SBGN-ER vs rule-based modeling

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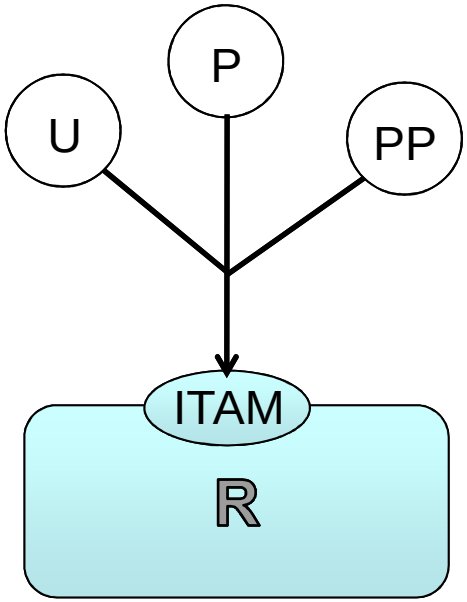
Models and SBGN-ER are sometimes orthogonal, and annotations can connect them!



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)

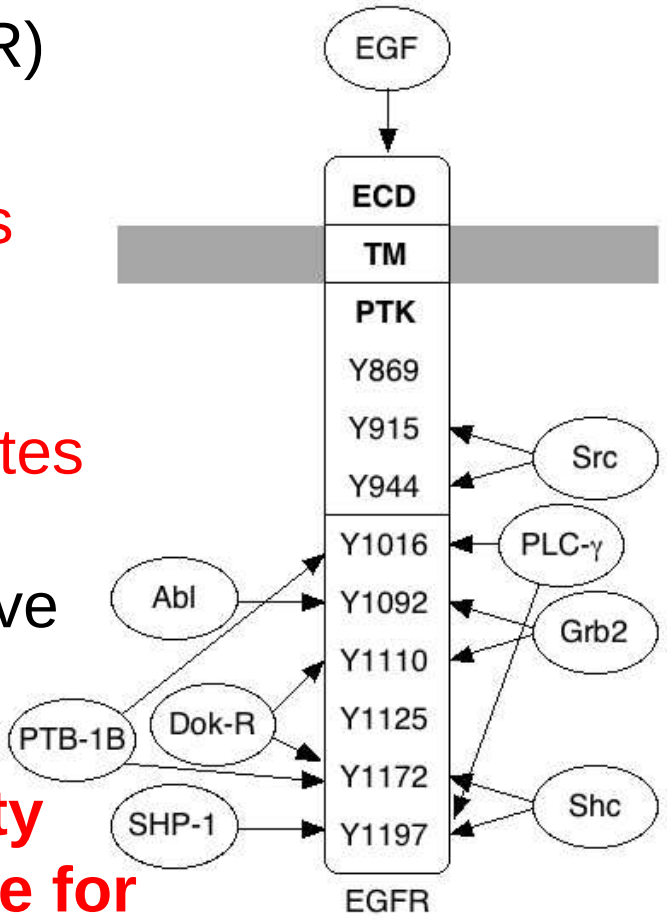
9 sites $\Rightarrow$ 2^9=512 phosphorylation states

