What Drosophila's gap genes teach us about redundancy, robustness and epigenesis

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Outline

- Introduction: complex systems amendments to Laplacian determinism
- A theory of robustness
- Model reduction of hierarchical systems
- Critical parameters and robustness, a case study: NFκB signalling
- Drosophila gap genes: redundancy and canalization
- Conclusion

Organism as a computable system

Sidney Brenner, DNA is self-sufficient: given the DNA sequence of an organism, we can compute the organism.

Functional genomics: protein A binds to promoter region of gene B which can be methylated or not, in the presence of protein C, which can be phosphorylated or not, ...
Developmental biology: identify all developmental genes, compute the network of interactions (an oriented graph with +/-) take a Teraflop computer, determine fate.

Morphogenesis is unfolding information on genes and interaction between genes stored on DNA.

First epigenetic amendment: environment

The fate is not specified only by genes, but also by the sequence of environments in which morphogenesis takes place.

Environment = external conditions (resulting eventually from interacting organisms: ecosystem), but also state of other internal variables resulting from the history of the processes.

An organism is continuously reacting to the outer world, creating its own, homeostatic environment.

Second epigenetic amendment: noise

division is neither rigorously symmetric, nor deterministic

stochastic molecular processes

separating a subsystem from the rest of the world generically demands replacing the rest of the world by noise

noise is multiple causality, as opposed to unique causality

Q1: What guarantees reliable functioning in epigenetic noisy landscape?

Q2: Can we account for (stochastic) multiple causality in biological models?

Systems approach

Complexity theory (cybernetics, synergetics, control theory, catastrophe theory, etc.)

Law of requisite variety

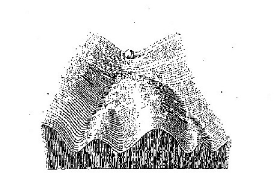
W.Ross Ashby: the variety in the control system must be equal to or larger than the variety of the perturbations in order to achieve control.

Order from noise

Heinz von Foerster: noise or random perturbations will help a self-organizing system to find more stable states in its fitness landscape.

Systems approach

Principle of asymmetric transitions: is variety possible?



transitions go from unstable to stable : state reduction, Waddington's chreods.

spontaneous decrease of variety is possible (canalization)

Catastrophes and structural stability

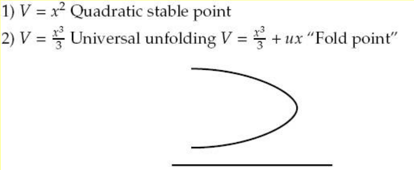


Figure 1. "Fold point"

Structural stability of attracting sets.

Flexibility: the set of attractors change at bifurcations.

Beyond René Thom: Prédire n'est pas expliquer

Nowadays, we feel more confident. The state of an organism (or part of it) is a point in a high dimensional space of genes and gene products concentrations.

This point satisfies some dynamics (differential equations, finite-state cellular automata), eventually stochastic (Gillespie dynamics). If all parameters are known, the dynamics is computable.

Biological systems are open, multi-scale, heterogeneous systems. Information can be very detailed on some parts, extremely scarce on others. Parameters are unknown.

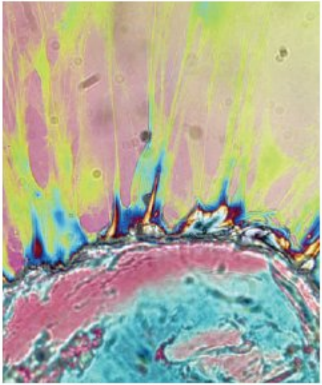
Q3: What is computable?

Prolegomena for a theory of robustness

- Parameter insensitivity
  - some parameters and perturbations have little effect on system functioning
  - redundancy, r-robustness
  - critical and non-critical parameters
- distributed robustness, r-robustness, Gromov concentration
- model reduction
- robust properties, critical targets, and robust simplifications are computable

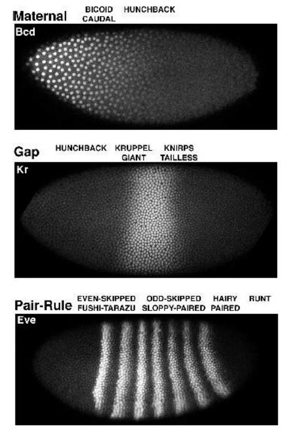
Robustness as general principle

Cancer and robustness



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

Development and Robustness



Two types of robustness

$M = f(K_1, K_2, \dots, K_n)$
Definition 1: M is *robust with respect to distributed variations* if the log-variance of M is much smaller than the log-variance of any of the parameters:

$$Var(\log M) \ll Var(\log K)$$

$K_i = K_i^0 s_i, i \in I_r$
Definition 2: M is *robust with respect to r variations* or *r-robust* if for any I_r:

$$Var(\log M) \ll Var(\log s)$$

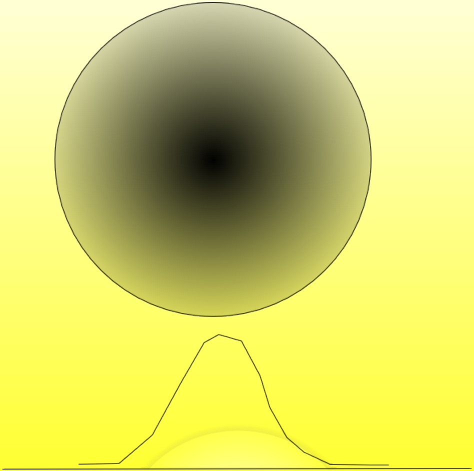
Cube or sphere concentration

Sums of small effects $M = \sum_{i=1}^{N} K_i$

Distributed robustness $Var(\log M) \sim Var(\log K)/N$

r-robustness $Var(\log M) \sim rVar(\log s)/N^2$

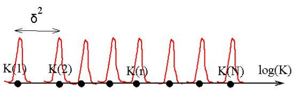
Gromov concentration



Objects in high-dimension look small when projected in low dimension.

Simplex concentration

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

- 

$Var(\log K) << \delta^2$, no overlap $Var(\log M) \sim Var(\log K)$

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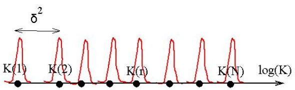
- 

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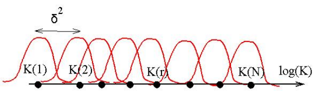
- 

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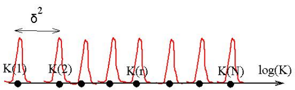
- 

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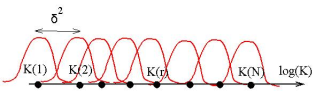
- 

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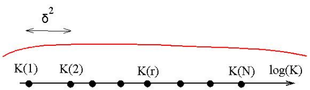
- 

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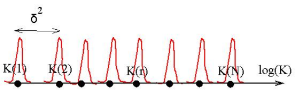
- 

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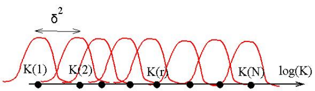
- 

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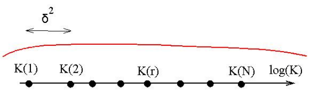
- 

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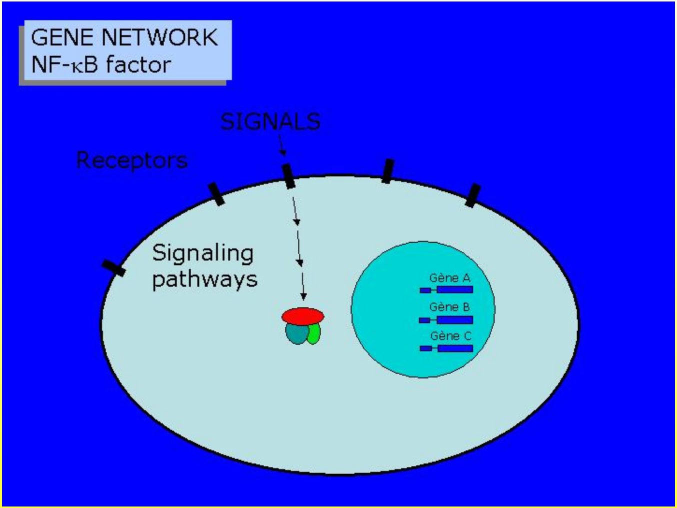
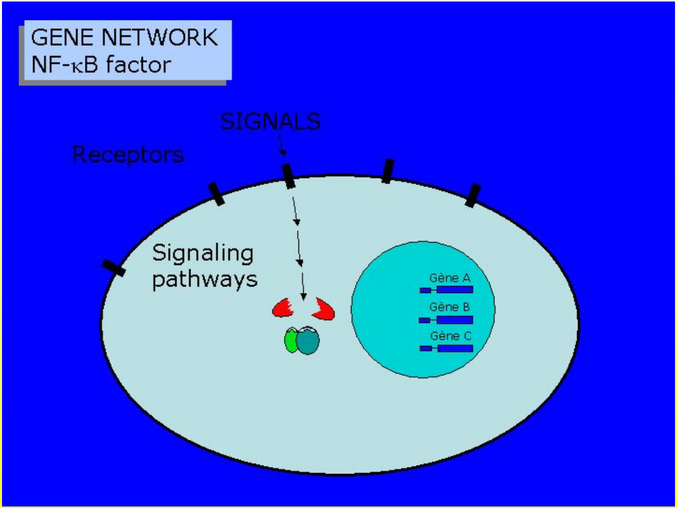
Critical parameters and weak r-robustness

one critical target, known, choose it, change it
$Var(\log M) \sim Var(\log k)$

unknown, pick at random. probability to pick it
$1-(1-1/n)^r \approx 1-exp(-r/n)$,
$Var(\log M)/Var(\log k_i) \approx 1-(1-1/n)^r \approx 1-exp(-r/n)$

r_0 critical targets, $Var(\log \tau)/Var(\log k_i) \approx C^2(1-(1-r_0/n)^r) \approx C^2(1-exp(-rr_0/n))$, where $C > 0$ is a sensitivity.


