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Analysis of Biological Clock May Lead to Greater Understanding of Human Disease

Our biological clock, or circadian rhythm, is upset by travelling across time zones, but very soon the body adjusts to the new day/night cycle. New studies of the computational models of the circadian rhythm of fruit flies show that the internal clock is robust, that is, not easily perturbed. These studies may eventually lead to greater understanding of human jet lag as well as human disease states.

Engineers at the University of California, Santa Barbara's new Institute for Collaborative Biotechnologies and the Max Planck Institute (MPI) for Dynamics of Complex Technical Systems, in Magdeburg, Germany have analyzed the mechanism of genetic circuits by which the fruit fly regulates its circadian rhythm. The results are published in the August 30 Proceedings of the National Academies of Science. The mechanism controlling the biological clock generates a complicated dynamic behavior, oscillating back and forth and making it difficult to study, but also making it a good prototypical dynamic cellular system.

The circadian rhythm of the fruit fly is a regulatory system that takes its cues from the sun. When the sun rises it affects the light-sensitive neurons of the brain of the fruit fly, setting off reactions of proteins at a certain rate depending on the amount of light. The reactions set the clock. There are key proteins and two key feedback loops involved, making the system a hierarchical control scheme, a design tool often

used in engineering.

The mechanism is called a negative feedback loop similar to that employed by an air conditioning thermostat system. It reacts when the temperature gets too cold by reducing the cooling.

The engineers are looking for the principles underlying the architecture of the fruit fly's system that enables it to be so robust, according to co-author Frank Doyle, a chemical engineer who holds UCSB's Duncan and Suzanne Mellichamp Endowed Chair in Process Control. "We are very excited about this collaborative work, and how systems engineering ideas and tools can be used to unravel design principles in a complex biological system."

The authors chose to analyze the circuitry of the fruit fly because it is one of the most studied of all organisms. They were able to take mathematical information from the scientific literature on fruit flies and perform computations to derive their findings.

They made systematic changes to the mathematical model in a sensitivity analysis of all parameters to find the points of greatest fragility. They found that the trade-off between robustness and fragility is largely determined by the architecture of the regulatory system, and that the design for precision at keeping accurate time may be at the expense of the fragility of the global machinery. They also discovered that sensitivity analysis confirms the theoretical insight that hierarchical control is important for achieving robustness.

Moving up the hierarchy of the system, searching for points of fragility, looking for the weak links, may be a way to show how disease is a failure of a robust system, according to the authors.

"The huge progress of the last three decades in molecular biology, viewed through the lens of modern systems analysis, is now supplying biological systems engineers, such as this collaborative team, with the ingredients to understand and explain biological and physiological functionality in an unprecedented, comprehensive way," said Dean Matthew Tirrell of the College of Engineering at UCSB.

In Germany, co-author and lead MPI researcher Joerg Stelling commented, "Implications of the systems approaches we followed in this collaborative work are to shed light on the function of individual control circuits in biology, with a long-term

perspective to rationally understand causes of diseases, and to design strategies for their treatment."

The work was partially funded by the U.S. Army Research Office through the Institute for Collaborative Biotechnologies at UCSB.

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