Sensitivity Analysis of Mammalian Circadian Clocks

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Key words: circadian, deterministic, stochastic, Fisher Information
Matrix, BioSens, hierarchies, noise, network

Prepared for Presentation at the 2006 Annual Meeting, San Francisco, CA, Nov. 12-17

November 2006
Unpublished

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A circadian clock is a common feature among eukaryotes and an occasional feature among prokaryotes, imparting an ~24 hour period to many biological behaviors at the molecular, tissular, and organismal levels [1]. Some of the molecular aspects of the clock have been elucidated for organisms as diverse as Neurospora [2,3], Arabidopsis [4], Drosophila [5] and mouse [6-8]. In consequence, models of varying complexity, both deterministic [9-17] and stochastic [18,19], have been proposed.

In mammals, the "master clock" is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalmus. This cluster of ~20,000 neurons receives light via the retinohypothalmic tract (RHT) to entrain the clock. The master clock then directs the timing of peripheral oscillators in other parts of the body [6].

Circadian rhythms are known to be robust, in that variations in kinetics (due to, for example, temperature fluctuations) do not appreciably affect performance. Applied to models of circadian rhythm, formal sensitivity analysis provides a tool to assess robustness. The sensitivity of a system to perturbations in parameters is given, for each state and each parameter in the system, as the infinitesimal change in each state with respect to each parameter. The smaller this value, the greater the robustness of this state to perturbations in this parameter. When these values are taken over all states and all parameters, one can determine the relative effect of perturbations in each parameter on the whole system. Sensitivities can then be used to generate the Fisher Information Matrix (FIM) and a rank-ordering of parameter effects on the circadian system.

BioSens software [20], part of BioSPICE, has been used to determine the rank-order of parameter sensitivities on two models of the mouse circadian clock – the 19-state model proposed by Leloup and Goldbeter [12] and the 74-state model proposed by Forger and Peskin [9].

For each model, rank-ordered sensitivities were grouped by parameter type. Parameters were separated into "global" and "local" sets [21]. Global parameters are those that affect many processes in addition to the circadian clock (e.g. transcription rates, translation rates), and local parameters are those that influence only the circadian clock (e.g. phosphorylation of clock proteins). A third category, "mixed" was provided for those parameters that are neither truly global nor local. It was found that for both the Leloup and Goldbeter model and the Forger and Peskin model the circadian system is statistically more sensitive to perturbations in "global" parameters than to perturbations in "mixed" or "local" parameters. This was previously found to be the case for the Leloup and Goldbeter *Drosophila* model [21]. Therefore, the current work extends the previous hypothesis into another phylum.

To further test this conclusion we introduced extraneous noise into selected reactions in the stochastic version of the Forger and Peskin model [18]. It was found that noise introduced into reaction propensities governed by circadian system-sensitive parameters propagates through the system and appears as a change in the distribution of level in miscellaneous clock components. However, noise introduced into reaction propensities governed by circadian system-insensitive parameters does not lead to this effect.

To assess the possibility that noise propagation is due to proximity between the points of noise introduction and the measured states, rather than arising when noise is introduced at highly sensitivity points, we determined the correlation between noise propagation and node distance. We found that no such correlation exists.

An examination of the timecourses of various states indicates that noise functions in the clock by damping oscillations. To achieve an unaltered mean propensity for any given reaction with multiplied lognormal noise, the propensity will either cluster close to zero or be very high. When the propensity is driven high, that reaction channel becomes very likely to "fire." And if, for example, the reaction is a degradation, then the level of the degraded species will be driven to very low levels.

In addition to explorations of system sensitivities with the nominal parameter set, we performed Monte Carlo assessments of system sensitivities in a sweep of parameter space. It was found that for both the Leloup and Goldbeter model and the Forger and Peskin model, the mean rank-ordered sensitivities to parameter perturbations observed throughout the explored portions of parameter space are well correlated with the rank-ordered sensitivities found in the nominal models. Therefore, the separation of robustnesses and fragilities in the circadian systems is the same for all parameter sets investigated. And thus, the separation of robustnesses and fragilities in the circadian systems are inherent in the hierarchical network structure, not in the choice of parameter sets.

Acknowledgements

References

1.   Dunlap, J. C. (1999), "Molecular bases for circadian clocks," *Cell*, vol. 96, no. 2, pp. 271-290.

2.   Lee, K., J. J. Loros, and J. C. Dunlap (2000), "Interconnected feedback loops in the *Neurospora* circadian system," *Science*, vol. 289, no. 5476, pp. 107-110.

