SBGN-ER vs rule-based modeling

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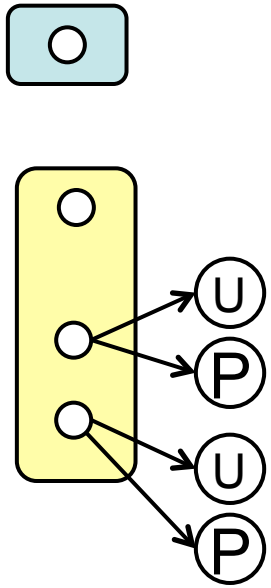
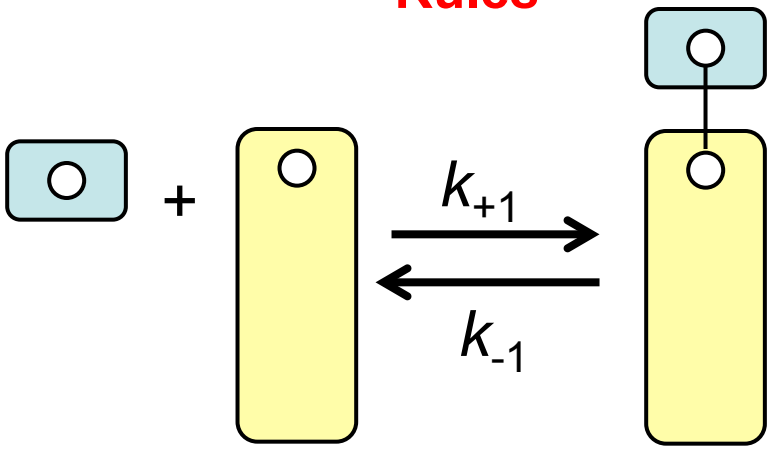
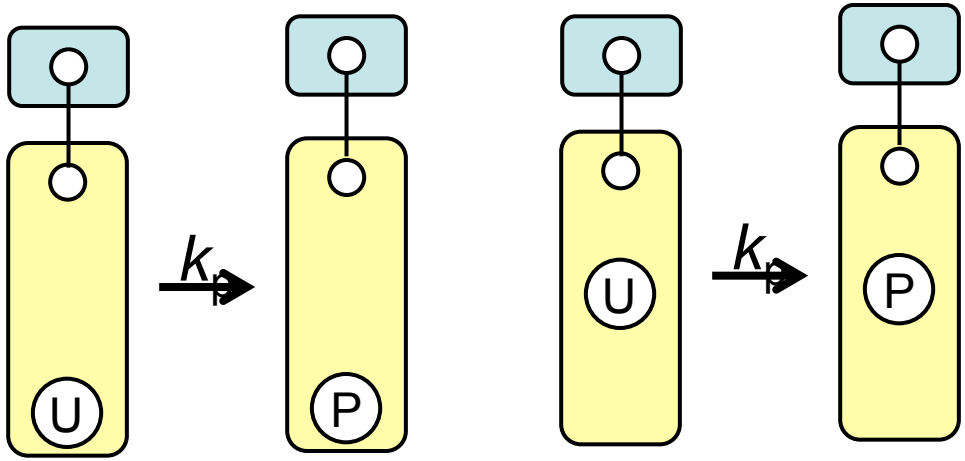
Molecules, components and rules

