Inverse Dynamical Analysis: Applications to Gene Networks

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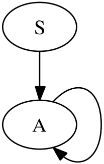
From Bio to Math and back

The Forward Problem:

interaction graph $\rightarrow$ reactions $\rightarrow \frac{dx}{dt} = f(x, q) \rightarrow x(t) \rightarrow$ bifurcations

interactions



experimental work

reactions

$$S_{\text{nuclear}} \longrightarrow S_{\text{nuclear}} + A_{\text{RNA}}$$
$$A_{\text{RNA}} \longrightarrow A_{\text{mRNA}}$$
$$A_{\text{mRNA}} \longrightarrow A_{\text{mRNA}} + A_{\text{protein}}$$
$$A_{\text{protein}} \longrightarrow A_{\text{nuclear}}$$
$$A_{\text{nuclear}} \longrightarrow A_{\text{nuclear}} + A_{\text{RNA}}$$

classical chemical kinetics

From Bio to Math and back

The Forward Problem:

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$$\begin{aligned}
\frac{drA}{dt} &= N \cdot \left(V_a^b + V_a^A \cdot \left(\frac{A}{\left(K_a^A + A\right)} \right)^{hA} + V_a^S \cdot \left(\frac{S}{\left(K_a^S + S\right)} \right)^{hS} \right) - (kex_a + \Phi_r A) \cdot rA \\
\frac{dmA}{dt} &= kex_a \cdot rA \cdot c1/c2 - \Phi_m A \cdot mA \\
\frac{dAc}{dt} &= ktl_a \cdot mA - (kim_A \cdot Ac - kex_A \cdot A) \cdot c1/c2 - \Phi_A c \cdot Ac \\
\frac{dA}{dt} &= kim_A \cdot Ac - (kex_A + \Phi_A) \cdot A
\end{aligned}$$

From Bio to Math and back

The Forward Problem:

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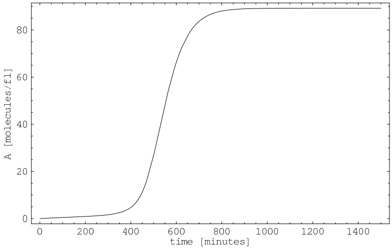
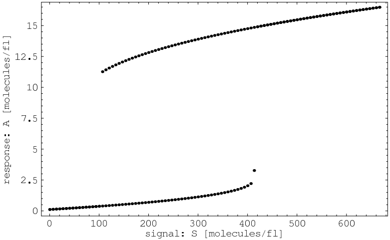
time courses: $x(t)$



stability and bifurcation analysis



From Bio to Math and back : *bifurcation phenotypes*

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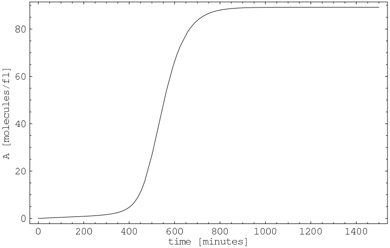
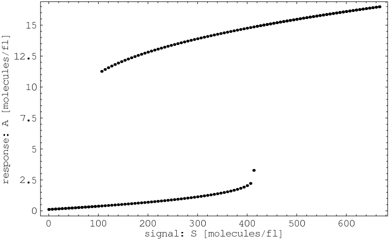


stability and bifurcation analysis
w.r.t. physiological signals



$\approx$ signal/response curves / titration experiments

From Bio to Math and back

The Inverse Problem: matching model to data

interaction graph $\leftarrow$ reactions $\leftarrow$ $\frac{dx}{dt} = f(x, q) \leftarrow x(t) \leftarrow$ bifurcations

match desired time-courses: $x(t)$

From Bio to Math and back

The Inverse Problem: matching model to data

$$\text{interaction graph} \leftarrow \text{reactions} \leftarrow \frac{dx}{dt} = f(x,q) \leftarrow x(t) \leftarrow \text{bifurcations}$$

