# Mathematical framework for studying biological robustness

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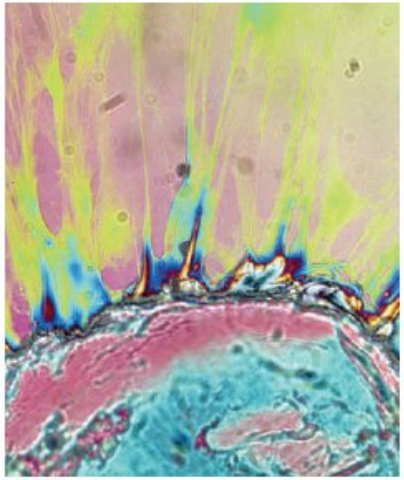
INRIA, Symbiose Project

University of Chicago, April 2nd, 2009

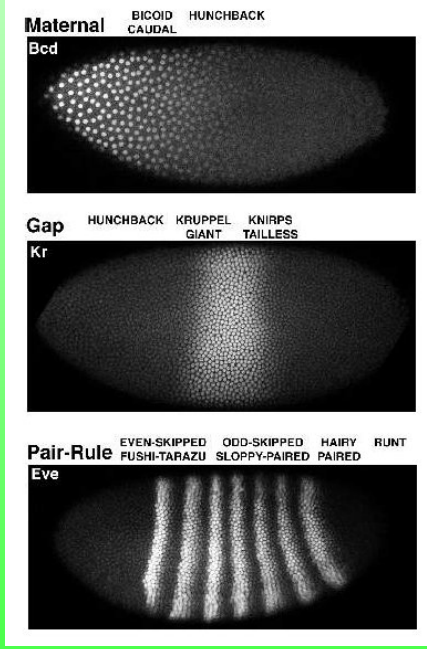
# The many faces of biological robustness

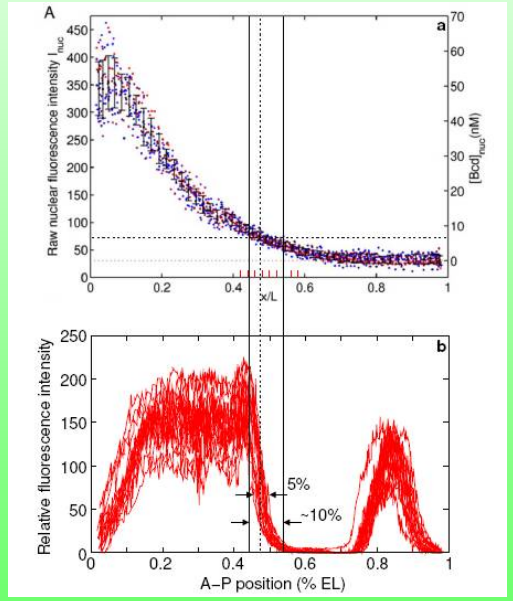
## Cancer and robustness



Hunt for fragility: weaknesses in tumour growth dynamics could yield new anti-cancer therapies.

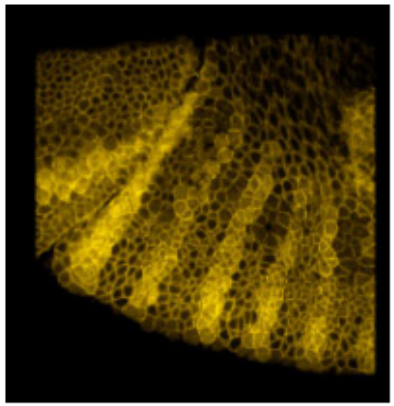
## Development and Robustness

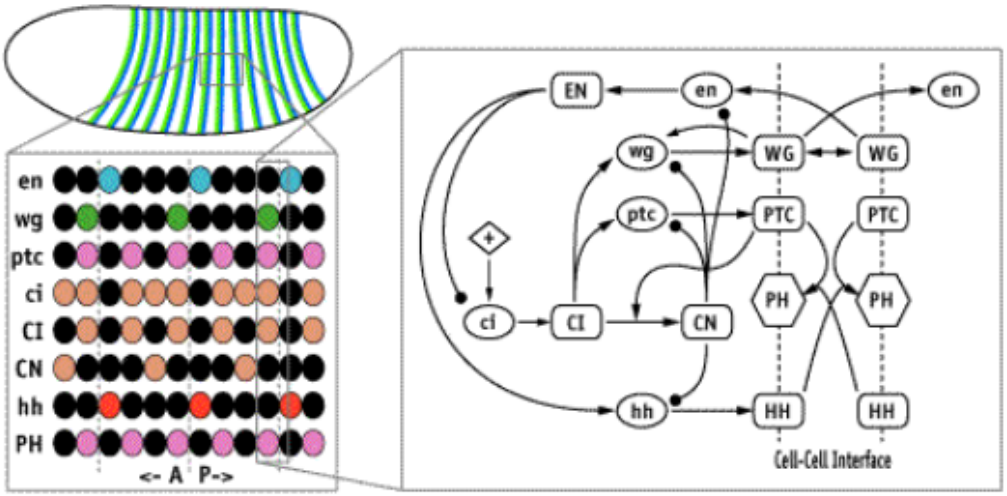



**How Does "Robust, Yet Fragile" Manifest Itself in the Example Systems?** Biological organisms are highly robust to uncertainty in their environments and component parts yet can be catastrophically disabled by tiny perturbations to genes or the presence of microscopic pathogens or trace amounts of toxins that disrupt structural elements or regulatory control networks. The 777 is robust to

# von Dassow's robustness






**von Dassow et al Nature 00**

# Redundancy and distribution of fragility: k robustness

## Multiple knockout analysis of genetic robustness in the yeast metabolic network

David Deutscher[1], Isaac Meilijson[2], Martin Kupiec[3] & Eytan Ruppin[1,4]

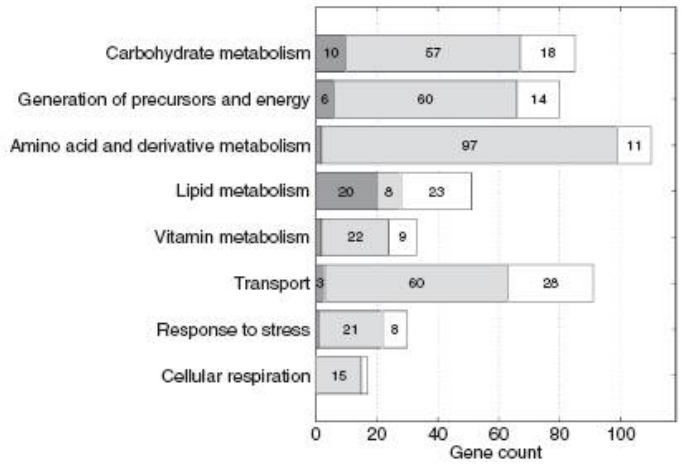



**Figure 3** Metabolic network robustness across different functional GO-Slim categories on rich medium, showing for each category the proportions of essential genes (dark), backed up genes (light), and genes not found to contribute in our analysis (white). Superimposed numbers indicate gene counts (for clarity, only counts of 3 or more are indicated). Only categories annotated with at least ten genes are included. The respective measurements in glucose minimal medium are very similar, except that many more of the genes involved in amino acid and derivative metabolism are essential (45/110).

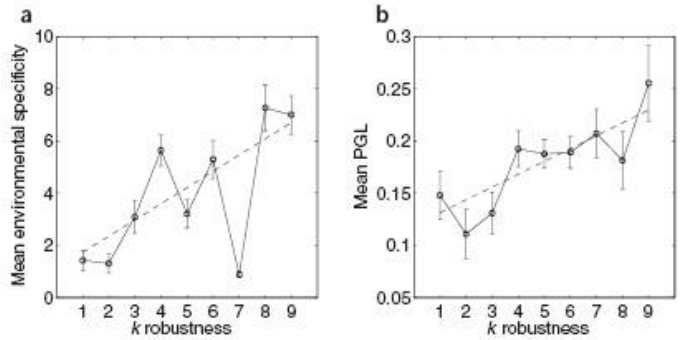


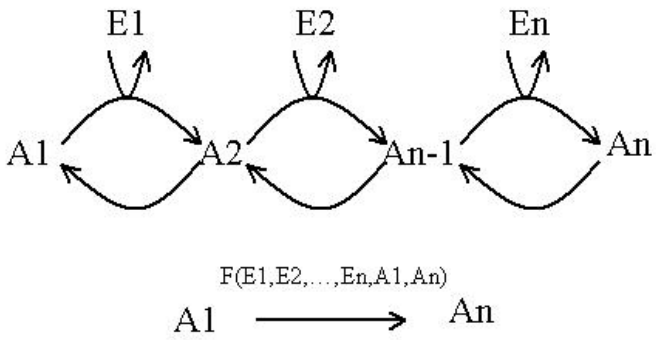

**Figure 5** Environmental specificity (ES) and propensity for gene loss (PGL) as a function of robustness level. Means ± s.e.m. are shown for the ES (**a**) and PGL (**b**) measures at each *k* robustness level. The dashed lines are the least squares linear regression through the original data points. Owing to their small number and the uncertainty in their robustness level estimation, we do not consider genes with *k* robustness >9, although the significant correlations found remain valid across *k* robustness thresholds from 5–12. The correlation between *k* robustness and PGL goes beyond the previously reported correlation between essentiality and evolutionary conservation[21–24], as it remains significant even when considering only nonessential genes ($R = 0.26$, $P = 5 \times 10^{-5}$, $N = 235$).

# Prolegomena for a mathematical theory of biological robustness

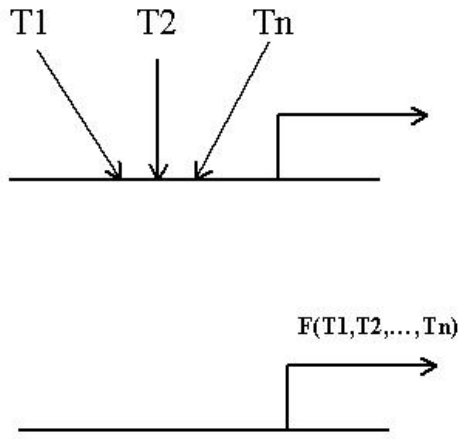
- Robustness by dimension reduction : from von Dassow to Gromov
- Model reduction : a framework for studying robustness
- Multi-fold robustness : a lesson from the fly

# Robustness by dimension compression

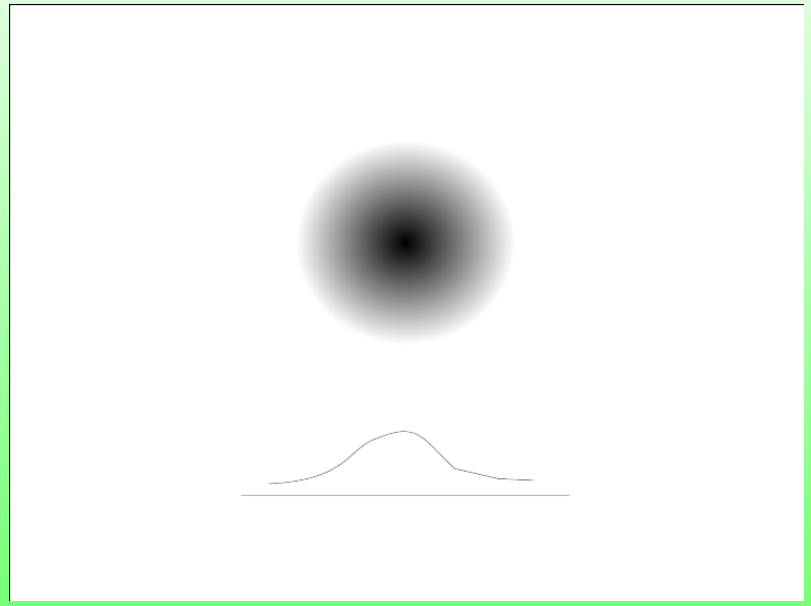
## Chain of catalysed transformations




## Transcription models



# Gromov-Levy cube concentration



Objects in high-dimension look small in projection.

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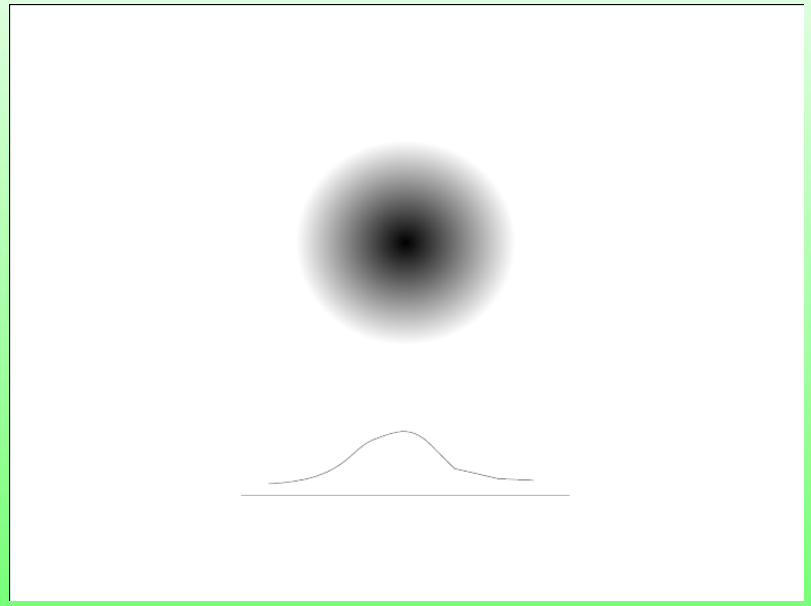

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Levy theorem (cube concentration): $F(k1, k2, ..., kn)$ with $F$ 1-Lipschitzian on $S^n(1)$ concentrates (roughly $Var(F) \sim 1/n$).

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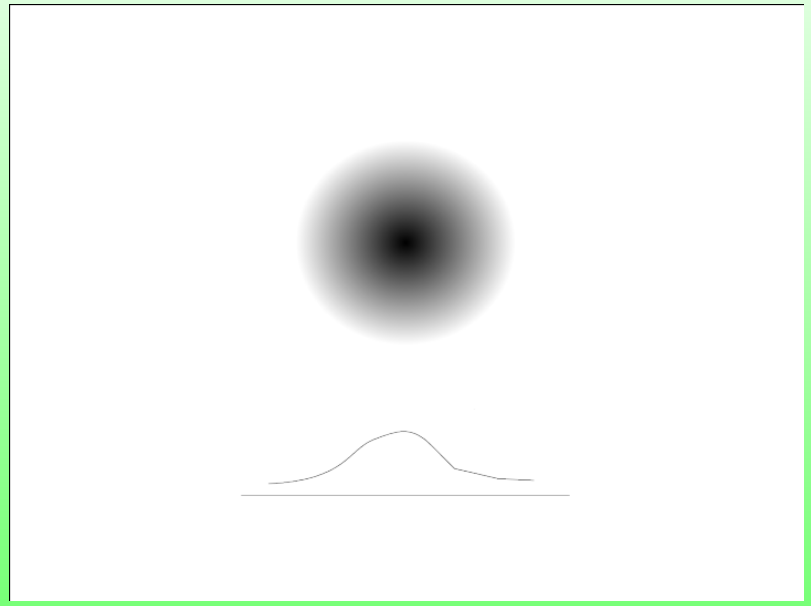

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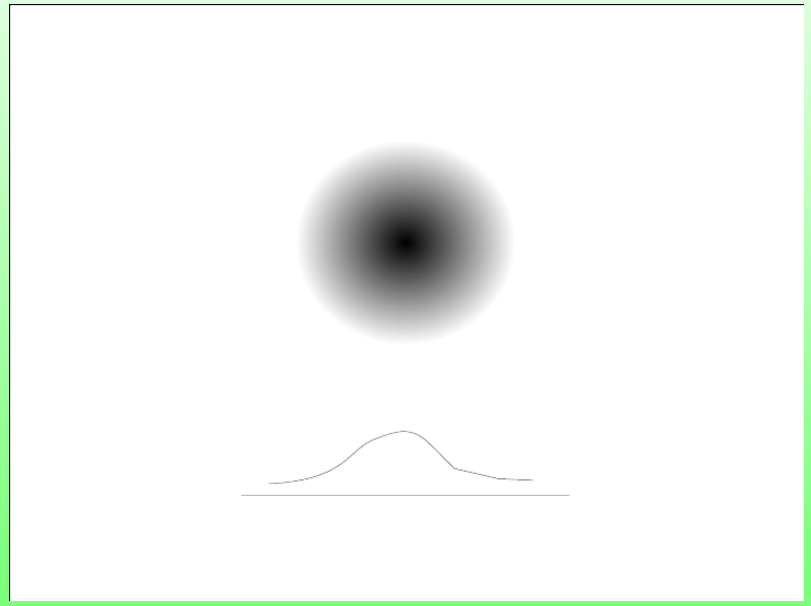

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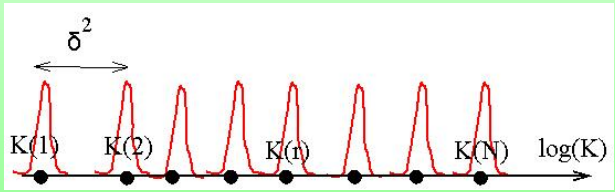
$f_{i[m_i,n_i;a]} = \frac{K_i v_a}{1+K_i v_a+K_j v_b}$, $\mathcal{F}^A_{i[a;m_i,n_i]} = f^A_{i[a;m_i,n_i]} \prod_k \left(1 - q(d_{ik}).E_b f^Q_{k[b;m_k,n_k]}\right)$,
$\sum_a C_a \sum_i \mathcal{F}^A_{i[a;m_i,n_i]}$

# Simplex concentration

order statistics $K_{(1)} >> K_{(2)} >> ...K_{(r)} >> ...K_{(n)}$, $M = K_{(r)}$
log-uniform parameters with average spacing $\delta$ in log-scale