Each site has ≥ 1 binding partner

$\Rightarrow$ more than 3^9=19,683 total states

EGFR must form *dimers* to become active

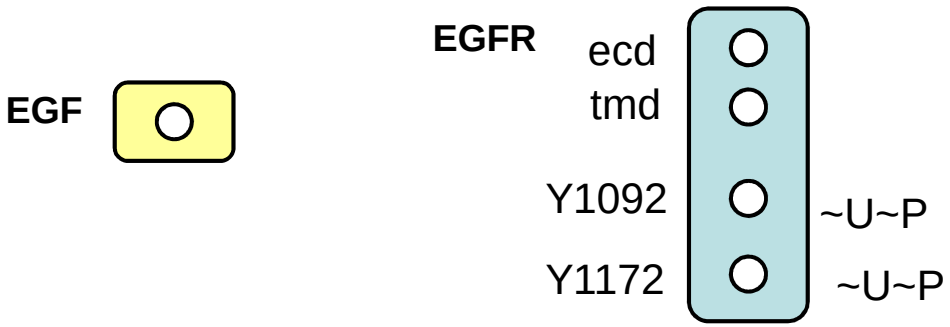
$\Rightarrow$ more than 1.9×10^8 states



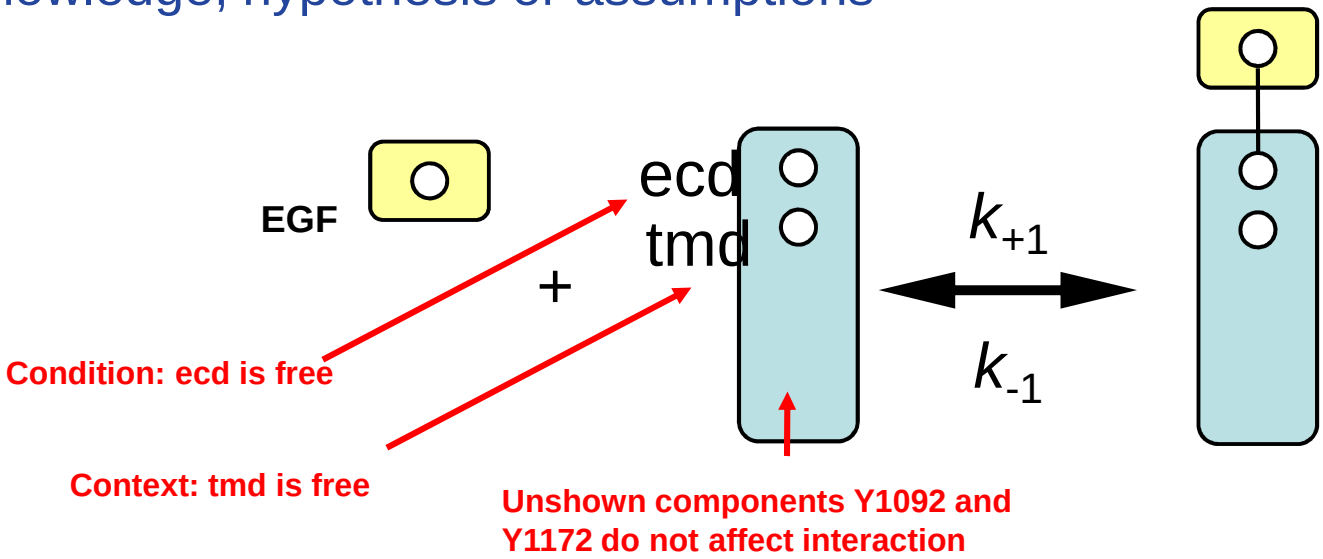
…but the number of entities and entity relationships is relatively small – case for SBGN-ER and rule0based modeling.

Rule-based approach

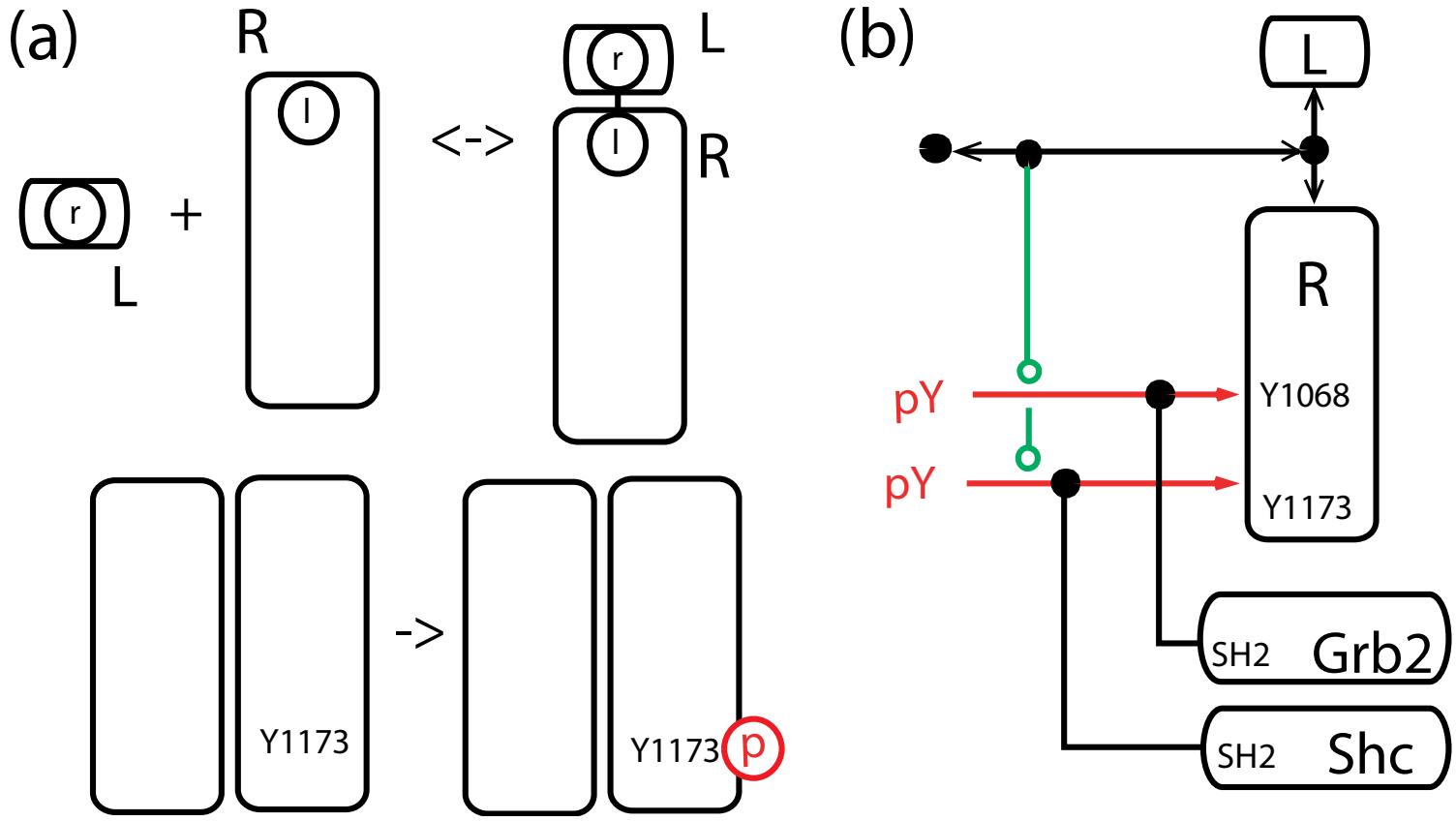
Biomolecules represented as collections of functional components



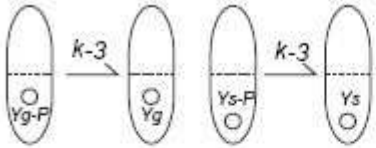
System evolves by reaction rules, that specify which biomolecules and their components affect kinetics of interactions. Rules correspond to knowledge, hypothesis or assumptions



Models and SBGN-ER seem to work perfectly together!

