Entrainment of synthetic gene oscillators by a noisy stimulus

Nicholas C. Butzin[1], Philip L. Hochendoner[1], Curtis T. Ogle[1], Paul Hill[1], William Mather[1,2]

***Short Abstract* —We investigate experimentally and theoretically the entrainment of an ensemble of synthetic gene oscillators by a noisy stimulus. Stochastic simulations suggested that a synthetic gene oscillator would be strongly entrained by two aperiodic signals: telegraph noise and phase noise. This simulation-based prediction was tested by a combination of microfluidic and microscopy using a real synthetic circuit in *Escherichia coli*. We use delayed feedback models to analyze these cells. We show that cells are entrained by two noisy signals: telegraph and phase noise. Cells are entrained when either signal period or amplitudes are varied.**

***Keywords* — Entrainment, oscillators, synthetic and systems biology, aperiodic and periodic noise.**

I. Purpose

Most organisms (bacteria to humans) regulate processes using molecular clocks to synchronize their physiology and behavior to stimuli from their environment [1]. When individual components that oscillate on their own (self-sustaining) are forced to synchronize to an outside signal (matching their period and phase to the external signal) they are said to be entrained (the signal is independent of the oscillator). The rhythm of gene expression can be entrained where by the expression of the gene correlates with an environmental signal e.g. our natural circadian rhythm oscillator is entrained to a 24 hour period by the daily cycle of sunlight and darkness [1,2]. Periodic signals have been intensively studied in this regard, but most natural signals contain a strong aperiodic (noisy) component, and it has been long known that aperiodic signals can entrain systems to common a behavior, e.g. in the stimulation of independent neurons [3], or even in the random forcing of material particles [4]. Synchronized cells may produce an amplified response by activating in unison. Entrainment of neurons by aperiodic signal is well documented [3,5,6]; however, we failed to identify other biological examples in the literature with experimental support. This is likely due to the difficulty in doing such experiments and the underestimation of the importance of this phenomenon in the biological community.

A synthetic biology approach has already proven useful in understanding the entrainment of oscillators by periodic signaling [7,8], which can mimic the response of a number of noisy oscillating systems: cell cycles [9], and NFkB response [10], for example. We used stochastic simulations to predict that a synthetic gene oscillator would be strongly entrained by two aperiodic signals: telegraph noise and phase noise. We tested our *in silico* prediction with *in vivo* experiments using the model organism *Escherichia coli* and showed that cells can be entrained by such signals. Oscillator entrainment via aperiodic signaling has been well documented and simulated in physics journals [11-13], but this phenomenon has rarely been studied in living cells. It is likely that oscillator entrainment of cells via aperiodic signaling happens all the time. Many natural signals contain a strong aperiodic component, but it is difficult to study this in a natural ecosystem (biofilm, eukaryotic cells, etc.). Here we demonstrate that an aperiodic signal can drive entrain a synthetic oscillator; however, this work may have broader impact on future studies of other organisms and natural ecology's.

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[1]Department of Physics, Virginia Tech. ncb@vt.edu, plh5012@vt.edu, cogle@vt.edu, metta@vt.edu, wmather@vt.edu.

[2]Department of Biology, Virginia Tech. wmather@vt.edu.

II. References

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