Molecules, binding sites, components and states

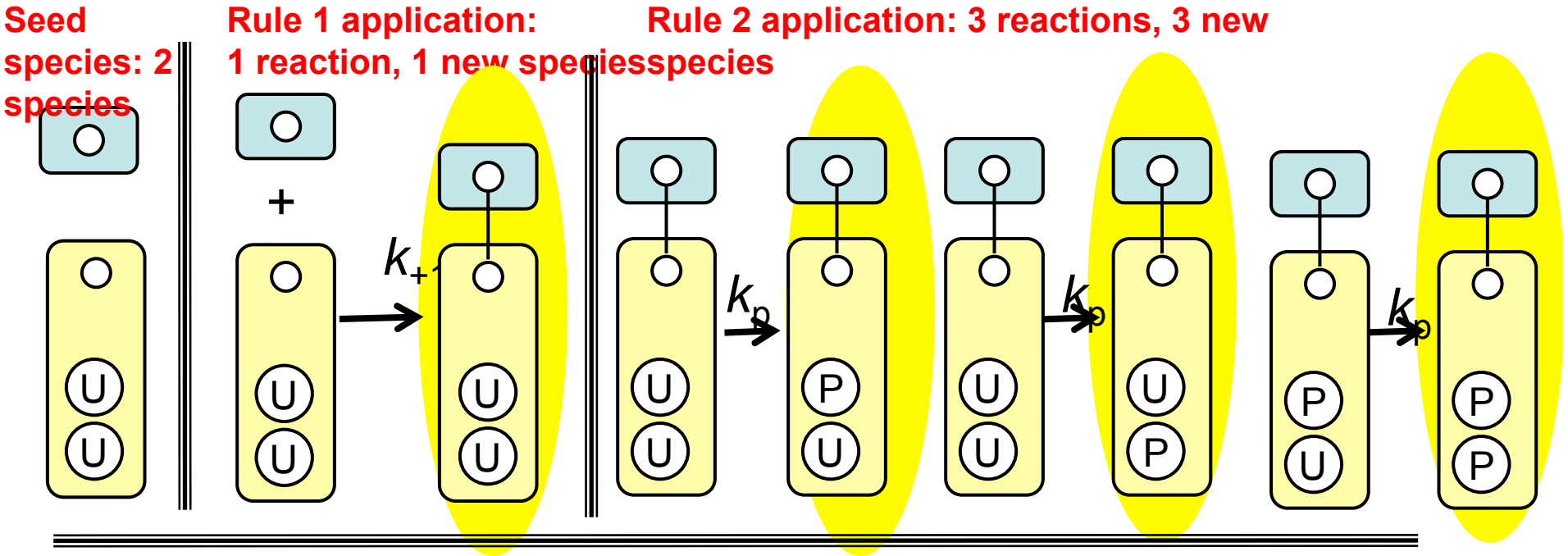


Rules

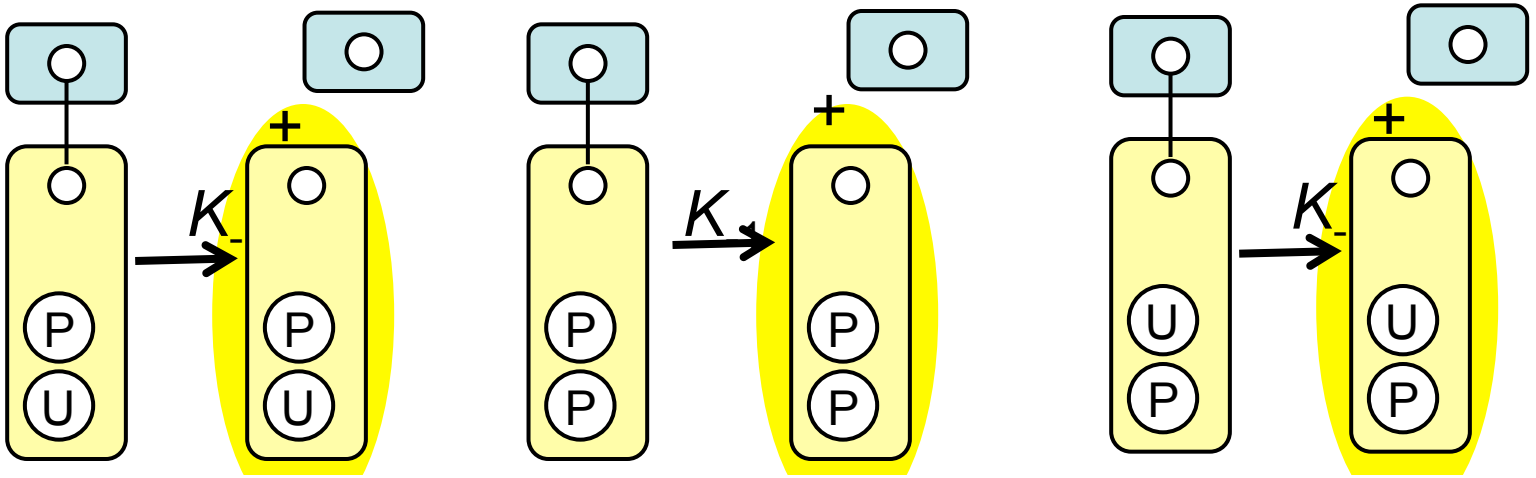




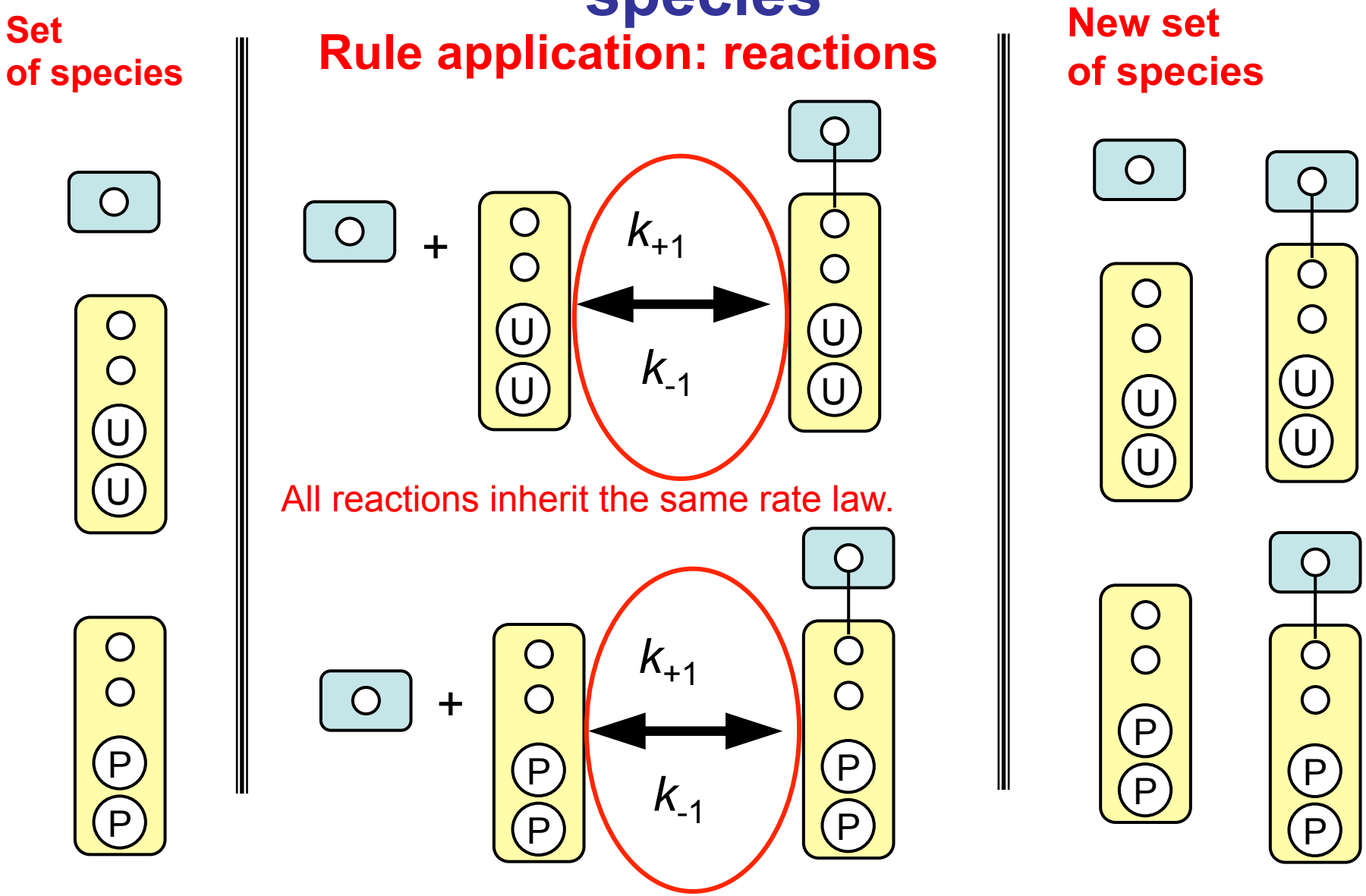
Rules generate reactions and species



Rule 1R application: 3 reactions, 3 new species



Rules generate reactions and new chemical species



Rule-based model generation

Input: initial species S_0

Input: reaction rules $\mathcal{R}$

Rules application 1 $\mathcal{R}(S_0) = R_0, S_1$

Rules application 2 $\mathcal{R}(S_0 \cup S_1) = R_1, S_2$

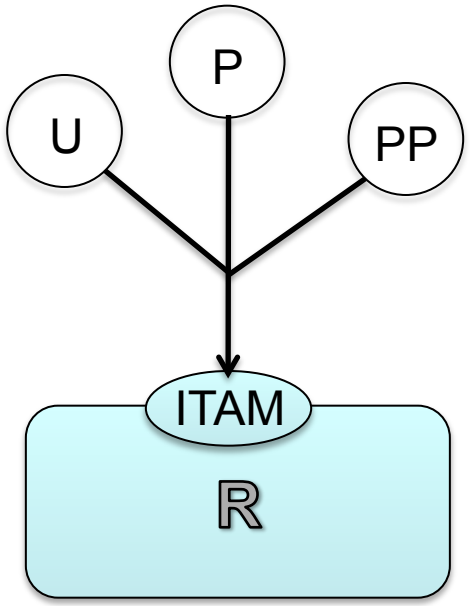
....

Rules application n $\mathcal{R}(S_n) = R_{n+1}, S_{n+1}$

Termination Terminate if $S_n = S_{n+1}$

Model: species S_n and reactions R_{n+1}

Models and SBGN-ER are sometimes orthogonal, and annotations can connect them!



R(ITAM~U) <-> R(ITAM~P) p,d

R(ITAM~P) <-> R(ITAM~PP) 0.1*p,0.1*d

R(ITAM~PP) -> R(ITAM~U) 0.01*d

How SBGN-ER can handle combinatorial complexity?

Epidermal growth factor receptor (EGFR)

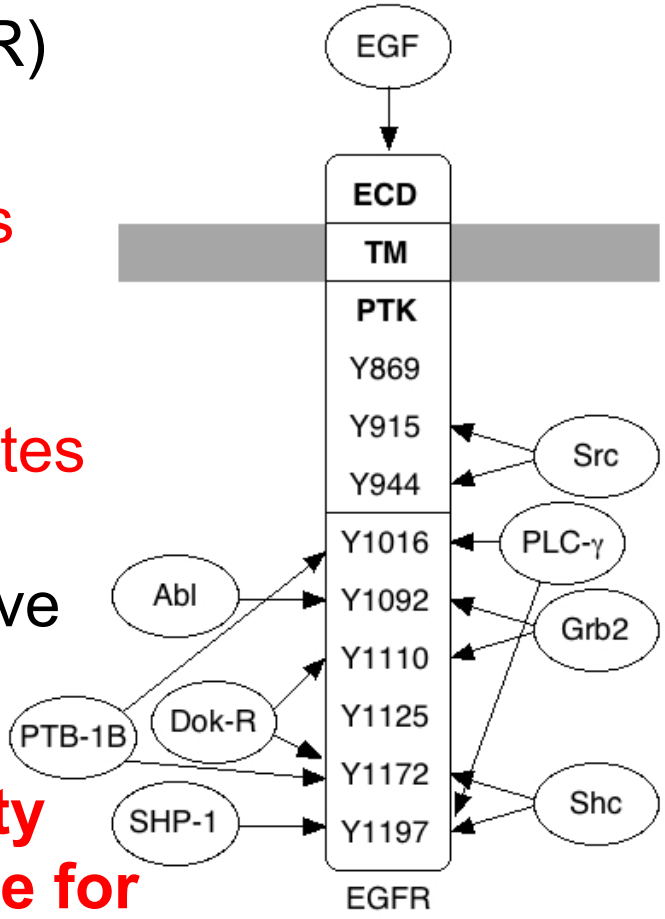
9 sites ⇒ 2^9=512 phosphorylation states