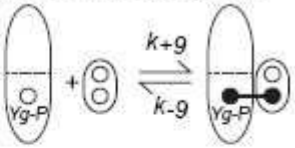


Dephosphorylation of unprotected tyrosine residues



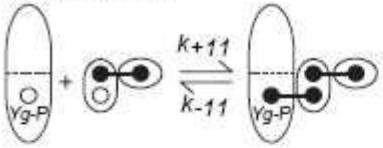
R(,*,1,*)* <-> R(*,*,0,*)**
R(,*,*,1)* <-> R(*,*,*,0)**

Grb2 binding to receptor phosphotyrosine



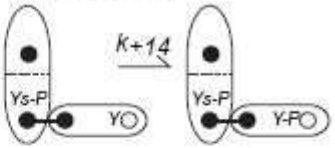
R(,*,1,*)* + Grb2 <-> R(*,*,2,*)**

Grb2-Sos binding to receptor phosphotyrosine



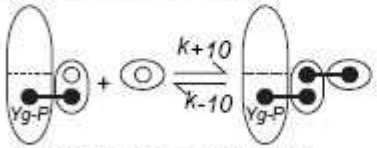
R(,*,1,*)* + Grb2-Sos <-> R(*,*,3,*)**

Shc transphosphorylation by receptor kinase



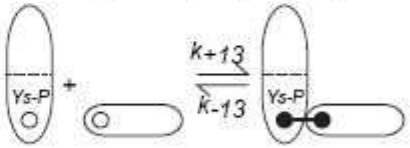
R(,*,*,2).* -> R(*,*,*,3).**

Sos binding to Grb2 associated with receptor phosphotyrosine



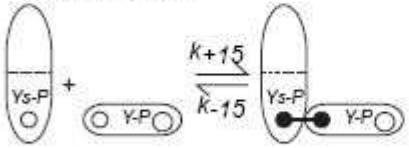
R(,*,2,*)* + Sos <-> R(*,*,3,*)**

Shc binding to receptor phosphotyrosine



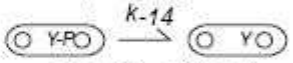
R(,*,*,1)* + Shc <-> R(*,*,*,2)**

ShcP binding to receptor phosphotyrosine



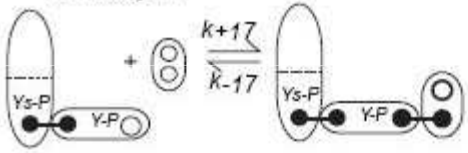
R(,*,*,1)* + ShcP <-> R(*,*,*,3)**

Shc dephosphorylation



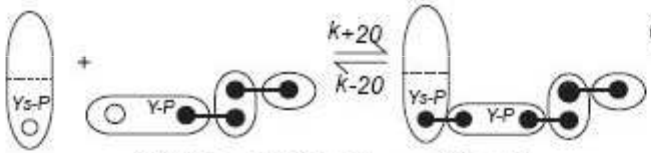
R(,*,*,3) -> R(*,*,*,2)*
ShcP-> Shc

Grb2 recruited to ShcP associated with receptor



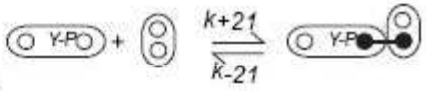
R(,*,*,2)* + Grb2 <-> R(*,*,*,4)**

Shcp-Grb2-Sos binding to receptor phosphotyrosine



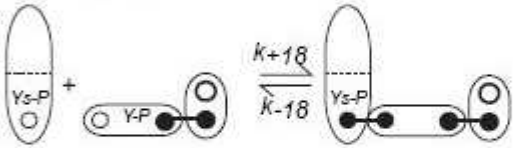
R(,*,*,1)* + ShcP-Grb2-Sos <-> R(*,*,*,5)**

