Performance Limitations in Autocatalytic Pathways

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Fundamental Issue in Controlled Networks

Robustness

How do external disturbances propagate in large-scale dynamical networks?
Overview

- Networks with Autocatalytic Structure
- Minimal Autocatalytic Pathway Model
- Characterization of Hard Limits
  - Hard Limits on Disturbance Attenuation
  - Hard Limits on Output Energy
- Autocatalytic Pathways with Multiple Intermediate Metabolite Reactions
- Ongoing Work
Networks with Autocatalytic Structure

The network’s product (output) is necessary to power and catalyze its own production

**Ex.** Biological, engineered, economic networks

Autocatalytic feedbacks are

- Positive feedbacks
- Destabilizing
Motivating Examples: Glycolysis Pathway

Glycolysis pathway is a central energy producer in a living cell

Gly, G1P, G6P, F6P, F1-6BP, Gly3p, 13BPG, 3PG, 2PG, NADH, TCA, Oxa, Cit, ACA, Pyr, PEP
Motivating Examples: Glycolysis Pathway

Glycolysis pathway is a central energy producer in a living cell
Motivating Examples: Glycolysis Pathway

Glycolysis pathway is a central energy producer in a living cell.
Motivating Examples: Glycolysis Pathway

Glycolysis pathway is a central energy producer in a living cell.

Cell Consumption of ATP

Autocatalysis

Allosteric Regulation

Catalyzing Enzymes

ATP

Gly

G1P

G6P

F6P

F1-6BP

Gly3p

13BPG

3PG

2PG

PK

PEP

Pyruvate

Oxa

Cit

TCA
Motivating Examples: Glycolysis Pathway

Cell Consumption of ATP
Motivating Examples: Glycolysis Pathway

Cell Consumption of ATP

- F6P → F1-6BP → Gly3p → 13BPG → 3PG
- ATP

PFK

PK
A minimal Autocatalytic Pathway Model

Cell Consumption of ATP

\[ s + qy \xrightarrow{PFK} x \xrightarrow{PK} (q + 1)y + x' \]

\[ y \xrightarrow{Consumption} \emptyset \]
A minimal Autocatalytic Pathway Model

Equilibrium point:

\[ x^* = \frac{1}{k} \quad \text{and} \quad y^* = 1 \]

\[
\begin{bmatrix}
\dot{x} \\
\dot{y}
\end{bmatrix}
= \begin{bmatrix}
1 & 2 \\
-q & 1 + y^{2h}
\end{bmatrix} + \begin{bmatrix}
-1 & 2kx \\
q + 1 & 1 + y^{2g}
\end{bmatrix} - \begin{bmatrix}
0 \\
1 + \delta
\end{bmatrix}
\]

PFK

PK

Consumptions
A minimal Autocatalytic Pathway Model

\[
\begin{bmatrix}
\dot{x} \\
\dot{y}
\end{bmatrix} = 
\begin{bmatrix}
1 \\
-q
\end{bmatrix} y^a \frac{2}{1 + y^{2h}} + 
\begin{bmatrix}
-1 \\
q + 1
\end{bmatrix} \frac{2kx}{1 + y^{2g}} - 
\begin{bmatrix}
0 \\
1 + \delta
\end{bmatrix}
\]

PFK
PK
Consumptions
A minimal Autocatalytic Pathway Model

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\begin{bmatrix}
0 \\
1 + \delta
\end{bmatrix}
\]

Feedback designed by Nature

Feedback designed by Nature
A minimal Autocatalytic Pathway Model

\[
\begin{bmatrix}
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\dot{y}
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-q
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-1 \\
q + 1
\end{bmatrix} \frac{2kx}{1 + y^{2g}} - \begin{bmatrix}
0 \\
1 + \delta
\end{bmatrix}
\]

- PFK
- PK
- Consumptions
Previous Works

Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,1* Gentian Buzi,2 John C. Doyle2

