Parametric robustness in gene networks: reliable functioning with unreliable components

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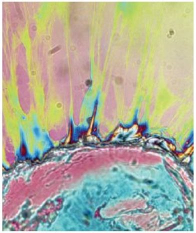
JOBIM, Montpellier, September 9, 2010

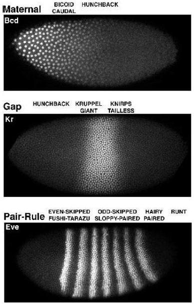
The many faces of biological robustness

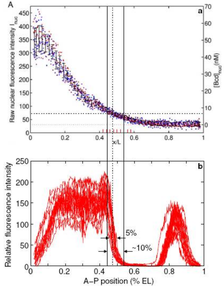
Cancer and robustness



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

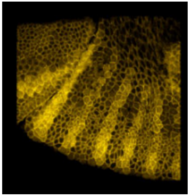
Development and Robustness

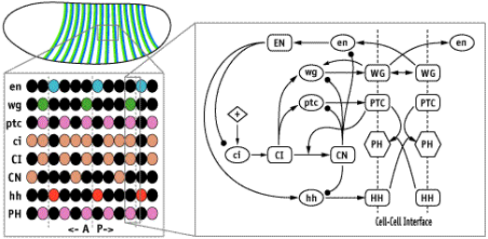




How Does "Robust, Yet Fragile" Manifest Itself in the Example Systems? Biological organisms are highly robust to uncertainty in their environments and component parts yet can be catastrophically disabled by tiny perturbations to genes or the presence of microscopic pathogens or trace amounts of toxins 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]

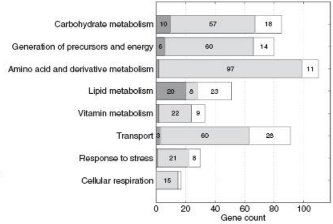


Figure 3 Metabolic network robustness across different functional GO-Slim categories on rich medium, showing for each category the proportions of essential genes (dark), backed up genes (light), and genes not found to contribute in our analysis (white). Superimposed numbers indicate gene counts (for 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).

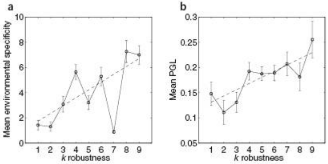


Figure 5 Environmental specificity (ES) and propensity for gene loss (PGL) as a function of robustness level. Means ± s.e.m. are shown for the ES (**a**) and PGL (**b**) measures at each *k* robustness level. The dashed lines are the least squares linear regression through the original data points. Owing 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 ($R = 0.26$, $P = 5 \times 10^{-5}$, $N = 235$).

von Neumann's Caltech lectures

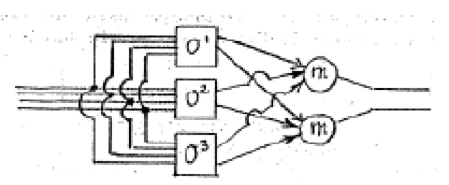
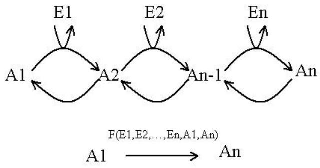


Fig. 26

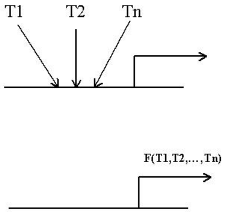
- reliable functioning with unreliable components.
- multiplexing, redundancy : instead of running in a single machine, the same information is fed into a number of identical machines.
- this technique can be used to control error.

Robustness by dimension compression

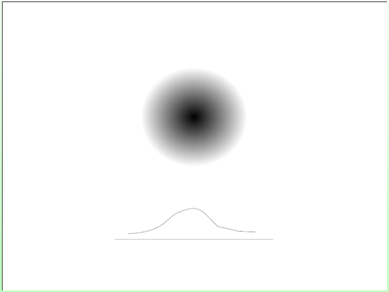
Chain of catalysed transformations



Transcription models

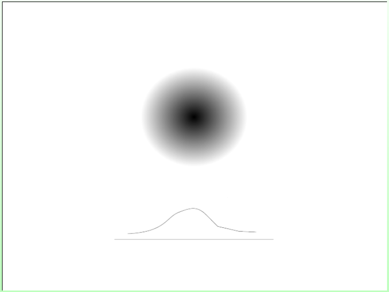


Gromov-Levy cube concentration



Objects in high-dimension look thin in projection.

