DYNAMIC MODELING AND OPTIMIZATION OF CIRCADIAN CLOCK

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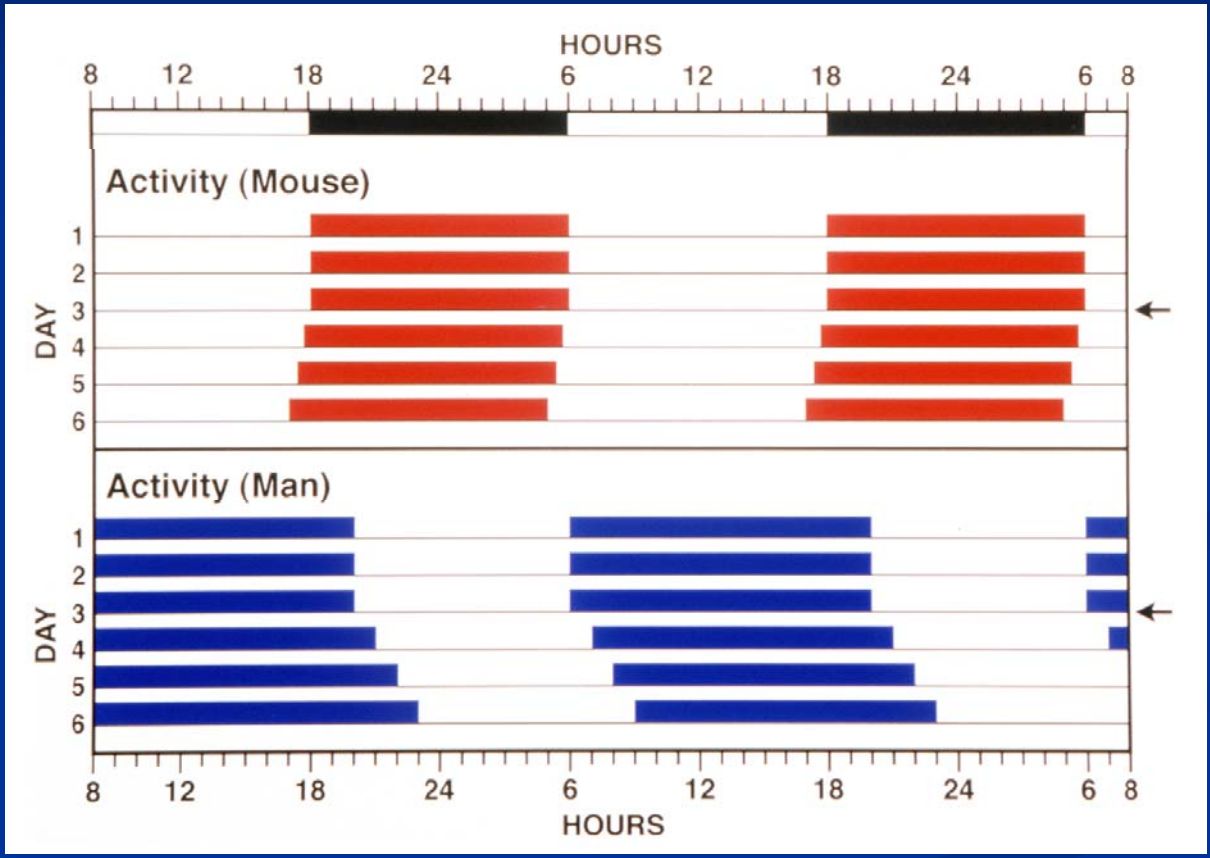
Biological Clock and Circadian Clock

A **clock** is a mechanical or an electronic device that measures time. There are several such systems in nature. However, the most pervasive clock in biology is the one like the clock we use in our daily lives, that is, the clock that measures the time of day. This is the clock that is often referred to as the "**Biological Clock**". In fact, its more precise name is the "**Circadian Clock**".

