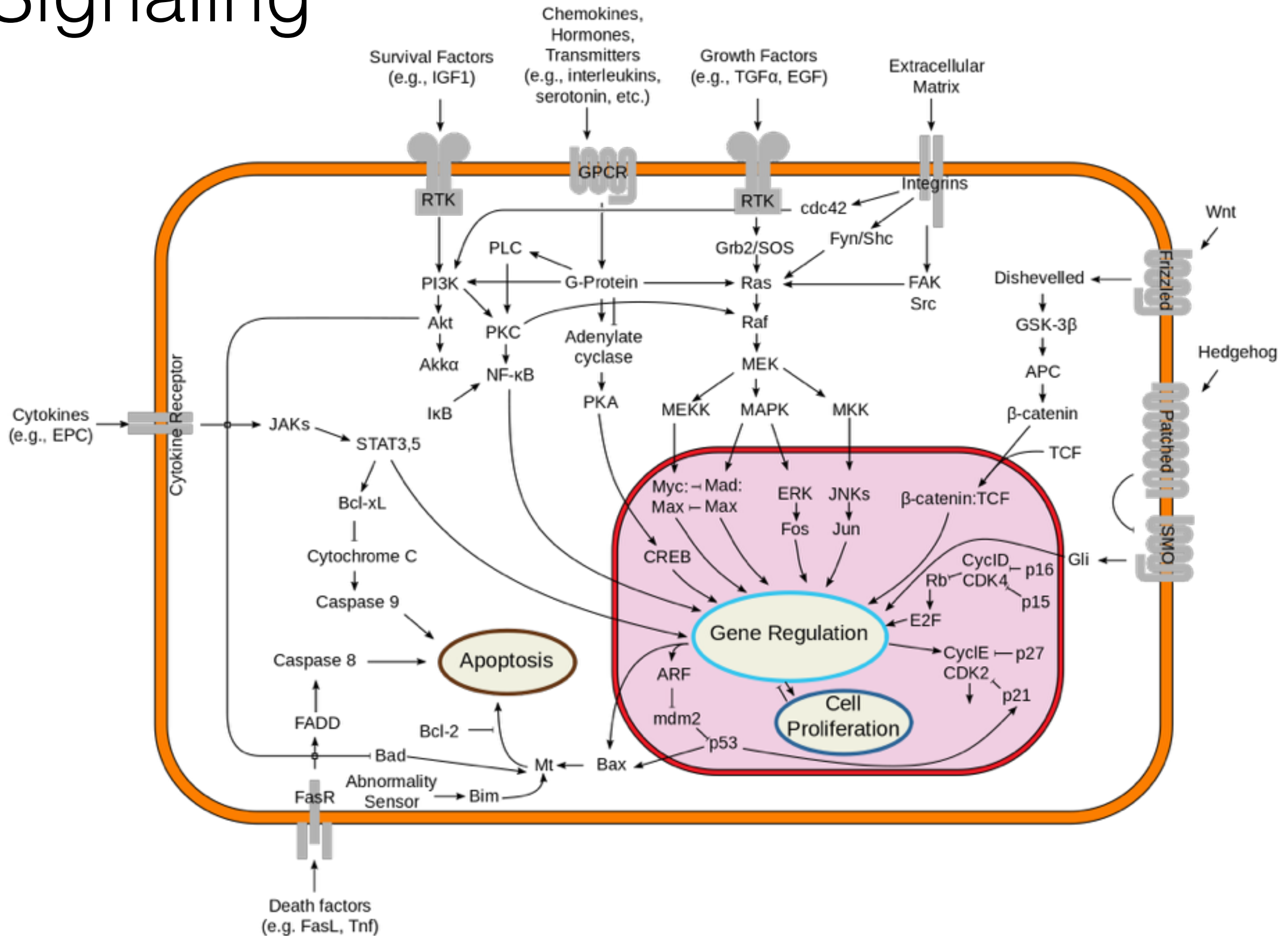


Executable knowledge representation in Systems Biology

The rule-based approach

Systems biology

Signaling



Proteins

- Synthesis
- Domains, residues (C-N terminus)
- Interactions (PPI)
- Post translational modification (Kinases)



How to build a network?



How to build a network?

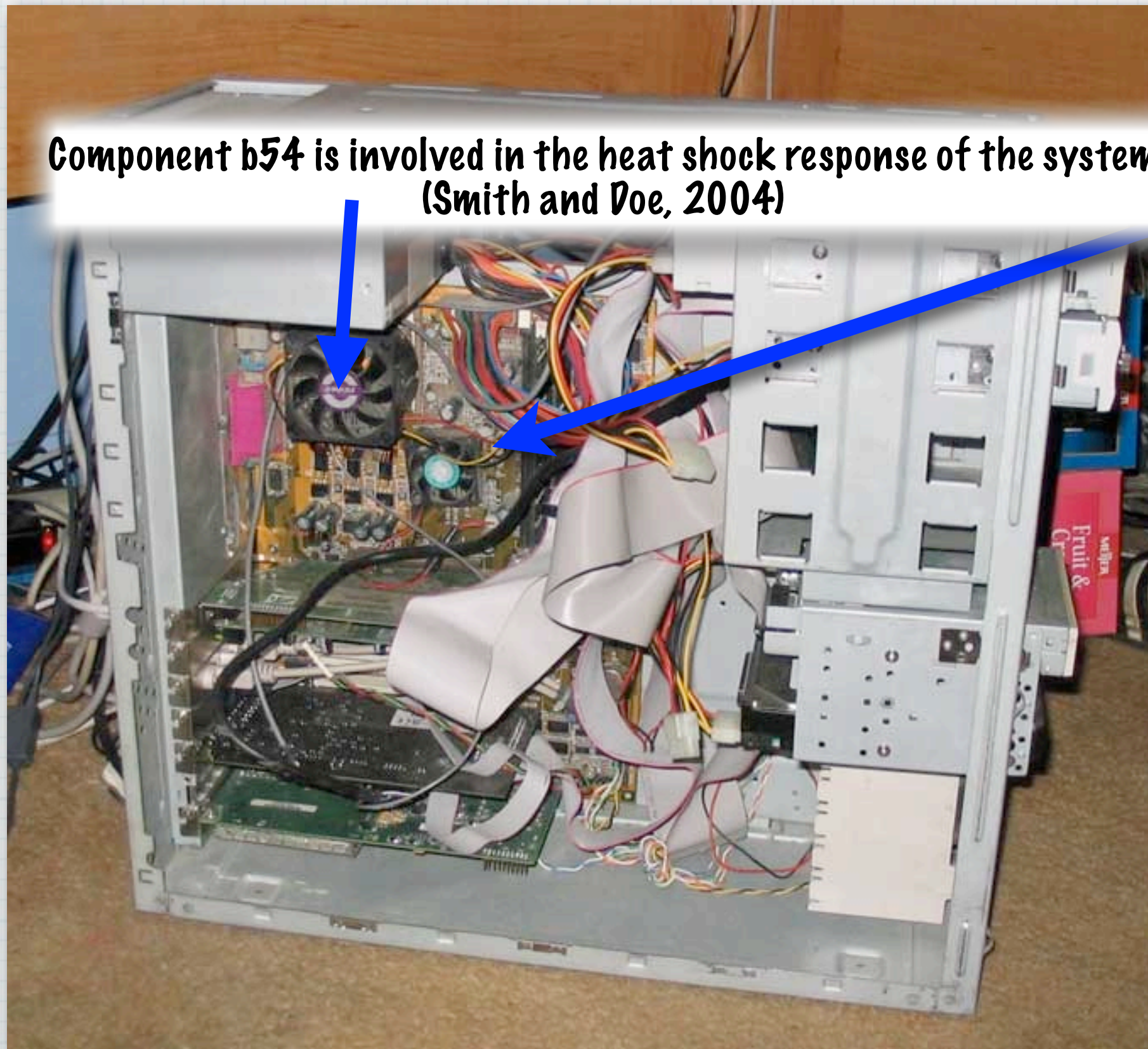
Component b54 is involved in the heat shock response of the system
(Smith and Doe, 2004)