Gromov-Levy cube concentration



Objects in high-dimension look thin in projection.

Levy theorem (cube concentration):

$F(k1, k2, ..., kn)$ defined on $S^n(1)$

$|F(k) - F(k')| < |k - k'|$ F is 1-Lipschitzian, for instance $F = (k1 + k2 + ... + kn)/n$

$Var(F) \sim 1/n$ F concentrates

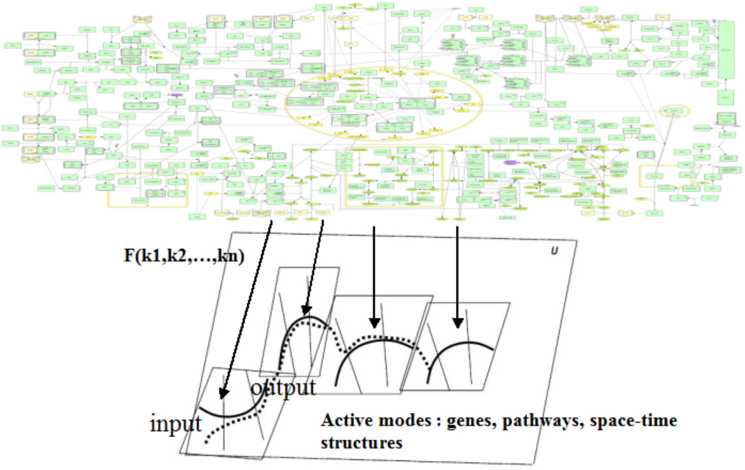
Simplex concentration : order statistics

ordered parameters $K_{(1)} > K_{(2)} > ...K_{(r)} > ...K_{(n)}$,

$$F = K_{(r)} \quad \text{F is the r-th order statistic}$$

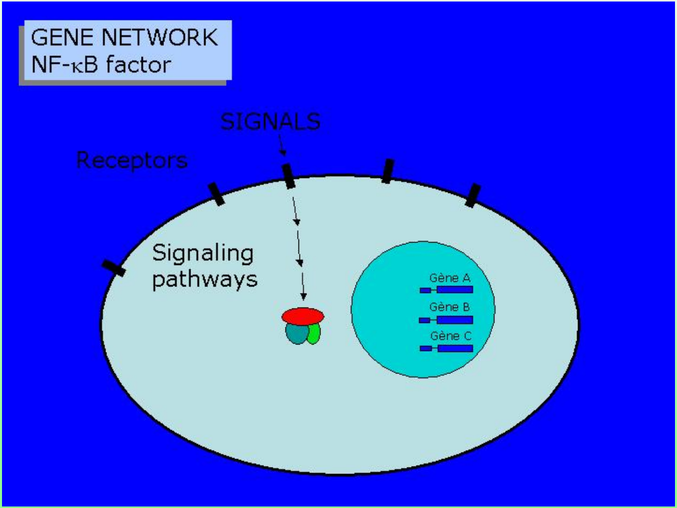
$$Var(F) \sim 1/n^2 \quad \text{F has simplex concentration}$$

