Inverse Methods in Systems Biology

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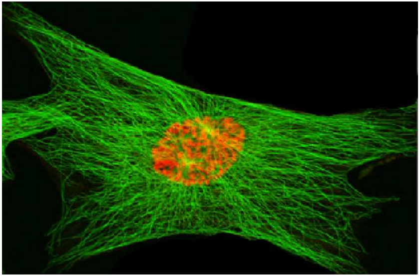
Systems Biology

- Cells are complex systems



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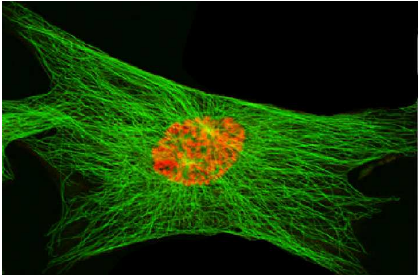

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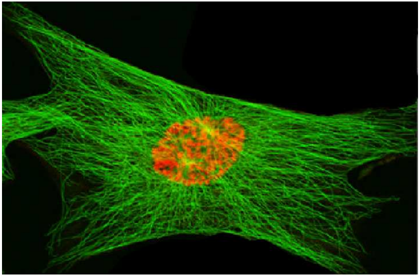
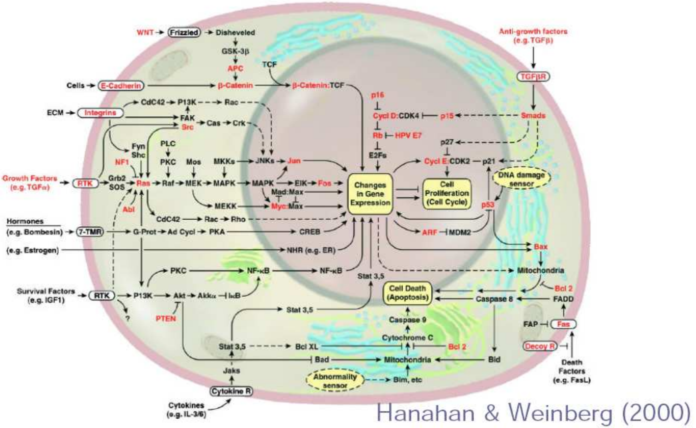


- In the face of continuously changing environments and its state, cells need to respond appropriately:
  - inputs: nutrients, repellants, heat shock, DNA damage, ...
  - responses: movement, growth, protein production, death

Systems Biology

- Complex networks of genes and pathways are involved in mediating the various inputs to the appropriate responses



Signal transduction network: Hanahan and Weinberg, *Cell* (2000)

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- The Forward analysis may include:
  - numerical integration for a set of given parameters
  - sensitivity analysis
  - bifurcation analysis

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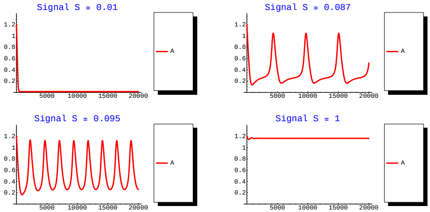

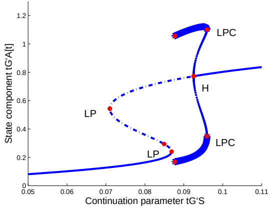

Inverse Problems

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- To numerically tackle inverse problems, *regularization strategies* are needed

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- For biological problems, usually want to find solutions that are *sparse*, i.e., having as few non-zero entries as possible: Ockam's razor

Sparsity-Promoting Regularization

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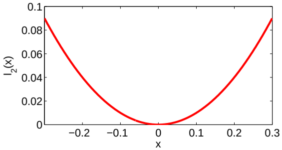

