

How periodic signals can tell time

Michele Monti¹ and Pieter Rein ten Wolde¹

Abstract — The coordination of biological activities in daily cycles provides an important advantage for the fitness of several organisms. The circadian clock in cyanobacteria *S. elongatus* drives daily genome-wide oscillations in mRNA expression levels, controls genome compaction and supercoiling, and modulates cell division. The clock contains a core oscillator consisting of the proteins KaiA, KaiB, and KaiC, which together generate circadian oscillations in the four phosphorylation states of KaiC. This clock controls the circadian expression of the transcriptome via phosphorylation of a single protein, RpaA. In this project we address how reliably temporal information can be transmitted from the clock to downstream genes. We have developed a mathematical model that describes how cells can infer the time from an ensemble of oscillatory genes. Using techniques of Statistical Mechanics and Information theory, we are able to compute how many time-states cells can uniquely distinguish. This enables us to analytically derive the error in measuring the perception of time.

Keywords — Circadian Clocks, Mutual Information, cyanobacteria, noise

PURPOSE

Circadian clock is one of the main ways to keep track of time for a wide range of biological organisms [1]. Generating rhythms in metabolic and behavioral processes helps cells distinguish between different moments in time [2] and this in turn optimizes the cells' biochemical functionality. Clocks are connected to the genome and drive oscillations in the whole transcriptome [3]. This connection is generally mediated by a single linking protein that oscillates along with the clock and triggers the expression of downstream genes. The purpose of this work was to study the dynamical features of this read out system that lead to an accurate perception of time in cells. To analyze this network we used information theory and statistical analysis [4]. We defined some of the relations occurring between oscillatory genes that maximize the information on time. Moreover, using analytical tools we were able to derive the error relative to the measure of time for each

moment of the day [5].

CONCLUSION

In the study of the behaviour of genes that read out the clock we found the optimal region in the parameter space that optimizes the information and minimizes the error on time. It turned out that the key parameter is the phase shift between the oscillatory genes. The insertion of cross correlation among the noises [6] induces changes in the optimal phase shift. Therefore, having cross correlation could help cells infer better information on time. Since oscillations in both time and space are very common in biology, our analysis has a general validity and can be equally applied to all the systems that need to infer information from oscillatory signals.

REFERENCES

- [1] Takao Kondo and Masahiro Ishiura. Circadian Rhythms of Cyanobacteria: Monitoring the Biological Clocks of Individual Colonies by Bioluminescence. *Journal of bacteriology*, 176(7): 1881-1885, 1994.
- [2] Taeko Nishiwaki, Yoshinori Satomi, Yohko Kitayama, Kazuki Terauchi, Reiko Kiyohara, Toshifumi Takao, and Takao Kondo. A sequential program of dual phosphorylation of KaiC as a basis for circadian rhythm in cyanobacteria. *The EMBO journal*, 26(17):4029–37, September 2007.
- [3] Joseph S Markson, Joseph R Piechura, Anna M Puszynska, and Erin K O'Shea. Circadian Control of Global Gene Expression by the Cyanobacterial Master Regulator RpaA. *Cell*, 155(6):1396–408, December 2013.
- [4] Gašper Tkačik and Aleksandra M Walczak. Information transmission in genetic regulatory networks: a review. *Journal of physics. Condensed matter : an Institute of Physics journal*, 23(15):153102, April 2011.
- [5] Julien O Dubuis, Gasper Tkacik, Eric F Wieschaus, Thomas Gregor, and William Bialek. Positional information, in bits. *Proceedings of the National Academy of Sciences of the United States of America*, 110(41):16301–8, October 2013.
- [6] Yuichi Taniguchi, Paul J. Choi, Gene-Wei Li, Huiyi Chen, Mohan Babu, Jeremy Hearn, Andrew Emili, and X. Sunney Xie. Quantifying *E. coli* Proteome and Transcriptome with Single-Molecule Sensitivity in Single Cells. *Science*, (533), 2011

□ Acknowledgements: This work is part of the research program of the “Stichting voor Fundamenteel Onderzoek der Materie FOM” which is financially supported by the “Nederlandse organisatie voor Wetenschappelijk Onderzoek NWO.”

¹ FOM institute AMOLF monti@amolf.nl