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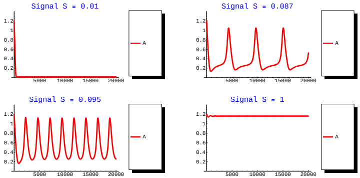

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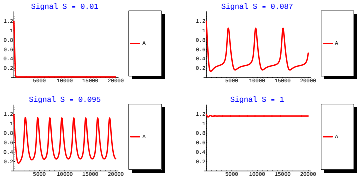
match desired bifurcation diagram



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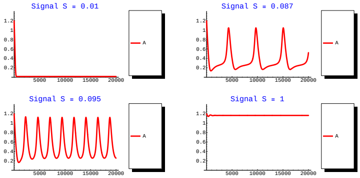

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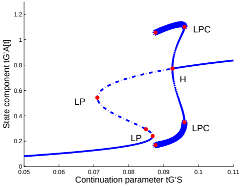

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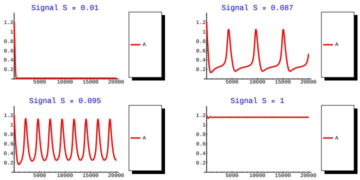

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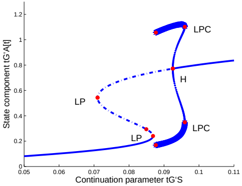

- Non-uniqueness of solution

From Bio to Math and back

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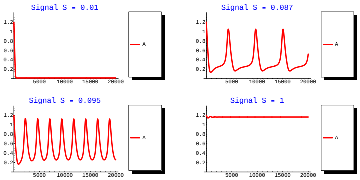

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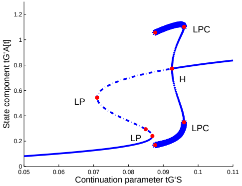


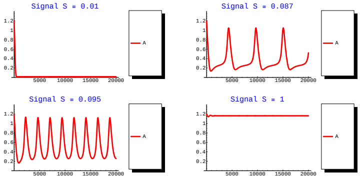
- Non-uniqueness of solution
- use the principle of *Ockham's razor*, i.e., sparsity constraints

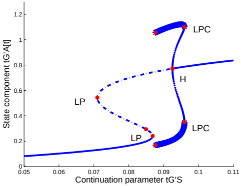
From Bio to Math and back

The Inverse Problem: matching model to data

interaction graph $\leftarrow$ reactions $\leftarrow$ $\frac{dx}{dt} = f(x,q) \leftarrow x(t) \leftarrow$ bifurcations

predict the parametric dependency of time-courses: $x(t)$





From Bio to Math and back

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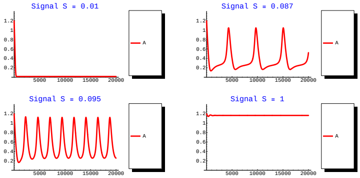
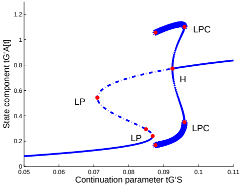


infer influential mechanisms controlling bifurcation points



From Bio to Math and back

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interaction graph ← reactions ← $\frac{dx}{dt} = f(x, q)$ ← $x(t)$ ← bifurcations

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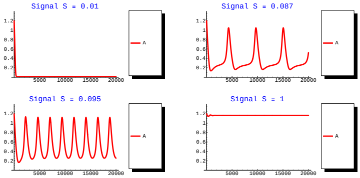

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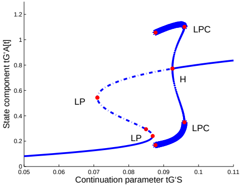

- Infer important predictions of model to be experimentally verified/falsified

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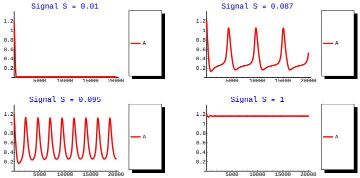

