Visualization of Rule-based Modeling – Virtual Cell & Systems Biology Graphical Notations (SBGN) approaches

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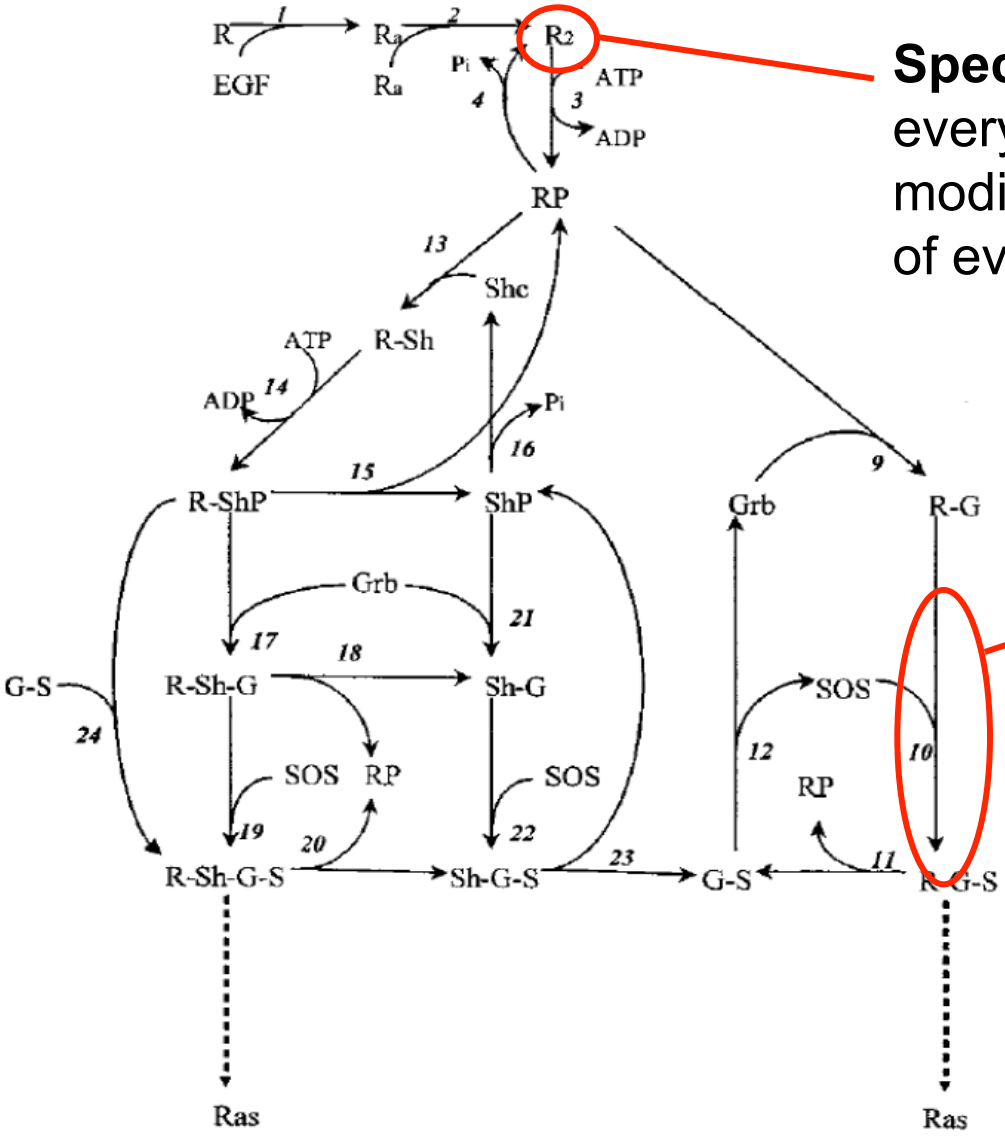
Acknowledgement

- Jim Schaff & Ion Moraru for brainstorming sessions
- Fei Gao and Dan Vasilescu for code implementation
- Stuart Moody and Anatoly Sorokin for discussions at SBGN meetings
- CCAM team
- SBGN community

A typical reaction network

18 species
34 reactions

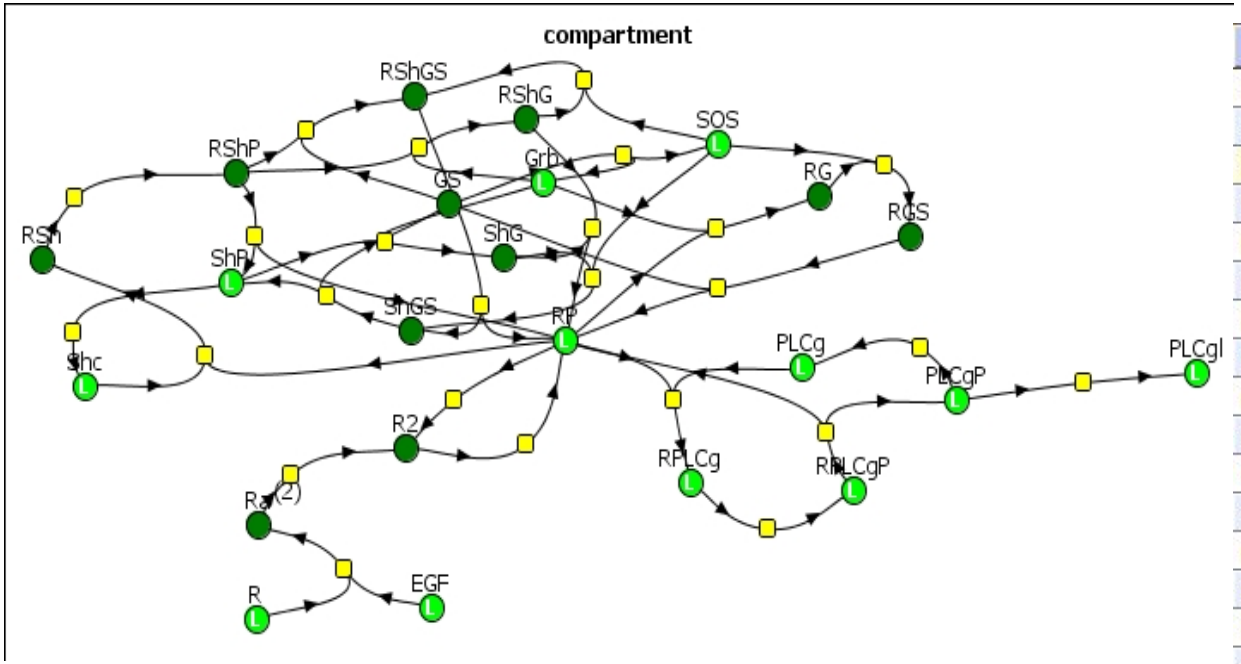


Species: One for every possible modification state of every complex

Reactions: One for every transition among species

Kholodenko et al., J. Biol. Chem. **274**, 30169 (1999)

Reaction network visualization



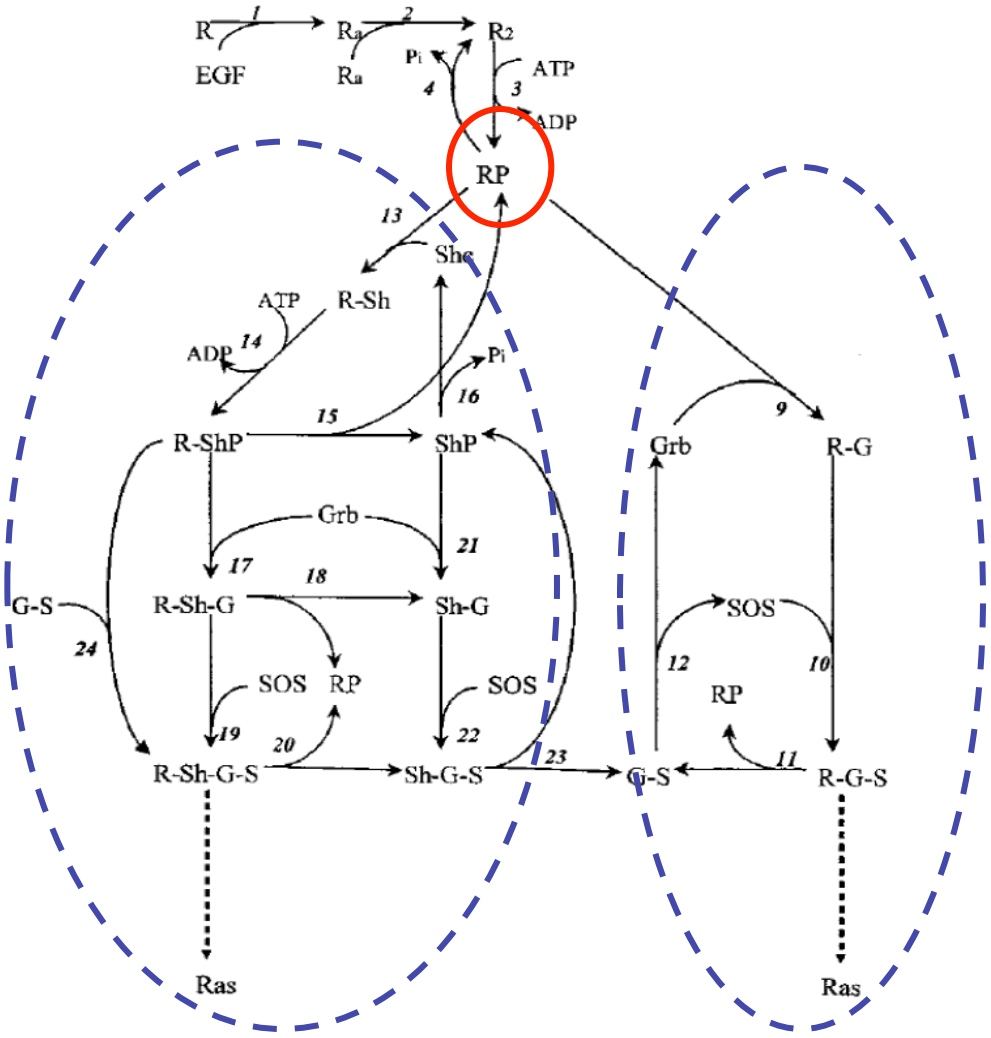
Reaction
EGF + R -> Ra
2Ra -> R2
R2 -> RP
RP -> R2
RP + PLCg -> RPLCg
RPLCg -> RPLCgP
RPLCgP -> RP + PLCgP
PLCgP -> PLCg
RP + Grb -> RG
RG + SOS -> RGS
RGS -> RP + GS
GS -> Grb + SOS
RP + Shc -> RSh
RSh -> RShP
RShP -> RP + ShP
ShP -> Shc
Grb + RShP -> RShG
RShG -> RP + ShG
SOS + RShG -> RShGS
RShGS -> RP + ShGS
Grb + ShP -> ShG
SOS + ShG -> ShGS
ShGS -> GS + ShP
GS + RShP -> RShGS
PLCgP -> PLCgI

VCell provides “minimalistic” description:

- –Bipartie graph (species and reaction nodes)
- –Single type of species nodes and two types of arrows
- –Many automatic layouts

Assumptions made

- **Phosphorylation inhibits dimer breakup**
  - No phosphorylated monomers
  - No association of monomers with other proteins complexes
  - To become dephosphorylated, all proteins should dissociate and dimer should break up
- **No individual phosphosites are considered**
  - Phosphorylation is identical for all phosphosites
  - Same phosphorylation timecourses
  - At most single adapter protein can bind to a dimer



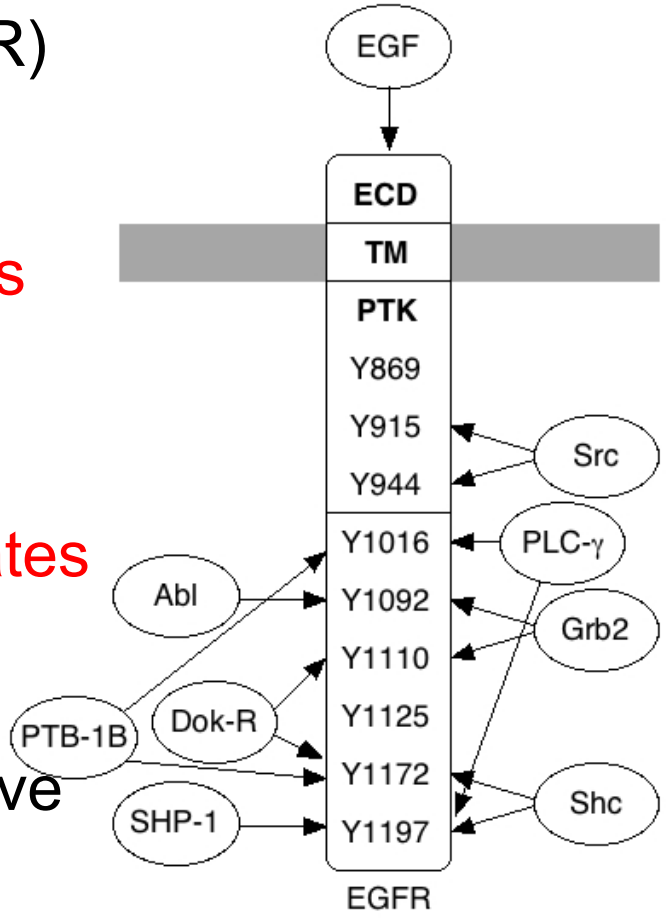
The problem: multiplicity of sites and binding partners gives rise to combinatorial complexity

Epidermal growth factor receptor (EGFR)

9 sites ⇒ 2^9=512 phosphorylation states

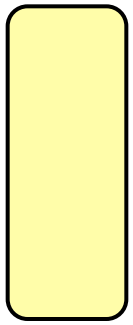
Each site has ≥ 1 binding partner
⇒ more than 3^9=19,683 total states