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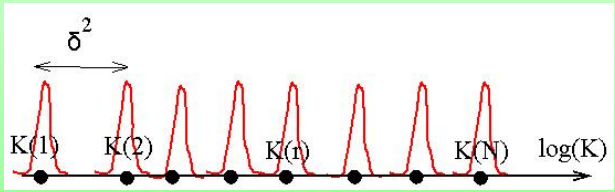


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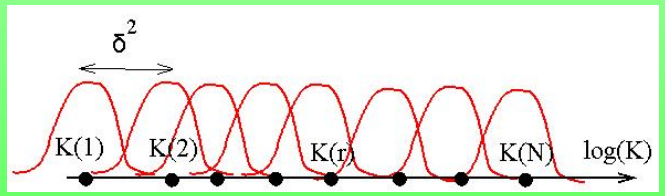


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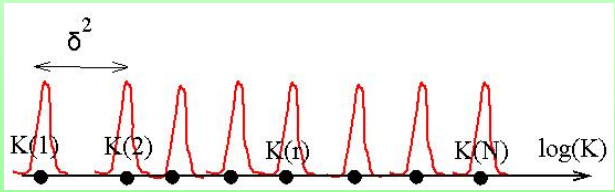


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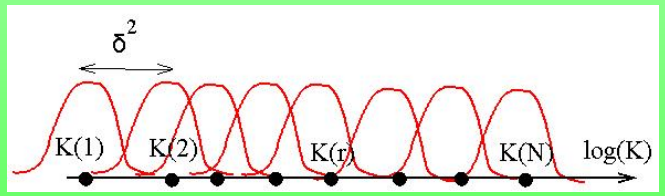


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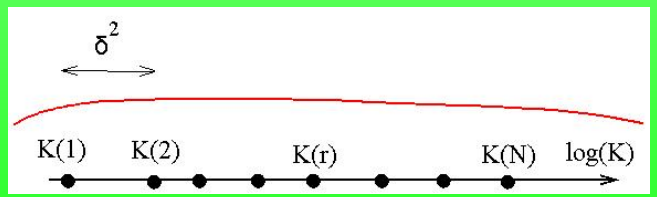


$Var(\log K) >> \delta^2$, simplex concentration
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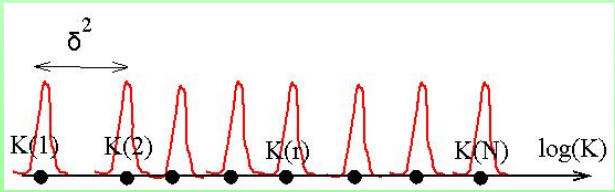


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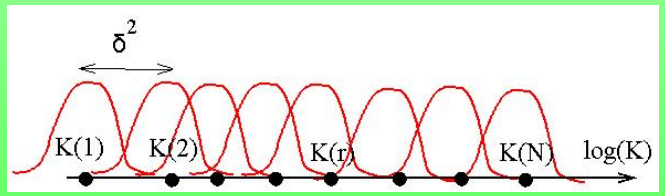


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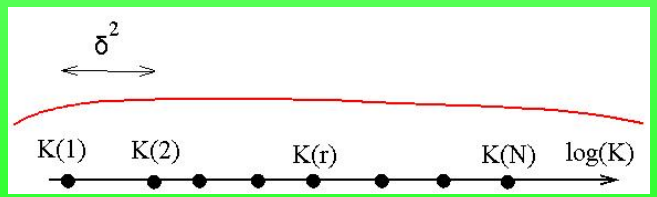


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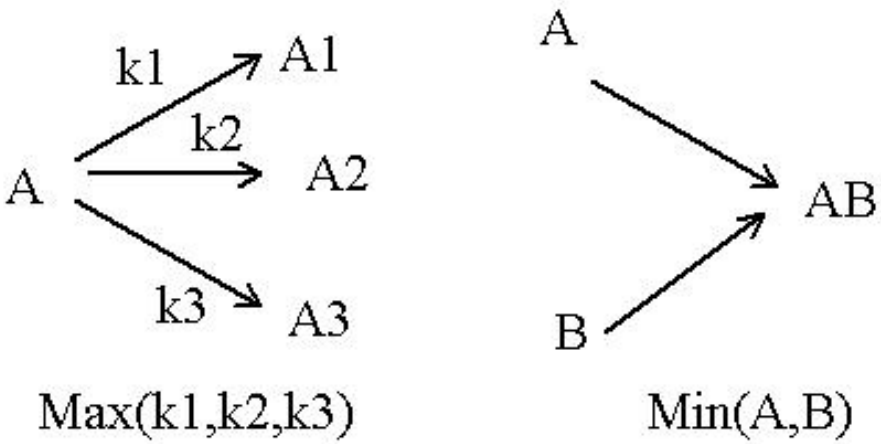
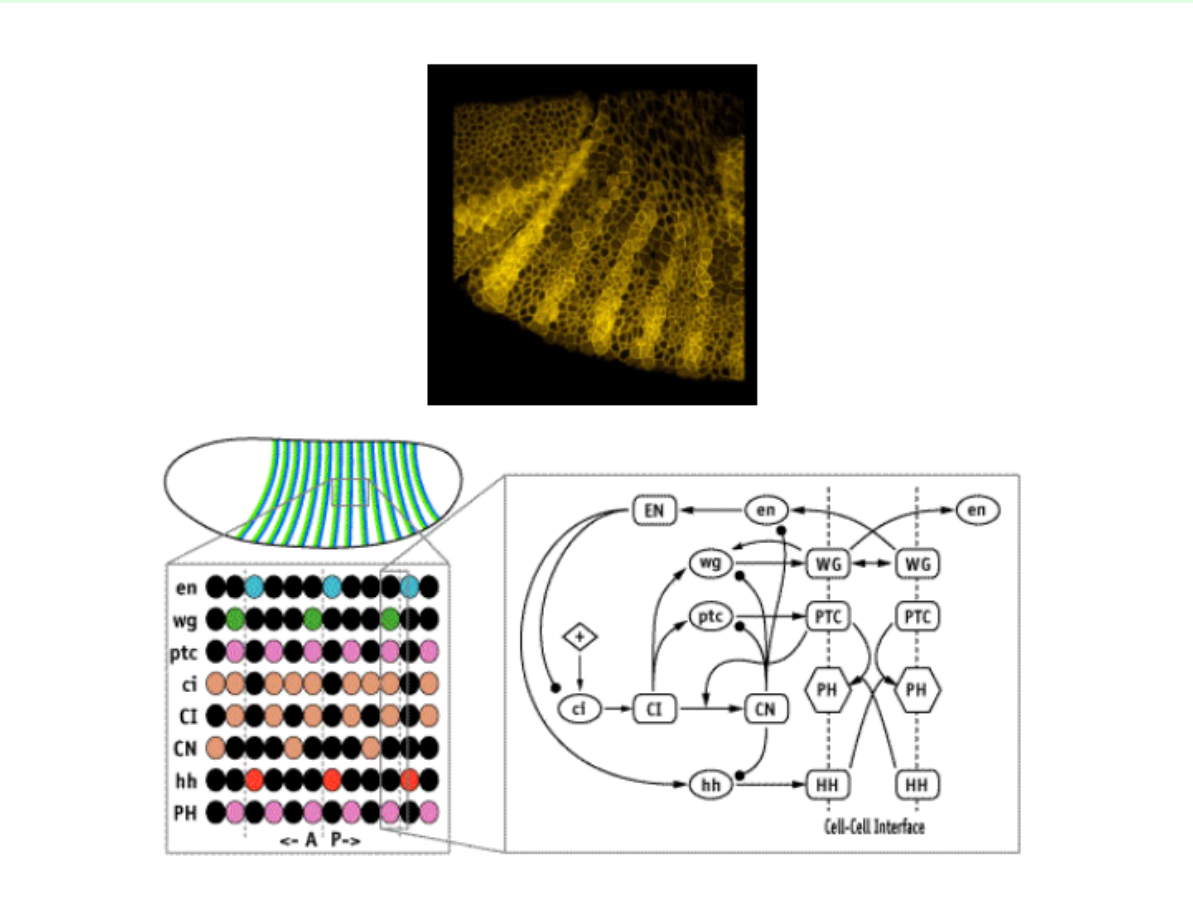
# Min - max combinations



# Von Dassow's robustness

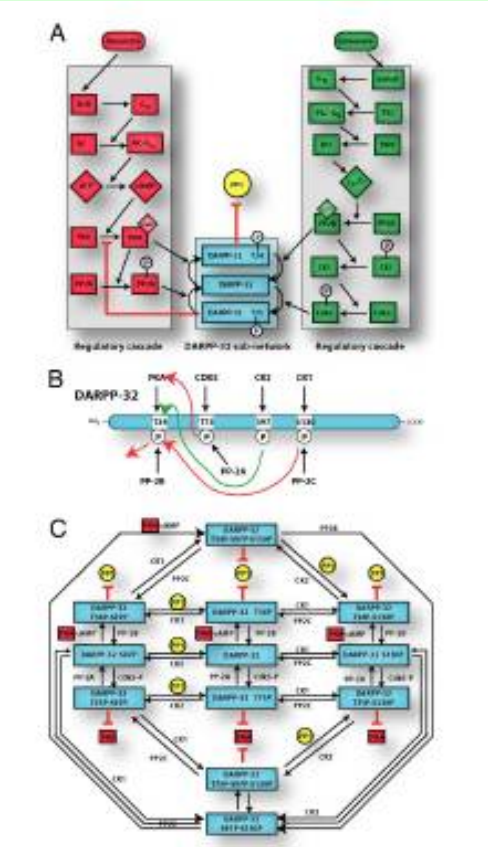



**von Dassow et al Nature 00**

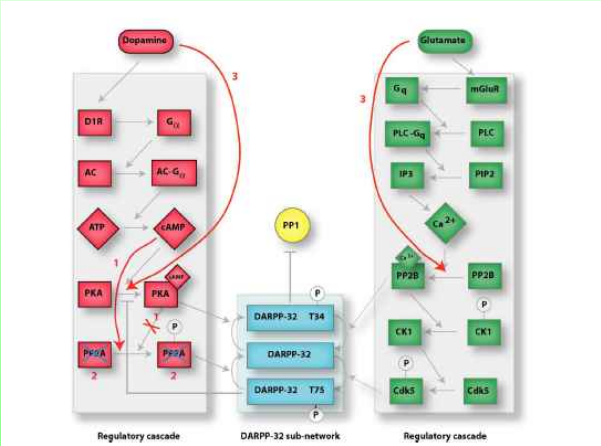
Hypothesis: robustness by dimension compression.

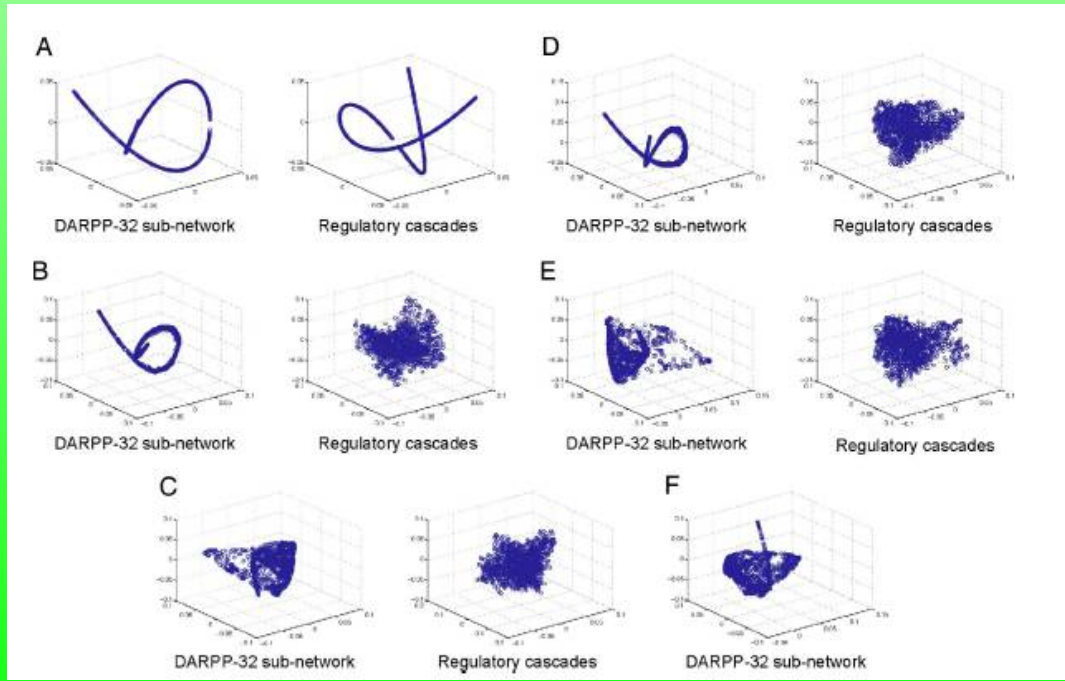
To prove this: a) dynamics is low dimensional (possible). b) there are only a few critical parameters (true). c) construct the coarse graining mapping (difficult).

# DARPP-32 pathway: dynamics is low dimensional




**Barbano et al., PNAS 2007.**



# Model reduction for Linear Networks of Chemical Reactions

All the reactions are of the type $A_i \to A_j$

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Kinetic equation

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$$c(t) = (I^0, c(0)) + \sum_{k=1}^{n-1} r^k (I^k, c(0)) \exp(-\lambda_k t)$$

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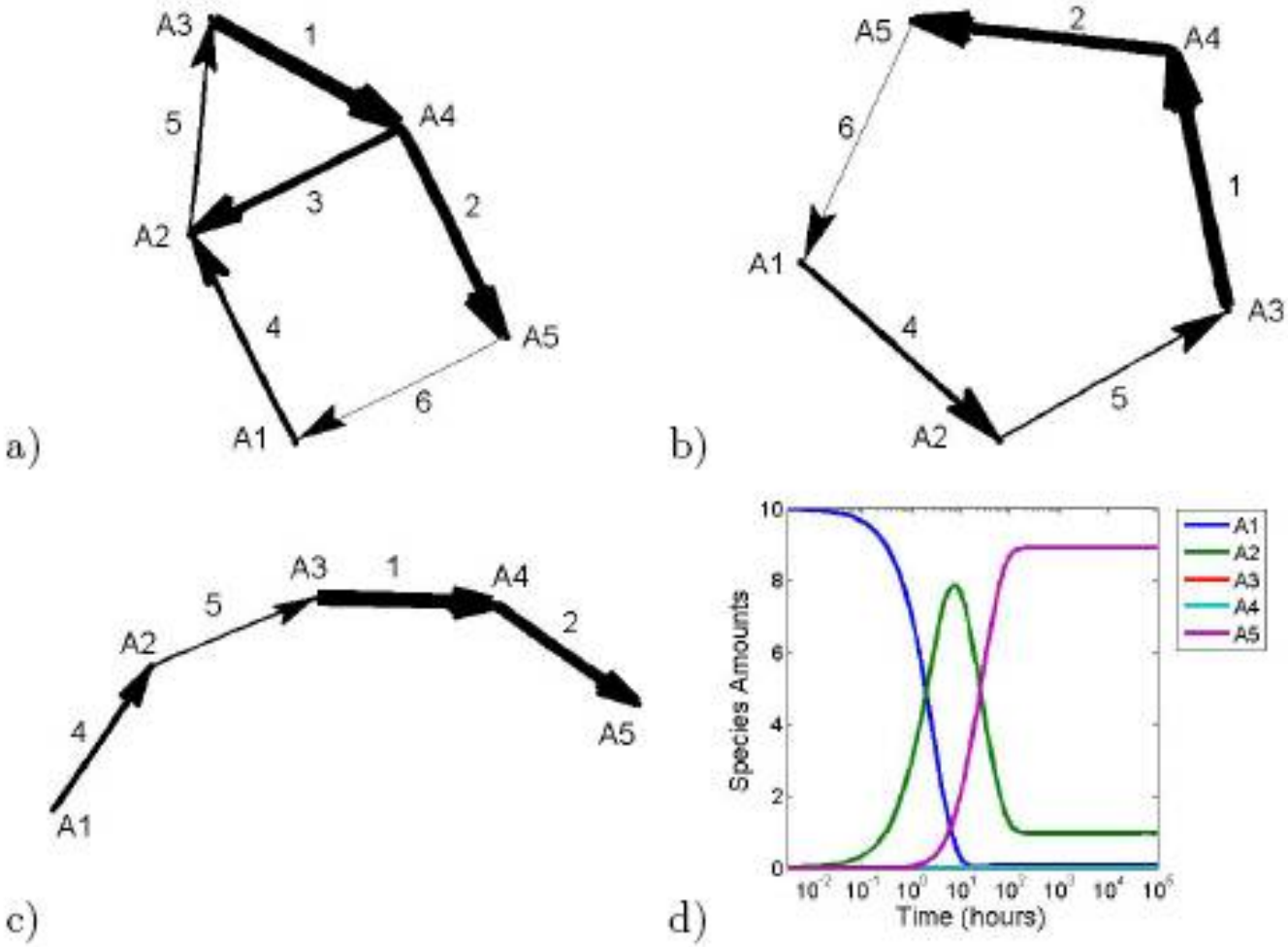
dominant subsystems: reduced models providing approximations to eigenvectors and eigenvalues.
goal: Compute dominant subsystems for arbitrary reaction networks with well separated constants

# Limitation theory for linear, hierarchical models: an example

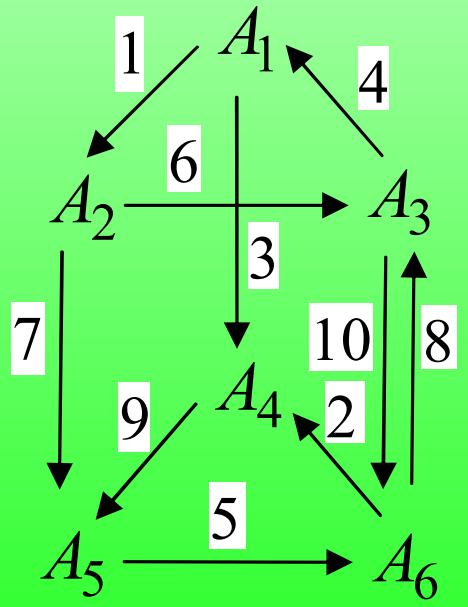



**Gorban and Radulescu Adv.Chem.Eng.08, Radulescu et al BMC Systems Biol. 08**

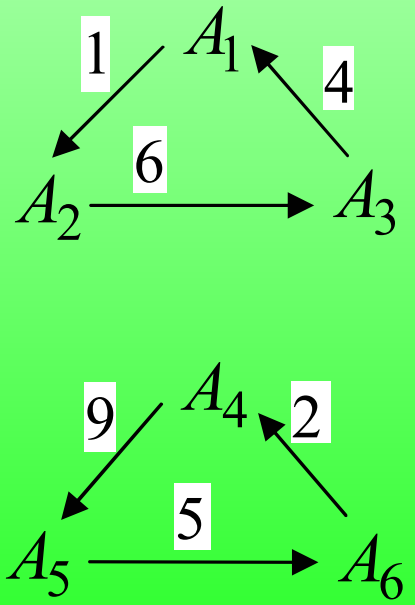
# A more complicated example: the prism

The prism is a model used in biophysics (Kurzynski Prog.Biophys.Mol.Biol. 98).