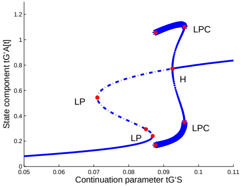

- Infer important predictions of model to be experimentally verified/falsified
- would like to vary only a few important reactions: sparsity constraints

Inverse Dynamical Analysis: Methodology

- In the initial modelling of gene networks to capture the observed qualitative behaviors
  - probe the possibility for the model to exhibit known pattern of up/down regulation or oscillations
  - characterize parameter variations that can give rise to these dynamical behaviors
- Computational methods:
  - inverse eigenvalue analysis

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- Given a plausible model of biological system of interest
  - identify mechanisms in model that can give rise to various *bifurcation phenotypes*: verify or falsify experimentally
  - design for desired dynamical characteristics
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  - inverse bifurcation analysis
  - sparsity constraint

Inverse Eigenvalue Problems: ODE setting

Illustration: design of gene switch w.r.t. signal

- gene 1: up-regulated

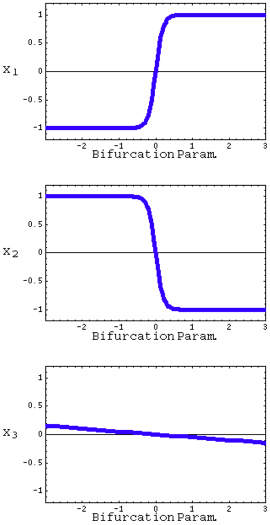

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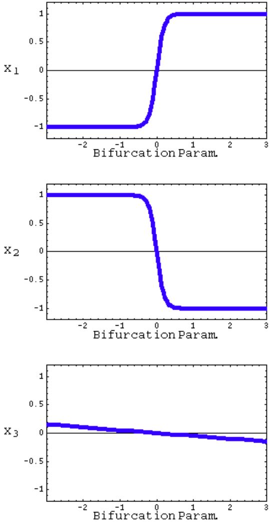
Illustration: design of gene switch w.r.t. signal

- gene 1: up-regulated
- gene 2: down-regulated



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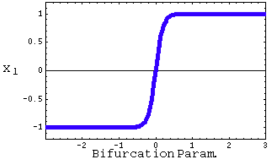
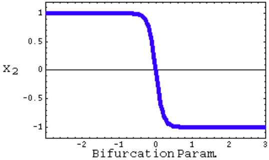
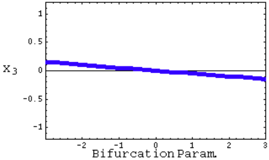


- gene 2: down-regulated



- gene 3: essentially unchanged



Inverse Eigenvalue Problems: ODE setting

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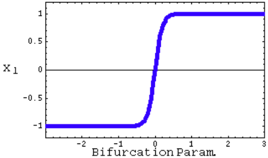
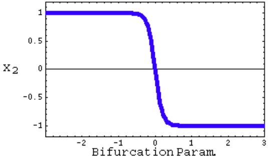
- gene 1: up-regulated



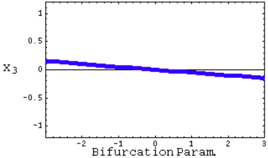
$\uparrow (v^*)_1$

- gene 2: down-regulated



$\downarrow (v^*)_2$

- gene 3: essentially unchanged

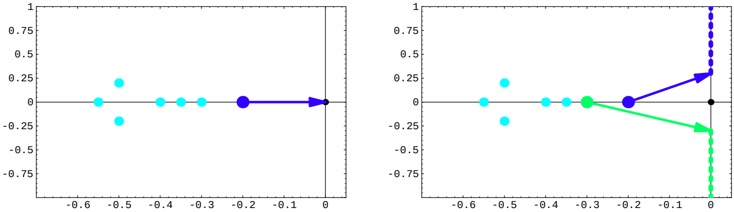


$\bullet (v^*)_3$

Inverse Eigenvalue Problems (IEP): ODE setting

Definition (IEP for Locating Saddle-Node and Hopf Bifurcations)