ShcP and Grb2 binding in cytosol



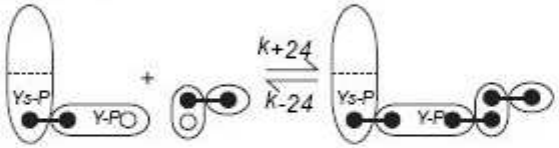
ShcP + Grb2 <-> ShcP-Grb2

ShcP-Grb2 binding to receptor phosphotyrosine



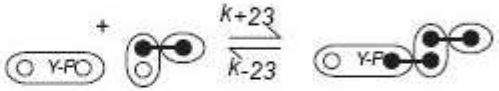
R(,*,*,1)* + ShcP-Grb2 <-> R(*,*,*,4)**

Grb2-Sos binding to ShcP associated with receptor phosphotyrosine



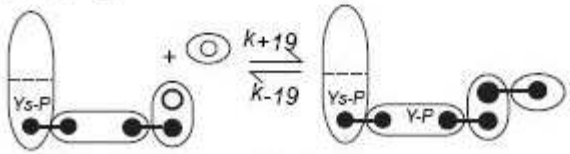
R(,*,*,3)* + Grb2-Sos <-> R(*,*,*,5)**

ShcP and Grb2-Sos binding in cytosol



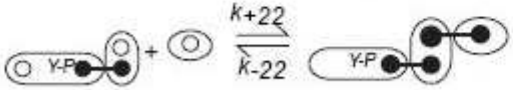
ShcP + Grb2-Sos <-> ShcP-Grb2-Sos

Sos binding to ShcP-Grb2 associated with receptor phosphotyrosine

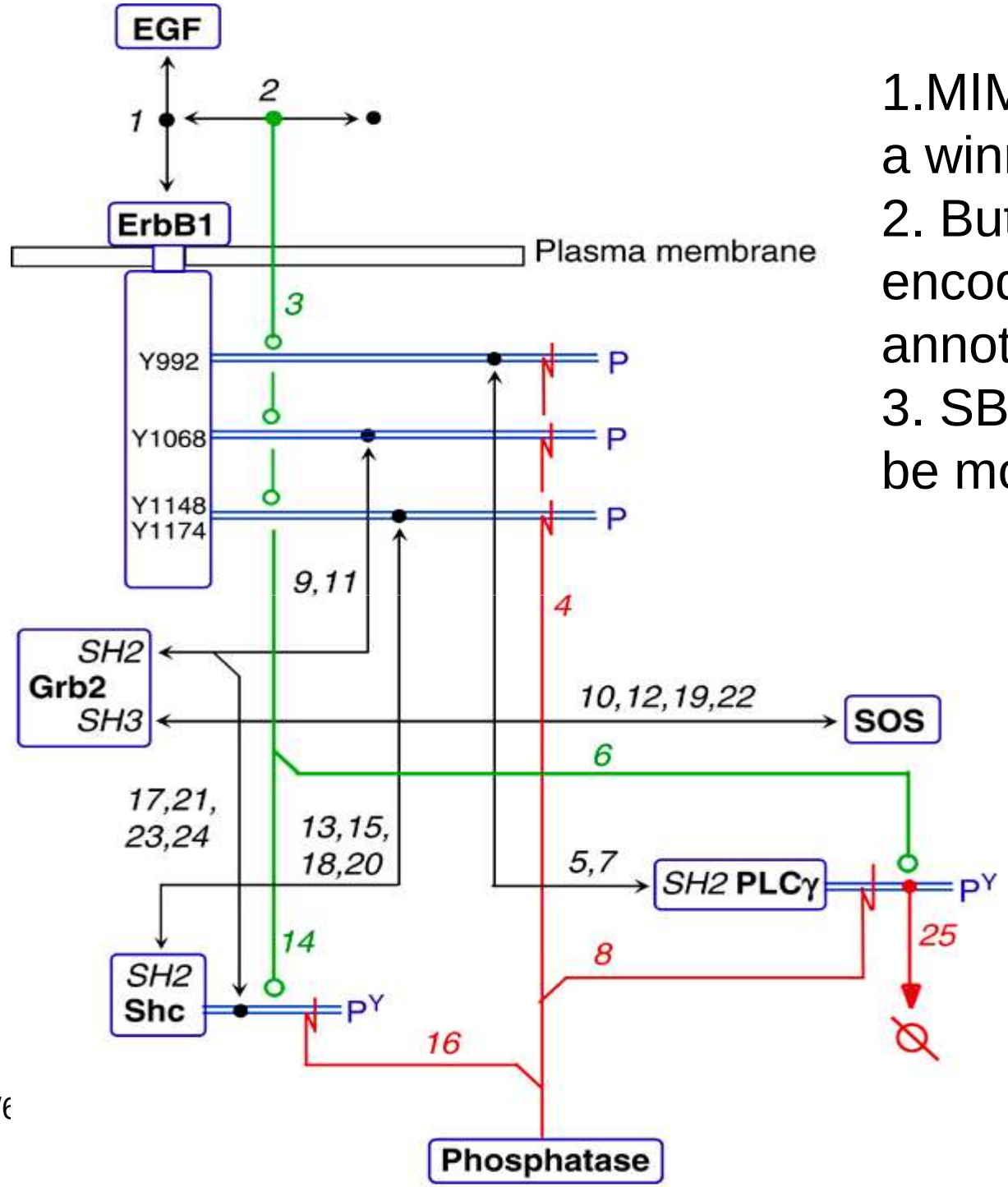


R(,*,*,4)* + Sos <-> R(*,*,*,5)**

ShcP-Grb2 and Sos binding in cytosol

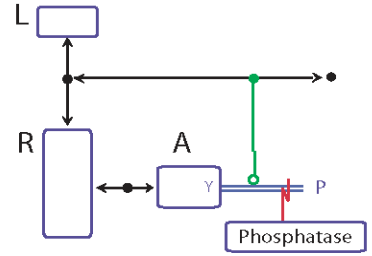


ShcP-Grb2 + Sos<-> ShcP-Grb2-Sos

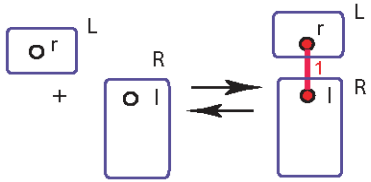


1.MIM seems to be a winner.
2. But details are encoded in annotations
3. SBGN-ER would be more cluttered…

