

Simulation analysis for the effect of light-dark cycle on the entrainment in circadian rhythm

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Introduction

The topic of this presentation

Simulation for the effects of light in circadian rhythm

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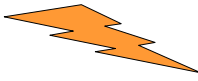
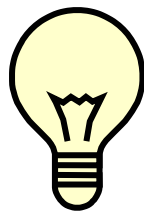
- Circadian rhythm
 - Gene regulatory network of circadian rhythm
- HFPN model for molecular circadian clock
 - Simulation under free-running conditions
- Light induced phase response simulation
 - Phase Response Curve obtained from simulation
- Entrainment to LD cycles
 - Simulation with the extended HFPN model
 - Jet lag simulation : Flying from Tokyo to N.Y

Circadian Rhythm

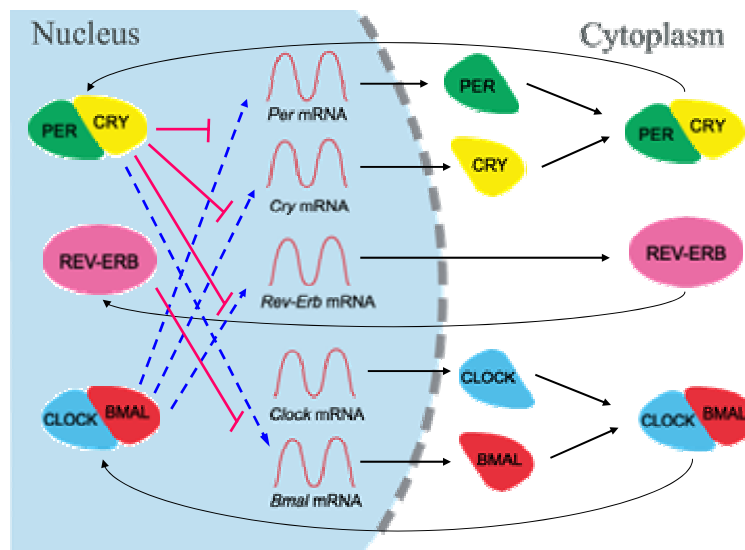
- An approximate daily periodicity
- Entrained by external cues, called Zeitgebers





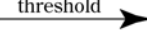


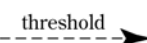
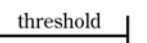
Daylight



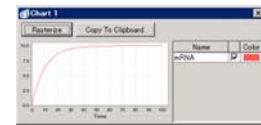
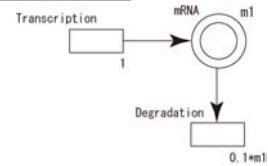
Gene Regulatory Network of Circadian Clock



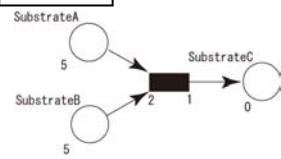
Hybrid Functional Petri Net (HFPN)

Places	Transitions	Arcs
<p>real number</p>  <p>Continuous Place</p>	<p>speed</p>  <p>Continuous Transition</p>	<p>threshold</p>  <p>Normal Arc</p>
<p>integer</p>  <p>Discrete Place</p>	<p>delay speed</p>  <p>Discrete Transition</p>	<p>threshold</p>  <p>Test Arc</p> <p>threshold</p>  <p>Inhibitory Arc</p>

