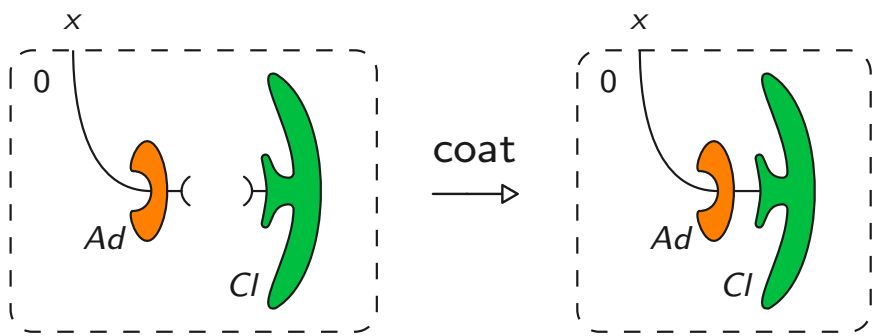
$$\langle C(1) * R_e(1 + 2^x), R_c(1^y + \bar{2}) \mid R_m(1^x + 2^y)\rangle \xrightarrow{\text{rec}} \nu z.\langle C(1^z) * R_e(1^z + 2^x)\,, R_c(1^y + 2) \mid R_m(1^x + 2^y)\rangle$$



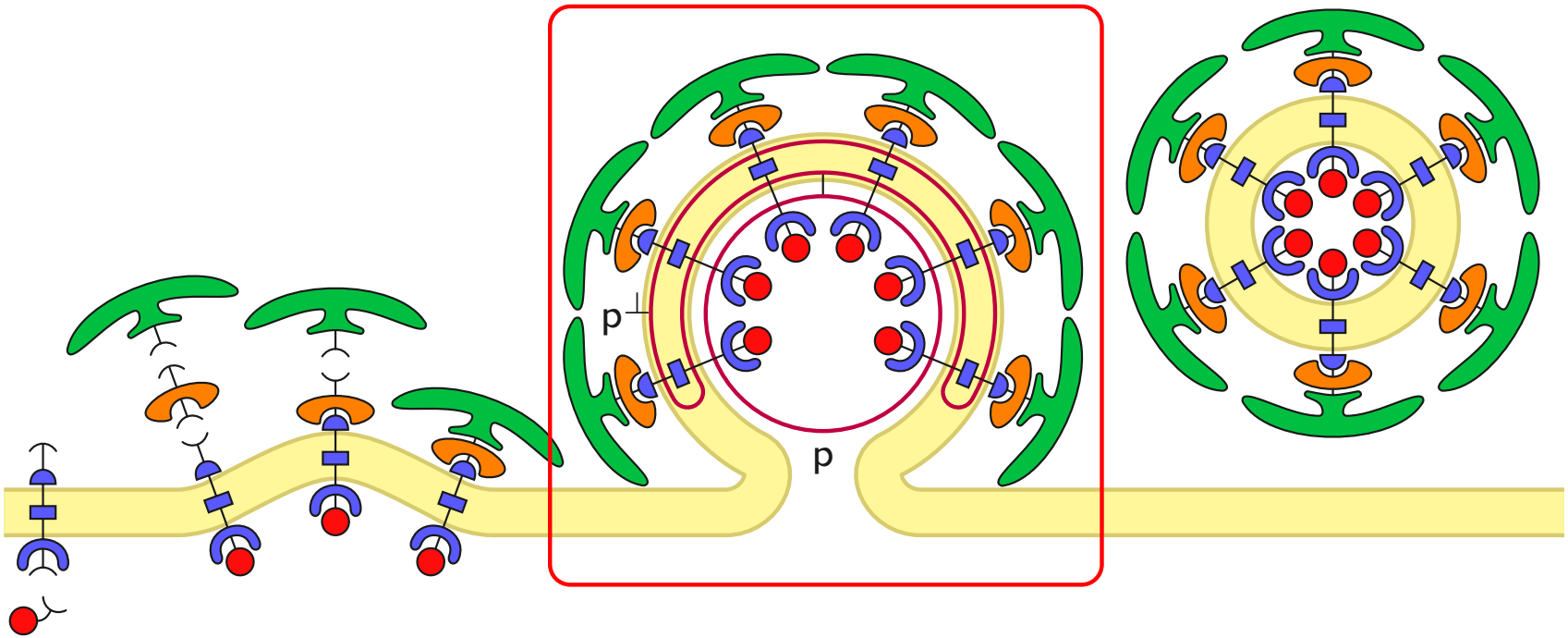


$$\langle R_c(1^x + 2) * Ad(1 + \bar{2}) \mid\rangle \xrightarrow{\text{adpt}} \nu y.\langle R_c(1^x + 2^y) * Ad(1^y + 2) \mid\rangle$$