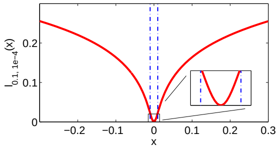

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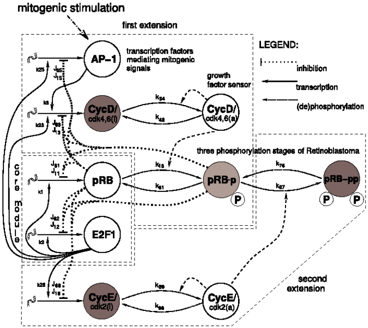
- Recent applications of sparse solutions using non-convex penalty:
  - *Exact reconstruction of sparse signals via nonconvex minimization*, R. Chartrand (2007)
  - Compressive sensing using l_1 re-weighting, E. Candes, S. P. Boyd, M. Wakin *et al.* (2007)
  - *Log-det heuristic for matrix rank minimization with applications to Hankel and Euclidean distance matrices*, M. Fazel, H. Hindi and S. P Boyd (2003)

Inverse Bifurcation: the G_1/S module of cell cycle



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

Inverse Bifurcation: the G_1/S module of cell cycle

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{pRB}] = k_1 \frac{[\mathrm{E2F1}]}{K_{m1} + [\mathrm{E2F1}]} \frac{J_{11}}{J_{11} + [\mathrm{pRB}]} \frac{J_{61}}{J_{61} + [\mathrm{pRB}_p]} - k_{16}[\mathrm{pRB}][\mathrm{CycD}_a] + k_{61}[\mathrm{pRB}_p] - \phi_{\mathrm{pRB}}[\mathrm{pRB}].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{E2F1}] = k_p + k_2 \frac{a^2 + [\mathrm{E2F1}]^2}{K_{m2}^2 + [\mathrm{E2F1}]^2} \frac{J_{12}}{J_{12} + [\mathrm{pRB}]} \times \frac{J_{62}}{J_{62} + [\mathrm{pRB}_p]} - \phi_{\mathrm{E2F1}}[\mathrm{E2F1}].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{CycD}_i] = k_3[\mathrm{AP\text{-}1}] + k_{23}[\mathrm{E2F1}] \frac{J_{13}}{J_{13} + [\mathrm{pRB}]} \times \frac{J_{63}}{J_{63} + [\mathrm{pRB}_p]} + k_{43}[\mathrm{CycD}_a] - k_{34}[\mathrm{CycD}_i] \frac{[\mathrm{CycD}_a]}{K_{m4} + [\mathrm{CycD}_a]} - \phi_{\mathrm{CycD}_i}[\mathrm{CycD}_i].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{CycD}_a] = k_{34}[\mathrm{CycD}_i] \frac{[\mathrm{CycD}_a]}{K_{m4} + [\mathrm{CycD}_a]} - k_{43}[\mathrm{CycD}_a] - \phi_{\mathrm{CycD}_a}[\mathrm{CycD}_a].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{AP\text{-}1}] = F_m + k_{25}[\mathrm{E2F1}] \frac{J_{15}}{J_{15} + [\mathrm{pRB}]} \frac{J_{65}}{J_{65} + [\mathrm{pRB}_p]} - \phi_{\mathrm{AP\text{-}1}}[\mathrm{AP\text{-}1}].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{pRB}_p] = k_{16}[\mathrm{pRB}][\mathrm{CycD}_a] - k_{61}[\mathrm{pRB}_p] - k_{67}[\mathrm{pRB}_p][\mathrm{CycE}_a] + k_{76}[\mathrm{pRB}_{pp}] - \phi_{\mathrm{pRB}_p}[\mathrm{pRB}_p].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{pRB}_{pp}] = k_{67}[\mathrm{pRB}_p][\mathrm{CycE}_a] - k_{76}[\mathrm{pRB}_{pp}] - \phi_{\mathrm{pRB}_{pp}}[\mathrm{pRB}_{pp}].$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{CycE}_i] = k_{28}[\mathrm{E2F1}] \frac{J_{18}}{J_{18} + [\mathrm{pRB}]} \frac{J_{68}}{J_{68} + [\mathrm{pRB}_p]} + k_{98}[\mathrm{CycE}_a] - k_{89}[\mathrm{CycE}_i] \frac{[\mathrm{CycE}_a]}{K_{m9} + [\mathrm{CycE}_a]} - \phi_{\mathrm{CycE}_i}[\mathrm{CycE}_i].$$

