An artificial cell-cycle system: how network structures modulate the clock functions

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***Short Abstract* — Although central architectures drive robust oscillations, networks containing the same core vary drastically in their potential to oscillate. What peripheral structures contribute to the variation remains elusive. Systematically analyzing network structures and functions showed that, while certain core topologies are essential for robust oscillations, local structures substantially modulate the degree of robustness. Strikingly, nodes receiving incoherent or coherent inputs promote or attenuate the robustness, additively. These may explain why auxiliary structures not required for oscillation are evolutionarily conserved. We developed an artificial mitotic oscillator, combined with single-cell analysis and modeling, to understand how network structures are linked to clock functions.**

***Keywords* — Biological oscillators, robustness, network structures, motifs, microfluidics, cell cycle, synthetic circuit, time-lapse fluorescence microscopy.**

I. Introduction

In principle, a single negative feedback is required and sufficient to generate self-sustained oscillations [1]. However, known biological oscillators are organized into more complex network structures. Some of the additional structures, such as positive feedback loops, are not required for generating oscillations but are evolutionary conserved, which has raised a question of what functional role they may play. Computational studies on several biological oscillators such as cell cycles have shown that adding a self-positive feedback loop to a core oscillatory circuit can increase the oscillator's robustness [2-4]. However, whether positive feedback is necessary or sufficient to increase robustness has remained controversial. While both Wee1 and Cdc25 form positive feedbacks in embryonic cell cycles, only the one from Cdc25 is critical for robustness of oscillation period [5]. A recent study using synthetic circuits [6], has shown that adding a negative feedback to an oscillator could also increase its robustness. These studies reveal the difficulty of identifying generalizable mechanisms through analyzing only a subset of oscillators. To obtain a complete picture beyond any chosen systems, a comprehensive mapping from the entire topology space to the function space is necessary. Moreover, it is challenging but critical to test the computational predictions by experimentally dissecting clock circuit and analyzing clock behaviors at the single-cell level.

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II. Results

We computationally generate an atlas of oscillators and systematically analyzed robustness of all oscillatory topologies. We found that, two key local structures, incoherent inputs and coherent inputs, can modify a core topology to increase and decrease its robustness respectively [7] (*Cell Systems 2017*), underscoring the important role of local modifications in robustness. It also suggests a convenient way to design robust synthetic circuits. Experimentally, we develop an artificial cell-cycle system to mimic the real cell mitotic oscillatory processes in microfluidic droplets [8] (*eLife 2018*). With nanofabrication and long-term time-lapse fluorescence microscopy, this system has enabled high-throughput single-cell analysis of clock dynamics and functions. We now apply the experimental platform together with mathematical modeling to investigate how network structures are linked to the essential functions of early embryonic cell cycles, such as tunability and robustness.

References

[1] Novak, B., and Tyson, J.J. (2008). Design principles of biochemical oscillators. Nat Rev Mol Cell Biol 9, 981-991.

[2] Tsai, T.Y., Choi, Y.S., Ma, W., Pomerening, J.R., Tang, C., and Ferrell, J.E., Jr. (2008). Robust, tunable biological oscillations from interlinked positive and negative feedback loops. Science 321, 126-129.

[3] Ananthasubramaniam, B., and Herzel, H. (2014). Positive feedback promotes oscillations in negative feedback loops. PLoS One 9, e104761.

[4] Gerard, C., Gonze, D., and Goldbeter, A. (2012). Effect of positive feedback loops on the robustness of oscillations in the network of cyclin-dependent kinases driving the mammalian cell cycle. FEBS J 279, 3411-3431.

[5] Tsai, T.Y., Theriot, J.A., and Ferrell, J.E., Jr. (2014). Changes in oscillatory dynamics in the cell cycle of early Xenopus laevis embryos. PLoS Biol 12, e1001788.

[6] Z. Li, S. Liu, and Q. Yang (2017). Incoherent Inputs Enhance the Robustness of Biological Oscillators. Cell Systems 5, 72.

[7] Y. Guan, Z. Li, S. Wang, P. M. Barnes, X. Liu, H. Xu, M. Jin, A. P. Liu, and Q. Yang (2018). A robust and tunable mitotic oscillator in artificial cells. eLife 7, e33549.