Continuous



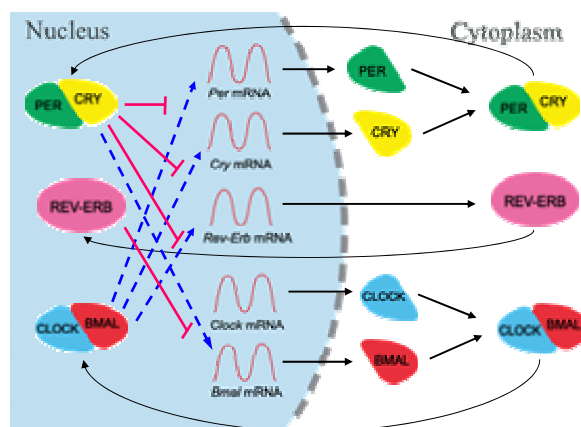
Discrete



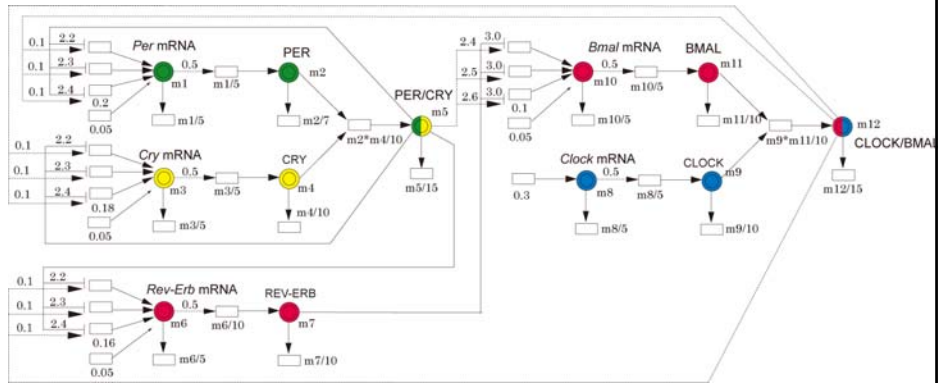
Matsuno, H., *et al.*, Biopathways Representation and Simulation on Hybrid Functional Petri Net., *In Silico Biol.*, 3(3):389-404,2003.

<http://www.cellillustrator.org/>

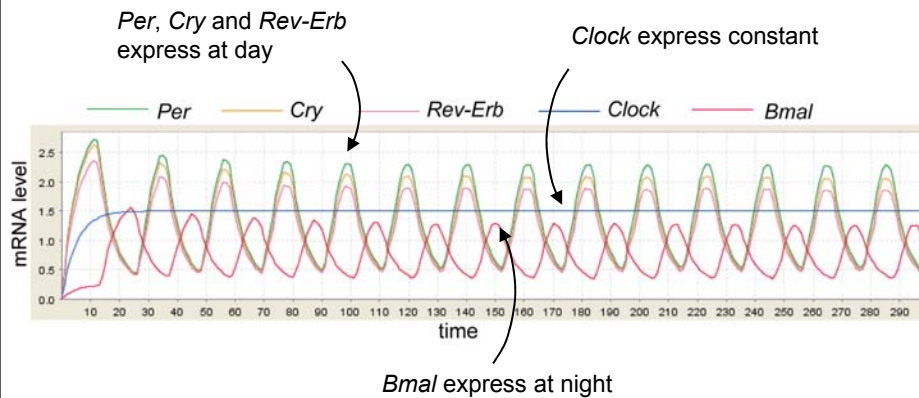
Hybrid Functional Petri Net (HFPN) Model of Circadian Gene Clock



Hybrid Functional Petri Net (HFPN) Model of Circadian Gene Clock



Oscillations of mRNAs in the HFPN model

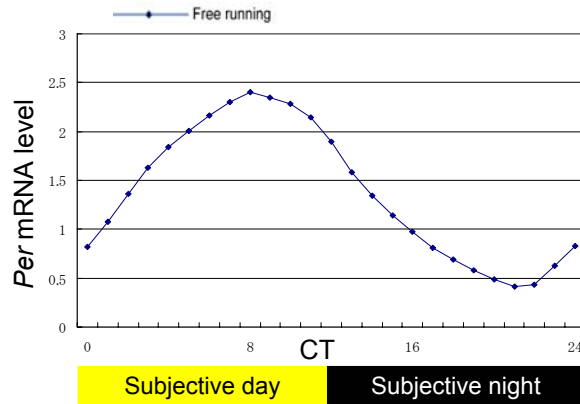
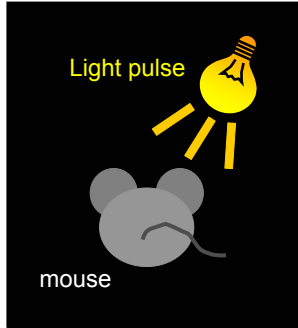


Generating stable rhythms called free-running rhythms in constant condition.