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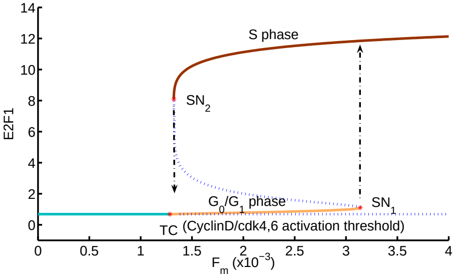

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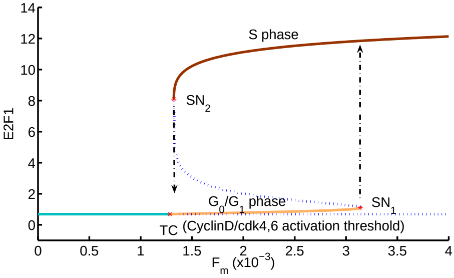

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- Which of the interactions play important roles in controlling the geometry of the bifurcation diagram?

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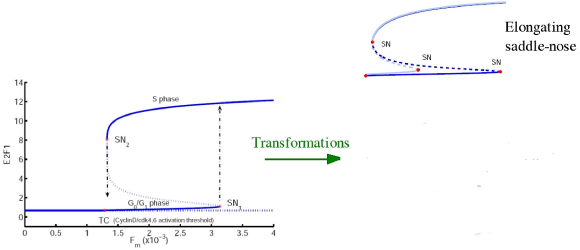

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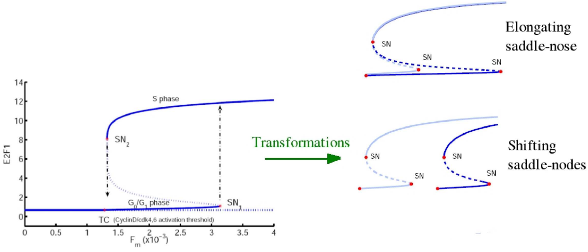

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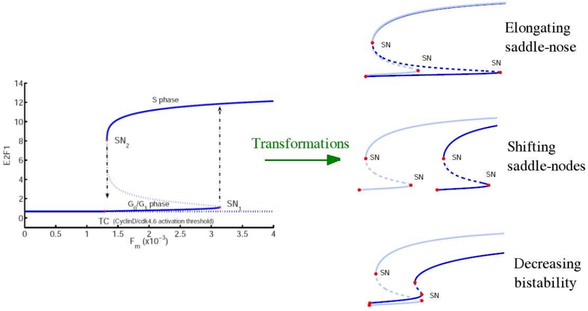

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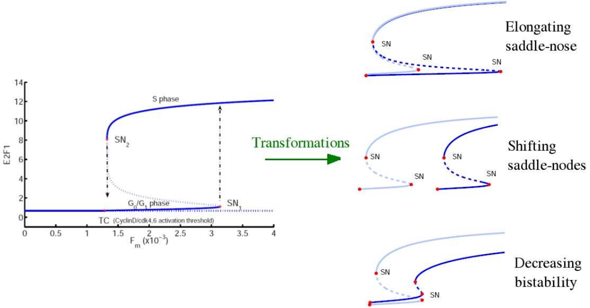
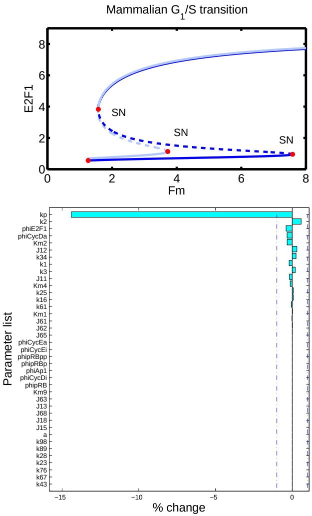


- Inverse bifurcation problem: from conditions on bifurcation diagrams, infer the governing mechanisms

