

# Conservation of Robustness in a Gene Regulatory Network Underlying Circadian Rhythms

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The cellular genetic networks which underlie circadian rhythms in the fly and the mouse have generated lots of attention in experimental and modeling studies in the last 5 years. This architecture is remarkable from an engineering perspective, as it exhibits an enviable level of robustness in the face of uncertain stochastic perturbations, such as those which arise from intracellular constituents that are present in small numbers.

The robustness of this period generator in *Drosophila* has been postulated to arise from the rich regulatory architecture emerging from the experimental studies, which consists of: (i) a pair of negative feedback loops involving the genes period (*per*) and timeless (*tim*), (ii) a positive feedback loop involving the gene *dClock*, and (iii) the formation of a complex involving the protein products of several of the aforementioned genes and the delay of this process by the protein kinase doubletime (*DBT*). Perturbation analyses of various published models suggest that each preserves an element of parametric robustness, but each also contains points of fragility, which are surprisingly different for different model structures.

Sensitivity analyses have been done with a deterministic model that assumes symmetry in the *per/tim* feedback loops (Leloup and Goldbeter, 1998), employing tools from systems engineering. The Fisher information matrix, and the singular value decomposition (SVD) are utilized to obtain insight into the tradeoffs between robustness and fragility in this elegant biological regulatory system. It will be shown that the ordered sensitivity of various parameters in the model is invariant with respect to operating regime, covering a wide range of behavior, such as steady-state, simple periodicity, and chaos. The SVD yields insight into the weakest directions for systematic perturbations. The results are consistent with a biological interpretation of the role of the various feedback loops, furthermore, they also point to a design principle of cellular regulation, namely to 'export' a specialized control circuit's points of fragility to a global, well-controlled regulatory system like general transcription. Ongoing efforts include the application of the above methods to a comprehensive model that incorporates known asymmetries in the *per* and *tim* feedback loops for greater understanding of the robustness properties of the actual system.

## References

Leloup JC, Goldbeter A. A model for circadian rhythms in *Drosophila* incorporating the formation of a complex between the PER and TIM proteins. *J Biol Rhythms*. 1998 Feb;13(1):70-87.