Knock out:
Cut wire 'w'

Observation:
computer's heat goes up!

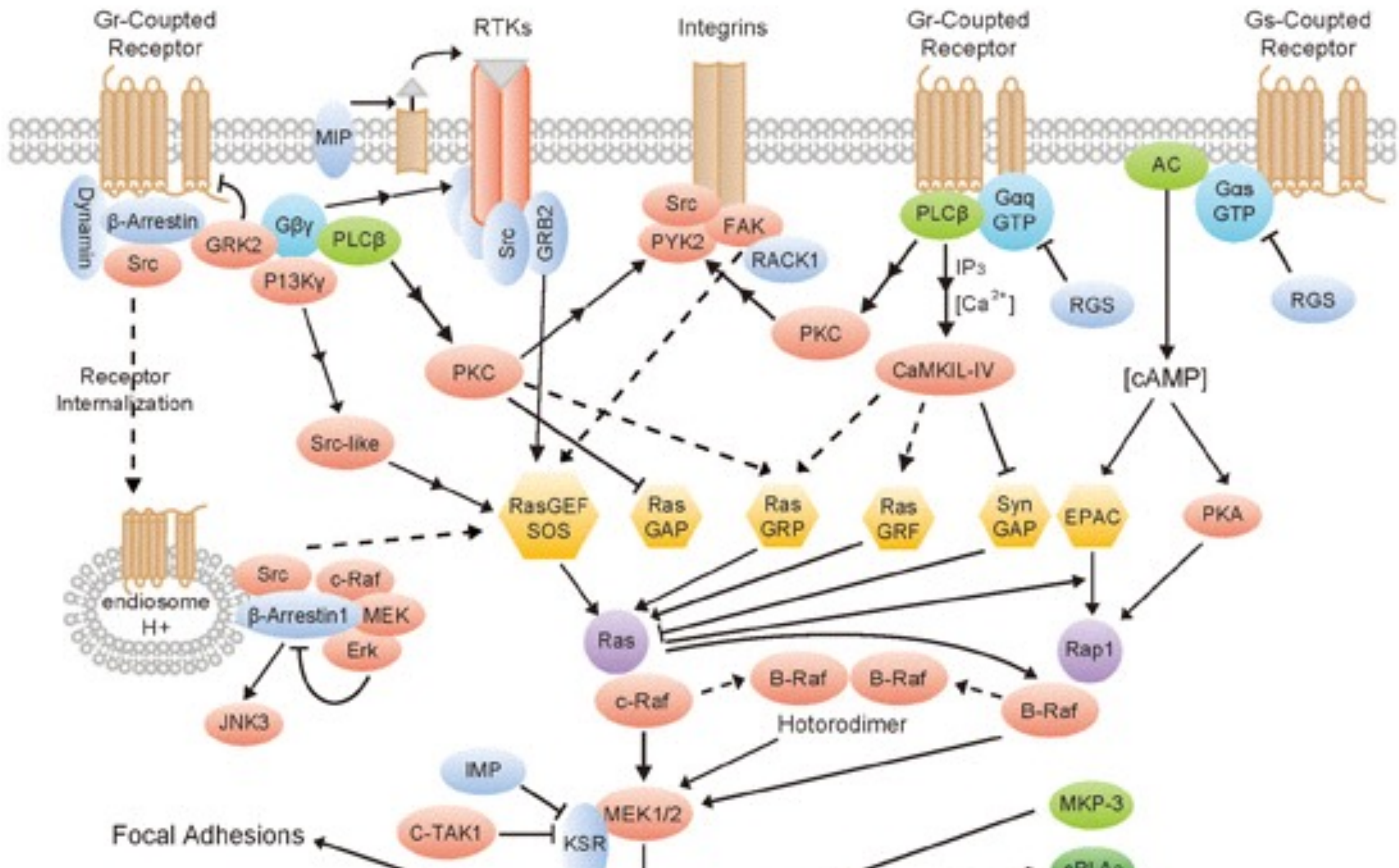
wire w

Cooling system

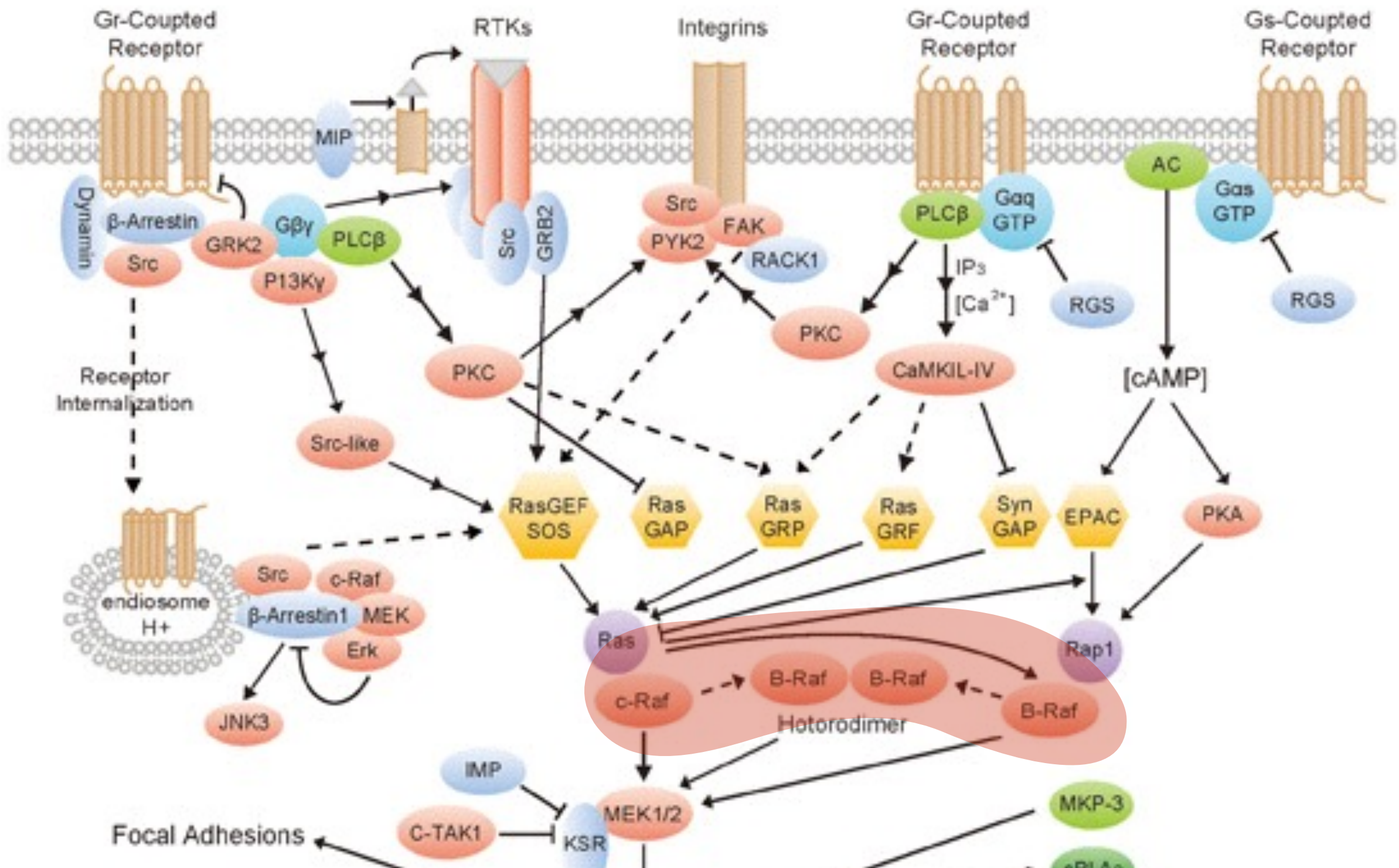


Make me a model of
RAF signaling!