Inverse Bifurcation: effect of sparsity-promiting penalty



(a) $l_{0.1,10^{-4}}$ regularization

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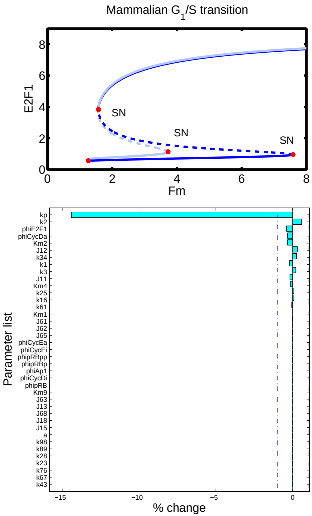

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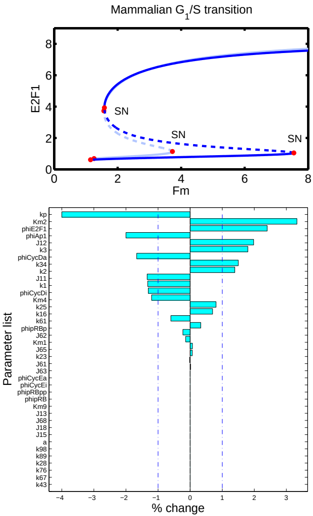

(c) l_2 regularization

Inverse Bifurcation: identified module

Table: Result of hierarchical algorithm with $p = 0.1, \varepsilon = 10^{-4}$

Modification Case	Level $j = 1$	Level $j = 2$	Level $j = 3$
Elongating SN_1 nose	$k_p \downarrow 14.3\%$	$k_{34} \uparrow 31.7\%$ $K_{m2} \uparrow 6.4\%$	$\phi_{\text{AP-1}} \downarrow 20.9\%$ $\phi_{\text{E2F1}} \uparrow 7.3\%$
Moving $SN_{1,2}$ to right	$K_{m4} \uparrow 269.3\%$	$J_{11} \uparrow 191.7\%$ $k_p \uparrow 17.3\%$	$k_2 \downarrow 39.9\%$ $\phi_{\text{E2F1}} \downarrow 11.7\%$ $K_{m2} \downarrow 10.3\%$
Decreasing bistabiliy	$J_{11} \uparrow 128.5\%$ $k_p \uparrow 33.8\%$	$k_1 \uparrow 169.1\%$ $K_{m2} \downarrow 21.7\%$ $J_{12} \downarrow 20.1\%$	$k_2 \downarrow 43.7\%$ $\phi_{\text{E2F1}} \downarrow 28.3\%$

Inverse Bifurcation: identified module

$$
\begin{aligned}
\frac{d}{dt}[\mathrm{pRB}] &= k_1 \frac{[\mathrm{E2F1}]}{K_{m1}+[\mathrm{E2F1}]} \frac{J_{11}}{J_{11}+[\mathrm{pRB}]} \frac{J_{61}}{J_{61}+[\mathrm{pRB}_p]} \\
&- k_{16}[\mathrm{pRB}][\mathrm{CycD}_a] + k_{61}[\mathrm{pRB}_p] - \phi_{\mathrm{pRB}}[\mathrm{pRB}], \\
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\end{aligned}
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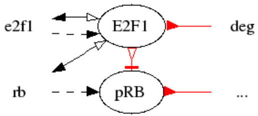

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\frac{d}{dt}[\mathrm{CycD}_i] &= -k_{34}[\mathrm{CycD}_i]\frac{[\mathrm{CycD}_a]}{K_{m4}+[\mathrm{CycD}_a]} + \cdots \\
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Application: Circadian Rhythm Model

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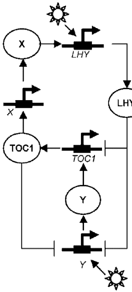
- Circadian model for *Arabidopsis thaliana* proposed by Locke et al, *Molecular Systems Biology* (2005)



