Modeling the dynamics and function of cellular interaction networks

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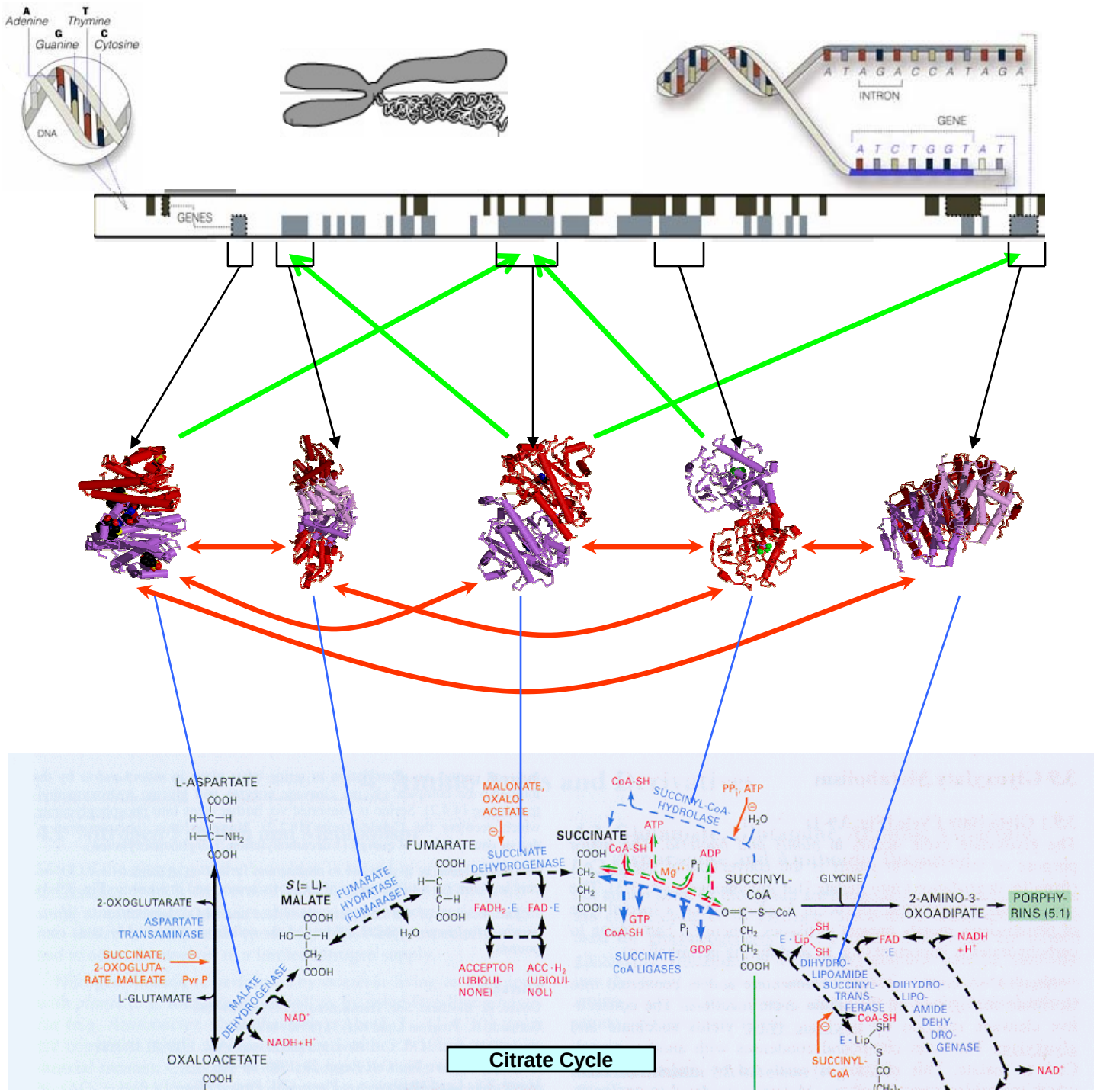


GENOME

protein-gene interactions

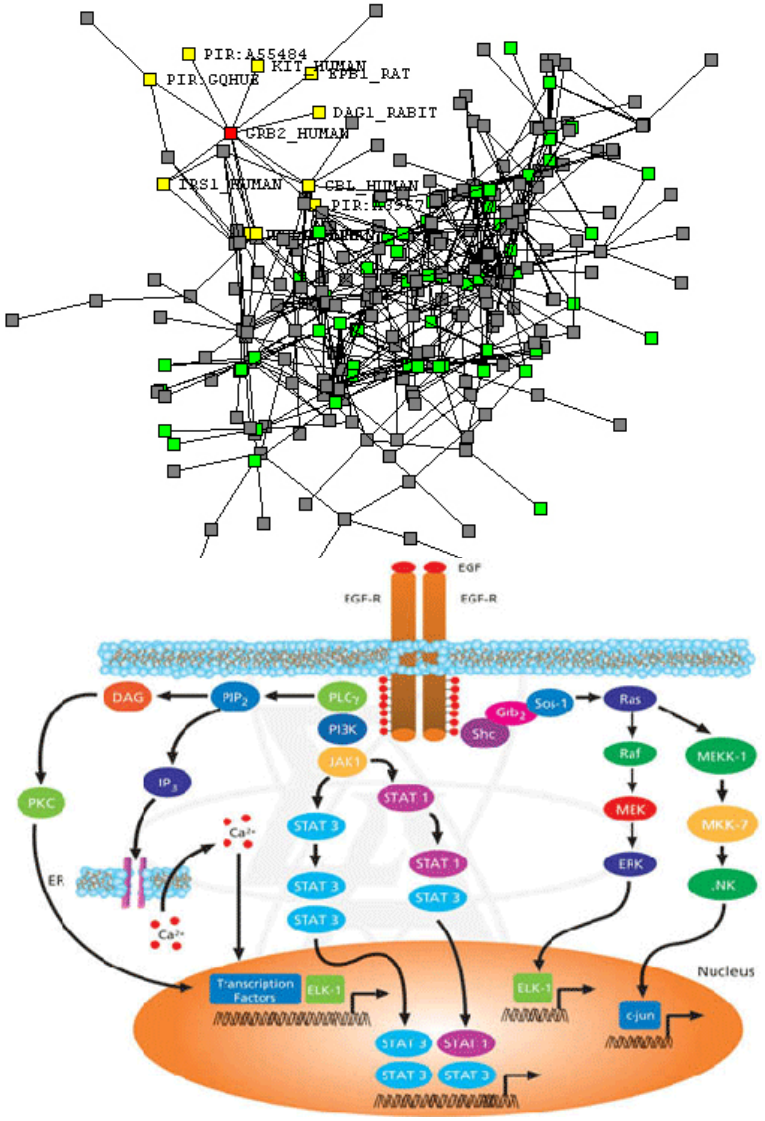
PROTEOME

protein-protein interactions

METABOLISM

Bio-chemical reactions

Cellular processes form networks on many levels



Protein interaction networks

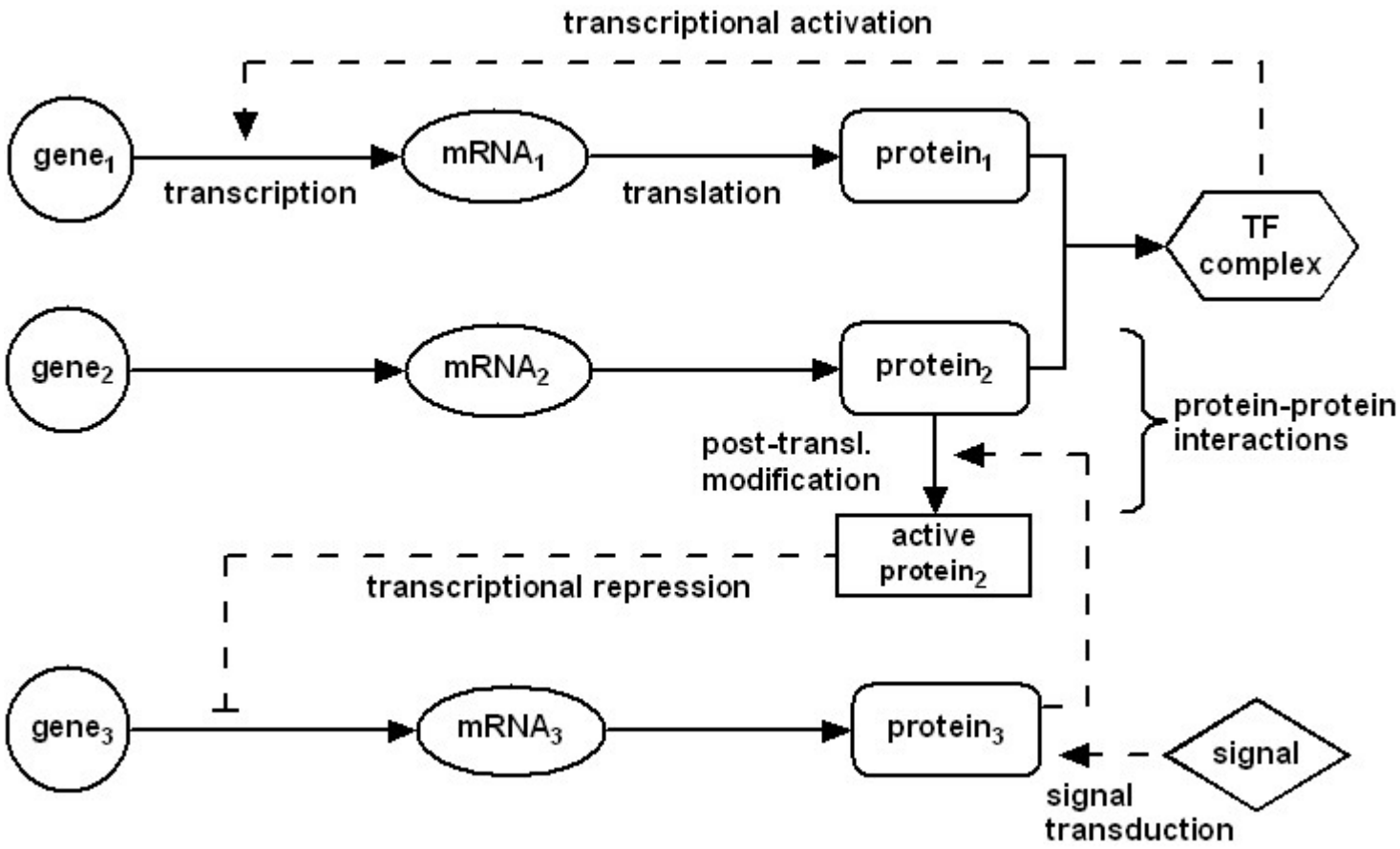
- Nodes: proteins
- Edges: protein-protein interactions (binding)

