

Hierarchies and modules in complex biological systems

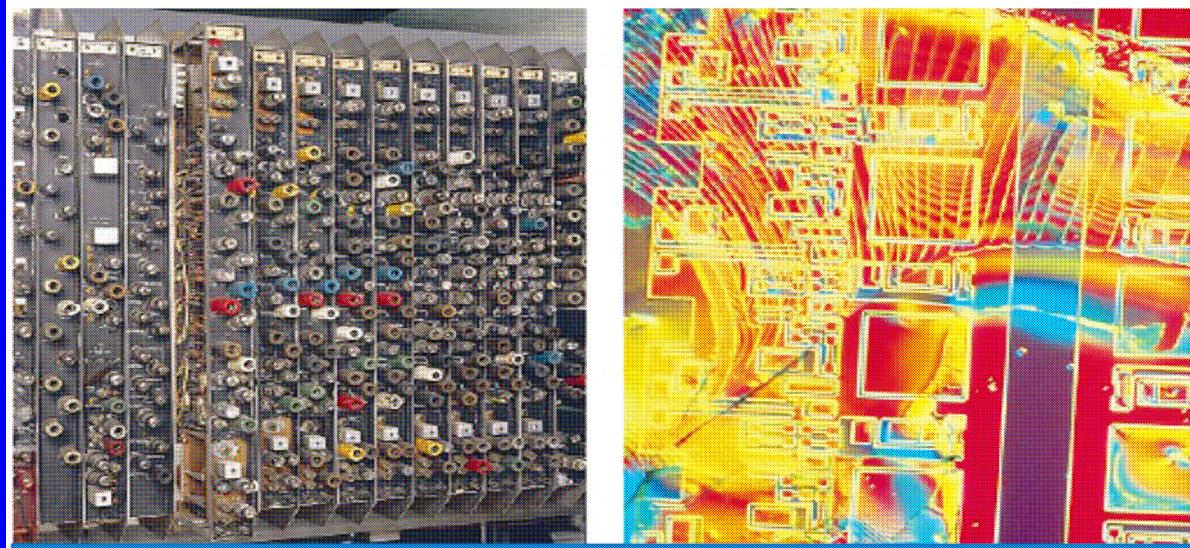
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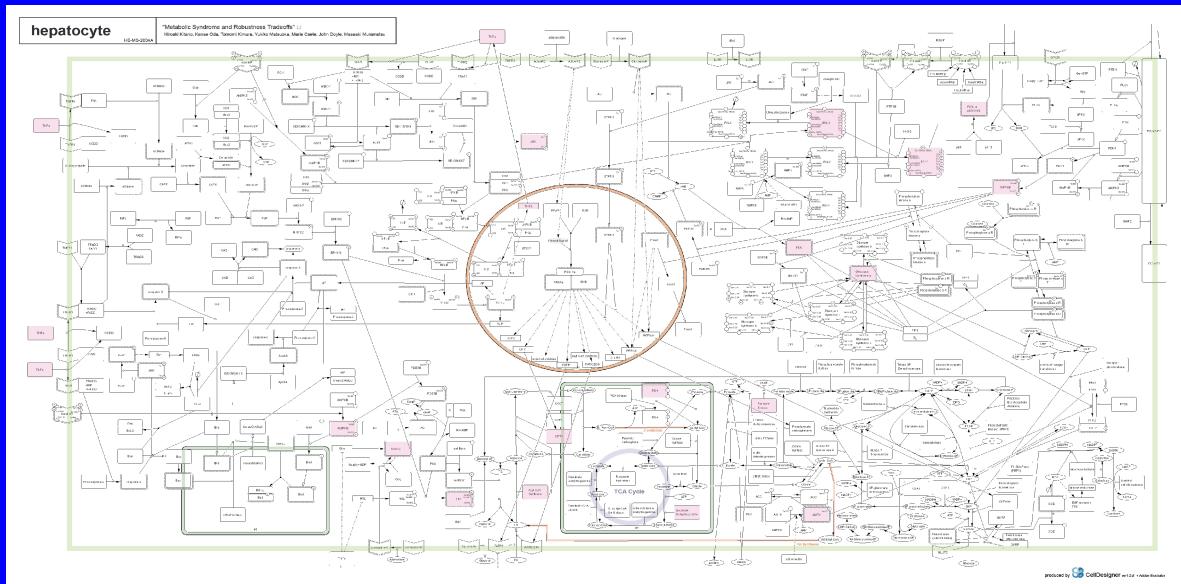
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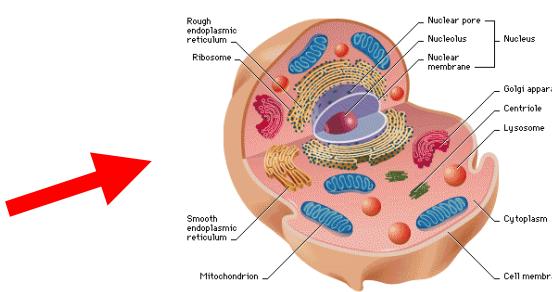
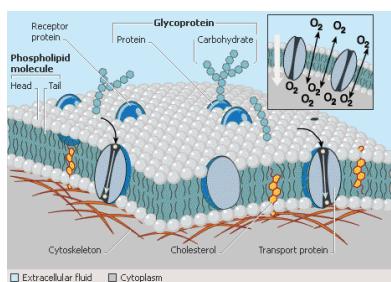
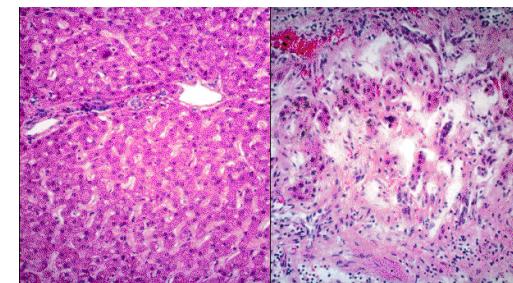
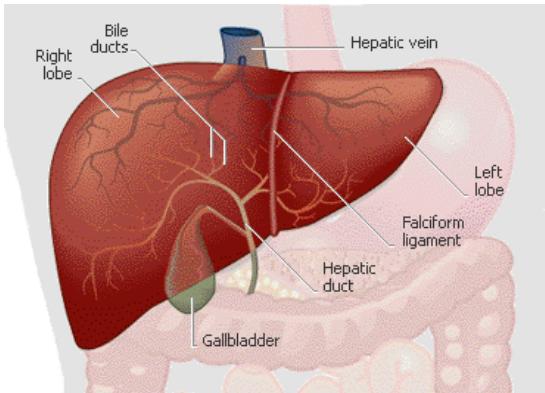
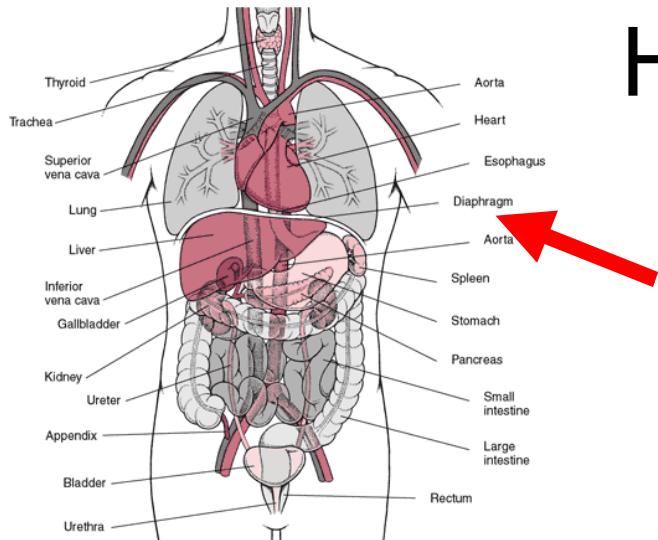
Modularity