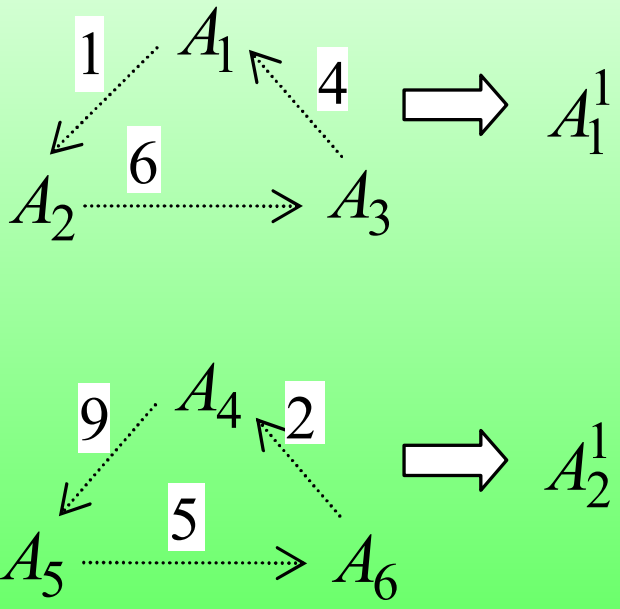
The full model

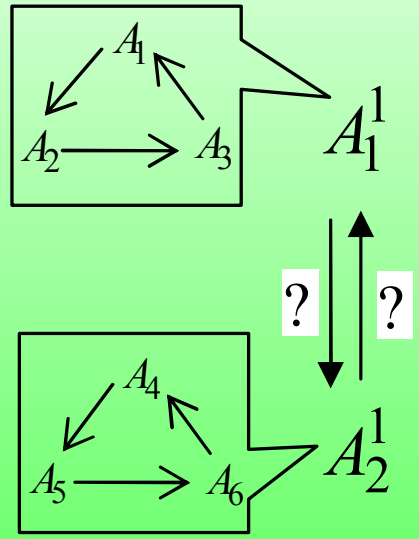



The auxiliary dynamical system



# Glue cycles




The limiting constant is $k_{32}$ for the upper cycle, $k_{54}$ for the lower cycle.

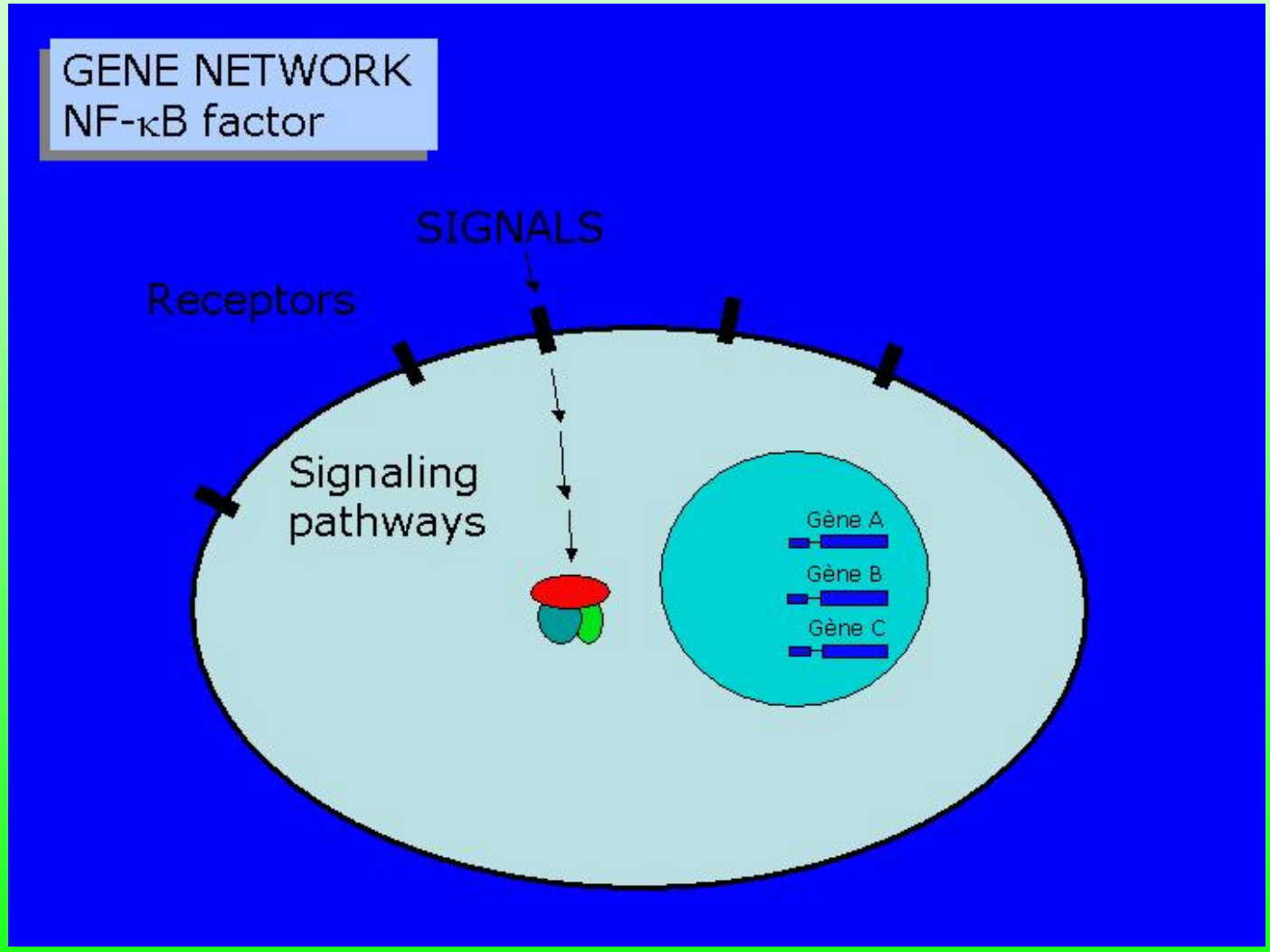
$k_{21}^1 = \max\{k_{41}k_{32}/k_{21},\ k_{52},\ k_{63}k_{32}/k_{13}\},\ k_{12}^1 = k_{36}k_{54}/k_{46}$

six possible orderings, each one a different simplification (different acyclic auxiliary dyn. system or different dominant (critical) parameters)

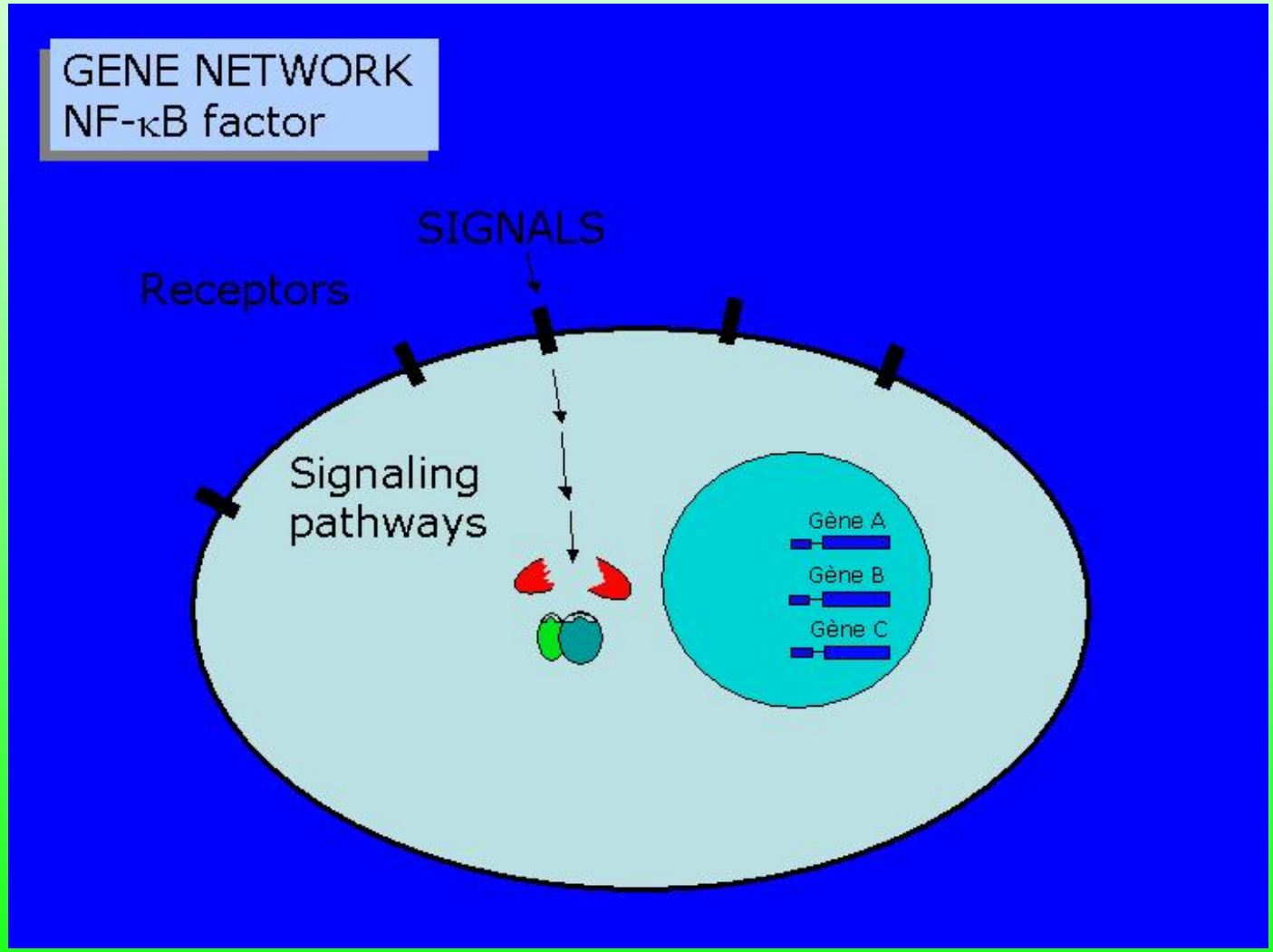
# Robustness of linear models

- Topology is not everything. Order integration ...
- Slowest relaxation time is an r-th order statistics (under some conditions). Concentration...
- Kinetic constants of dominated reactions are not critical (only order matters). Max rule...
- Dimension of dynamics (number of active modes) is low and can change with time and with orders.

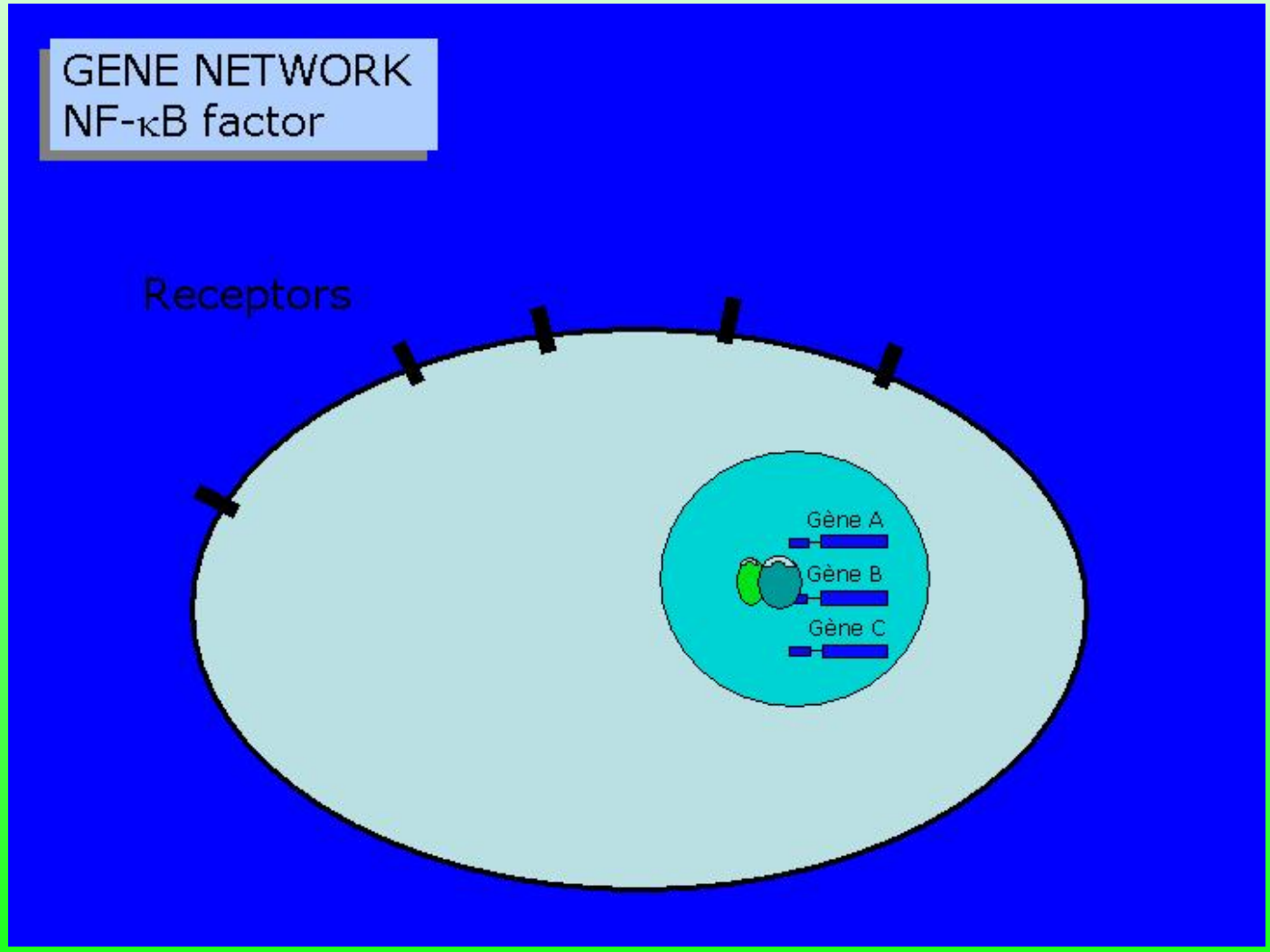
# Signalling of NF$\kappa$B: a case study