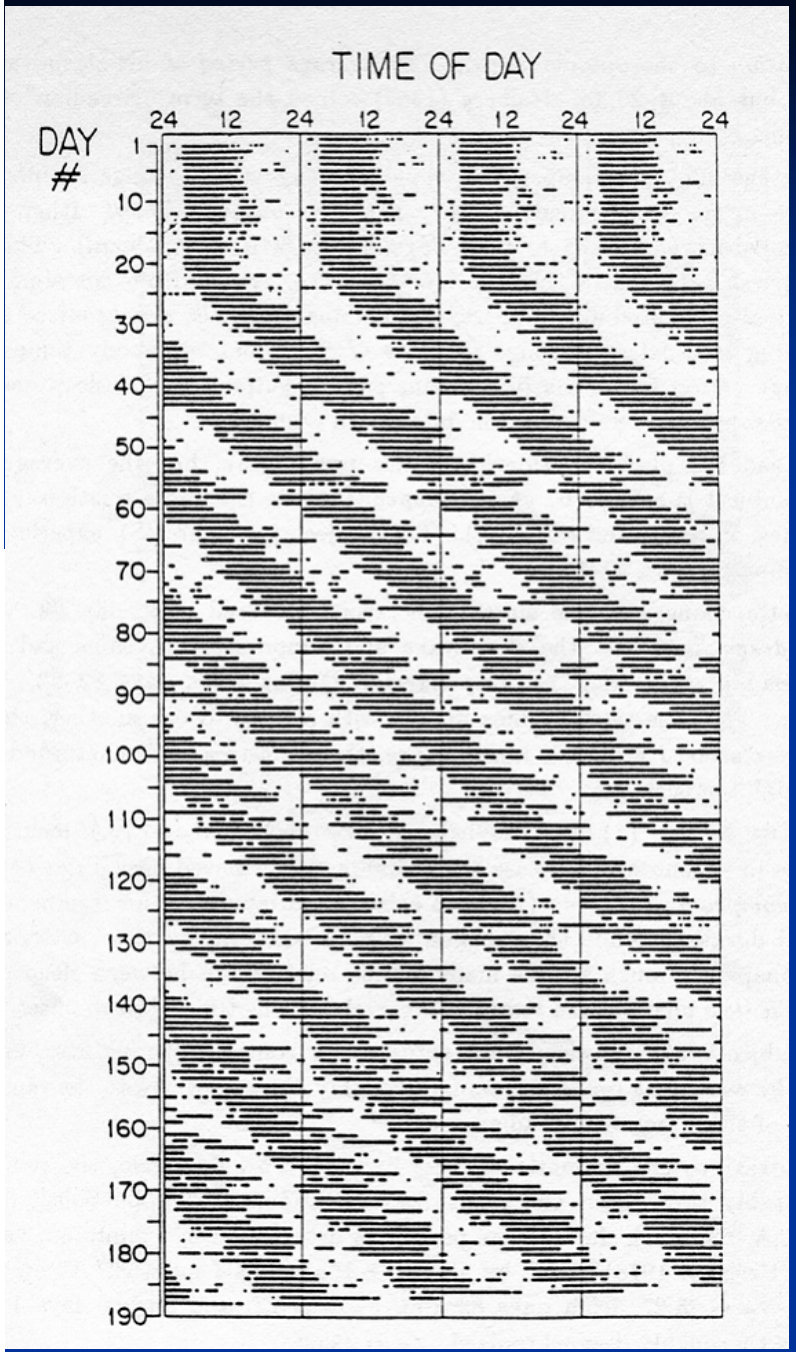
Circadian = circa (about) + dies (day)

CIRCADIAN PLOT



Sancar A (**2000**) Annu. Rev. Biochem.69:31-67

Circadian Rhythm of Body Temperature in Man



Colin J et al (**1968**) J. Appl. Physiol. 25:170-176

Circadian Rhythm

•It is the oscillation with the periodicity of about a day (*circa dies*) in the biochemical, physiological and behavioral functions of organisms; *t*=25 hrs (human); 23.7 hrs (mouse)

•It is generated by an innate time keeping mechanism (“biological clock”) independent of external input.

•The circadian clock is synchronized with the solar clock by light. In mammals the input to the clock is through the eye.

Why is the Circadian Clock Important :

