Theoretical Performance Limit of the Autocatalytic Glycolysis System

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Short Abstract **— Autocatalysis is necessary and ubiquitous in both engineered and biological systems but can aggravate control performance and cause instability. We analyze the properties of autocatalysis in the universal and well studied glycolytic pathway. A simple two-state model incorporating ATP autocatalysis and inhibitory feedback control captures the essential dynamics, including limit cycle oscillations, observed experimentally. System performance is limited by the inherent autocatalytic stoichiometry and higher levels of autocatalysis exacerbate stability and performance. We show that glycolytic oscillations are not merely a "frozen accident" but a result of the intrinsic stability tradeoffs emerging from the autocatalytic mechanism.**

Keywords **— Glycolysis, oscillations, Bode integral formula, autocatalysis**

I. Purpose

In metabolic systems the destabilizing effects of "positive" autocatalytic feedback is often countered by negative feedback loops. Although negative feedback may stabilize autocatalytic systems, we argue that there is a theoretical limit to the optimal performance of such systems. The purpose of this research is to explore the hard limits of stability and performance that arise from such autocatalytic and regulatory mechanisms using the well-understood example of glycoylsis.

II. Results

A. Two-State Model

Consider a two-state model with ATP (x) and a lumped intermediate metabolite (y) as states:

$$\dot{x} = -q\frac{Vx^q}{1+\gamma x^h} + (q+1)k_y y - k_x$$

$$\dot{y} = \frac{Vx^q}{1+\gamma x^h} - k_y y$$

where q is the autocatalytic stoichiometry of the system.

B. Theoretical Performance Limits

Consider a sensitivity function S defined as the system response to noise/perturbation. In the ideal situation, S is zero or very small (response is unaffected by noise). However, if $S(z)=1$ for a right half plane (RHP) "zero" z, a constraint on the sensitivity function can easily be shown to be:

$$\frac{1}{\pi}\int_0^\infty \ln\left|S_{\hat{h}=\hat{h}}(j\omega)\right|\frac{z}{z^2+\omega^2}d\omega \geq \max\left\{0, \ln\left|\frac{z+p}{z-p}\right|\right\}$$

Where p is a right half plane pole s.t. $S(p)=0$.

For our model, when $q>0$, i.e. there is autocatalysis, we find that the zero indeed lies on the RHP and given by:

$$z = \frac{k_y}{q}$$

Similarly, there is always one RHP pole given by:

$$p = RHPzero\left\{s^2 + \left(q^2 + k_y\right)s - qk_y\right\}$$

$$= \frac{-q^2 - k_y \pm \sqrt{(q^2+k_y)^2 + 4qk_y}}{2}$$

Therefore the constraint given above holds for glycolysis. Note that both z and p depends only on autocatalytic stochiometry q and reaction rate k_y and cannot be lifted by changing the negative feedback.

III. Conclusion

We show that glycolytic oscillations are rather a result of the hard tradeoff that emerges from the autocatalytic mechanism of glycolysis, which is necessary for the downstream reactions to proceed. The constraint on the system performance depends only on the architecture of the system. This means that evolving a more complex enzyme with tighter regulation will not change the optimal performance limit.

References

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Acknowledgements: This work was funded by Institute for Collaborative Biotechnologies through grant DAAD19-03-D-0004 from the U.S. Army Research Office.

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