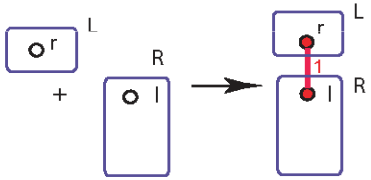
(a)

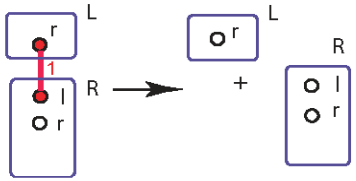


(b1) Ligand-binding independent on dimerization

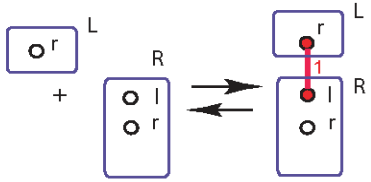


(b2) Ligand binds to any receptor, but can not dissociate in a dimer

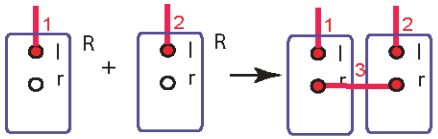




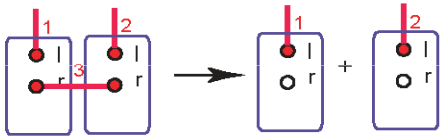
(b3) Ligand can interact with monomers only



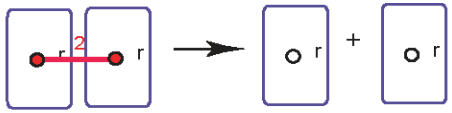
(c1) Dimer formation is ligand-induced



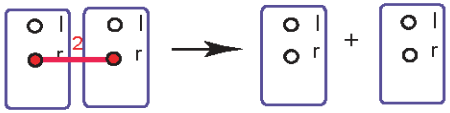
(c2) Dimer can break-up only when both ligands are present



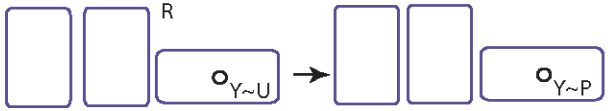
(c2) Dimer break-up is spontaneous



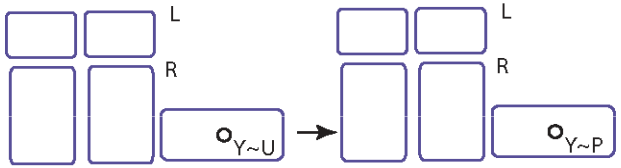
(c4) Dimer can break-up only after both ligand are gone.



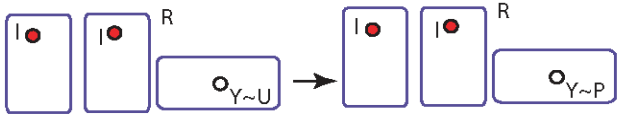
(d1) A is phosphorylated in a dimer



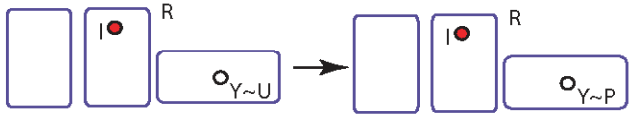
(c2) Phosphorylation requires 2 ligands L



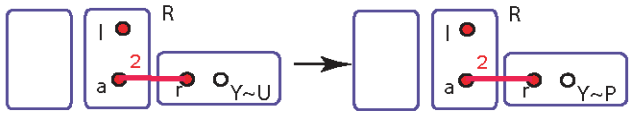
(d3) Phosphorylation requires two ligands



(d4) Phosphorylation requires at least one ligand

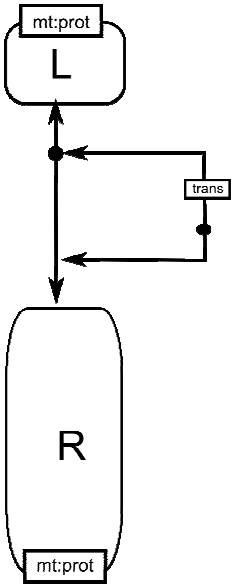


(d5) Explicit requirement which ligand is required

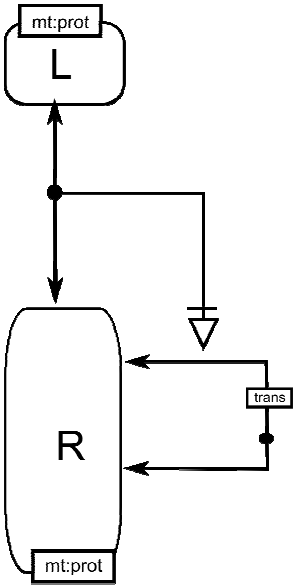


Specifying stoichiometry

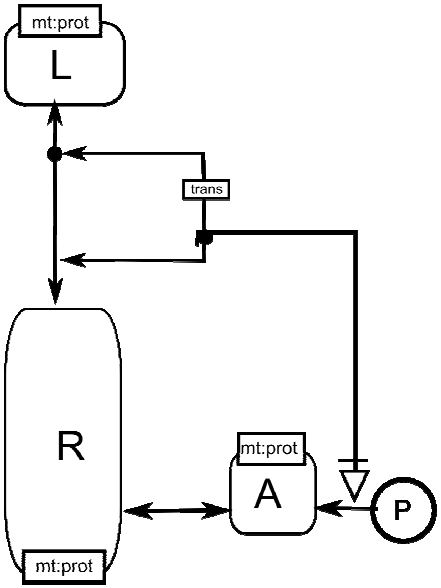
Two ligands are required for dimerization