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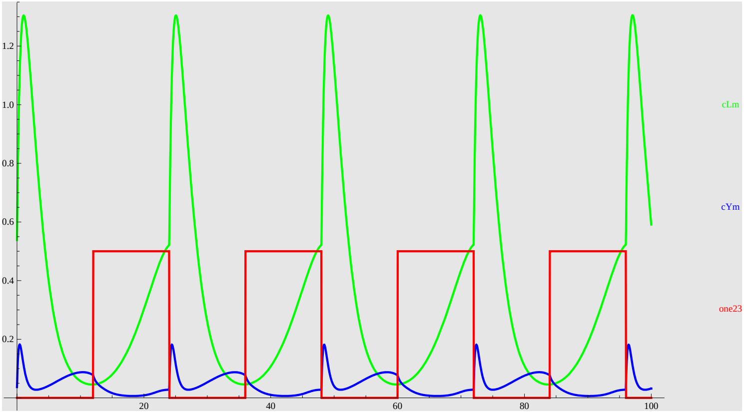
$$
\begin{aligned}
&\mathrm{cLc}'[t] == -r1\,\mathrm{cLc}[t] - \frac{m2\,\mathrm{cLc}[t]}{k2+\mathrm{cLc}[t]} + p1\,\mathrm{cLm}[t] + r2\,\mathrm{cLn}[t]\\
&\mathrm{cLm}'[t] == -\frac{m1\,\mathrm{cLm}[t]}{k1+\mathrm{cLm}[t]} + \frac{n1\,\mathrm{cXn}[t]^{a}}{g1^{a}+\mathrm{cXn}[t]^{a}} + q1\,\mathrm{cPn}[t]\,\mathrm{LD}[t, \mathrm{dayLength}]\\
&\mathrm{cLn}'[t] == r1\,\mathrm{cLc}[t] - r2\,\mathrm{cLn}[t] - \frac{m3\,\mathrm{cLn}[t]}{k3+\mathrm{cLn}[t]}\\
&\mathrm{cPn}'[t] == -\frac{m15\,\mathrm{cPn}[t]}{k13+\mathrm{cPn}[t]} + p5\,(1-\mathrm{LD}[t, \mathrm{dayLength}]) - q3\,\mathrm{cPn}[t]\,\mathrm{LD}[t, \mathrm{dayLength}]\\
&\mathrm{cTc}'[t] == -r3\,\mathrm{cTc}[t] + p2\,\mathrm{cTm}[t] + r4\,\mathrm{cTn}[t] - \frac{\mathrm{cTc}[t]\,(m6+m5\,(1-\mathrm{LD}[t,\mathrm{dayLength}]))}{k5+\mathrm{cTc}[t]}\\
&\mathrm{cTm}'[t] == -\frac{m4\,\mathrm{cTm}[t]}{k4+\mathrm{cTm}[t]} + \frac{g3^{c}\,n2\,\mathrm{cYn}[t]^{b}}{(g3^{c}+\mathrm{cLn}[t]^{c})\,(g2^{b}+\mathrm{cYn}[t]^{b})}\\
&\mathrm{cTn}'[t] == r3\,\mathrm{cTc}[t] - r4\,\mathrm{cTn}[t] - \frac{\mathrm{cTn}[t]\,(m8+m7\,(1-\mathrm{LD}[t,\mathrm{dayLength}]))}{k6+\mathrm{cTn}[t]}\\
&\mathrm{cXc}'[t] == -r5\,\mathrm{cXc}[t] - \frac{m10\,\mathrm{cXc}[t]}{k8+\mathrm{cXc}[t]} + p3\,\mathrm{cXm}[t] + r6\,\mathrm{cXn}[t]\\
&\mathrm{cXm}'[t] == \frac{n3\,\mathrm{cTn}[t]^{d}}{g4^{d}+\mathrm{cTn}[t]^{d}} - \frac{m9\,\mathrm{cXm}[t]}{k7+\mathrm{cXm}[t]}\\
&\mathrm{cXn}'[t] == r5\,\mathrm{cXc}[t] - r6\,\mathrm{cXn}[t] - \frac{m11\,\mathrm{cXn}[t]}{k9+\mathrm{cXn}[t]}\\
&\mathrm{cYc}'[t] == -r7\,\mathrm{cYc}[t] - \frac{m13\,\mathrm{cYc}[t]}{k11+\mathrm{cYc}[t]} + p4\,\mathrm{cYm}[t] + r8\,\mathrm{cYn}[t]\\
&\mathrm{cYm}'[t] == -\frac{m12\,\mathrm{cYm}[t]}{k10+\mathrm{cYm}[t]} + \frac{g6^{f}\left(q2\,\mathrm{cPn}[t]\,\mathrm{LD}[t,\mathrm{dayLength}] + \frac{g5^{e}\,(n5+n4\,\mathrm{LD}[t,\mathrm{dayLength}])}{g5^{e}+\mathrm{cTn}[t]^{e}}\right)}{g6^{f}+\mathrm{cLn}[t]^{f}}\\
&\mathrm{cYn}'[t] == r7\,\mathrm{cYc}[t] - r8\,\mathrm{cYn}[t] - \frac{m14\,\mathrm{cYn}[t]}{k12+\mathrm{cYn}[t]}
\end{aligned}
$$