Each site has ≥ 1 binding partner

⇒ more than 3^9=19,683 total states

EGFR must form *dimers* to become active

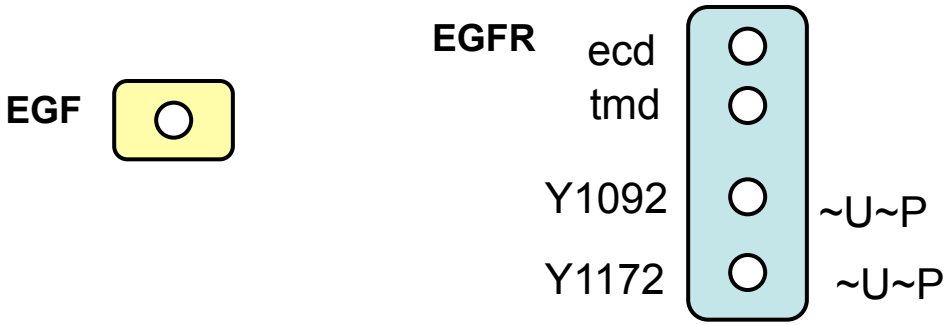
⇒ more than 1.9×10^8 states



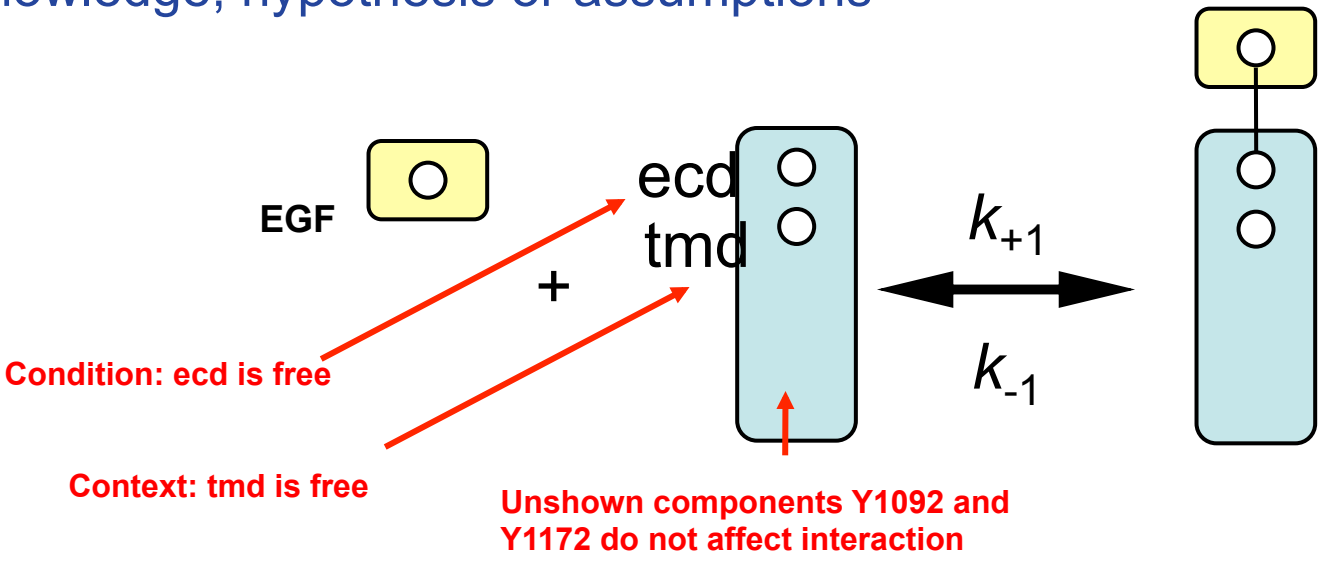
…but the number of entities and entity relationships is relatively small – case for SBGN-ER and rule0based modeling.

Rule-based approach

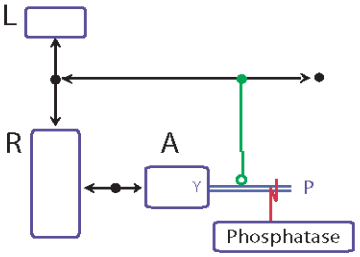
Biomolecules represented as collections of functional components



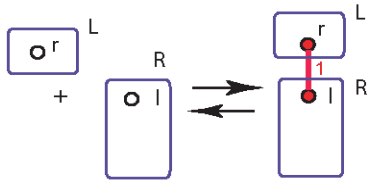
System evolves by reaction rules, that specify which biomolecules and their components affect kinetics of interactions. Rules correspond to knowledge, hypothesis or assumptions



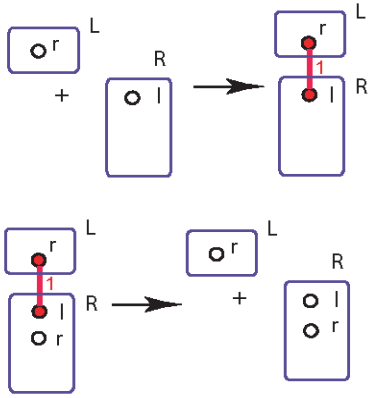
(a)



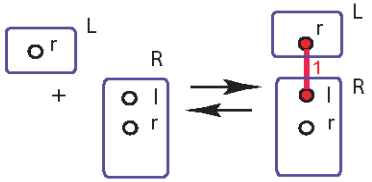
(b1) Ligand-binding independent on dimerization



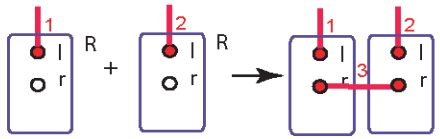
(b2) Ligand binds to any receptor, but can not dissociate in a dimer



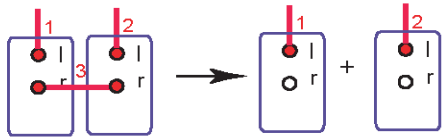
(b3) Ligand can interact with monomers only



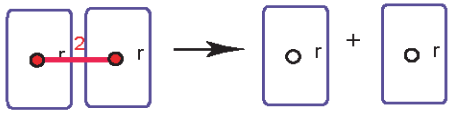
(c1) Dimer formation is ligand-induced



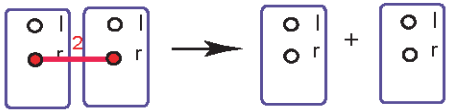
(c2) Dimer can break-up only when both ligands are present



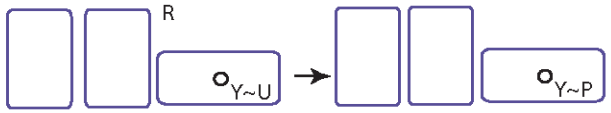
(c2) Dimer break-up is spontaneous



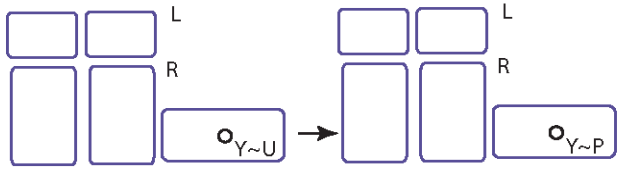
(c4) Dimer can break-up only after both ligand are gone.



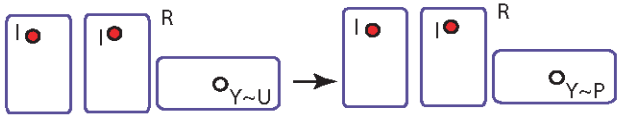
(d1) A is phosphorylated in a dimer



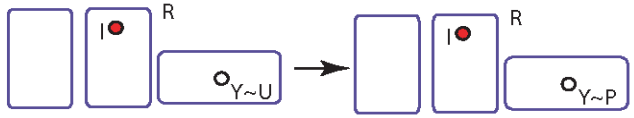
(c2) Phosphorylation requires 2 ligands L



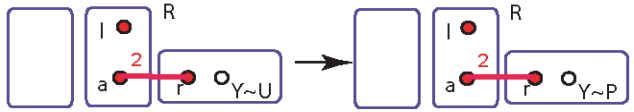
(d3) Phosphorylation requires two ligands



