Dynamical Models of Biological Networks.

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Overview

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

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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

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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
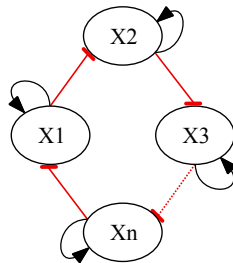
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Elowitz and Leibler (2000)
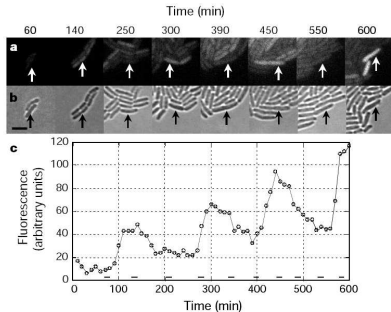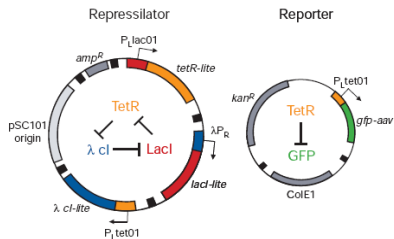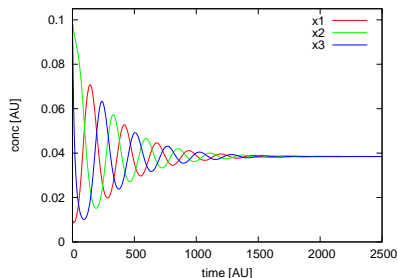
Two Systems

Classical Repressilator

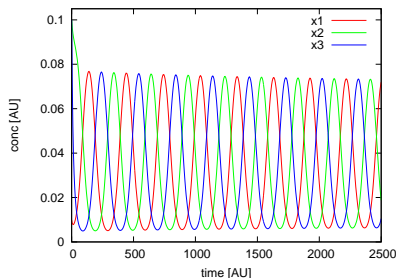Repressilator with Autoactivation

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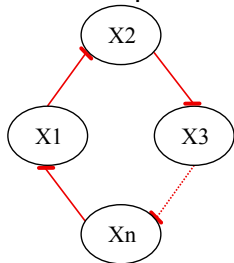
Dynamics for Odd Genenumbers
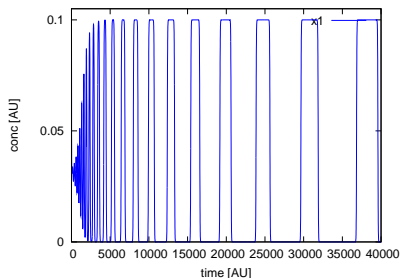
Stable Equilibrium

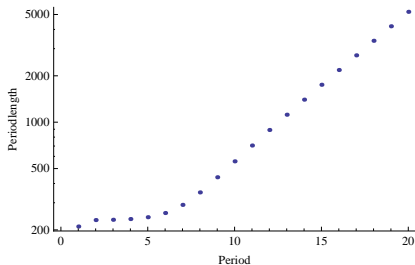Limit Cycle Oscillations

Repressilator with Autoactivation

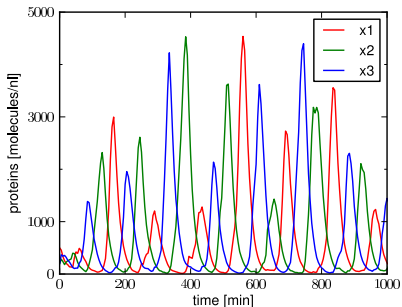## Stable Heteroclinic Cycle

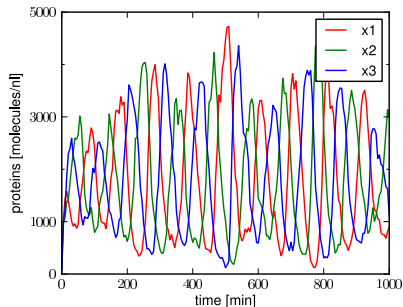## Increasing Period Length

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Stochastic Simulation
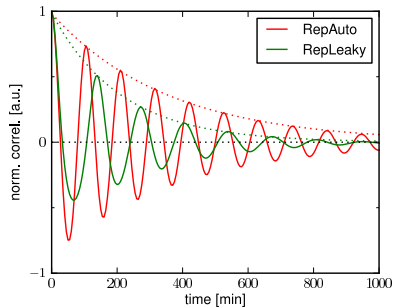

Classical Repressilator

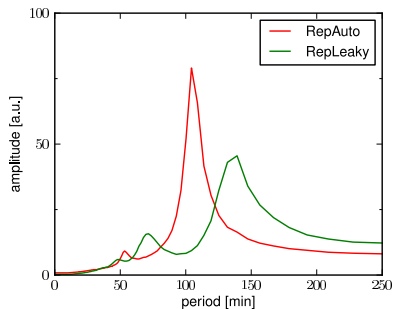Repressilator with Autoactivation

Variability of Oscillations

Autocorrelation

Period Spectrum

Autocorrelationtime (τ_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

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GATA Type Transcription Factors

