

Modelling the Dynamics of Cell Networks using Inverse Methods

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Inverse Problems in Cell Biology

Inverse Problems is a field of applied mathematics where one looks for causes of **observed** or **desired** effects [1]. Mathematically, inverse problems may be formulated in terms of operator equations of the form: determine $p \in P$ from $y \in Y$, such that

$$F(p) = y,$$

where $F : P \rightarrow Y$ is a (in general, nonlinear) parameter-to-output map acting between Hilbert spaces P and Y . Such problems are typically ill-posed and hence regularization techniques have to be developed [1].

For many problems in cellular control, systems of first-order ordinary differential equations (ODEs) can adequately model the underlying processes. Denoting by x and p the biochemical concentrations and parameters, respectively, the instantaneous change in x is described by the vector field f :

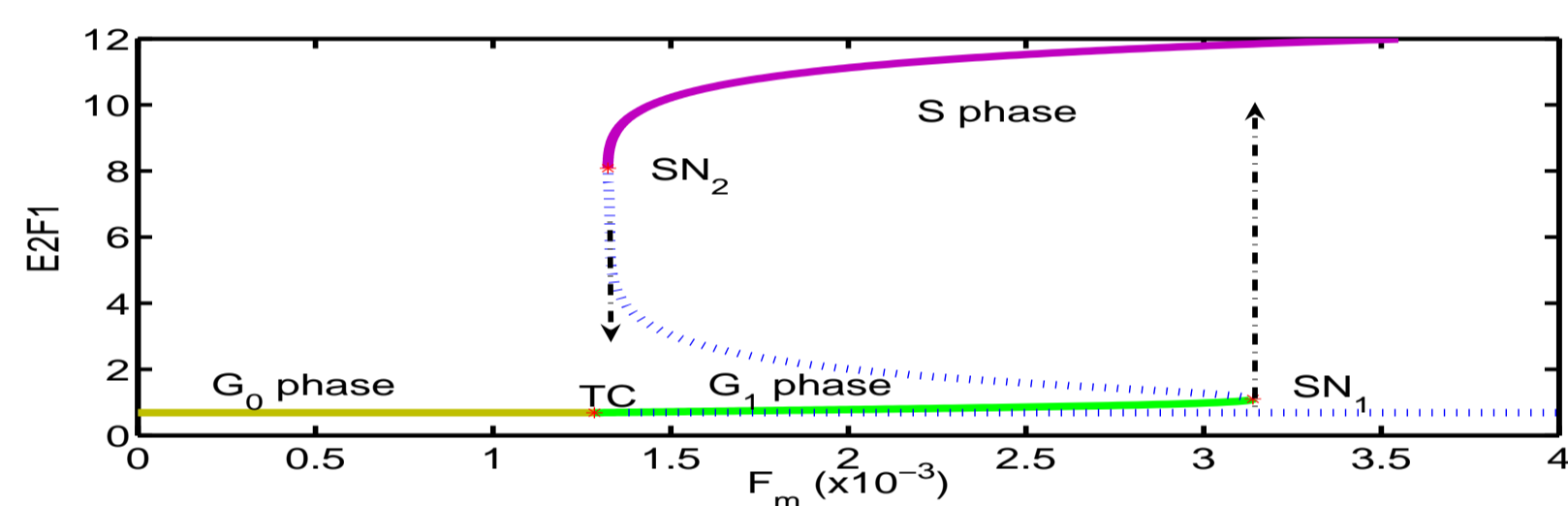
$$\dot{x} = f(x, p).$$

Inverse problems at the *first level* include **parameter and network identification**: what mathematical models and parameters can give rise to the quantitative observed system behavior? What is the topology of the network involved in a given regulatory process? Mathematically, appropriate regularization techniques involving **sparsity**, as well as **hierarchical** approaches may need to be developed.

At the *second level*, one would like to address problems of biological **reverse engineering**: what underlies the **qualitative properties** of the observed gene system, the **biochemical parameters** or **network topology**? How to genetically engineer qualitative behavior into the gene system via parameter variations? These problems may be studied via the (inverse) mapping from the space of bifurcation diagrams to the space of parameters.

Forward Bifurcation Analysis

The forward bifurcation analysis maps **parameter values** \rightarrow **bifurcation diagram**. Via the bifurcation diagram, the parameter space is partitioned into "qualitatively different" regions. Bifurcation analysis has been applied to provide an understanding into a wide variety of gene regulatory networks, including cell cycle, circadian rhythm and metabolic switches.