Robustness by dimension compression

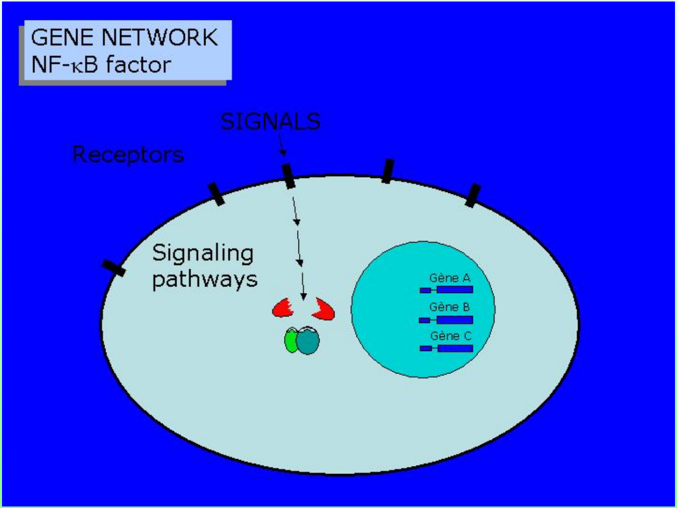


Crazy quilt: sequence of robust simplifications in abstract spaces

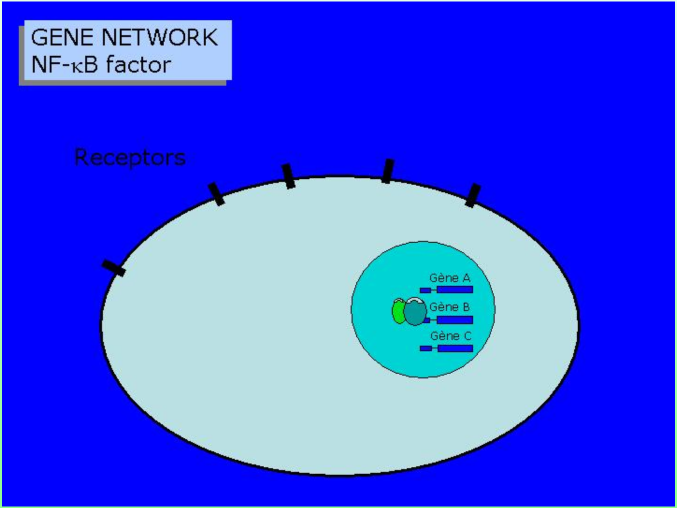
Signalling of NFκB: a case study



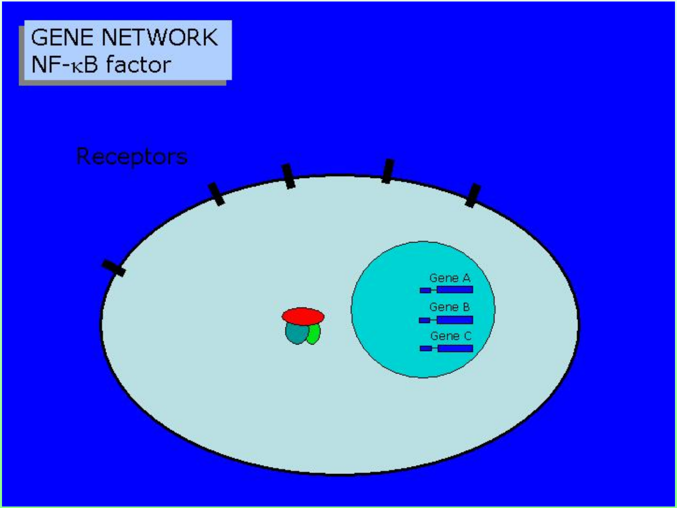
NFκB response to signals



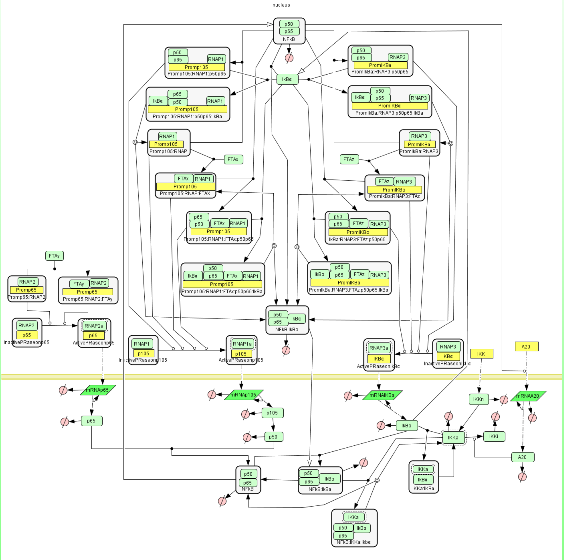
NFκB controls over 100 genes



NFκB controls over 100 genes

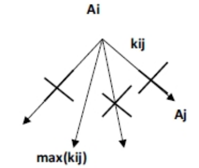


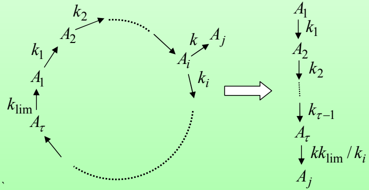
A complex model

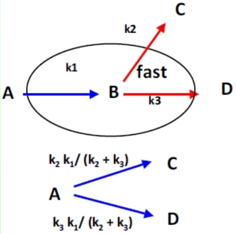


Model reduction for multiscale systems

Total or partial separation of timescales $k_i << k_j$.