Cross talks



Cross talks



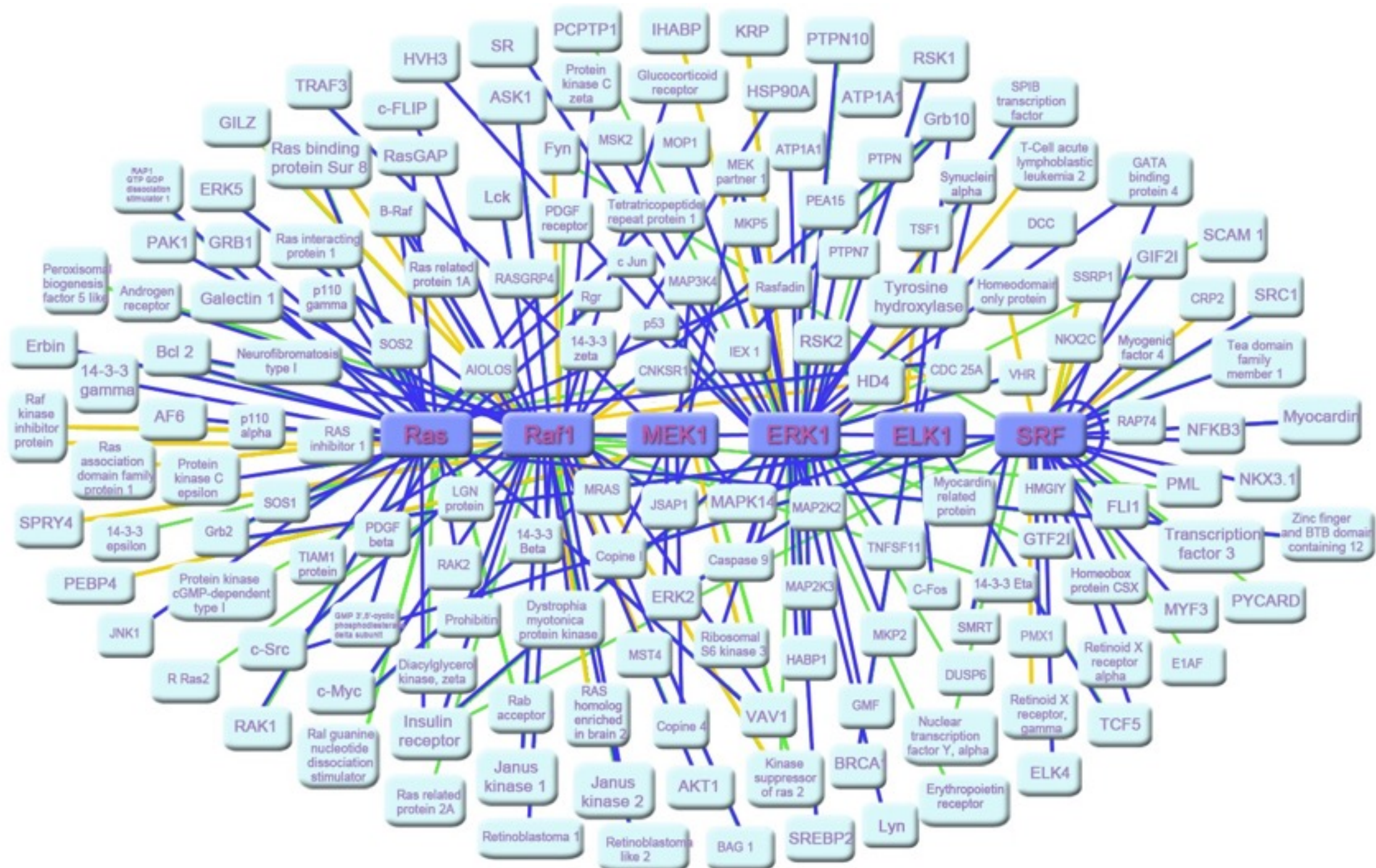
Reading papers

In the absence of an upstream stimulus, RAF kinases adopt a closed conformation, in which the N terminus inhibits the catalytic C terminus^{8,9}. This inactive conformation is stabilized through phosphorylation of key residues on RAF (such as S259 on CRAF and S365 on BRAF)¹⁰. These residues serve as docking sites for the adaptor protein 14-3-3 (refs. 11,12), and their dephosphorylation by phosphatases such as protein phosphatase 2A results in the displacement of 14-3-3, thus facilitating RAF activation^{13,14}.

More papers

Activated RAF kinases phosphorylate and activate MEK1 and MEK2 (ref. 2). These are dual-specificity kinases that in turn phosphorylate and activate ERK1 and ERK2 in what constitutes the RAF-MEK-ERK signaling cascade (or classical MAPK cascade). Active ERK phosphorylates serine or threonine residues within the Ser/Thr-Pro motif in many cytoplasmic and nuclear proteins³⁸

Wait a second...