EGFR must form *dimers* to become active
⇒ more than 1.9×10^8 states

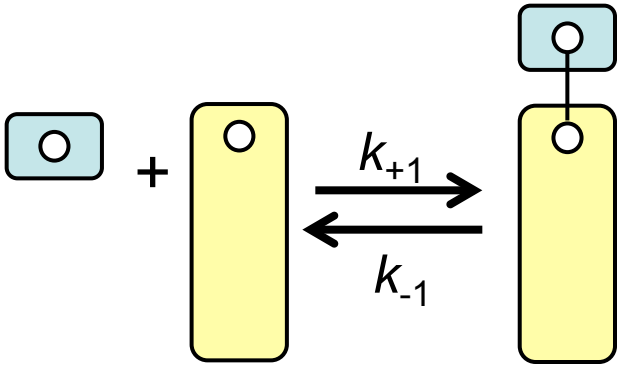


Molecules, components and rules

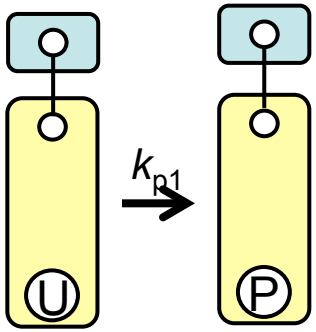
Molecules



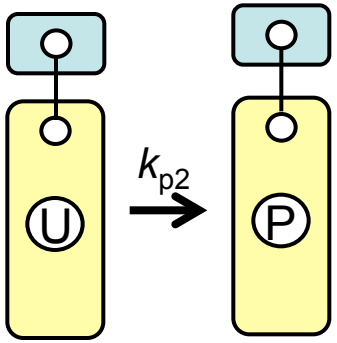
Rule 1



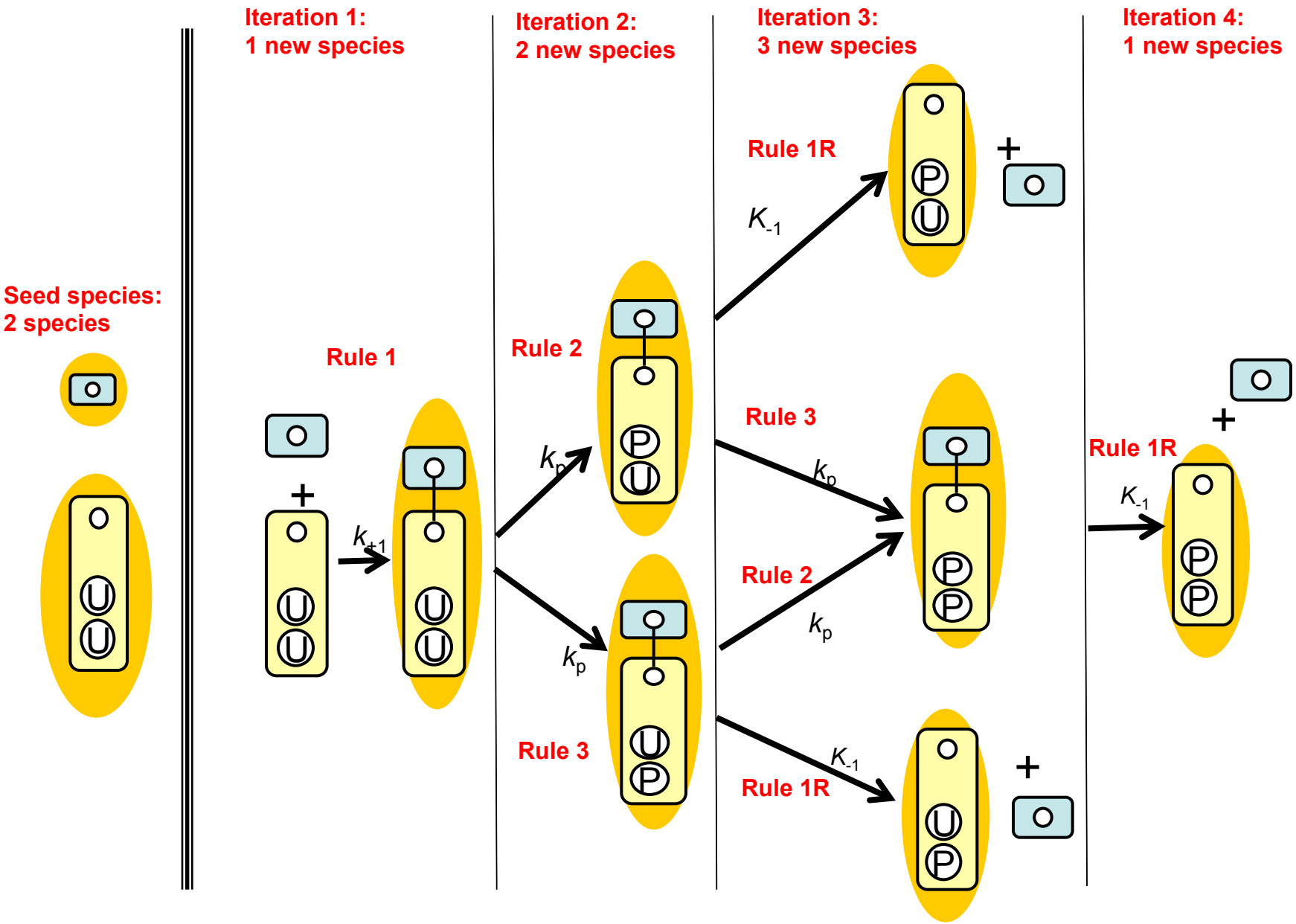
Rule 2



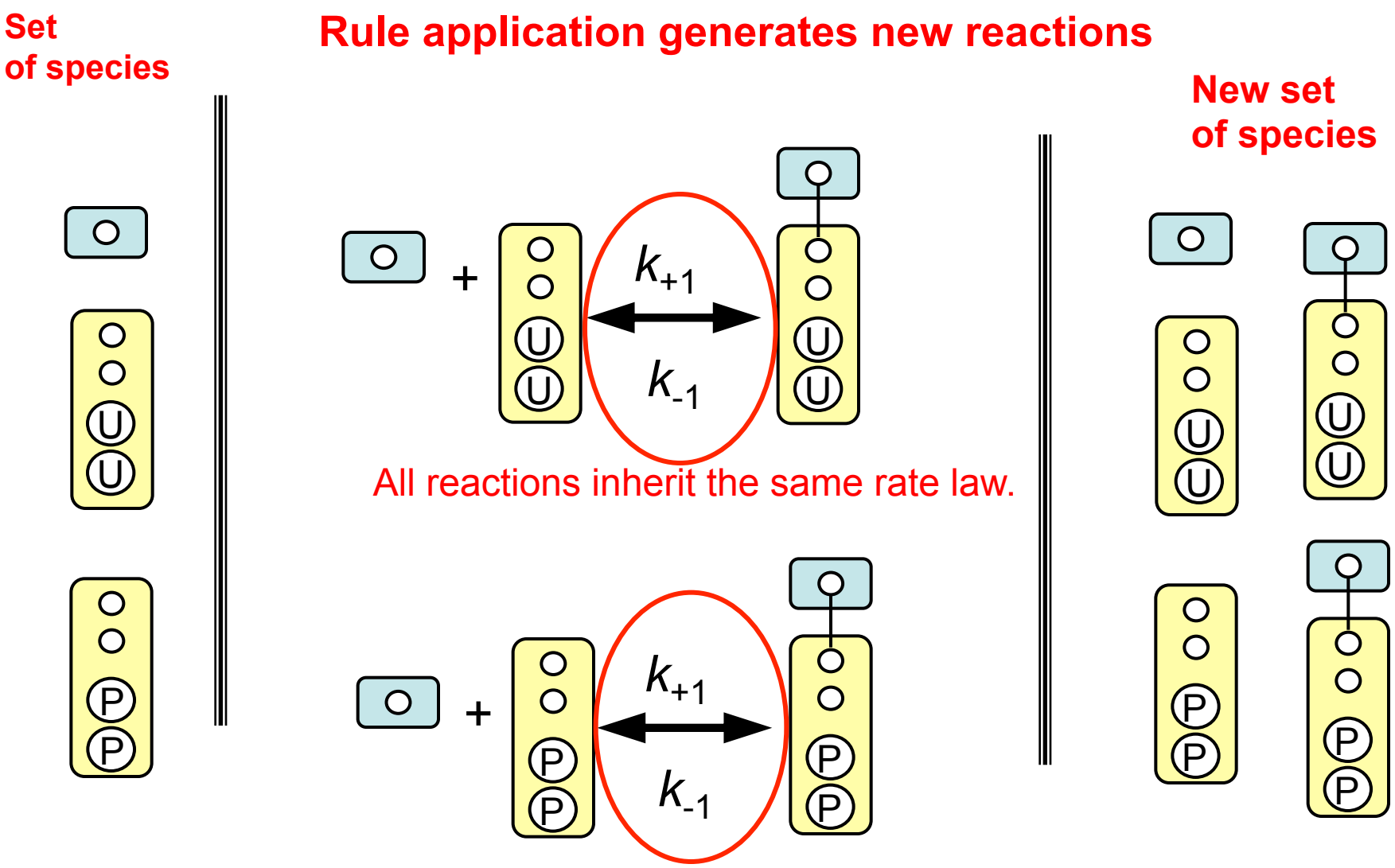
Rule 3



Rules generate reactions and 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 $\mathcal{R}(S_0 \cup S_1) = R_1, S_2$

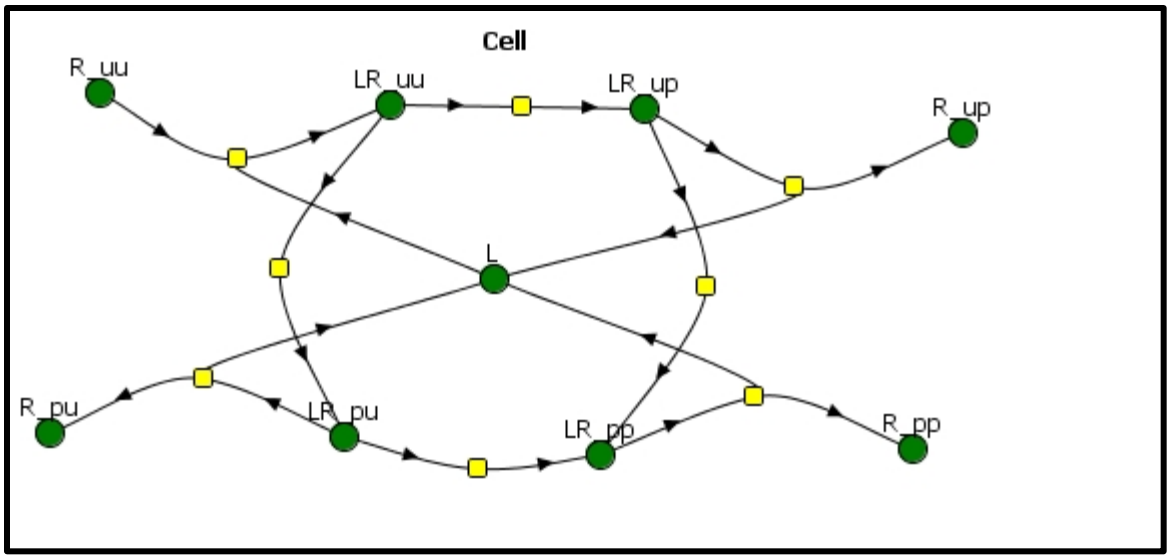
....

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

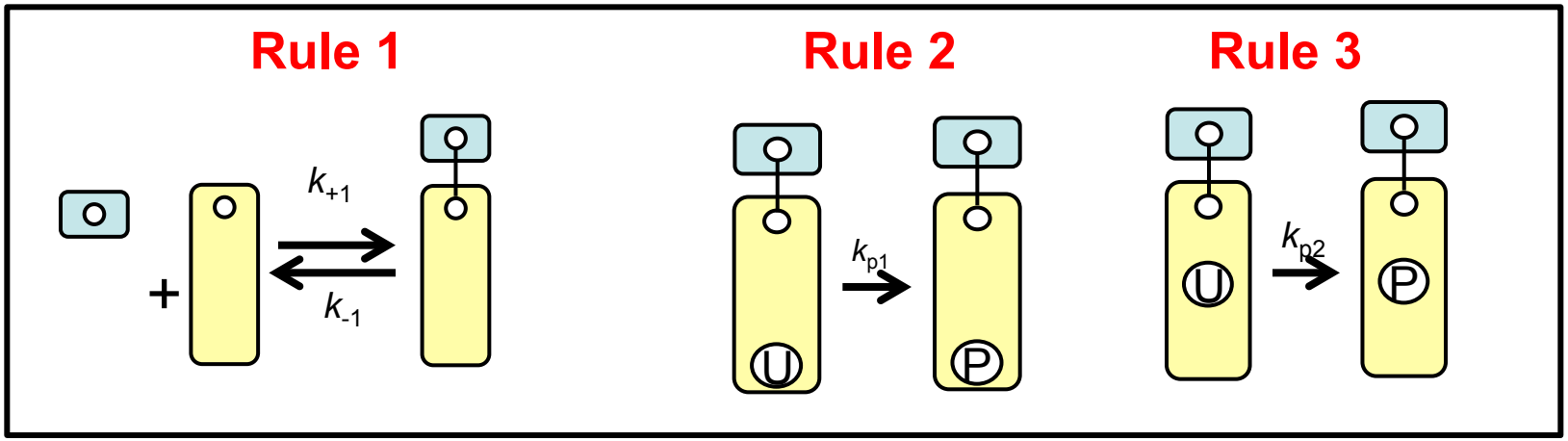
Termination Terminate if $S_n = S_{n+1}$

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

Visualization



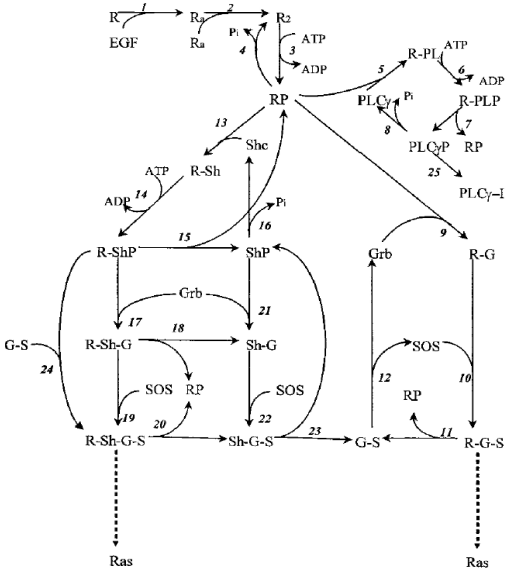
VS



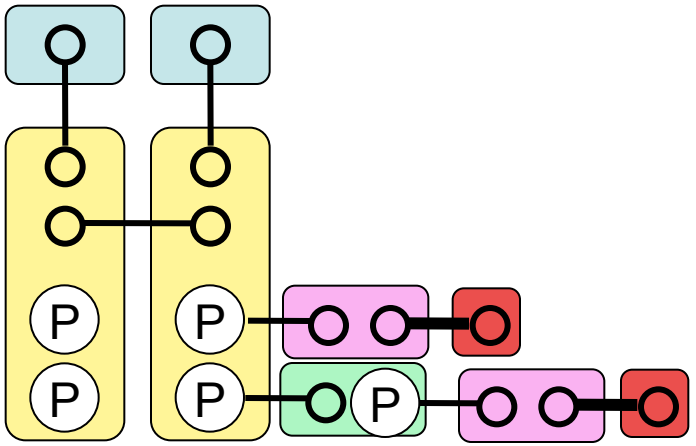
Expanded version of the Kholodenko model

- 5 molecule types
- 23 reaction rules
- No new rate parameters (!)

