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March 15, 2015

Ruth Nussinov, Editor-in-Chief

Dear Editor,

Please find enclosed our manuscript entitled "Quantifying stochastic noise in cultured circadian reporter cells" by Peter C. St. John and Francis J. Doyle III, which we are submitting for publication in *PLOS Computational Biology* as a Research Article.

Circadian rhythms are cell-autonomous 24-hour oscillations in gene transcription and play an integral role in coordinating metabolic processes in many species. Due to low molecular counts at the single-cell level, stochastic noise plays an important role in determining the output of the circadian gene regulatory network. However, quantifying the amount of noise present, specifically in response to a perturbation, is experimentally difficult. In this study we demonstrate that a reasonable description of the cell-autonomous noise can be gained by analyzing the damping profiles of data collected from entire cell cultures. Such a method is particularly useful for its applicability to the large wealth of existing experimental data from which new insights might be gained. We feel that this article would be an excellent fit for *PLOS Computational Biology* not only due to the journal's large readership in circadian rhythms specifically, but also since our article demonstrates the importance of multi-scale systems biology: incorporating elements from molecular-level simulations up through high-throughput biological screens.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to *PLOS Computational Biology*. We look forward to hearing back from you.

Sincerely,

Francis J. Doyle III
Professor and Department Chair
Associate Dean for Research, College of Engineering