# NF$\kappa$B response to signals



# NF$\kappa$B controls over 100 genes



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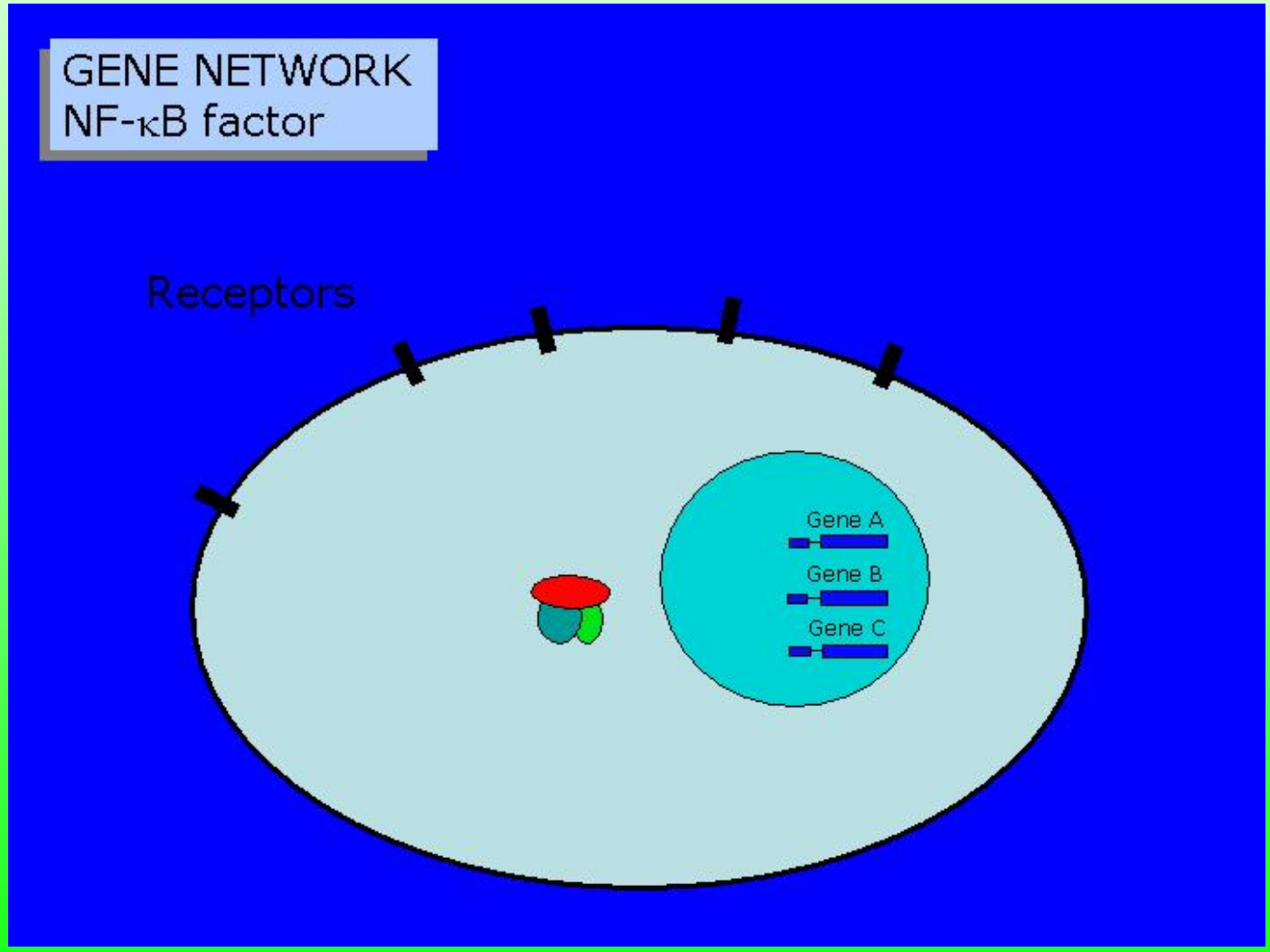
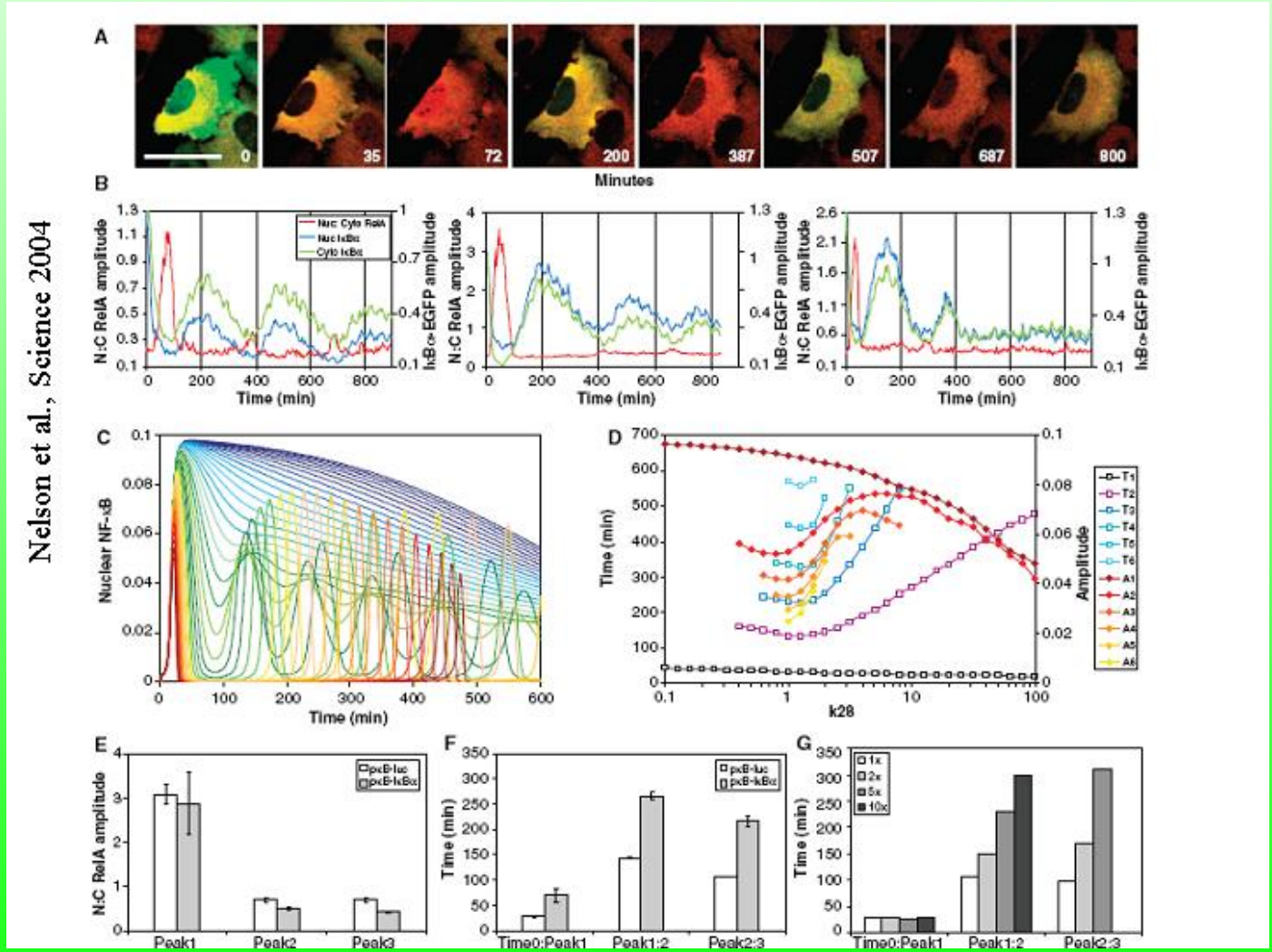
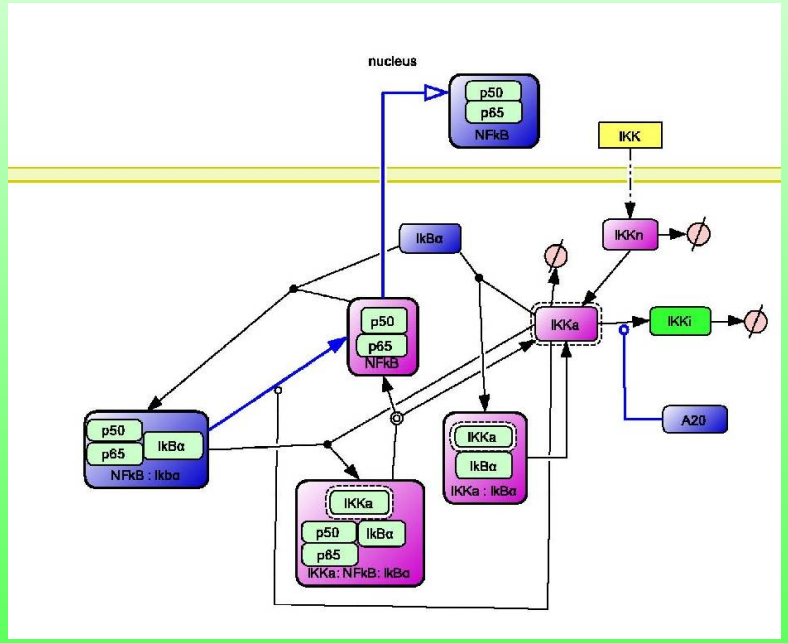


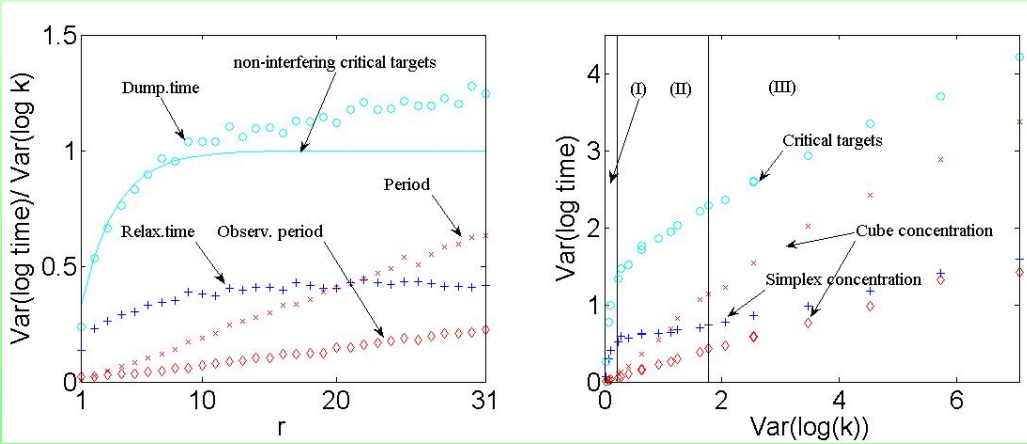
# Delayed negative feed-back produce oscillations

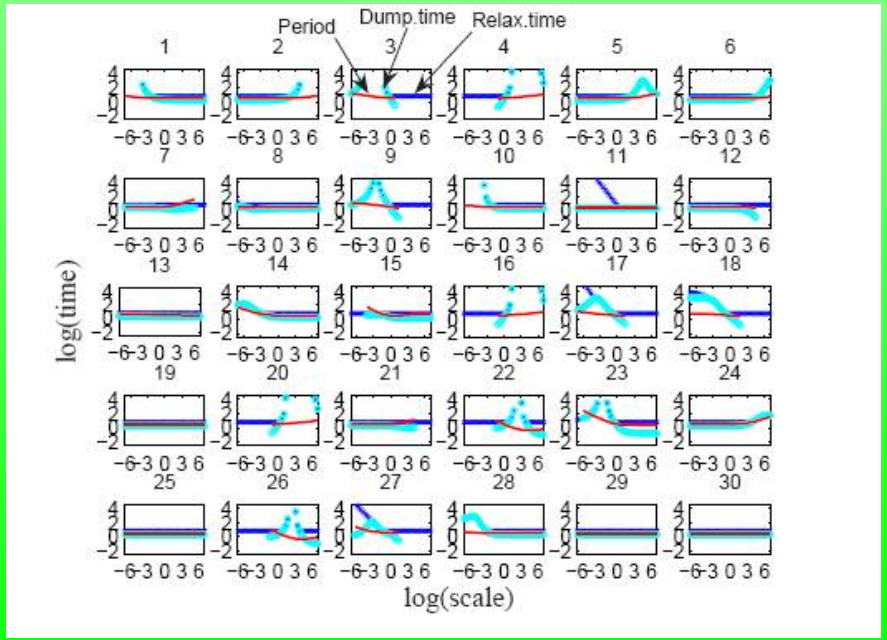


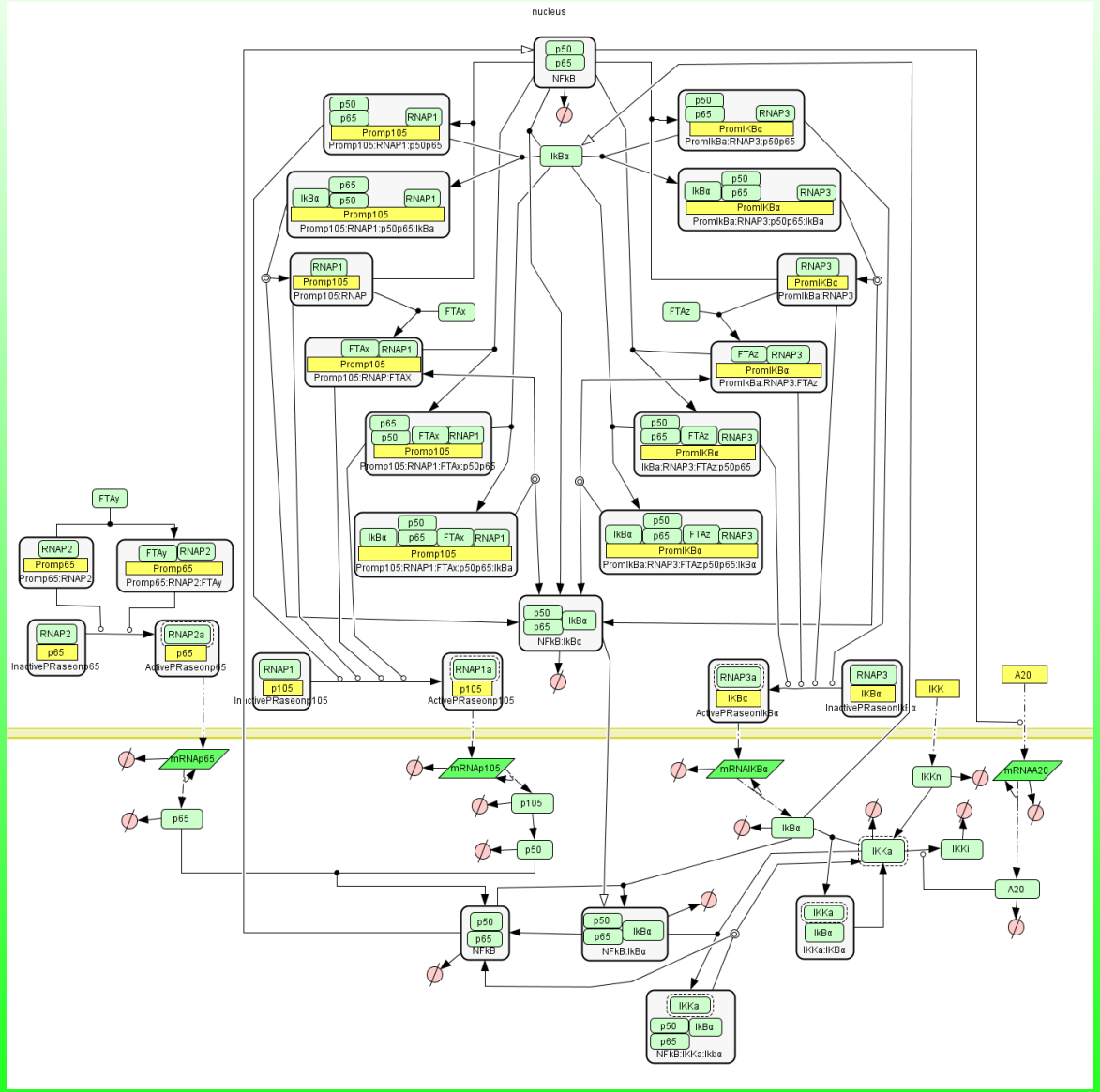
# NF$\kappa$B pathway: testing generic robustness for nonlinear models