18 species
34 reactions

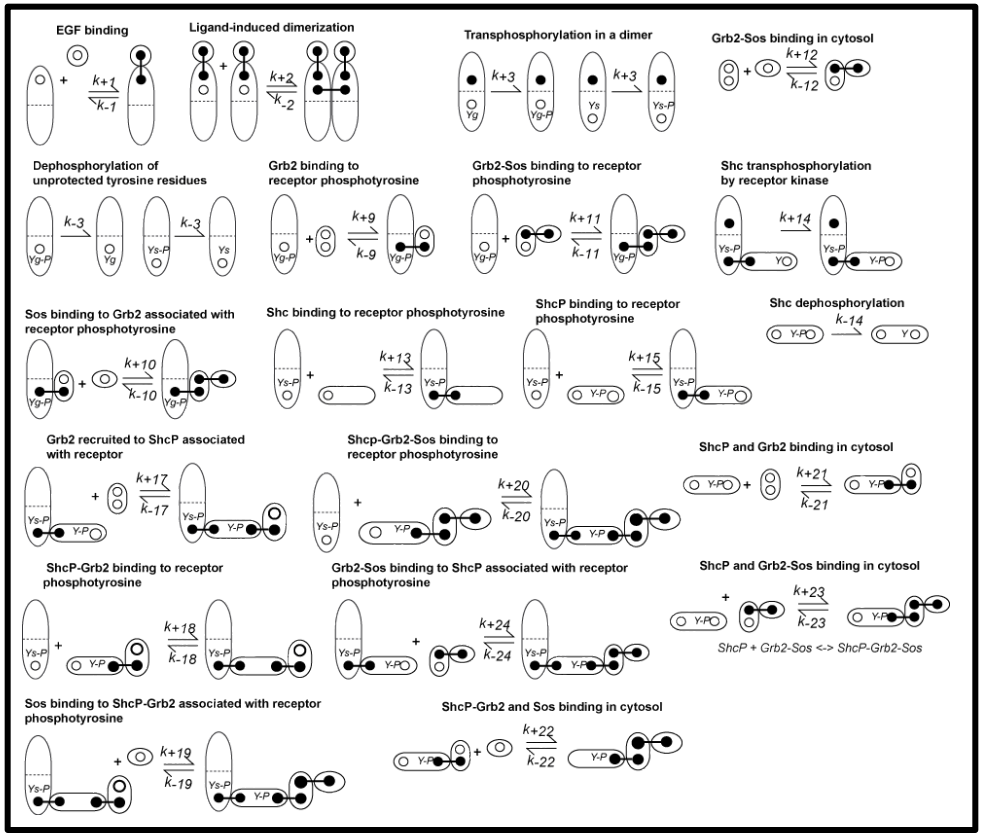


356 species
3,749 reactions

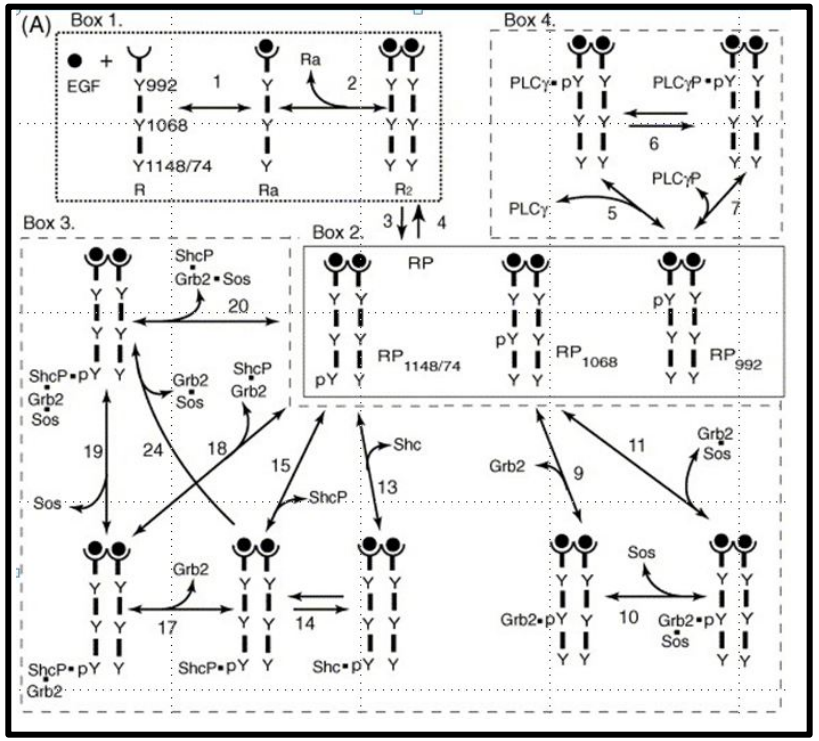


Blinov et al. *Biosystems* **83**, 136 (2006)

Visualization of rule-based models…



Drawing cartoons is not easy…



Visualization of rule-based models…

Reaction Diagram | Reactions | Structures | Species | Species Types | Observables

Reaction
egfr(l,r)+egf(r) <-> egfr(!1,r).egf(r!1)
egfr(!1,r)+egfr(!2,r) <-> egfr(!1,r!3).egfr(!2,r!3)
egfr(r!1,Y1068~Y) -> egfr(r!1,Y1068~pY)
egfr(r!1,Y1148~Y) -> egfr(r!1,Y1148~pY)
egfr(Y1068~pY) -> egfr(Y1068~Y)
egfr(Y1148~pY) -> egfr(Y1148~Y)
egfr(r!2,Y1148~pY!1).Shc(PTB!1,Y317~Y) -> egfr(r!2,Y1148~pY!1).Shc(PTB!1,Y317~pY)
Shc(PTB!1,Y317~pY) -> Shc(PTB!1,Y317~Y)
egfr(Y1068~pY)+Grb2(SH2,SH3) <-> egfr(Y1068~pY!1).Grb2(SH2!1,SH3)
egfr(Y1068~pY)+Grb2(SH2,SH3!2) <-> egfr(Y1068~pY!1).Grb2(SH2!1,SH3!2)
egfr(Y1068~pY!1).Grb2(SH2!1,SH3)+Sos(dom) <-> egfr(Y1068~pY!1).Grb2(SH2!1,SH3!2).Sos(dom!2)
egfr(Y1148~pY)+Shc(PTB,Y317~Y) <-> egfr(Y1148~pY!1).Shc(PTB!1,Y317~Y)
egfr(Y1148~pY)+Shc(PTB,Y317~pY) <-> egfr(Y1148~pY!1).Shc(PTB!1,Y317~pY)
egfr(Y1148~pY)+Shc(PTB,Y317~pY!1).Grb2(SH2!1,SH3) <-> egfr(Y1148~pY!2).Shc(PTB!2,Y317~pY!1).Grb2(SH2!1,SH3)
egfr(Y1148~pY)+Shc(PTB,Y317~pY!1).Grb2(SH2!1,SH3!3).Sos(dom!3) <-> egfr(Y1148~pY!2).Shc(PTB!2,Y317~pY!1).Grb2(SH2!1,SH3!3).Sos(dom!3)
egfr(Y1148~pY!1).Shc(PTB!1,Y317~pY)+Grb2(SH2,SH3) <-> egfr(Y1148~pY!1).Shc(PTB!1,Y317~pY!2).Grb2(SH2!2,SH3)
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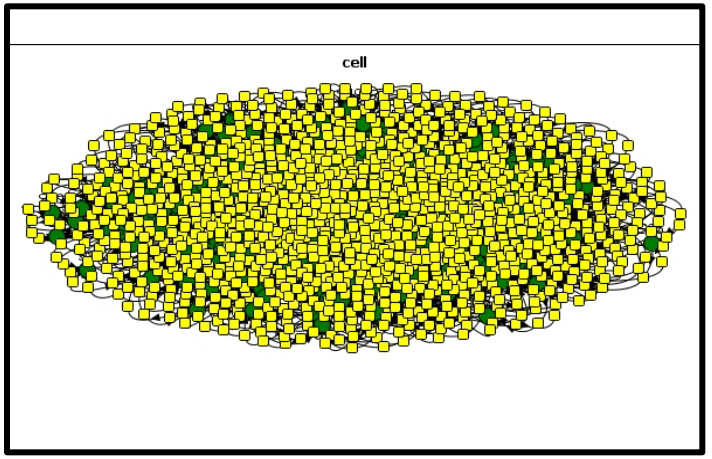
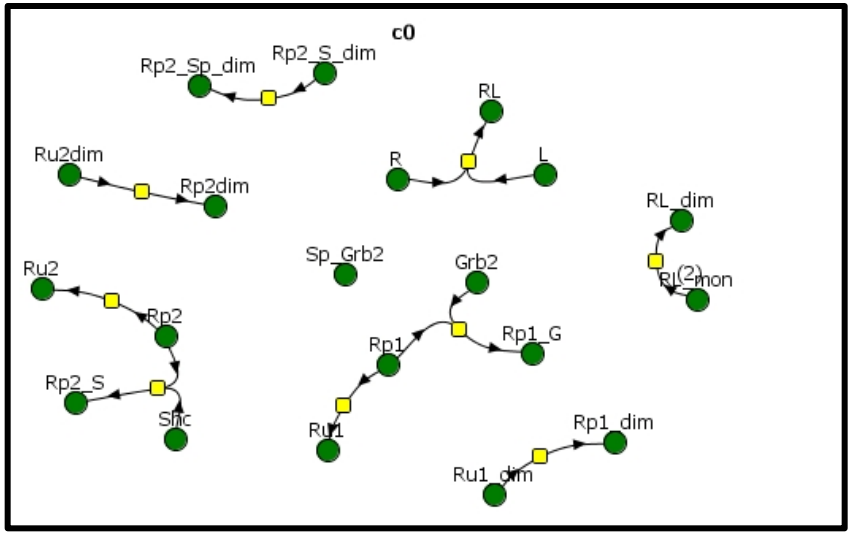
Shc(PTB!1,Y317~pY!2).Grb2(SH2!2,SH3)+Sos(dom) <-> Shc(PTB!1,Y317~pY!2).Grb2(SH2!2,SH3!3).Sos(dom!3)
Shc(PTB,Y317~pY)+Grb2(SH2,SH3) <-> Shc(PTB,Y317~pY!1).Grb2(SH2!1,SH3)
Shc(PTB,Y317~pY)+Grb2(SH2,SH3!2) <-> Shc(PTB,Y317~pY!1).Grb2(SH2!1,SH3!2)
Shc(PTB,Y317~pY) -> Shc(PTB,Y317~Y)
Grb2(SH2,SH3)+Sos(dom) <-> Grb2(SH2,SH3!1).Sos(dom!1)
Shc(PTB,Y317~pY!2).Grb2(SH2!2,SH3)+Sos(dom) <-> Shc(PTB,Y317~pY!2).Grb2(SH2!2,SH3!3).Sos(dom!3)