Signal transduction networks

- Nodes: proteins, molecules
- Edges: reactions and processes reflecting information transfer (e.g. ligand/receptor binding, protein conformational changes)

R. Albert, Scale-free networks in cell biology, J. Cell Science 118, 4947 (2005)

Signaling, gene regulation and protein interactions are intertwined



Mapping of cellular interaction networks

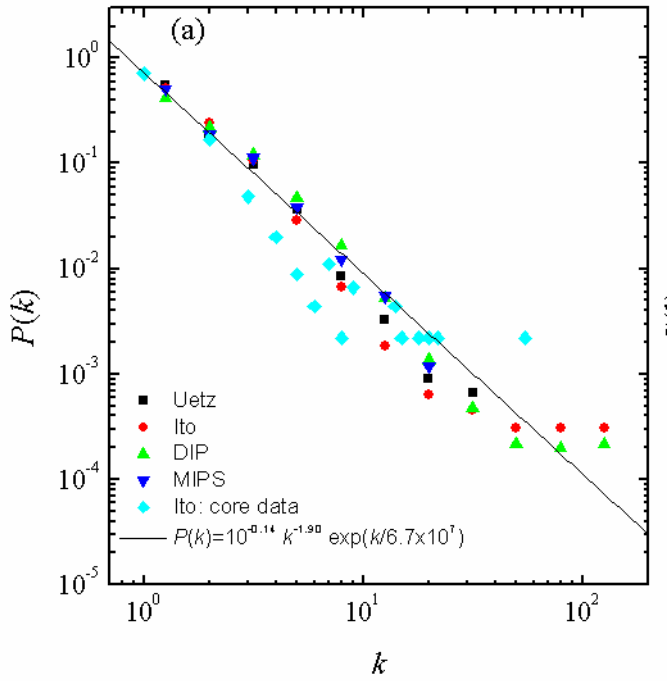
Experimental advances allow the construction of genome-wide cellular interaction networks

- Protein networks:
  Uetz et al. 2000, Ito et al., 2001, Krogan et al. 2006 – *S. cerevisiae,*
  Giot et al. 2003 – *Drosophila melanogaster* , Li et al. 2004 – *C. elegans*
  Human interactome
- Transcriptional regulatory networks
  Shen-Orr et al. 2002 – *E. coli*,
  Guelzim et al 2002, Lee et al. 2002 - *S. cerevisiae,*
  Davidson *et al.* 2002 – sea urchin
- Signal transduction networks
  Ma'ayan et al. 2005 – mammalian hippocampal neuron

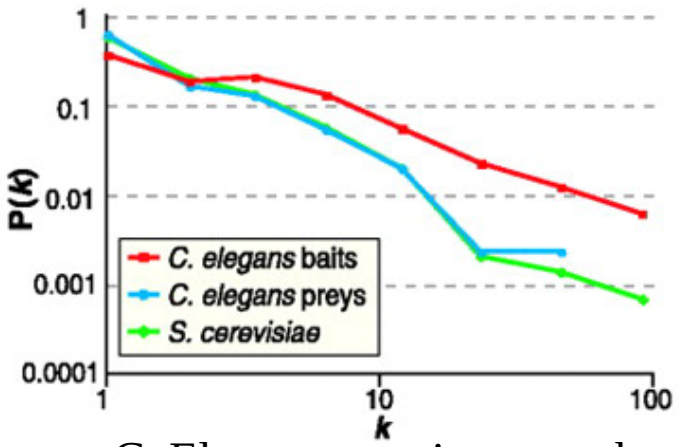
Graph analysis uncovered common architectural features of cellular networks: Connected, short path length, heterogeneous (scale-free), conserved interaction motifs

node degree: number of edges (indicating regulation by/of multiple components)

degree distribution: fraction of nodes with a given degree



S. cerevisiae protein network

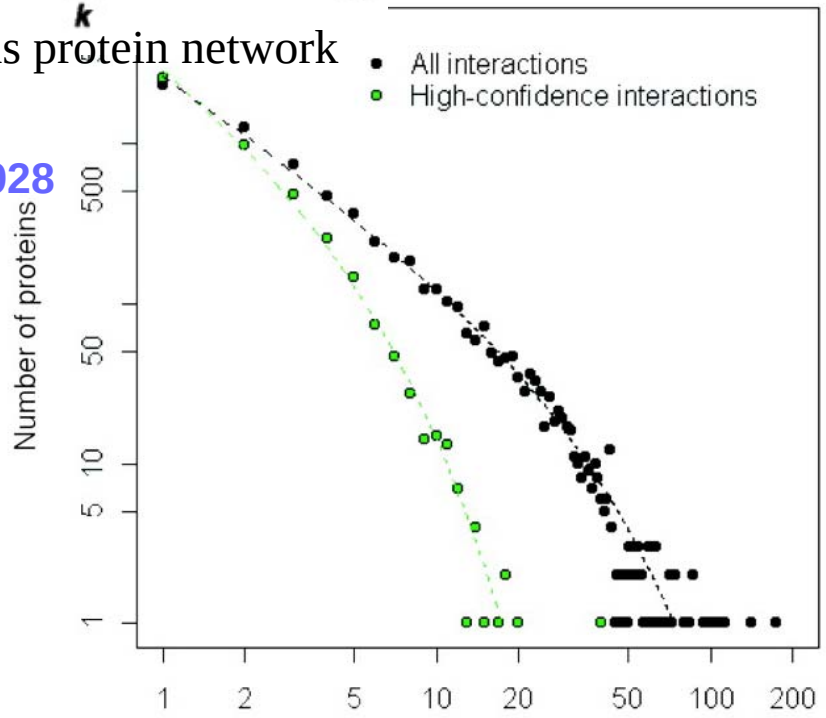


C. Elegans protein network

Li *et al.*, Science 303, 540 (2004)

D. melanogaster protein network

Yook *et al.*, Proteomics 4, 928 (2004)



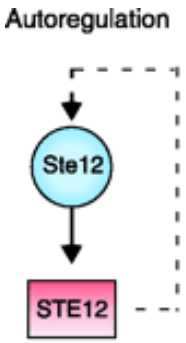
Giot *et al.*, Science 302, 1727 (2003)

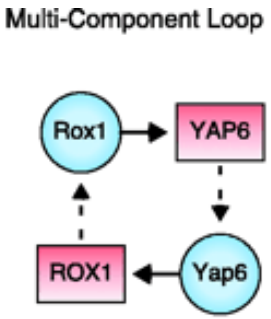
Biological networks are highly heterogeneous

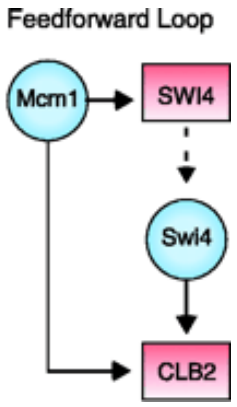
This suggests robustness to random mutations, but vulnerability to mutations in highly-connected components.

R. Albert, A.L. Barabasi, Rev. Mod. Phys. 74, 47 (2002)

Abundant regulatory motifs

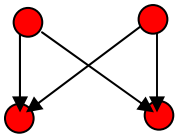




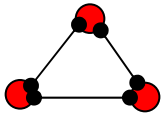


Positive and negative feedback loops

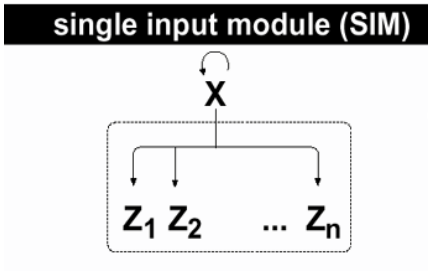
bifans



scaffolds



Positive and negative feedforward loops



Shen – Orr et al., Nature Genetics (2002)

Lee et al, Science 298, 799 (2002)

Ma'ayan et al, Science 309, 1078 (2005)

Feedforward loop: convergent direct and indirect regulation; noise filter

Single input module: one TF regulates several genes; temporal program

Bifans: combinatorial regulation

Scaffold: protein complexes

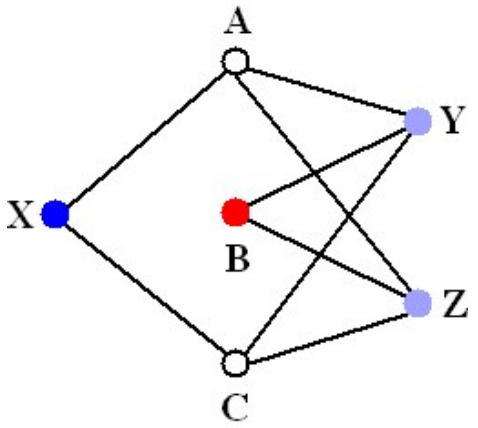
Positive and negative motifs:

Balance: homeostasis

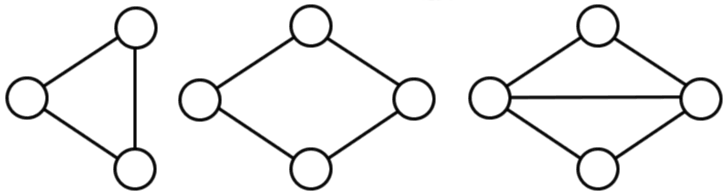
More positive: long-term info storage

Interaction prediction using abundant motifs

- The interaction pattern of each protein forms a signature
- Find most similar proteins
- Suggest as interaction partners the signature elements that the most similar proteins have, but the target protein does not

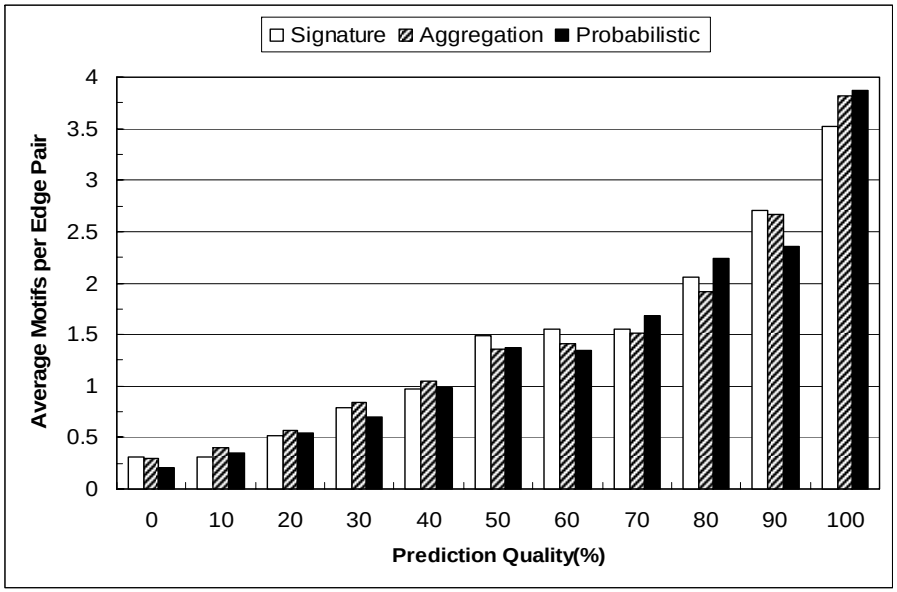


Signature of X: (A,C)
Most similar to Y (A,B,C) and Z (A,B,C)
Both share the element B that X does not have
Suggested interaction partner for X: B



A leave-one-out approach on the DIP PIN indicates an 8-25% success rate of the first 1-10 candidate (compare to <0.1% for random selection)

Prediction success based on the abundance of network motifs in the neighborhood of node.



I Albert & R. Albert, Bioinformatics (2004)

Importance of a dynamical understanding

Only subsets of the genome-wide interaction networks are active in a given external condition

Han et al. 2004 – dynamical modularity of protein interaction networks
Luscombe et al. 2004 – endogeneus and exogeneus transcriptional subnetworks

Proteins, mRNAs and small molecules have time-varying abundances.

Network topology needs to be complemented by a description of network dynamics – states of the nodes and changes in the state

Complete dynamical description is only feasible on smaller networks (modules):
Signal transduction in bacterial chemotaxis, NF-kB signaling module, the yeast cell cycle, Drosophila embryonic segmentation

Access dynamics through modeling

First step: define the system; collect known states or behavior

Input: components; states of components

Hypotheses: interactions; kinetics (rates, parameters).

Validation: capture known behavior.

Explore: study cases that are not accessible experimentally

change parameters, change assumptions

The role of protein interactions in

1. The Drosophila segment polarity gene network

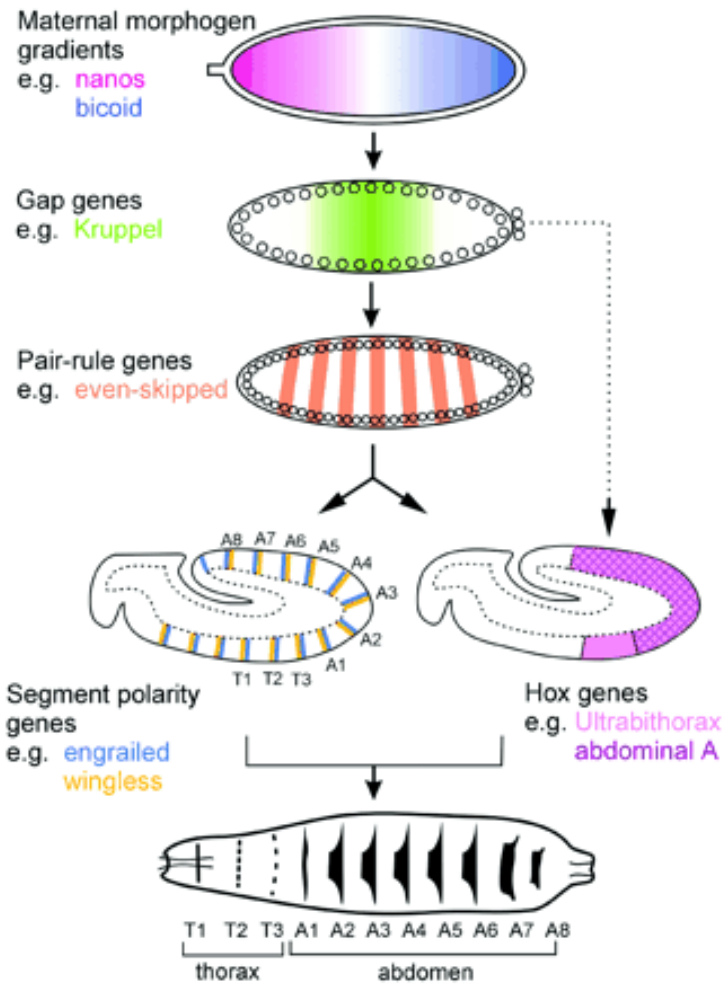
R. Albert, H. G. Othmer, Journ. Theor. Biol. 223, 1 (2003)

M. Chaves, R. Albert, E. Sontag Journ. Theor. Bio. 235, 431 (2005).

2. Signal transduction in plant guard cells

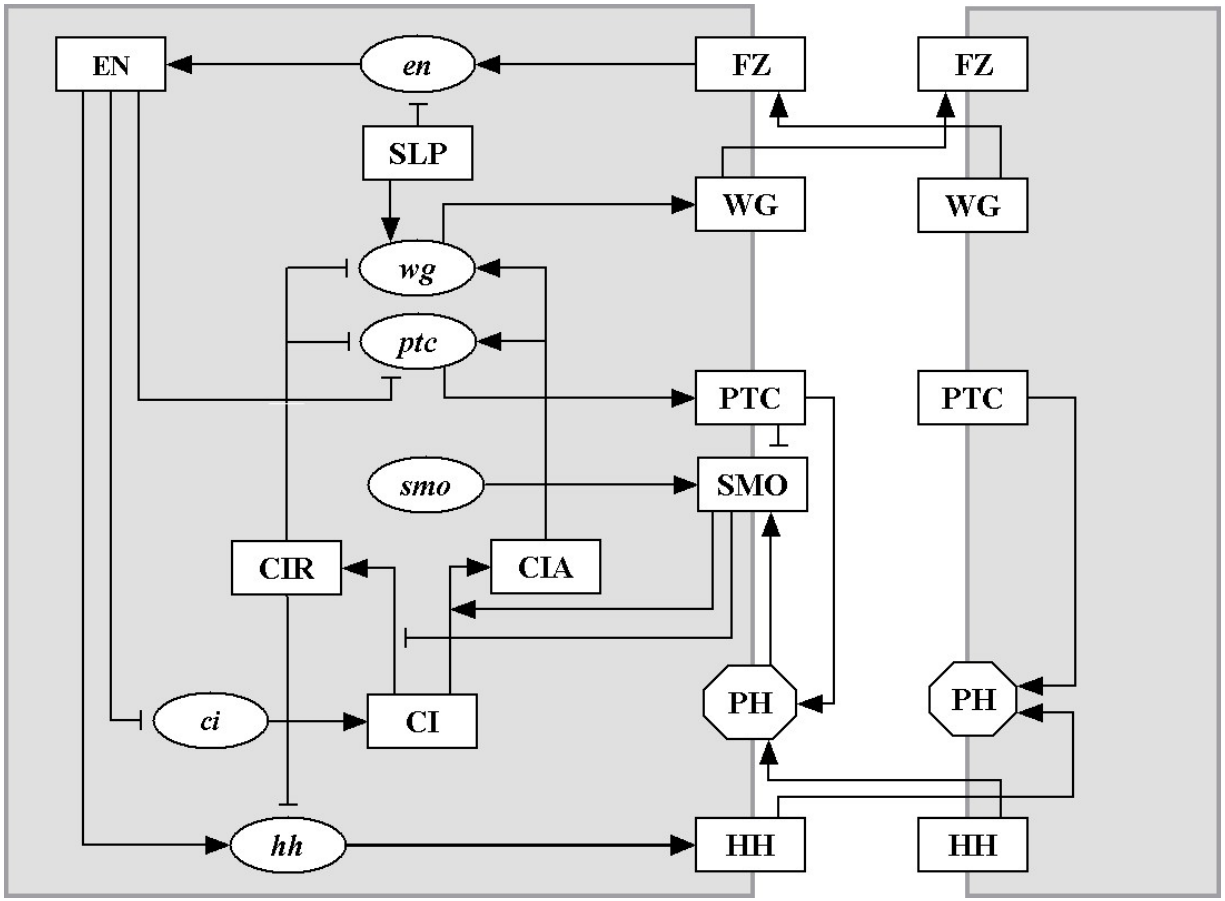
S. Li, S. M. Assmann, R. Albert (2006).