**Gorban and Radulescu, IET Systems Biol. 07**

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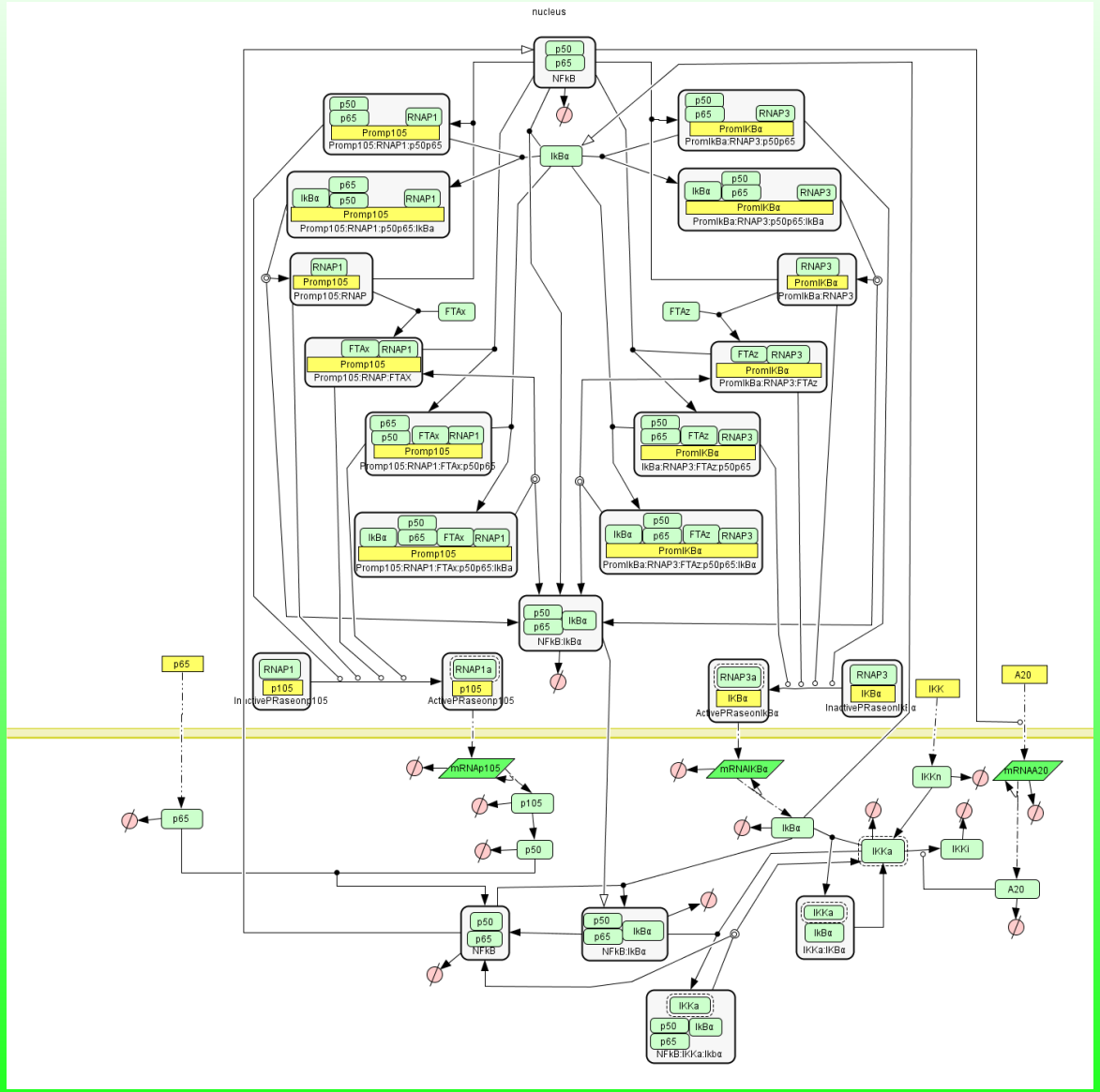
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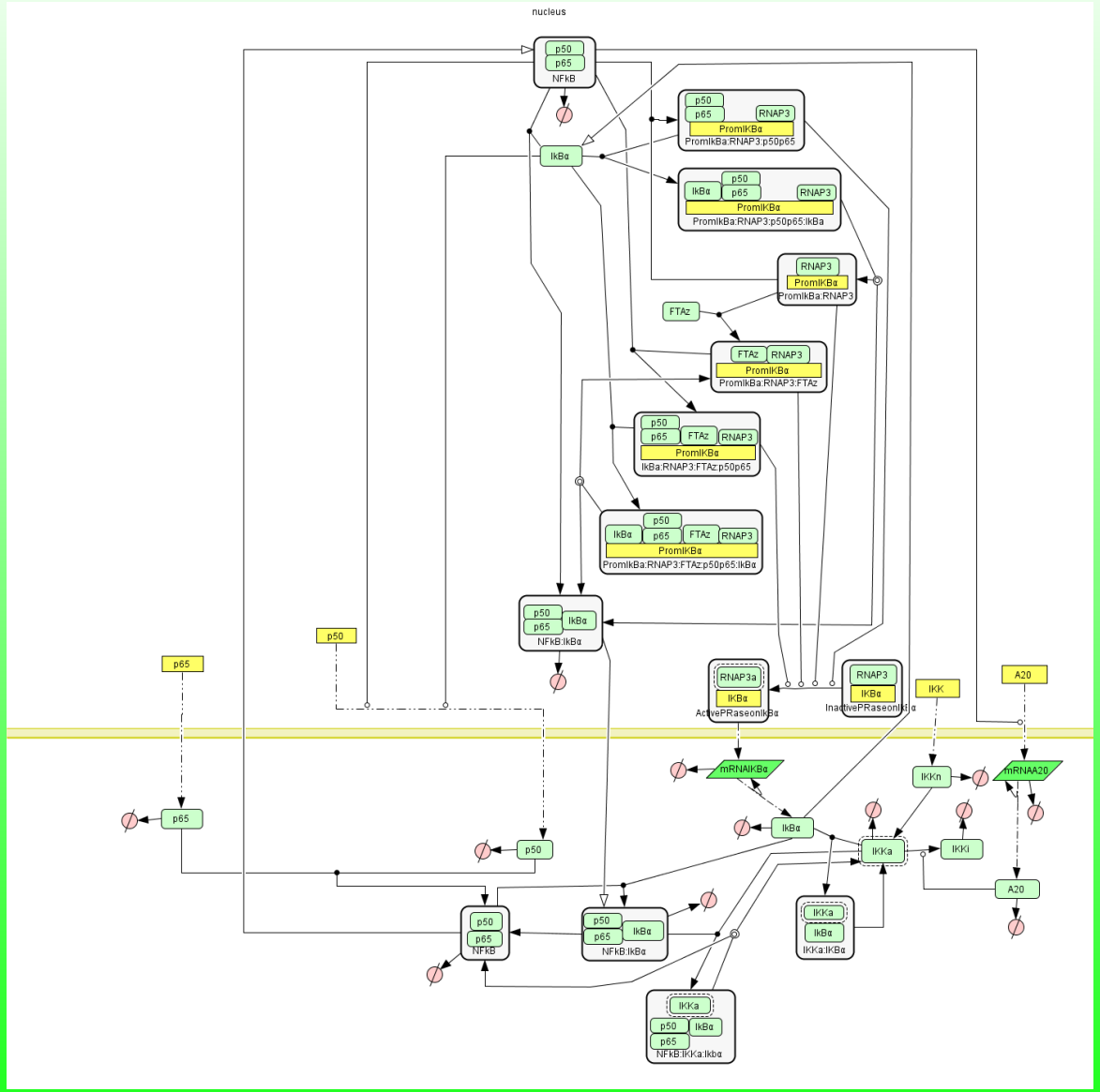
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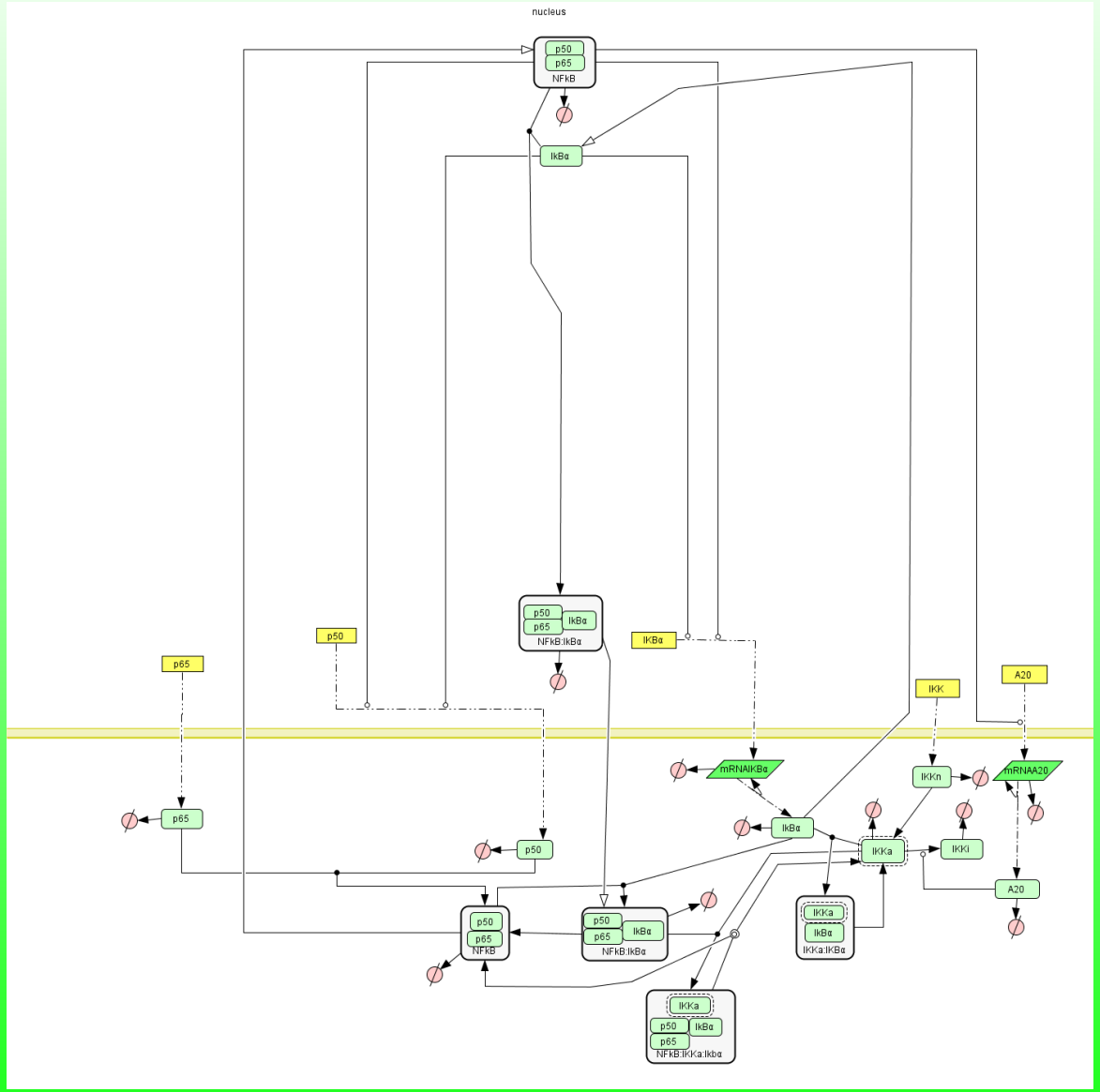
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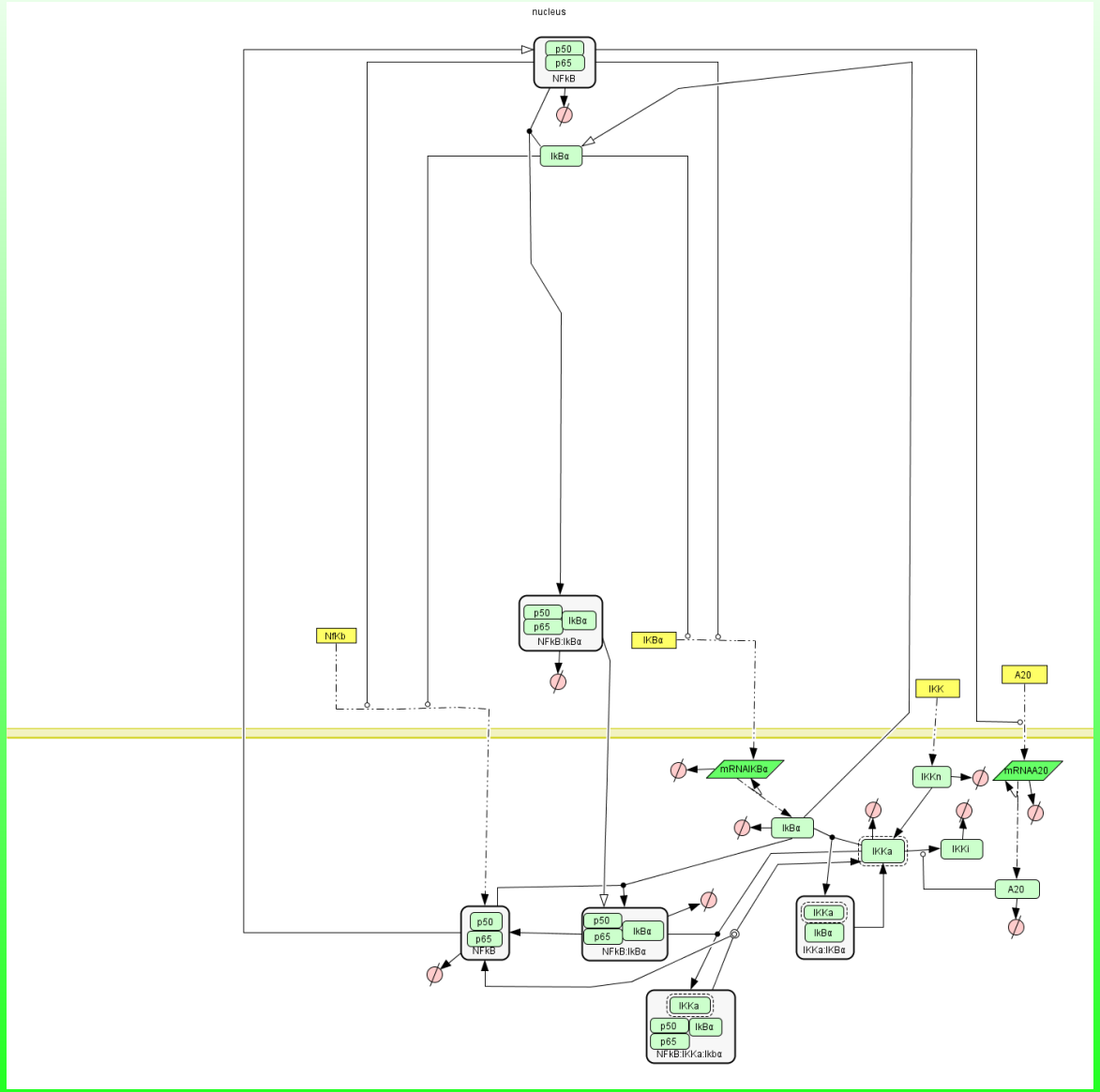
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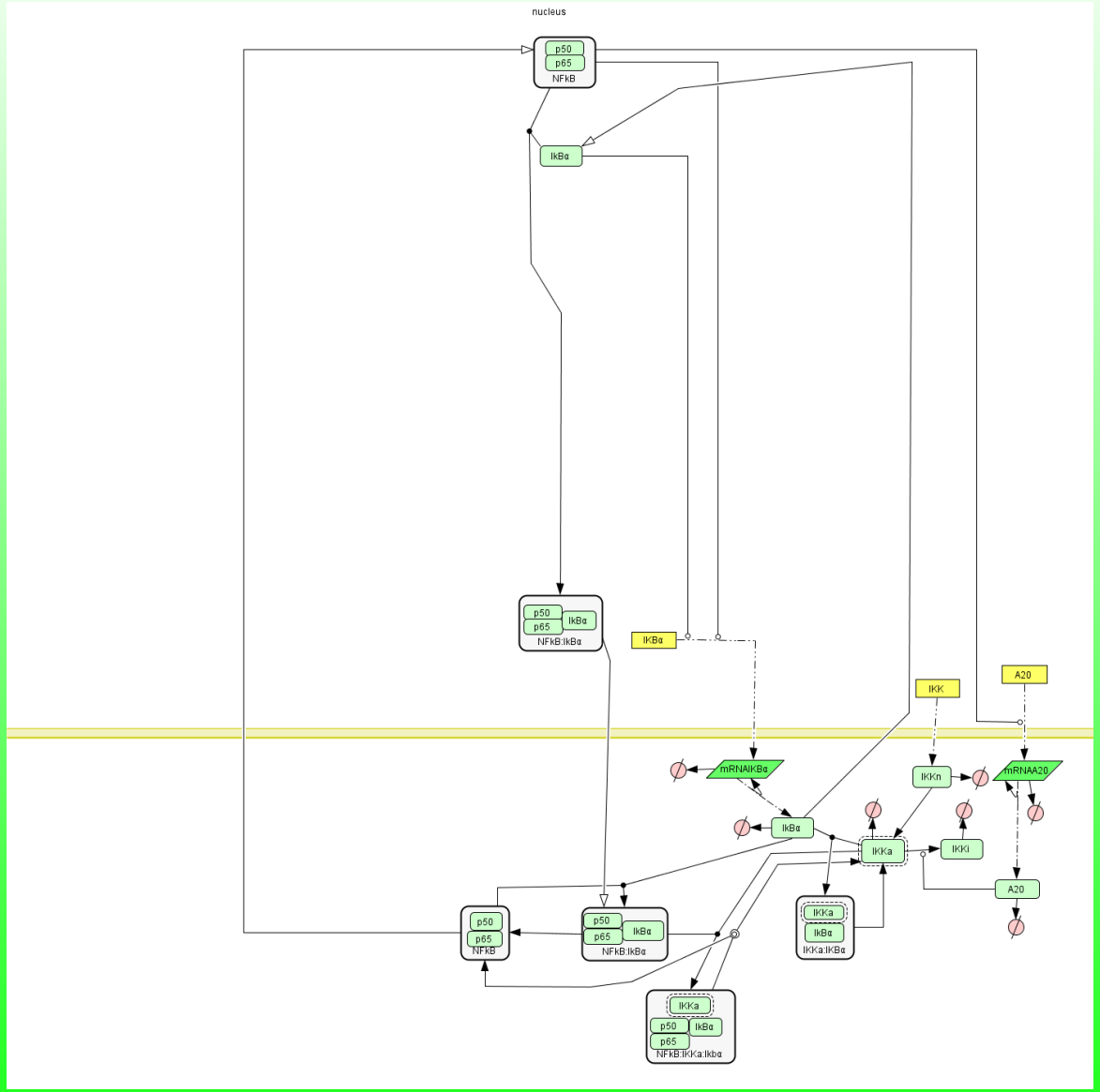
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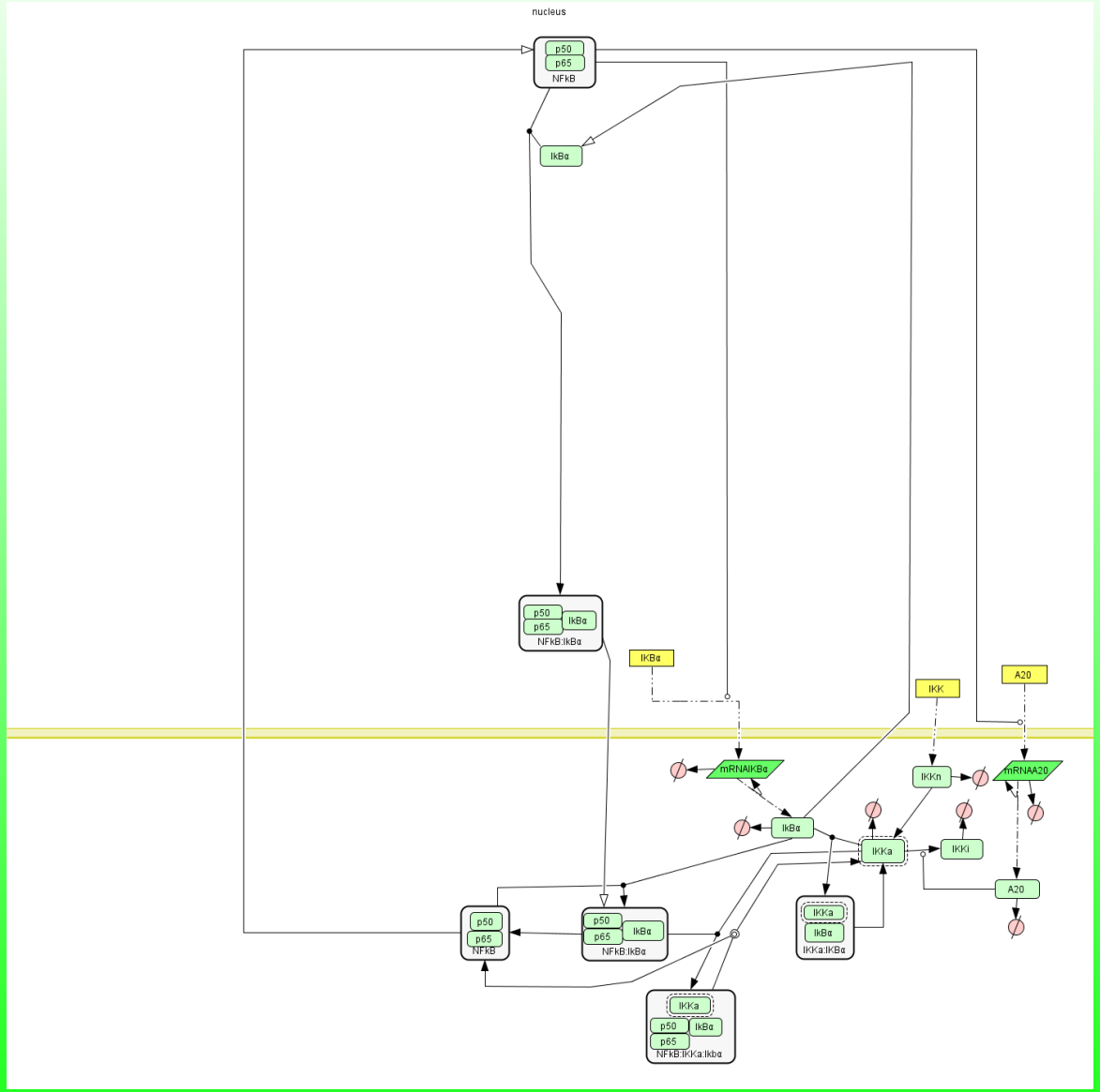
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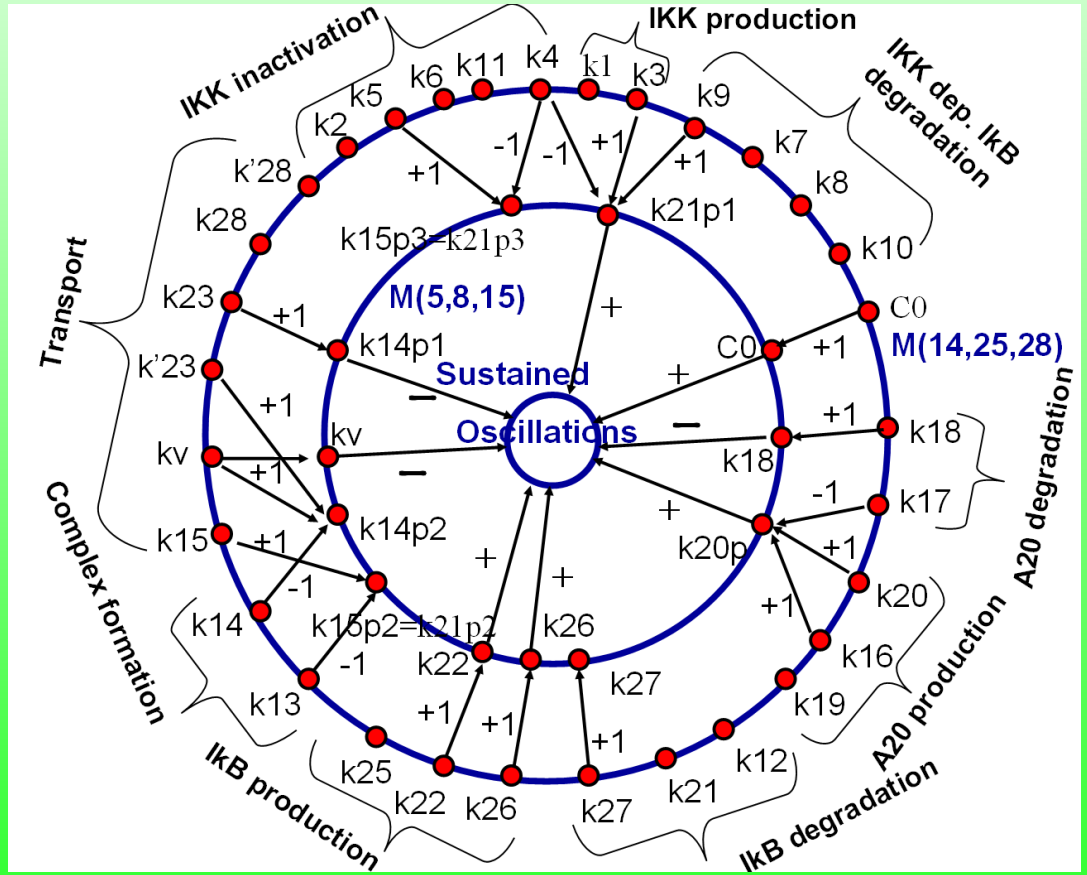
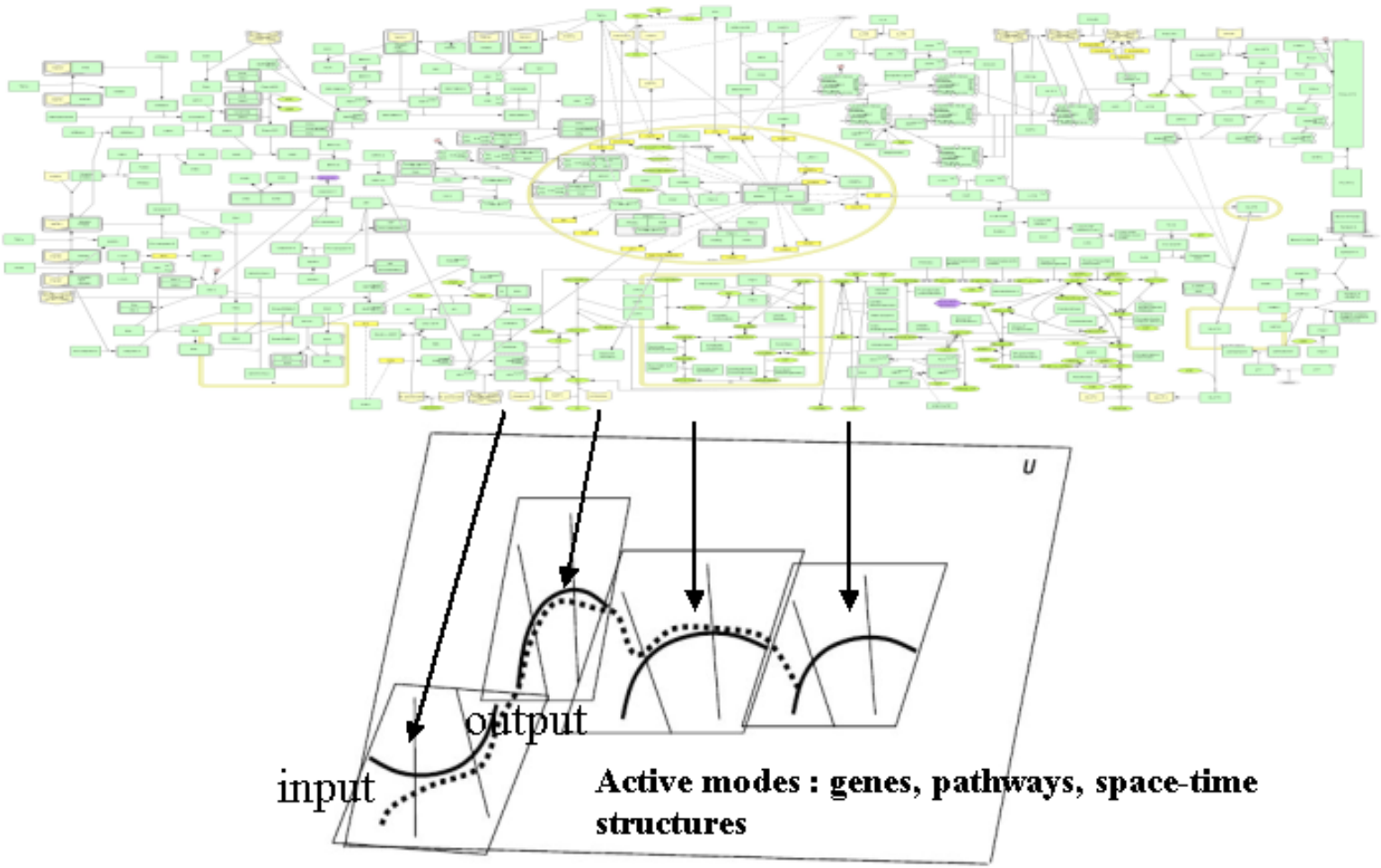
# Model reduction and critical parameters