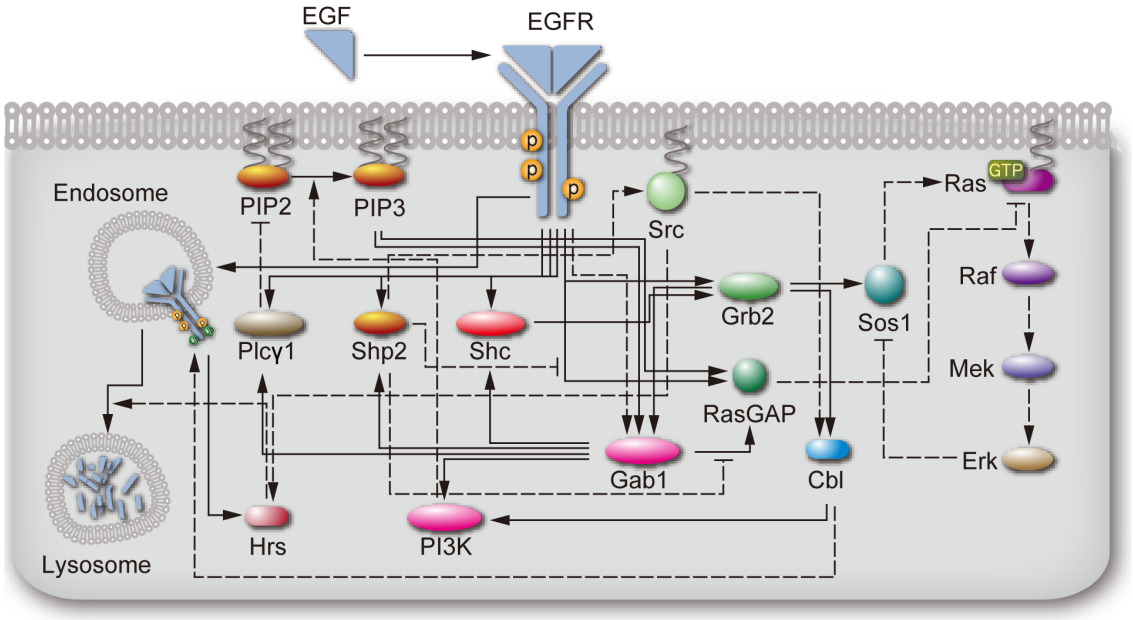


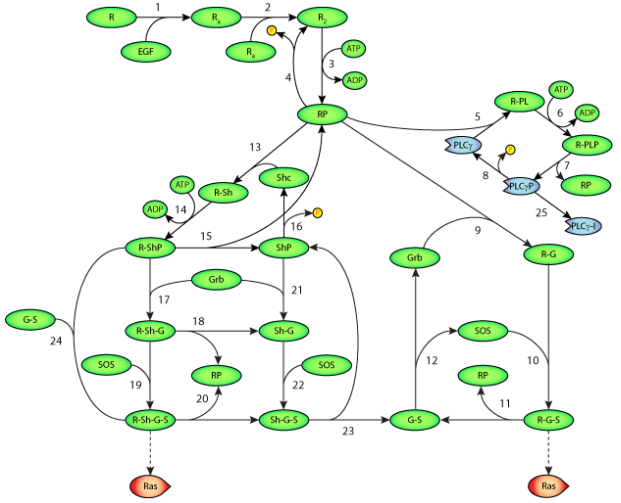


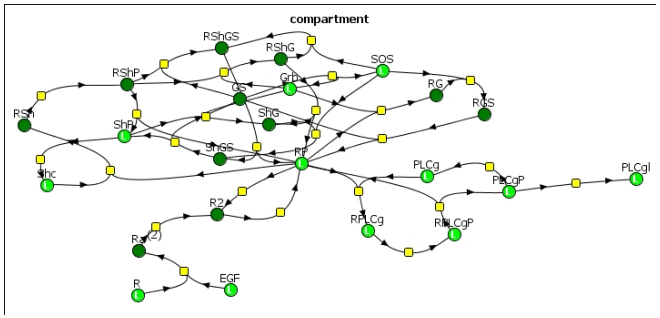
Reading/writing code is not easy…

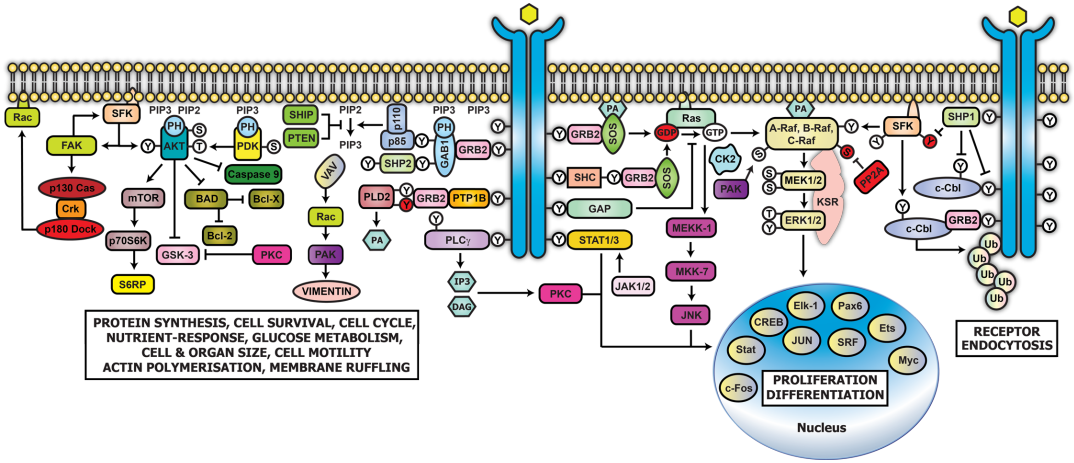
Almost all reactants and products in patterns are distinct, so cartoons can not be assembled into a network…

Variety of model visualizations: EGFR signaling



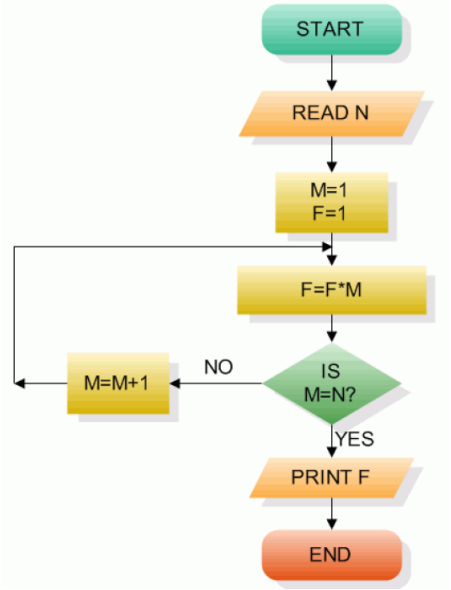




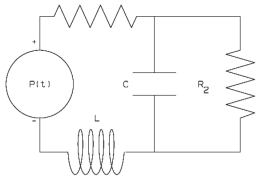


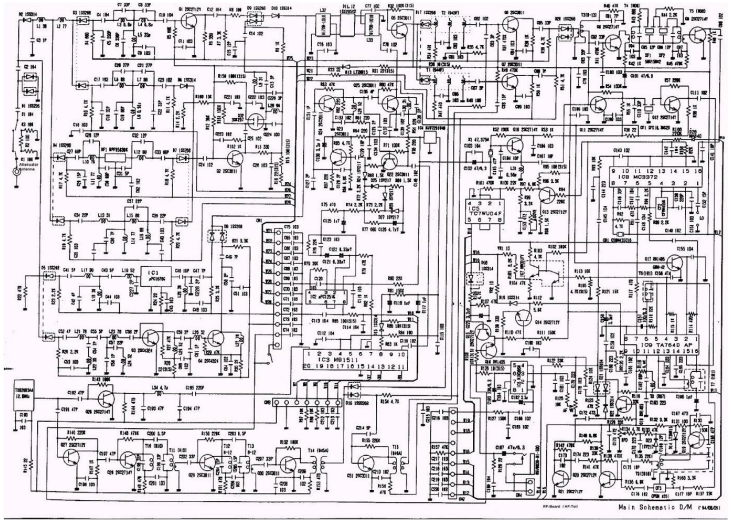
Visualization in Exact Sciences

Standard CS notations



Standard EE notations





Biology Electrical Engineering, Pathways Electronic Circuits

- Circuits and algorithms are designed by humans
  - Follow a defined set of rules
  - Boundaries well defined
- Pathways
  - Don't know all the "rules"
  - Boundaries not clear
  - Knowledge often incomplete

Ideal visual representation

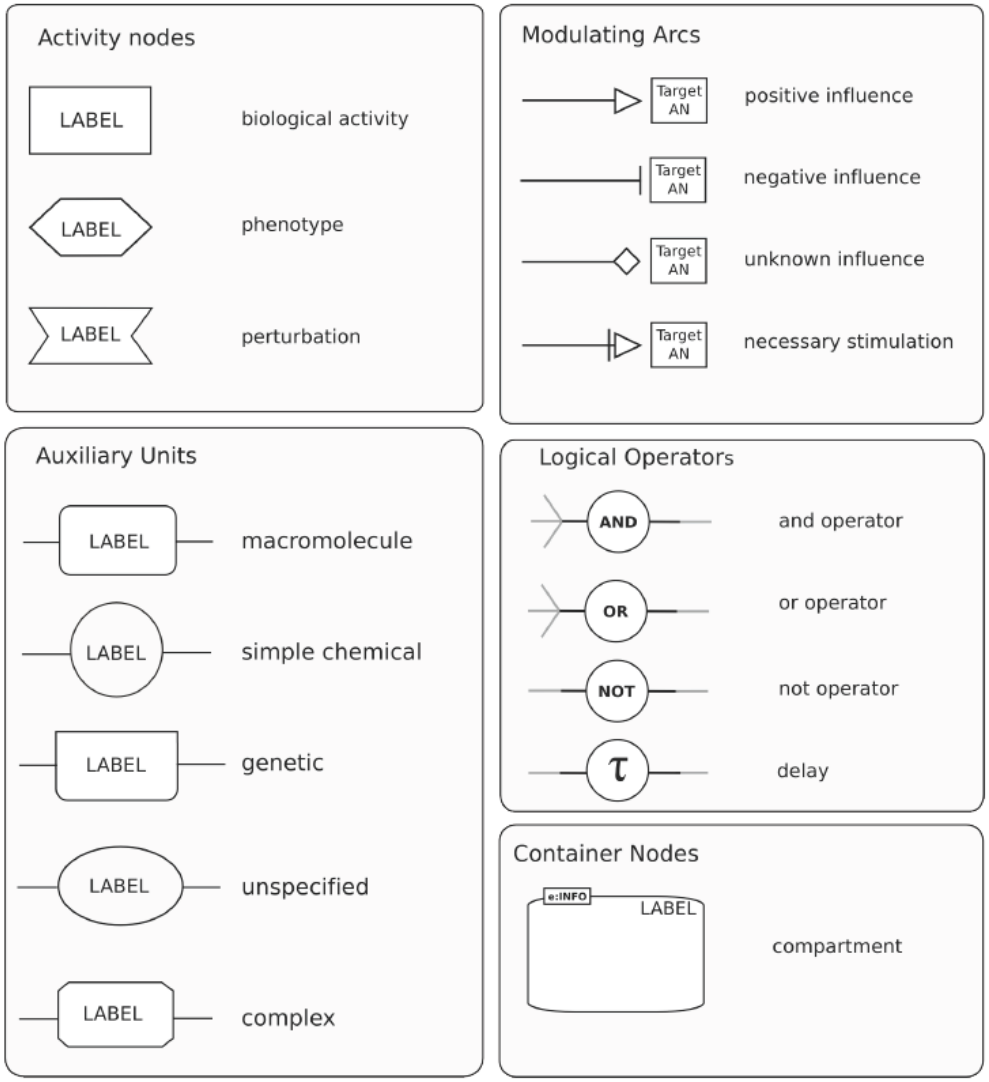
- Visual Language:
  - rich to capture adequately complex biological information
  - represent both mechanistic and qualitative relationships
  - support hierarchical representation, modularization and encapsulation
- Rules and guidelines ensure:
  - reader can unambiguously understand what writer meant
  - machine readable and writable, allow computer manipulation/analysis
- Has an underlying conceptual abstraction
  - a model of its world
  - vocabulary (symbols/**glyphs**)
  - **syntax** (basic assembly or glyphs)
  - **grammar** (rules based on meaning - **semantics**)

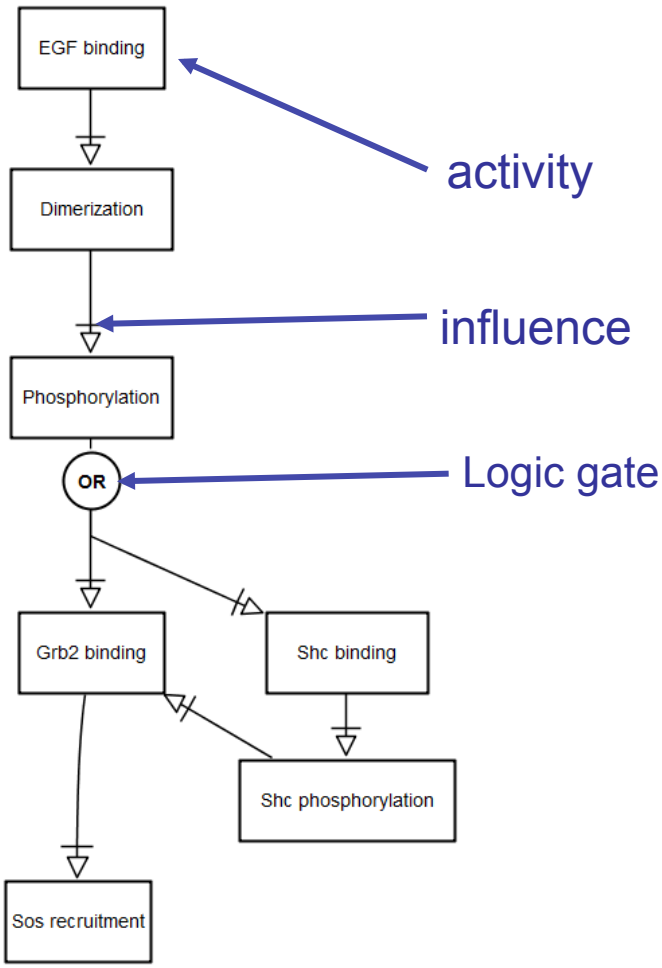
What is SBGN?