Segmentation is governed by a cascade of genes



Transient gene products, initiate the next step then disappear.

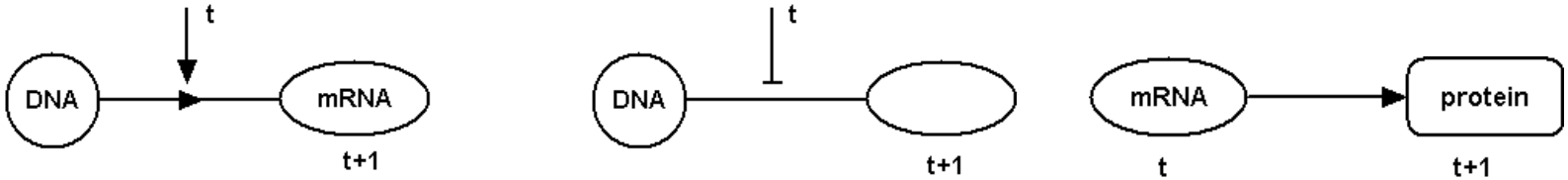
Network of the Drosophila segment polarity genes



R. Albert, H. G. Othmer, Journ. Theor. Biol. 223, 1 (2003)

Qualitative (Boolean) model

- Transcripts and proteins are either ON (1) or OFF(0).
- Transcription depends on transcription factors; inhibitors are dominant.



- Translation depends on the presence of the transcript.
- Transcripts and most proteins decay if not produced.

$$hh_i^* = EN_i \quad \textit{and not } CIR_i$$

$$EN_i^* = en_i$$

- Synchronous update: transcription, translation, mRNA/protein decay on the same timescale, protein binding faster

  R. Albert, H. G. Othmer, Journ. Theor. Bio. 223, 1 (2003).

- Asynchronous update & hybrid model: post-translational processes faster than pre-translational

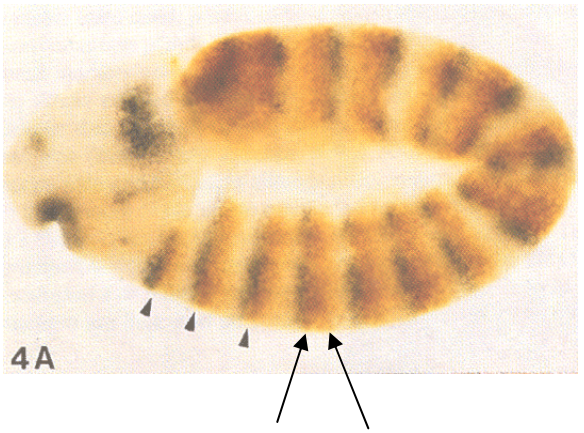
  M. Chaves, R. Albert, E. Sontag Journ. Theor. Bio. 235, 431 (2005).

  M. Chaves, E. Sontag, R. Albert, IEE Proc. Syst. Bio. (2006).

The model reproduces the wild type steady state

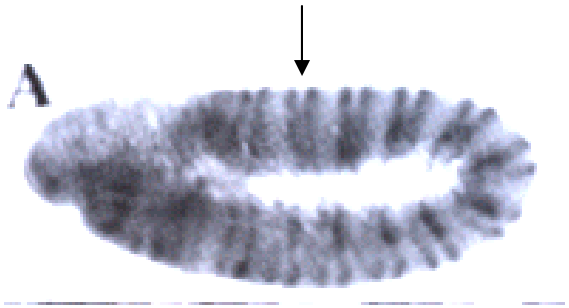
Synchronous model

initial state steady state



wg en

ptc

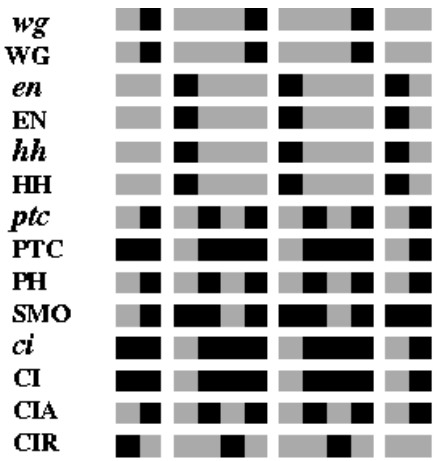


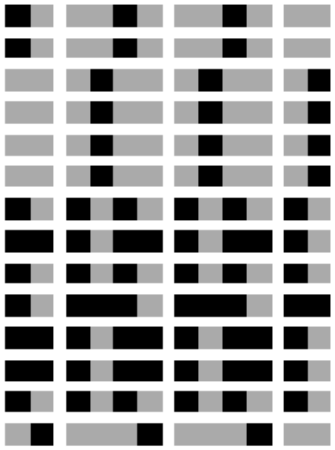
The net effect of the interactions is enough to capture the functioning of the network.

The kinetic details of the interactions can vary as long as their overall effect is maintained – robustness.