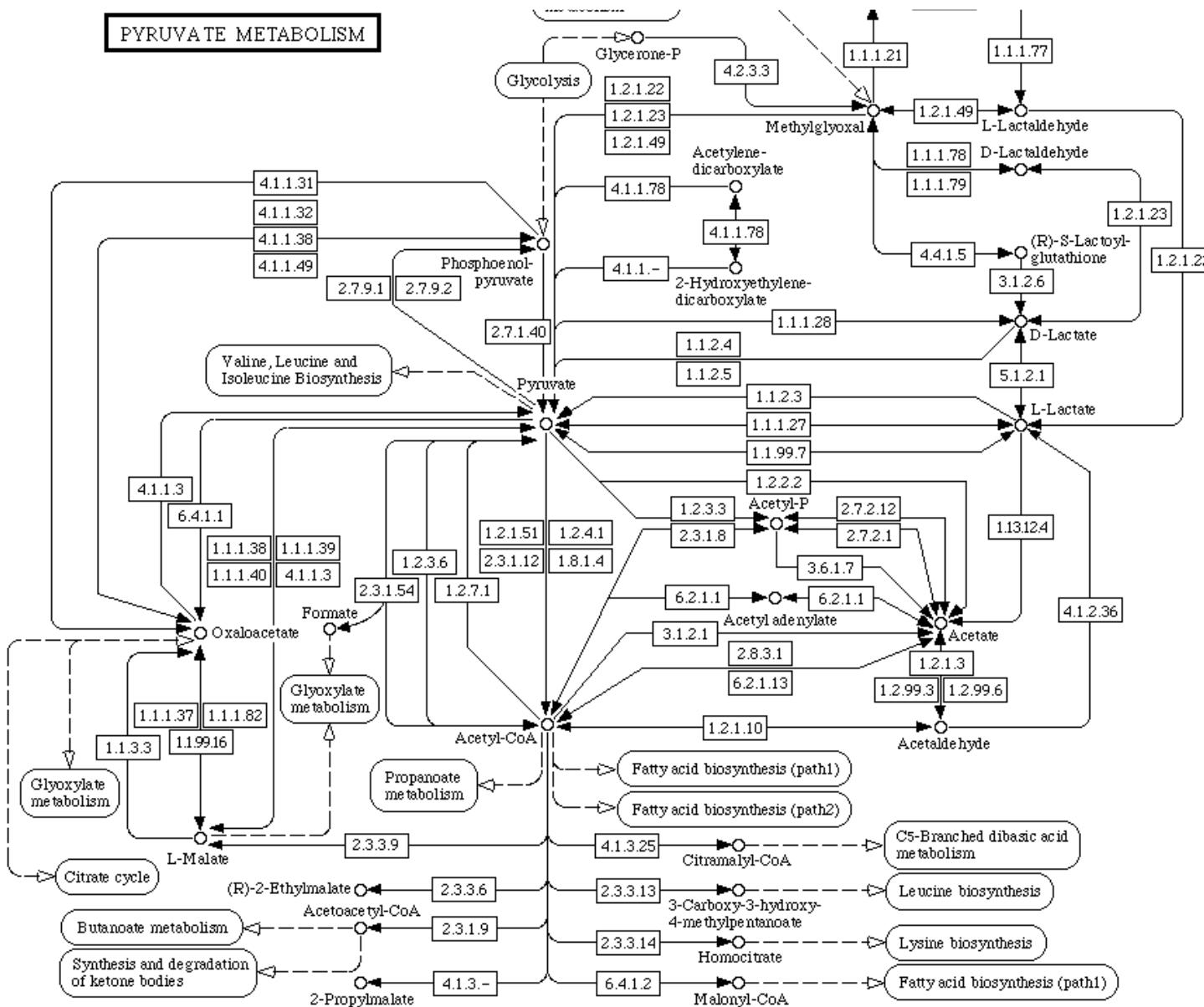
From Hartwell et al, Nature 1999



Hierarchies



Pathways

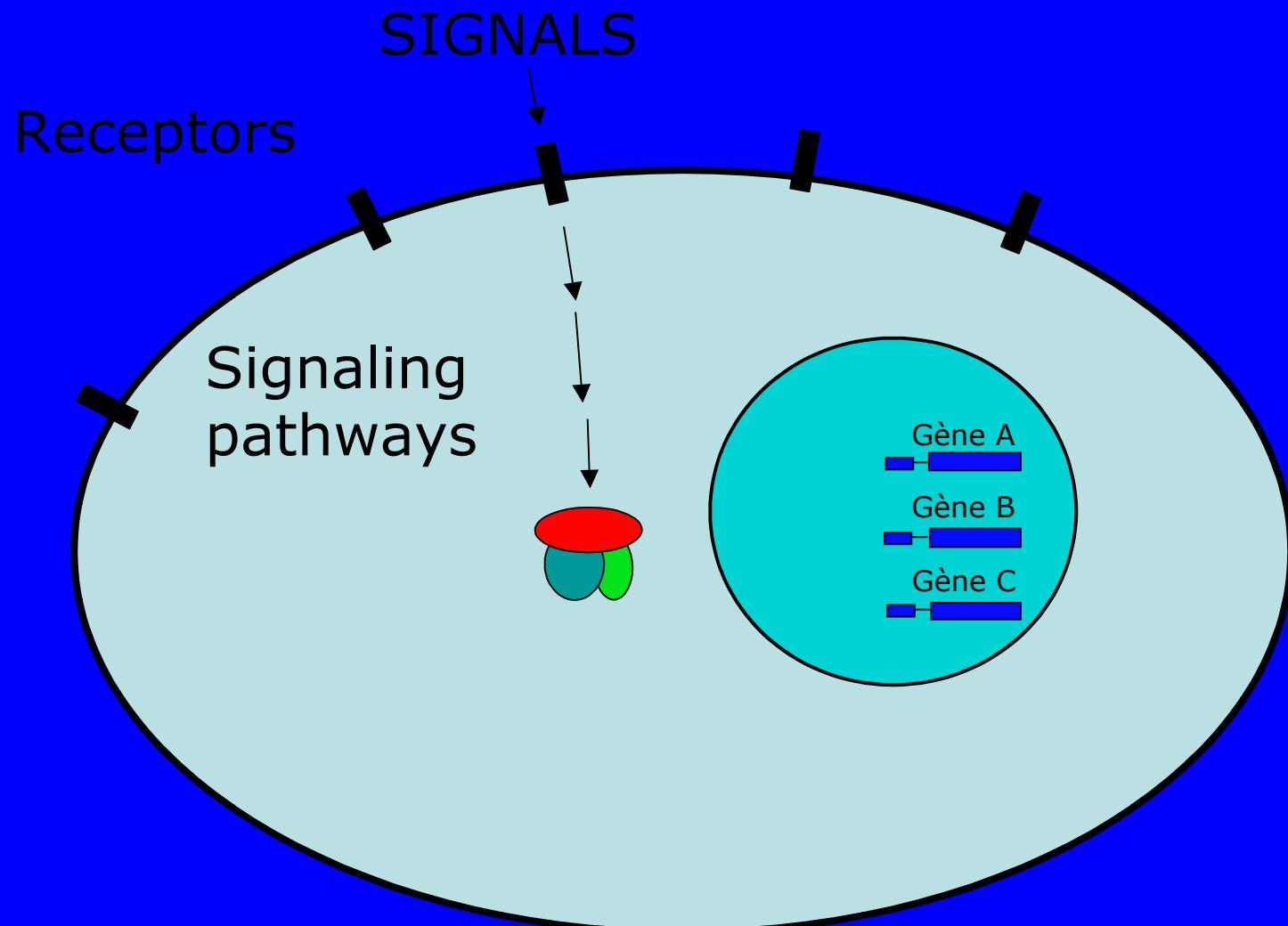


Hierarchies and robustness

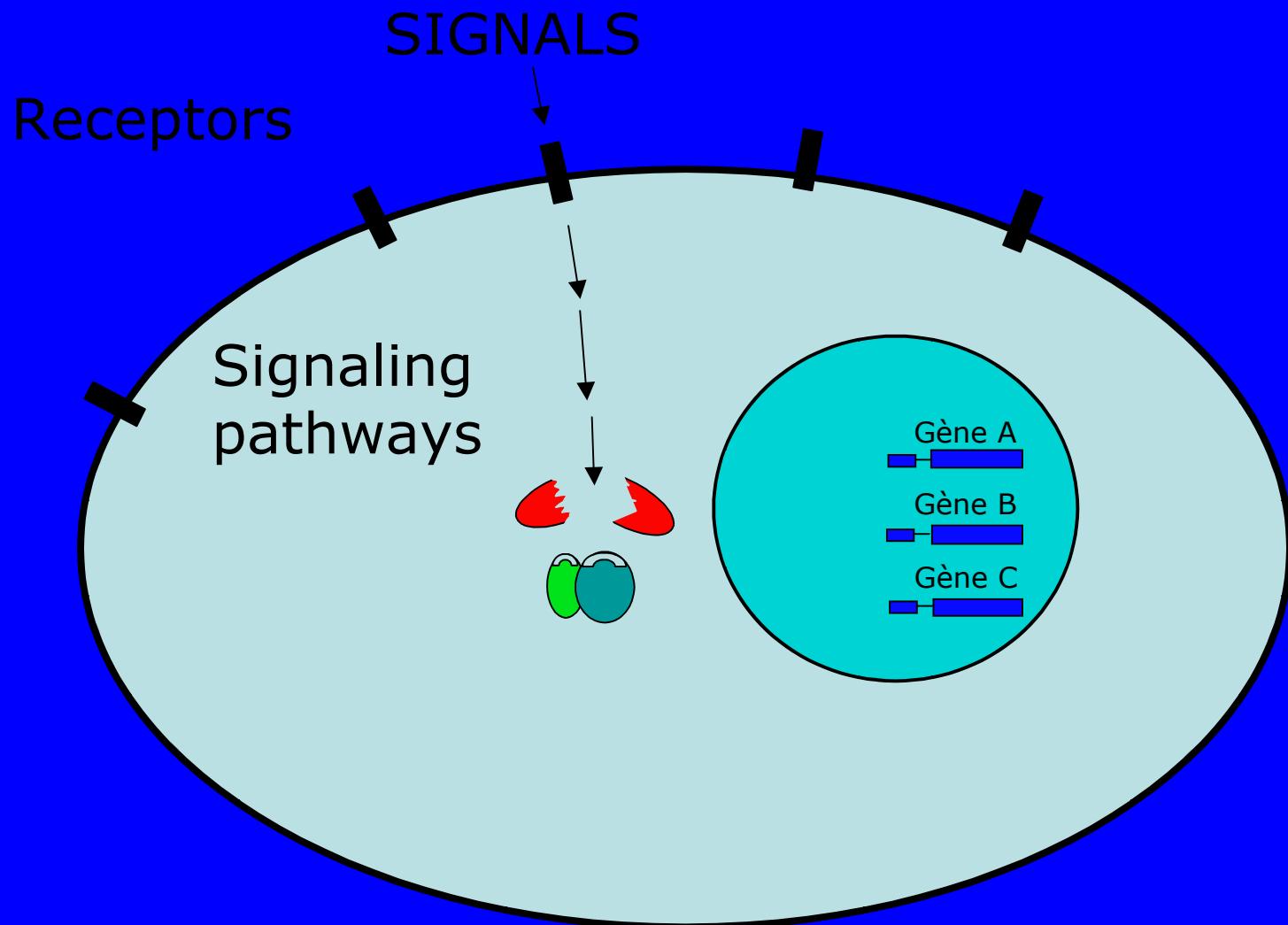
1. How to represent the hierarchical structure of biological systems?
 - a) hierarchy of models
 - b) modular reduction technique
2. Which is the relation between robustness and the hierarchical structure?
 - a) distributed robustness
 - b) r-robustness