- A community effort initiated by Hiroaki Kitano in late 2005.
- Three orthogonal languages to unambiguously describe biochemical and cellular events in graphs:
  - Activity Flow (SBGN AF)
  - Process diagrams (SBN PD)
  - Entity Relationships (SBGN ER)
- Limited amount of symbols (32 in PD, 21 in ER)
- Can graphically represent quantitative models, biochemical pathways, genetic interactions, at different levels of granularity.

Language of SBGN: Activity flow

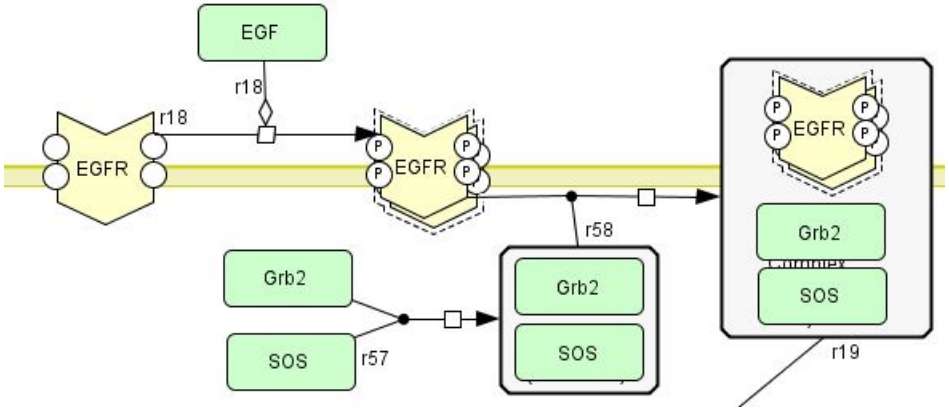
- Flux of information going from one entity to another



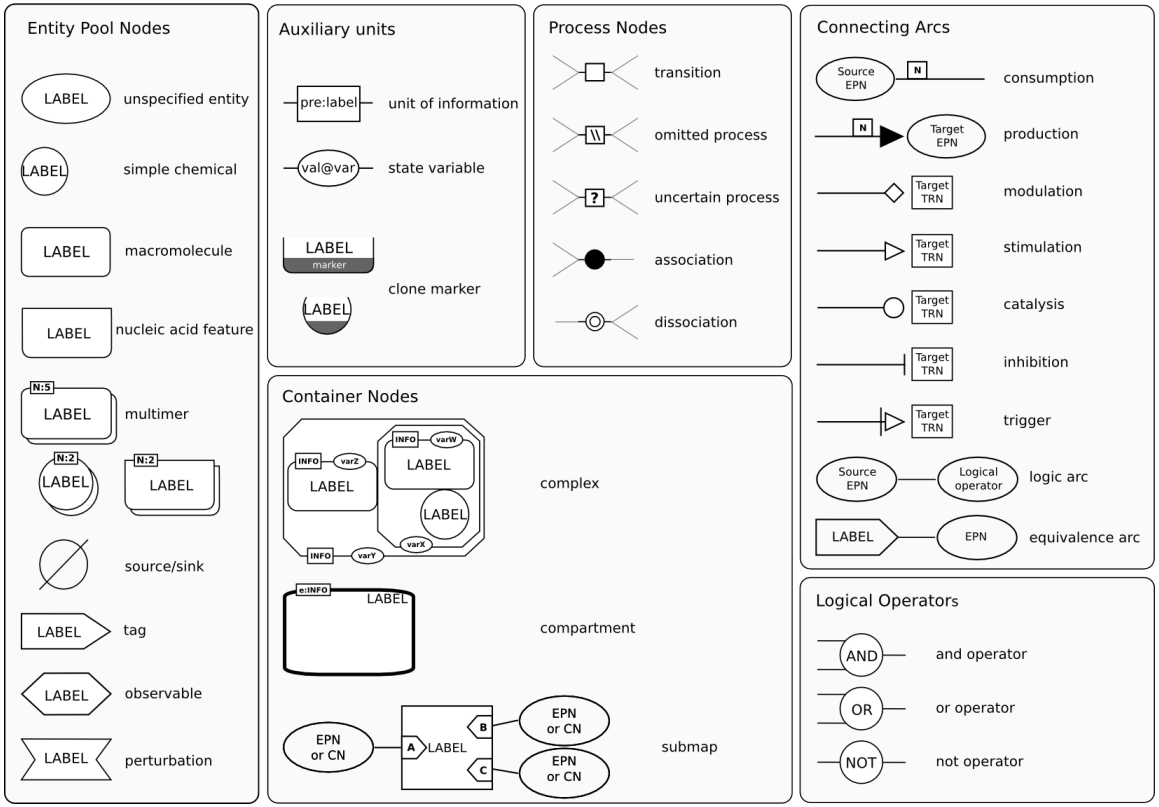


Language of SBML: Process Diagrams

- "Glorified" representation of reaction networks:
  - Multiple types of arrows and nodes
  - complexes
  - User-specified colors, multiple attributes, etc
- Adapted for machine-reading, e.g.
  - no dashed lines
  - Independent on colors and widths
  - Logic
- Used in CellDesigner and PantherDB
- Widely used for poster presentations

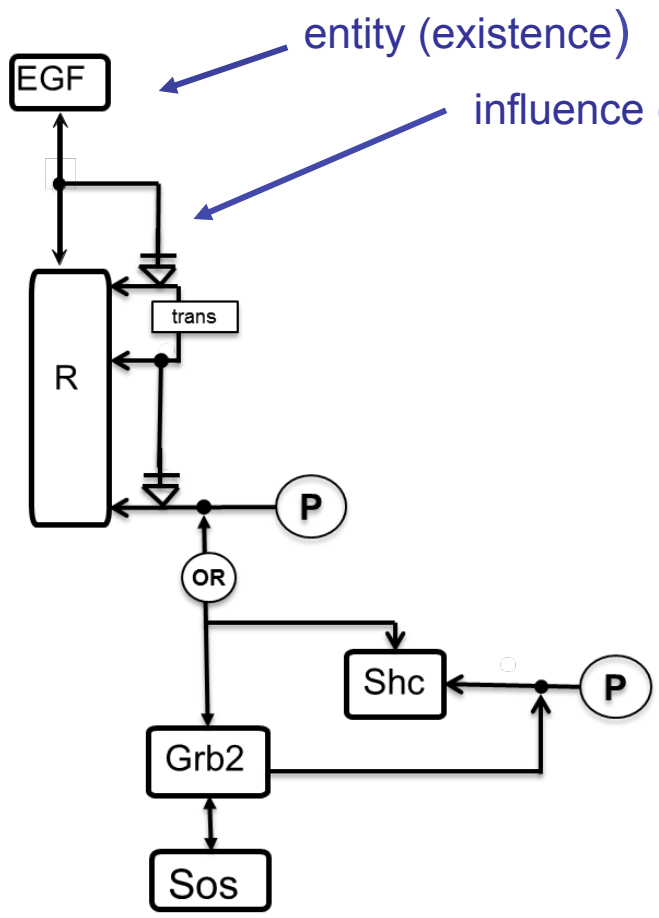


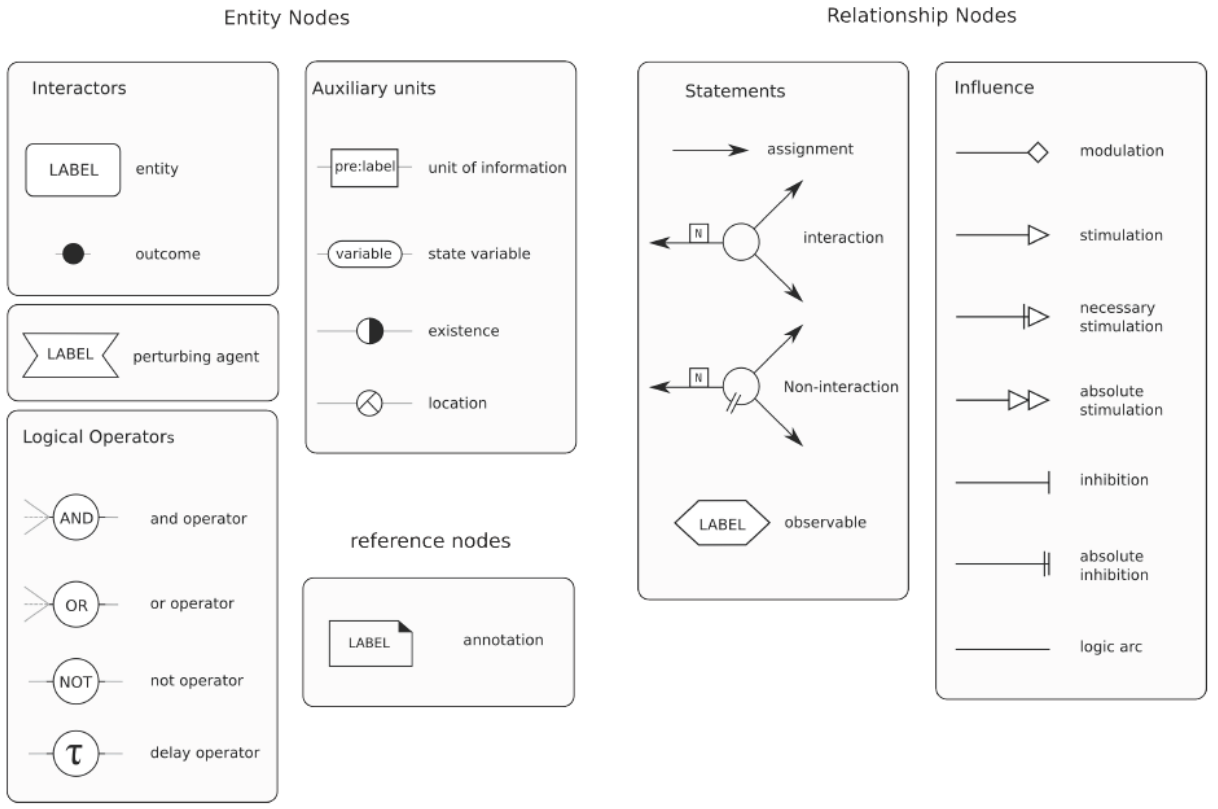
SYSTEMS BIOLOGY GRAPHICAL NOTATION REFERENCE CARD



Language of SBGN: Entity relationships

- Generalization of Molecular Interaction Maps (MIM)
- Describe interactions between entities and the rules that control them

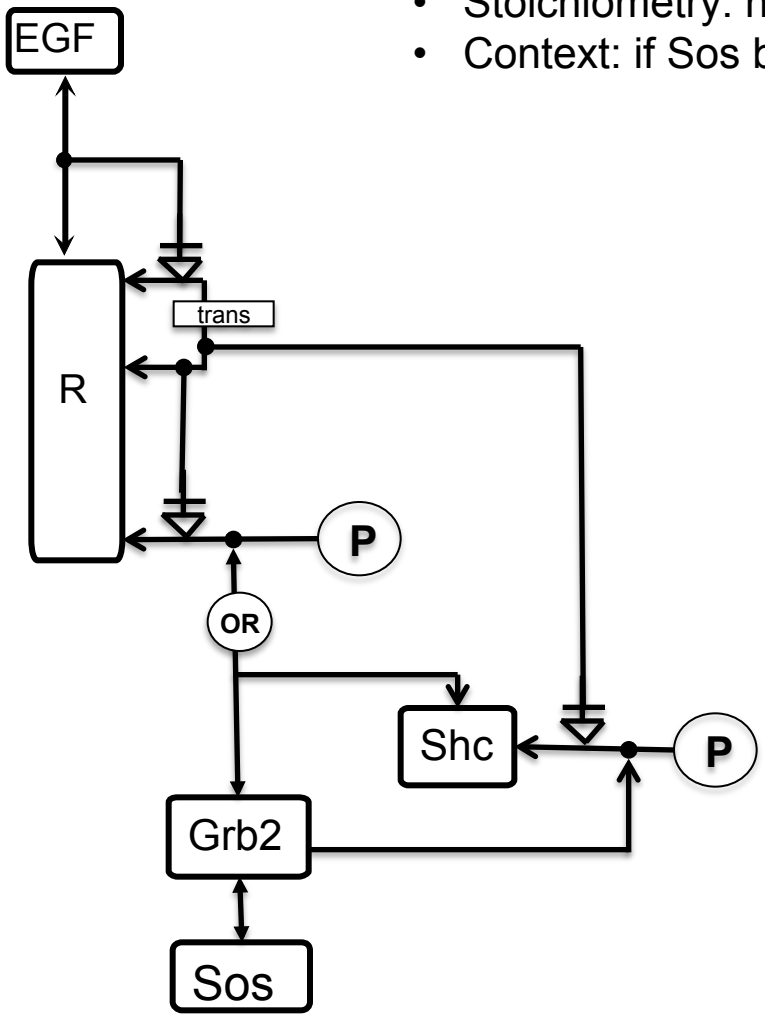




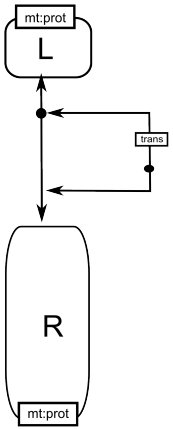
Problems of SBGN-ER or MIM

Not enough information to recover a model:

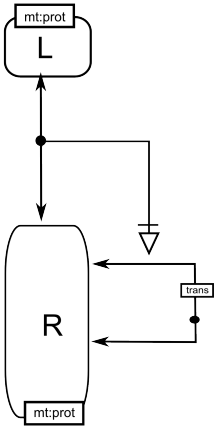
- Reverse interactions are not defined
- Stoichiometry: how many R in dimer are phosphorylated?
- Context: if Sos binds complexes Grb2 in complex with EGFR, Shc?