Dynamical repertoire: four steady states

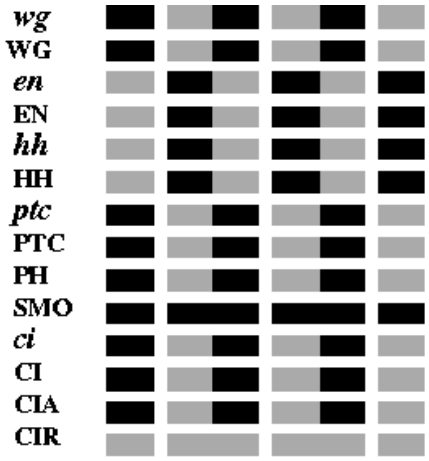
wild type



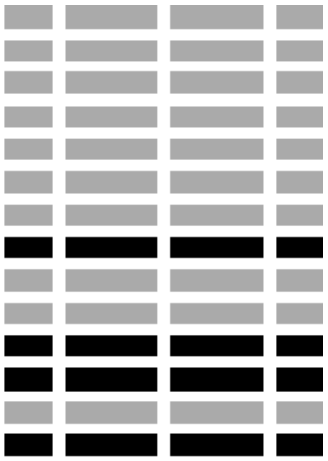


displaced

broad



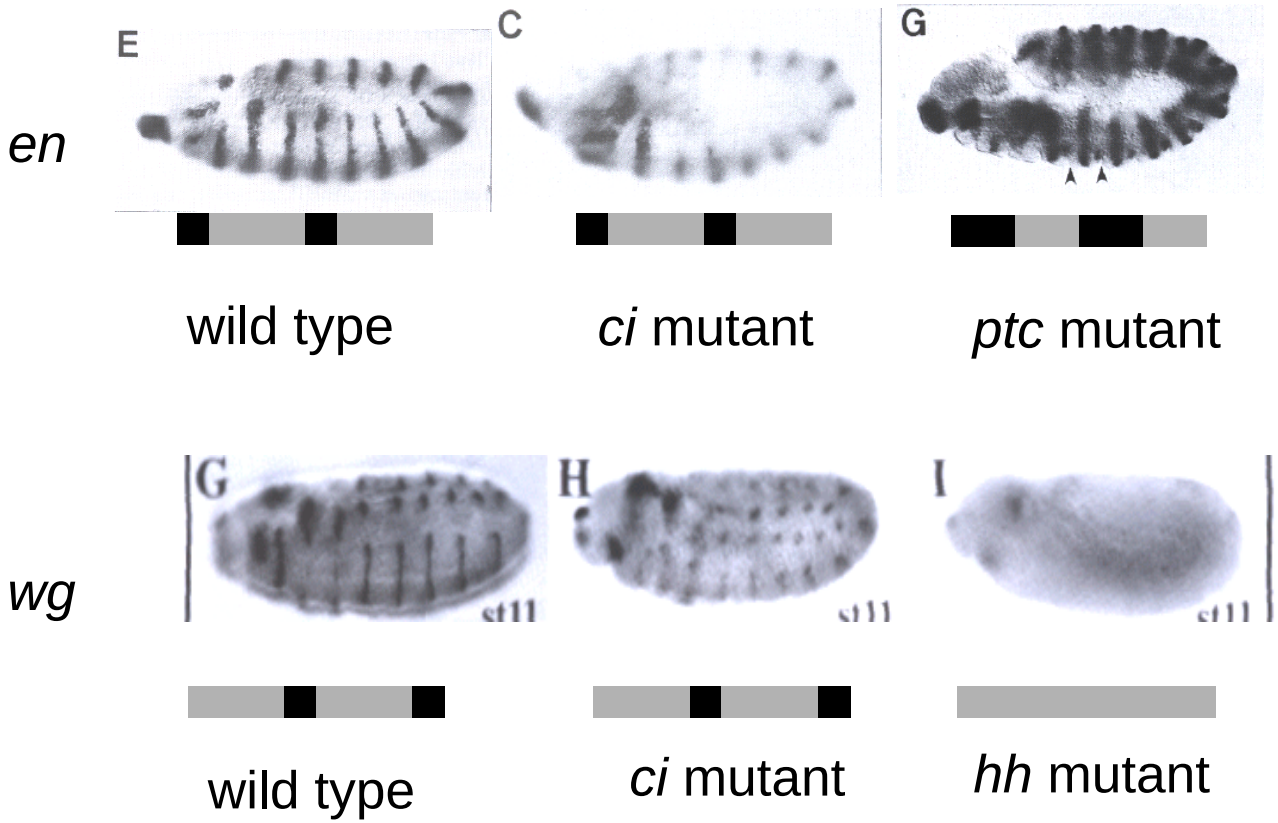
ectopic furrow



no segmentation

lethal

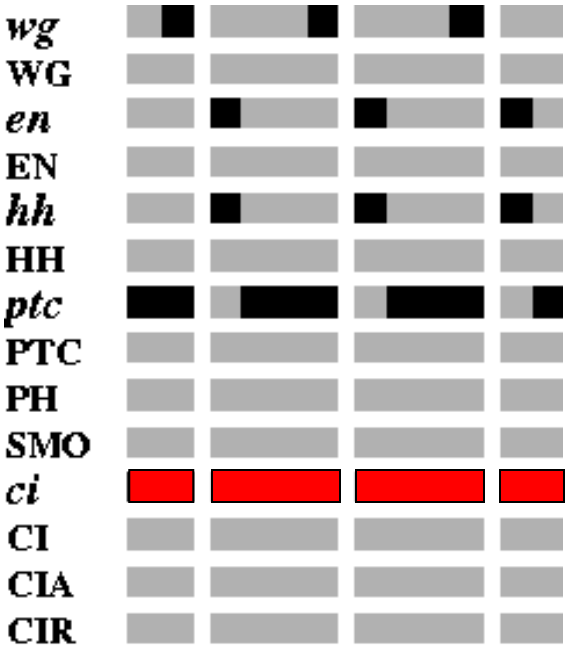
Model correctly reproduces experimental results on knock-out mutants



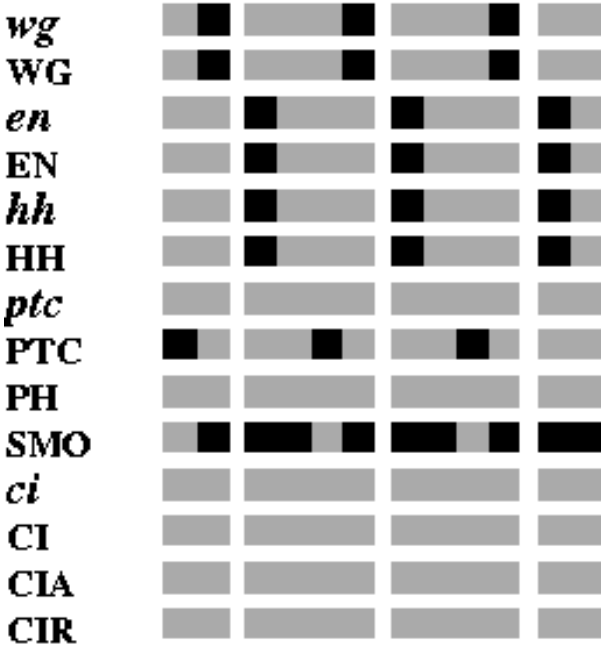
Tabata, Eaton, Kornberg, Genes & Development 6, 2635 (1992)

Gallet et al., Development 127, 5509 (2000)

ci mutation can preserve the prepattern



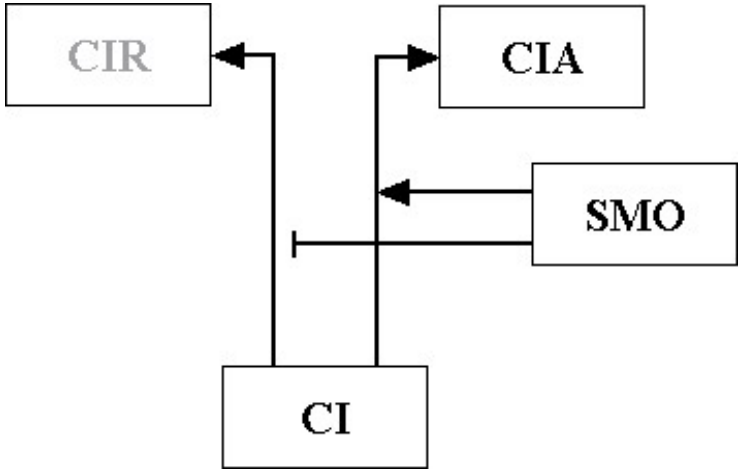
initial state



final state

The effect of *ci* mutation depends on the initial state.
For wild type prepattern, the *wg, en, hh* stripes remain.

Regulation of post-translational modifications crucial for correct dynamic behavior

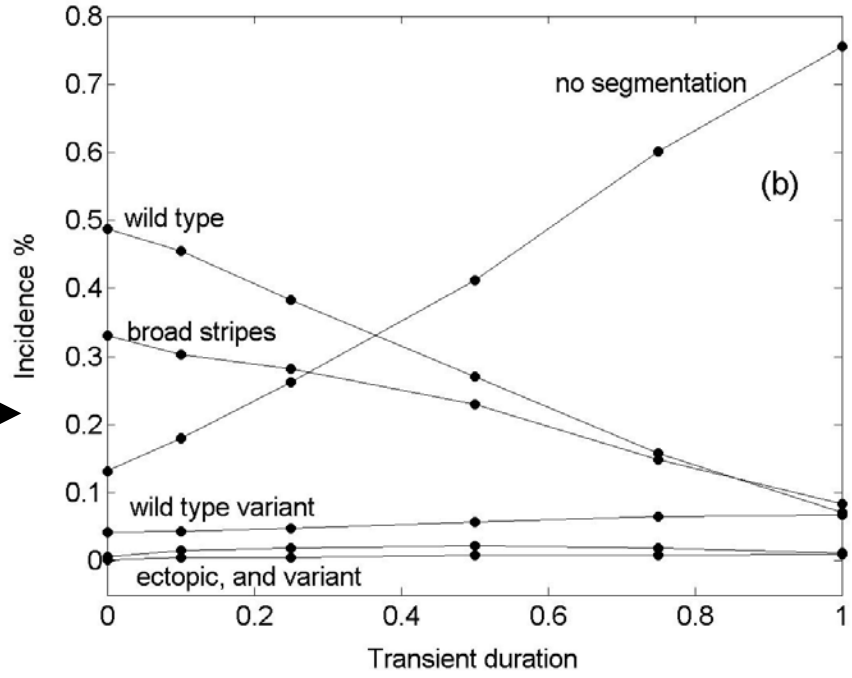


The two CI transcription factors have opposite regulatory roles. The post-translational modification of CI is regulated in a binary fashion. The expression of CIA and CIR needs to be complementary in all CI-expressing cells

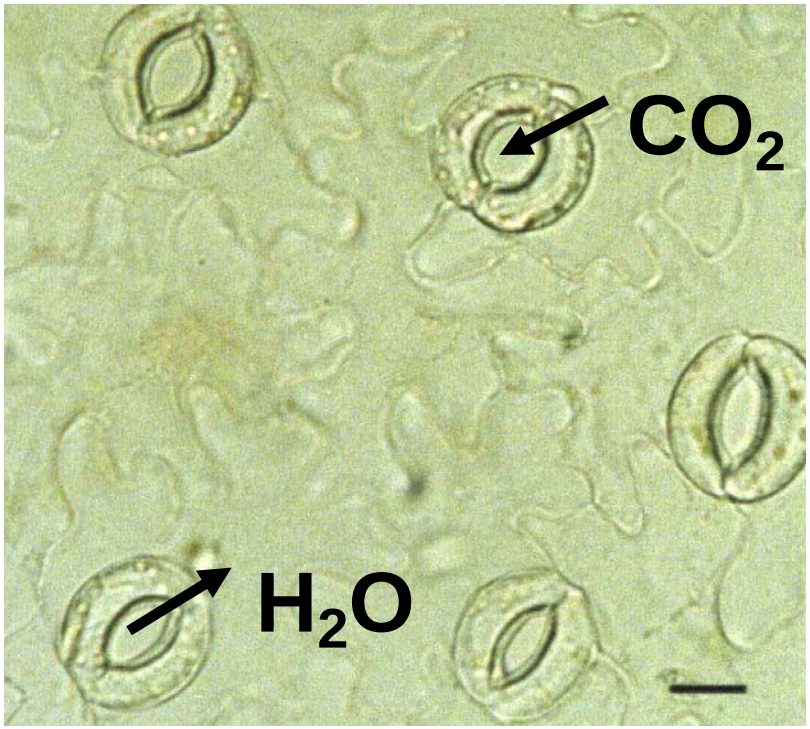
If a perturbation leads to a transient imbalance between CIA and CIR, the wild type steady state becomes unreachable.

Only CIA - broad stripes;
Only CIR - no segmentation

The condition of CIA/CIR complementarity is that PTC be initiated before SMO – true



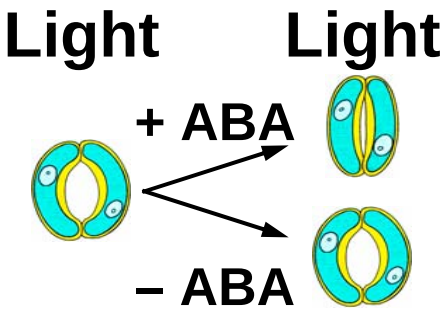
Modeling abscisic acid (ABA) signaling in plants



The exchange of oxygen and carbon dioxide in the leaf occurs through pores called **stomata**.

Stomata open in the morning and close during the night. The immediate cause is a change in the turgor (fullness) of the **guard cells**.