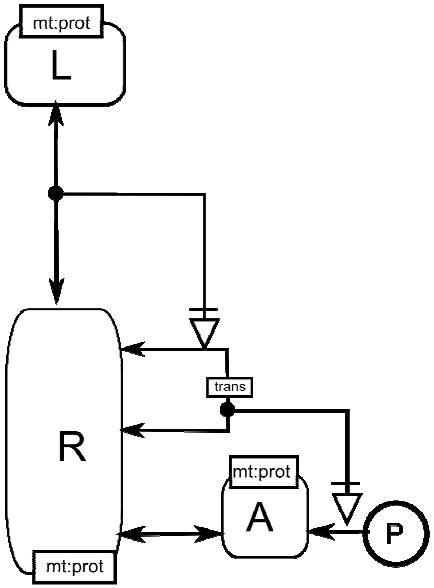
At least one ligand is required for dimerization



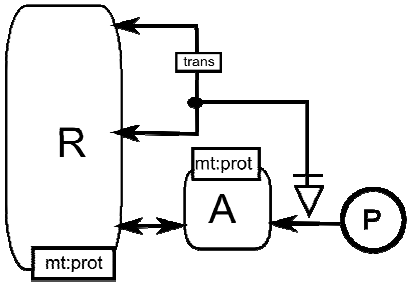
Two ligands are necessary for phosphorylation



One ligands is required for phosphorylation

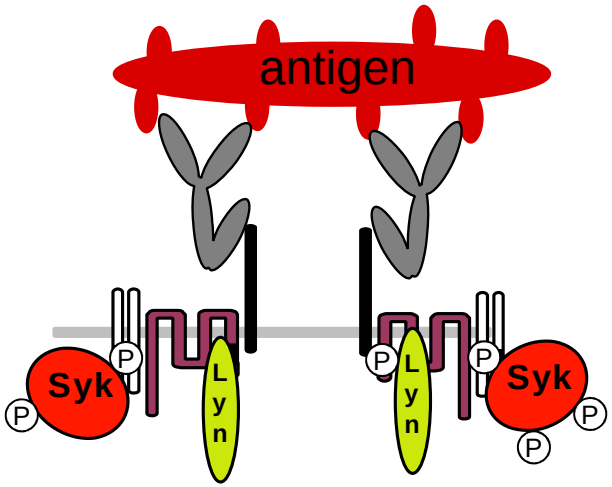


Two receptors are required for phosphorylation

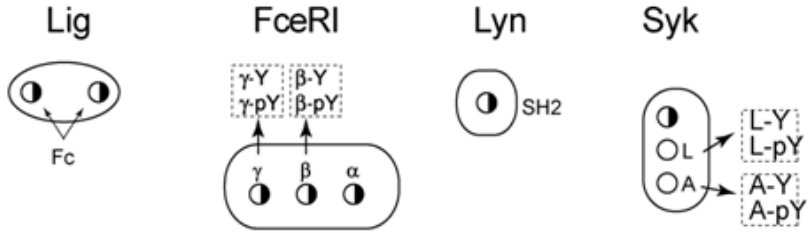


Early Events in FcεRI receptor Signaling

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”)

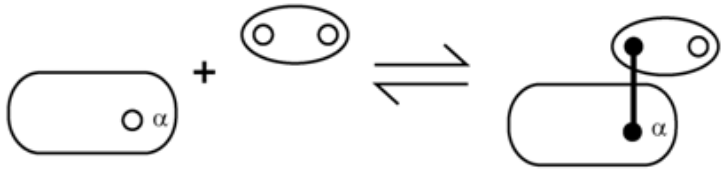


Molecules



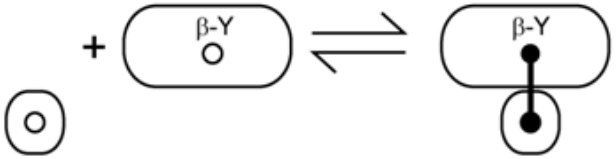
Reaction Rules

1. Ligand binding

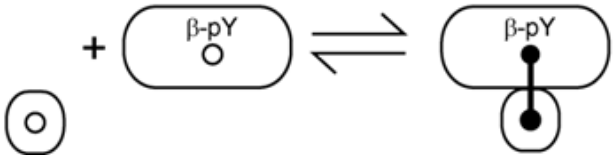


2. Ligand-induced aggregation

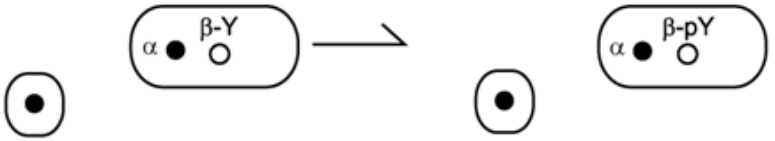
3. Binding of Lyn to unphosphorylated receptor