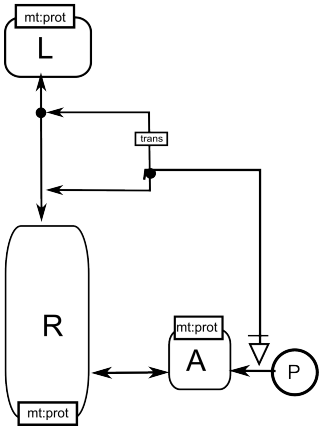
Two ligands are required for dimerization



At least one ligand is required for dimerization



Two ligands are necessary for phosphorylation



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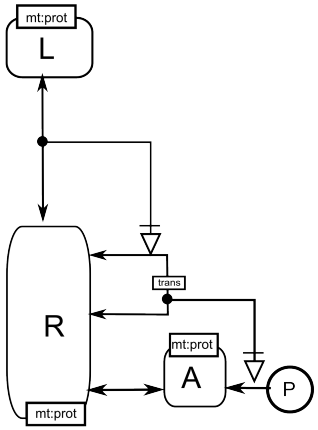
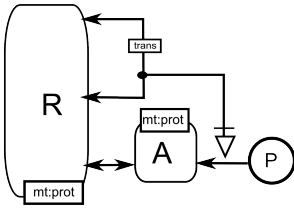


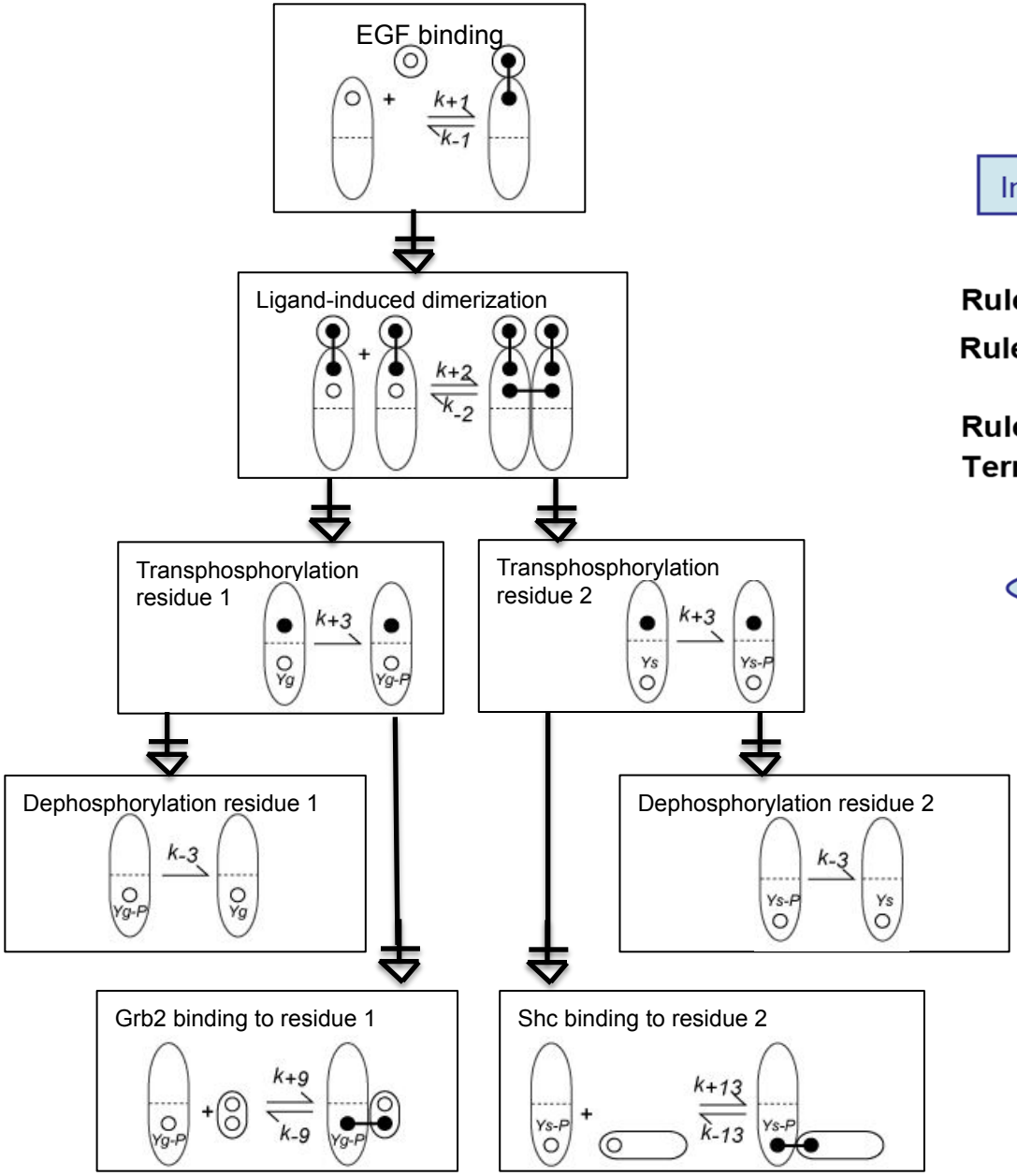
Two receptors are required for phosphorylation



Compare SBGN Languages

	AF	PD	ER
Describes:	Influence of biological activities on each other	Conversion physical entities into other entities, change their states or location	Interactions between entities and the rules that control them
Level of description:	Conceptual description of influences	Mechanistic	Mechanistic
Building blocks:	Different activities of physical entities are represented separately	Different states of physical entities are represented separately	Physical entities are represented only once
Ambiguity:	Ambiguous interpretation in biochemical terms	Completely unambiguous	Ambiguous
Temporality:	Sequential influences	Sequential	Non-sequential
Pitfalls:	Not suitable to represent association, dissociation, multi-state entities	Sensitive to combinatorial explosion	Creation, destruction, translocation and stoichiometry are not easily represented

Rule-based Activity Flow Diagram



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

....

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

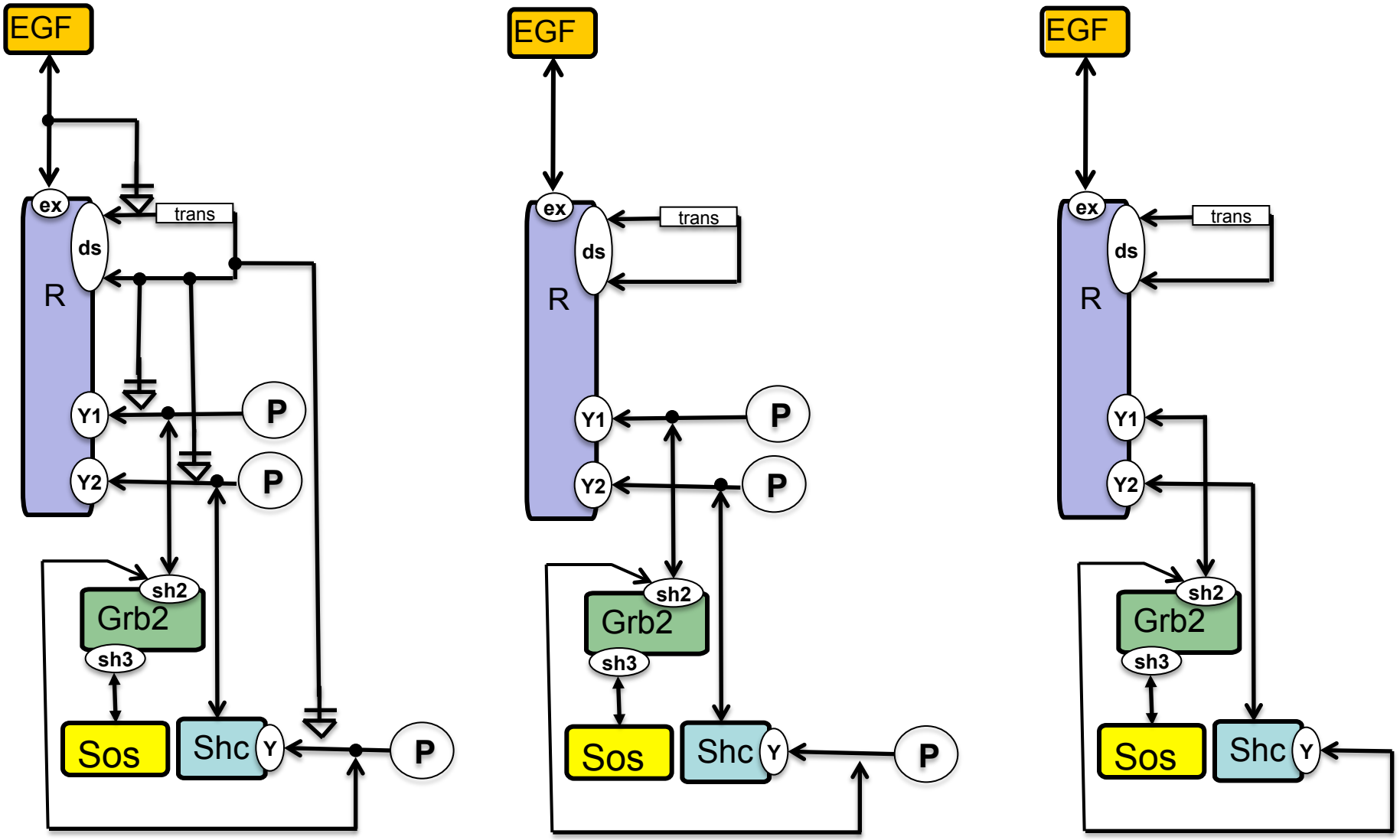
Termination Terminate if $S_n = S_{n+1}$

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

Drawing cartoons is not easy…

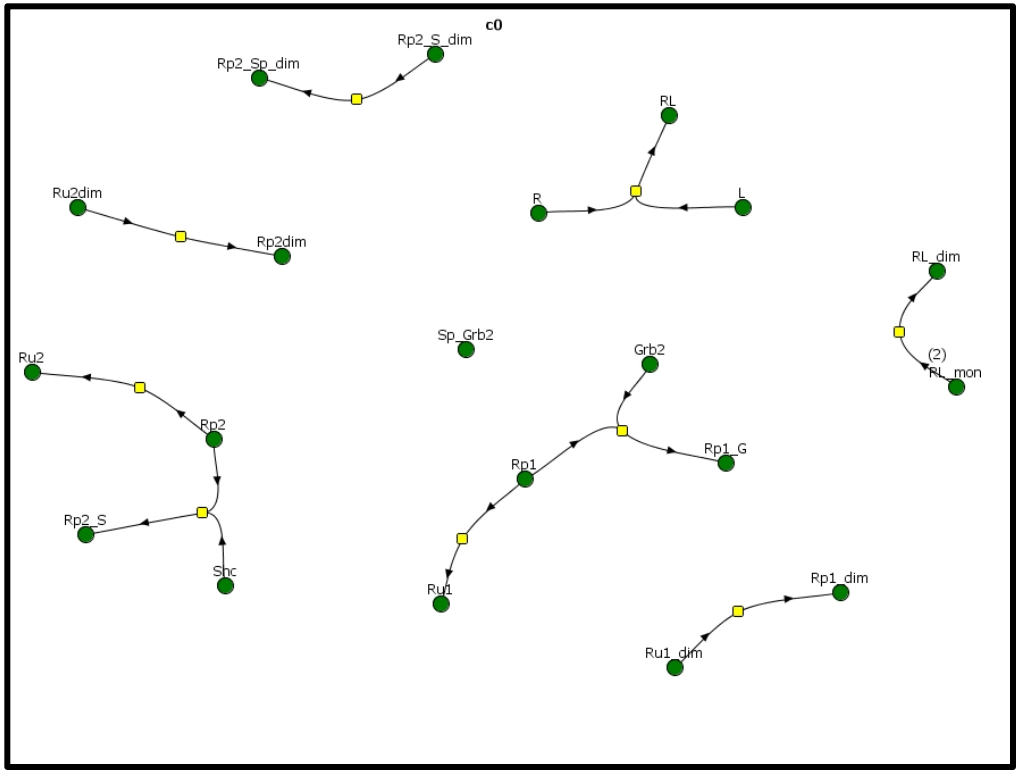
Such visualization can be done only after rules specification, not before