$k' = \max(k_{ij})$

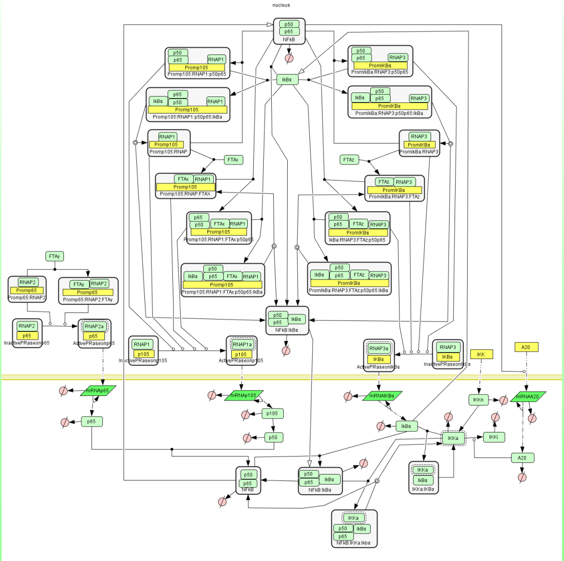
Dominance, pruning

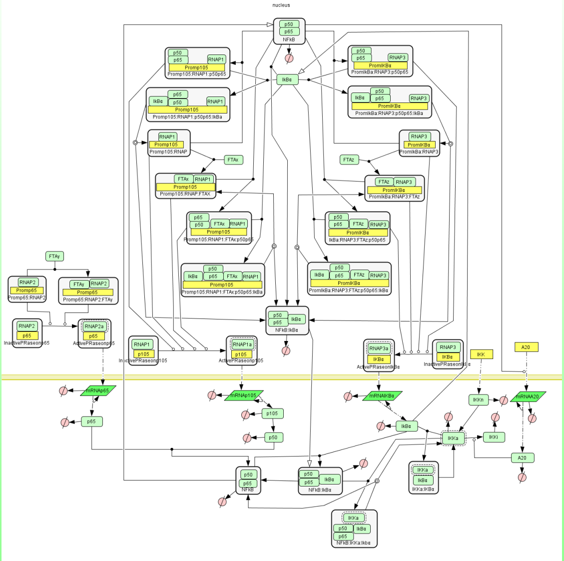
$\log(k') =$

$\log(k) + \log(k_{lim}) - \log(ki)$

Averaging

Pooling


nucleus
NFkB
IkBα
Promp105:RNAP1:p50p65
Promp105:RNAP1:p50p65:IkBα
Promp105:RNAP
PromIkBa:RNAP3:p50p65
PromIkBa:RNAP3:p50p65:IkBa
PromIkBa:RNAP3
FTAx
FTAz
FTAy
Promp105:RNAP:FTAx
PromIkBa:RNAP3:FTAz
Promp105:RNAP1:FTAx:p50p65
IkBa:RNAP3:FTAz:p50p65
Promp105:RNAP1:FTAx:p50p65:IkBa
PromIkBa:RNAP3:FTAz:p50p65:IkBα
Promp65:RNAP2
Promp65:RNAP2:FTAy
InactivePRaseonp65
ActivePRaseonp65
NFkB:IkBα
InactivePRaseonp105
ActivePRaseonp105
ActivePRaseonIkBα
InactivePRaseonIkBα
IKK
A20
mRNAp65
mRNAp105
mRNAIkBα
mRNAA20
p65
p105
p50
IKKn
IKKa
IKKi
IKKa:IKBα
NFkB:IKKa:Ikbα


