Entrainment of synthetic genetic oscillators in *E. coli* to an external periodic signal.

Octavio Mondragón-Palomino[1], Lev Tsimring[2], and Jeff Hasty[1,2]

We have previously built a robust, persistent and tunable genetic oscillator in *E. coli* that consists of two feedback loops of opposite sign. As cells divide, their oscillations become quickly desynchronized within a few generations. Using a microfluidic platform, we force the oscillator with a periodically modulated concentration of an inducer of transcription. Different strengths and frequencies of forcing are explored. Our results indicate that the synthetic oscillations are frequency-locked to the forcing signal within a range of frequencies and for different amplitudes.

***Keywords* — synthetic oscillator – frequency locking.**

I. Motivation

A fast, robust and persistent genetic oscillator in *Escherichia coli* was built in our lab [1,2]. The oscillatory expression of its components results from the interaction between two feedback loops of opposite sign. The period of oscillations can be tuned through the concentration of inducers of transcription, Arabinose and IPTG (isopropyl b-D-1-thiogalactopyranoside), in cell media. Each cell behaves as an independent oscillator and although the phase of oscillations is partly inherited from mother to daughter cells, it drifts quickly within a few generations. A natural next step in the advancement of synthetic biological oscillations is to achieve their coordinated behavior.

One way to synchronize multiple independent oscillators is by entraining them with an external rhythm [3]. In this work we study the forced oscillations of this system through experiments and numerical simulations.

II. Experiments and results

The double feedback oscillator can receive external dynamic input in the form of periodic variations in the concentration of inducers of transcription Arabinose and IPTG. To do this, we use a microfluidic platform that combines long term confinement of *E.coli* monolayers with a dynamic fluidic switch. In this way we obtain single cell data for long periods of time, while investigating different forcing amplitudes for a wide range of frequencies.

When the concentration of Arabinose is modulated sinusoidally, our experiments show that as the forcing period gets closer to the average natural period, a colony of oscillators behaves more coherently and it becomes locked to the entraining signal.

To account for the effects of forcing at the single cell level, we calculate two quantities as a function of the forcing period. The first one is detuning and the second one is the average cross-correlation calculated over all the pairs of independent oscillators. Detuning is defined as the subtraction of the forcing period from the measured period of the oscillator.

For different amplitudes, we find that detuning decreases nonlinearly as a function of the forcing period, and flattens around the natural period of the oscillator. The average pair cross-correlation reaches a maximum within the same interval.

Our mathematical models can explain qualitatively the observed behavior and predict that entrainment is also possible through a modulated signal of the transcription activator IPTG that interacts with the oscillator through the negative feedback loop.

III. Conclusion

We have demonstrated through single-cell experimentation the entrainment of a synthetic genetic oscillator in *E. coli* to an external periodic chemical signal. Our mathematical models are able to qualitatively explain the observed behavior and predict that the oscillator can also be entrained through the modulation of IPTG.

References

[1] Stricker J *et al.* (2008) A fast, robust and tunable synthetic gene oscillator. *NATURE* 456(7221), 516-519.

[2] Mather W *et al.* (2009) Delay-Induced Degrade-and-Fire Oscillations in Small Genetic Circuits. *PRL* 102(6):068105(4).

[3] Pikovsky A, Rosenblum M and Kurths J (2001) Synchronization. A universal concept in nonlinear sciences. Cambridge University Press, Cambridge, UK.

Acknowledgements: Octavio Mondragon is financially supported by CONACyT (México) and the Hasty Lab.

[1]Department of Bioengineering, University of California, San Diego, E-mail: omondrag@ucsd.edu

[2]Center for Nonlinear Science, University of California, San Diego.