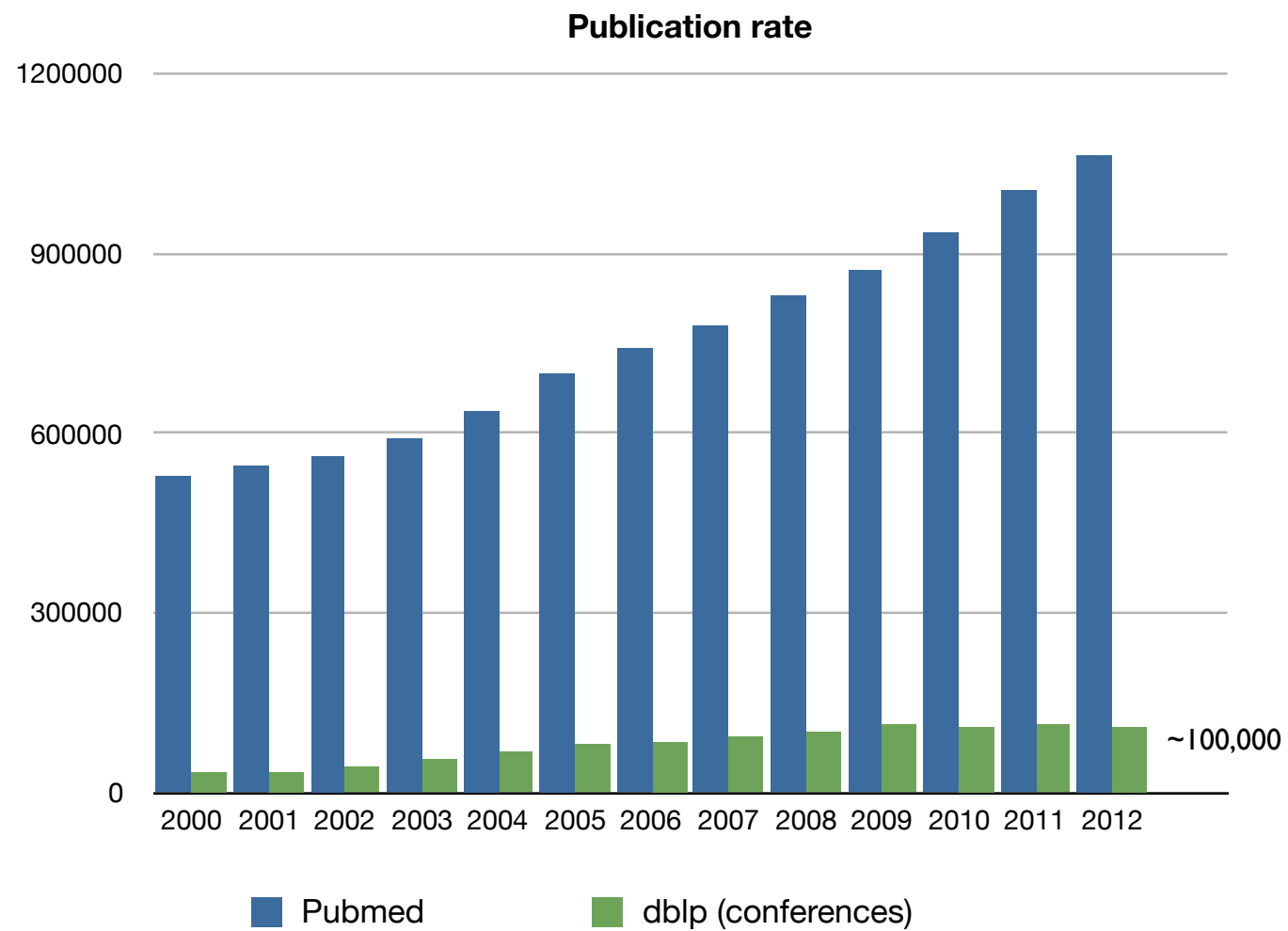


(1) The Systems Bid