How light effect function?

Per mRNA levels in free-running and induced after light from biological experiment

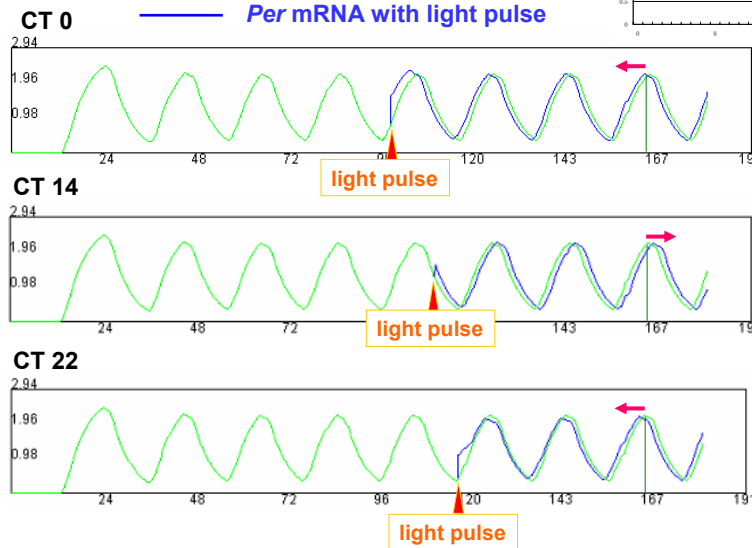
Biological experiment



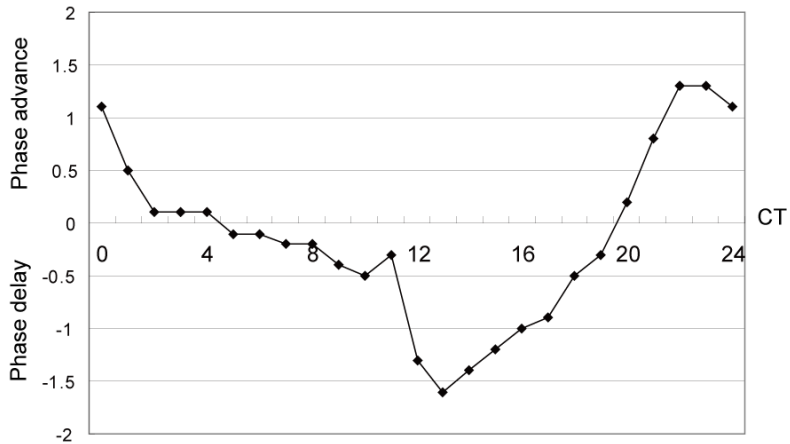
Miyake *et al.*, Neuroscience Letters 294 (2000)

