Robust synchronization of coupled circadian and cell cycle oscillators in single mammalian cells

Rosamaria Cannavo¹, Jonathan Bieler¹, Kyle Gustafson¹, Cedric Gobet¹, David Gatfield⁵, Felix Naef¹

¹The Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, SWITZERLAND
⁵Center for Integrative Genomics, Génopole, University of Lausanne, Lausanne, Switzerland, SWITZERLAND

Circadian oscillators and cell cycles are two fundamental periodic processes with a period in the range of one day. Consequently, when they run in parallel in the same cell, their coupling may lead to synchronization. Long-standing observations of circadian variations in mitotic indices in mammalian cells and more recent studies on the daytime-dependence of cell division in mouse liver and cultured fibroblasts have led to the intriguing hypothesis that the circadian cycle might gate cell-cycle progression. Interestingly, even Cyanobacteria exhibit circadian coupling of the cell cycle, indicating that it may be of fundamental biological importance. A better understanding of how the two systems mutually interact is currently of great interest as new findings on the role of circadian clocks in proliferating tissues are reported, notably in the epidermis and in stem cells. Here, we performed a large-scale time-lapse imaging of single mammalian NIH3T3 fibroblasts during several days to further analyze the mutual interactions between the two oscillators and their dynamical consequences. The analysis of over 80'000 single cell traces showing circadian cycles in dividing cells clearly indicated that both oscillators tick in a tightly synchronized state, with cell divisions occurring tightly five hours before the peak in circadian Rev-Erbα-YFP reporter expression. In principle, such synchrony may be caused by coupling in either direction, or both.

While gating of cell division by the circadian cycle has been most studied, our data combined with stochastic modeling unambiguously show that reverse coupling is predominant in NIH3T3 cells. Moreover, genetic and pharmacological perturbations showed that the two interacting cellular oscillators adopt a synchronized state that is highly robust over a wide range of parameters. These findings have implications for circadian function in proliferative tissues, including epidermis, immune cells, and cancer.