Bifurcation diagram of a genetic switch model for cell cycle [6]

Inverse Bifurcation Analysis

The inverse bifurcation analysis maps **geometric properties of bifurcation diagrams** \rightarrow **parameters**. For biological applications arising in homeostasis and genetic switches, the geometric condition of principal interests is the **distance to bifurcation manifold**. Consider the splitting of m -dimensional parameter space $P \subset \mathbb{R}^m$ into input and system parameters, $p = (p_i, p_s) \in P_i \times P_s$. Let the *forward operator* $F : P \rightarrow P$ be a mapping in parameter space, taking a given point to its orthogonal projection on the bifurcation manifold, $\Sigma(p_s)$. That is,

$$F(p) = (\mathbb{P}_{\Sigma(p_s)} p_i, p_s).$$

Using $F(p)$, inverse bifurcation can be formulated as the constrained optimization problem:

$$\begin{aligned} \min_{p_s} J(p) &= \|F(p)_i - p_i\| \\ \text{subject to: } & p_{\text{low}} \leq p \leq p_{\text{upp}} \\ & 0 \leq c(F(p)_i), \end{aligned}$$

where $\|\cdot\|$ denotes the l_2 -norm and $c : P_i \rightarrow \mathbb{R}^k$ represents k -dimensional nonlinear constraints. With the right and left eigensystems of the Jacobian for the vector field $f(x, p)$ denoted as $f_x v = \omega_{\text{crit}} v$, $f_x^T w = \bar{\omega}_{\text{crit}} w$, the expressions for **adjoint solution** in the case of saddle-node and Hopf bifurcations are given by:

$$\begin{aligned} \text{Saddle - node : } & w^H f_p, \\ \text{Hopf : } & \text{Re} \left\{ \frac{1}{w^H v} (w^H f_{xp} v - \lambda^H f_p) \right\}, \end{aligned}$$

where superscript H denotes conjugate transpose and $\lambda \equiv f_x^{-T}(w^H f_{xx} v)$.

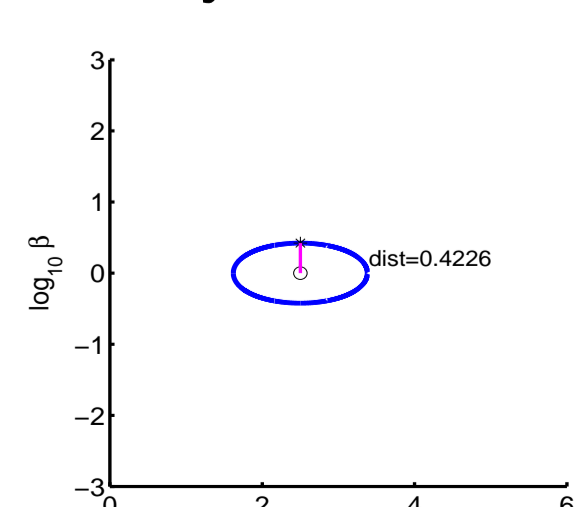
Example Applications

Maximizing Region of Oscillations in Repressilator

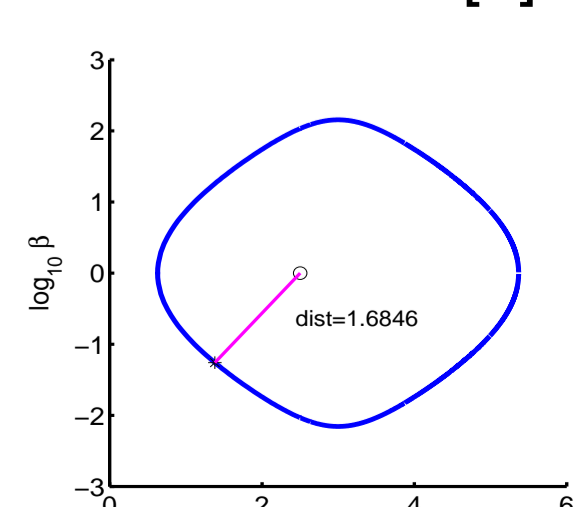
The ODE system for the protein and RNA concentrations x_i and y_i is given by [5]:

$$\begin{aligned} \dot{x}_i &= \beta(y_i - x_i) \\ \dot{y}_i &= \alpha \left(\frac{1 - \delta}{1 + x_{i-1 \bmod n}^h} + \delta \right) - y_i, \quad i = 0, \dots, 2, \end{aligned}$$

with the following dimensionless parameters: α the efficiency of gene expression, β the ratios of degradation rates, δ the leakiness of gene transcription, h the Hill-coefficient reflecting the degree of cooperativity of repressor binding. Using inverse analysis, the region of oscillations with respect to an operating point may be **maximized** under appropriate constraints [4].