Radulescu et al BMC Systems Biol. 08

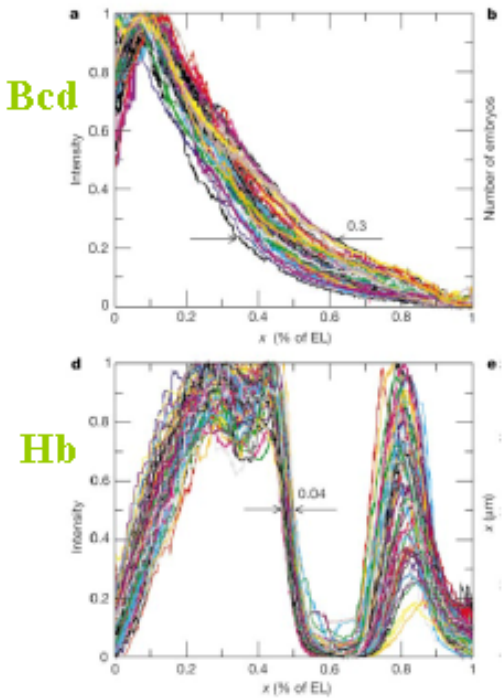
# Multi-fold robustness

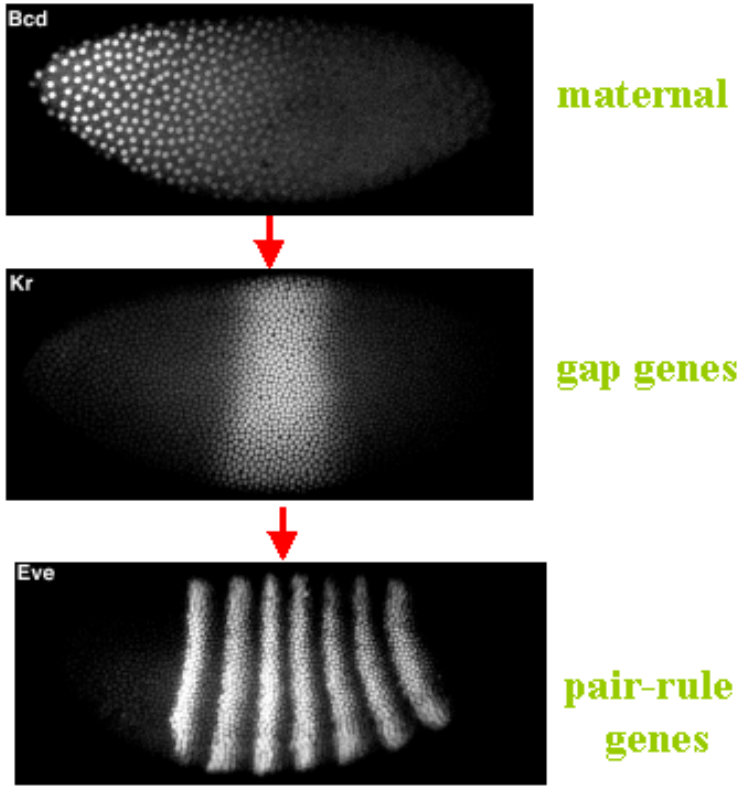



Crazy quilt: sequence of robust simplifications in abstract spaces

# Multi-fold robustness - A lesson from the fly

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




**Houchmandzadeh, Wieschaus, Leibler, 2002: unexplained reduction of variance**

# Complex, but not bottom level: the gene circuit model

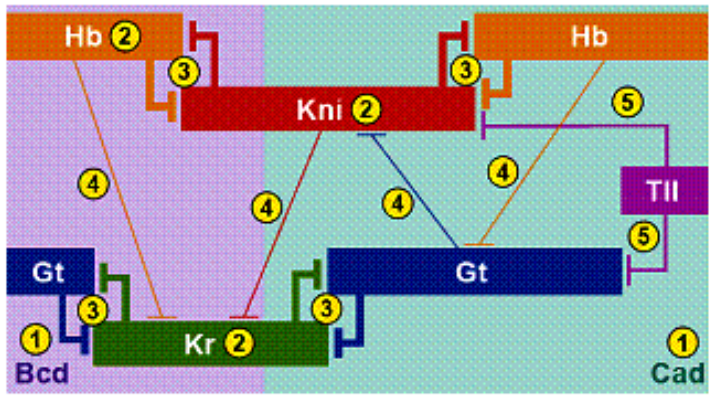
## Model: Hopfield + diffusion

Synthesis

$$\frac{\partial u_a(x,t)}{\partial t} = R_a g_a\left(\sum_{b=1}^{N} T_{ab} u_b(x,t) + T_a m(x) + h_a\right)$$

Transport

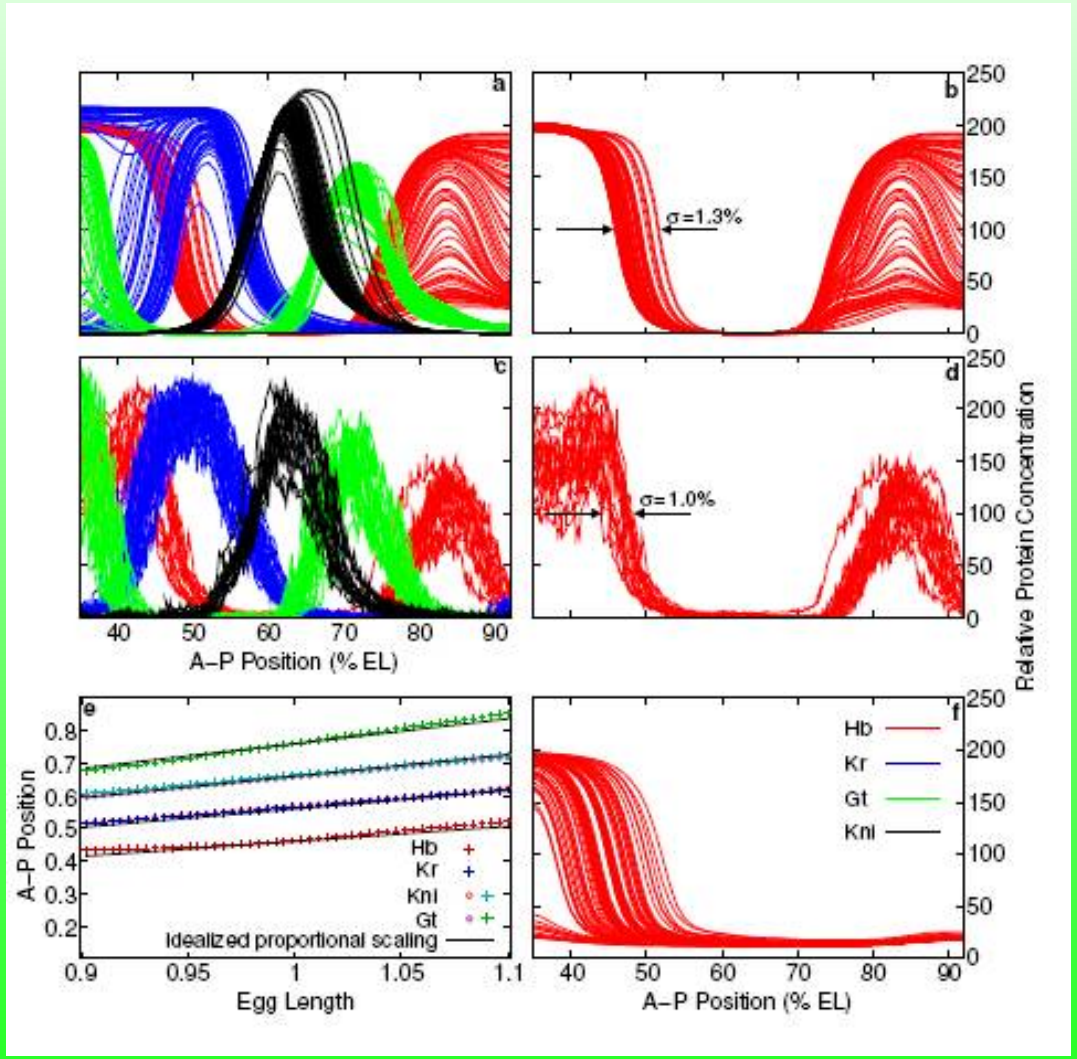
$$+ D_a \nabla^2 u_a(x,t)$$




Degradation

$$-\lambda_a u_a(x,t)$$

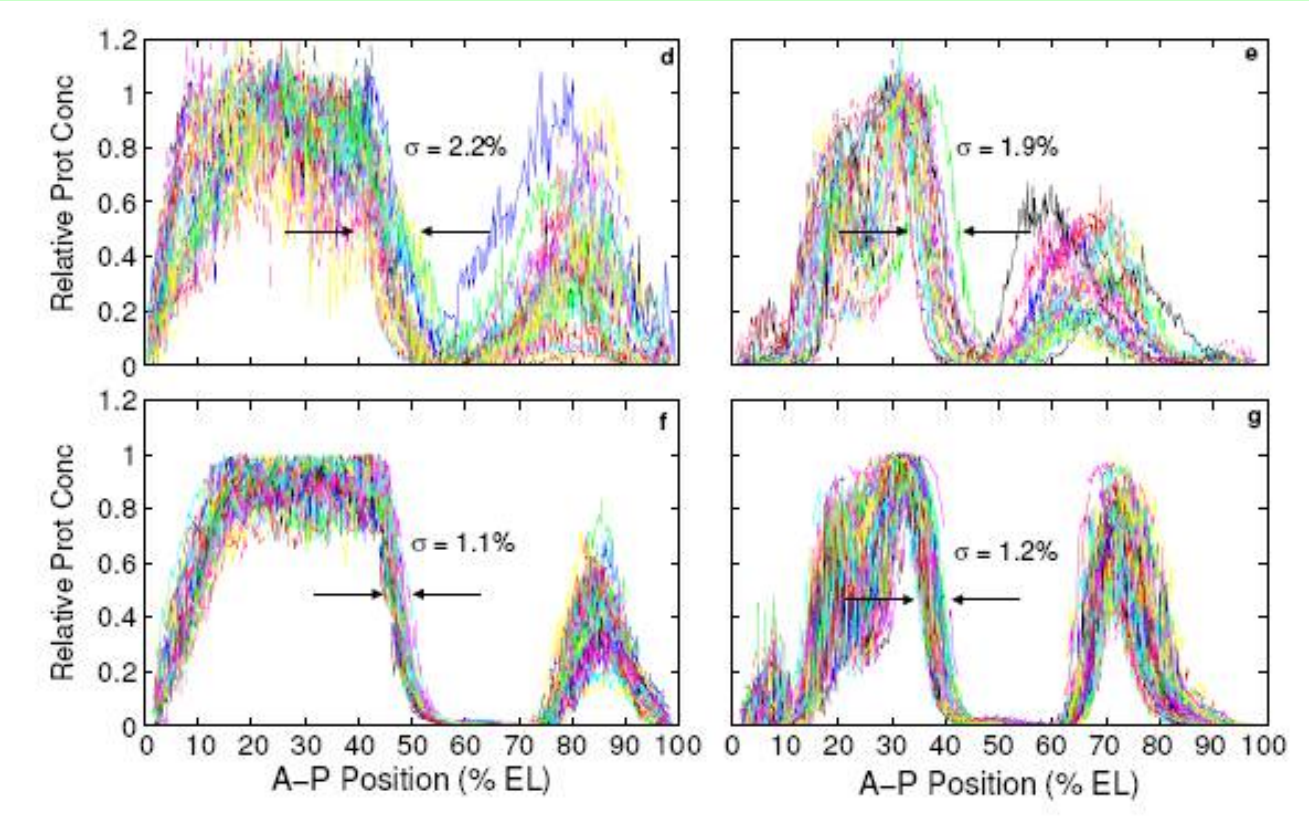
# Reproduces canalization properties of the patterns




Gap genes domains are stabilized by gene interactions.