(d4) Phosphorylation requires at least one ligand

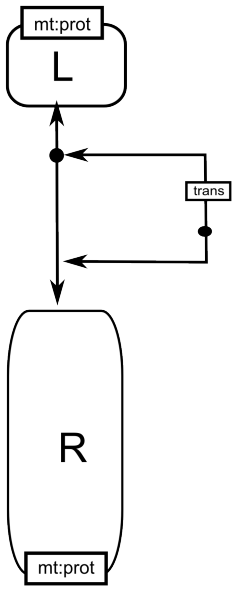


(d5) Explicit requirement which ligand is required

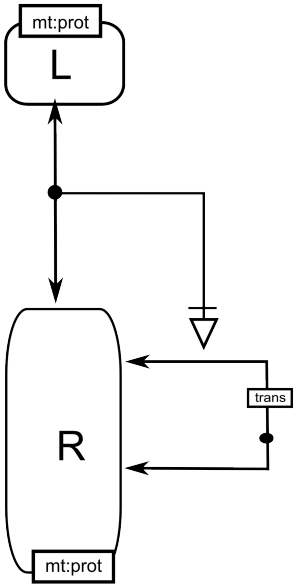


Specifying stoichiometry in ER is a problem…

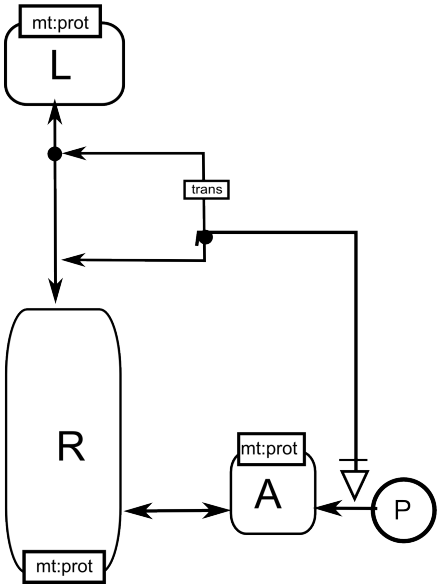
Two ligands are required for dimerization



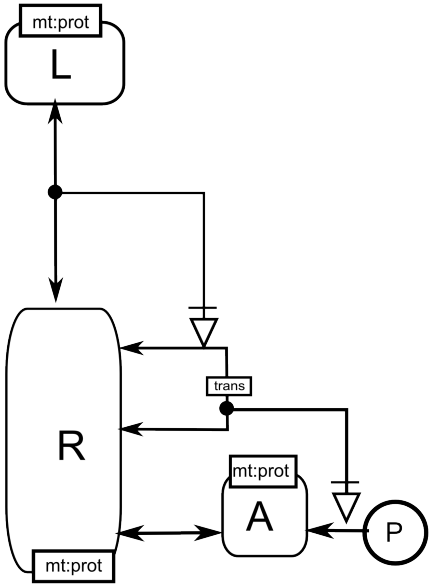
At least one ligand is required for dimerization



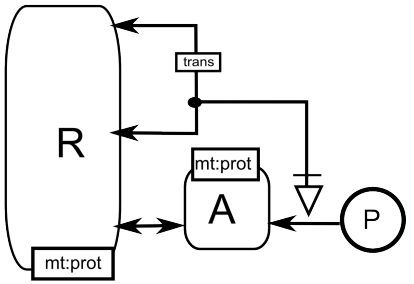
Two ligands are necessary for phosphorylation



