Inverse qualitative problems from computational design in synthetic biology

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Nottingham, March 2010

Overview

1. Space of Gene Circuits
2. Inverse Qualitative Problems
   - Dynamical systems and bifurcations
   - Sparsity Promoting Regularization
3. Numerical Examples
   - Minimal Oscillator
   - Modulated Oscillator
   - Phase Relationship

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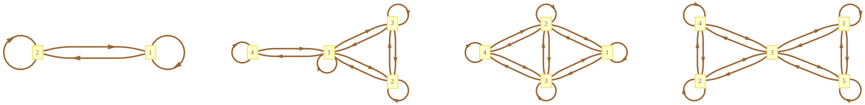
Space of Gene Circuits



Given a directed graph $G = (X, A)$, we consider the following space of regulatory networks:

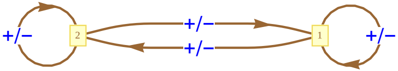
$$X(i)'(t) = \gamma(i) - \beta(i)X(i) + \alpha(i) \prod_{(j,i)\in A} 2^{\mathsf{nOn}(j,i)} \left(\frac{X(i)^{\mathsf{nH}(j,i)}}{(1 + X(j)^{2-\mathsf{nH}(j,i)})(1 + X(j)^{\mathsf{nH}(j,i)})} \right)^{\mathsf{nOn}(j,i)}$$

where

- $\mathsf{nOn}(j,i) \in [0,1]$: whether gene j affects the transcription of gene i
- $\mathsf{nH}(j,i) \in [0,2]$: whether gene j represses ($\mathsf{nH} = 0$) or activates ($\mathsf{nH} = 2$) gene i

Space of Gene Circuits

For instance, a two-dimensional network where each of the node is able to repress or activate itself as well as the other node:



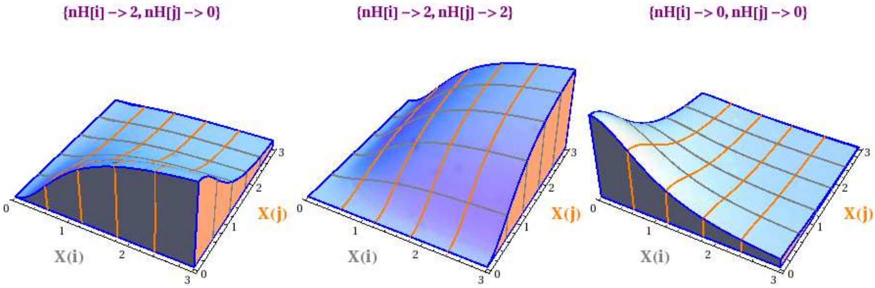
The ODE system is given by the following:

$$X(1)'(t) = \gamma(1) - \beta(1)X(1) + \alpha(1)2^{\mathsf{nOn}(1,1)+\mathsf{nOn}(2,1)} \times$$
$$\left(\frac{X(2)^{\mathsf{nH}(2,1)}}{\left(X(2)^{2-\mathsf{nH}(2,1)}+1\right)\left(X(2)^{\mathsf{nH}(2,1)}+1\right)}\right)^{\mathsf{nOn}(2,1)} \left(\frac{X(1)^{\mathsf{nH}(1,1)}}{\left(X(1)^{2-\mathsf{nH}(1,1)}+1\right)\left(X(1)^{\mathsf{nH}(1,1)}+1\right)}\right)^{\mathsf{nOn}(1,1)}$$

$$X(2)'(t) = \gamma(2) - \beta(2)X(2) + \alpha(2)2^{\mathsf{nOn}(1,2)+\mathsf{nOn}(2,2)} \times$$
$$\left(\frac{X(2)^{\mathsf{nH}(2,2)}}{\left(X(2)^{2-\mathsf{nH}(2,2)}+1\right)\left(X(2)^{\mathsf{nH}(2,2)}+1\right)}\right)^{\mathsf{nOn}(2,2)} \left(\frac{X(1)^{\mathsf{nH}(1,2)}}{\left(X(1)^{2-\mathsf{nH}(1,2)}+1\right)\left(X(1)^{\mathsf{nH}(1,2)}+1\right)}\right)^{\mathsf{nOn}(1,2)}$$