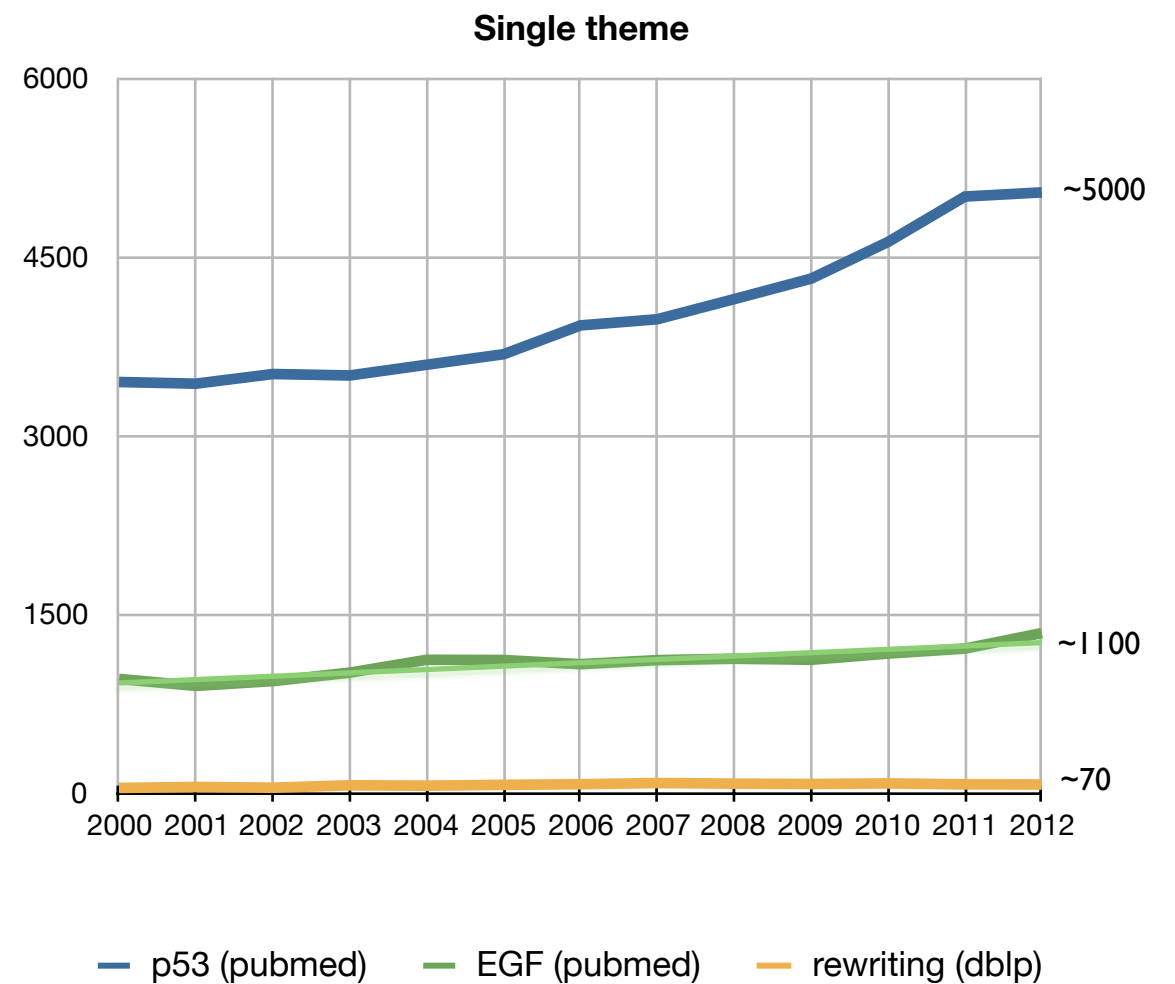
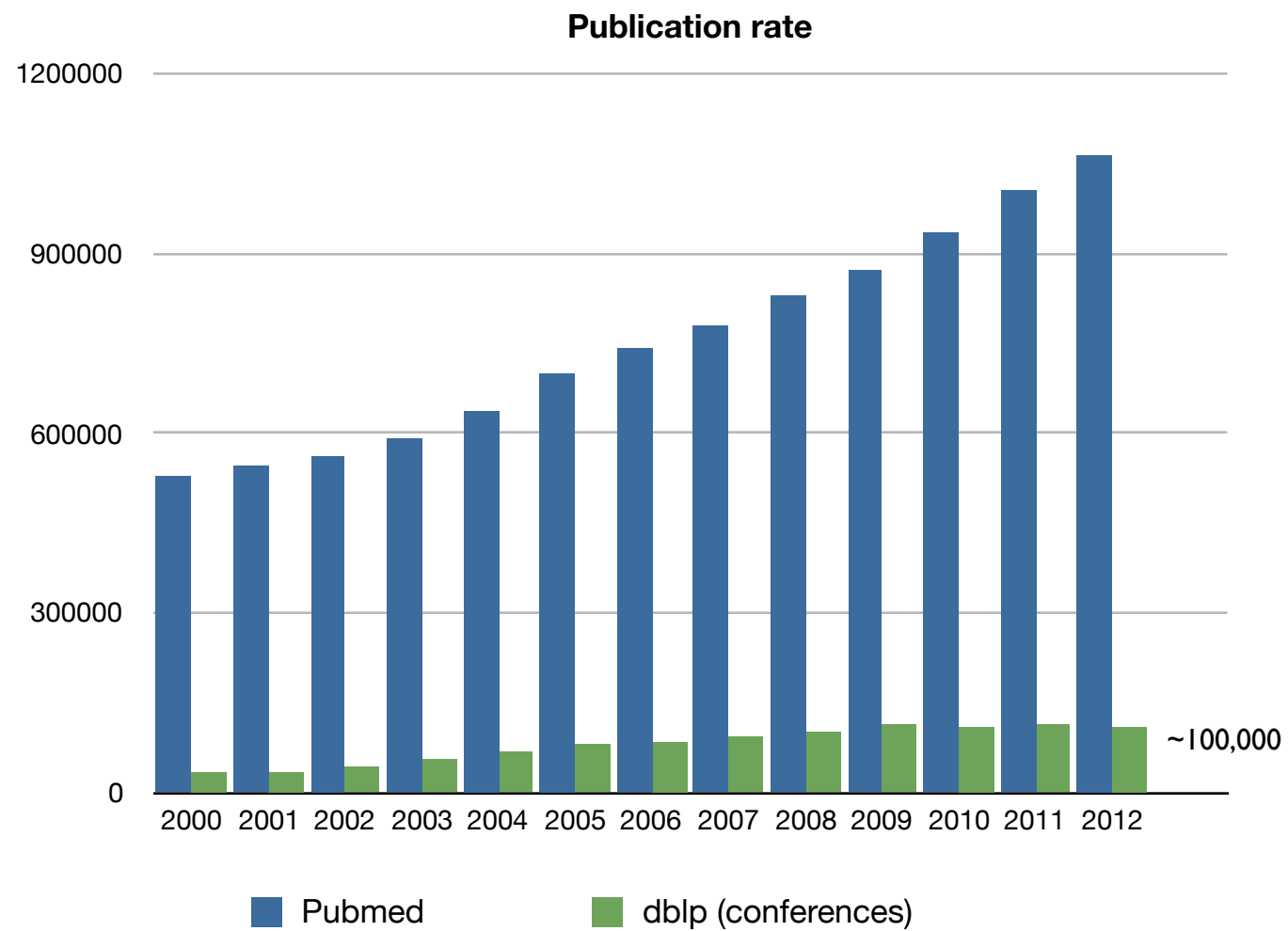