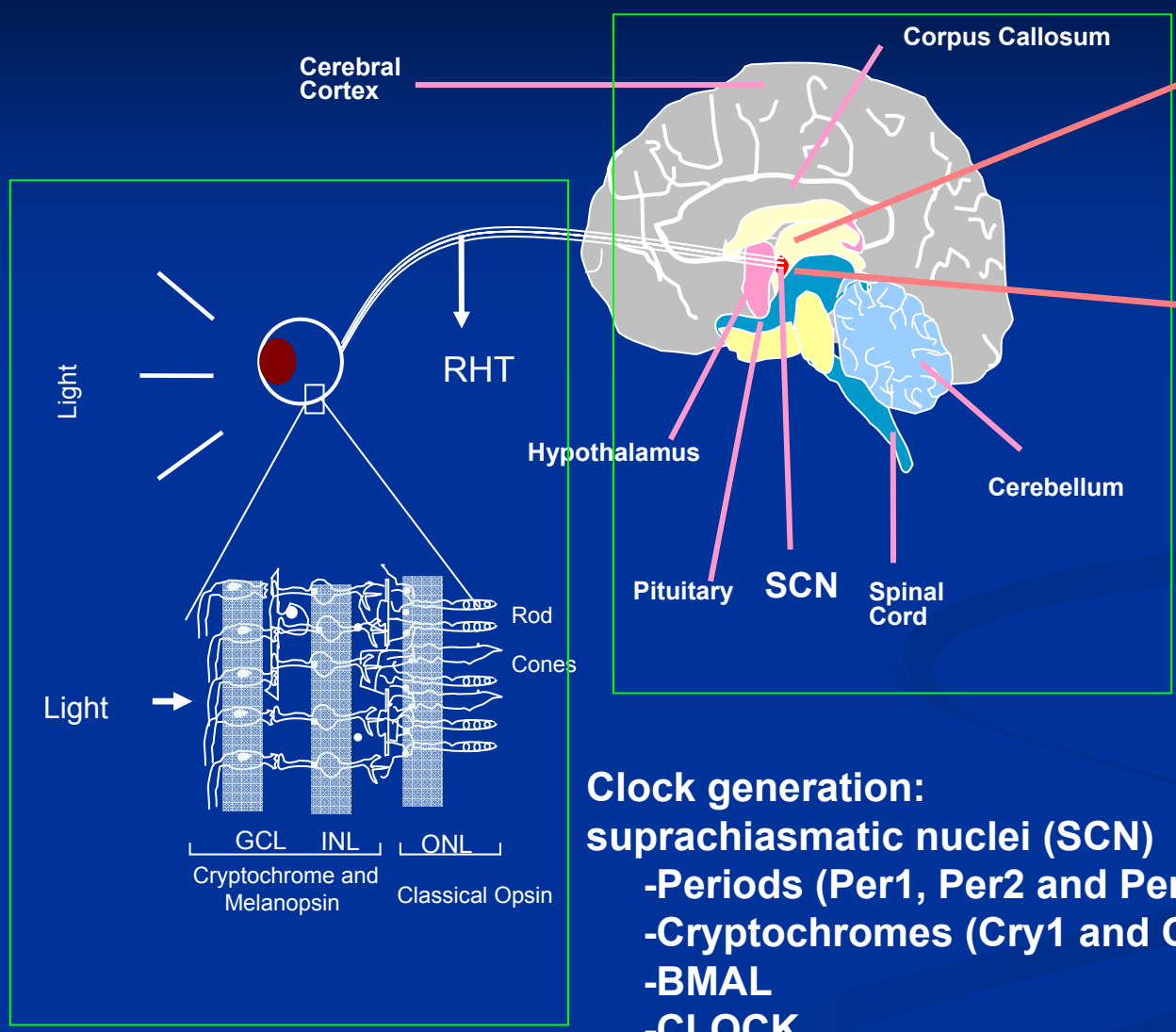
Chronotherapy: Administering anticancer drugs at specific times of day for optimal efficacy

Treatment of Ovarian Cancer with **Cisplatin (C)** and **Doxorubicin (D)**

Group	Time of Drug Delivery	5-Year Survival
1	Random	0%
2	D: 6:00 C: 18:00	11%
3	C: 6:00 D: 18:00	44%

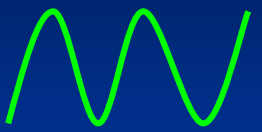
Hrushesky W (**1985**) Science **228** :73-85

Understanding Mechanism of Biological Clock in Human



Input elements

Clock generation:
suprachiasmatic nuclei (SCN)
- **-Periods (Per1, Per2 and Per3)**
- **-Cryptochromes (Cry1 and Cry2)**
- **-BMAL**
- **-CLOCK**
- **-Casein kinase Iε**