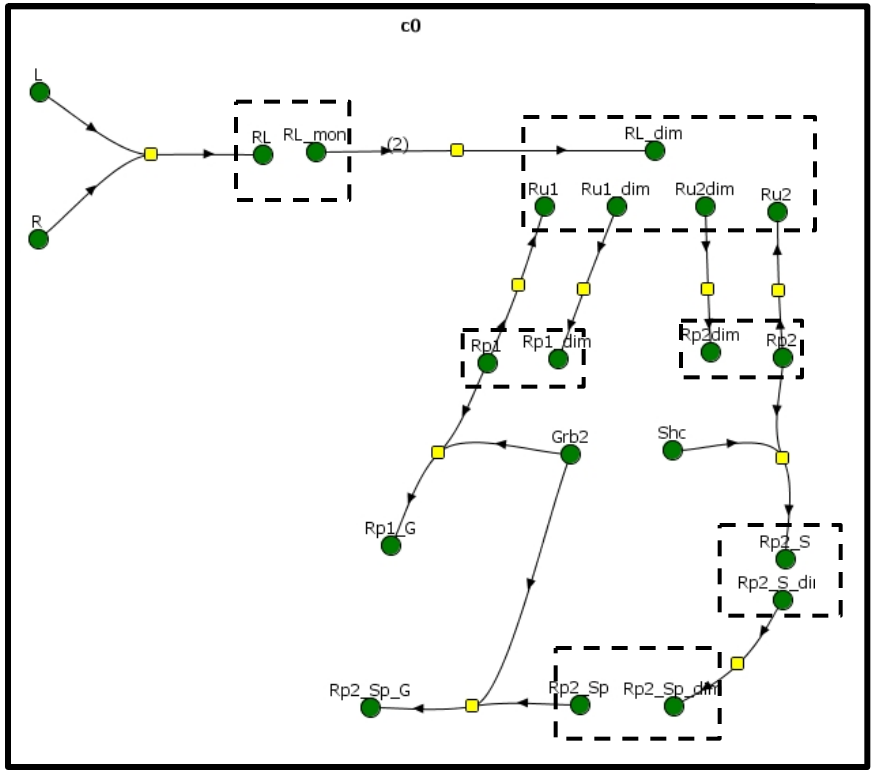
Rule Based Entity Relationships Diagram



Reaction-network visualization of rule-based models…

Approach: Species templates and rules as graph nodes



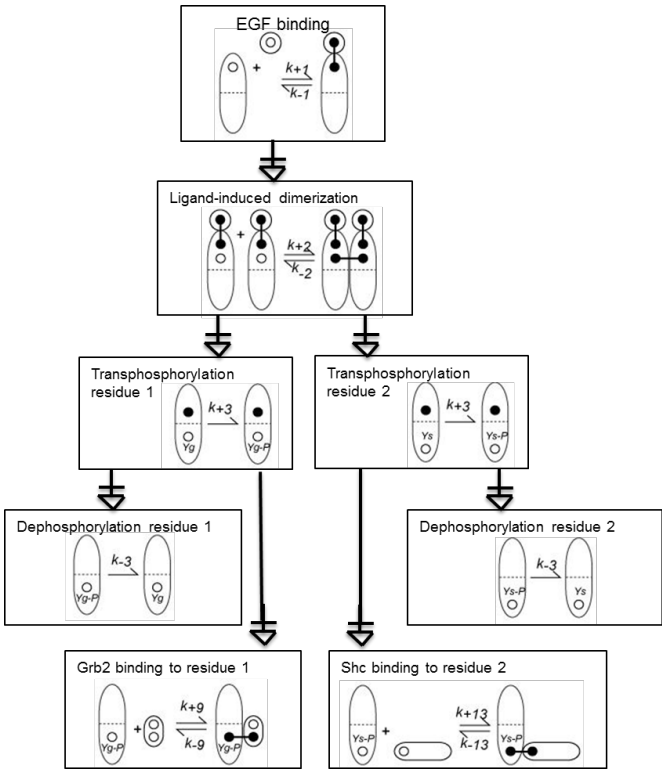


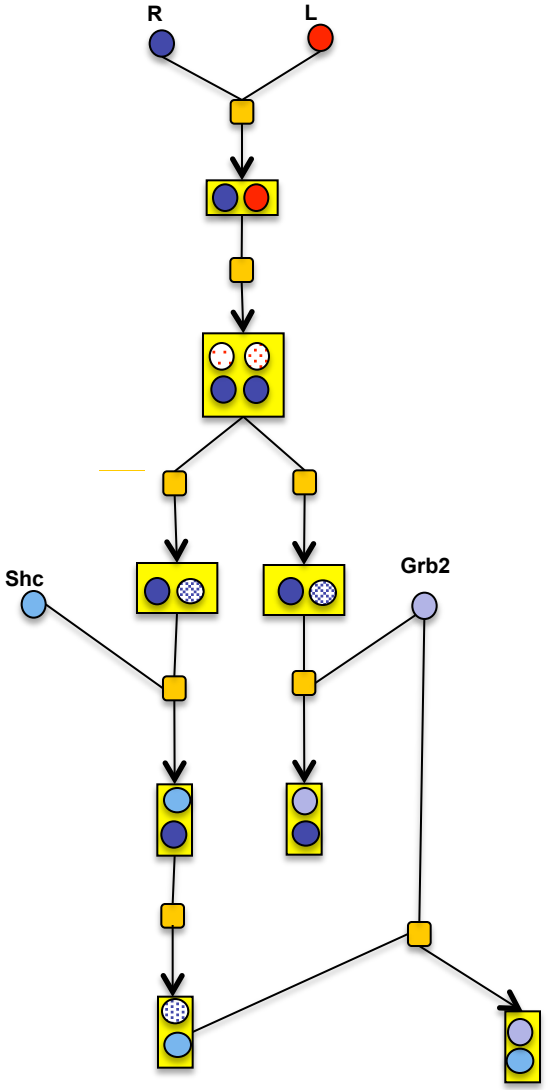
Options:

- user-specified grouping
- Algorithm to find similarities among patterns and automatically group them

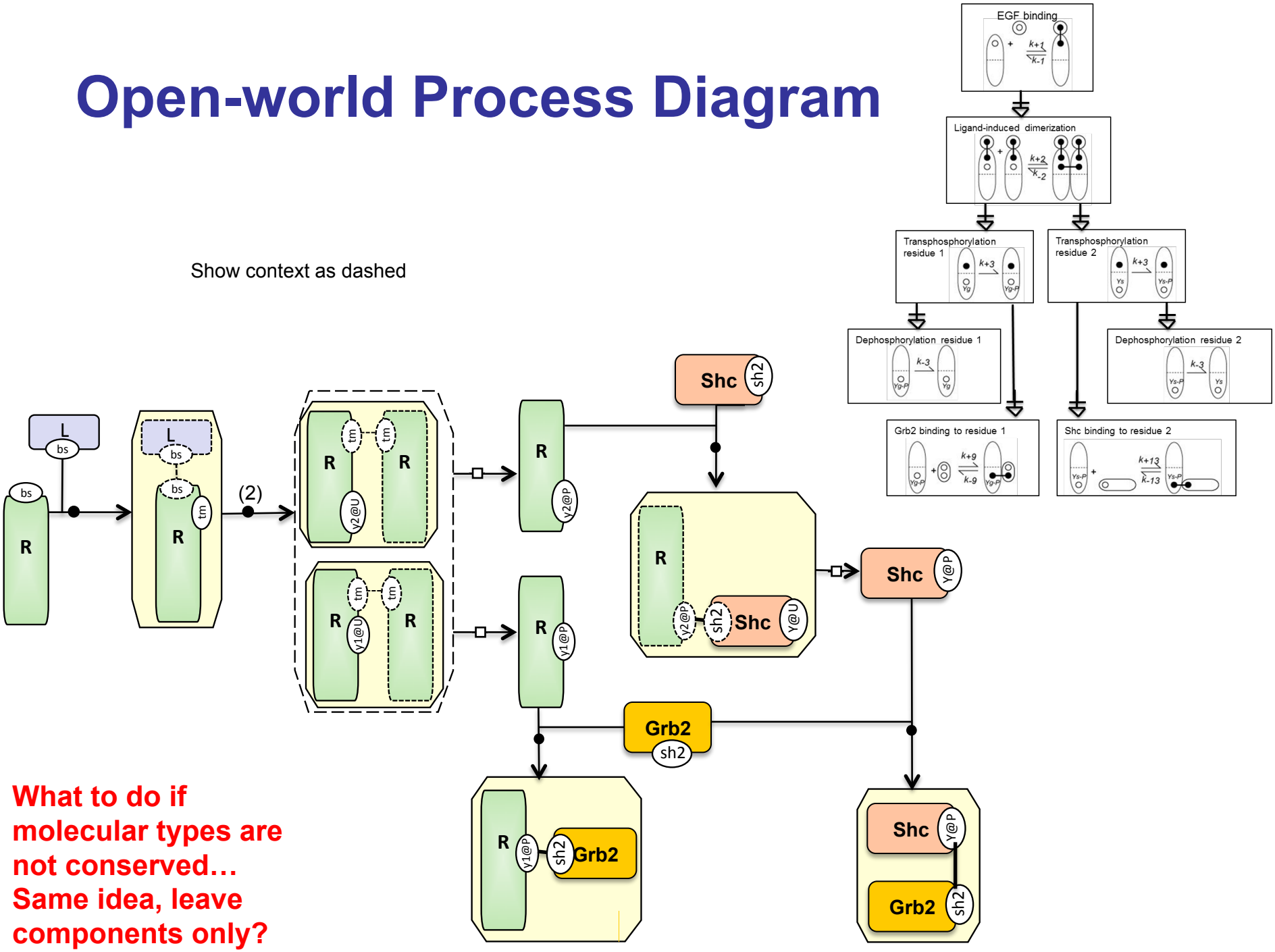
Still postprocessing!

VCell reaction diagram proposal – drop molecular types

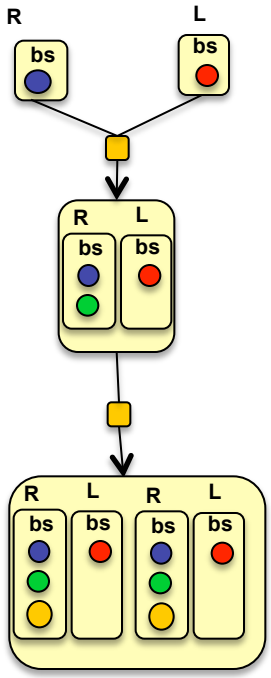


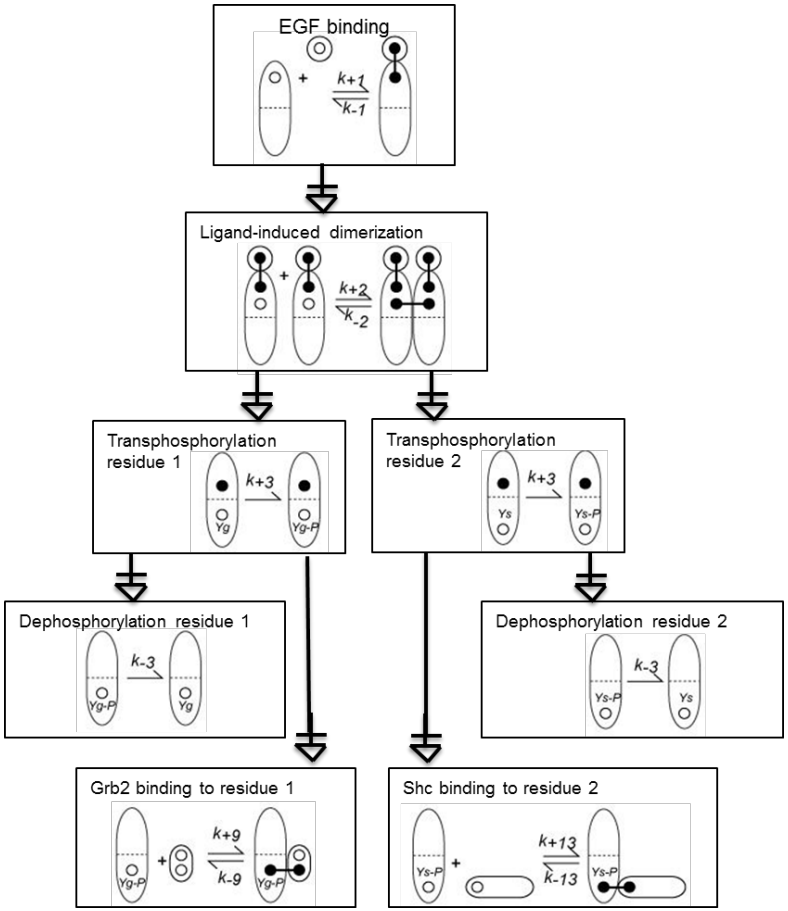


Open-world Process Diagram



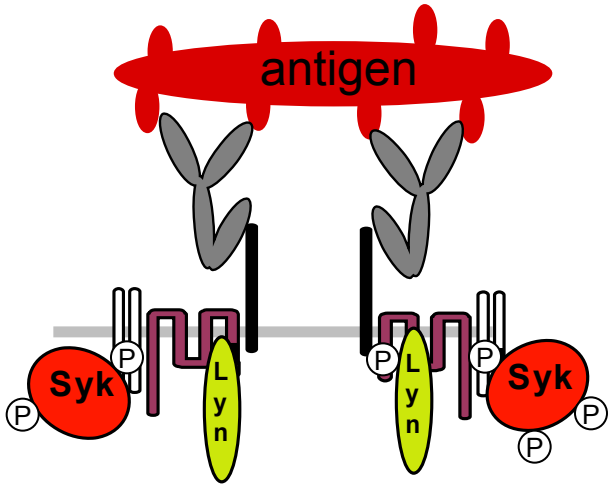
VCell reaction diagram proposal - drop components