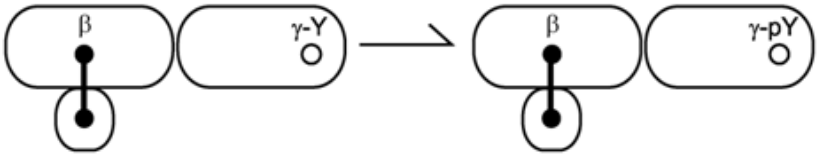
4. Binding of Lyn to phosphorylated receptor



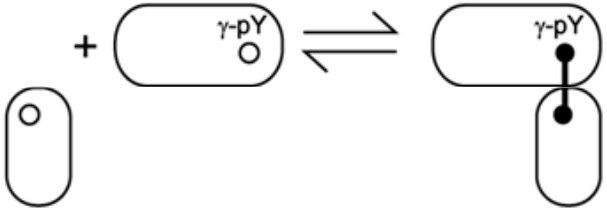
5. Transphosphorylation of β by Lyn



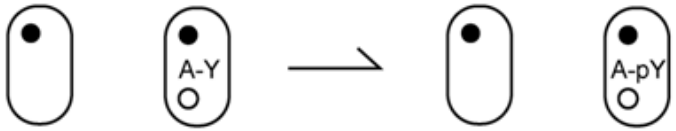
6. Transphosphorylation of γ by Lyn



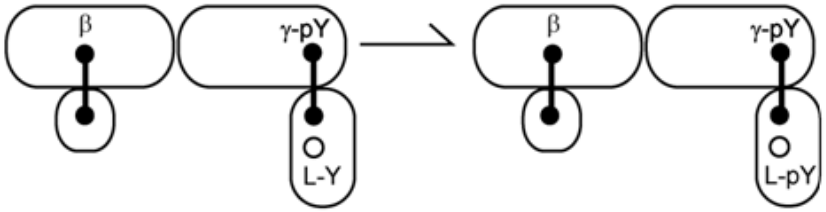
7. Binding of Syk to phosphorylated receptor