GENE NETWORK
NF-κB factor
SIGNALS
Receptors
Signaling pathways
Gène A
Gène B
Gène C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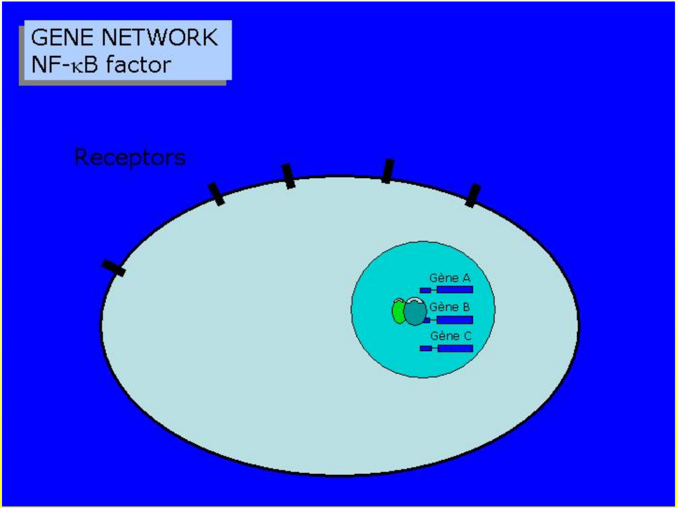
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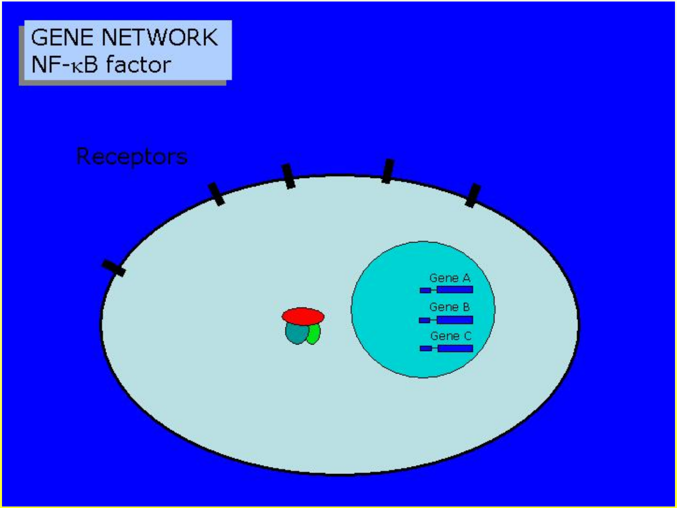
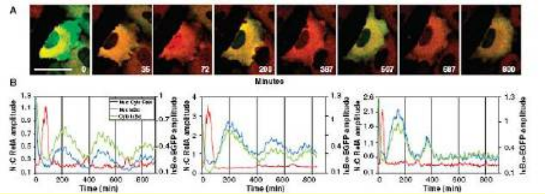
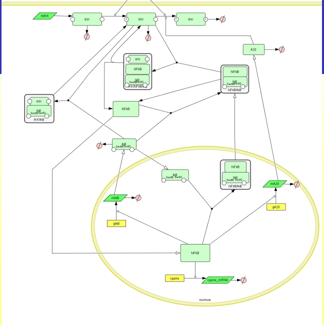
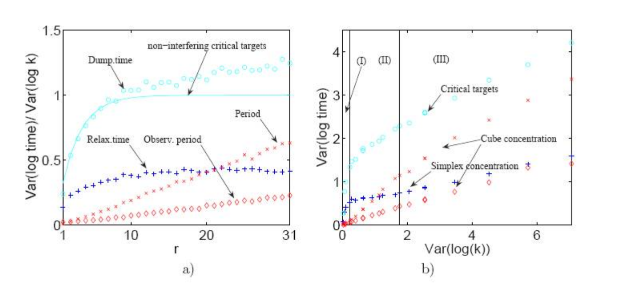

GENE NETWORK
NF-κB factor
Receptors
Gene A
Gene B
Gene C

NFκB oscillations







Limitation theory for linear hierarchical models

A_i are reagents, c_i is concentration of A_i.
All the reactions are of the type $A_i \to A_j$.
$k_{ji} > 0$ is the reaction $A_i \to A_j$ rate constant.
The reaction rates: $w_{ji} = k_{ji} c_i$.

