Simulation mammalian molecular circadian oscillators by dynamic gene network

Yanhong Tong[1], Hava Sieglemann[2].

Keywords: circadian rhythms, gene network

1 Introduction.

Internal biological rhythms that are entrainable to the 24-hr light-dark cycle are driven by endogenous oscillators called circadian clocks. At the molecular level, circadian oscillators are controlled by autoregulatory feedback loops. The transcriptional-translational feedback loops involve transcriptional activation/inhibition and translocation to the nucleus. Several of the genes and proteins involved in the feedback loops have been well studied in different organisms, such as the mouse and drosophila, although questions remain to be answered.

Although approximately 10 genes/proteins (Bmal, Clock, Per1-3, Cry1-2, Rev-erbα in mouse) are involved in the regulation of core clock to generate circadian rhythms, hundreds of genes cycle in different organs such as the suprachiasmatic nuclei and liver. The relationships among the core clock genes/proteins and the cycling genes/proteins in different organs are not yet well understood because of the system's complexity.

Several computational approaches to model biological clocks have been proposed [1]. However, there has not been a model which is basic enough to be of help for molecular biologists in the discovery of new genes or proteins related to circadian rhythms.

This study implements a gene network to model the circadian oscillator at the molecular level. The model is simple and can be easily updated in accordance to new experimental data. While the basic data used was collected from mice, not many modifications would be required to apply it to the human biological clock. This network should prove useful in the discovery of new genes/proteins related to circadian rhythms as well as in the analysis of drug's effects on the biological clock and in understanding of the most effective timing for administering various medications.

2 Methods and Results.

The molecular data for circadian clocks, including the data for gene mutant/deletion mice, are collected from hundreds of studies based on the list of references at http://stke.sciencemag.org/cgi/cm/stkecm;CMP_13296[2].

Our gene network is a directed graph, consisting of three kinds of nodes: a gene node (circle), a protein node (rectangle), or a protein complex (diamond). An edge A → B connects two nodes A and B, and its direction represents the message transmission: A activates/inhibits B via passing

[1] Computer Science Department, University of Massachusetts at Amherst, Computer. E-mail:ytong@cs.umass.edu

[2] Computer Science Department, University of Massachusetts at Amherst, Computer. E-mail:hava@cs.umass.edu

messages of start /stop activation or start/stop inhibition at certain points in time. Each node is associated with an expression function which describes how it is affected by its input; this is based on biological data or published computational models. A node can receive message(s) from its direct upstream node(s), when it reaches a certain threshold, it sends out activation/inhibition message(s) to its direct downstream node(s). The node representing the protein complex is associated with a more complex function that simulates the multi-level regulation according to biological data, such as simulation of light driven, simulation of transcription regulation by protein compound, and simulation of nuclear translocation.

In our model we make the assumption that when a node reaches its peak level, it remains there until it receives a message of stop activation or start inhibition from its direct upstream node(s). Similarly, we assume that when a node reaches its trough level it stays there until a message is received to start activating or stop inhibition. To simplify the model, we incorporate the functions of some other regulate genes/proteins (such as Clock, Cry1 and Cry 2) in the core clock system as part of the regulate functions in node M or N.

Figure 1 shows our gene network of the wild type mammalian biological clock. It includes two feedback loops. Solid lines represent positive feedback and dash lines represent negative feedback. M and N are protein complexes, and are used to simplify the simulation. Bmal_M_Rev-erbα feedback loop is non-light driven and cannot be affected by light directly. M_Per_N feedback loop is more important and directly regulated by light. We use this same network to simulate the genes/proteins behaviors in gene mutant/deletion animal, by putting the node representing the dysfunction gene/protein in a "sleep state," rendering it incapable of receiving and sending messages.

In future work we will consider our network of the single cell synchronization as the first step in explaining the synchronization in the different levels of the clock hierarchy. This should also include synchronizations among cells in same tissue/organ, synchronization among tissues, etc. Such a network structure would enable the simulation of the sophisticated relationships among core clock genes/proteins and hundreds of clock controlled genes/proteins, and therefore may be useful in analyzing health problems related to the system level confusion in the circadian rhythms, such as work shift, time zone effect and jet lag.

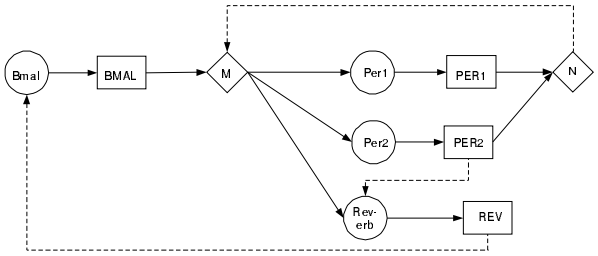

Figure 1: simulation wild type mammalian clock

References

[1] Leloup J. and Goldbeter A. 2003. Toward a detailed computational model for the mammalian circadian clock. PNAS. Vol. 100. pp. 7051-7056.

[2] Van Gelder, R. N. , Herzog, E. D. , Schwartz, W. J. and Taghert P. H. 2003. Circadian rhythms: In the loop at last. Science. Vol .300. pp. 1534-1535.