Simulation of phase shift by light pulse

— Per mRNA without light pulse
— Per mRNA with light pulse

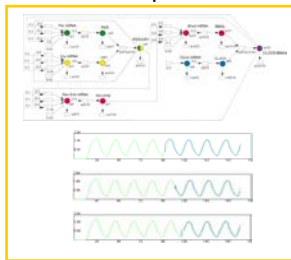


Phase Response Curve obtained from simulation

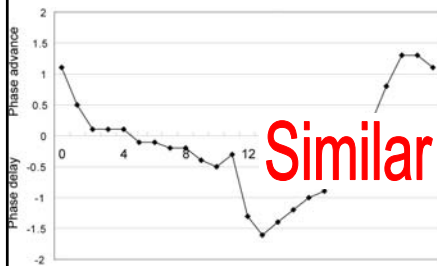


Phase response curve obtained from the simulation and biological literature

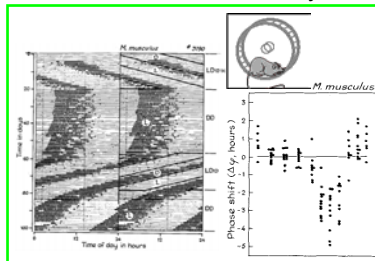
Gene expression



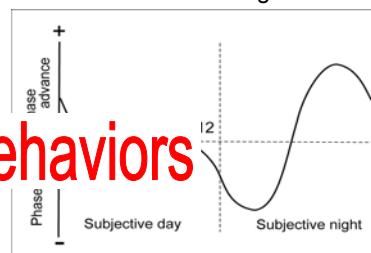
PRC obtained from simulation



Animal locomotor activity



PRC described in biological literature*

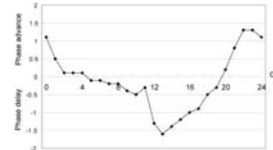


Similar behaviors

* Pittendrigh, C.S. and Daan, S., J.Comp.Physiol (1976)

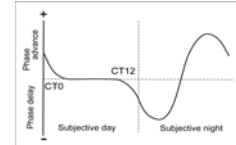
Summary on the way

1. Successfully and quantitatively simulating the behavioral phase shift of the circadian clock.
(Light induction of one kind of clock gene (Per) was taken into consideration.)

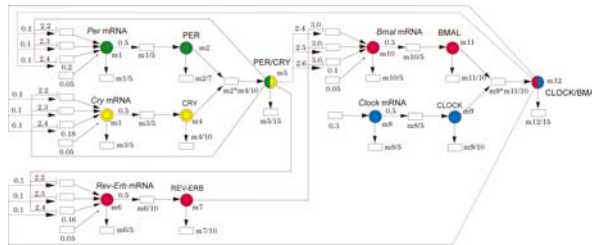


Simulation

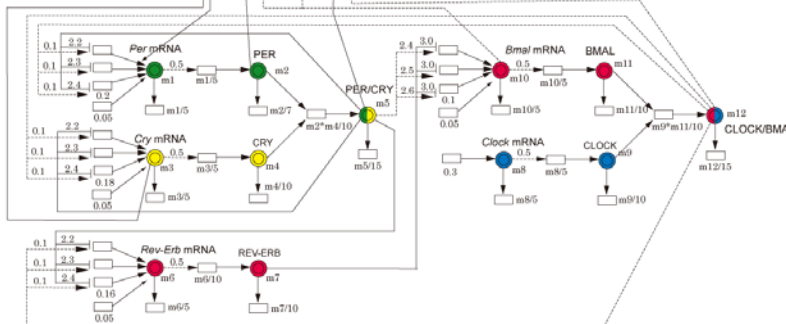
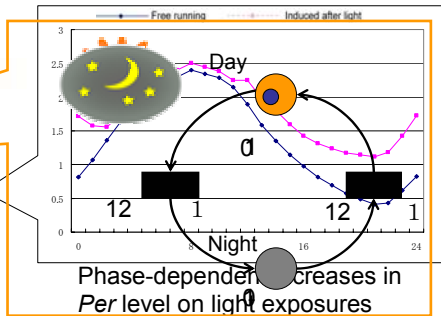
2. Suggesting that the five genes feedback mechanism is essential for phase response behavior.