nucleus
NFkB
IkBα
Promp105:RNAP1:p50p65
Promp105:RNAP1:p50p65:IkBa
Promp105:RNAP
FTAx
Promp105:RNAP:FTAX
Promp105:RNAP1:FTAx:p50p65
Promp105:RNAP1:FTAx:p50p65:IkBa
PromIkBa:RNAP3:p50p65
PromIkBa:RNAP3:p50p65:IkBa
PromIkBa:RNAP3
FTAz
PromIkBa:RNAP3:FTAz
IkBa:RNAP3:FTAz:p50p65
PromIkBa:RNAP3:FTAz:p50p65:IkBa
NFkB:IkBα
FTAy
Promp65:RNAP2
Promp65:RNAP2:FTAy
InactivePRaseonp65
ActivePRaseonp65
InactivePRaseonp105
ActivePRaseonp105
ActivePRaseonIkBα
IKK
A20
mRNAp65
mRNAp105
mRNAIkBα
mRNAA20
p65
p105
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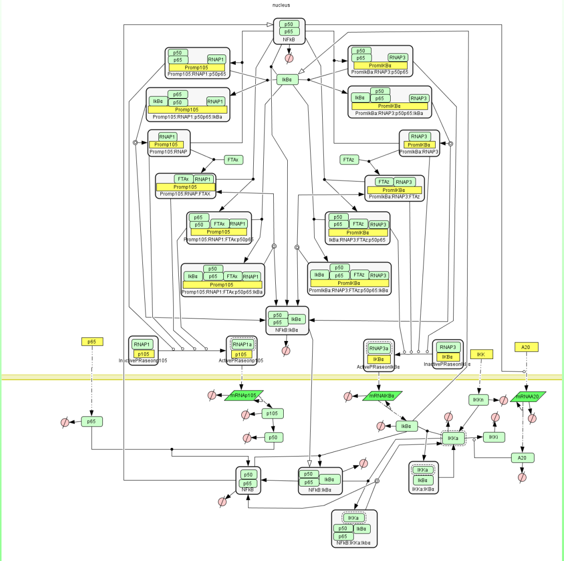
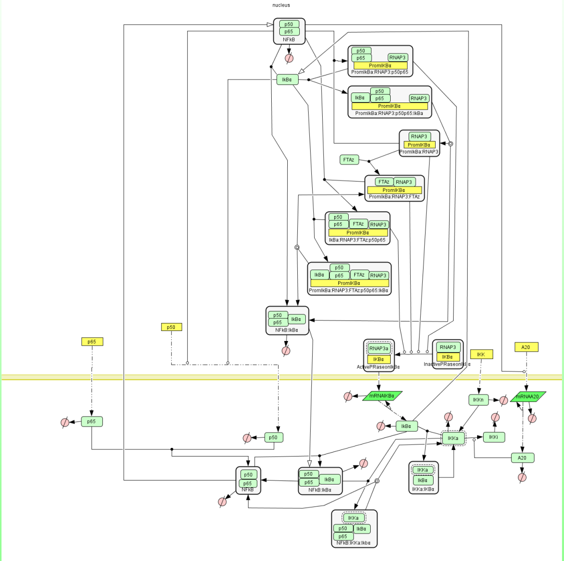
IKKn
IKKa
IKKi
IKKa:IkBα
NFkB:IkBα
NFkB:IKKa:Ikbα




nucleus
NFkB
PromIkBa:RNAP3:p50p65
PromIkBa:RNAP3:p50p65:IkBa
PromIkBa:RNAP3
FTAz
PromIkBa:RNAP3:FTAz
IkBa:RNAP3:FTAz:p50p65
PromIkBa:RNAP3:FTAz:p50p65:IkBa
NFkB:IkBa
ActivePRaseonIkBa
IKK
A20
mRNAIkBa
mRNAA20
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IKKa
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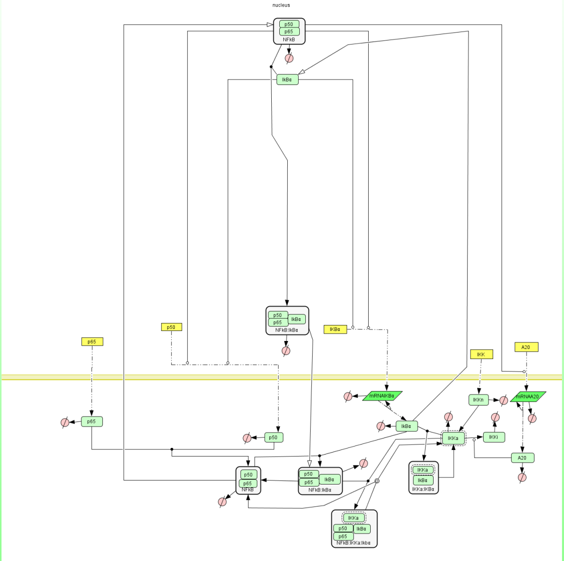
NFkB:IKKa:Ikba