ODE system

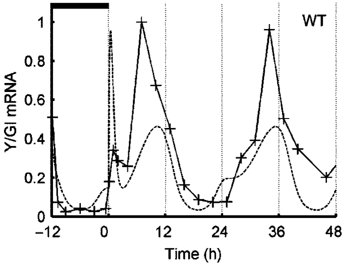
Application: Circadian Rhythm Model

- Simulation of model with nominal parameters under 12 hr light-dark cycle



Application: Circadian Rhythm Model

- Evidence suggests GIGANTEA could be gene Y



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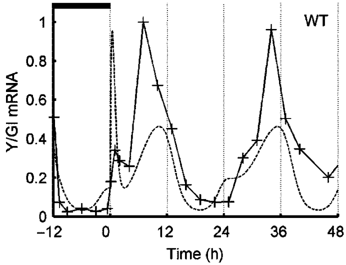

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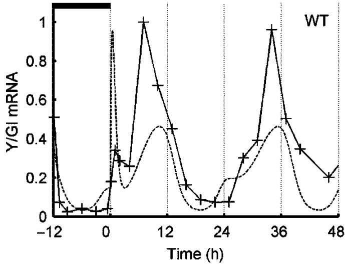

Phase misfit with experimental data

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- Inverse problem: vary parameters so that Y mRNA peaks at ZT7 rather than ZT11

Application: Circadian Rhythm Model

- The peak time $\hat{t}$ for the level of Y mRNA, satisfies

$$\begin{aligned} \dot{y}(t) &= f(y,q) \\ f_{YmRNA}(y(\hat{t}),q) &= 0 \end{aligned}$$

Application: Circadian Rhythm Model

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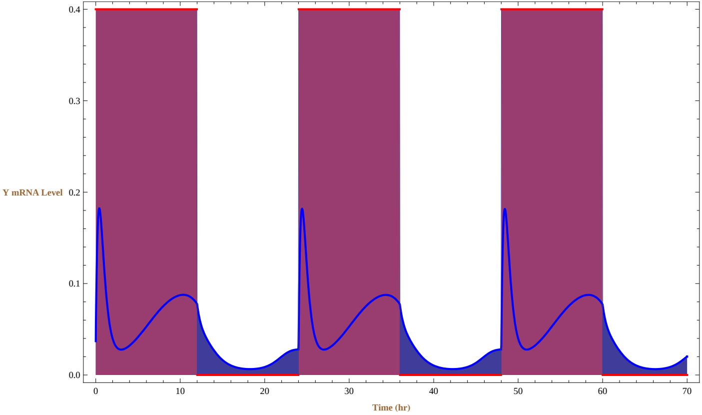
- Minimization of the objective:

$$\|\hat{t}(q) - \hat{t}^*\|^2 + \mu l_{p,\varepsilon}(q - q^*) \to \min_q$$

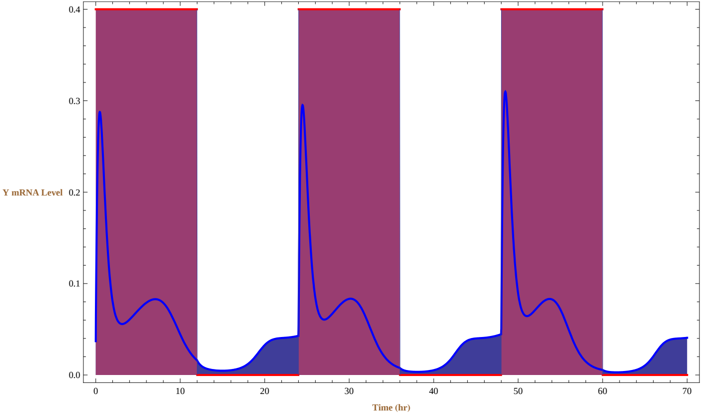
Application: Circadian Rhythm Model

- Y mRNA solution profile for the original parameter set

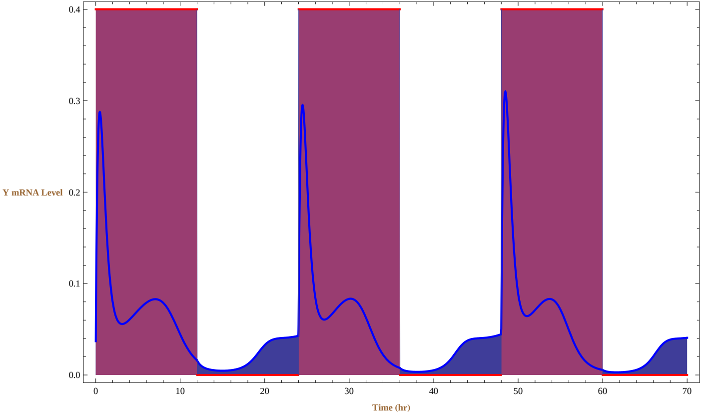


Application: Circadian Rhythm Model

- Y mRNA solution profile for the identified parameter set



- Y mRNA solution profile for the identified parameter set
- 1 out of 54 parameters is identified



Application: Circadian Rhythm Model

- Identified parameter: g6, Hill-constant in repression of gene Y by LHY

$$cLc'[t] == -r1\, cLc[t] - \frac{m2\, cLc[t]}{k2+cLc[t]} + p1\, cLm[t] + r2\, cLn[t]$$

$$cLm'[t] == -\frac{m1\, cLm[t]}{k1+cLm[t]} + \frac{n1\, cXn[t]^{a}}{g1^{a}+cXn[t]^{a}} + q1\, cPn[t]\, LD[t, dayLength]$$

$$cLn'[t] == r1\, cLc[t] - r2\, cLn[t] - \frac{m3\, cLn[t]}{k3+cLn[t]}$$

$$cPn'[t] == -\frac{m15\, cPn[t]}{k13+cPn[t]} + p5\,(1 - LD[t, dayLength]) - q3\, cPn[t]\, LD[t, dayLength]$$

$$cTc'[t] == -r3\, cTc[t] + p2\, cTm[t] + r4\, cTn[t] - \frac{cTc[t]\,(m6+m5\,(1-LD[t,dayLength]))}{k5+cTc[t]}$$

$$cTm'[t] == -\frac{m4\, cTm[t]}{k4+cTm[t]} + \frac{g3^{c}\, n2\, cYn[t]^{b}}{(g3^{c}+cLn[t]^{c})\,(g2^{b}+cYn[t]^{b})}$$

$$cTn'[t] == r3\, cTc[t] - r4\, cTn[t] - \frac{cTn[t]\,(m8+m7\,(1-LD[t,dayLength]))}{k6+cTn[t]}$$

$$cXc'[t] == -r5\, cXc[t] - \frac{m10\, cXc[t]}{k8+cXc[t]} + p3\, cXm[t] + r6\, cXn[t]$$

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- Infer mechanisms governing the spectrum of the dynamical system: *inverse eigenvalue problems*