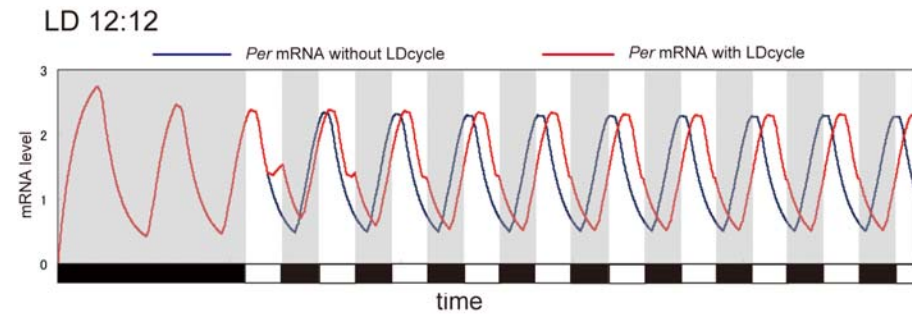
Animal experiments



Entrainment to LD Cycles



Entrainment Simulation in LD 12:12

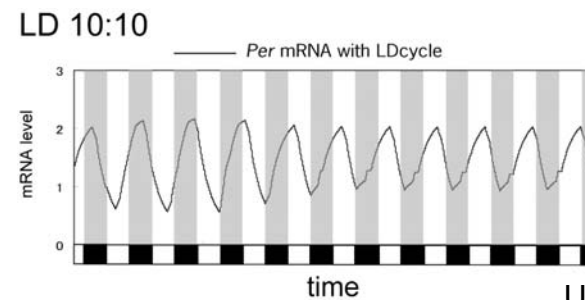


Mouse free-running period < 24

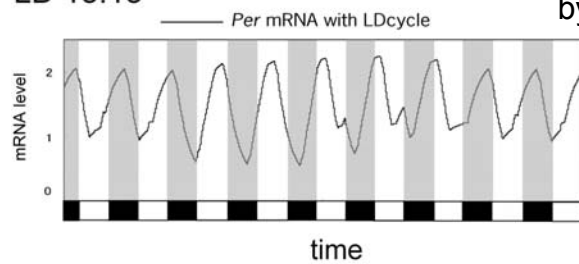
Per without LDcycle is not lined up LDcycle(24h)

Per with LDcycle is entrain LDcycle(24h)

Entrainment Simulation in far from 24h LD cycle



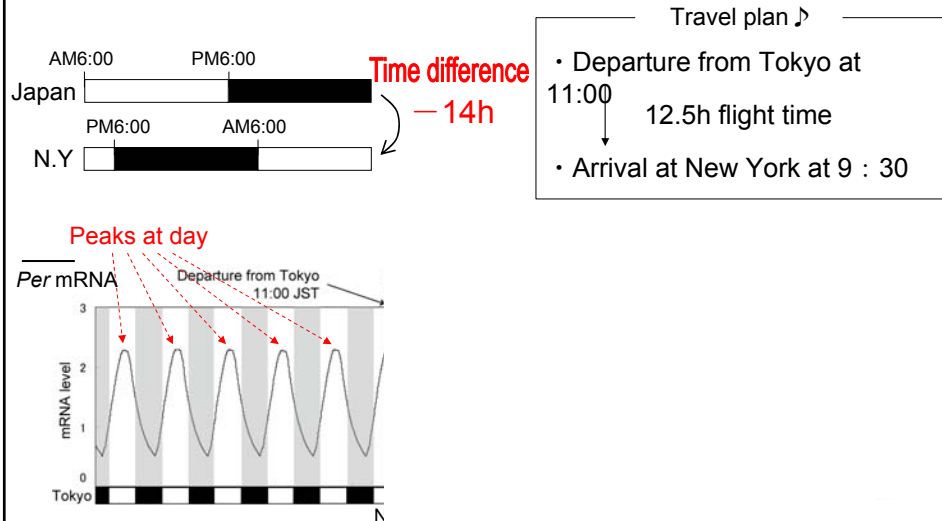
LD 13:13



Unable to be entrained
by far from 24h LDcycles.

Confirmed the biological fact

Jet Lag Simulation: Flying from Tokyo to New York



Summary

- Suggesting that the five genes feedback mechanism is essential for phase response behavior.
 - Entrainment was found possible only when periodicity of the external LD cycle was close to 24hr.
- ➡ Found in the biological observation strengthens the usefulness of our HFPN model.
- Our model successfully reproduced unstable transition period corresponding physiological symptoms of malaise during the jet lag.

Thank you for listening !

Actgram Obtained from the Jet Lag Simulation