Regulation Functions

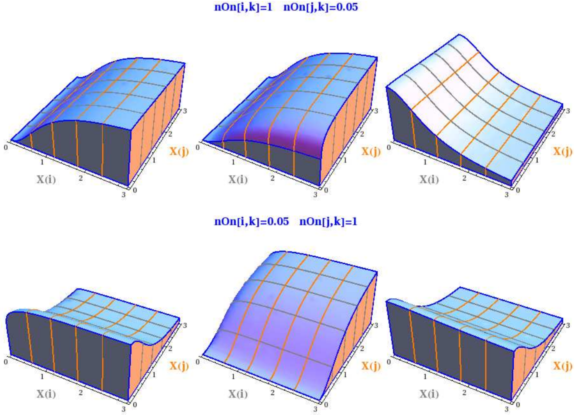
By choosing nH from 0 to 2, the regulation function goes from representing a repressor to activator:



$$\left(\frac{X(i)^{\mathsf{nH}(i)}}{\left(X(i)^{2-\mathsf{nH}(i)}+1\right)\left(X(i)^{\mathsf{nH}(i)}+1\right)}\right)\left(\frac{X(j)^{\mathsf{nH}(j)}}{\left(X(j)^{2-\mathsf{nH}(j)}+1\right)\left(X(i)^{\mathsf{nH}(i)}+1\right)}\right)$$

Regulation Functions

Regulation by TF i can be switched off setting $\mathsf{nOn}(i)$ close to 0:



$$\left(\frac{X(i)^{\mathsf{nH}(i)}}{\left(X(i)^{2-\mathsf{nH}(i)}+1\right)\left(X(i)^{\mathsf{nH}(i)}+1\right)}\right)^{\mathsf{nOn}(i)} \left(\frac{X(j)^{\mathsf{nH}(j)}}{\left(X(j)^{2-\mathsf{nH}(j)}+1\right)\left(X(i)^{\mathsf{nH}(i)}+1\right)}\right)^{\mathsf{nOn}(i)}$$

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Function of networks connected to their dynamical characteristics

We wish to design gene networks that exhibit the desired dynamical behaviors; e.g.,

- gene switches / oscillators
- networks that can transit between the types of dynamics
- oscillators: encoding multiple frequencies; genes turned on after a desired time difference

Sparse networks!

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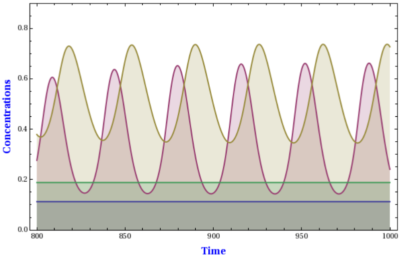
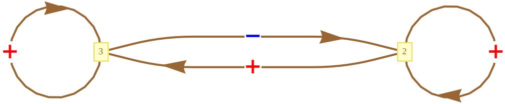
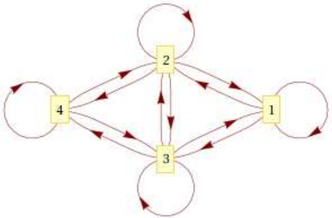




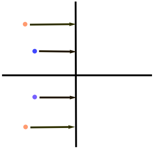
$$
\begin{aligned}
X(1)'(t) &= 0.11 - X(1)(t) \\
X(2)'(t) &= 1.56\left(\frac{(X(2)(t))^2}{(X(2)(t))^2+1}\right)^{0.54}\left(\frac{1}{(X(3)(t))^2+1}\right)^{0.83} - 1.082X(2)(t) \\
X(3)'(t) &= 1.26\left(\frac{(X(2)(t))^2}{(X(2)(t))^2+1}\right)^{0.07}\left(\frac{(X(3)(t))^2}{(X(3)(t))^2+1}\right)^{0.67} - 0.71X(3)(t) \\
X(4)'(t) &= 0.19 - X(4)(t)
\end{aligned}
$$

Modulated oscillation: Topology 1

Consider the following topology of gene interactions in a 4 gene network:

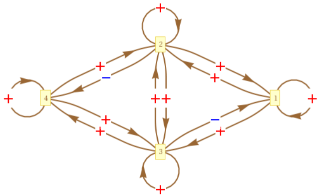


Can we find a network of repressors/activators, constrainted by the above network topology, that can give rise to modulated oscillations?
Find a Hopf-Hopf bifurcation:

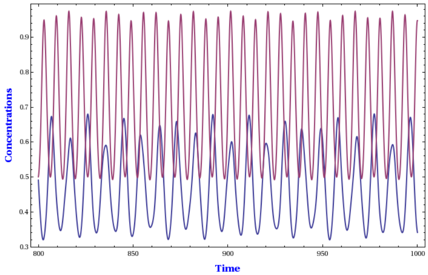


Modulated oscillation: Topology 1

Identified network of interactions:

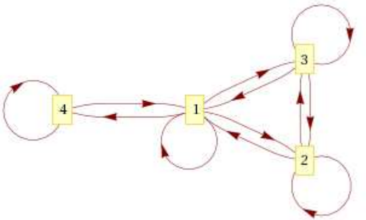


Solution behavior: genes 1 & 4

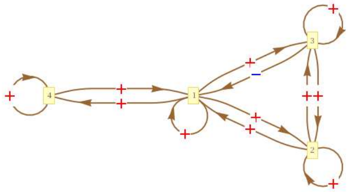


Modulated oscillation: Topology 2

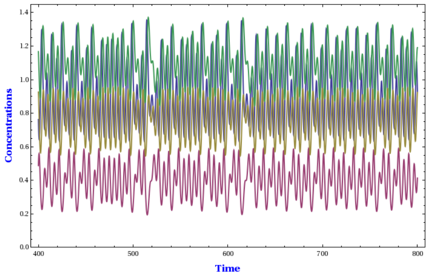
Consider an alternative topology:



Identified network of interactions:

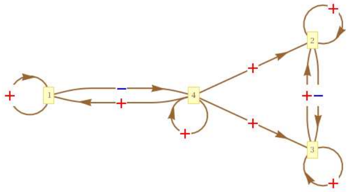


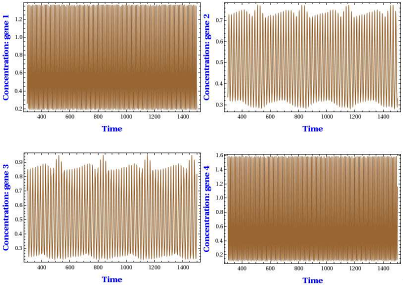
Solution behavior:



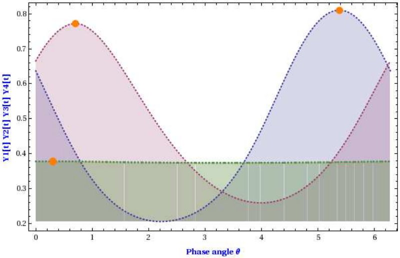
Modulated oscillation: Topology 2

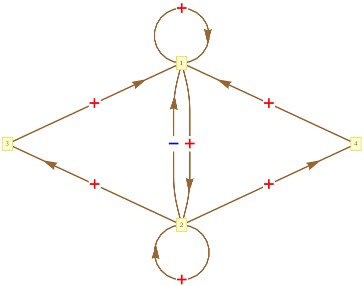
By choosing an appropriate range of frequencies, with the same topology one can get a slow oscillatory mode out of fast oscillations



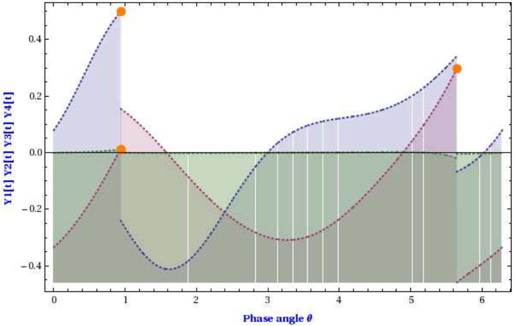


Phase in Limit Cycle Oscillator





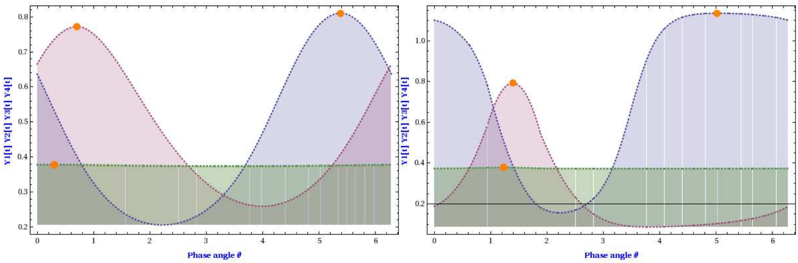
Adjoint Solution for Phase Difference

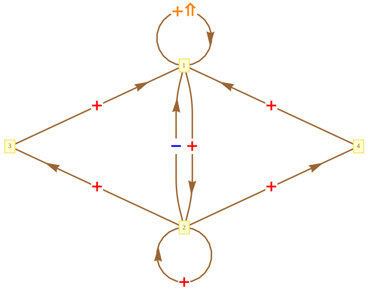


$$\dot{\psi}(t) = T \left[\frac{df}{dx}\right]^T \psi(t) + Sv(t), \;\; t \in [0,1],$$
$$\psi(\hat{t}_i^+) = \psi(\hat{t}_i^-) + g(x(\hat{t}_i), \alpha),$$

expression for the gradient: $T \int_{[0,1]} \psi(t) \cdot \frac{df}{d\alpha} dt$

Phase in Limit Cycle Oscillator





Acknowledgements

Funding provided by Vienna Science and Technology Fund (WWTF) is gratefully acknowledged

WWTF

Wiener Wissenschafts-, Forschungs- und Technologiefonds

Project Nr. MA07