Biochemical reactions models

GENE NETWORK NF- κ B factor

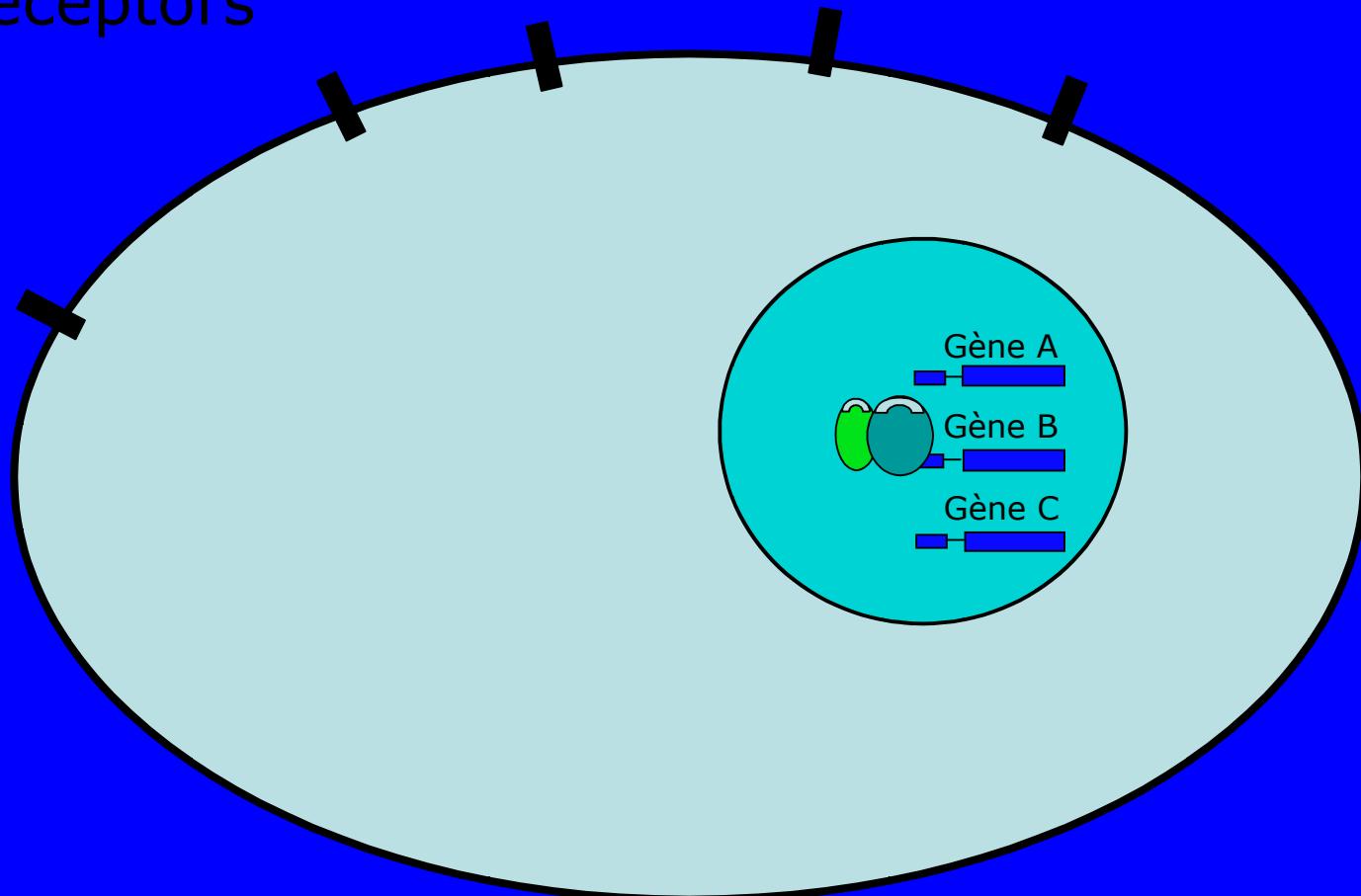


GENE NETWORK NF- κ B factor

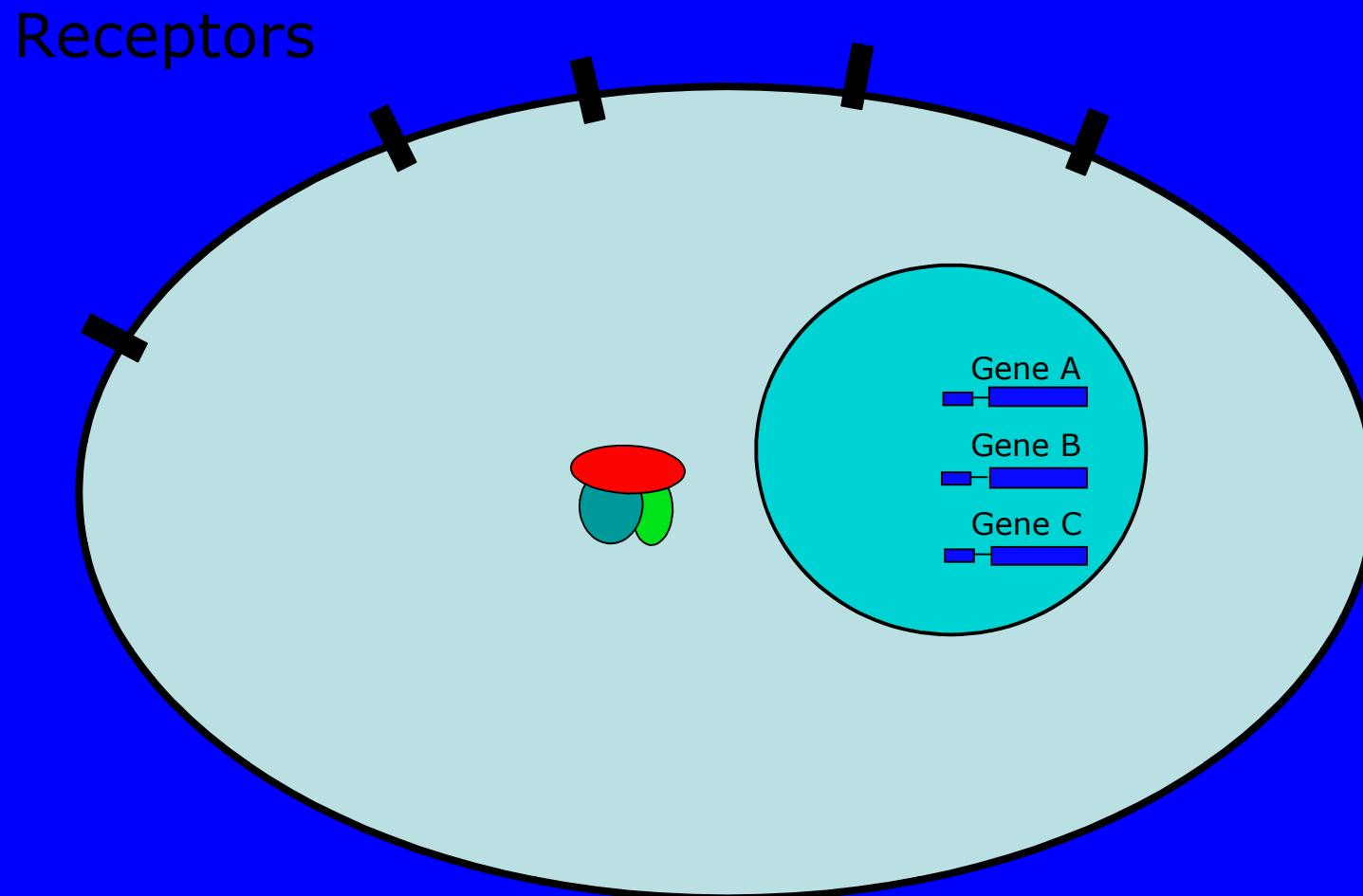


GENE NETWORK NF- κ B factor

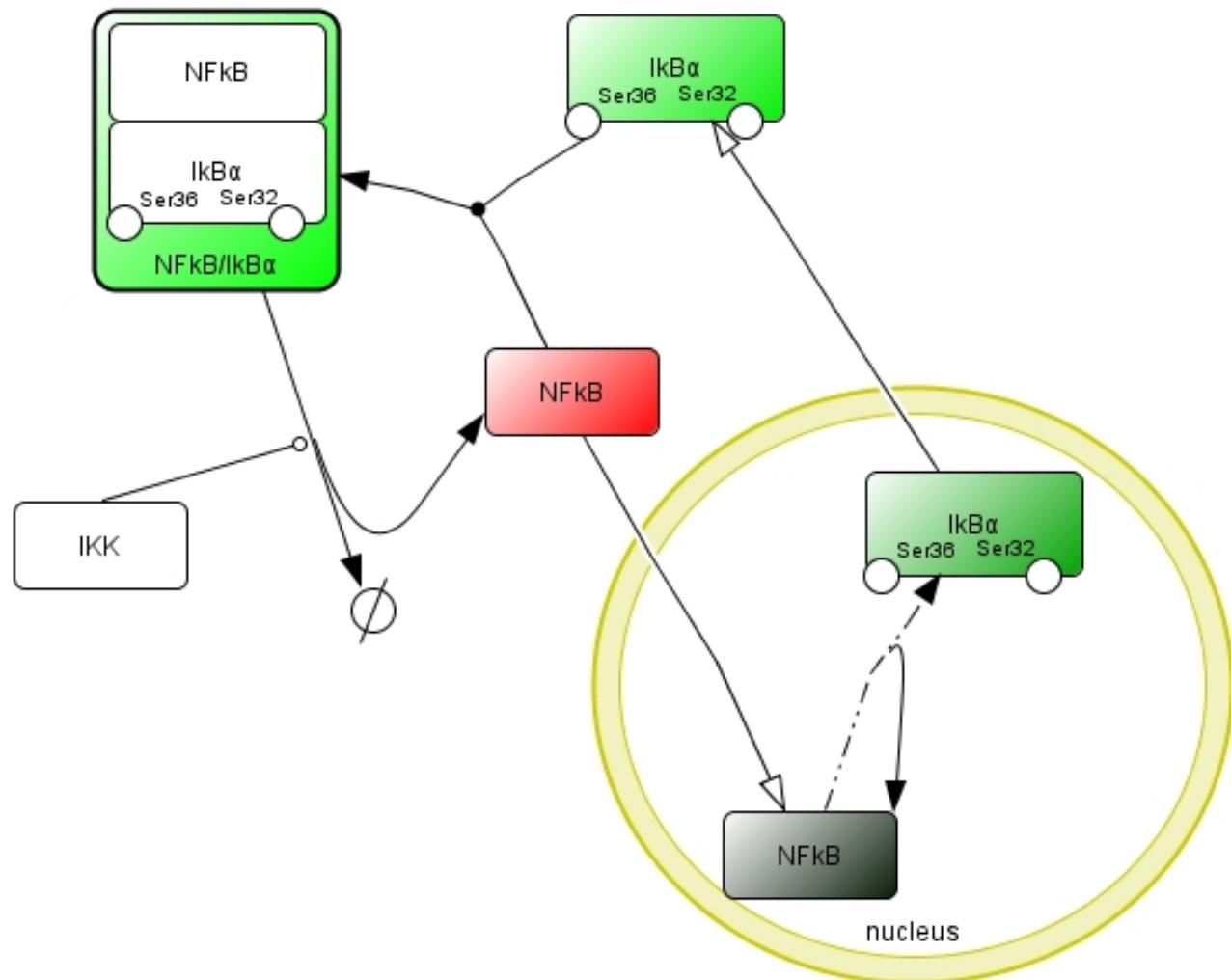
Receptors

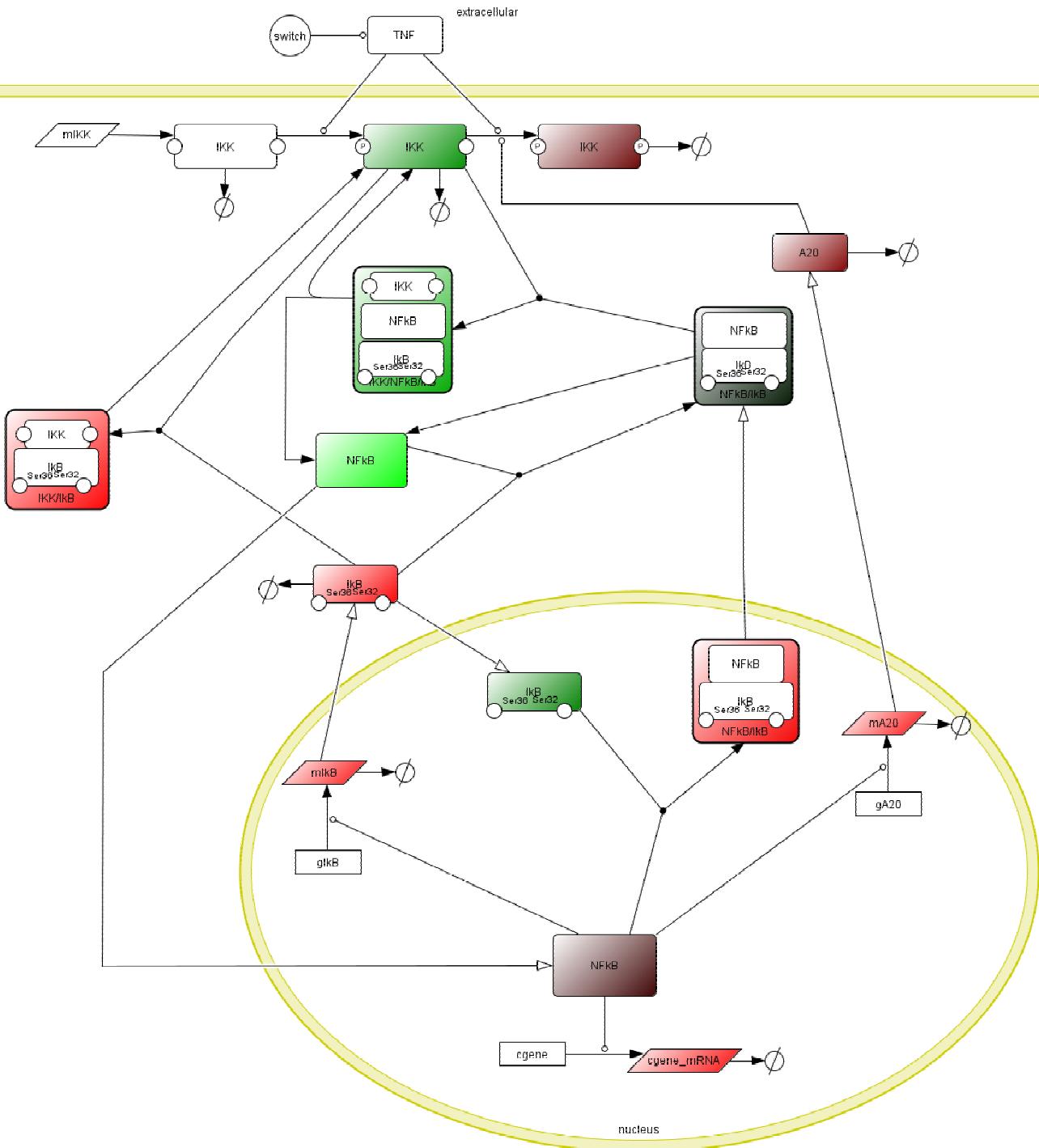


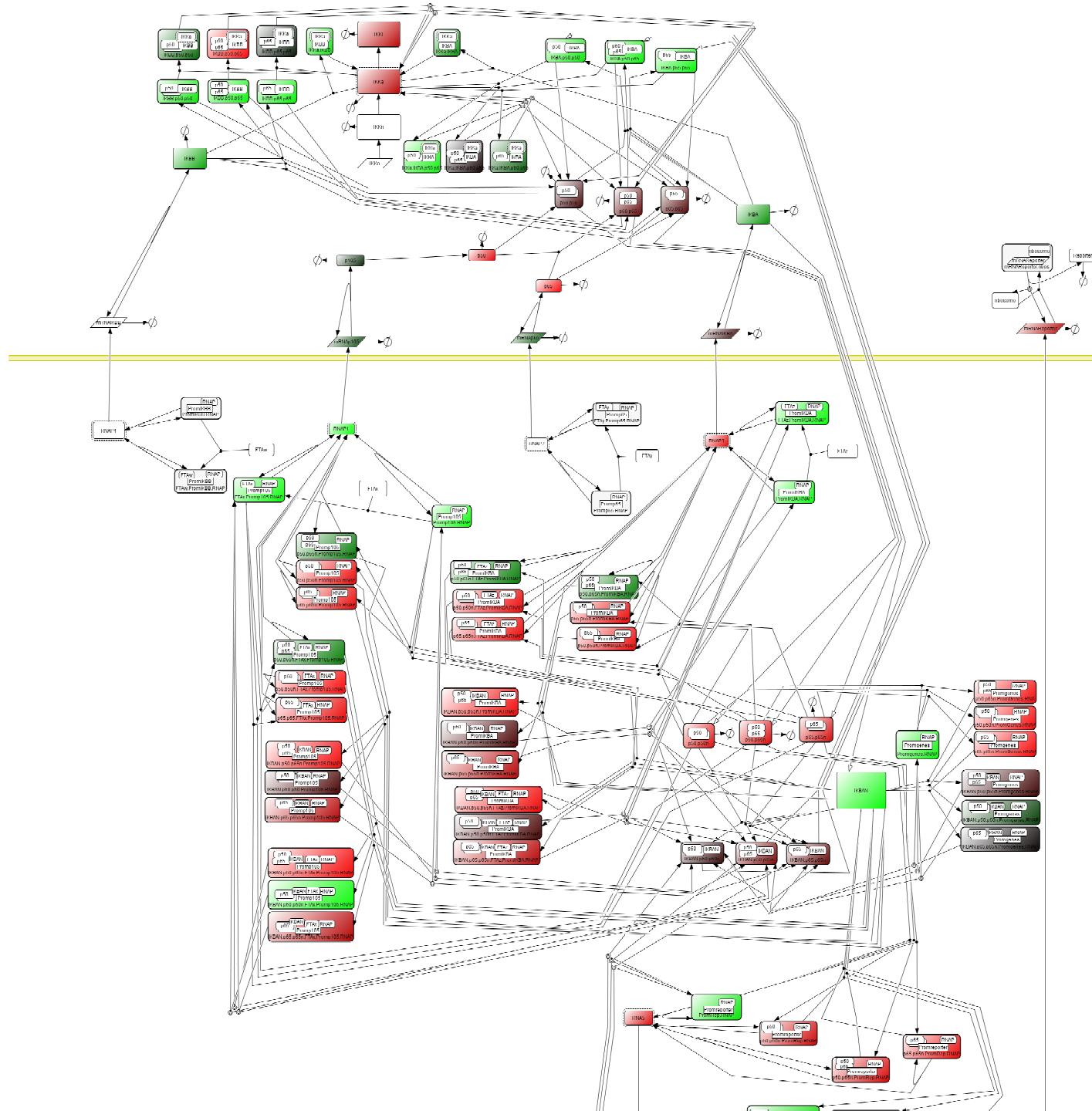
GENE NETWORK NF- κ B factor

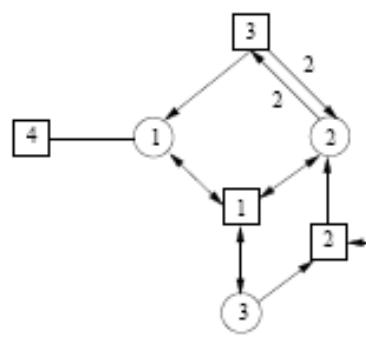


Hierarchical models, model hierarchies

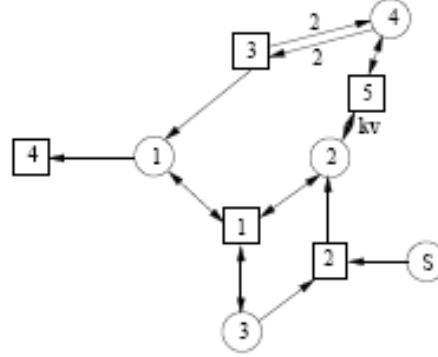




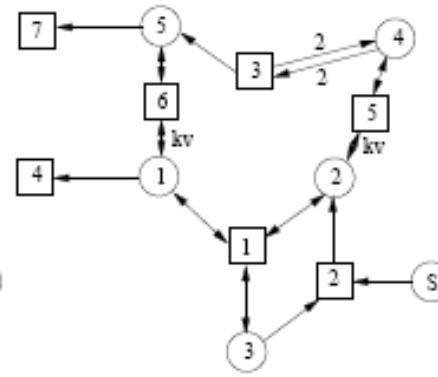




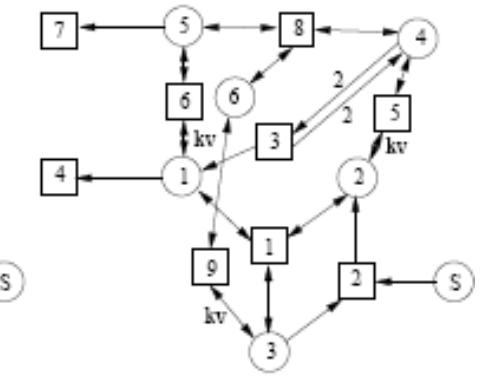
$M(3,4,5)$



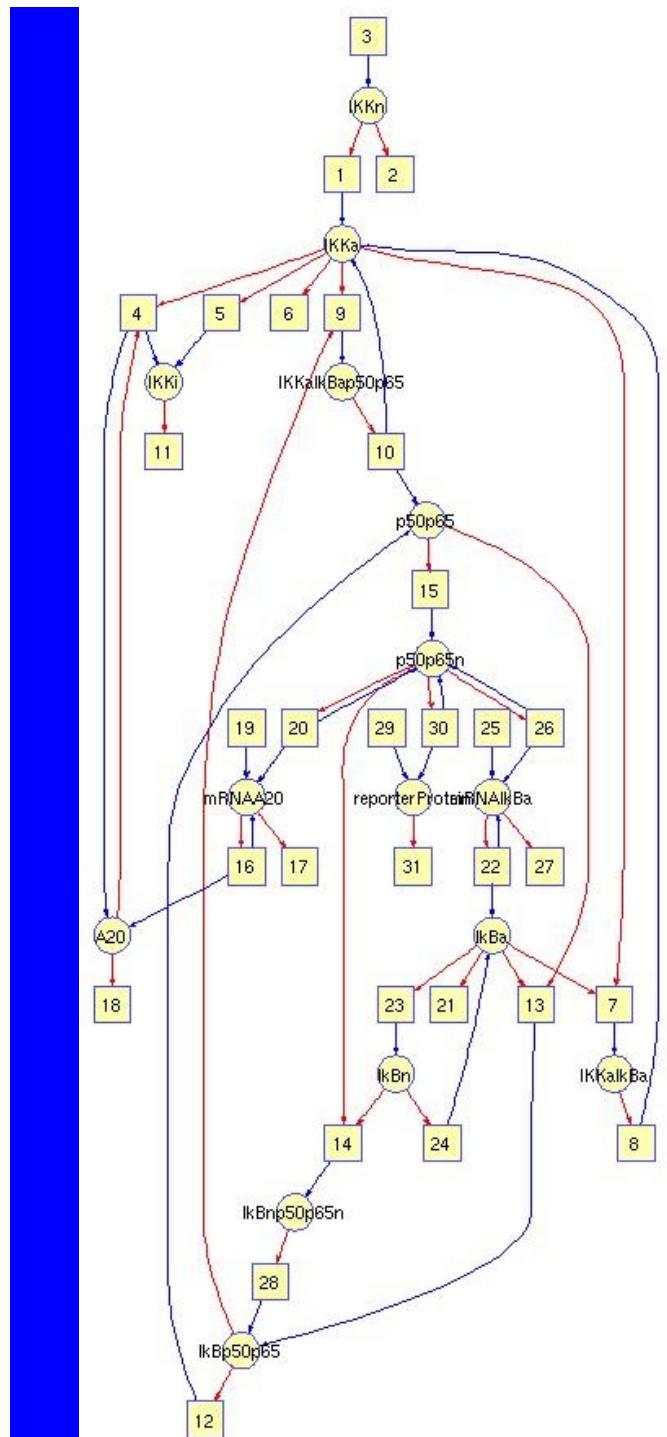
$M(4,5,7)$



$M(5,7,10)$