One ligands is required for phosphorylation

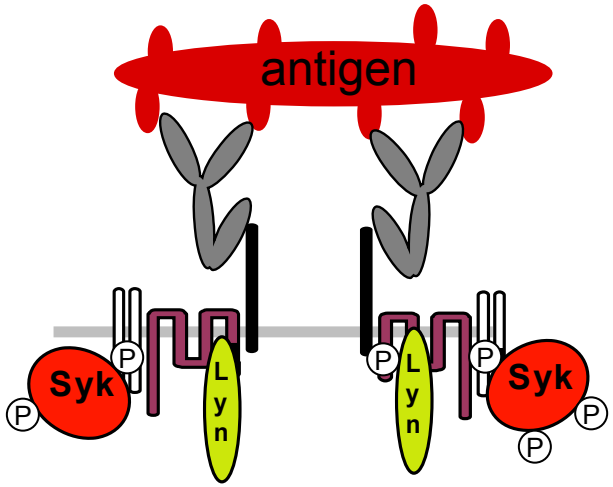


Two receptors are required for phosphorylation

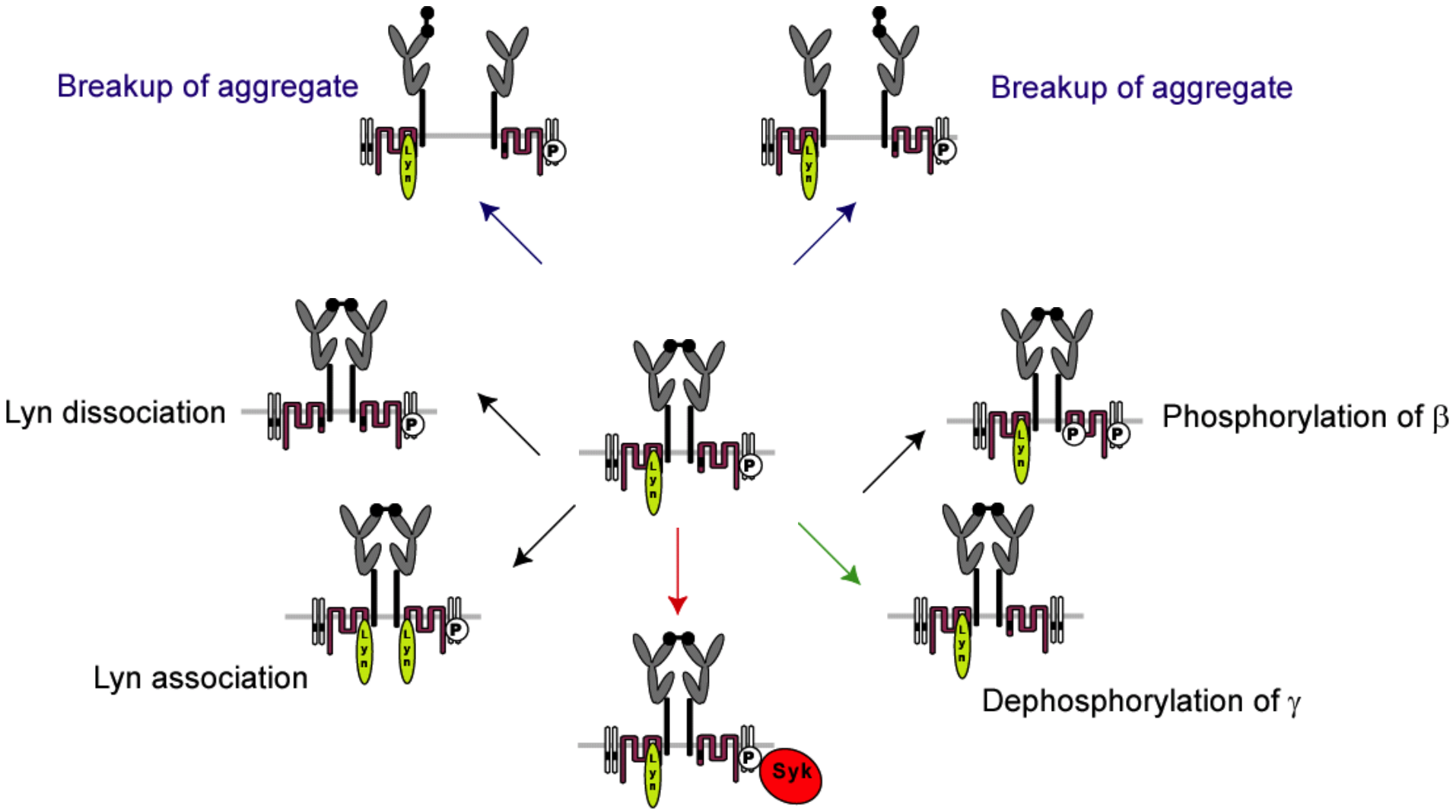


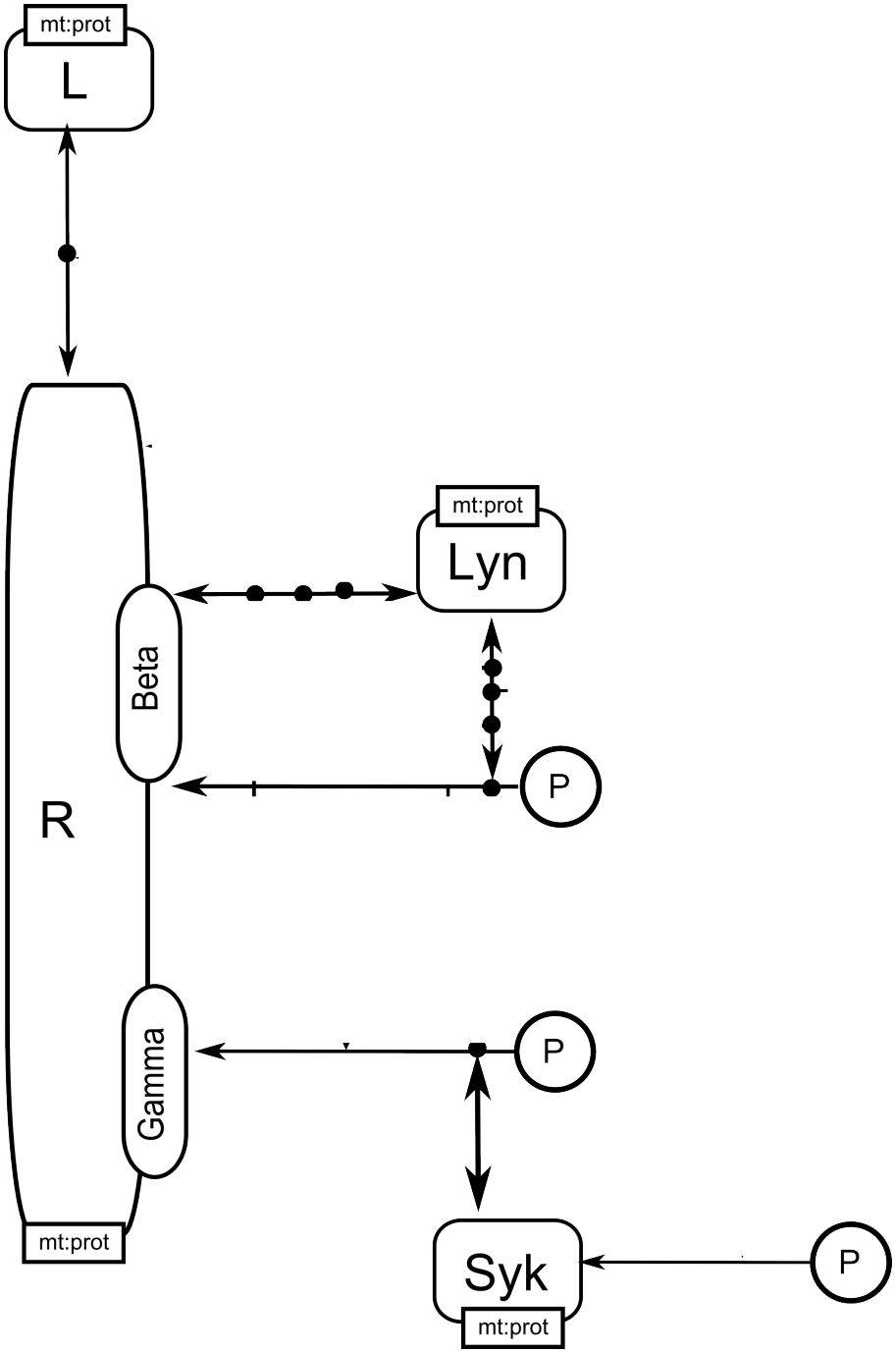
Early Events in FcεRI receptor Signaling

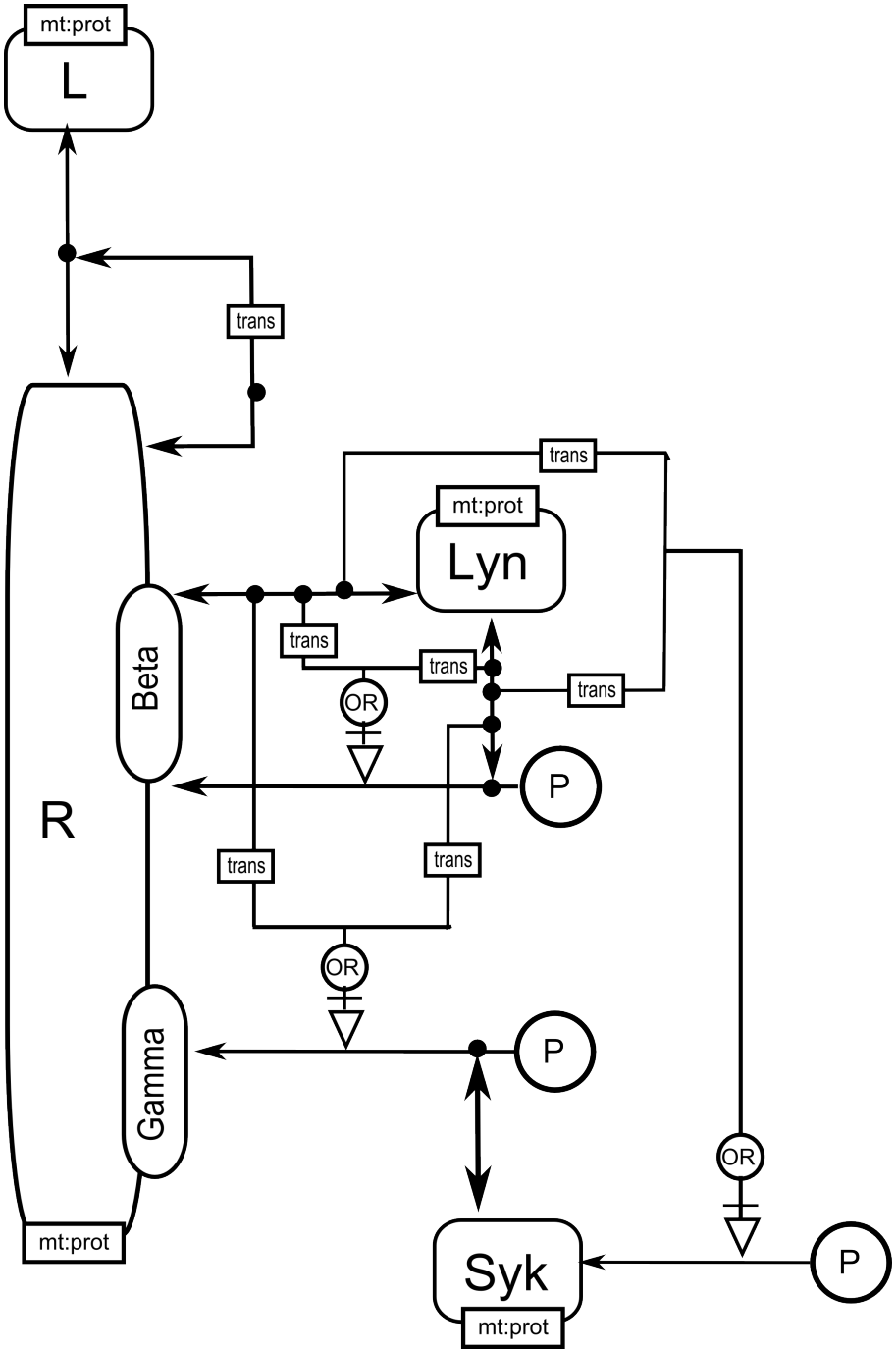
1. Multivalent antigen binds to IgE on cell surface forming aggregates
2. Tyrosine kinase Lyn associates with receptors and **transphosphorylates** ITAM tyrosines
3. Phosphorylated ITAMs recruit Syk and additional Lyn
4. Syk is transphosphorylated by Lyn or Syk
5. Phosphorylation of Syk is critical for downstream events ("activation")



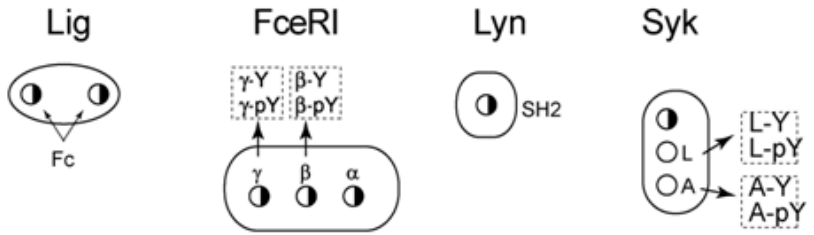
Not a pathway!