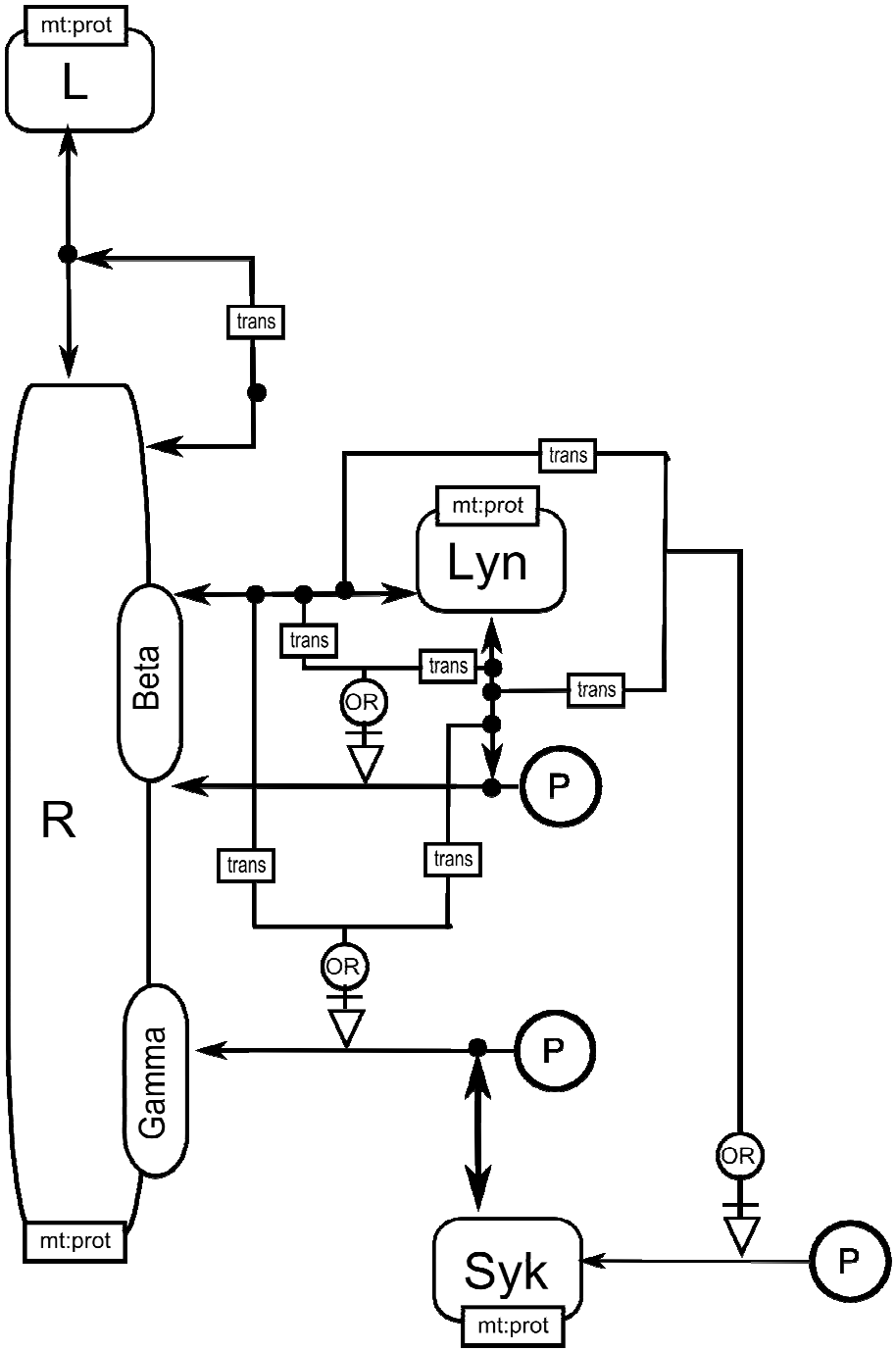


8. Transphosphorylation of Syk by Syk



9. Transphosphorylation of Syk by Lyn

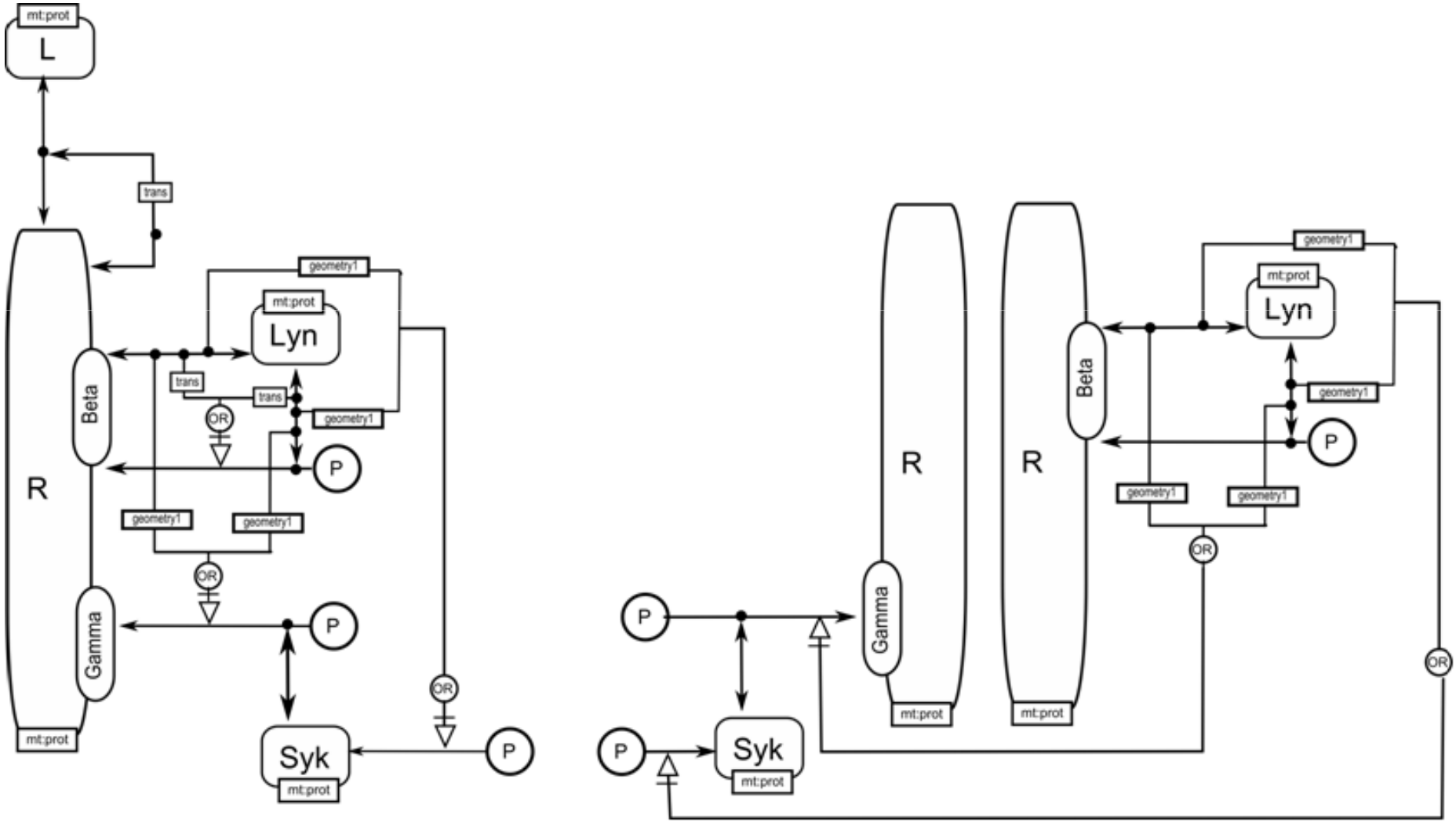



mt:prot
L
trans
R
Beta
trans
mt:prot
Lyn
trans
trans
trans
OR
P
trans
trans
OR
Gamma
P
mt:prot
OR
Syk
P
mt:prot

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.

Specifying topology



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.

Suggestions for libSBGN:

- Draw SBGN-PD for BioPAX
- Draw simplest unconditional ER diagrams – analogue of contact maps.