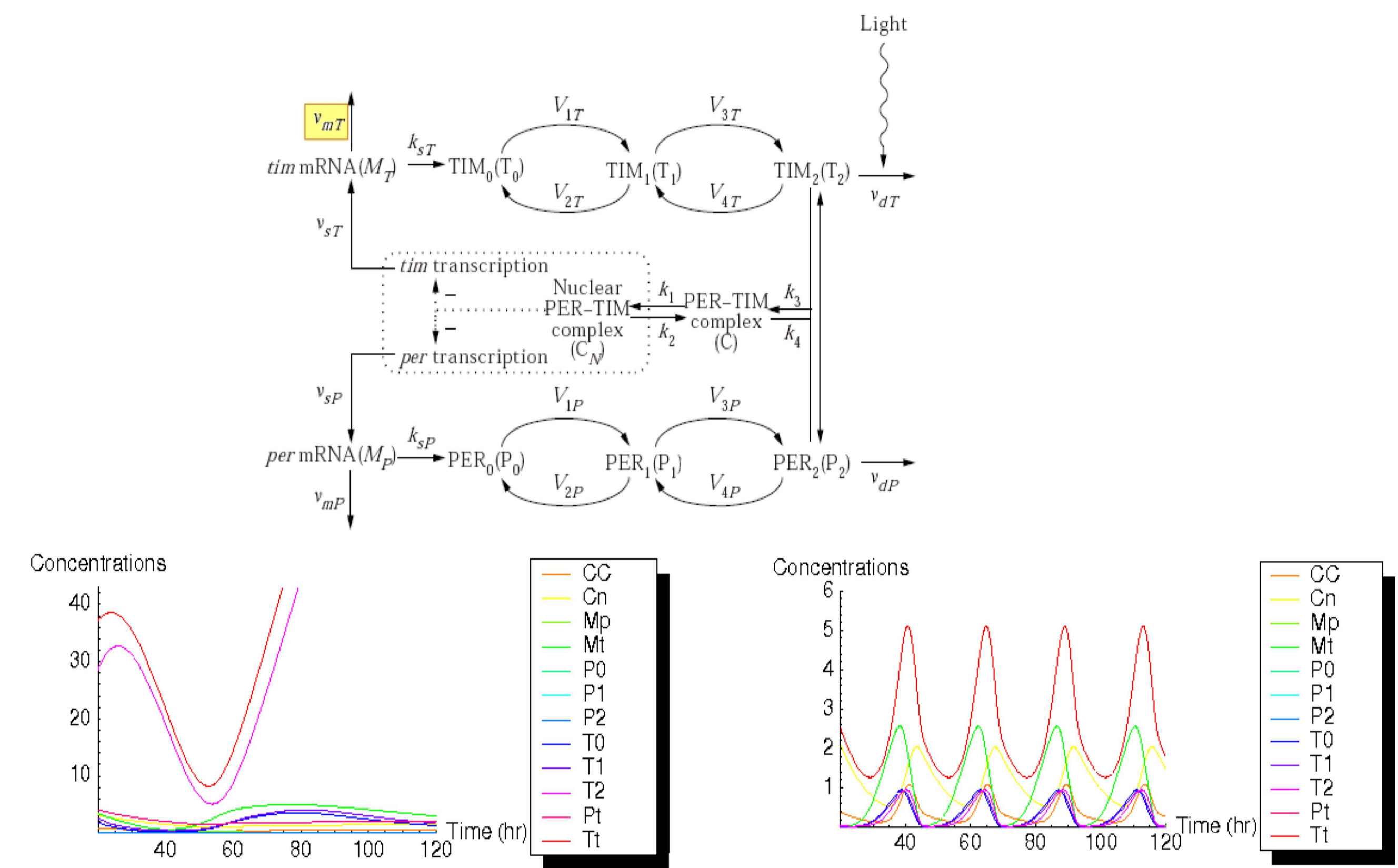
Initial bifurcation diagram:
 $\delta = 10^{-3}$, $h = 1.5$