Denote the desired eigenvalues $\lambda_{SN} = \{0\}$ or $\lambda_H = \{\pm\omega i\}$. With equilibrium condition $f(x,q) = 0$, determine parameter values q such that $\sigma(\frac{df}{dx}) \supset \lambda_{SN,H}$, subject to some additional inequality constraints on the associated eigenvectors $C \cdot V^{\text{crit}} \geq 0$

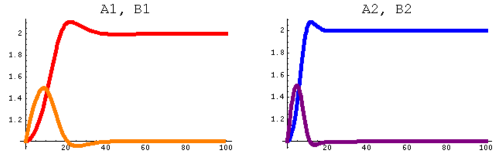


(a) IEP for Saddle-Node (b) IEP for Hopf

Inverse Eigenvalue Problems: Coupled Brusselator

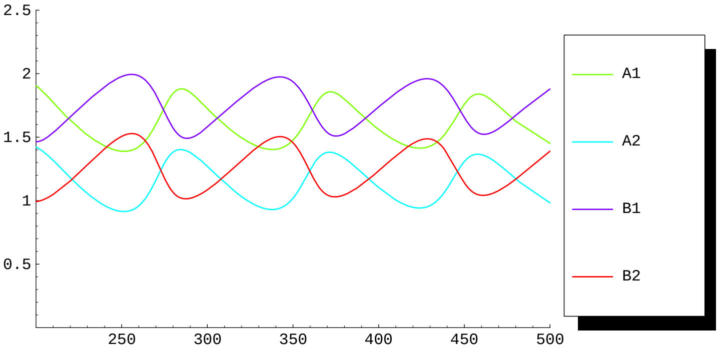
- Initial damped behavior in coupled Brusselators

		Forward rate	Backward rate
Production/degradation: system 1	$\emptyset \rightleftarrows A1$	$k(1, 1)$	$k(1, 2)$
	$2\,A1 + B1 \rightarrow 3\,A1$	$k(1, 3)$	
	$A1 \rightarrow B1$	$k(1, 4)$	
Production/degradation: system 2	$\emptyset \rightleftarrows A2$	$k(2, 1)$	$k(2, 2)$
	$2\,A2 + B2 \rightarrow 3\,A2$	$k(2, 3)$	
	$A2 \rightarrow B2$	$k(2, 4)$	
Coupling: systems 1, 2	$A1 \rightleftarrows A2$	C12	C12



Inverse Eigenvalue Problems: ODE setting

- Application: design of oscillation pattern in coupled Brusselators

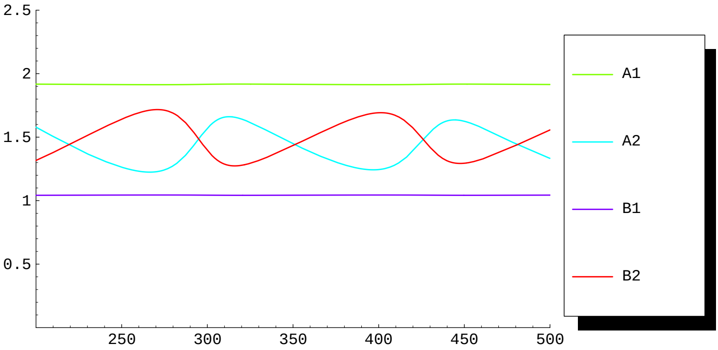


Equal amplitude of oscillation in {A1,B1} and {A2, B2}:

$$V_{A1}^{\text{crit}} = V_{A2}^{\text{crit}}, V_{B1}^{\text{crit}} = V_{B2}^{\text{crit}}$$