nucleus
p50
p65
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NFkB:IkBα
p50
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A20
mRNAIkBα
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mRNAA20
p65
IkBα
p50
IKKa
IKKi
A20
p50
p65
NFkB
p50
p65
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IKKa
IkBα
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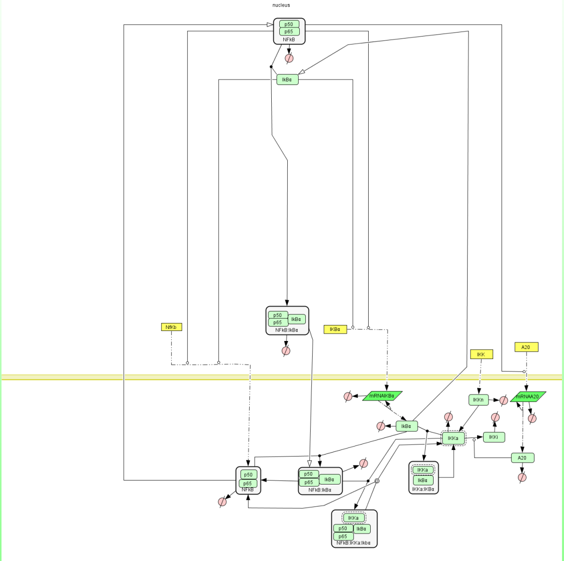
IKKa
p50
IkBα
p65
NFkB:IKKa:Ikbα


nucleus
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IkBα
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IkBα
NFkB:IkBα
NfKb
IKBα
IKK
A20
mRNAIKBα
mRNAA20
IKKn
IkBα
IKKa
IKKi
A20
IKKa
IkBα
IKKa:IkBα
p50
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NFkB
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IkBα
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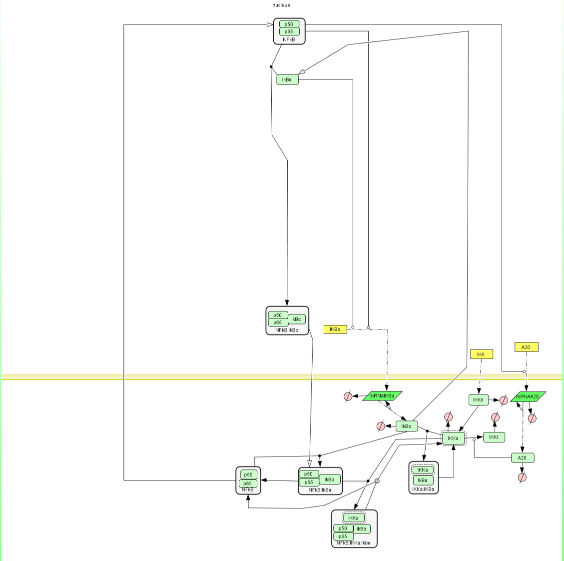
p50
IkBα
p65
NFkB:IKKa:Ikbα


nucleus
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mRNAA20
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IkBα
IKKa:IKBα
p50
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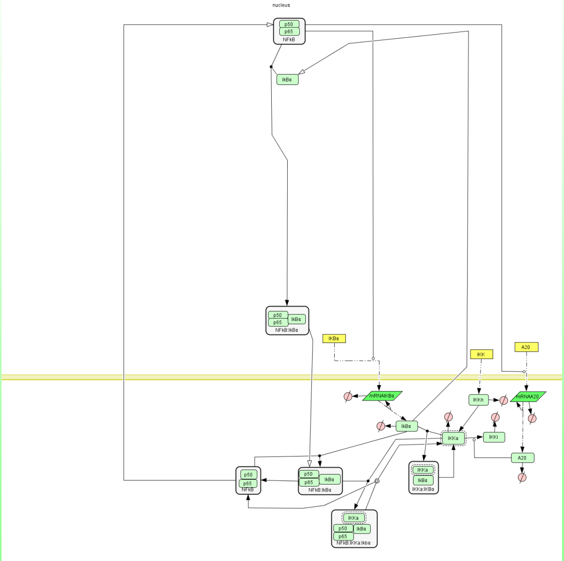
p65
NFkB:IKKa:Ikbα