mt:prot
L
mt:prot
Lyn
Beta
P
R
Gamma
P
mt:prot
Syk
P
mt:prot

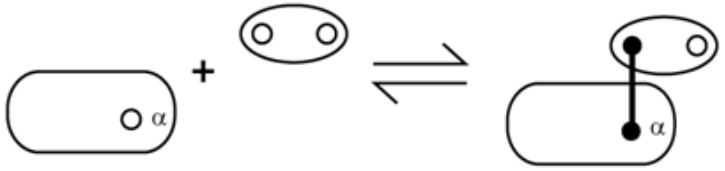

mt:prot
L
trans
trans
mt:prot
Lyn
Beta
trans
trans
trans
OR
P
R
trans
trans
OR
Gamma
P
OR
mt:prot
Syk
P
mt:prot

Molecules



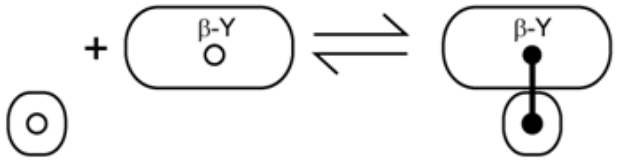
Reaction Rules

1. Ligand binding

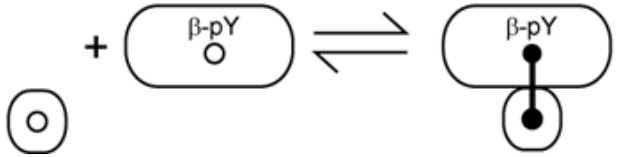


2. Ligand-induced aggregation

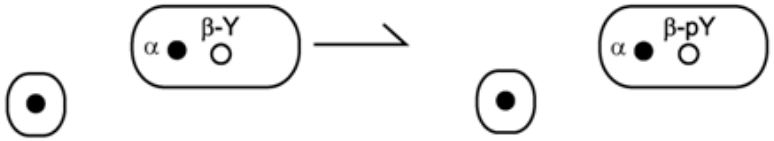
3. Binding of Lyn to unphosphorylated receptor



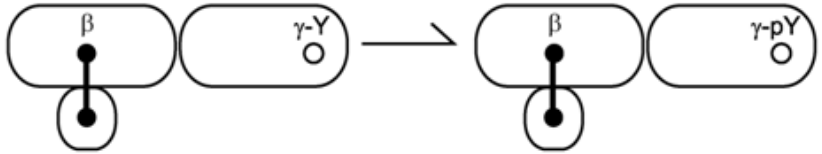
4. Binding of Lyn to phosphorylated receptor



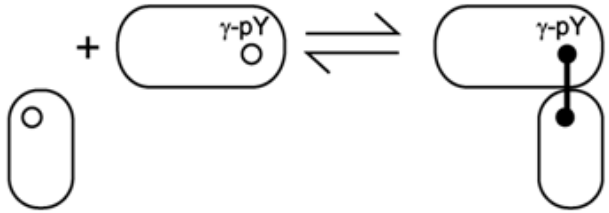
5. Transphosphorylation of β by Lyn



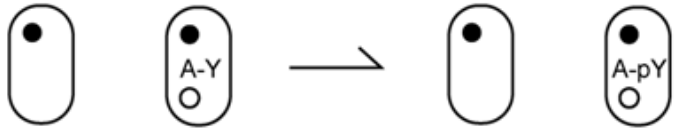
6. Transphosphorylation of γ by Lyn



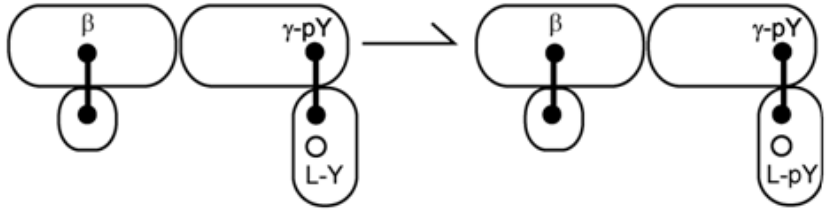
7. Binding of Syk to phosphorylated receptor