Inverse Eigenvalue Problems: ODE setting

- Application: design of oscillation pattern in coupled Brusselators



No oscillation in A1, B1: $V_{A1}^{\text{crit}} = V_{B1}^{\text{crit}} = 0$

Sparsity-promoting regularization: l_p, $p \leq 1$

- Consider (smoothed) functionals $\mathbb{R}^n \to \mathbb{R}$:
  $l_{p,\epsilon}(x) = \sum_i (x_i^2 + \epsilon)^{p/2}$

Sparsity-promoting regularization: l_p, $p \leq 1$

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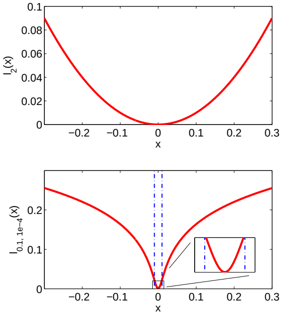
- Convex only within the box $\{x : |x_i| < \sqrt{\epsilon},\ 0 < i \leq n\}$



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- Convex only within the box $\{x : |x_i| < \sqrt{\epsilon},\ 0 < i \leq n\}$
- Recent applications of sparse solutions using non-convex penalty:
  - *Exact reconstruction of sparse signals via nonconvex minimization*, R. Chartrand (2007)
  - Compressive sensing using l_1 re-weighting, E. Candes, S. P. Boyd, M. Wakin *et al.* (2007)
  - *Log-det heuristic for matrix rank minimization with applications to Hankel and Euclidean distance matrices*, M. Fazel, H. Hindi and S. P Boyd (2003)

Inverse Eigenvalue Problem: ODE setting

- Hybrid solution algorithm:
  - Lift-and-Project (LP)

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  - Lift-and-Project (LP)
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- Hybrid solution algorithm:
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- Least square formulations with sparsity constraint:

$$\begin{aligned} \text{LP} &: \quad J(q) = \|A(q) - A_{\text{proj}}\|_{\mathcal{F}}^2 + \alpha \|\boldsymbol{q} - \boldsymbol{q}^*\|_{l_p}^p \\ \text{QN} &: \quad J(q) = \sum_i |\lambda_i(q) - \lambda_i^d|^2 + \alpha \|\boldsymbol{q} - \boldsymbol{q}^*\|_{l_p}^p , \end{aligned}$$

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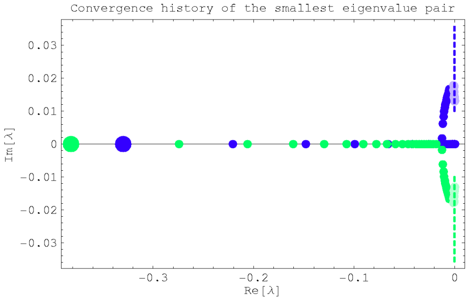
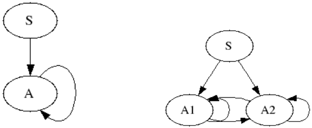
$$\text{QN} \quad : \quad J(q) = \sum_i |\lambda_i(q) - \lambda_i^d|^2 + \alpha \|\boldsymbol{q} - \boldsymbol{q}^*\|_{l_p}^p,$$

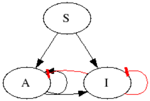


Emergence of New Dynamical Repertoir: from a Bistable Switch to an Oscillator

- Consider a model for GATA transcription factors, which play important role in Th2 cell differentiation and nitrogen catabolite repression (NCR)
- Modelling assumption: auto-activating transcription factor A with 2 binding sites in regulatory region of its gene
- Scenario: duplication of gene A



- Subsequent mutation scenario: loss of activating domain



- Can oscillations emerge via a few additional mutations?