Big data

Big data



Big data

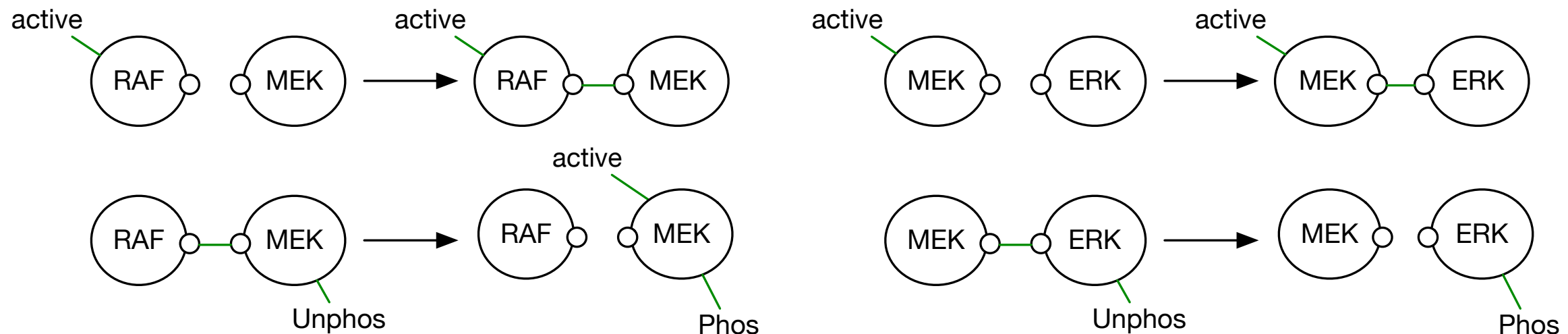


Systems biology 2.0

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Systems biology 2.0

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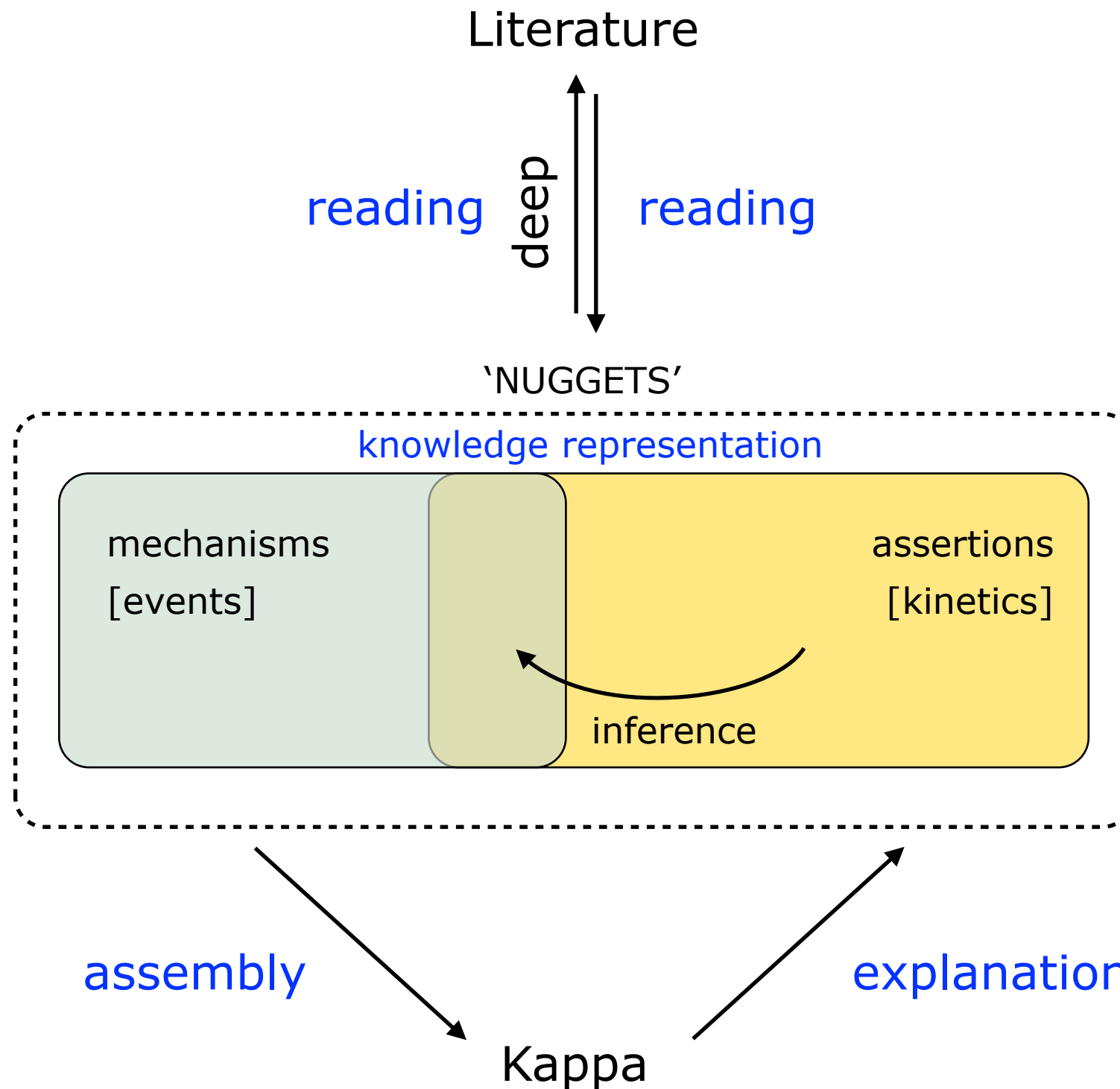
Formal reasoning vs. formal languages

ELEMENT.