90% of the water taken up by a plant is lost in transpiration, while the stomata are open.

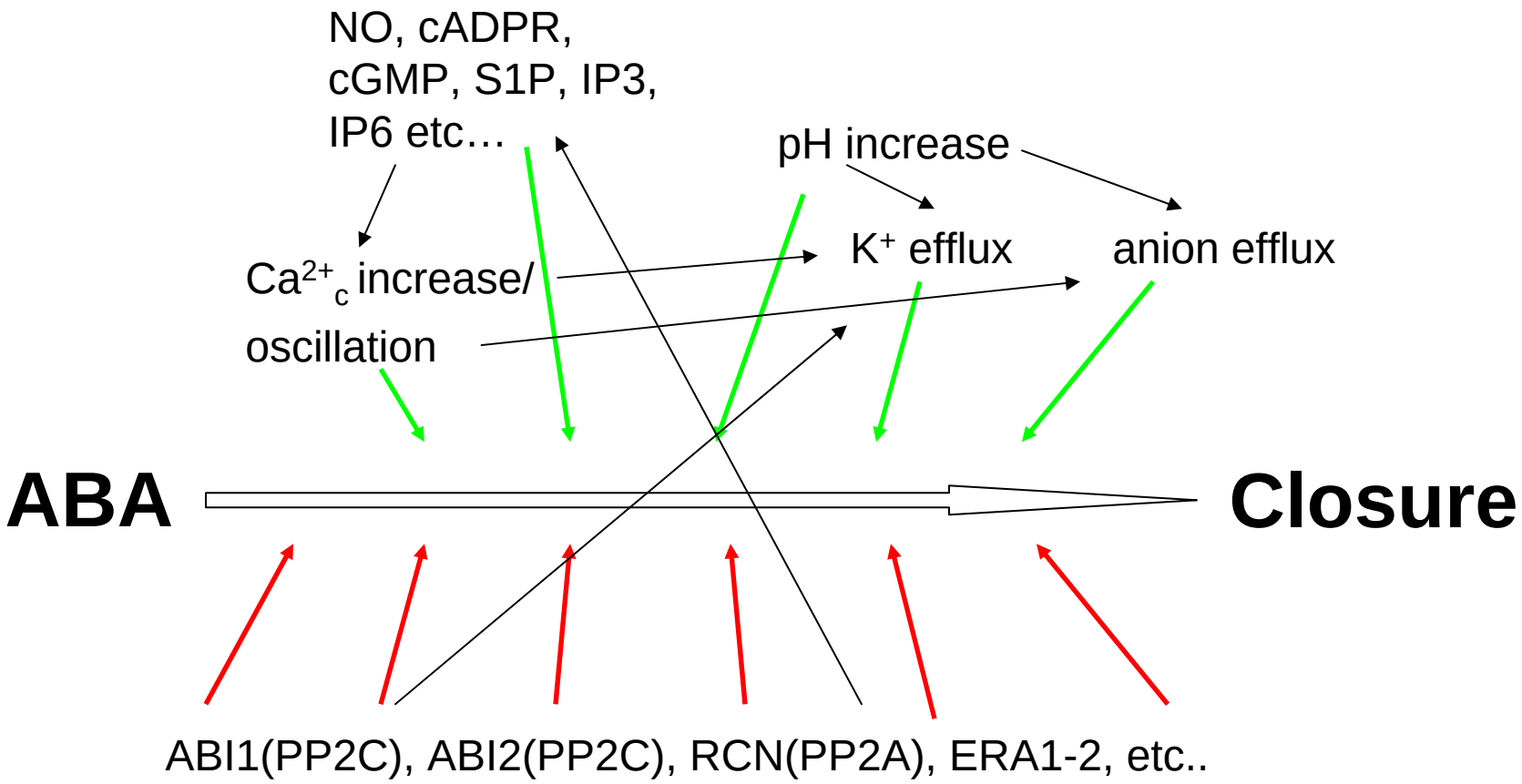


During drought conditions the hormone abscisic acid (ABA) triggers the closing of the stomata.

More than 20 proteins and molecules participate in ABA-induced closure, but their interaction network has not been synthesized yet.

Mediators of ABA-induced stomatal closure

Inference methods: genetic & pharmacological perturbations
biochemical evidence



Database construction

- Literature mining & curation - Song Li
- Define network
  - nodes: proteins, chemical messengers, ion channels, concepts

  Examples: ABA, SphK, K efflux, pH, depolarization, closure
  - edges: interactions, activating or inhibiting effects on nodes or other edges
  - classify biological information into activation or inhibition

  Examples: ABA ⟶ SphK, SphK ⟶ (ABA ⟶ closure)

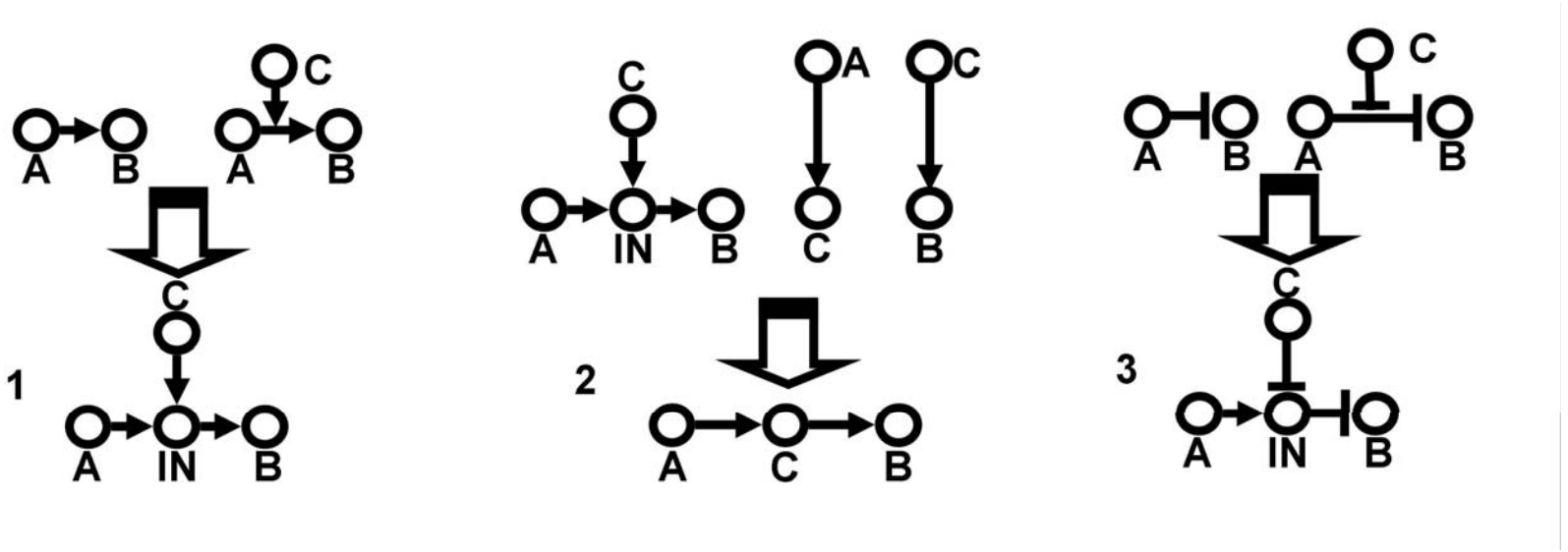
Node A	**Node/Process B**	**interaction**	**species**	**ref**
ROS	ABA → closure	promotes	*Vicia faba*	*(1)*
PLC	ABA → closure	promotes	*Commelina communis*	*(3)*
SphK	ABA → AnionEM	partially promotes	*Arabidopsis*	*(4)*
ABA	SphK	promotes	*Arabidopsis*	*(4)*

Network construction

Need to synthesize experimental inferences into the simplest network that incorporates all effects.