Emergence of New Dynamical Repertoir: from a Bistable Switch to an Oscillator

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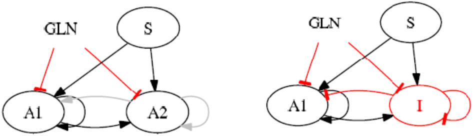

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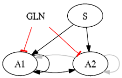

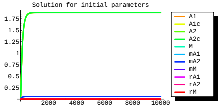

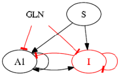

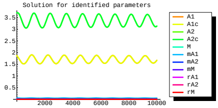

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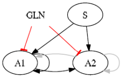
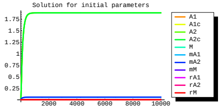
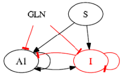
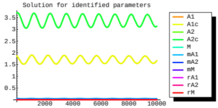
- Evolutionary scenario







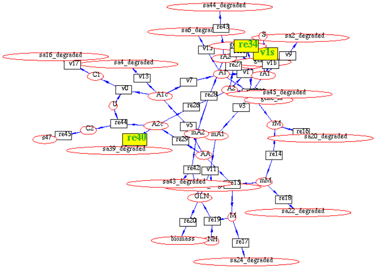


- Identified reactions:

AI\`v1s[t] == AI\`s AI\`Va1_S (0.04→0.011) / (AI\`S+AI\`Ka1_S[t])

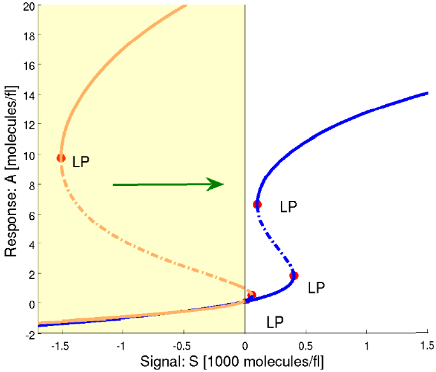
AI\`re34[t] == AI\`s AI\`Va2_S (0.04→0.001) / (AI\`S+AI\`Ka2_S[t])

AI\`re40[t] == 24 AI\`A2c[t] AI\`D_A2c (0.03→0.0046)



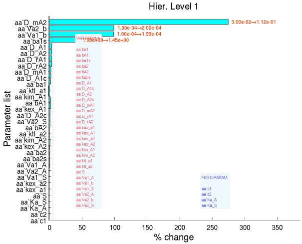
Inverse Bifurcation Analysis: GATA Example

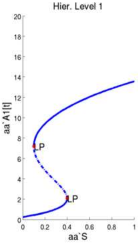
- Consider the duplicated, dual-activator GATA system
- System is an irreversible switch after duplication
- Which mutations can relieve the hypersensitivity to signal?

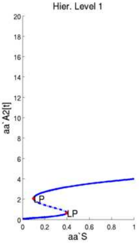


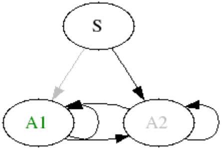
Inverse Bifurcation Analysis: GATA Example

- Identified parameters for relieving hypersensitivity









Hierarchical Approach: Identifying Multiple Solutions

- In general, multiple solutions exist even under sparsity constraint
- Use an hierarchical approach to identify a sequence of solutions to the inverse bifurcation problem

Algorithm

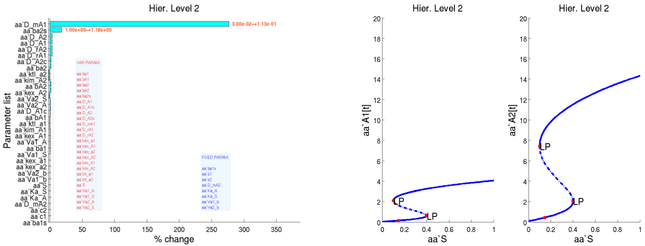
HIERARCHICAL-IDENTIFICATION($q_s^0 \in \mathbb{R}^m$, MaxLevel, p, ϵ)