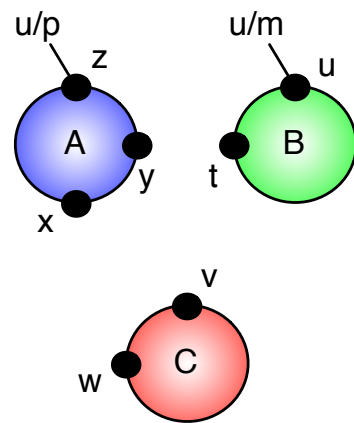
77

font droicts , si on leur adjouste le commun ABC ; le total $FB C$ sera egal au total ABD . Le triangle ABD a donc les deux costez AB, BD , egaux aux deux costez FB, BC du triagle CBF , chacun au sien, & les angles ABD , CBF contenus d'iceux costez, egaux, & par la 4. p. les triangles ABD, CBF seront egaux. Mais le quarré AF est double du triangle $FB C$ par la 41. prop. car ils sont sur mesme base BF , & entre mesmes paralleles BF, GC : il sera donc aussi double de son egal ABD , duquel le parallelogramme BK est aussi double par la mesme 41. prop. & par consequent le quarré AF sera egal au parallelogramme BK : car les choses doubles d'une mesme sont egales entr'elles. Par mesme discours on prouvera que le parallelog. CK est egal au quarré AI : partant les deux parallelogrammes ensemble BK & CK , seront egaux aux deux quarez ensemble AF & AI . Donc le quarré BE qui est composé d'iceux parallelogrammes BK, CK , sera aussi egal aux mesmes quarez AF, AI . Parquoy aux triangles rectangles, le quarré du costé, &c. Ce qu'il falloit prouver.

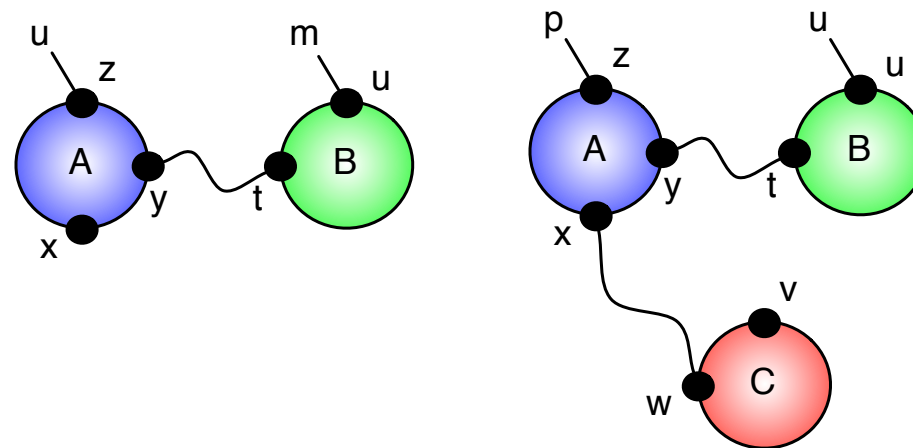
Big mechanism project



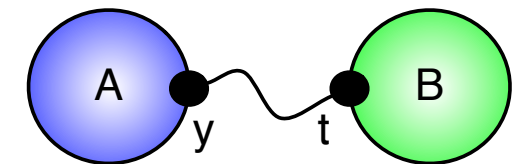
The cell as a graph



Proteins (nodes)