$$\langle Ad(1^x + 2) * Cl(1) \mid\rangle \xrightarrow{\text{coat}} \nu y.\langle Ad(1^x + 2^y) * Cl(1^y) \mid\rangle$$



$$\{(P, P', S, S', Q)\}$$

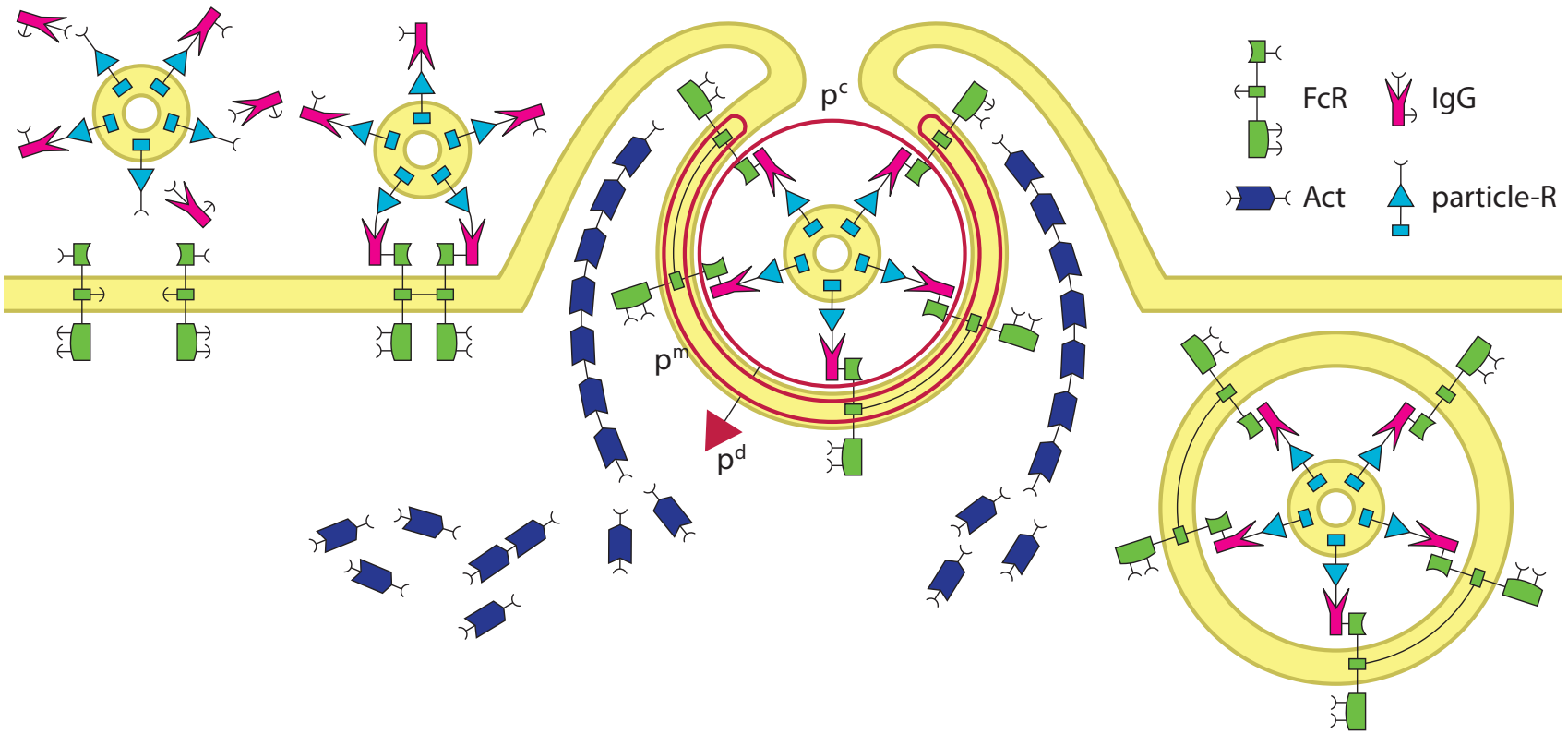
$$P = \sum_{i=1}^{6} \left(C(1^x) * R_e(1^x + 2^y)\right) \qquad P' = \diamond$$

$$S = \sum_{i=1}^{6} \left(R_m(1^y + 2^w)\right) \qquad S' = \mathbf{0}$$

$$Q = \sum_{i=1}^{6} \left(R_c(1^w + 2^a) * Ad(1^a + 2^b) * Cl(1^b)\right)$$

Another example: Fc receptor-mediated phagocytosis

Even more complex biological pathways can be specified...

