Dynamical Models of Biological Networks.

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Vienna, October 15th 2012
Overview

- Introduction
- Repressilator Like Systems
- GATA-type Gene-Regulatory Networks
  - Nitrogen Catabolite Repression in Yeast
  - Effects of Gene Duplication on an Autoactivator
Models of Biological Networks

- help to understand and predict behaviours of complex networks
- allow conduct *in silico* experiments
- allow to investigate robustness of behaviours
- provide hints on the evolution of network topologies
- help to design novel functions or optimize existing ones
Dynamical Models in Molecular Biology

- Deterministic Differential Equation Based Models
  - computationally efficient to solve
  - simple networks can be analytically explored
  - cannot account for stochastic fluctuations
    eg. at low molecule numbers

- Stochastic Reaction Models
  - often only way to explore stochastic fluctuations
  - analytical solutions only for very simple systems
  - simulation algorithms give only potential trajectories
  - need to obtain statistics over many simulations
Two Systems

Classical Repressilator

Repressilator with Autoactivation
Dynamics for Odd Genenumbers

Stable Equilibrium

Limit Cycle Oscillations

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Repressilator with Autoactivation

Stable Heteroclinic Cycle

Increasing Period Length
Stochastic Simulation

Classical Repressilator

Repressilator with Autoactivation
Variability of Oscillations

**Autocorrelation**

![Autocorrelation graph](image)

Autocorrelation time ($\tau_A$)

- RepLeaky: $\tau_A = 210$ min (1.6 periods)
- RepAuto: $\tau_A = 352$ min (3.4 periods)
Comparison

- apart from a central equilibrium and limit cycle oscillations, the Repressilator with autoactivation can also exhibit oscillations with increasing period lengths
- with autoactivation, oscillations are possible without cooperative transcription factor binding
- the combination of repression and autoactivation lead to more uniform oscillations in stochastic simulations
GATA Type Transcription Factors

- ubiquitous eucaryotic transcription factors
- most bind a \((A/T)\text{GATA}(A/G)\) sequence
- can be both transcriptional activators and repressors
- only few, closely related GATA TFs in most species
- involved in metabolism, immune response, and development
- regulatory motifs consisting of GATA TF: autoregulation, feed-back and -forward loops, cascades
regulatory network of 4 GATA factors
- Gat1p, Gln3p: activators
- Dal80p, Gzf3p: competitive repressors

at high N: Gat1p and Gln3p sequestered in cytoplasm by Ure2p

at low N: Gat1p and Gln3p trans locate to nucleus

adapted after Cooper (2002)
Validation

from Boczko et al. 2005

GAT1 mRNA

DAL80 mRNA
Potential Function of Negative Feed-Back

- decreasing inhibition leads to sigmoid behaviour
- gradual response fits differential expression in dependence of nitrogen source found experimentally
Single Autoactivator

- based on GAT1
- additional signal S activating A
- posttranscriptional regulation by Gln
- parameters adapted to exhibit bistability
Switching Behaviour

Gln → S → target genes

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Gene Duplication

\[ \text{Gln} \rightarrow \text{S} \rightarrow \text{A} \rightarrow \text{target genes} \]

\[ \Rightarrow \]

\[ \text{Gln} \rightarrow \text{S} \rightarrow \text{A}_1 \rightarrow \text{A}_2 \rightarrow \text{target genes} \]

\[ \Rightarrow \]

Graphical representation with arrows showing the flow of information.

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Feedback Loop Disruption - Neofunctionalization

![Diagram]

- Gln
- S
- A1
- A2
- Old targets
- New targets

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Cascade Formation

\[ \text{Gln} \rightarrow \text{S} \rightarrow \text{target genes} \]

\[ \Rightarrow \]

\[ \text{Gln} \rightarrow \text{S} \rightarrow \text{target genes} \]

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**No mut.**
**One mut.**
**Two mut.**

\[ \text{A1 [molecules/fl]} \]

\[ \text{S [molecules/fl]} \]
Loss of Trans-activational Domain
Slow Oscillations

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Fast Oscillations

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NCR model qualitatively reproduces time-course data and predicts results of knock out experiments even though parameters were from diverse sources.

- Repressors DAL80 and GZF3 could be responsible for creating a gradual, rather than a sigmoid response to nitrogen availability.
- Another function of the repressors could be mitigation of gene copy number variation.
Autoactivator

gene duplication would lead to hypersensitivity or irreversibility of switching

some mutations leading relieving the gene dosage effect lead to network motifs found in GATA type gene networks

gene dosage could be a driving factor in the evolution of such auto-regulatory networks

loss of the trans-activating domain in one paralogue could lead to an oscillator with only a few additional mutations
Thanks to

Peter Schuster
Christoph Flamm
Stefan Müller, Rainer Machné
Stefanie Widder, James Lu, Josef Hofbauer
Ulrike Mückstein