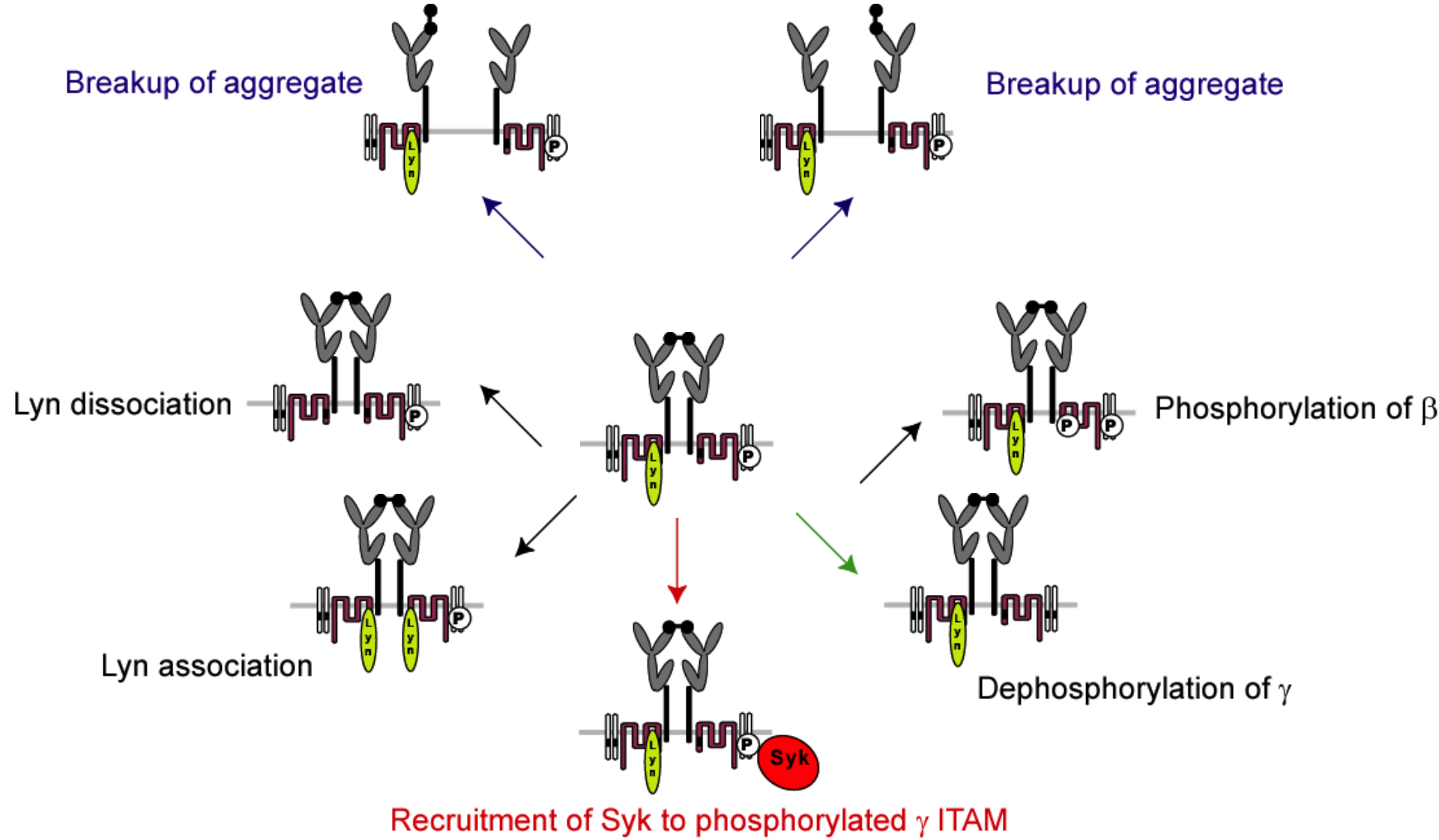


Early Events in FcεRI receptor Signaling

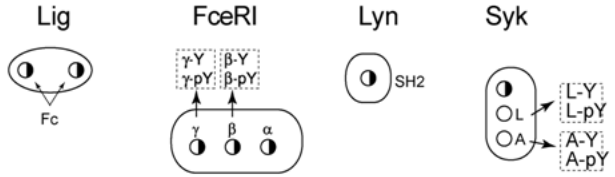
1. Multivalent antigen binds to IgE on cell surface forming aggregates
2. Tyrosine kinase Lyn associates with receptors and **transphosphorylates** ITAM tyrosines
3. Phosphorylated ITAMs recruit Syk and additional Lyn
4. Syk is transphosphorylated by Lyn or Syk
5. Phosphorylation of Syk is critical for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



Not a pathway!

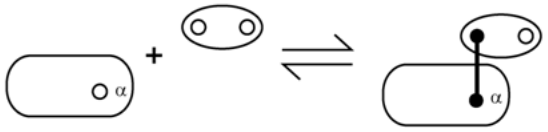


Molecules



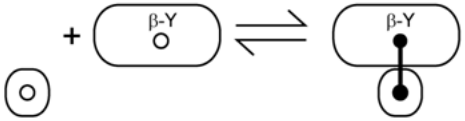
Reaction Rules

1. Ligand binding

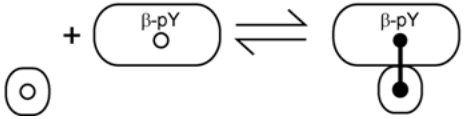


2. Ligand-induced aggregation

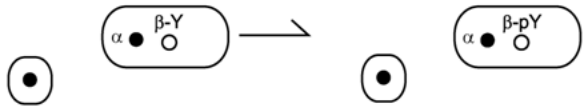
3. Binding of Lyn to unphosphorylated receptor



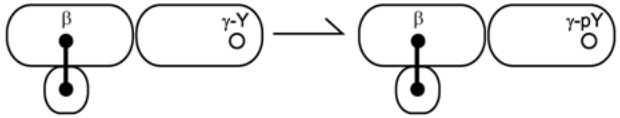
4. Binding of Lyn to phosphorylated receptor



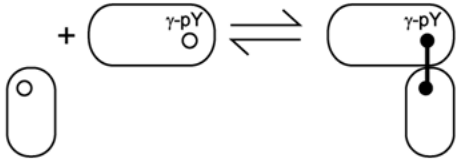
5. Transphosphorylation of β by Lyn



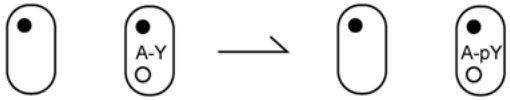
6. Transphosphorylation of γ by Lyn



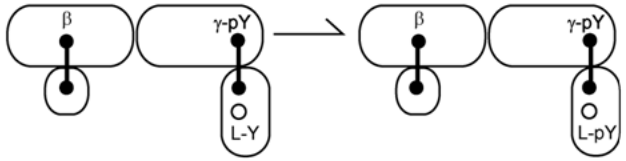
7. Binding of Syk to phosphorylated receptor

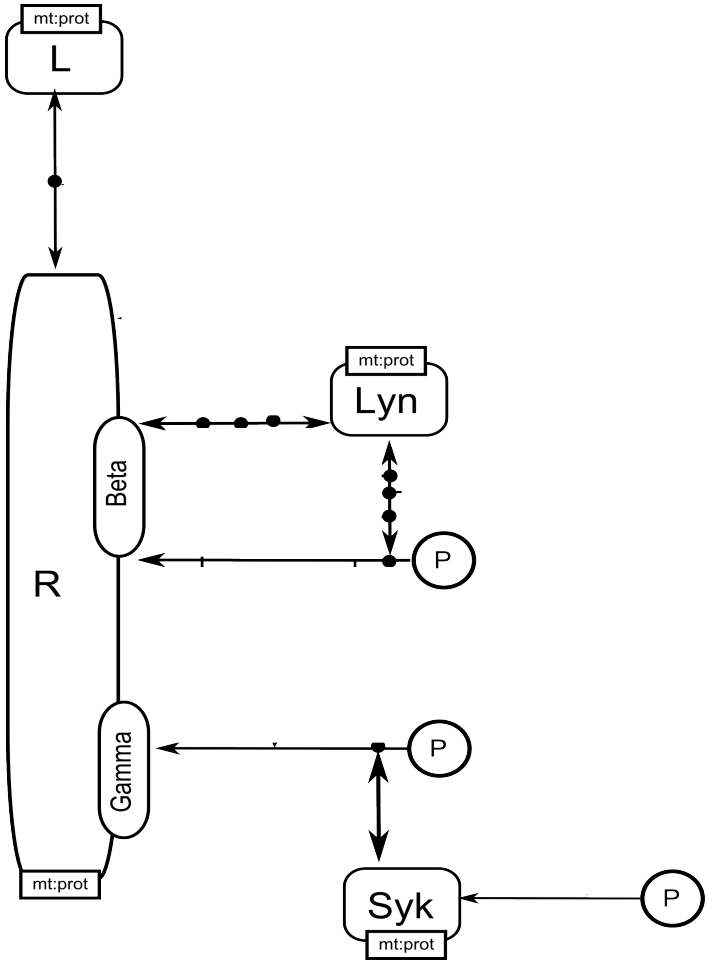


8. Transphosphorylation of Syk by Syk



9. Transphosphorylation of Syk by Lyn

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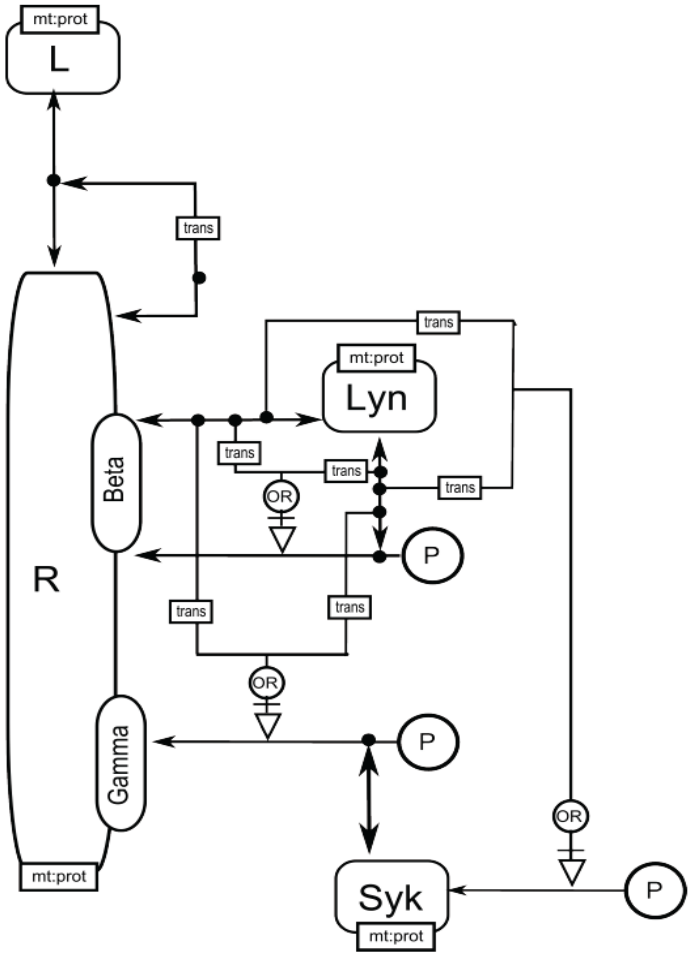
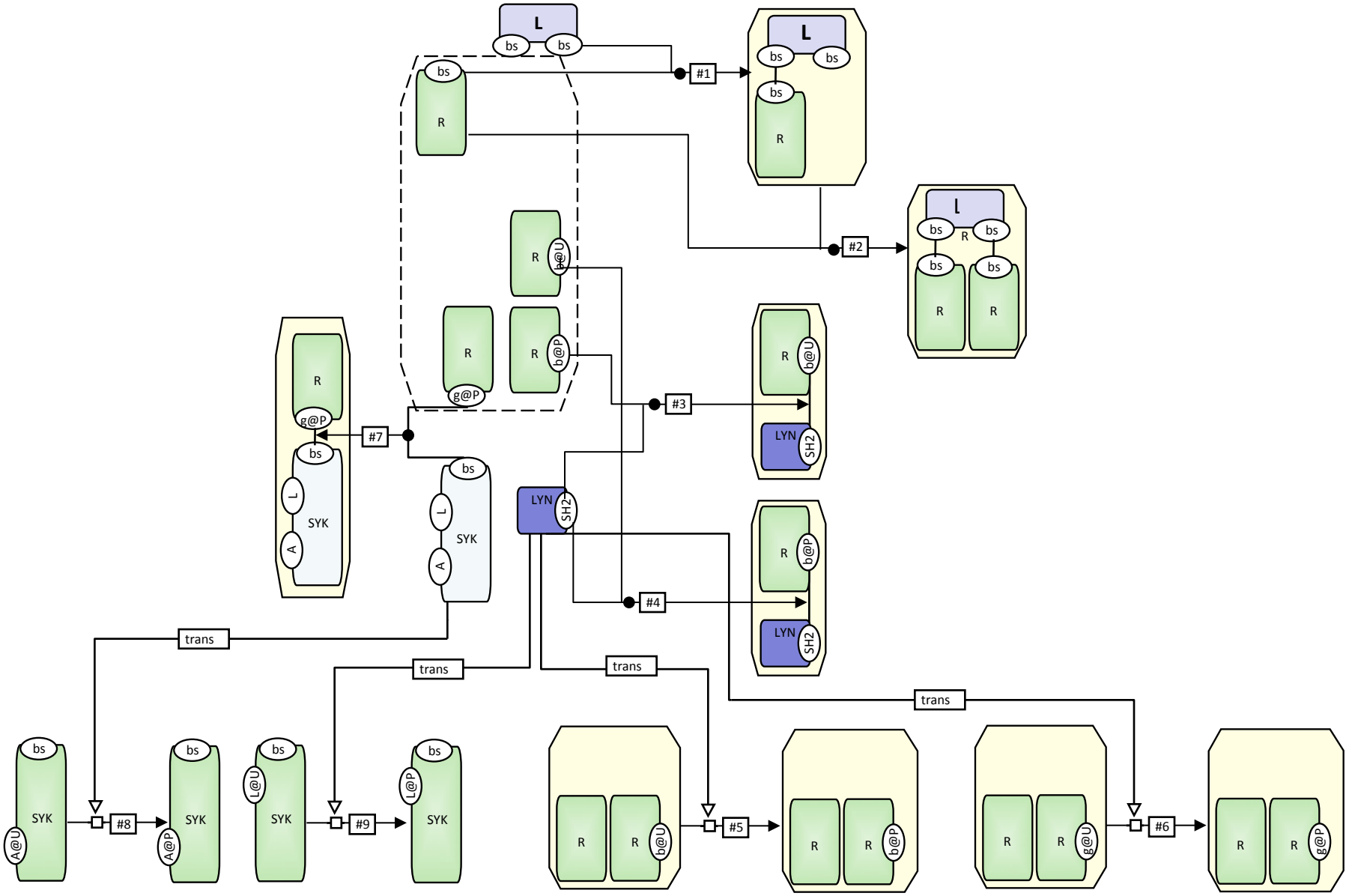
Beta
Gamma
mt:prot
Lyn
P
P
mt:prot
Syk
mt:prot
P


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


L
bs
bs
R
#1
#2
b@U
b@P
g@P
#3
LYN
SH2
#4
#7
SYK
L
A
trans
#8
#9
A@U
A@P
L@U
L@P
#5
#6
g@U