nucleus
p50
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p50
p65
IkBα
NFkB:IkBα
IKBα
IKK
A20
mRNAIKBα
IKKn
mRNAA20
IkBα
IKKa
IKKi
A20
IKKa
IkBα
IKKa:IKBα
p50
p65
NFkB
p50
p65
IkBα
NFkB:IkBα
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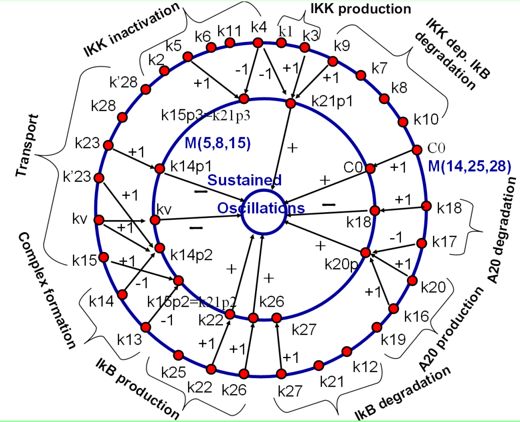
p50
IkBα
p65
NFkB:IKKa:Ikbα

The function $F(k1, ..., kn)$



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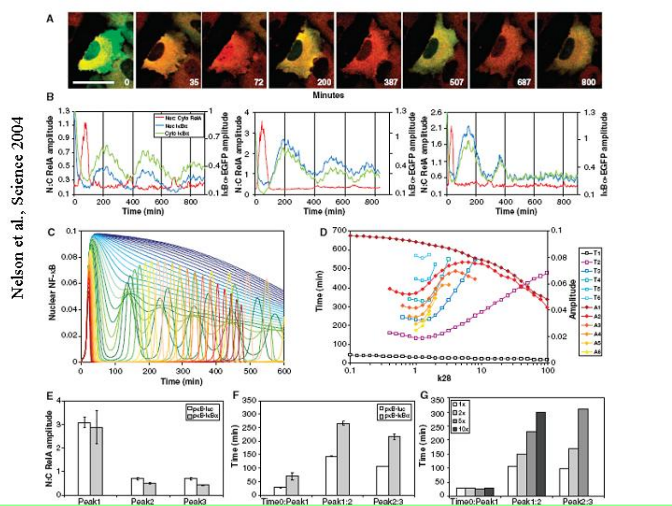
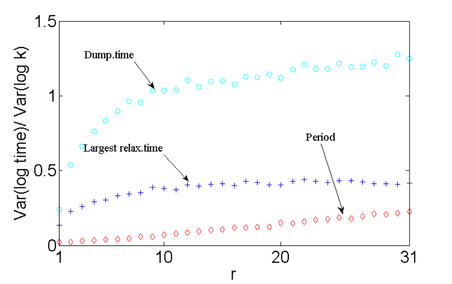
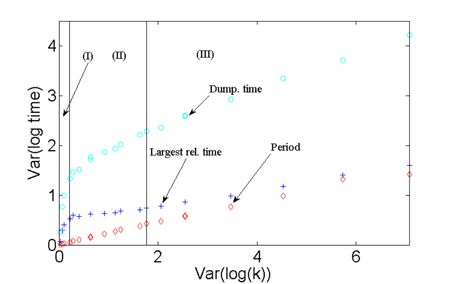
Delayed negative feed-back produce oscillations



Testing robustness

- Pick a random set I_r of r parameters.
- $k_i \to k_i s_i, i \in I_r$, where s_i are r random iid positive variables of log-variance $Var(logk)$.
- Monte-Carlo estimate for $Varlog(property)$.
- Produce two plots: $Varlog(property)$ vs. $Var(logk)$ and vs. r.