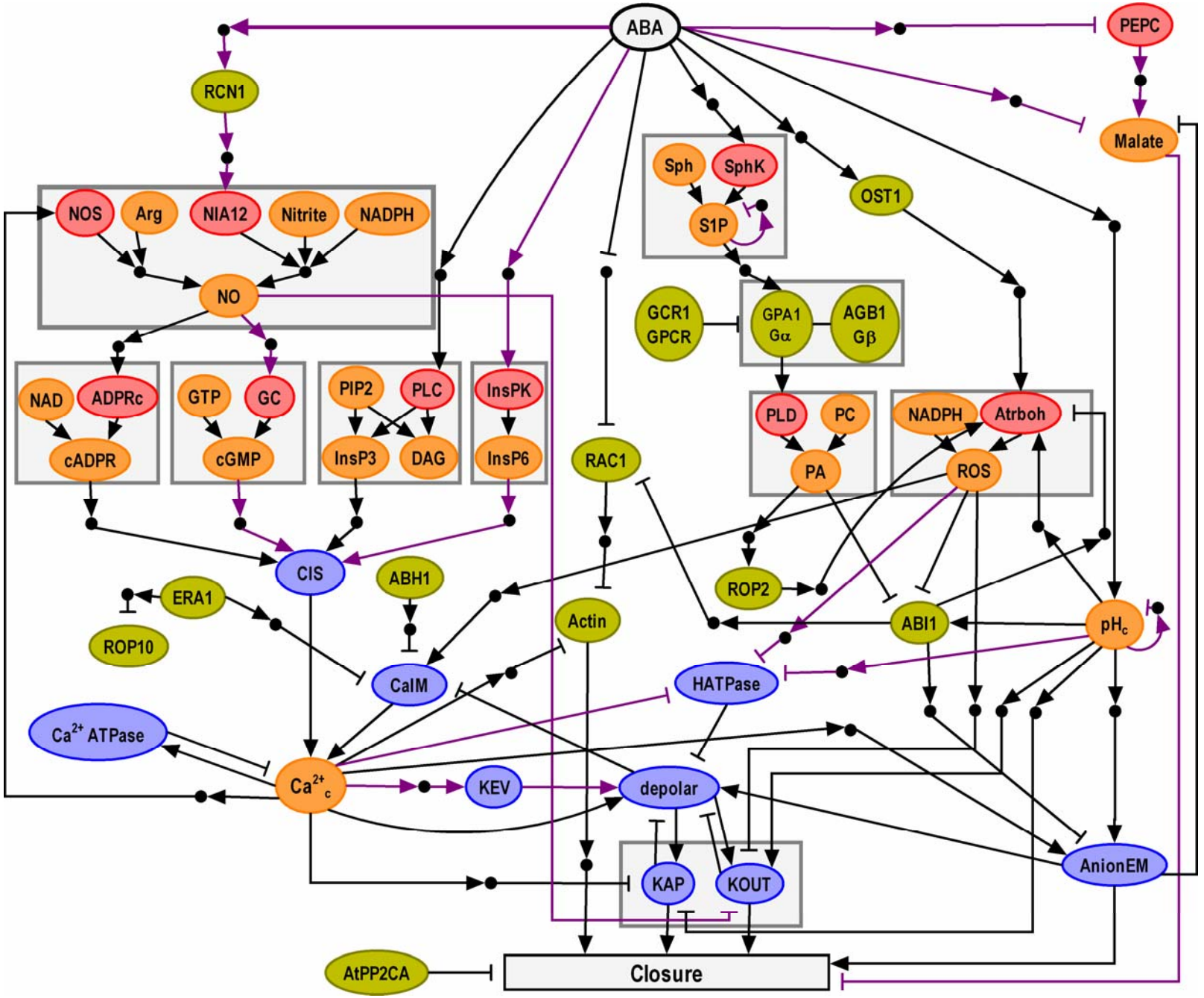
Edges should connect pairs of nodes: introduce intermediary nodes (1,3)

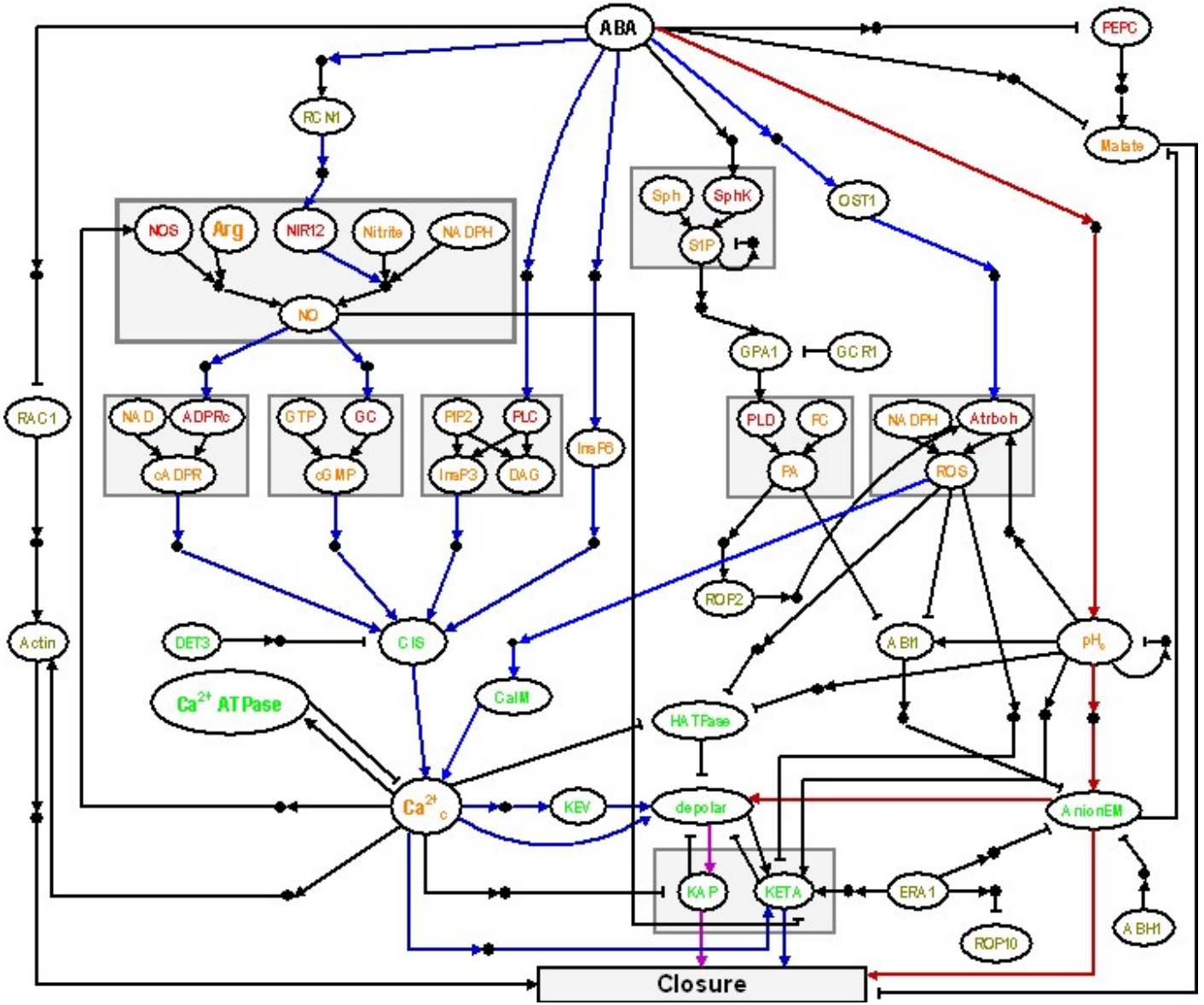
Limit redundancy to minimal supported: contract intermediary nodes (2)



The full algorithm is an example of a binary transitive reduction problem.

R. Albert, B. Dasgupta, R. Dondi and E. D. Sontag 2006.


ABA
PEPC
RCN1
Malate
Sph
SphK
S1P
OST1
NOS
Arg
NIA12
Nitrite
NADPH
NO
GCR1
GPCR
GPA1
Gα
AGB1
Gβ
NAD
ADPRc
cADPR
GTP
GC
cGMP
PIP2
PLC
InsP3
DAG
InsPK
InsP6
PLD
PC
PA
NADPH
Atrboh
ROS
RAC1
CIS
ABH1
ERA1
ROP10
CaIM
Actin
ROP2
ABI1
pHc
HATPase
Ca2+ ATPase
Ca2+c
KEV
depolar
AnionEM
KAP
KOUT
AtPP2CA
Closure
enzymes
sign. trans. proteins
transport
small molecules
• interm. node
— inf. edges



Two pathways of Ca^{2+} activation

At least two separate ABA-closure pathways, one through Ca^{2+}, the other through pH_c.

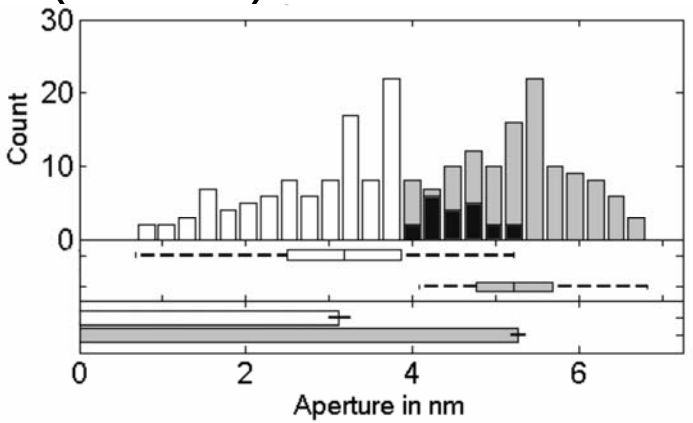
Pathway redundancy suggests robustness to perturbations.

Actin reorganization, pHc increase, malate breakdown, membrane depolarization need to be simultaneously disrupted to block all ABA- closure paths.

Qualitative model of network dynamics

• Each node has two states: 1 (active) and 0 (inactive)

•“closure=1” does not mean “stomata are closed” because “open” and “closed” stomatal apertures are both distributions



• Synergy -- AND; independence -- OR; inhibitors -- NOT.

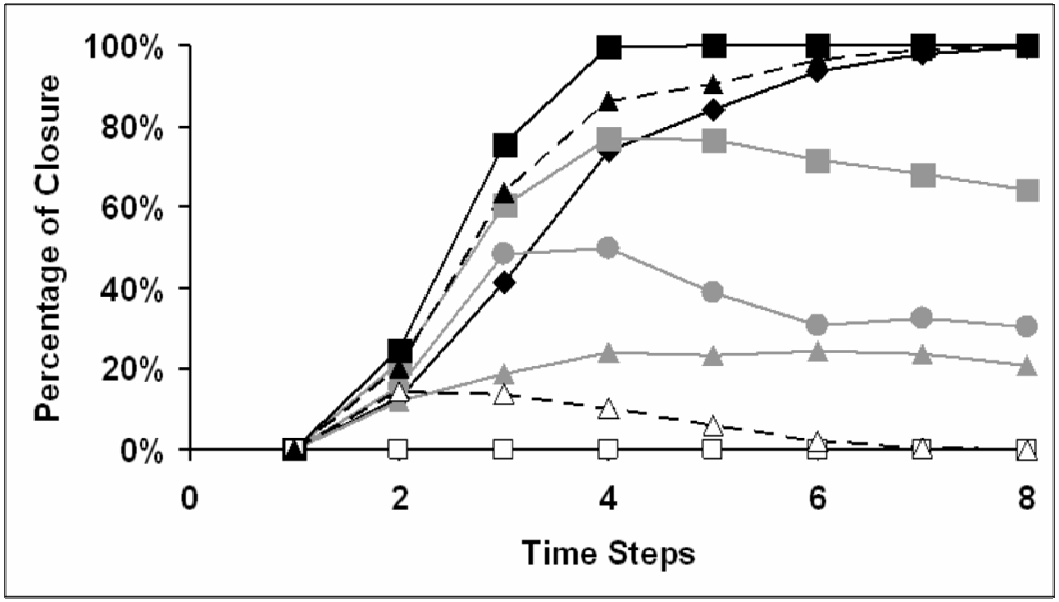
Closure* = (KOUT or KAP) and AnionEM and Actin and not Malate

• Asynchronous algorithm with randomly selected timing/order. That is changed after each round

• Randomize the initial states of all the nodes to mimic the noise in the internal environment of the guard cell.