**Manu et al., Plos Biology 09**

# Experimental proof




**Manu et al., Plos Biology 09**

# Kink dynamics

$$u_t = du_{xx} + R\sigma(Tu + M(x)) - \lambda u$$

kink solution

$$U(x,q) = \frac{R}{\lambda} \times \begin{cases} 1 - \frac{1}{2}\exp(\gamma(x-q)), & x < q, \\ \exp(-\gamma(x-q)), & x > q, \end{cases}$$

# Whitham's principle

variational form

$$\frac{\delta D[u_t]}{\delta u_t} = -\frac{\delta F[u]}{\delta u},$$

$D = \frac{1}{2}\int {u_t}^2 dx$ dissipation functional
$F = \int [\frac{1}{2} d {u_x}^2 + \Phi(u, x)] dx$. energy functional
$\Phi_u = -R\sigma(Tu + M(x)) + \lambda u$ potential

# One kink

Potential for a step function

$$\Phi = \begin{cases} RM/T + \lambda u^2/2, & u < -M/T \\ -Ru + \lambda u^2/2, & u > -M/T \end{cases}$$

Whitham averaged functionals

$$\bar{D} = D[U], \quad \bar{F} = F[U].$$

Whitham's principle

$$\frac{d\bar{D}(q_t)}{dq_t} = -\frac{d\bar{F}(q)}{dq}.$$

Model re-writing

$$r\frac{dq}{dt} = \frac{M(q)}{RT} + \frac{1}{2\lambda},$$

where $r = R^{-2}\int_{-\infty}^{\infty} U_x^2 dx = \frac{3}{4}\gamma\lambda^{-2}$.

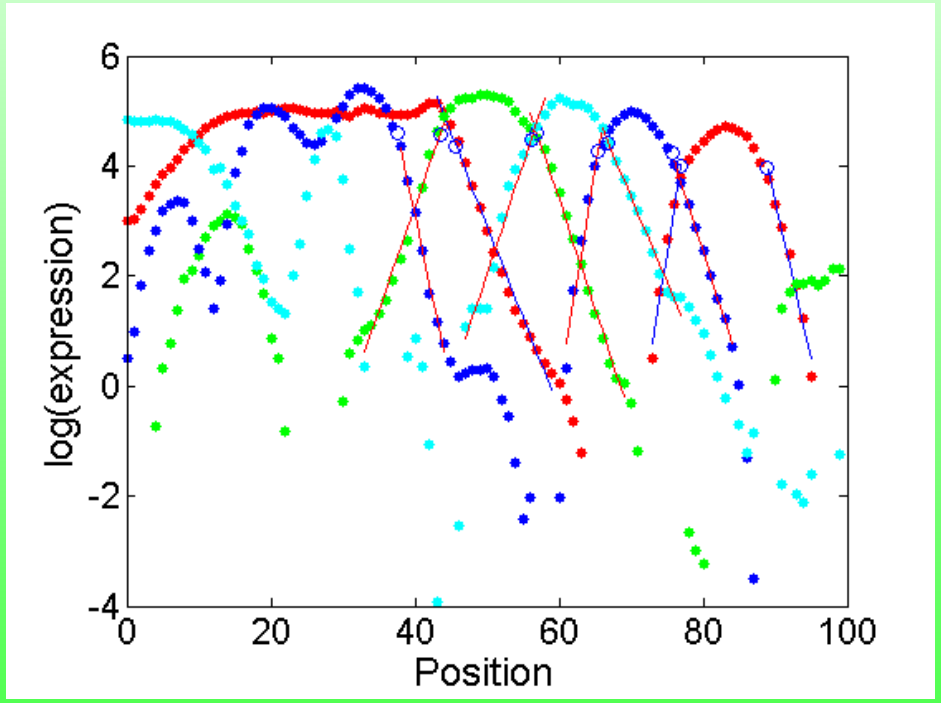
# Several interacting kinks

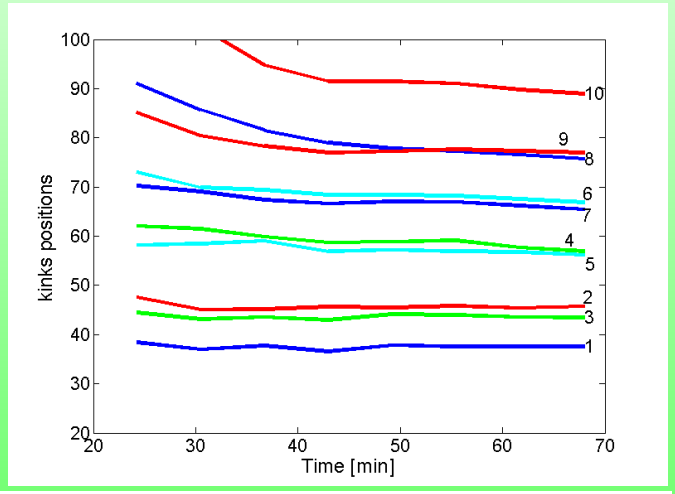
$$g_i(x, q_1, ..., \quad q_n) = m_k\mu(x) + h_k + T_{kk}[\tilde{U}_{l(k)}(x) - R_k/\lambda_k] +$$
$$+ \sum_{m \neq k} T_{km} \qquad [\tilde{U}_{l(m)}(x) + \tilde{U}_{r(m)}(x) - R_m/\lambda_m],$$

where $\tilde{U}_i = U_i(q_i + s_i(x - q_i))$.

$$r_i \frac{dq_i}{dt} = s_i\left(\frac{g_i}{R_k T_{kk}} + \frac{1}{2\lambda_k}\right).$$

# Kink representation of data: robustness of domain positions

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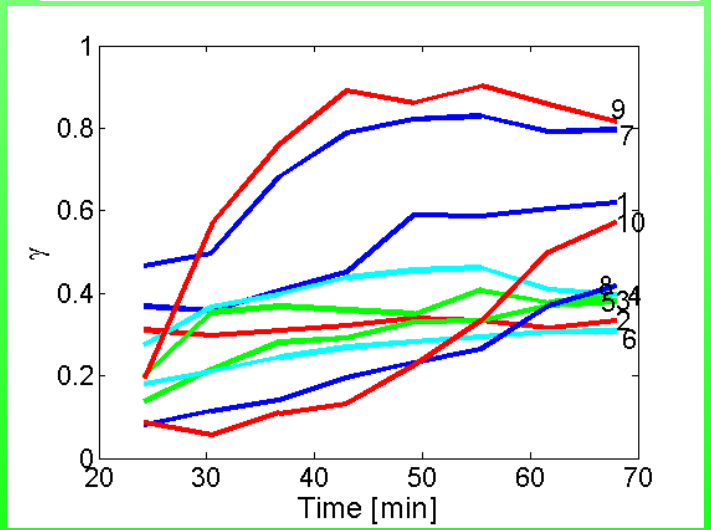
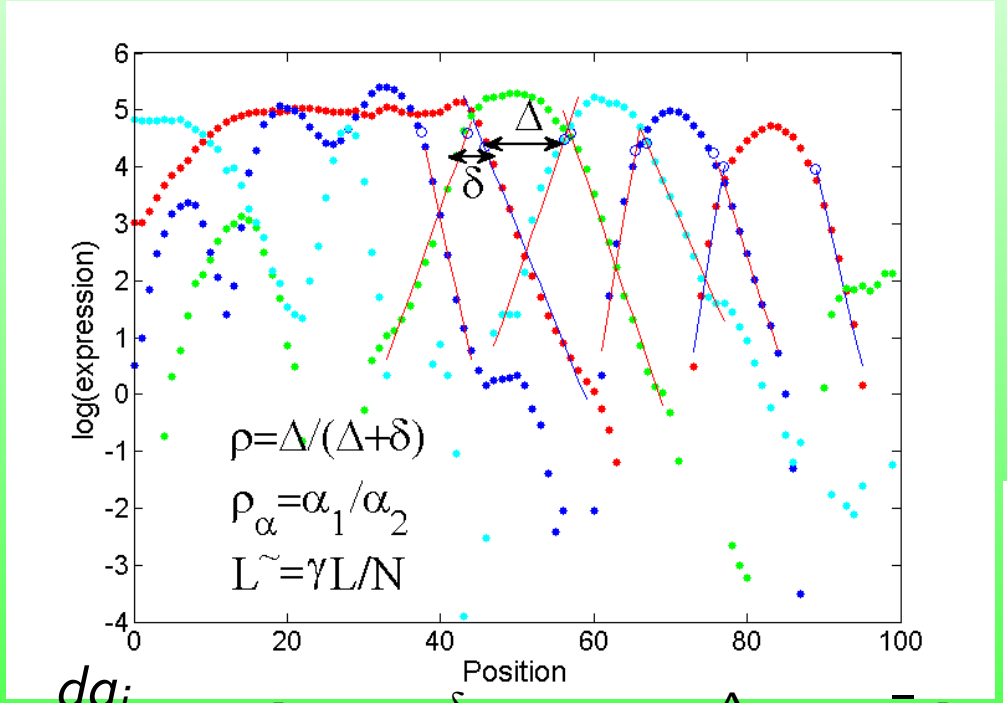
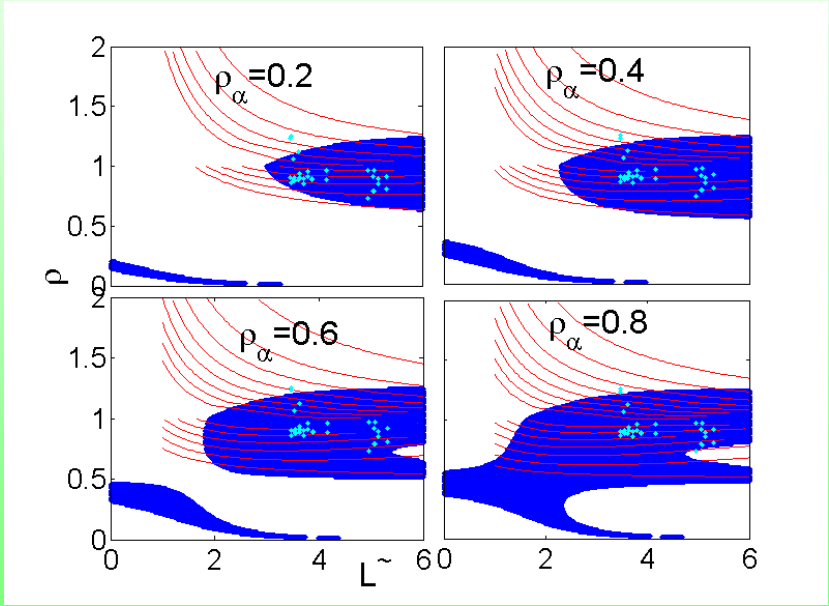
Kink profile



# Elastic (springy) morphogenesis

Alternating cushion

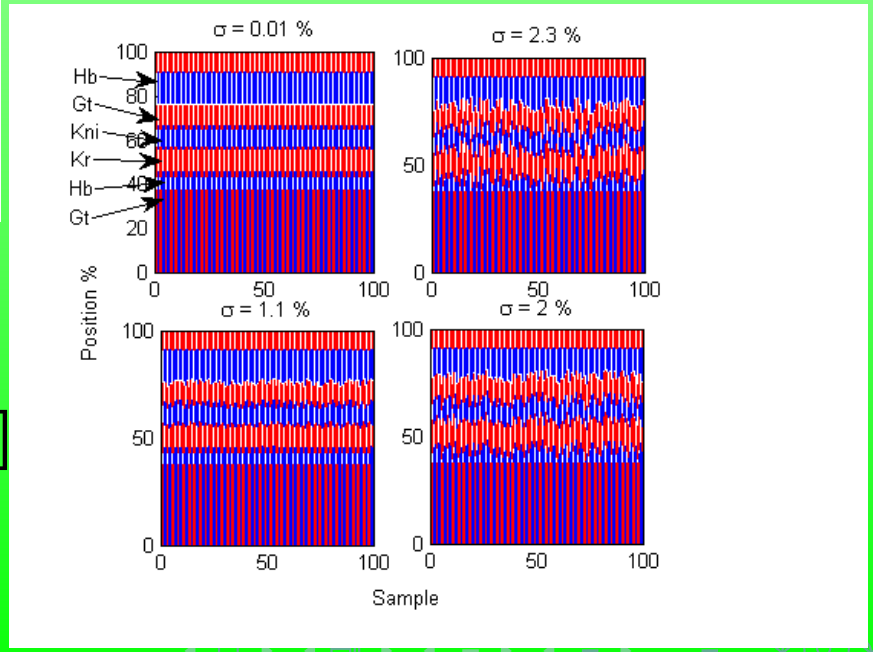



$$\frac{dq_i}{dt} = v_i[\alpha_1 e^{-\gamma\delta_i} - \alpha_2 e^{-\gamma\Delta_{i+2}} + \bar{h}_i]$$

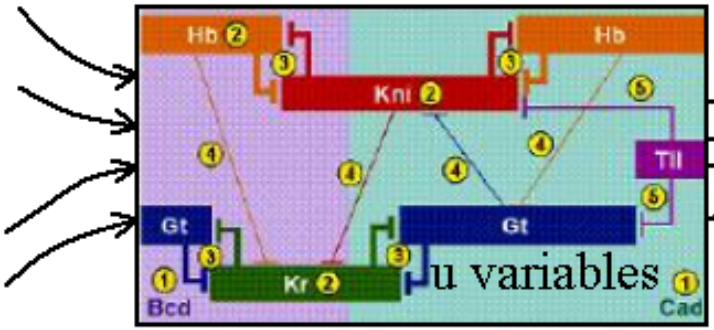
$$\frac{dq_{i+1}}{dt} = v_{i+1}[\alpha_2 e^{-\gamma\Delta_i} - \alpha_1 e^{-\gamma\delta_i} - \bar{h}_{i+1}]$$

Interacting kink approximation of GCM

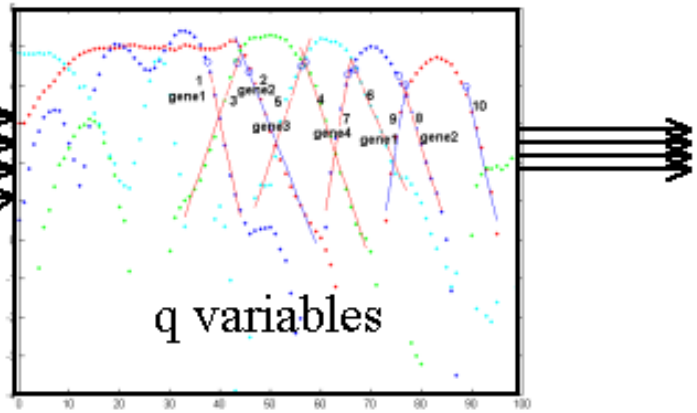


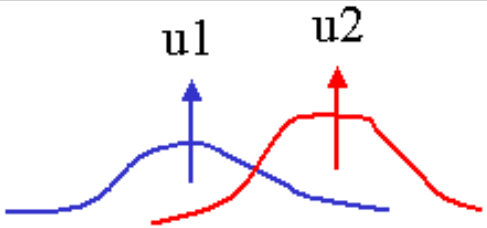
# The 2-scale robustness picture

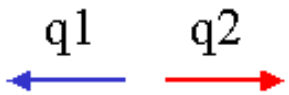
**Local gene interactions**



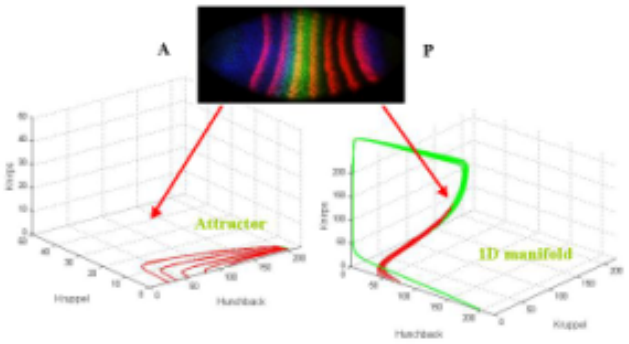

**Interactions between localized modes**

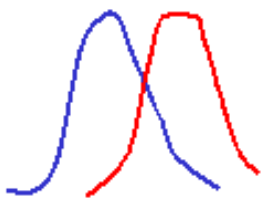



**Diffusionless approximation: domain formation**



**Interacting kinks: springiness**

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- Build hierarchical models.
- Develop mathematics to diagnose the situations either in data or in models: various coarse graining, G-scheme sensitivity, finite time Lyapunov, weak attractors and shadows of attractors...

