The Effect of Transcriptional Delays in Cyclic Biochemical Networks

German A. Enciso[1]

***Short Abstract* — Two complementary analyses of a cyclic negative feedback system with delay are considered in this poster. The first analysis applies the work by Sontag, Angeli, Enciso and others regarding monotone control systems under negative feedback, and it implies the global attractiveness towards an equilibrium for arbitrary delays. The second one concerns the existence of a Hopf bifurcation with respect to the delay parameter, and it implies the existence of nonconstant periodic solutions for special delay values.**

These ideas are applied to the study of a simple gene regulatory loop under negative feedback. A key idea is the use of the Schwarzian derivative, and its application for the study of Hill function nonlinearities. The positive feedback case is also addressed.

***Keywords* — Delay systems, Schwarzian derivative, Hill functions, negative feedback, Hopf bifurcation.**

I. Purpose

THE work in synthetic biology by Elowitz and Leibler [2] and many others has stressed the importance of self-inhibitory gene expression networks in the appearance of oscillations. It has been pointed out by Lewis and Monk [5][6] that delays in gene transcription and protein translation might have an essential role in tuning the period of the oscillation, as well as determining whether a persistent oscillation is at all present in the system. Examples of this idea have been given in the context of NF-kB and p53 oscillations, as well as the Hes1 gene involved in somitogenesis.

Two complementary analyses of a cyclic negative feedback system with delay are considered in this poster. The first analysis applies the work by Sontag, Angeli, Enciso and others regarding monotone control systems under negative feedback, and it implies the global attractivity towards an equilibrium for arbitrary delays. The second one concerns the existence of a Hopf bifurcation on the delay parameter, and it implies the existence of nonconstant periodic solutions for special delay values.

A key idea is the use of the so-called Schwarzian derivative, and its application for the study of Michaelis-Menten and Hill function nonlinearities. An important insight presented is that this particular choice of nonlinearities simplifies the behavior of the system, beyond that possible if other bounded sigmoidal nonlinearities are considered instead.

The results in this paper provide measurable tests for determining whether a stable negative feedback gene network can be destabilized into an oscillatory regime by a large enough time delay, such as that induced by large splicing events. They can similarly be used to determine whether time delays are essential to preserve an already present oscillatory behavior.

II. Conclusion

Even though a mathematical analysis is extremely difficult for most realistic gene regulatory networks, a simplified scenario can be studied to provide insight into possible regulation mechanisms, in this case the appearance of oscillations through time delays.

References

[1] D. Angeli, E.D. Sontag, Monotone controlled systems. *IEEE Trans. Autom. Control,* 48:1684-1698, 2003.

[2] M.B. Elowitz, S. Leibler, A synthetic oscillatory network of transcriptional regulators. *Nature*, 403:335-338, 2000.

[3] G.A. Enciso, A dychotomy for a class of cyclic delay systems. Arxiv, q-bio.MN/0601015. To appear in Mathematical Biosciences.

[4] G.A. Enciso, E.D. Sontag, Global attractivity, I/O monotone small-gain theorems, and biological delay systems. To appear in *Discrete and Continuous Dynamical Systems.*

[5] J. Lewis, Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator. *Current Biology*, 13:1396-1408.

[6] N.A.M. Monk, Oscillatory expression of Hes1, p53, and NF-kB driven by transcriptional time delays. *Current Biology*,13:1409-1413,2003.

Acknowledgements: *The MBI receives major funding from the National Science Foundation Division of Mathematical Sciences and is supported by the Ohio State University.*

[1]Mathematical Biosciences Institute, Columbus, OH, USA. E-mail: genciso@mbi.osu.edu