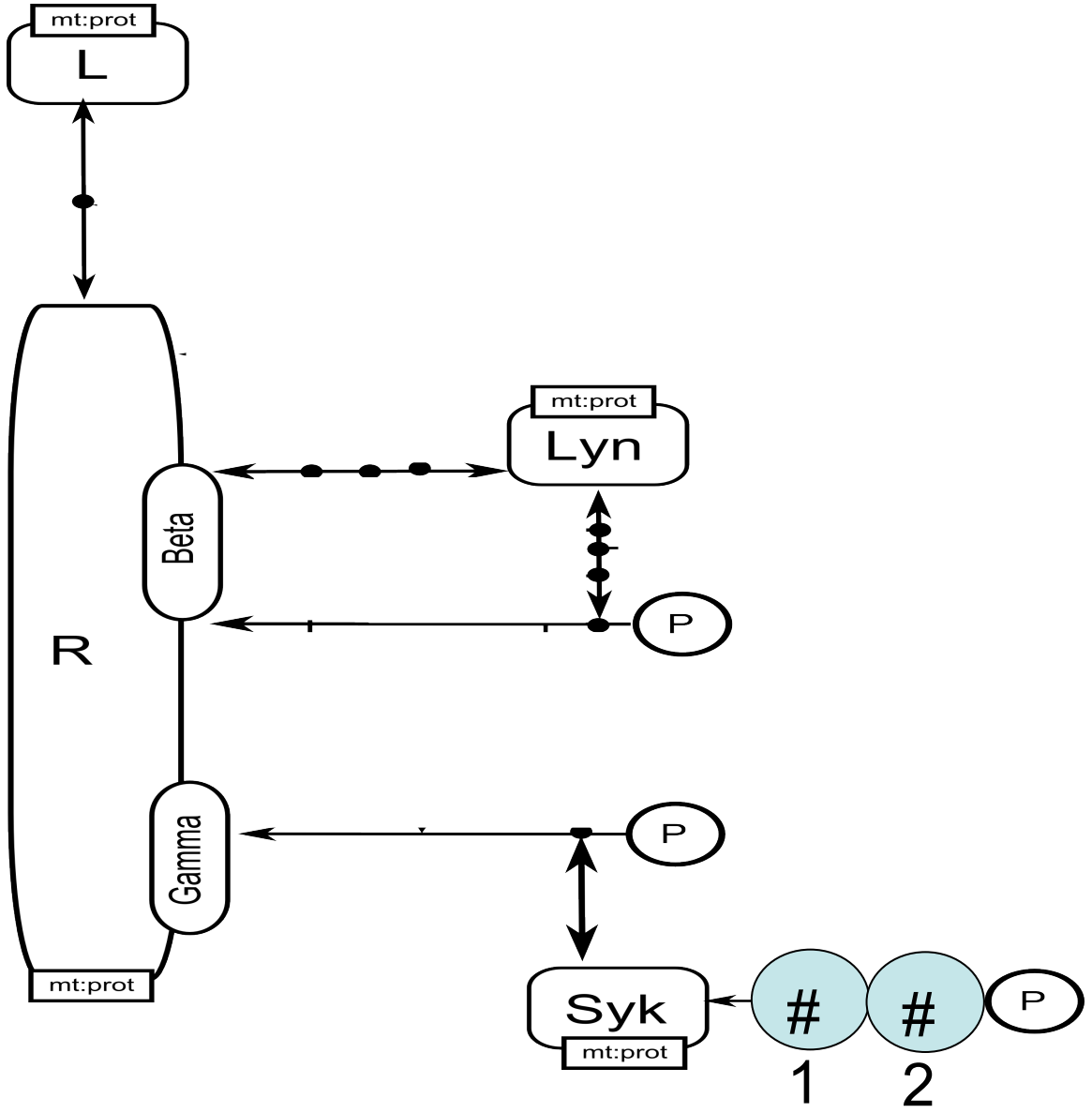


8. Transphosphorylation of Syk by Syk



9. Transphosphorylation of Syk by Lyn



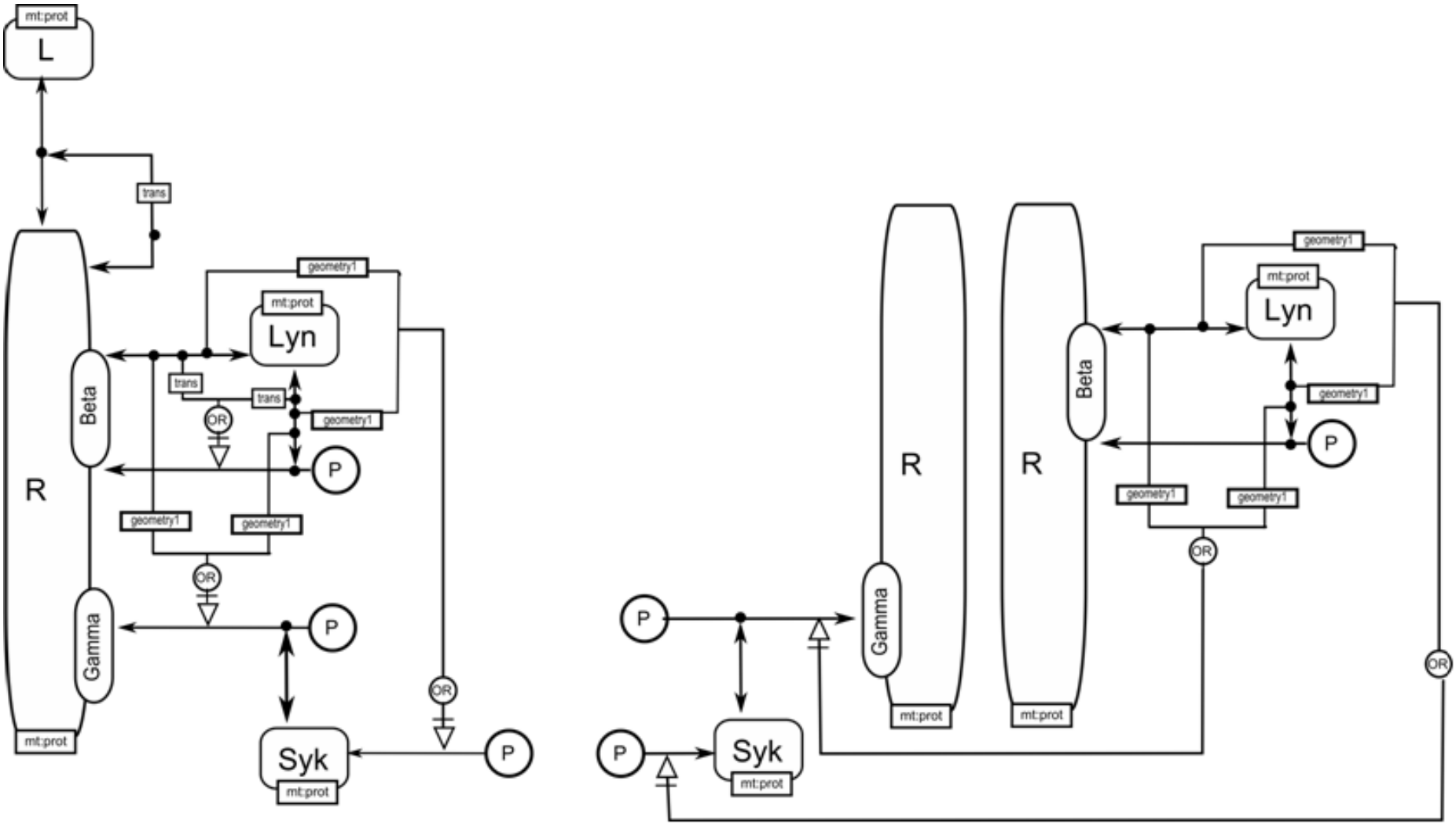


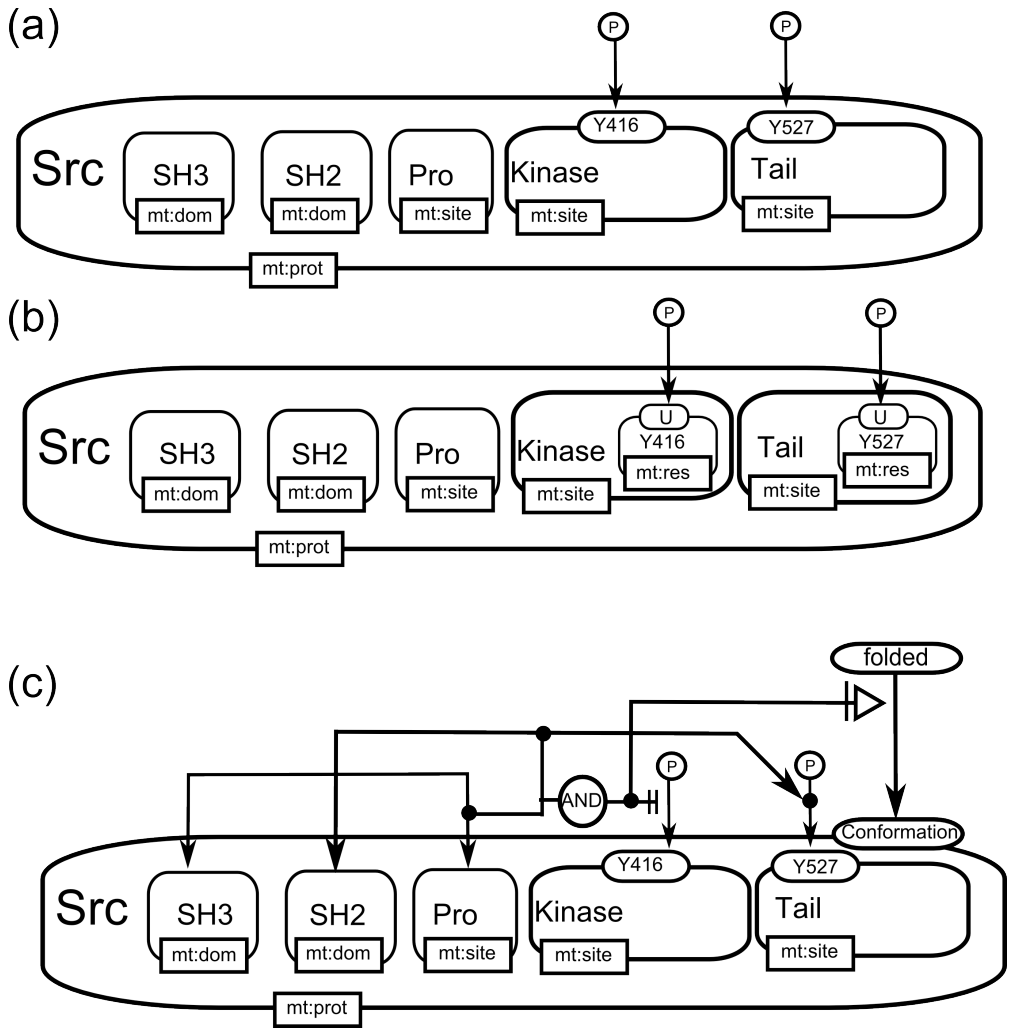
#1: R().R().Syk(Y~U) -> R().R().Syk(Y~P)