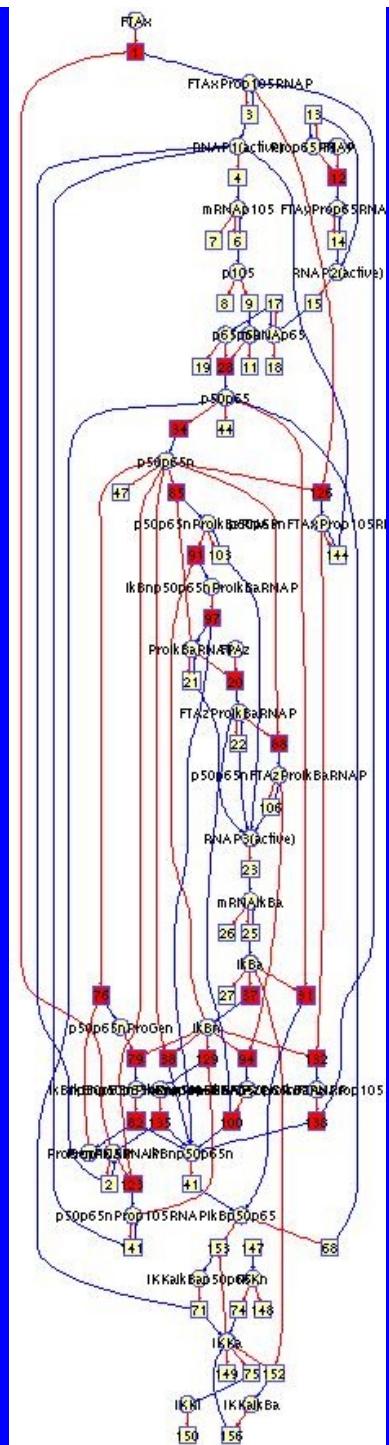


$M(6,9,13)$



Many to one mapping

- Reduce
 - Compare
 - Organize



Reduction method

$$\frac{dX}{dt} = \text{SR}(X, \lambda) = \sum_{i=1}^m S^i R_i(X, \lambda)$$

$$\mathcal{I} \subset \{1, \dots, n\}$$

$$\mathcal{B}_I = (\mathcal{I}, \mathcal{R}_I, \mathcal{A}_I)$$

p50p65n

26

25

mRNAlkBa

22

27

lBa

Terminal species

Intermediate species

$$S_I \gamma = 0$$

$\gamma_i \geq 0$, if R_i irreversible

Reaction route

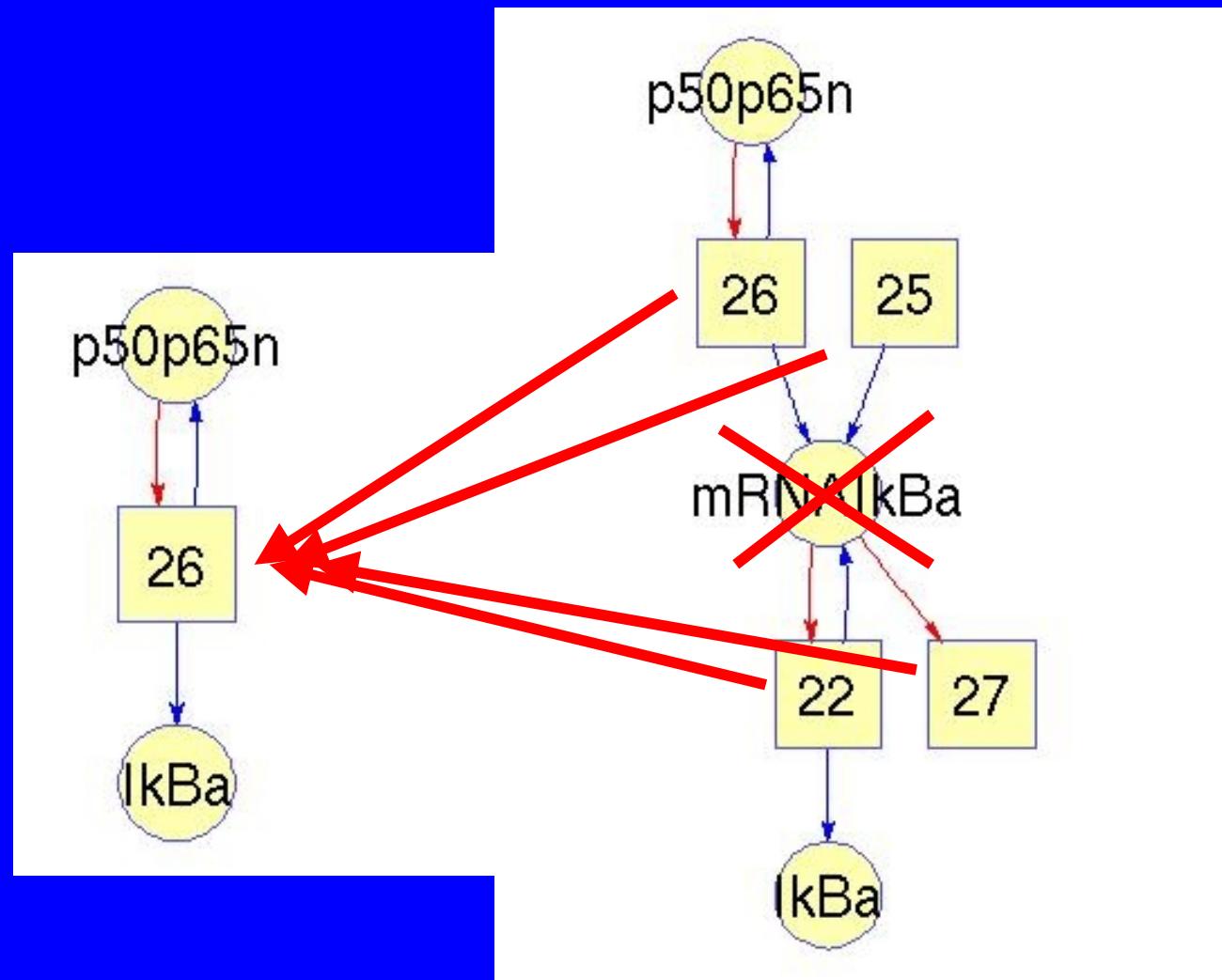
Submechanism = reactions in a RR

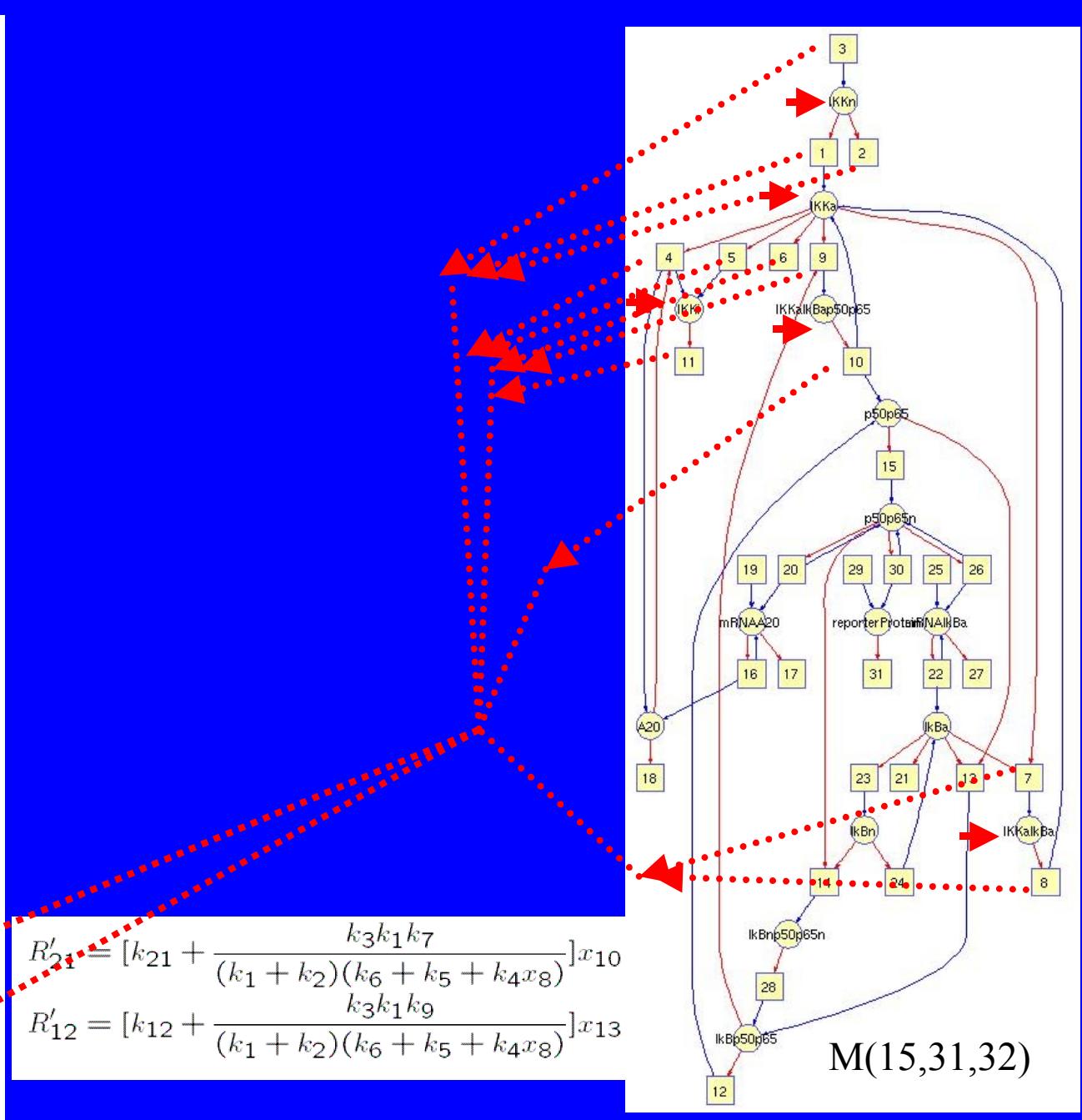
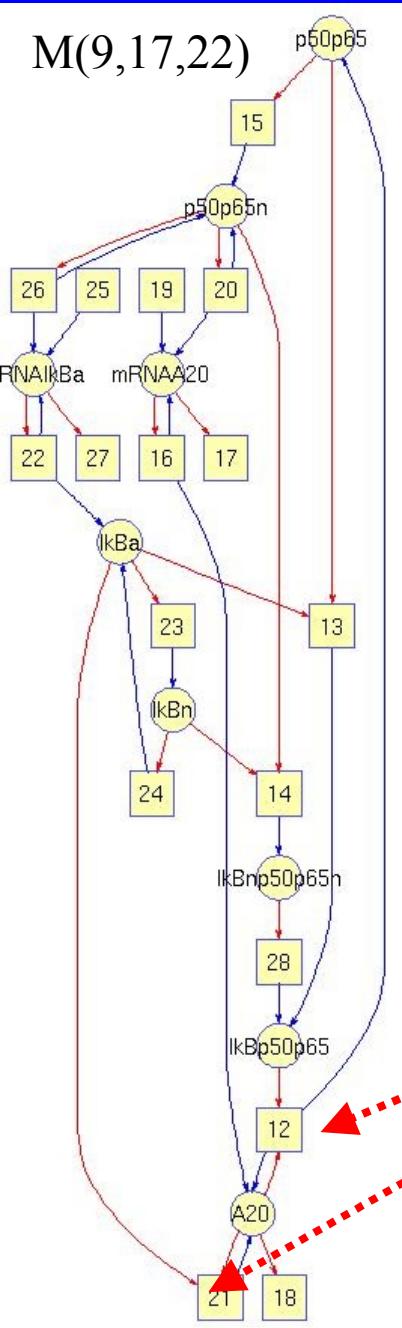
Simple mechanism = it does
not contain a smaller one