Optimized bifurcation diagram:
 $\delta = 10^{-4}$, $h = 2$

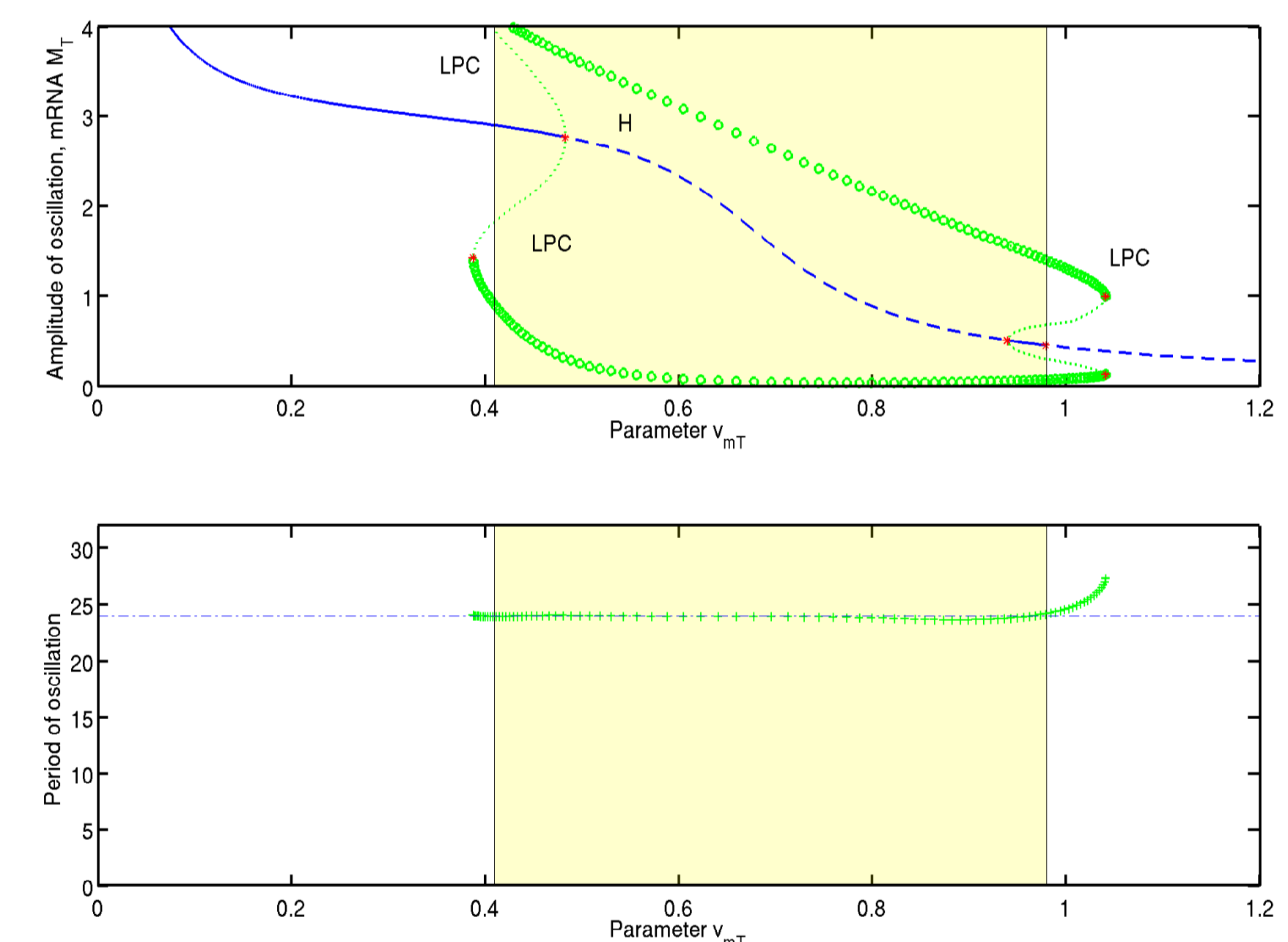
Constancy of Period in Circadian Rhythm

In the study of circadian rhythms an important biological question is how the **constancy of period** arises, with respect to variations in biochemical parameters and environmental factors such as temperature. The forward analysis entails the continuation and bifurcation of **limit cycles**, which may be formulated as boundary value problems on the unit circle [2]. Adjoint method for sensitivity analysis has been carried out to enable inverse analysis for the location of **limit point for cycles** (LPC) and **total variation** of period.