Both engineering and evolution are constrained by trade-offs between efficiency and robustness, but theory that formalizes this fact is limited. For a simple two-state model of glycolysis, we explicitly derive analytic equations for hard trade-offs between robustness and efficiency with oscillations as an inevitable side effect. The model describes how the trade-offs arise from individual parameters, including the interplay of feedback control with autocatalysis of network products necessary to power and catalyze intermediate reactions. We then use control theory to prove that the essential features of these hard trade-off “laws” are universal and fundamental, in that they depend minimally on the details of this system and generalize to the robust efficiency of any autocatalytic network. The theory also suggests worst-case conditions that are consistent with initial experiments.
Previous Works

Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,¹* Gentian Buzi,² John C. Doyle²

Both engineering science and biology have observed that cellular metabolism is characterized by the presence of oscillations in the concentration of key metabolites, and that these oscillations are driven by the interplay of positive and negative feedback loops. For example, oscillations in the concentration of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) are known to be a key feature of glycolysis, which is the first step in glucose metabolism. The authors of this paper use a linearized two-state model of glycolysis pathway to explore the robustness of these oscillations. They find that the presence of a single negative feedback loop is sufficient to stabilize the oscillations, and that the period of the oscillations is determined by the rate constants of the feedback loop. The authors also show that the oscillations can be perturbed by changes in the rate constants, and that the system is robust to these perturbations. The implications of these findings for the design of synthetic biological oscillators are discussed.
Previous Works

Linearized Model:

\[
\begin{bmatrix}
\Delta \dot{x} \\
\Delta \dot{y}
\end{bmatrix}
= \begin{bmatrix}
-k & a + g \\
(q + 1)k & -qa - g(q + 1)
\end{bmatrix}
\begin{bmatrix}
\Delta x \\
\Delta y
\end{bmatrix}
+ \begin{bmatrix}
0 \\
-1
\end{bmatrix} \delta
+ \underbrace{\begin{bmatrix}
-1 \\
q
\end{bmatrix} h \Delta y}_{\text{Control}}
+ \underbrace{\Delta y}_{\text{Disturbance}}
\]

The plant has a RHP zero, which imposes hard limits on performance.
Previous Works

Chandra, *et al.* showed that oscillation in glycolysis is due to the existence of autocatalytic feedback.

Our goal is to characterize hard limits due to autocatalytic structures in networks by using nonlinear models of such networks.
Characterization of Hard Limits

We interpret fundamental limitation of feedback by using

- Hard limits (lower bounds) on $L_2$-gain disturbance attenuation of the system
- Hard limits (Lower bounds) on $L_2$-norm of the output of the system
Hard Limits on $L_2$-gain Disturbance Attenuation

\[ \dot{x} = f(x) + g(x)u + p(x)\delta, \quad x \in \mathbb{R}^n, \quad u \in \mathbb{R}^m \]
\[ y = h(x), \quad \delta \in L^2(0, T) \]

The $L_2$-gain form $\delta$ to $y$ is less than or equal to $\gamma$

\[ \int_0^T |y(t)|^2 dt \leq \gamma^2 \int_0^T |\delta(t)|^2 dt, \quad \forall T > 0 \text{ and zero initial state} \]

Finding a stabilizing state feedback which minimizes $\gamma$

$\gamma^*$ : the best achievable $L_2$-gain
Theorem:

There exists a hard limit on the best achievable disturbance attenuation, \( \gamma^* \), for system (GP) such that the regional state feedback \( L_2 \)-gain disturbance attenuation problem with guaranteed stability is solvable for all \( \gamma > \gamma^* \), but is not solvable for all \( \gamma < \gamma^* \).

\[
\gamma^* \geq H(q, k, g) = \frac{q}{k + gq}
\]

\[
\begin{bmatrix}
\dot{x} \\
\dot{y}
\end{bmatrix} = \underbrace{\begin{bmatrix} 1 \\ -q \end{bmatrix}}_{PFK} y^a u + \underbrace{\begin{bmatrix} -1 \\ q + 1 \end{bmatrix}}_{PK} \frac{2kx}{1 + y^{2g}} - \underbrace{\begin{bmatrix} 0 \\ 1 + \delta \end{bmatrix}}_{Consumptions}
\]

Tradeoff Between Robustness and Efficiency

The glycolysis mechanism is more robust efficient if $k$ and $g$ are large.