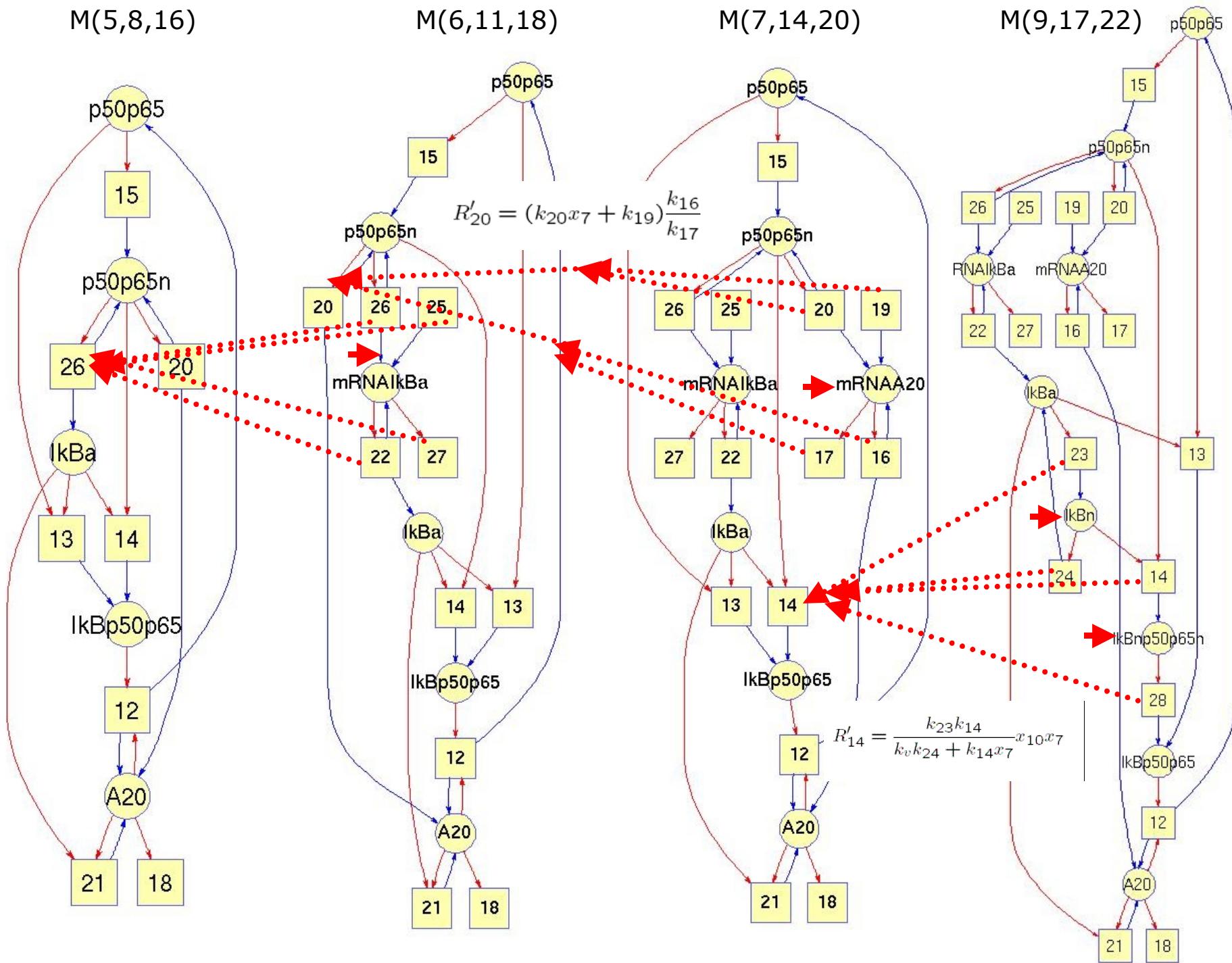
Reduction

a) Choose I

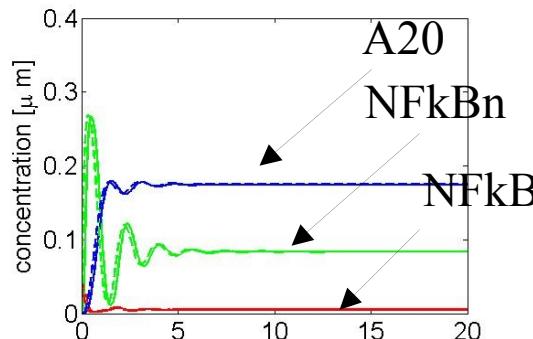
b) Replace R_I by simple submechanisms



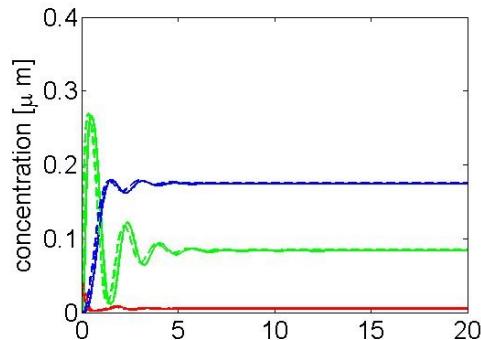




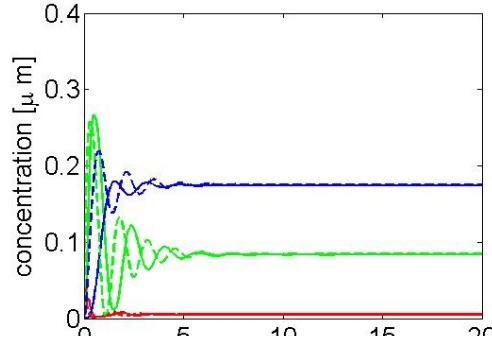
M(9,17,22)



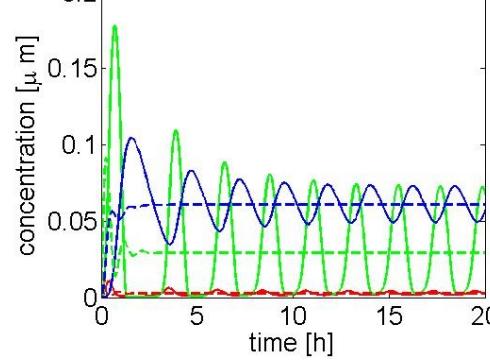
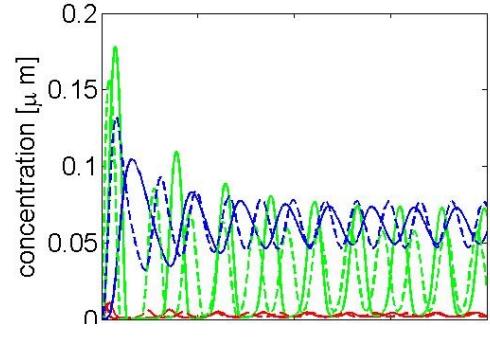
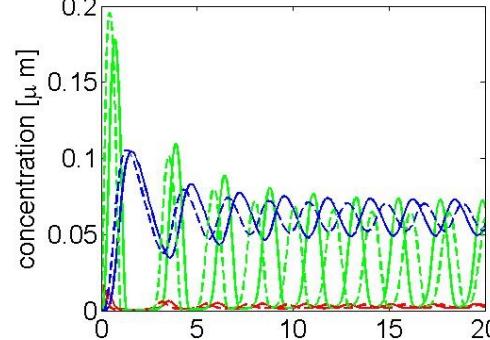
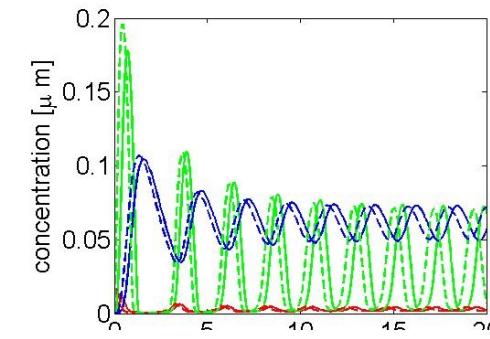
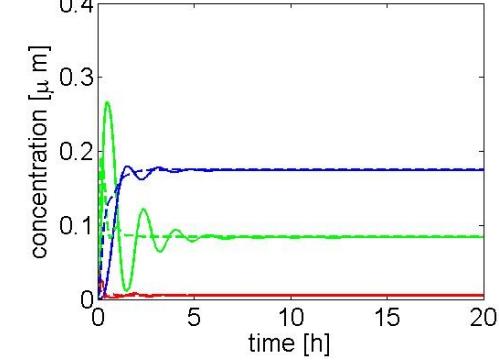
M(7,14,20)



M(6,11,18)



M(5,8,16)



Partial conclusions

1. Model reduction can be used for producing an hierarchy of models.
2. Reduction procedure is modular and is based on the choice of some Intermediate species. Several choices are possible:
 - a) rapid species (CSP method)
 - b) functional modules
 - c) monotone or Gale-Nikaido modules
 - d) species that are missing in lower complexity models
3. Some properties are common to many models in the hierarchy : steady states automatically, other under some conditions. Look for the minimal model, get rid of unnecessary details, but...don't forget the atoms. These are the source of variability.

Robustness of molecular networks

Distributed robustness

von Neumann: without randomness, situations may arise where errors tend to be amplified instead of cancelled out; for example it is possible, that the machine remembers its mistakes, and thereafter perpetuates them

A.Wagner: distributed robustness...emerges from the distributed nature of many biological systems where many (and different parts) contribute to system functions

$$M = f(K_1, K_2, \dots, K_n)$$

(K_1, K_2, \dots, K_n) independent random variables

$$\text{Var}(\log M) \ll \text{Var}(\log K_i)$$

$$\mathbb{P}[|M - M_c| > t] \leq 2\exp(-t^2/2D^2), t > 0$$

Gromov concentration

$f : E_n \rightarrow \mathbb{R}$ 1-Lipschitzian

$$\mu(\{x \in E_n | |f(x) - m_f| > t > 0\}) \leq 2\exp(-t^2/2D_n^2)$$

Cube concentration (sum of many effects)

$$f(X_1, \dots, X_n) = \frac{1}{n} \sum_{i=1}^n X_i$$

$$D_n \sim 1/\sqrt{n}, \text{Var}(f) \sim 1/n$$

Simplex concentration (extrema statistics)

$$X_{(1)} < X_{(2)} < \dots < X_{(n)}$$

$$f_i = X_{(i)} - X_{(i-1)}$$

$$D_n \sim 1/n, \text{Var}(f_i) \sim 1/n^2$$

Canalization of development by microRNAs



Eran Hornstein & Noam Shomron

nature
genetics (2006)

- post-transcriptional regulation
- networks controlling hundreds of mRNA

Example 1 (musculature differentiation)

Loss of miR-1 leads to loss of canalization in rapid growth phase of *D. Melanogaster*

Example 2 (scutellar bristles)

- the number is canalized.
- model by Meir, von Dassow, Munro and Odell is robust thanks to canalization of circuit comprising E[spl]-C genes
- the role of miRNA has to be proven

Example 3 (Ultrabitorax canalization)

- *Ubx* is a homeotic gene setting the fate of halteres
- Canalization is known for 50 years, related to 3'UTR domain
- This domain contains binding sites for miR-iab-4-5p, a Hox cluster miRNA.