- ubiquitous eucaryotic transcription factors
- most bind a `(A/T)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
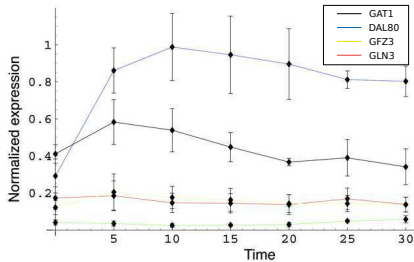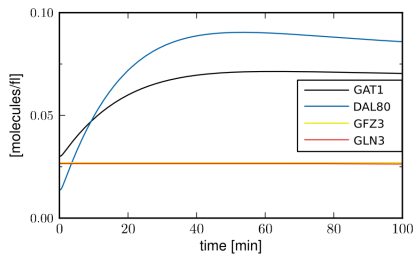
Yeast Nitrogen Catabolite Repression (NCR)

- 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
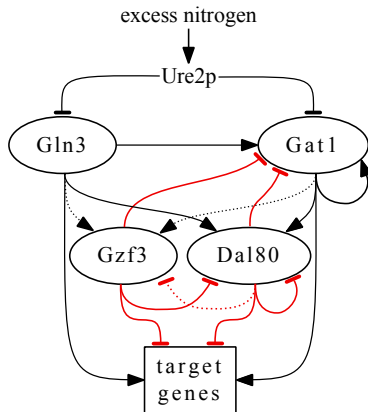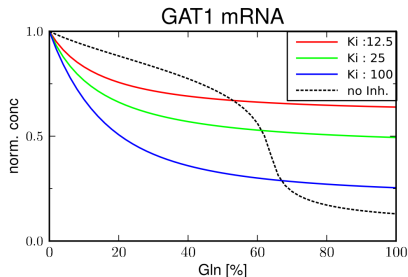

adapted after Cooper (2002)

Validation

from Boczko *et al.* 2005
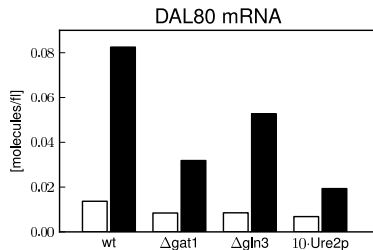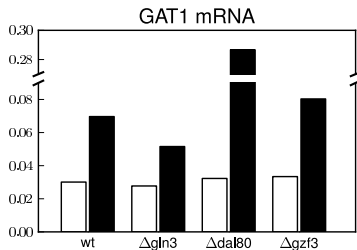
# Potential Function of Negative Feed-Back

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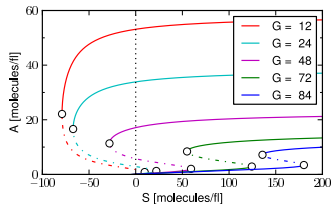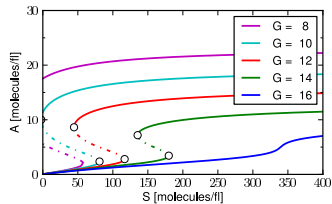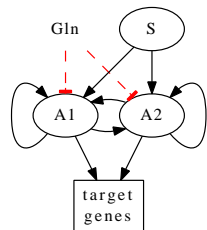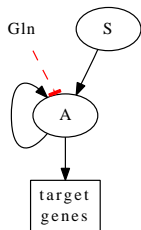
Single Autoactivator

