Spatiotemporal stochastic modeling reveals a hidden compensation mechanism for robust daily rhythms

Stephen Beesley[1, a], Dae Wook Kim[2, a], Matthew D'Alessandro[1], Yuanhu Jin[1], Kwangjun Lee[1], Hyunjeong Joo[1,3], Yang Young[3], Robert J. Tomko Jr[1], John Faulkner[4], Joshua Gamsby[4], Jae Kyoung Kim[2] and Choogon Lee[1]

1) *Department of Biomedical Sciences, College of Medicine, Florida State University, Tallahassee, FL 32306, USA*
2) *Department of Mathematical Sciences, KAIST, Deajeon 34141, KOR*
3) *Department of Systems Biology, Sookmyung Women's University, Seoul 04310, KOR*
4) *Department of Molecular Medicine, University of South Florida, Tampa, FL 33620, USA*
a) S.B. and D.W.K. contributed equally to this work

Corresponding Author: Jae Kyoung Kim, jaekkim@kaist.ac.kr
and Choogon Lee, choogon.lee@med.fsu.edu

ABSTRACT

Circadian (daily) physiological events, such as sleep and cell division, are essential for survival of humans. Their robust timekeeping capabilities are controlled by an endogenous pacemaker, the circadian clock. Its key molecular oscillatory mechanism has been identified by experimental work over the past decades whose significance was appreciated and thus the 2017 Nobel Prize in Physiology or Medicine was awarded to the three pioneer researchers. However, our understanding of this mechanism remains far from complete. How are the robust rhythms generated within a single cell with a heterogeneous cytoplasmic environment, which directly influences the manifestation of these rhythms? To address this question, which is challenging because it requires to consider *time*, *space* and *stochasticity* together, we have developed a spatiotemporal stochastic mathematical model of the system for the first time. By analyzing the model, we identified a potential mechanism for how the clock generates the robust rhythms over a wide range of cytoplasmic congestion levels: spatially coordinated collective behaviors of clock molecules. This provides a clear mechanistic insight into why sleep disorders arise under clinical conditions, such as Alzheimer's disease, obesity and aging, where the cytoplasmic environment can be severely disrupted. Surprisingly, these model predictions have been confirmed experimentally. This study sheds light on novel molecular dynamics for robust cellular rhythms and provides theoretical frameworks which can be broadly applied in cell physiology.