Longest relaxation time of a linear network

k_1, k_2, \dots, k_n : kinetical parameters

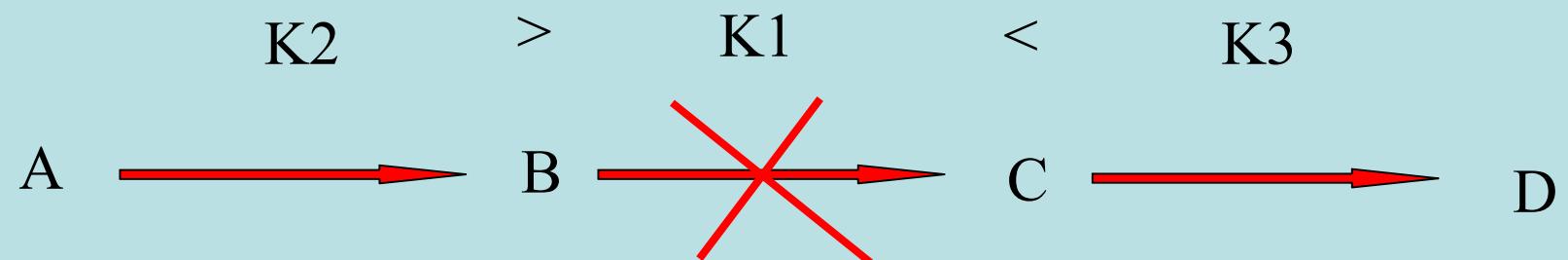
$k(1) \gg k(2) \gg \dots k(r-1) \gg k(r) \gg \dots \gg k(n)$

$$\tau \sim 1/k(r)$$

The longest relaxation time of a linear network is limited by the ergodicity boundary

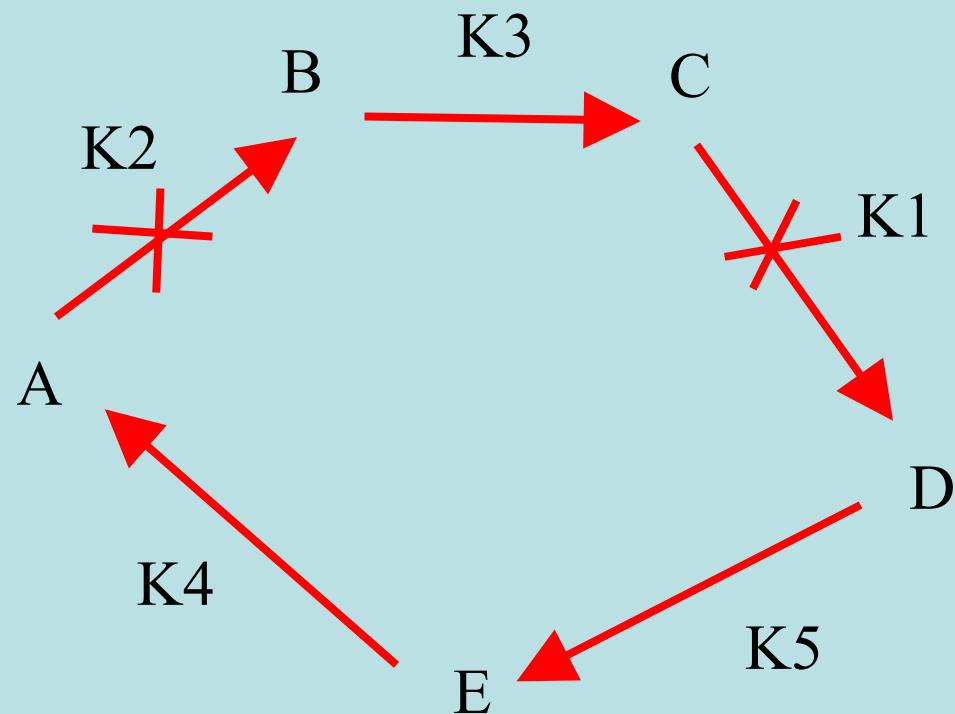
The relaxation time has distributed robustness as a consequence of the simplex concentration

$$\text{Var}[\log(k(r))] \sim 1/n^2$$



Limiting step rule for chains: the slowest reaction controls the relaxation time

$$K_1 < K_2 < K_3 < K_4 < K_5$$



Cycle rule: the second slowest reaction controls the relaxation time

r-robustness

$I_r = \{i_1, i_2, \dots, i_r\} \subset \{1, 2, \dots, n\}$ r is fixed

$K_i^0, i = 1, \dots, n$ central values

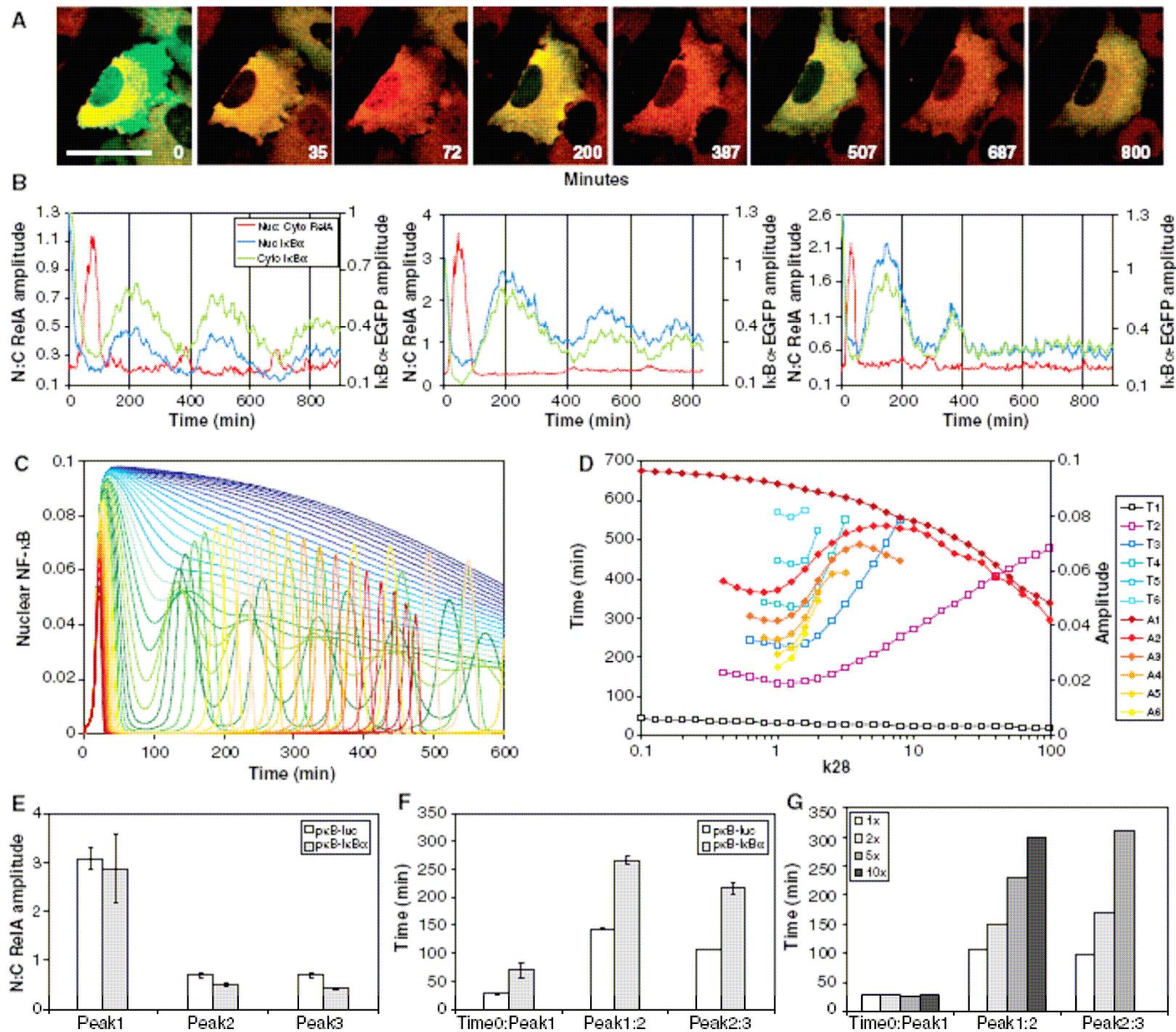
$s_i > 0, i = 1, \dots, r$ random scales

$$K_i = \begin{cases} K_i^0 s_i & i \in I_r \\ K_i^0 & i \notin I_r \end{cases}$$

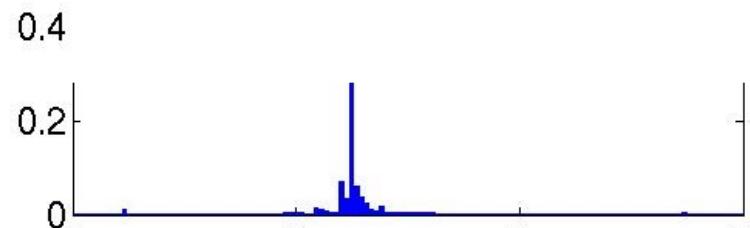
$Var(\log M) \ll Var(\log s_i), 1 \leq i \leq r$ r-robustness

if the choice of I_r is random, weak r-robustness

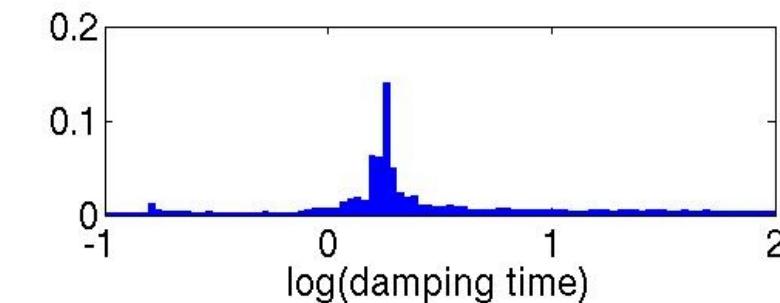
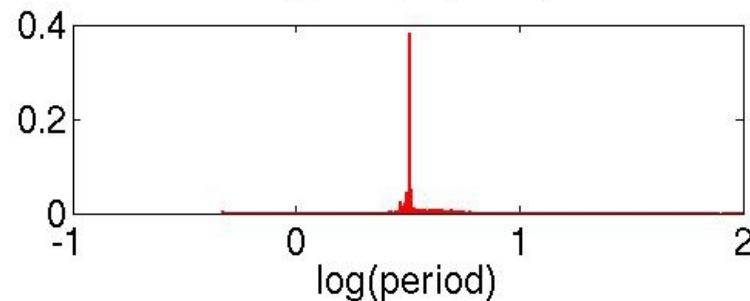
Timescales of NFkB example



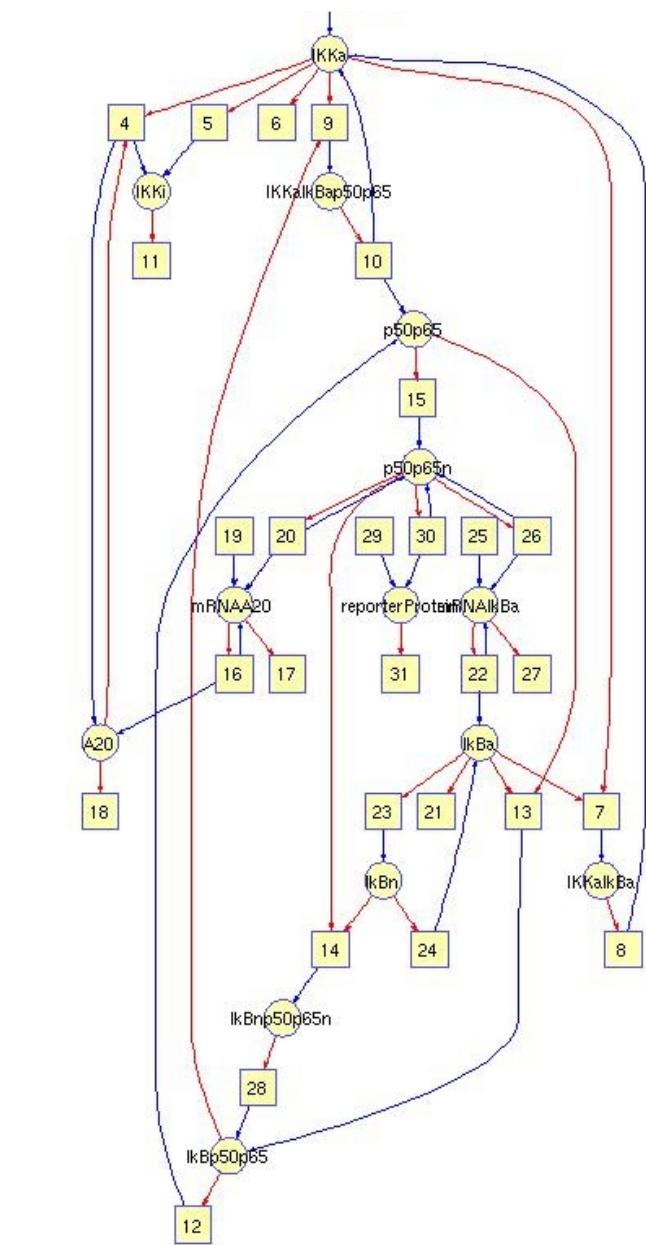
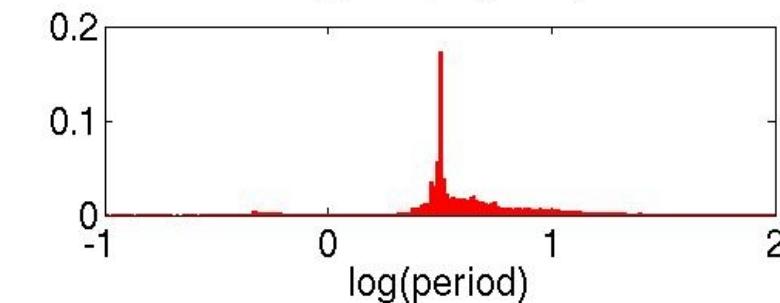
weak r-robustness