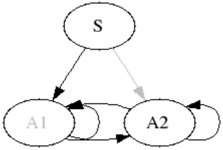
- Initialize: $s \leftarrow \{1, \cdots, m\}$, $I_{\text{identified}} \leftarrow \emptyset$
- FOR $j = 1, \cdots,$ MaxLevel
  - $I_{\text{remain}} \leftarrow s \setminus I_{\text{identified}}$
  - If $I_{\text{remain}} = \emptyset$, Exit
  - Solve $q^j_{I_{\text{rem}}} \leftarrow$ `ParamIden`$(q^0_{I_{\text{rem}}}, l^p_{p,\epsilon})$; if no solution, Exit.
  - $I_j \leftarrow \{i : |(q^j_{I_{\text{rem}}})_i| > \sqrt{\epsilon}\}$
  - $I_{\text{identified}} \leftarrow I_{\text{identified}} \cup I_j$

  END
- **Return** $\{q^1_{I_1}, q^2_{I_2}, q^3_{I_3}, \cdots\}$

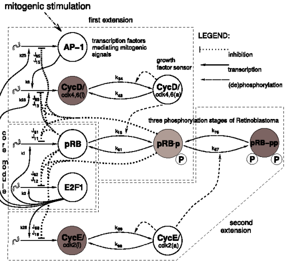
Inverse Bifurcation Analysis: GATA Example

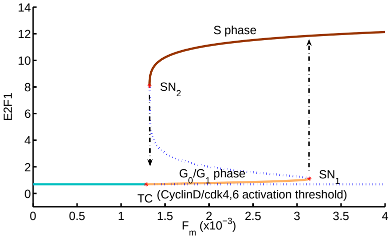
- Level 2: alternative parameters for relieving hypersensitivity





The G_1/S Module of Mammalian Cell Cycle





M. Swat, A. Kel, H. Herzel, *Bioinformatics* (2004)

- What can be said about the core regulatory mechanism of the bifurcation points?

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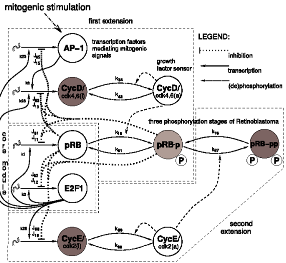

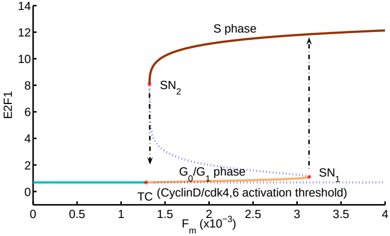

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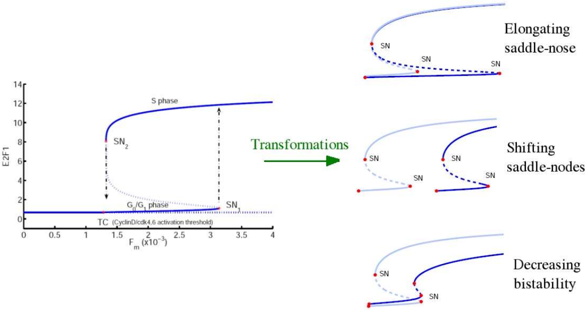
- What can be said about the core regulatory mechanism of the bifurcation points?
  - Inverse Bifurcation Analysis

Inverse Bifurcation Analysis: Mammalian G_1/S Transition

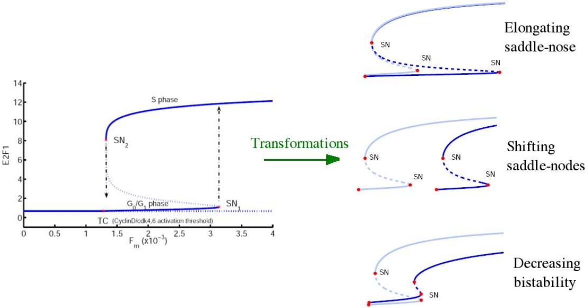
- Goal: infer core regulatory mechanism of the G_1/S genetic switch
- Method: *bifurcation phenotypes* $\longrightarrow$ parameter sets