- based on GAT1
- additional signal S activating A
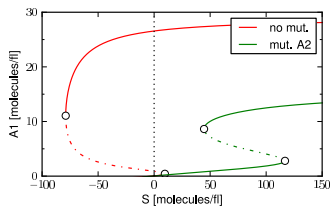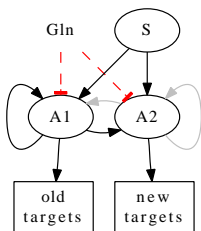- posttranscriptional regulation by Gln
- parameters adapted to exhibit bistability
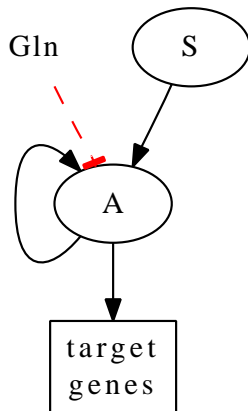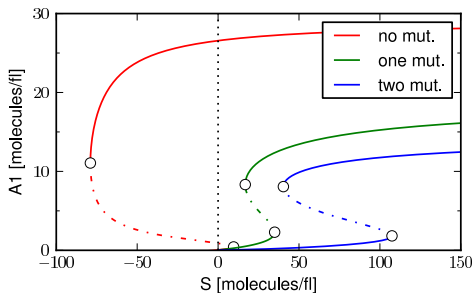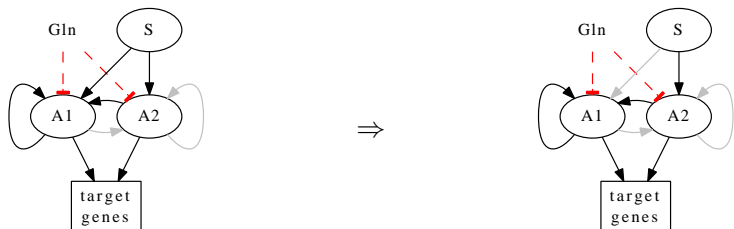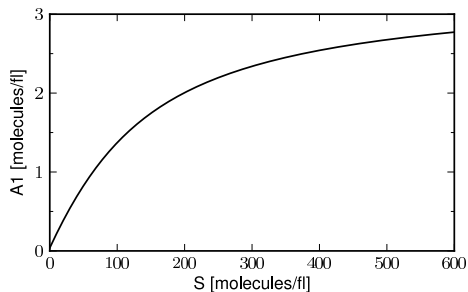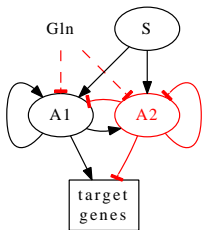
Switching Behaviour
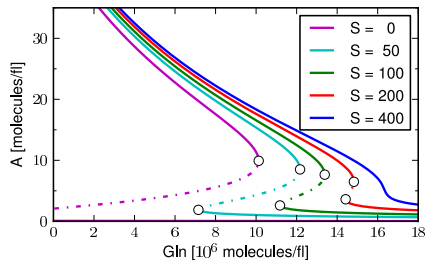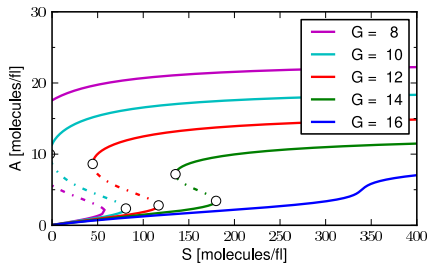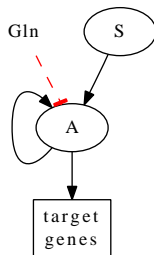
Gene Duplication
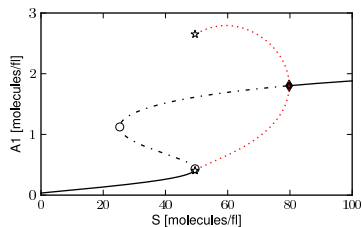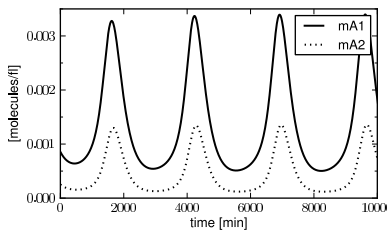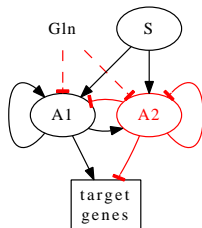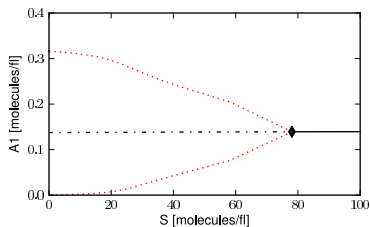
Feedback Loop Disruption - Neofunctionalization

Cascade Formation

Loss of Trans-activational Domain

Slow Oscillations

Fast Oscillations

NCR
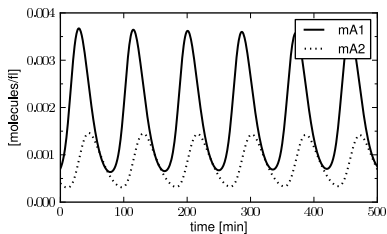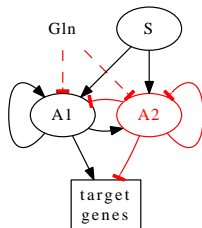
- NCR model qualitatively reproduces time-course data and predicts results of knock out experiments even though parameters were from diverse sources
- repressors DAL80 and GZF3 could be responsible for creating a gradual, rather than a sigmoid response to nitrogen availability
- another function of the repressors could be mitigation of gene copy number variation

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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

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Thanks to

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