Mathematical modeling and experimental validation of glucose and temperature compensation in the Neurospora circadian clock

Andrey Dovzhenok¹, Mokryun Baek², Jennifer Loros³, Jay Dunlap⁴, Sookkyung Lim⁵, Christian Hong²

¹Department of Mathematical Sciences, University of Cincinnati, Cincinnati, OH, UNITED STATES
²Department of Cellular and Molecular Physiology, University of Cincinnati College of Medicine, Cincinnati, OH, UNITED STATES
³Departments of Biochemistry and Genetics, Geisel School of Medicine at Dartmouth, Hanover, NH, UNITED STATES
⁴Genetics, Geisel School of Medicine at Dartmouth, Hanover, NH, UNITED STATES
⁵Department of Biochemistry, Geisel School of Medicine at Dartmouth, Hanover, NH, UNITED STATES

Circadian clock plays a vital role timing various facets of organisms' activity including physiology, cell cycle, metabolism etc. Autonomous circadian oscillations arise from transcriptional-translational feedback loops of core clock components. The period of circadian oscillator is relatively insensitive to changes in physiological temperature and nutrients (e.g. glucose), which are referred to as temperature and nutrient compensation, respectively. Recently, a transcription repressor, CSP-1, was identified as a component of the circadian system in Neurospora crassa. The transcription of csp-1 is under the circadian regulation. Intriguingly, CSP-1 represses a circadian transcription factor, WC-1, forming a negative feedback loop that can influence the core oscillator. This feedback mechanism is suggested to maintain the circadian period in a wide range of glucose concentrations. In this report, we constructed a mathematical model of the Neurospora circadian clock incorporating the above WC-1/CSP-1 feedback loop, and investigated molecular mechanisms of glucose and temperature compensation. Our model shows that glucose compensation is achieved by balancing the activation rates of csp-1 and wc-1, and that temperature compensation can be achieved by intricate balance of synthesis and degradation of FRQ and WC-1. More importantly, we experimentally validated loss of glucose compensation in wc-1ov mutant, and maintenance of the abundance of nuclear FRQ as a function of temperature as predicted in the model.