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Kinetic equation

$$\frac{dc_i}{dt} = k_{i0} + \sum_{j \geq 1} k_{ij} c_j - (\sum_{j \geq 0} k_{ji}) c_i, \tag{1}$$

or in vector form: $\dot{c} = K_0 + Kc$.

Hierarchical models

Systems biology models need constants and these are most of the time unknown.
We have some ideas about the network structure: reaction graph, influence graph, etc.
Usually, something is big, and something is small enough,
we can guess the constant *ordering* ($I = (i, j)$):

$$k_{I_1} \ll k_{I_2} \ll k_{I_3} \ll \dots$$

We say that the system has separated constants.

Limiting step

Linear chain of reactions $A_1 \rightarrow A_2 \rightarrow ...A_n$ with reaction rate constants k_i (for $A_i \rightarrow A_{i+1}$)

Let k_q be the smallest constant: $k_q \ll k_i$ $(i \neq q)$
In time scale $\sim 1/k_q$:
$A_1, ...A_{q-1}$ transform fast into A_q,
$A_{q+1}, ...A_{n-1}$ transform fast into A_n,
only two components, A_q and A_n, are present,
the whole chain behaves as a single reaction $A_q \xrightarrow{k_q} A_n$

Limiting Step for Irreversible Cycle

Irreversible Cycle $A_1 \to A_2 \to \dots A_n \to A_1$
with reaction rate constants k_i (for $A_i \to ...$)
Limiting step $A_n \to A_1$
with reaction rate constant $k_n \ll k_i$ $(i < n)$
kinetic matrix has one simple zero eigenvalue that corresponds to the conservation law $\sum c_i = b$ and $n - 1$ nonzero eigenvalues

$$\lambda_i = -k_i + \delta_i \; (i \leq n - 1),$$

where $\delta_i \to 0$ when $\sum_{i<n} \frac{k_n}{k_i} \to 0$.
In particular the largest relaxation time of a cycle $1/k_{n-1}$ is controlled by the second slowest constant.

Eigenvalues and eigenvectors specify dynamics of linear systems

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

- For systems with separated constants, each time an exponential goes to zero there is a jump $-r^k(l^k, c(0) - c_s)$ in concentrations, if $(l^k, c(0) - c_s) \neq 0$.

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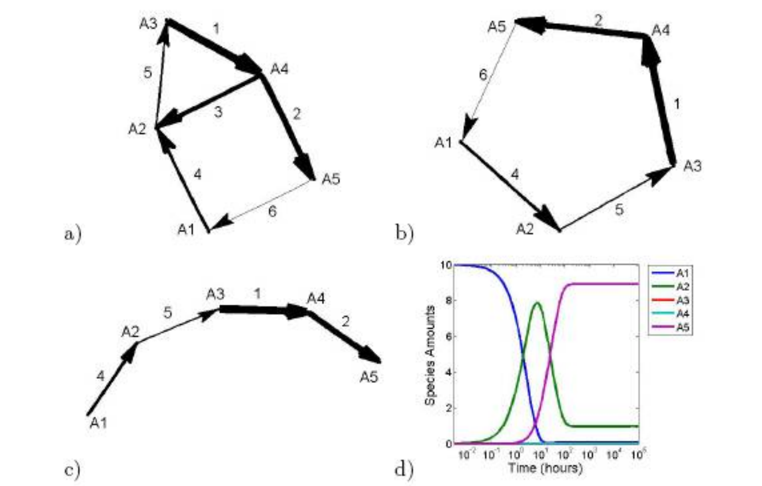
- The sequence of jumps codes the dynamics.
- The last jump represents the slowest relaxation process, the smallest (in absolute value) eigenvalue. Under some conditions this obeys to a order statistics.

An example

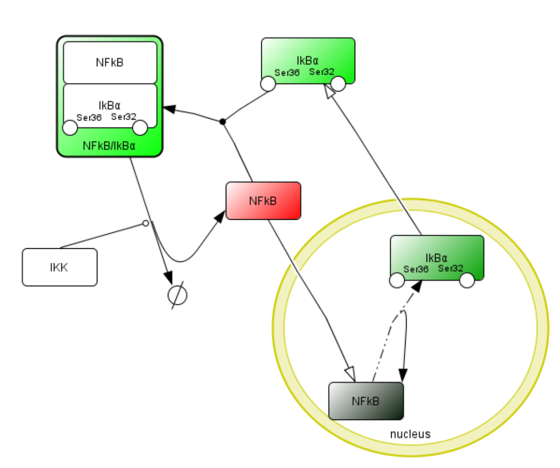

a)
A3
1
5
A4
3
2
A2
4
A5
6
A1
b)
A5
2
A4
6
1
A1
A3
4
5
A2
c)
A3
1
A4
5
2
A2
4
A5
A1
d)
Species Amounts
Time (hours)
A1
A2
A3
A4
A5

Limitation theory for non-linear systems?