Inverse Eigenvalue Problems

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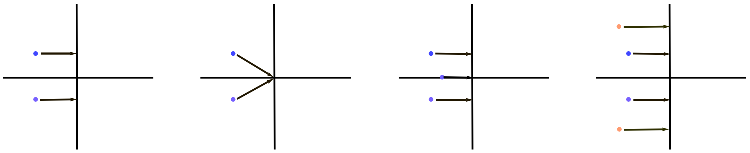
- For the dynamical system $\dot{y}(t) = f(y,q)$, many bifurcations of equilibrium correspond to various conditions on eigenvalues of $\frac{df(y,q)}{dy}$
- Inverse eigenvalue problems: identify the possible model mechanisms bringing about the desired change in the spectrum



(d) Hopf (e) BT (f) Fold-Hopf (g) Hopf-Hopf

Inverse Eigenvalue Problems

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$$
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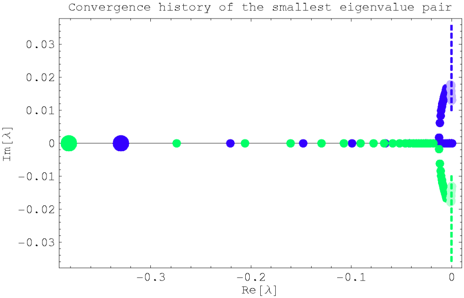

Transition of a Bistable Switch to an Oscillator

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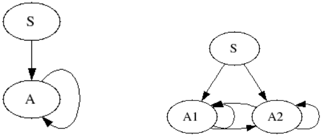

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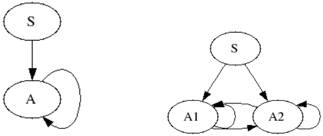
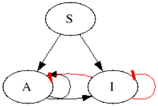


- Subsequent loss of the activating domain



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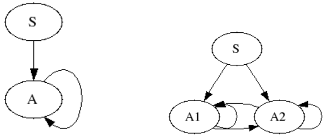

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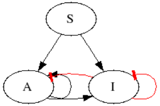
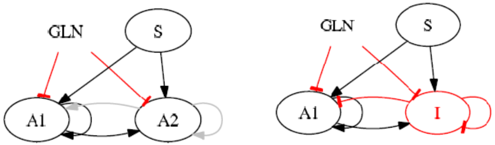


- Can oscillations emerge via a few additional mutations?

Transition of a Bistable Switch to an Oscillator

- Evolutionary scenario



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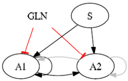

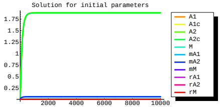

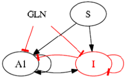

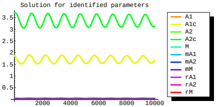

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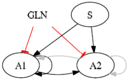
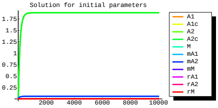
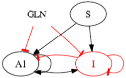
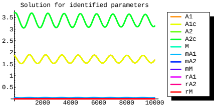
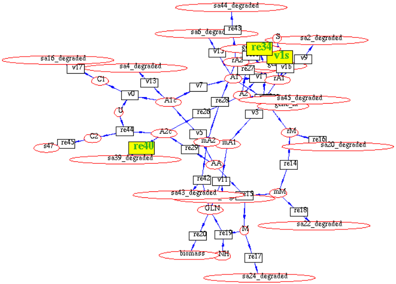








- Identified reactions:



$$A1`v1s[t] == \frac{A1`s\, A1`Va1\_S_{\,0.04\to 0.011}}{A1`S + A1`Ka1\_S[t]}$$

$$A1`re34[t] == \frac{A1`s\, A1`Va2\_S_{\,0.04\to 0.001}}{A1`S + A1`Ka2\_S[t]}$$

$$A1`re40[t] == 24\, A1`A2c[t]\; A1`D\_A2c_{\,0.03\to 0.0046}$$

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- Sparsity-promoting regularization can be effective in drawing useful insights from biological models

Acknowledgements

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University of Vienna: Peter Schuster, Christoph Flamm, Rainer Machné
Keio University: Douglas Murray

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