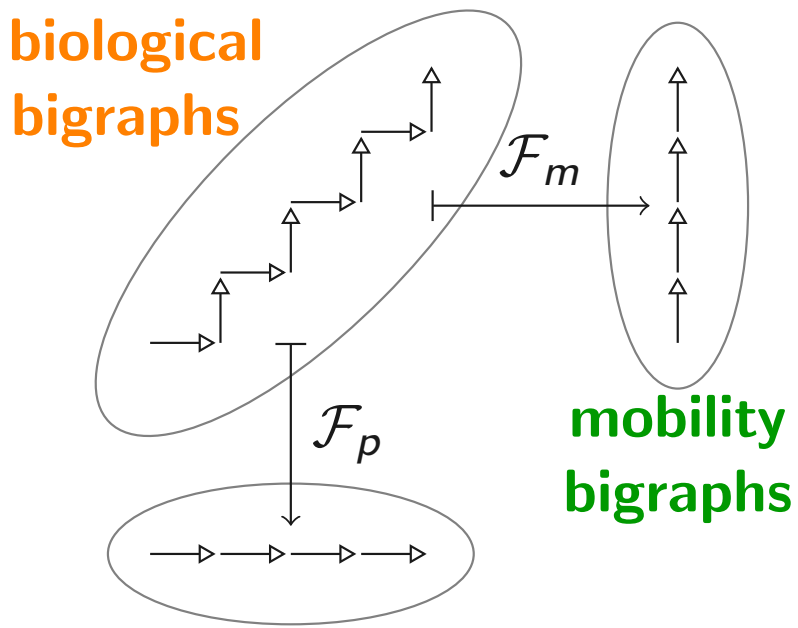


Talk outline

0. Introduction to Bigraphs
1. Biological Bigraphs and Bioβ framework
   + syntax
   + well-formedness
   + semantics
2. Example: **vesicle formation**
3. Formal comparison results

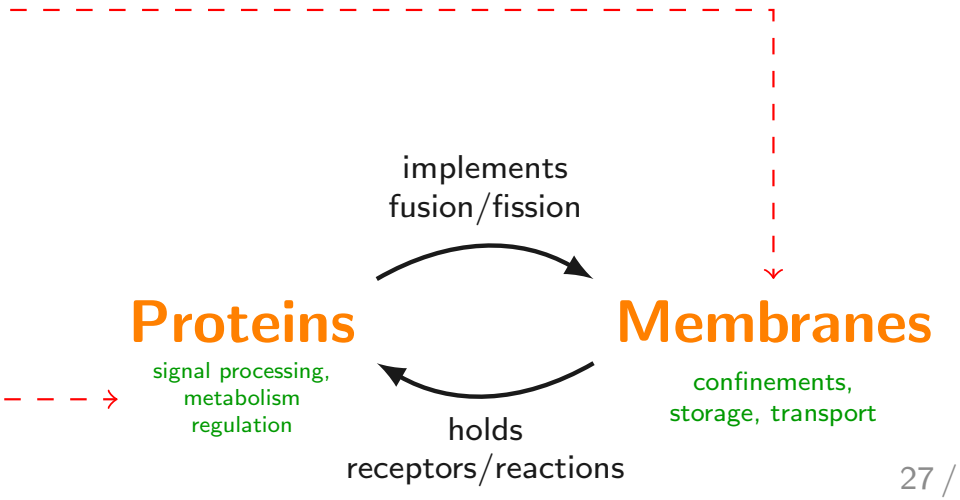
Formalizing connections between models

The formal Bioβ model allows to establish a **formal** connection between the protein-only and membrane mobility-only models:



Theorem

Each transition in biological bigraphs corresponds to either a protein-only transition or to a mobility-only transition



Conclusions & Future Work

Done:

- a bigraphical model for protein-membrane interactions
- a model-driven (and user-friendly) framework
- formalization of causality among mobility and protein interaction
- a formal type system for well-formedness

To do:

- stochastic refinement of reactions (**stochastic bigraphs**)
- adding molecular transporters/channels
- refinements on fluidity and distances
- tools (modeling and simulation)