Mathematical framework for studying biological robustness

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Outline

- Complex biological systems and Laplacian determinism
- Robustness by dimension compression
- Multiscale robustness
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.
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.

However, the organism and parts of organism are continuously reacting to the outer world, creating their own, homeostatic environment.
Second epigenetic amendment: noise

thermal noise: all interaction energies are of order $kT$

mesoscopic noise in multi-scale systems: low number species, slow variables

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

Q1: What guarantees reliable functioning in epigenetic noisy landscape?

Q2: Can we think at a mathematical framework for the study of robustness?
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

Structural stability of attracting sets. Flexibility: the set of attractors change at bifurcations.

1) \( V = x^2 \) Quadratic stable point
2) \( V = \frac{x^3}{3} \) Universal unfolding \( V = \frac{x^3}{3} + ux \) “Fold point”

Figure 1. “Fold point”
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.

Q0: What is computable?
Prolegomena for a theory of robustness

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

Chain of catalysed transformations

Transcription models

\[ A_1 \xrightarrow{F(E_1, E_2, \ldots, E_n, A_1, A_n)} A_n \]

\[ T_1 \xrightarrow{F(T_1, T_2, \ldots, T_n)} \]

Radulescu  Robustness
Gromov concentration

Objects in high-dimension look small in projection.
Levy theorem (cube concentration): \( F(k_1, k_2, \ldots, k_n) \) with \( F \) 1-Lipschitzian, concentrates \( \text{Var}(F) \sim 1/N \).
Examples of 1-Lipschitzian functions: \( \frac{1}{N} \sum_{i=1}^{N} x_i, \ f(x) = \frac{x}{K+x} \).
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

$\text{Var}(\log K) \ll \delta^2$, no overlap $\text{Var}(\log M) \sim \text{Var}(\log K)$
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

$\text{Var}(\log K) << \delta^2$, no overlap

$\text{Var}(\log M) \sim \text{Var}(\log K)$

$\text{Var}(\log K) \sim \delta^2$, saturation

$\text{Var}(\log M) = \delta^2$
order statistics $K_1 >> K_2 >> ... K_r >> ... K_n$, $M = K_r$

log-uniform parameters with average spacing $\delta$ in log-scale

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

$Var(\log K) \sim \delta^2$, saturation $Var(\log M) = \delta^2$

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

$Var(\log M) \sim Var(\log K) / N^2$
order statistics $K_1 >> K_2 >> ... K_r >> ... K_n$, $M = K_r$

log-uniform parameters with average spacing $\delta$ in log-scale

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

$\text{Var}(\log K) \sim \delta^2$, saturation $\text{Var}(\log M) = \delta^2$

$\text{Var}(\log K) \gg \delta^2$, simplex concentration $\text{Var}(\log M) \sim \text{Var}(\log K)/N^2$
Min - max combinations

\[ A \xrightarrow{k1} A1 \xrightarrow{k2} A2 \xrightarrow{k3} A3 \]
\[ \text{Max}(k1, k2, k3) \]

\[ A \xrightarrow{} AB \xrightarrow{} \text{Min}(A, B) \]

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

\[ \frac{dc_i}{dt} = k_{i0} + \sum_{j \geq 1} k_{ij}c_j - \left( \sum_{j \geq 0} k_{ji} \right)c_i, \] 
\[ \dot{c} = K_{0} + Kc. \]
Linear network of chemical reactions

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

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

(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 \( \text{ordering} (I = (i,j)) \):

\[
k_{I_1} \ll k_{I_2} \ll k_{I_3} \ll \ldots
\]

We say that the system has separated constants.
Limiting step

Linear chain of reactions $A_1 \rightarrow A_2 \rightarrow \ldots A_n$ 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 $\sim 1/k_q$:
- $A_1, \ldots A_{q-1}$ transform fast into $A_q$,
- $A_{q+1}, \ldots A_{n-1}$ transform fast into $A_n$,

only two components, $A_q$ and $A_n$, are present,
the whole chain behaves as a single reaction $A_q \xrightarrow{k_q} A_n$
Limitation theory for linear, hierarchical models: an example

Gorban and Radulescu Adv.Chem.Eng.08, Radulescu et al BMC Systems Biol. 08
NFκB pathway: testing concentration for nonlinear models

Gorban and Radulescu, IET Systems Biol. 07
Model reduction and critical parameters

Radulescu et al. BMC Systems Biol. 08
Model reduction and robustness

- Model reduction provides mathematical framework for robustness.
- Complex biological systems have simple, robust dynamics. Robust dynamics is computable. No need for full parameter identification.
- There are remaining critical parameters allowing control.
- Generic response to statistical perturbations (cube or simplex concentration) : need high compression, not necessarily high dimension.
- Robust system design: network topology is not all. Need also order relations among parameters.
Multiscale robustness

Crazy quilt: sequence of robust simplifications in abstract spaces

Active modes: genes, pathways, space-time structures
A lesson from the fly

Houchmandzadeh, Wieschaus, Leibler, 2002: unexplained reduction of variance
Complex, but not bottom level: the gene circuit model

Model: Hopfield + diffusion

\[
\frac{\partial u_d(x,t)}{\partial t} = R_a g_d \left( \sum_{b=1}^{N} T_{ab} u_b(x,t) + T_a m(x) + h_a \right) + D_a \nabla^2 u_d(x,t) - \lambda_d u_d(x,t)
\]
Reproduces canalization properties

Manu et al. 08, in review Plos

Radulescu

Robustness
Redundancy effect

Manu et al. 08, in review Plos
Interacting kink model

Vakulenko and Radulescu, manuscript
The 2-scale robustness picture

Local gene interactions

Interactions between localized modes

Diffusionless approximation: domain formation

Interacting kinks: springiness
Robustness can exist at many scales. Multi-scale model reduction allows to focus on a particular scale.

Biological dynamical systems can pass from one dynamical simplification to another one. All these simplifications can be robust.

The two simplifications for Drosophila gap gene system dynamics, the diffusionless approximation and the interacting kinks approximation explain stability at various times.

Alternating cushion ensures robust design of Drosophila gap gene system.
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