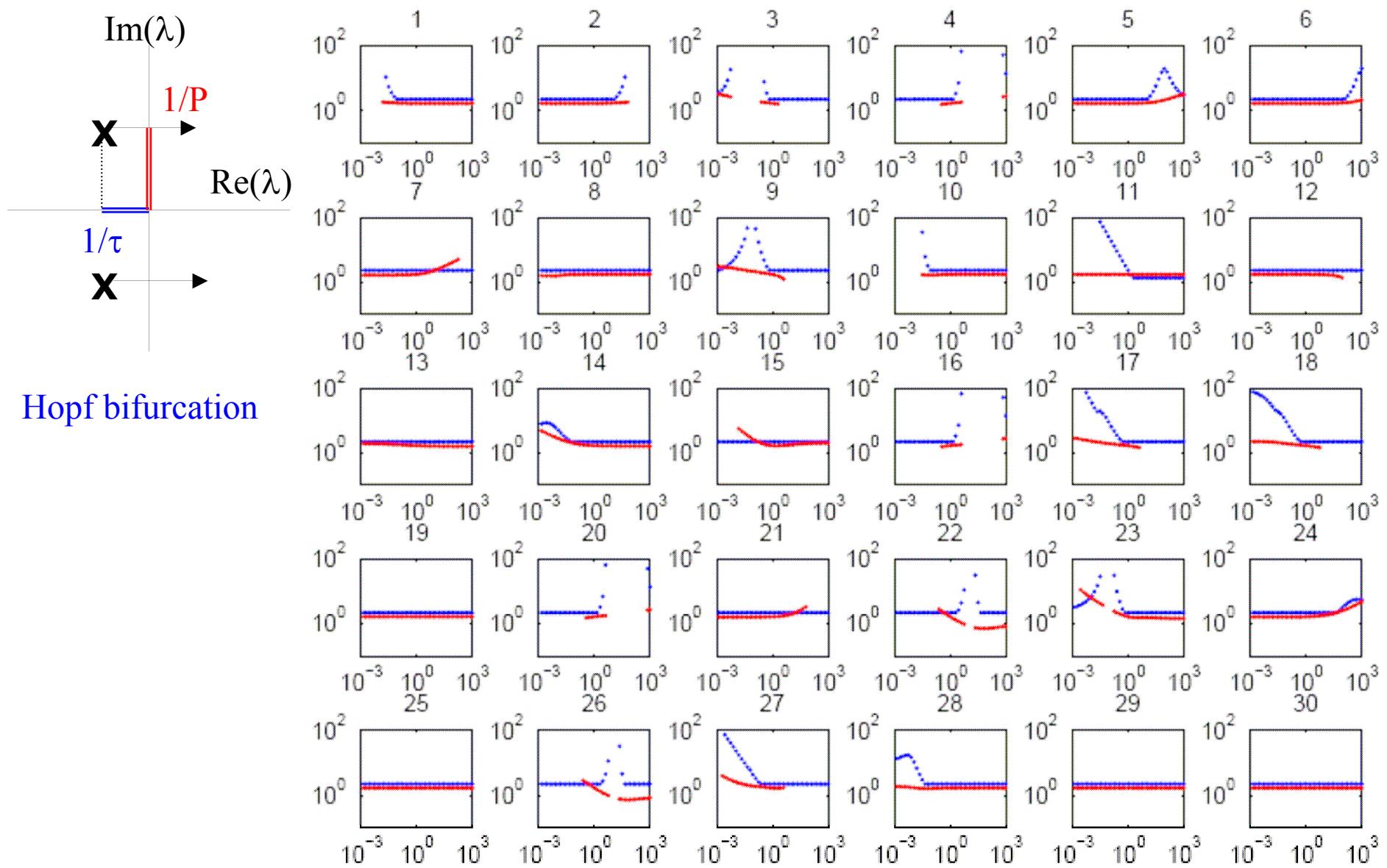
$r=1$



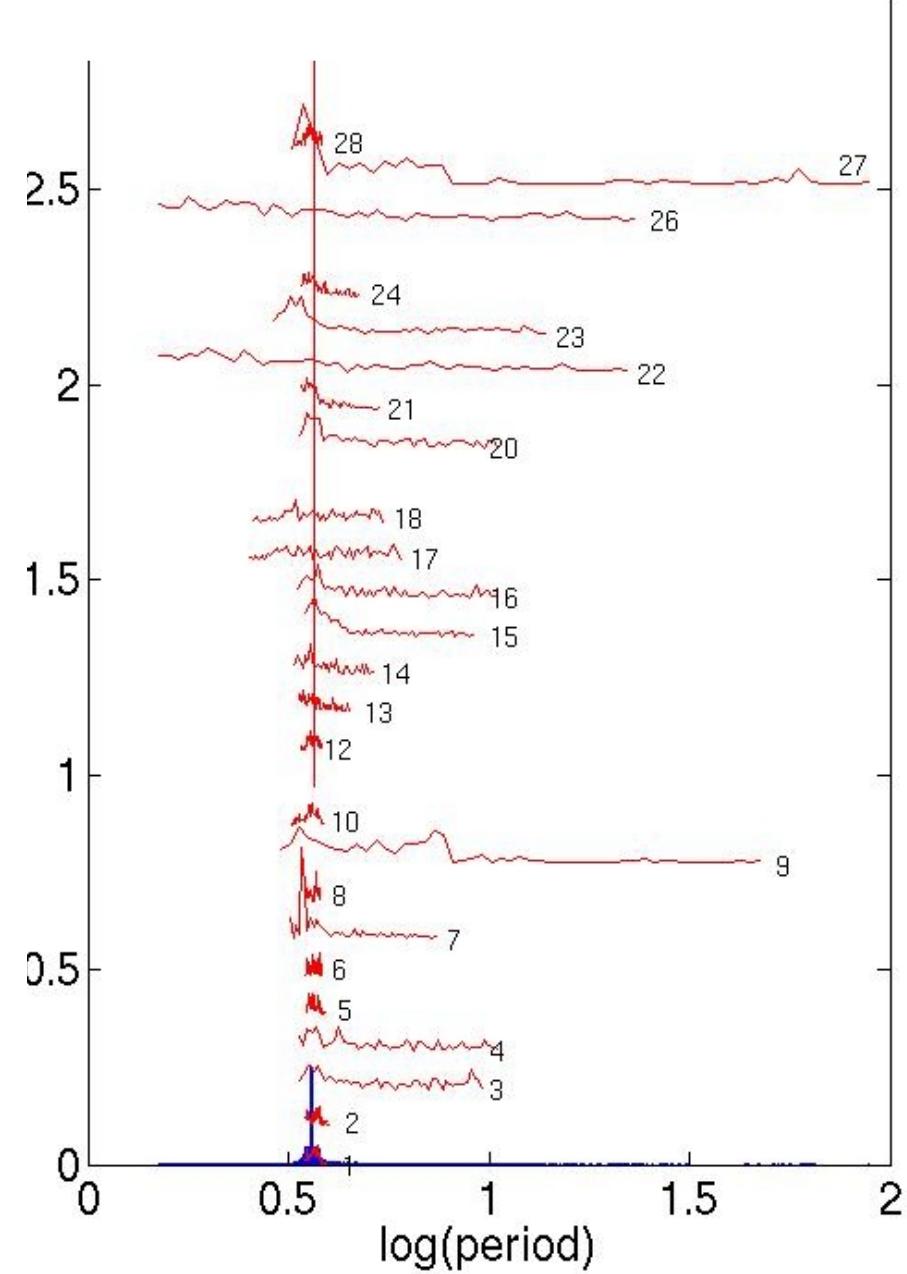
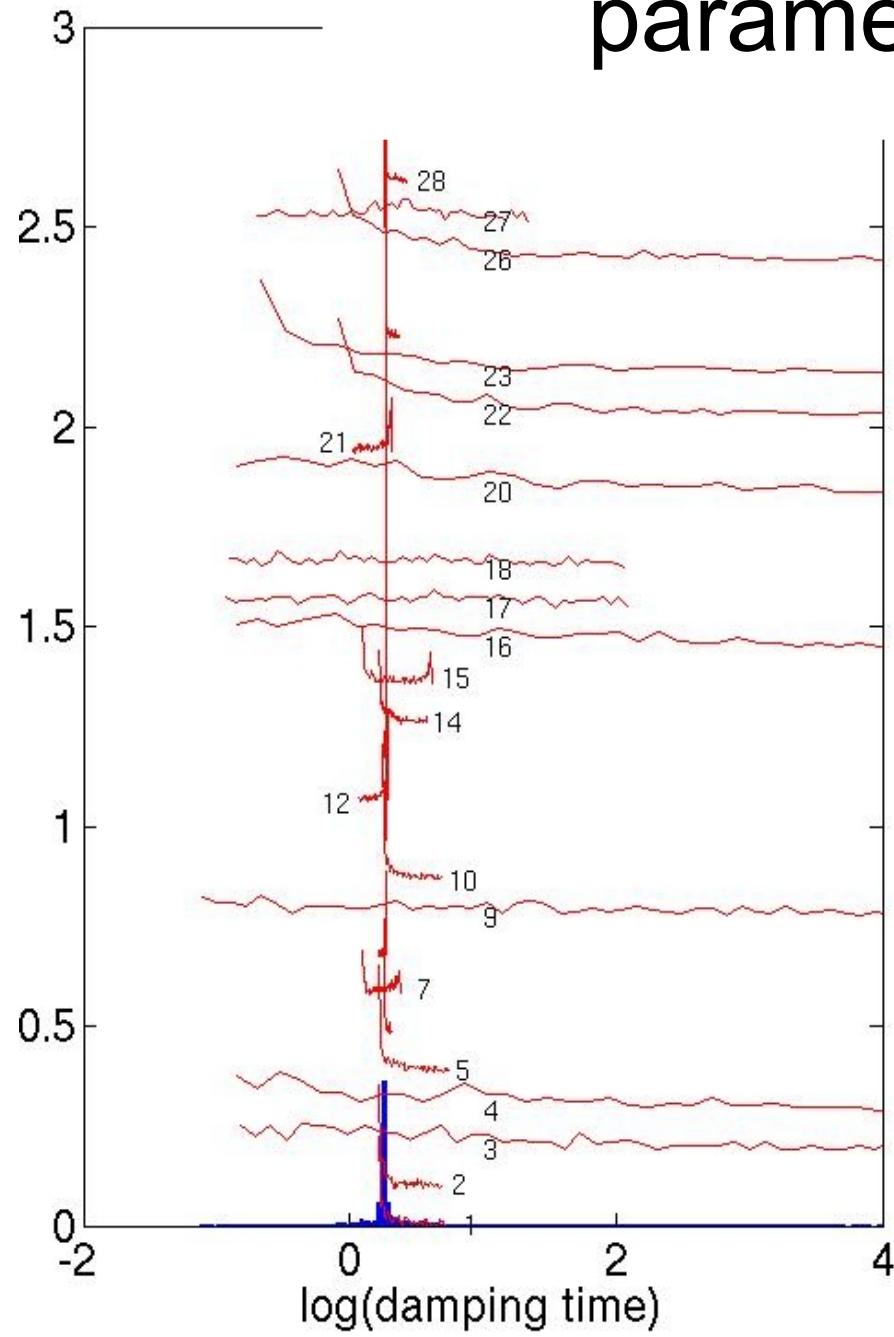
$r=2$



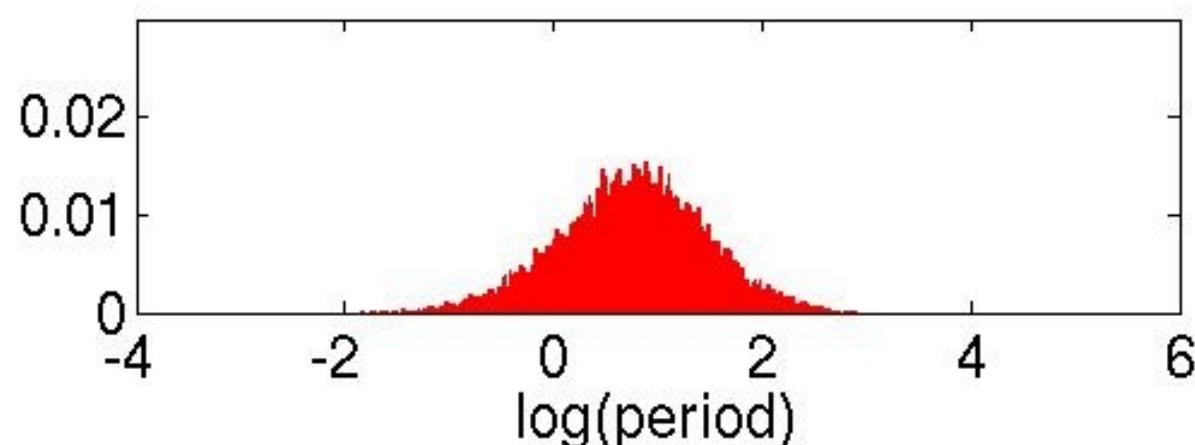
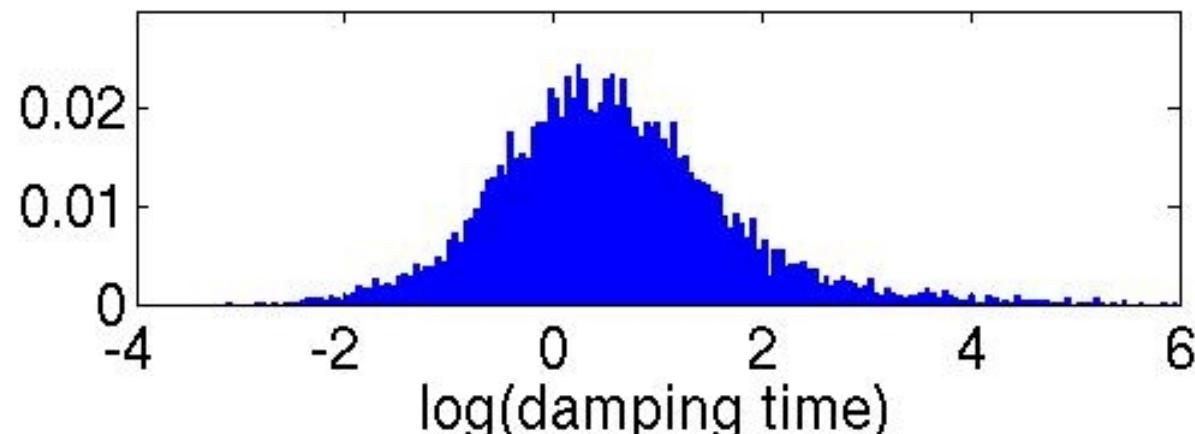
r-robustness



parameter sensitivity



distributed-robustness



Gap genes patterning of Drosophila example

thanks to Manu and John Reinitz

How accurately does Bcd specify fates? an experimental surprise..... ...a 1-robustness, twice redundancy case!