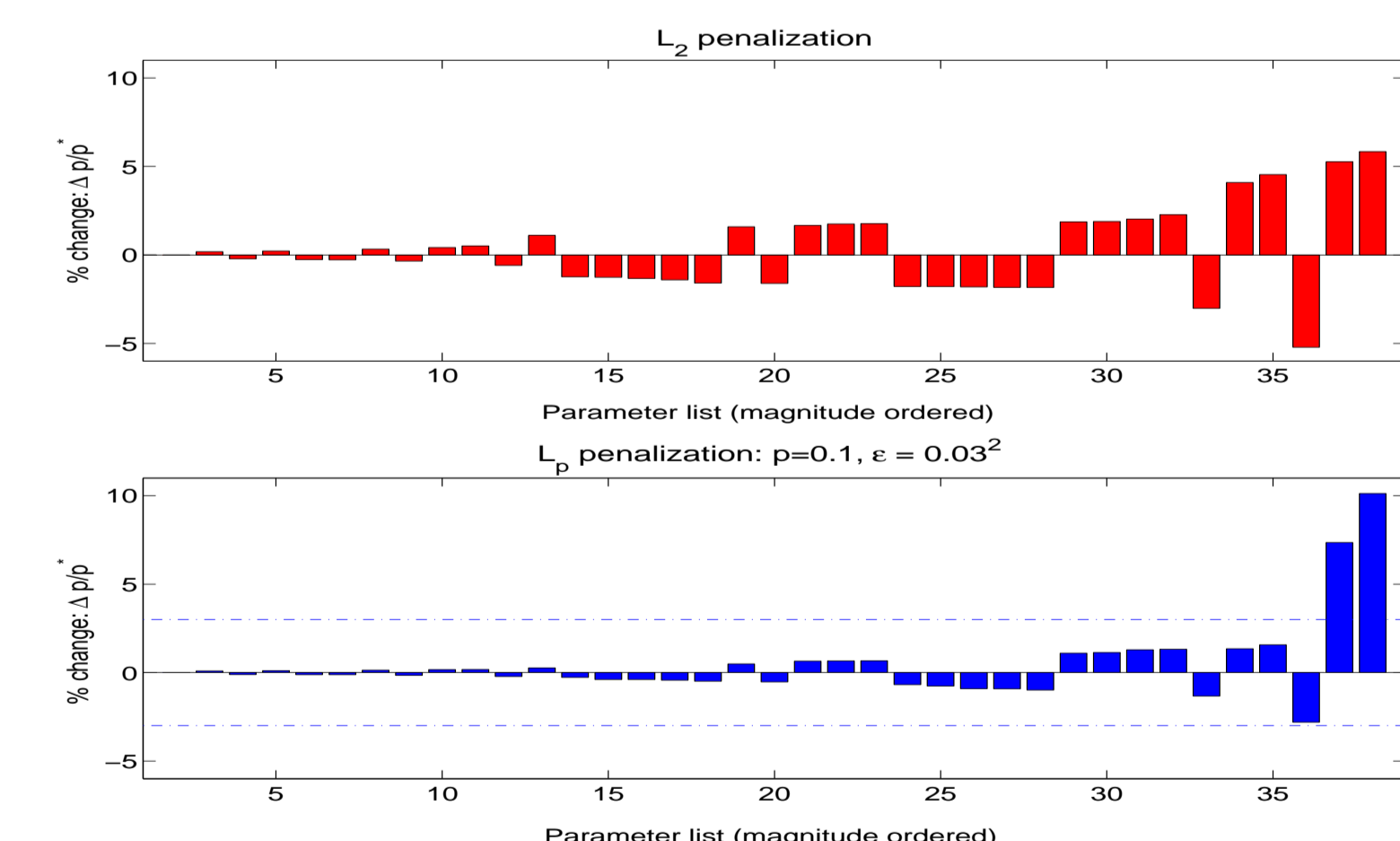


Circadian rhythm system (Leloup and Goldbeter [3]) and solutions for different values of parameter v_{mT}

When inverse bifurcation analysis is applied as a method for understanding *biological design principles* and *engineering* gene systems, the **sparsity of parameter change** may be a desirable property. Thus, penalty functionals involving l_p , $p \leq 1$, may be used as a way to obtain parameter solutions of small cardinality.



Result of inverse bifurcation for the constancy of oscillation period



Comparison of solutions obtained using l_2 and l_p penalty functionals

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