$$H(q, k, g) = \frac{q}{k + gq}$$

Large $k$ requires either a more efficient or a higher level of enzymes, and large $g$ requires a more complex controlled PK enzyme.
Hard Limits on $L_2$-Output Energy

\[
\begin{align*}
\dot{x} &= f(x) + g(x)u, \quad x \in \mathbb{R}^n, \quad u \in \mathbb{R}^m \\
y &= h(x),
\end{align*}
\]

Cheap optimal control problem:

Finding a stabilizing state feedback control which minimizes the functional

\[
J_\varepsilon(x_0; u) = \frac{1}{2} \int_0^\infty \left[ y^T y + \varepsilon^2 u^T u \right] dt
\]

As $\varepsilon \to 0$, the optimal value $J_\varepsilon^*(x_0)$ tends to $J_0^*(x_0)$

$J_0^*(x_0)$: The ideal performance
Hard Limits on $L_2$-norm Output Energy

Theorem:

There is a hard limit on the performance measure of the unperturbed ($\delta = 0$) system (GP) in the following sense

$$\int_0^\infty (y(t; u_0) - \bar{y})^2 \, dt \geq \frac{q^3}{k} \, z_0^2 + J(z_0, q, g),$$

where $z_0 = (x(0) - x^*) + \frac{1}{q}(y(0) - y^*)$, $u_0$ is an arbitrary stabilizing feedback control law for system (GP), and $J(0, q, g) = J(z, q, 0) = 0$ and $|J(z, q, g)| \leq c|z|^3$ on an open set $\Omega$ around the origin in $\mathbb{R}$.

Hard Limits on $L_2$-norm Output Energy

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Increasing $q$ (number of ATP molecules invested in the pathway), increases fragility of the network to small disturbances and it can result in undesirable transient behavior.

$H(q, k, z_0) = \frac{q^3}{k} z_0$

Increasing $q$, increases the production of the pathway.
Multiple Intermediate Metabolite Reactions

Cell Consumption of ATP
Multiple Intermediate Metabolite Reactions
Multiple Intermediate Metabolite Reactions

\[ \dot{x}_1 = y^a u - K_1 x_1, \]
\[ \dot{x}_2 = K_1 x_1 - K_2 x_2, \]
\[ \vdots \]
\[ \dot{x}_n = K_{n-1} x_{n-1} - \frac{2K_n x_n}{1 + y^{2g}}, \]
\[ \dot{y} = (q + 1) \frac{2K_n x_n}{1 + y^{2g}} - q y^a u - (1 + \delta), \]
Hard limits on $L_2$-gain Disturbance Attenuation

Theorem:

There exists a hard limit on the best achievable disturbance attenuation, $\gamma^*$, for system (GGP) such that the problem of disturbance attenuation with internal stability is solvable for all $\gamma > \gamma^*$, but is not solvable for all $\gamma < \gamma^*$, i.e.,

$$\int_0^T (y(t; u_0) - \bar{y})^2 dt \leq \gamma^2 \int_0^T \delta^2(t) dt.$$ 

Moreover, the hard limit function is given by

$$\gamma^* \geq H(q, K, g, n)$$

where

$$H(q, K, g, n) = \frac{1}{g(q + 1)(1 - \left(\frac{q}{q+1}\right)^\frac{1}{n}) + K\left((\frac{q+1}{q})^{\frac{1}{n}} - 1\right)}.$$ 

Multiple Intermediate Metabolite Reactions

**Ex.** The $L_2$-gain disturbance attenuation of autocatalytic pathways, and the obtained hard limit based on our Theorem.
Conclusion

- We characterize fundamental limits on robustness and performance measures of autocatalytic pathways
- We explicitly derive hard limits on the performance of the autocatalytic pathways with intermediate reactions
- We generalize our results to higher dimensional model of autocatalytic pathways
Related Work

- Robustness analysis of autonomous cyclic networks
  
  M. Siami and N. Motee, "Robustness and Performance Analysis of Cyclic Interconnected Dynamical Networks," The SIAM Conference on Control and Its Application, San Diego, CA, USA, 2013.

- Fundamental limitations of feedback control laws in cyclic dynamical networks
  


Ongoing Work

• Generalize our results for a class of directed networks

• Unification of network performance analysis
  - Adjusting coupling functions
  - Reconfiguring of an existing network
  - Establishing new couplings
  - Sparsification of existing networks