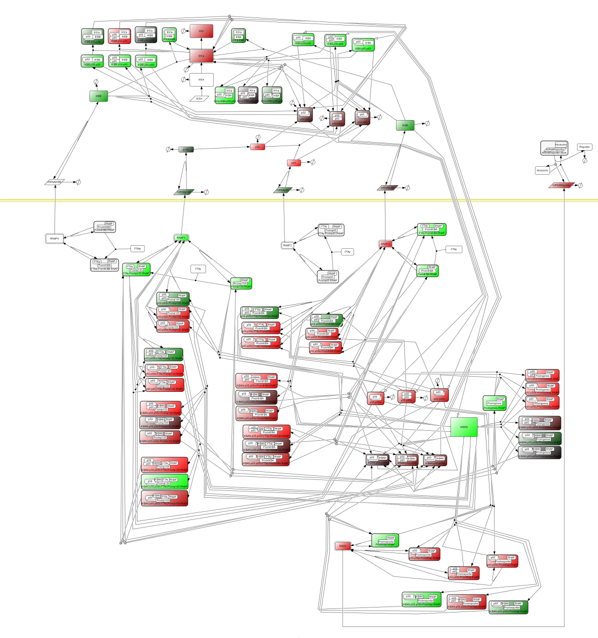
Difficulty: time scales tend to cluster, or diverge

- Singular behavior of the system at bifurcations, critical slow-down without limitation.
- Limit cycles and chaotic attractors are possible. Total separation is improbable. For instance Gershgorin theorem implies that kinetic matrices with totally separated elements have real eigenvalues: no oscillations.
- Invariant manifolds gather several degrees of freedom

Simplest model



Most complex model



Quasi-stationarity

Some species have small concentrations most of the time $x_\epsilon = \epsilon x$.
The system is of the type slow/fast.
$\epsilon \frac{dx}{dt} = f(x, y)$ (1)
$\frac{dy}{dt} = g(x, y)$ (2)

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Theorem (Tykhonov)

If for any y the dynamics (1) has a hyperbolic point attractor, then after a fast transition the system evolves according to:
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Theorem (Fenichel)

There is an invariant manifold $\mathcal{M}_\epsilon$ close to $\mathcal{M}_0$.

Averaging

Some species have oscillating behavior, others do not.
$\epsilon \frac{dx}{dt} = f(x, y)$ (1)
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For any y the fast dynamics (1) has an attractive hyperbolic limit cycle $x = \psi(\tau, y) = \psi(\tau + T(y), y)$, then

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$\frac{dy}{dt} = \frac{1}{T(y)} \int_0^{T(y)} g(\psi(\tau, y), y, 0) d\tau$

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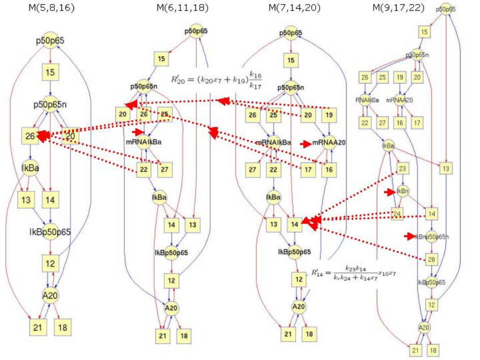
Stationarity equation for non-oscillating variables (to be solved for y).

$$\int_0^{T(y)} g(\psi(\tau, y), y) d\tau = 0$$

Reduction produces an hierarchy of models

Works for multiscale systems, uses max-plus algebra: if $x << y$ or $y << x$, then $x + y = max(x, y)$.

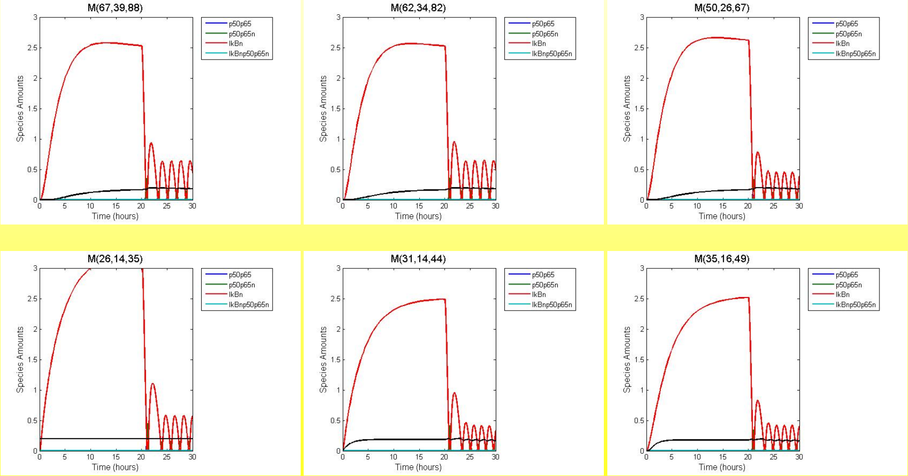


Identify critical parameters

Parameters of simple models are monomials of parameters of complex models

- Identify critical monomials
- Go back to initial parameters

Hierarchy of models, from M(67,39,88) to M(26,14,35)



What can we do with critical parameters?