# Acknowledgements

Alexander Gorban, University of Leicester
Andrei Zinovyev, Curie Institute
Alain Lilienbaum, Stress et Pathologies du Cytosquelette, Paris 7
Sergei Vakulenko, Institute of Print, St. Petersburg
Manu, John Reinitz, Stony Brook University
Maria Samsonova, St.Petersburg State Polytechnical University

# Simplicity of the dynamics

Palis conjecture: every system can be approximated by another having only finitely many attractors.

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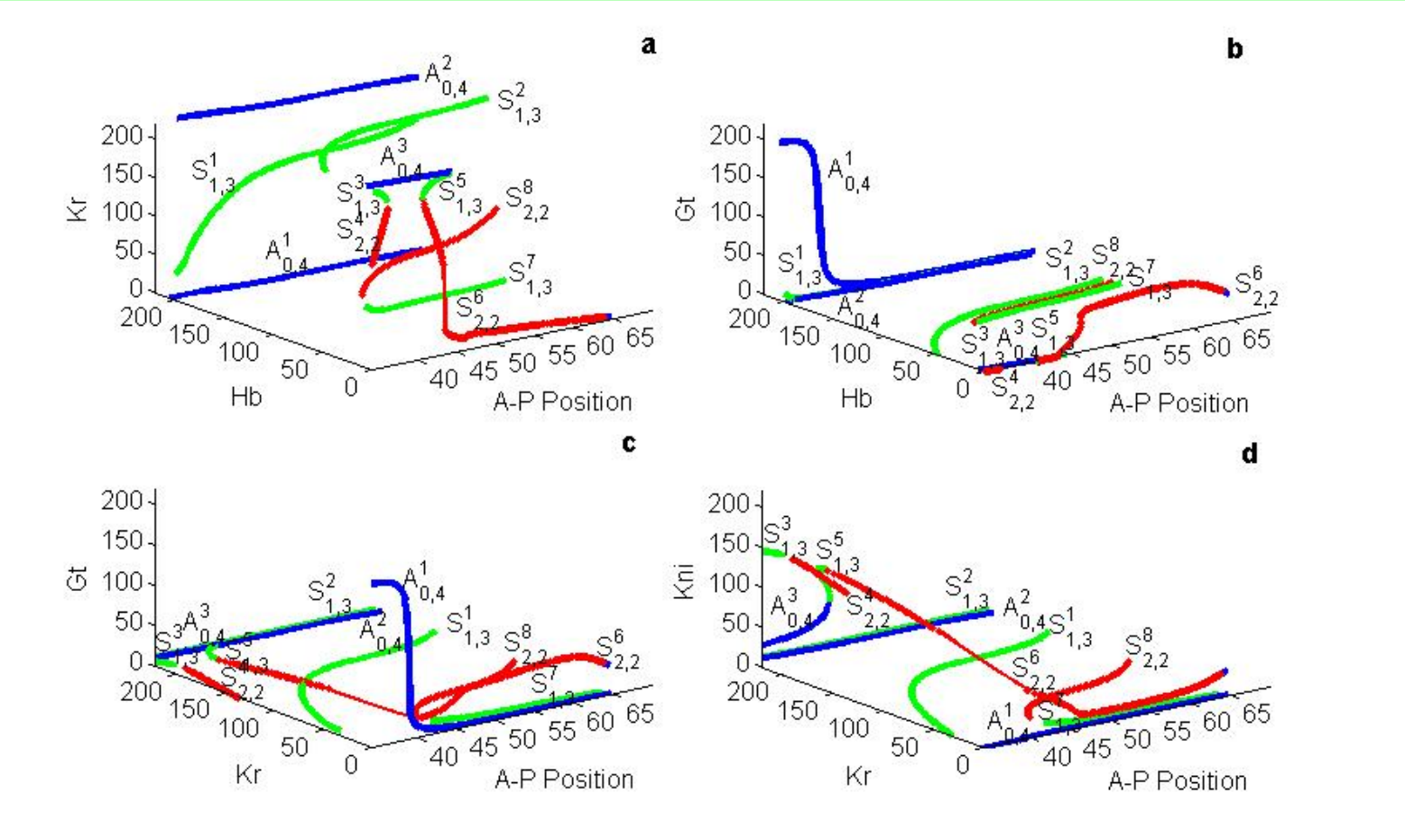
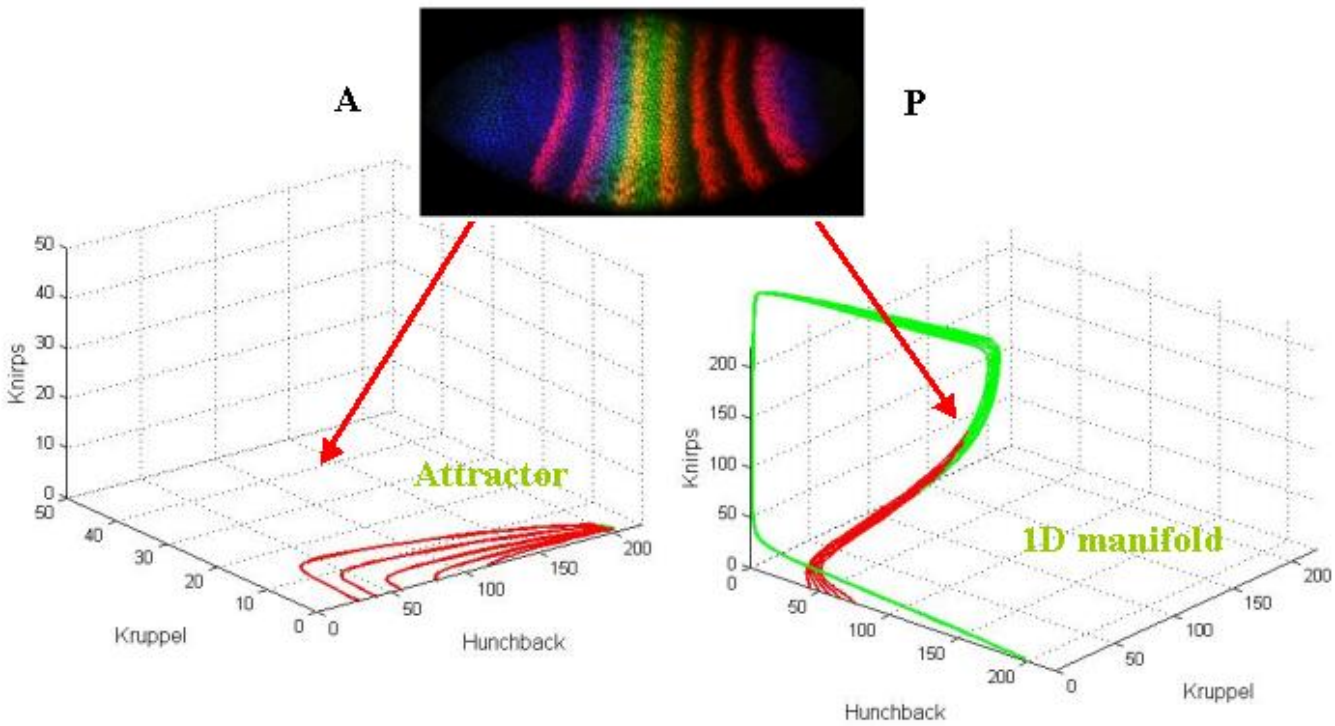
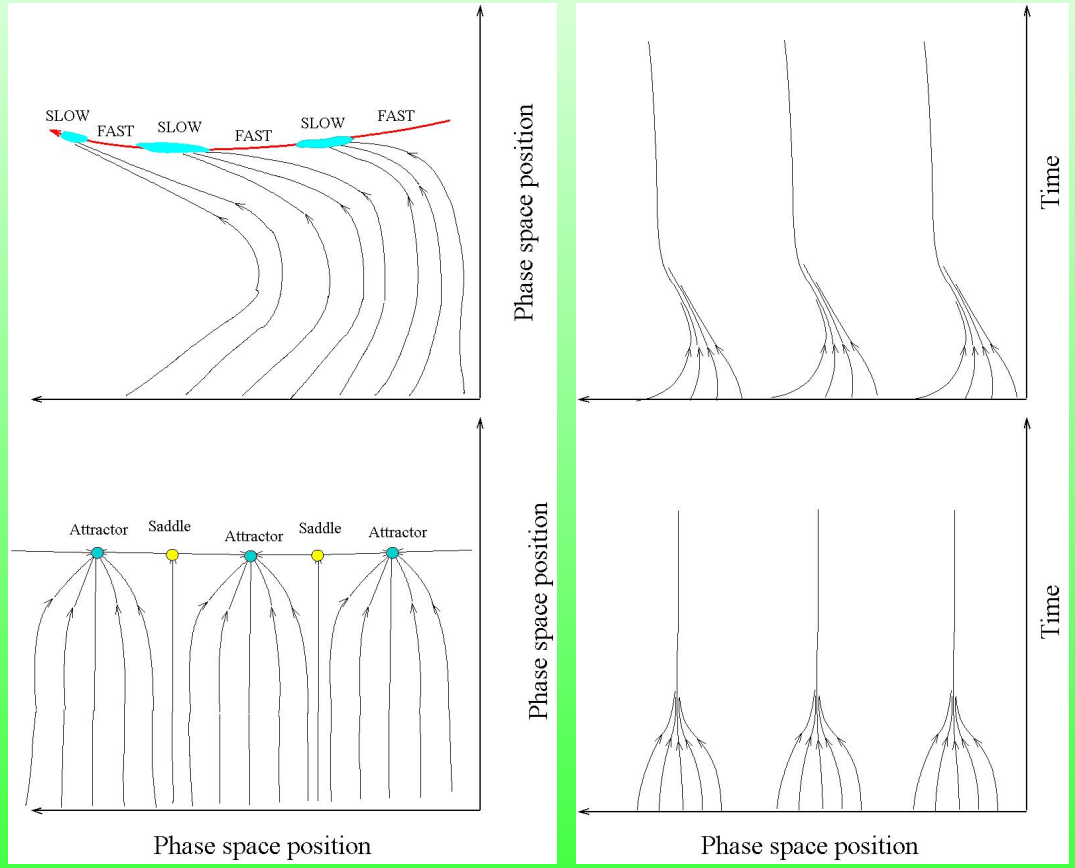


# Diffusionless approximation and canalization



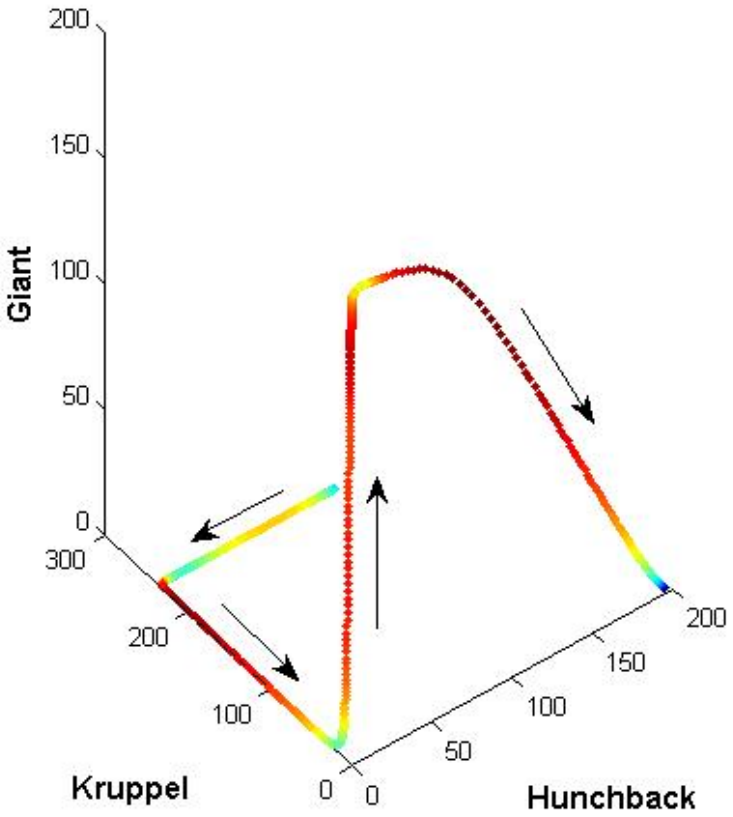

14

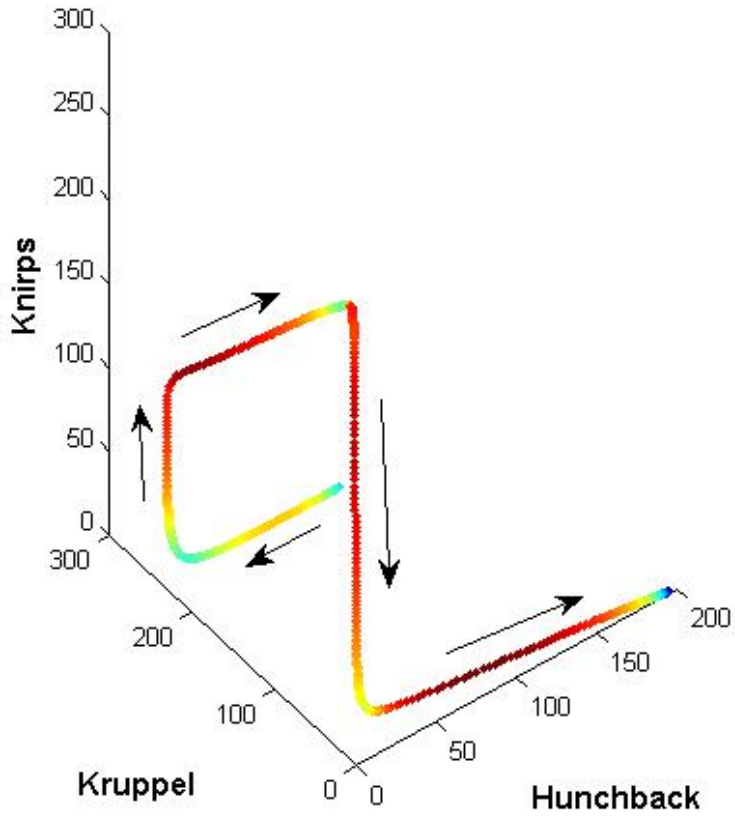
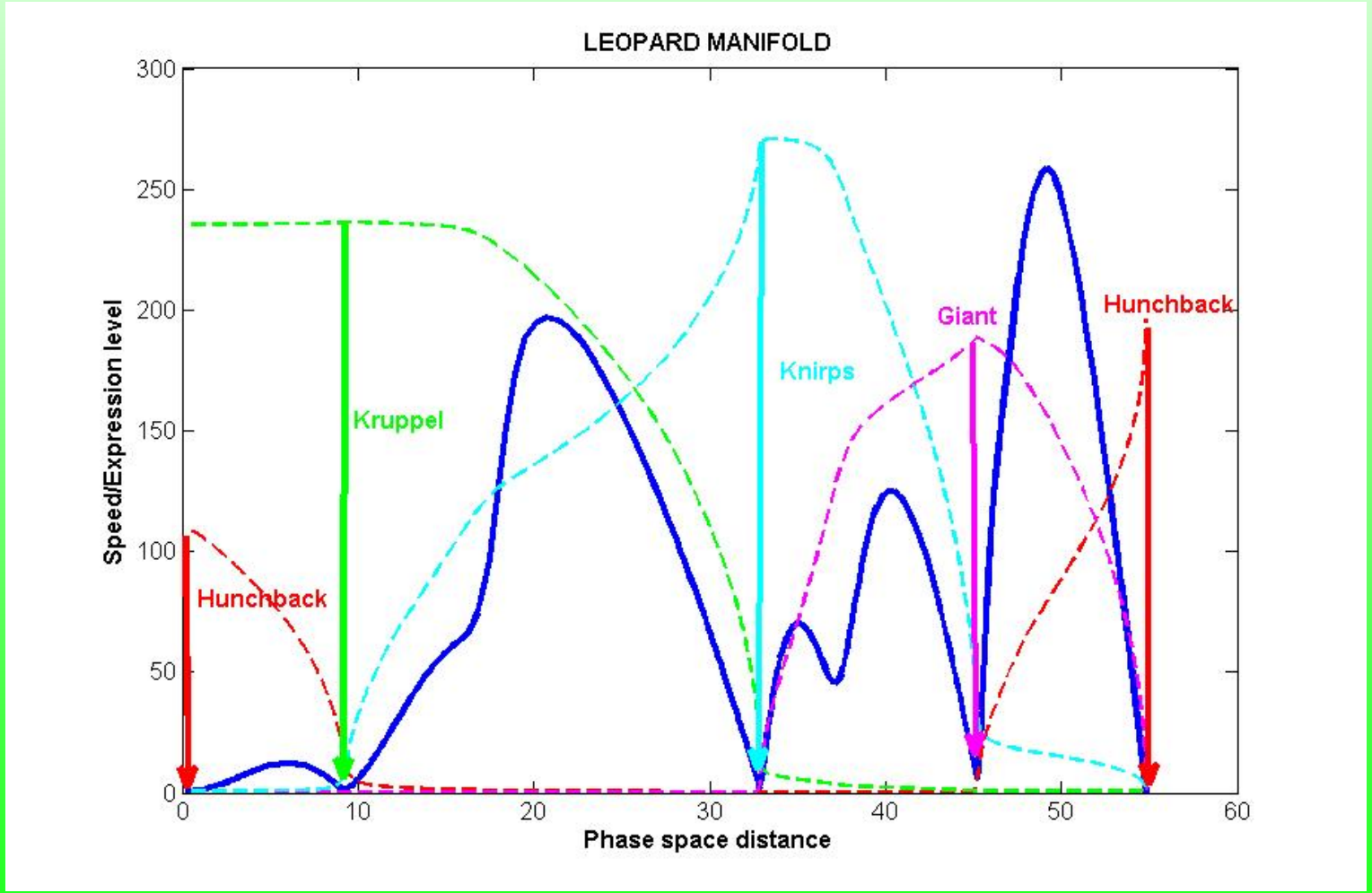
# Two canalization schemes




Attractors support SRB (Sinai-Ruelle-Bowen) probability measures. The SRB probability of a state is the inverse of the time spent in the neighborhood of the state.

# Leopard manifold






# Leopard manifold