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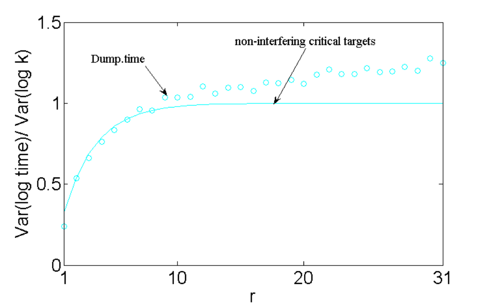
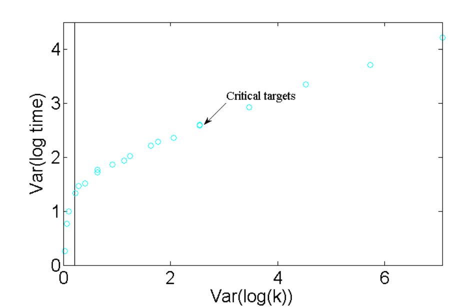
Critical parameters : fragility points

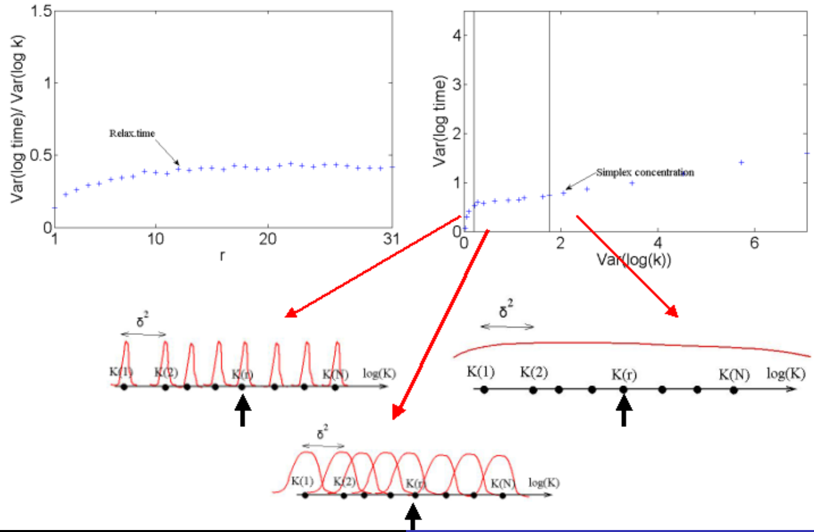




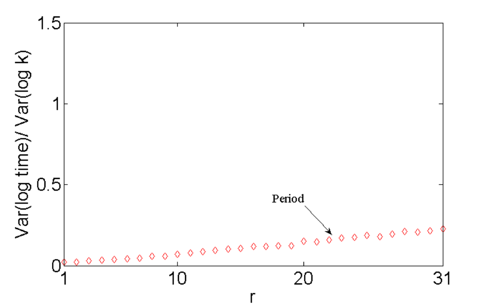
If a critical target is chosen by chance, then the sensitivity is C.

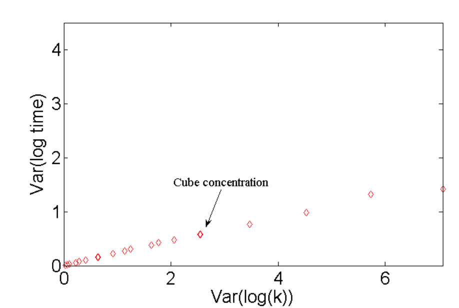
$$Var(\log \mathrm{time})/Var(\log k) = C^2[1-(1-r_c/n)^r] \approx C^2[1-exp(-rr_c/n)]$$

Simplex concentration : dominance, limiting step



Cube concentration : multiplication, addition





$$P \sim k_1^{\alpha_1} \dots k_n^{\alpha_n}$$

$$\log P = C + \alpha_1 \log k_1 + \dots + \alpha_n \log k_n$$

Conclusion and perspective

- A generic mechanism produce robustness in complex regulatory networks: size matters!
- Robustness by dimension compression: a few rely on many.
- Robustness and dynamical dimension (joint work with AN.Gorban and A.Zynoviev).
- Early expression patterns in Drosophila are robust with respect of variability of cis-regulatory modules (work in progress with J.Reinitz).
- Experimental robustness: quantify variability following perturbation (work in progress with Y.Arlot).

PhD position in malaria systems biology (DIMNP lab, Montpellier)