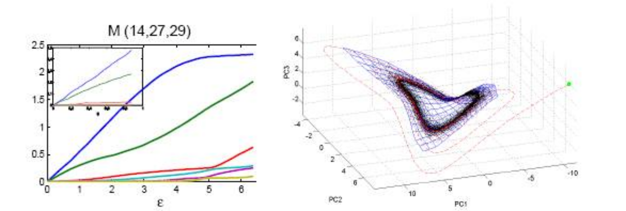
How to produce sustained oscillations?

$k_{20p} = k_{16}k_{20}/k_{17}$. Increasing k_{20p} stands for increasing the NFκB dependent A20 production.

Increasing k_{26},k_{22} stands for increasing the NFκB dependent IκB production.

A lot of parameters are not critical. For instance we don't have to know with precision the complex formation constant (allow variations of a factor 100).

Invariant manifold is 2D



Singular values curves and invariant manifold.

Molecular network have huge compression ratio from the size of the network (10^2 species) to the dimension of the invariant manifold: Gromov concentration's acts.

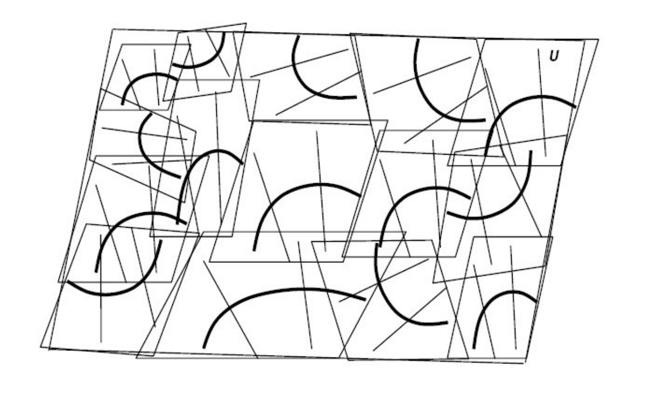
Invariant manifold

Existence of invariants could also follow from symmetry (Emmy Noether).

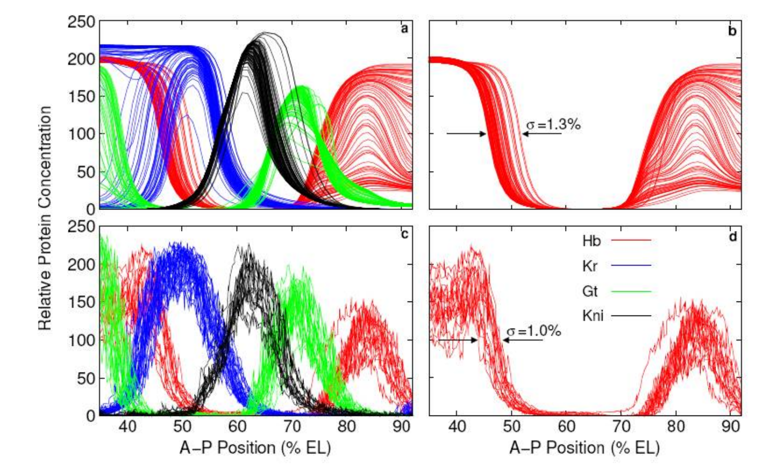
Invariants reduce the dimensionality of the system. The higher the symmetry, the lower the dimension of the invariant manifold.

For robustness we need low dimension, for flexibility we need something more.

Life is not simple: crazy quilt



First hours of Drosophila development



A model and two complementary model reduction techniques

$$\frac{\partial u_i}{\partial t} = d_i \frac{\partial^2 u_i}{\partial x^2} + R_i \sigma\left(\sum_{j=1}^{m} T_{ij} u_j + \sum_{k=1}^{p} M_{ik} v_k(x) + h_i\right) - \lambda_i u_i$$

diffusionless approximation : consider finite dimensional local dynamics, it applies to short time dynamics
center manifold approximation : reduce the infinite dimensional dynamics to dynamics on the finite dimensional center manifold (variables are position of kinks), it applies to long times.