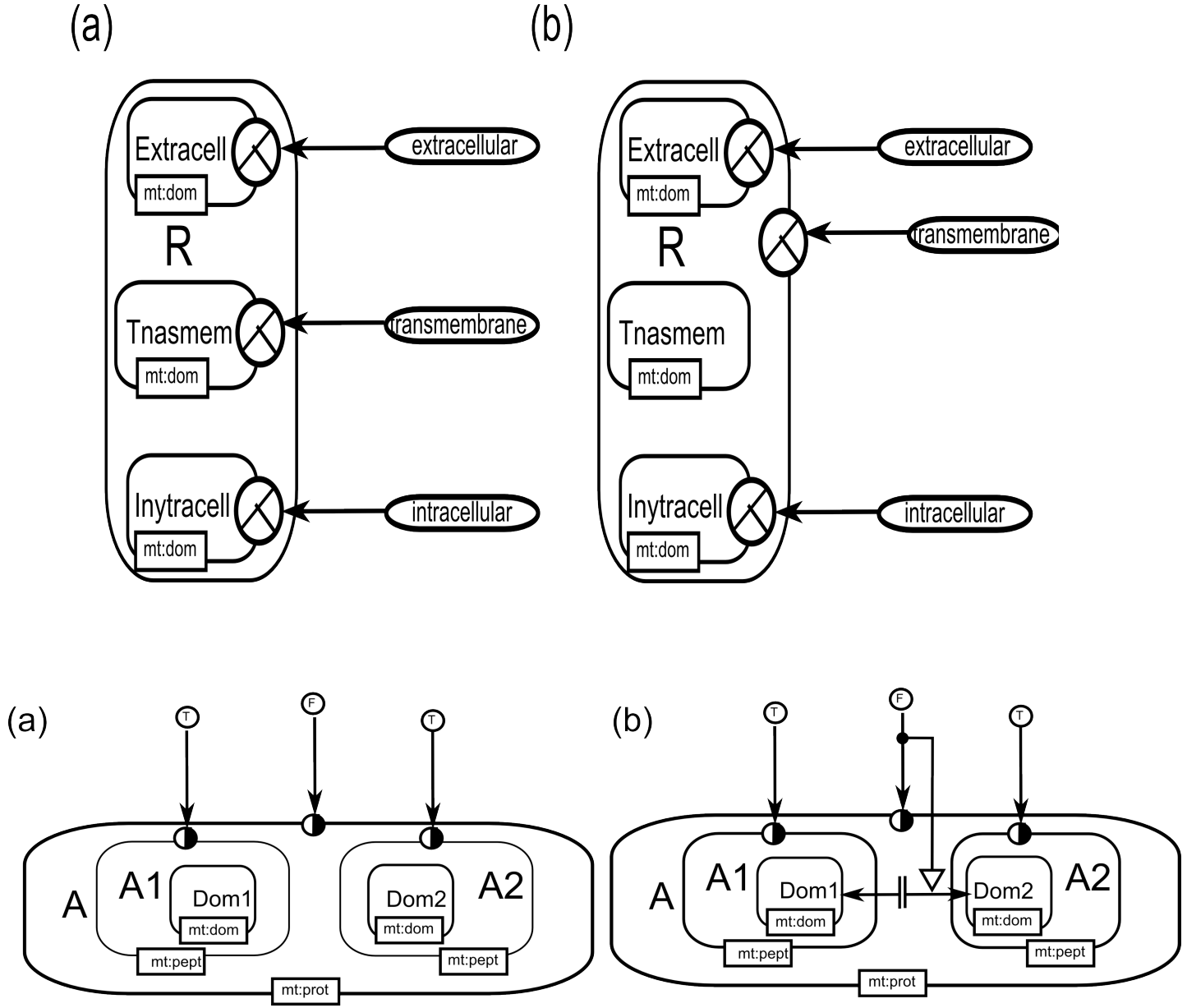
Issues

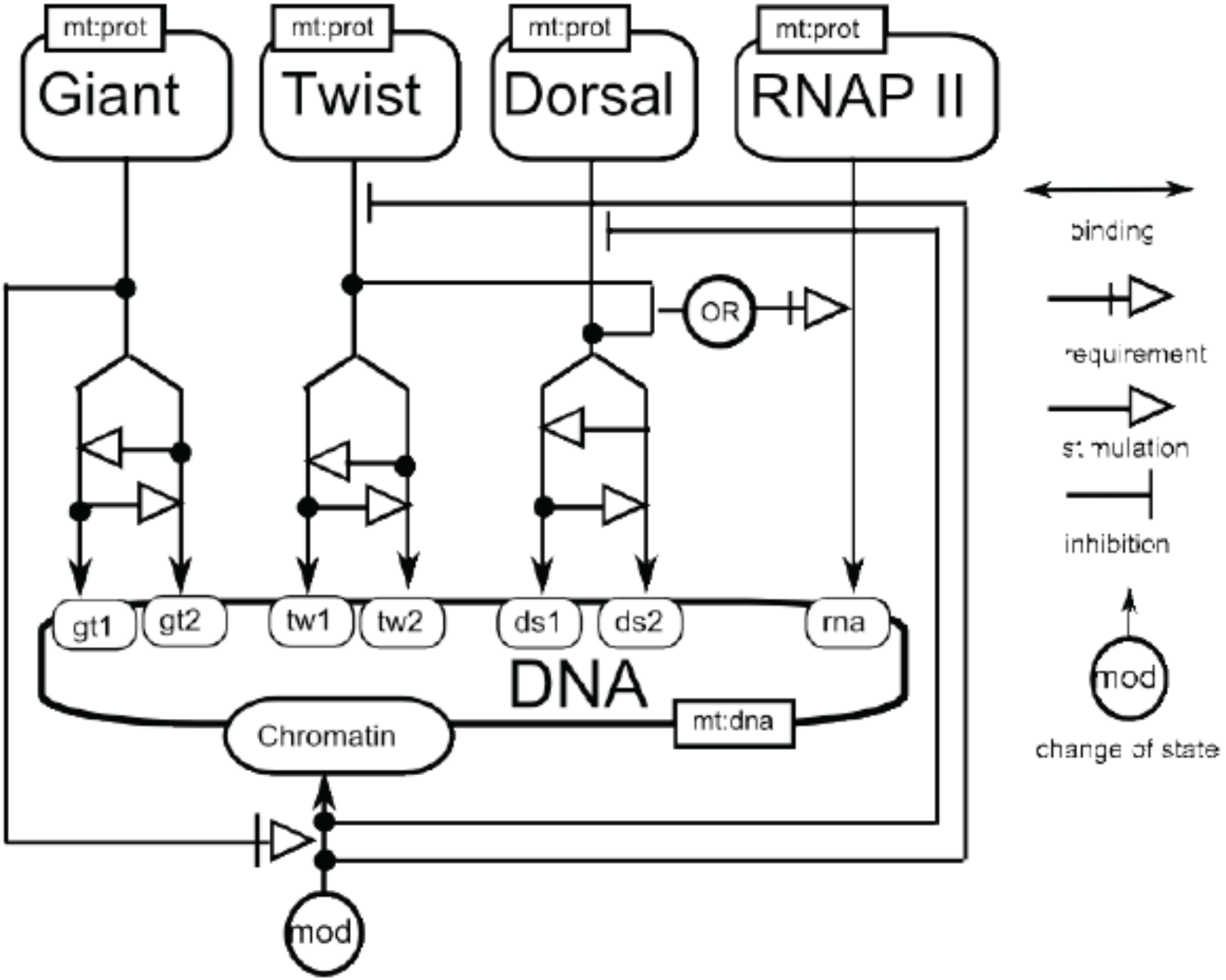
- Geometry is often essential, but cis and trans are not enough to express it.
- Separate interactions often require different context. Showing it on the same diagram is undesirable. How can we show what is essential and what is context?
- Domains are required.

Displaying oligomers




(a)
P
P
Src
SH3
mt:dom
SH2
mt:dom
Pro
mt:site
Y416
Kinase
mt:site
Y527
Tail
mt:site
mt:prot
(b)
P
P
Src
SH3
mt:dom
SH2
mt:dom
Pro
mt:site
U
Y416
mt:res
Kinase
mt:site
U
Y527
mt:res
Tail
mt:site
mt:prot
(c)
folded
AND
P
P
Conformation
Src
SH3
mt:dom
SH2
mt:dom
Pro
mt:site
Y416
Kinase
mt:site
Y527
Tail
mt:site
mt:prot


(a)
(b)
Extracell
mt:dom
R
Tnasmem
mt:dom
Inytracell
mt:dom
extracellular
transmembrane
intracellular
(a)
(b)
T
F
T
A
A1
Dom1
mt:dom
mt:pept
Dom2
mt:dom
mt:pept
A2
mt:prot


mt:prot
Giant
mt:prot
Twist
mt:prot
Dorsal
mt:prot
RNAP II
OR
gt1
gt2
tw1
tw2
ds1
ds2
rna
DNA
Chromatin
mt:dna
mod
binding
requirement
stimulation
inhibition
mod
change of state

Suggestions for SBGN

- Strict rules for annotations!
- Different levels of details (like MIM): Explicit, Heuristic, Combinatorial.
- Separate interactions often require different context. Showing it on the same diagram is undesirable. How can we show what is essential and what is context?
- Think about human vs machine readability.

SBGN-ER

1. SBGN-ER for pathway elements, protein pages, etc.
2. Different levels of details (like MIM): Explicit, Heuristic, Combinatorial.
3. **Logic nodes AND, OR for simultaneous events and making a map more concise - VOTE**
4. Oligomers, topology - submaps
5. Clones
6. **Strict rules for annotations, legends: uncertaincy, data - VOTE**
7. Submaps, compositionality
8. Hybrid maps: using PD, ER & AF together, linking different maps