Nature (2002)
415:798-802

Establishment of developmental precision and proportions in the early *Drosophila* embryo

Bahram Houchmandzadeh*,†, Eric Wieschaus* & Stanislas Leibler*‡§

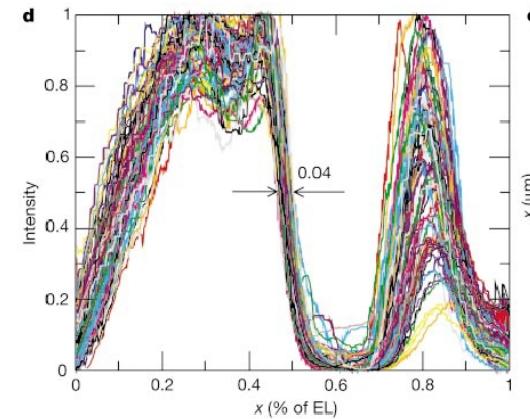
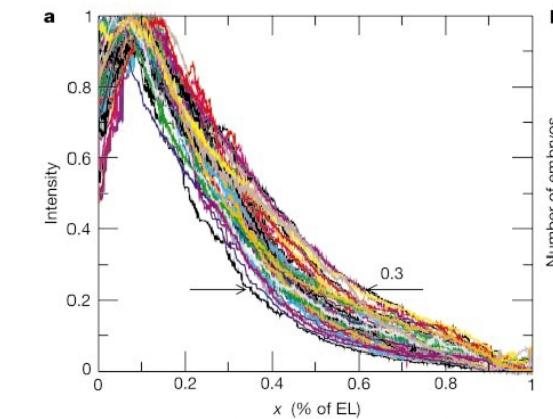
* Howard Hughes Medical Institute, Department of Molecular Biology,
Princeton University, Princeton, New Jersey 08544, USA

† CNRS, Laboratoire de Spectrométrie Physique, BP87, 38402, St-Martin D'Hères Cedex, France

‡ Department of Physics, Princeton University, Princeton, New Jersey 08544, USA

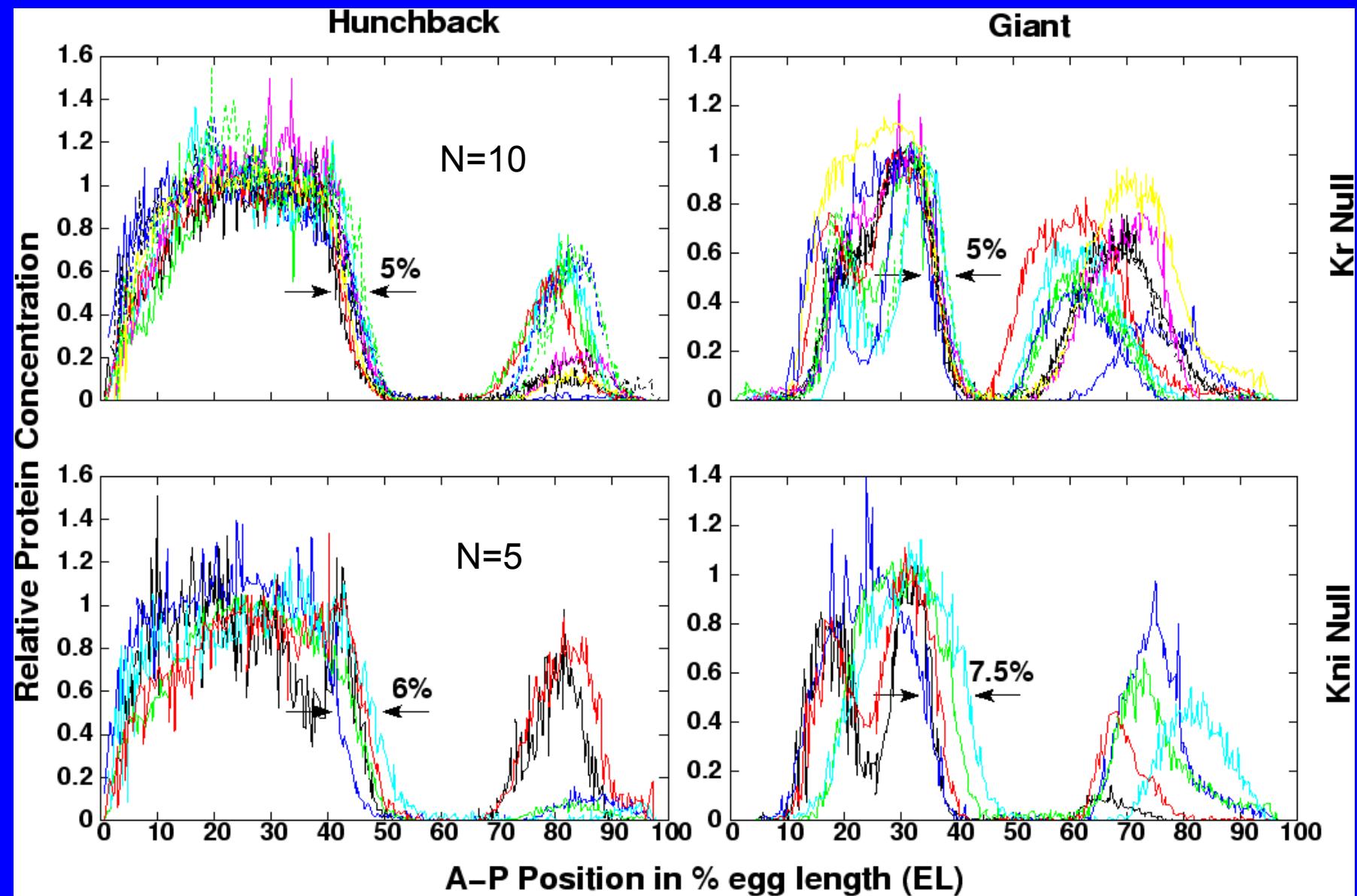
During embryonic development, orderly patterns of gene

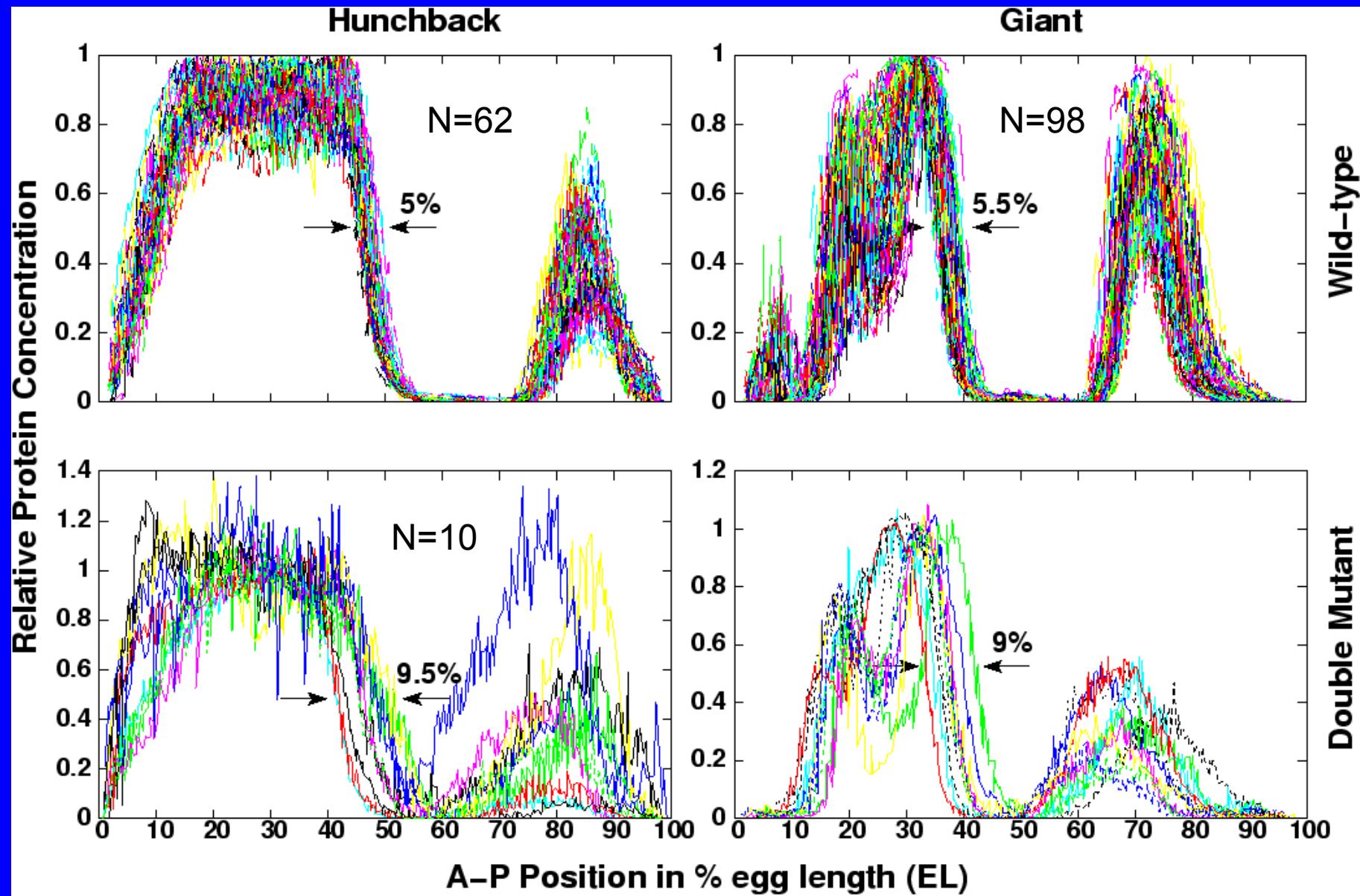
significantly smaller than that expected, even when the reduced efficiency we measure for the *bcd* transgenes is taken into consid-

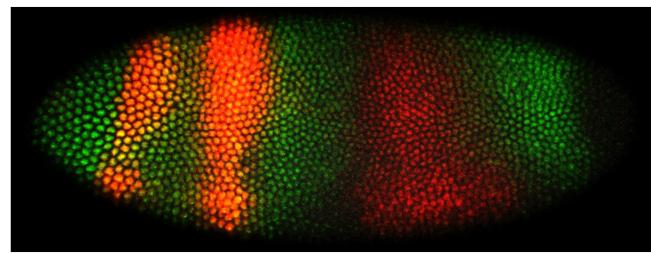
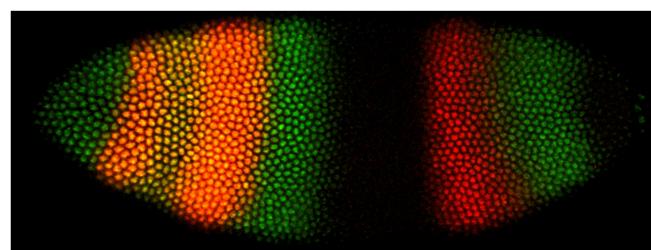
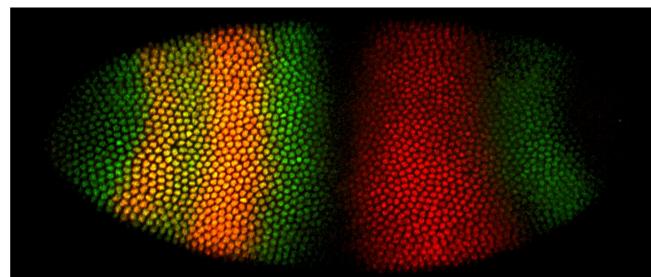
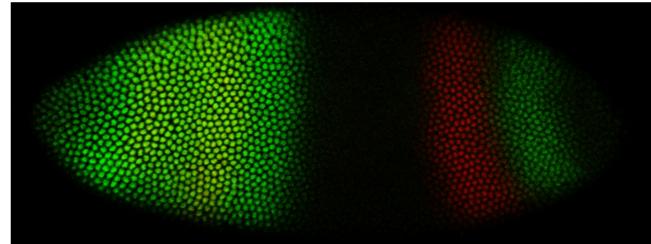


X_{bcd}

X_{hb}







Manu (Reinitz group)

Conclusions and future work

1. A simple reduction procedure has been applied to large molecular biology models to produce hierarchies.
2. These hierarchies can be used for:
 - a) parameter sensitivity studies
 - b) robustness studies
 - c) “unravelling” studies
3. Two types of robustness: distributed, r-robustness
4. Concentration effects: cube or sphere, simplex
5. To do : work more examples, more mathematics...