Simplicity of the dynamics

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

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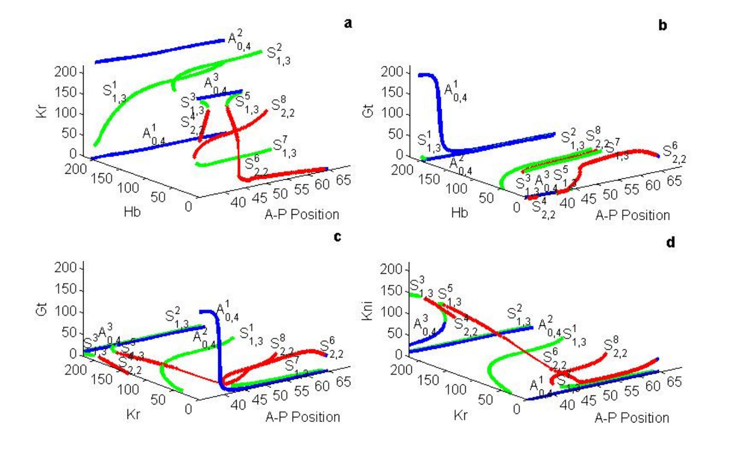
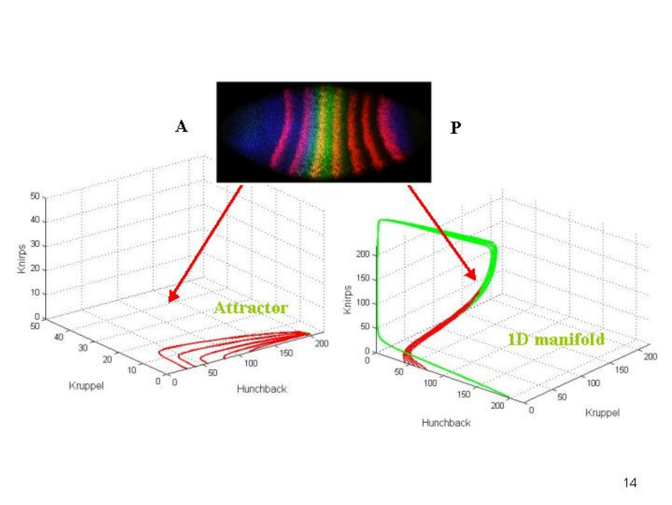
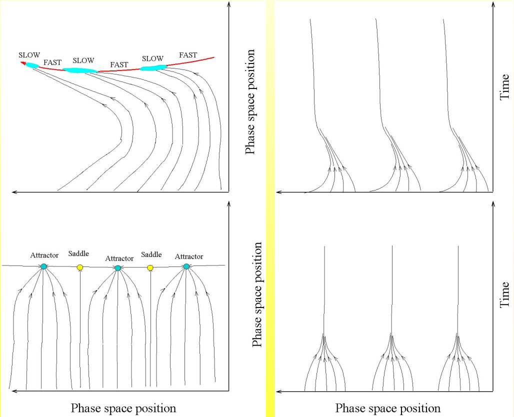


Diffusionless approximation and canalization

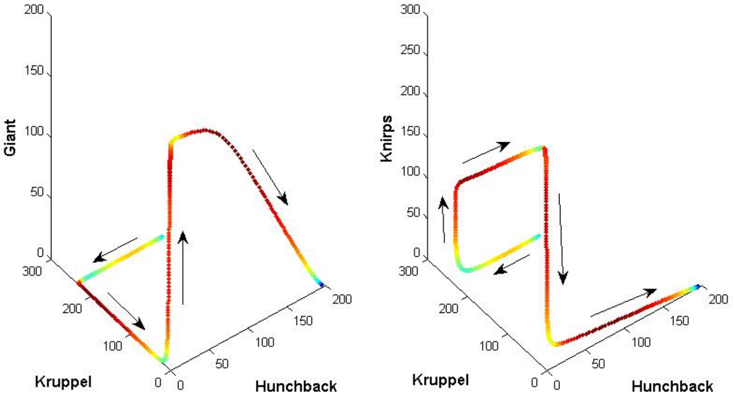


Two canalization schemes

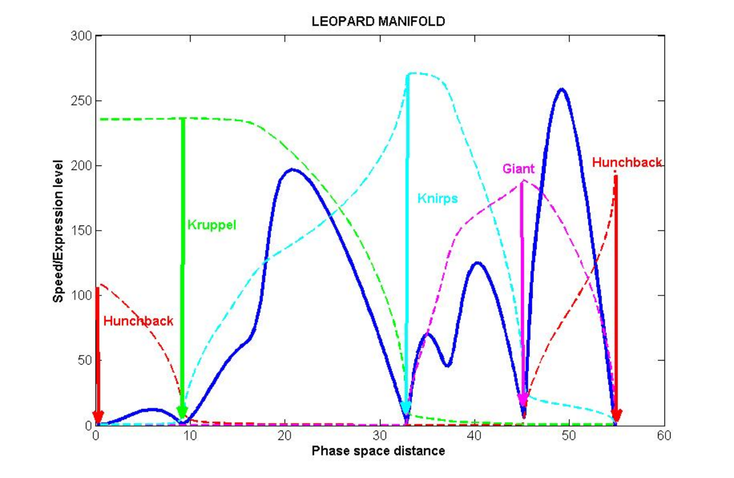


Attractors support SRB (Sinai-Ruelle-Bowen) probability measures. The SRB probability of a state is the inverse of the time spent in the neighborhood of the state.