Inverse Bifurcation Analysis: Mammalian G_1/S Transition

- Goal: infer core regulatory mechanism of the G_1/S genetic switch
- Method: *bifurcation phenotypes* $\rightarrow$ parameter sets
- Consider the following 3 modes of geometric transformations of the nominal bifurcation diagram:

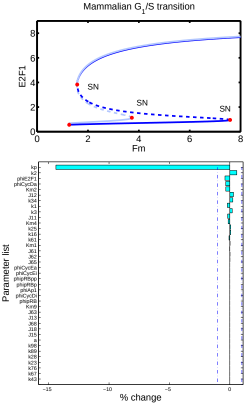


Inverse Bifurcation Analysis: Mammalian G_1/S Transition

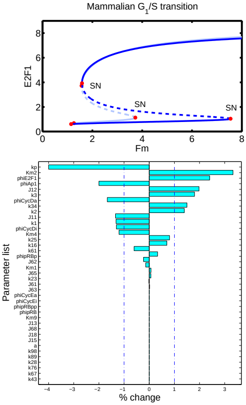


- Biological relevance of geometric perturbations:
    - observed in mutant phenotypes
    - checkpoint mechanism: delay of transition point
    - response of switch to additional signals

Inverse Bifurcation: Effect of Sparsity Constraint



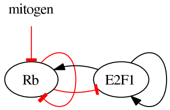
(g) $l^{0.1}_{0.1,10^{-4}}$ regularization



(h) l^2_2 regularization

Inverse Bifurcation: Identified Modules

$$\begin{aligned}\frac{d}{dt}[\text{pRB}] &= k_1 \frac{[\text{E2F1}]}{K_{m1} + [\text{E2F1}]} \frac{J_{11}}{J_{11} + [\text{pRB}]} \frac{J_{61}}{J_{61} + [\text{pRB}_p]} \\ &- k_{16}[\text{pRB}][\text{CycD}_a] + k_{61}[\text{pRB}_p] - \phi_{\text{pRB}}[\text{pRB}], \\ \frac{d}{dt}[\text{E2F1}] &= k_p + k_2 \frac{a^2 + [\text{E2F1}]^2}{{K_{m2}}^2 + [\text{E2F1}]^2} \frac{J_{12}}{J_{12} + [\text{pRB}]} \frac{J_{62}}{J_{62} + [\text{pRB}_p]} \\ &- \phi_{\text{E2F1}}[\text{E2F1}]\end{aligned}$$



$$\begin{aligned}\frac{d}{dt}[\text{CycD}_i] &= -k_{34}[\text{CycD}_i] \frac{[\text{CycD}_a]}{K_{m4} + [\text{CycD}_a]} + \cdots \\ \frac{d}{dt}[\text{CycD}_a] &= k_{34}[\text{CycD}_i] \frac{[\text{CycD}_a]}{K_{m4} + [\text{CycD}_a]} + \cdots\end{aligned}$$

Possible Biological Interprations: G_1/S Module

1. Modification 1 + 2 : move bistability
   - move SN_1 or SN_1/SN_2 : insensitivity to mitogen
     $\rightarrow$ E2F1/pRB $\leftrightarrow$ p53/Mdm2 involved in cell-cycle arrest

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     $\longrightarrow$ increase stochasticity of response

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3. Propose new experiments to check mathematical model
   - iterate the **Experiment-Model-Experiment** loop

Collaborators: Heinz Engl, Philipp Kuegler, Rainer Machné, Stefan Mueller, Peter Schuster

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