• Interpret the number of simulation runs having achieved closure at a certain timestep as the probability of closure.

Signal transduction is resilient to perturbations



▲ Normal response to ABA stimulus.
△ No stimulus
■ ABI1 knockout mutants respond faster (hypersensitivity).
◆ Ca^{2+} clamping leads to slower response (hyposensitivity)

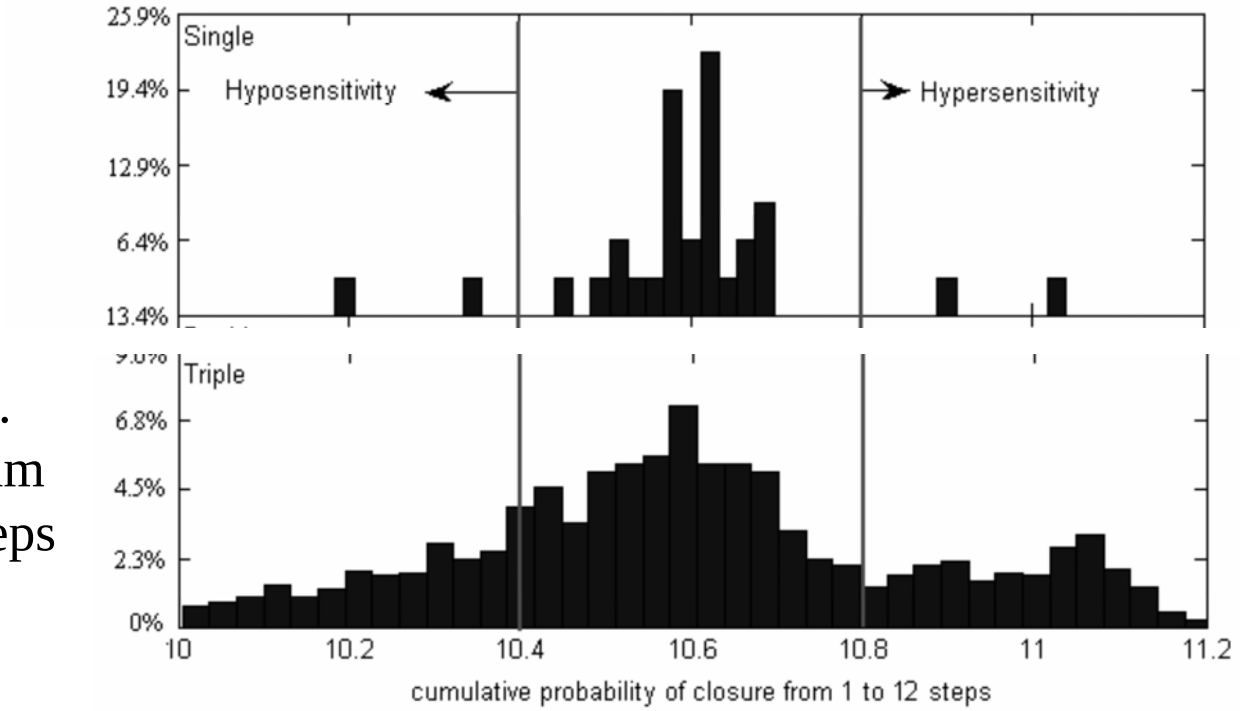
Perturbations in □ anion efflux or depolarization cause ABA insensitivity.
Perturbations in ■ SphK or S1P, ● GPA1, PLD or PA, or △ pH_c lead to decreased sensitivity.

Prediction: pH disruption more severe than Ca^{2+} disruption.

Model predicts remarkable robustness

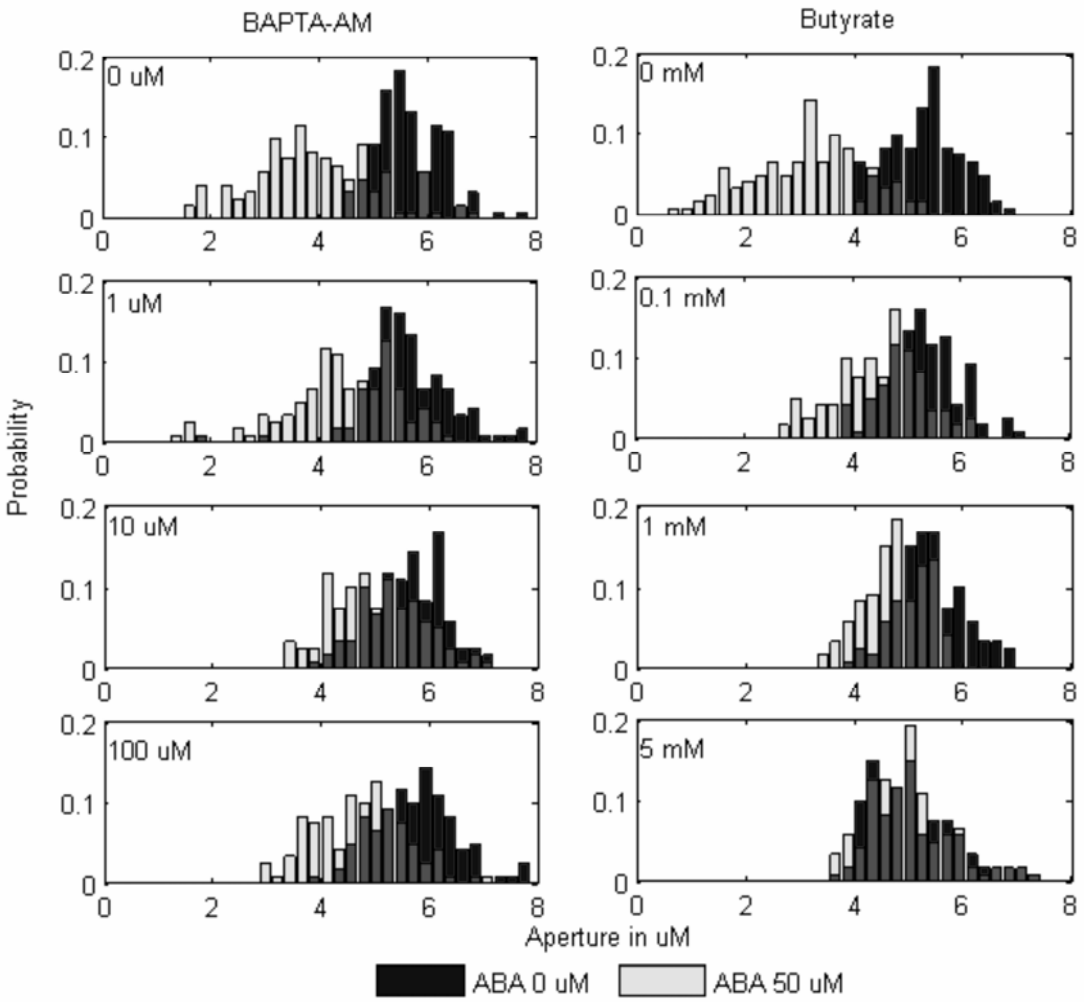
No. of nodes disrupted	Perc. with normal sensit.	Perc. causing hyper-sensit.	Perc. causing hypo-sensit.	Perc. causing reduced sensit.	Perc. causing insensit.
1	**65%**	5%	5%	17.5%	7.5%
2	**46%**	8.1%	8.1%	26.5%	15.8%
3	**32%**	9.8%	10.5%	29.6%	24.8%

Continuum of close-to normal sensitivity



Cumulative prob. of closure: the sum of PC over 12 steps

Experimental validation: disruption of Ca^{2+} versus pH



Normal: "open" and "closed" state distinguishable

pH disrupted: "open" and "closed" state indistinguishable

Ca^{2+} disrupted: "open" and "closed" state distinguishable

Qualitative agreement with theoretical prediction.

Conclusions and outlook

- Cellular interaction networks incorporate regulation at mRNA, protein and chemical level.
- The topology of regulatory networks has a major role in determining their dynamical behaviors.
- It is possible to make predictions based on qualitative models.

Protein interaction prediction:
István Albert

Drosophila segmentation:
Hans G. Othmer, Eduardo Sontag
Madalena Chaves

Pathogen-immune system interactions:
Eric Harvill, Jaewook Joo, Juilee Thakar

Gene regulation:
Anshuman Gupta, Claire Christensen
Costas Maranas, Yu-wen Chiu, Anton Nekrutenko, Kateryna Makova

ABA signaling in plants:
Sarah Assmann, Song Li

Graph inference:
Bhaskar Dasgupta
Riccardo Dondi
Eduardo Sontag

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