Leopard manifold

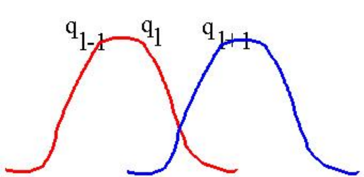


Leopard manifold



Center manifold reduction and domain springiness

$\frac{\partial u}{\partial t} = \mathcal{F}(u(x,t), x)$
$\mathcal{F}(\tilde{u}_q) = 0$, $q = (q_1, \ldots, q_n)$ (if translation invariance, q are center manifold degrees of freedom)
$u(x,t) = \tilde{u}_{q(t)} + w(x, q(t))$

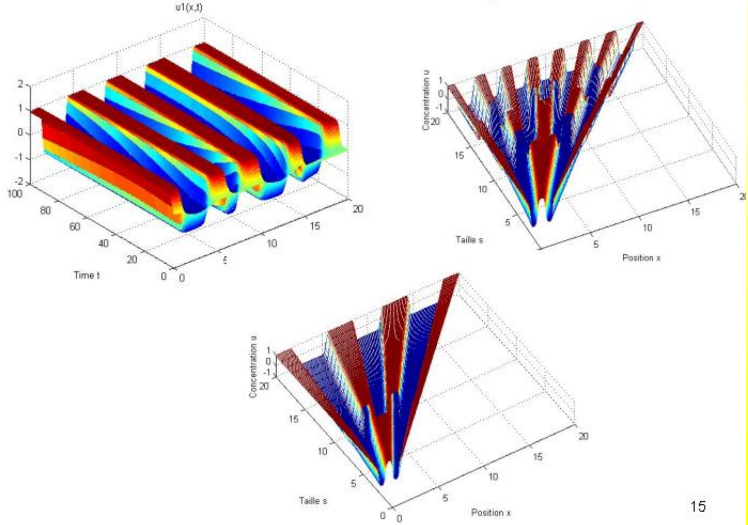


ODE for $q(t)$:

$$\mu \frac{dq_l}{dt} = \tilde{h}_i + m_i v(q_l) + C_l \exp(-\gamma(q_l - q_{l-1})) - C_{l+1} \exp(-\gamma(q_{l+1} - q_l))$$

$C_l = T_{i(l)j(l)} R_{j(l)} (\lambda_{j(l)})^{-1}$ Springs

Multistable, proportional patterns



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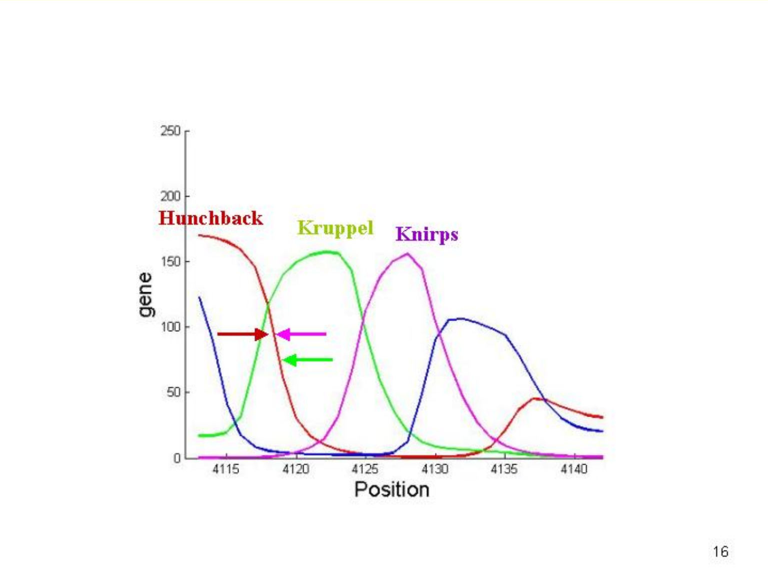
Redundancy of Drosophila gap genes



Summary of the two methods

Center manifold approximation predicts

- redundancy of the control: 2-robustness
- proportionality of patterning, genetic springs

Diffusionless approximation predicts:

- canalization of initial data
- 2 distinct types of patterning: point attractors, leopard manifold

Conclusion

Robustness = high structural complexity, low dynamical complexity, concentration phenomenon (NFκB), also redundancy (gap genes).

Flexibility = possibility to choose one of the many possible responses. Either multistability or multiple simplifications.

Law of requisite variety = necessity to have transitions between simple dynamical behaviors; the system is wandering in the set of possible robust simplifications or multistable solutions. Applications to physiology? to speciation?

Corollary : steady state is only a very simplified concept, need metastable and transition states. leopard manifold, crazy quilt are picturesque examples. Applications to morphogenesis? to signaling cascades?

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René Thom's landscape of sciences