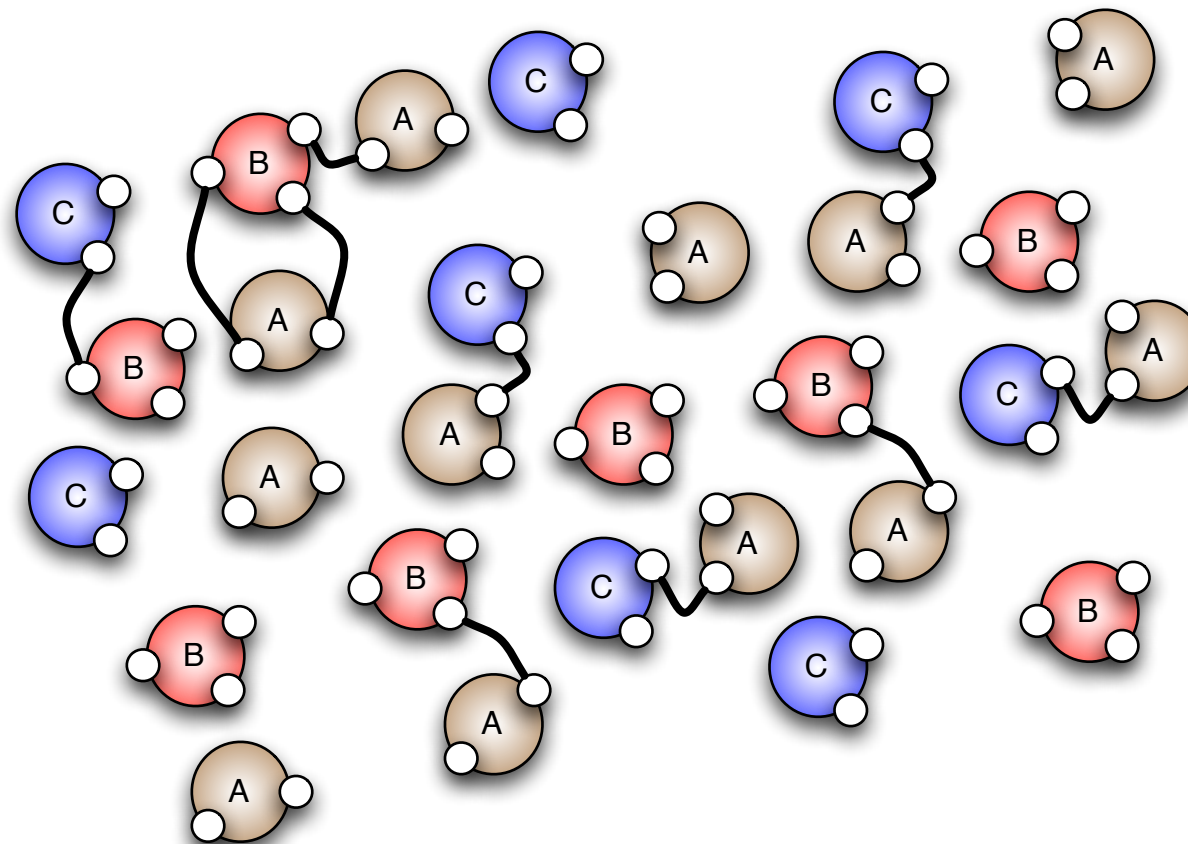
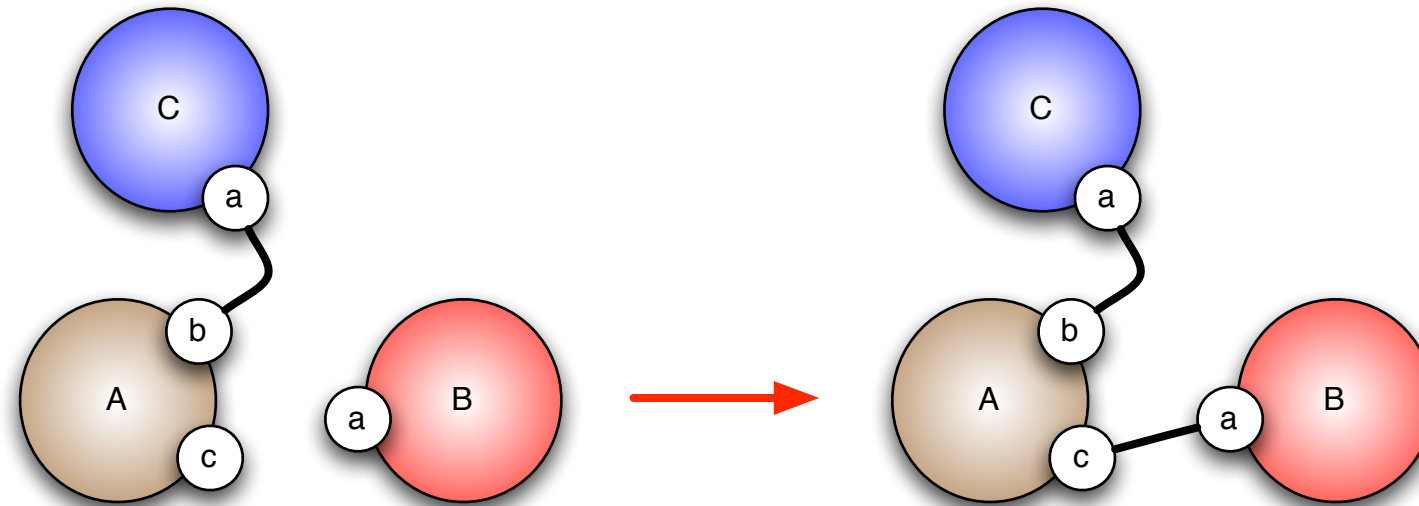
Species
(connected
components)



Expression
(pattern)

Rule application

A pattern



Syntax

- Agent signature **%agent:** $A(x \sim u \sim p \sim 0, y, z)$

- Simple rule

'my_rule' $A(x \sim u?, y), A(x \sim p?, z) \leftrightarrow A(x \sim u?, y!1), A(x \sim p?, z!1) @ 0.1, 1$

- Initial state

%init: 1000 $A()$

- Variables

%var: *'Bound A'* $|A(y!_, z)| + |A(y, z!_)| + |A(y!_, z!_)|$

%var: *'bndA/A'* $'Bound A' / |A()|$

Exo 1 (*)

K is a kinase for S phosphorylation

K is active when phosphorylated at residue Tyr605

P is a ubiquitous phosphatase

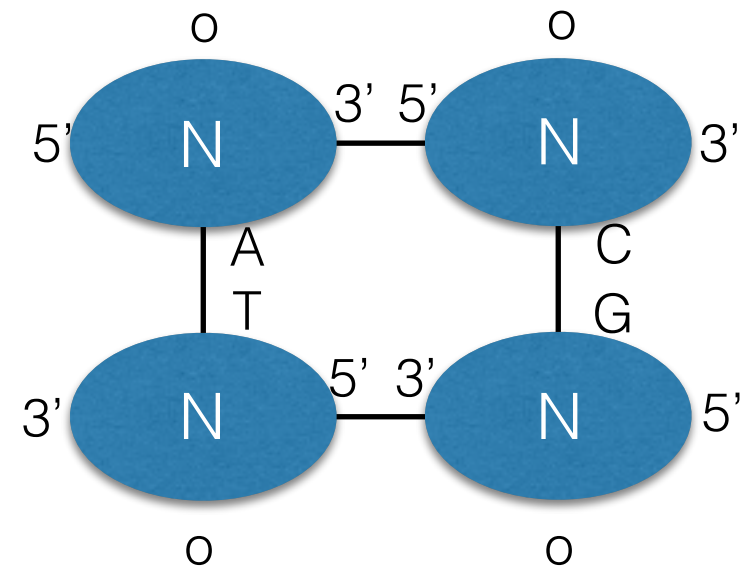
Exo 2 (***)

Encode double strand DNA
on which enzymes can bind

Use Kappa to generate a
circular oligomer of size n

Needed:

- longest prefix convention
- perturbation



Exo 3 (***)

Write a model of **deamination** and **repair**

Deamination: C → U (stop when 2% of the C bases are deaminated)

Repair:

- UDG binds and slides on DNA
- On a U/G it removes the faulty base and detaches (U→AP)
- The hole is then filled by BER enzymes (AP→C)

Needed the file dna.ka from (or generated from Exo 2):

[https://www.irif.univ-paris-diderot.fr/
~jkrivine/homepage/Teaching_files/dna.ka](https://www.irif.univ-paris-diderot.fr/~jkrivine/homepage/Teaching_files/dna.ka)

Static analysis and Simulation techniques