3.   Merrow, M., T. Roenneberg, G. Macino, and L. Franchi (2001), "A fungus among us: the *Neurospora crassa* circadian system," *Semin. Cell Dev. Biol.*, vol. 12, no. 4, pp. 279-285.

4.   Salom, P. A. and C. R. McClung (2004), "The *Arabidopsis thaliana* clock," *J. Biol. Rhythms*, vol. 19, no. 5, pp. 425-435.

5.   Williams, J. A. and A. Sehgal (2001), "Molecular components of the circadian system in Drosophila," *Brain Res. Rev.*, vol. 63, pp. 729-755.

6.   Reppert, S. M. and D. R. Weaver (2001), "Molecular analysis of mammalian circadian rhythms," *Annu. Rev. Physiol.*, vol. 63, pp. 647-676.

7.   Reppert, S. M. and D. R. Weaver (2002), " Coordination of circadian timing in mammals," *Nature*, vol. 418, no. 6901, pp. 935-941.

8.   Shearman, L. P., S. Sriram, D. R. Weaver, E. S. Maywood, I. Chaves, B. Zheng, K. Kume, C. C. Lee, G. T. van der Horst, M. H. Hastings, and S. M. Reppert (2000), "Interacting molecular loops in the mammalian circadian clock," *Science*, vol. 288, no. 5468, pp. 1013-1019.

9.   Forger, D. B. and C. S. Peskin (2003), "A detailed predictive model of the mammalian circadian clock," *Proc. Natl. Acad. Sci. USA*, vol. 100, no. 25, pp. 14806-14811.

10.   Leloup, J.-C. and A. Goldbeter (1998), "A model for circadian rhythms in *Drosophila* incorporating the formation of a complex between the PER and TIM proteins," *J. Biol. Rhythms*, vol. 13, pp. 70-87.

11.   Leloup, J.-C., D. Gonze, and A. Goldbeter (1999), "Limit cycle models for circadian rhythms based on transcriptional regulation in Drosophila and Neurospora," *J. Biol. Rhythms*, vol. 14, no. 6, pp. 433-448.

12.   Leloup, J.-C. and A. Goldbeter (2003), "Toward a detailed computational model for the mammalian circadian clock," *Proc. Natl. Acad. Sci. USA*, vol. 100, no. 12, pp. 7051-7056.

13.   Locke, J. C. W., A. J. Millar, and M. S. Turner (2005), "Modelling genetic networks with noisy and varied experimental data: the circadian clock in *Arabidopsis thaliana*," *J. Theor. Biol.*, vol. 234, no. 3, pp. 383-393.

14.   Ruoff, P., M. Vinsjevik, C. Monnerjahn, and L. Rensing (2001), "The Goodwin model: simulating the effect of light pulses on the circadian sporulation rhythm of *neurospora crassa*," *J. Theor. Biol.*, vol. 209, no. 1, pp. 29-42.

15.   Smolen, P., D. A. Baxter, and J. H. Byrne (2001), "Modeling circadian oscillations with interlocking positive and negative feedback loops," *J. Neurosci.*, vol. 21, no. 17, pp. 6644-6656.

16.   Tyson, J. J., C. I. Hong, C. D. Thron, and B. Novak (1999), "Simple model of circadian rhythms based on dimerization and proteolysis of PER and TIM," *Biophys. J.*, vol. 77, pp. 2411-2417.

17.   Ueda, H. R., M. Hagiwara, and H. Kitano (2001), "Robust oscillations within the interlocked feedback model of *drosophila* circadian rhythm." *J. Theor. Biol.*, vol. 210, no. 4, pp. 401-406.

18.   Forger, D. B. and C. S. Peskin (2005), "Stochastic simulation of the mammalian circadian clock," *Proc. Natl. Acad. Sci. USA*, vol. 102, no. 2, pp. 321-324.

19.   Gonze, D., J. Halloy, J.-C. Leloup, and A. Goldbeter (2003), "Stochastic models for circadian rhythms: effect of molecular noise on periodic and chaotic behavior," *C. R. Biologies*, vol. 326, pp. 189-203.

20.   Taylor, S., R. Gunawan, K. Gadkar, and F. J. Doyle III, "BioSens: a sensitivity analysis toolkit for BioSPICE," available at http://www.chemengr.ucsb.edu/~ceweb/faculty/doyle/biosens/BioSens.html.

21.   Stelling, J., E. D. Gilles, and F. J. Doyle III (2004), "Robustness properties of circadian clock architectures," *Proc. Natl. Acad. Sci. USA*, vol. 101, no. 36, pp. 13210-13215.