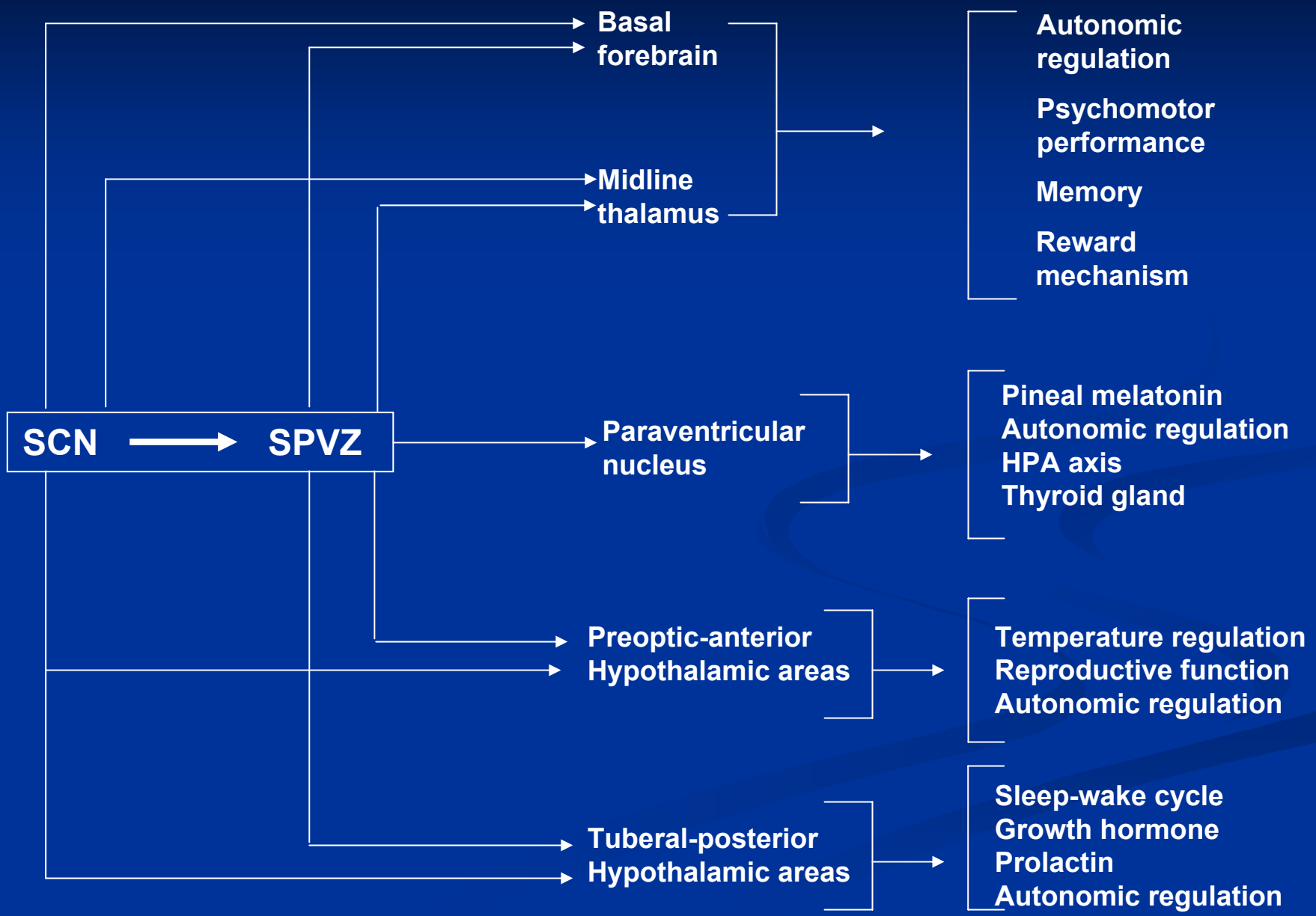


- **•sleep-wake cycles**
- **•neuroendocrine levels**
- **•mental alertness**
- **•physical strength**
- **•body temperature**
- **•blood pressure**
- **•blood viscosity and etc.**

Output elements

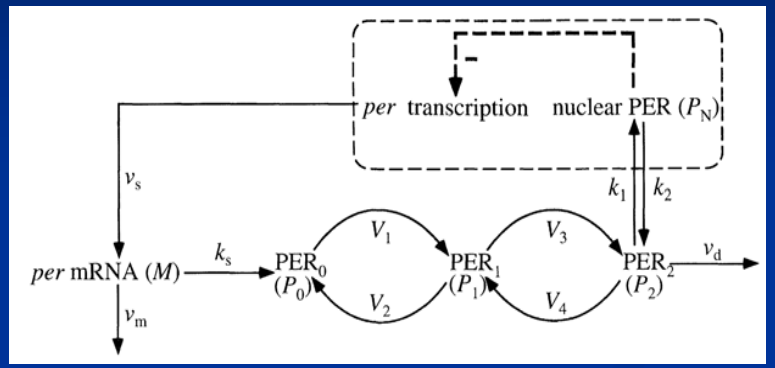
Kavakli and Sancar (2004) Mol. Inter.

SCN= suprachiasmatic nuclei
SPVZ=subparaventricular zone



MOLECULAR CLOCKS

- Drosophila



Goldbeter A. (1995) Proc. R. Soc. Lond. B 261: 319-324

- Neurospora

  Loros J.J. & Dunlap J.C. (2001) Annu. Rev. Physiol. 63: 757-794

- Bacteria

  Mori T. & Johnson C.H. (2001) Semin. Cell Dev. Biol. 12: 271-278

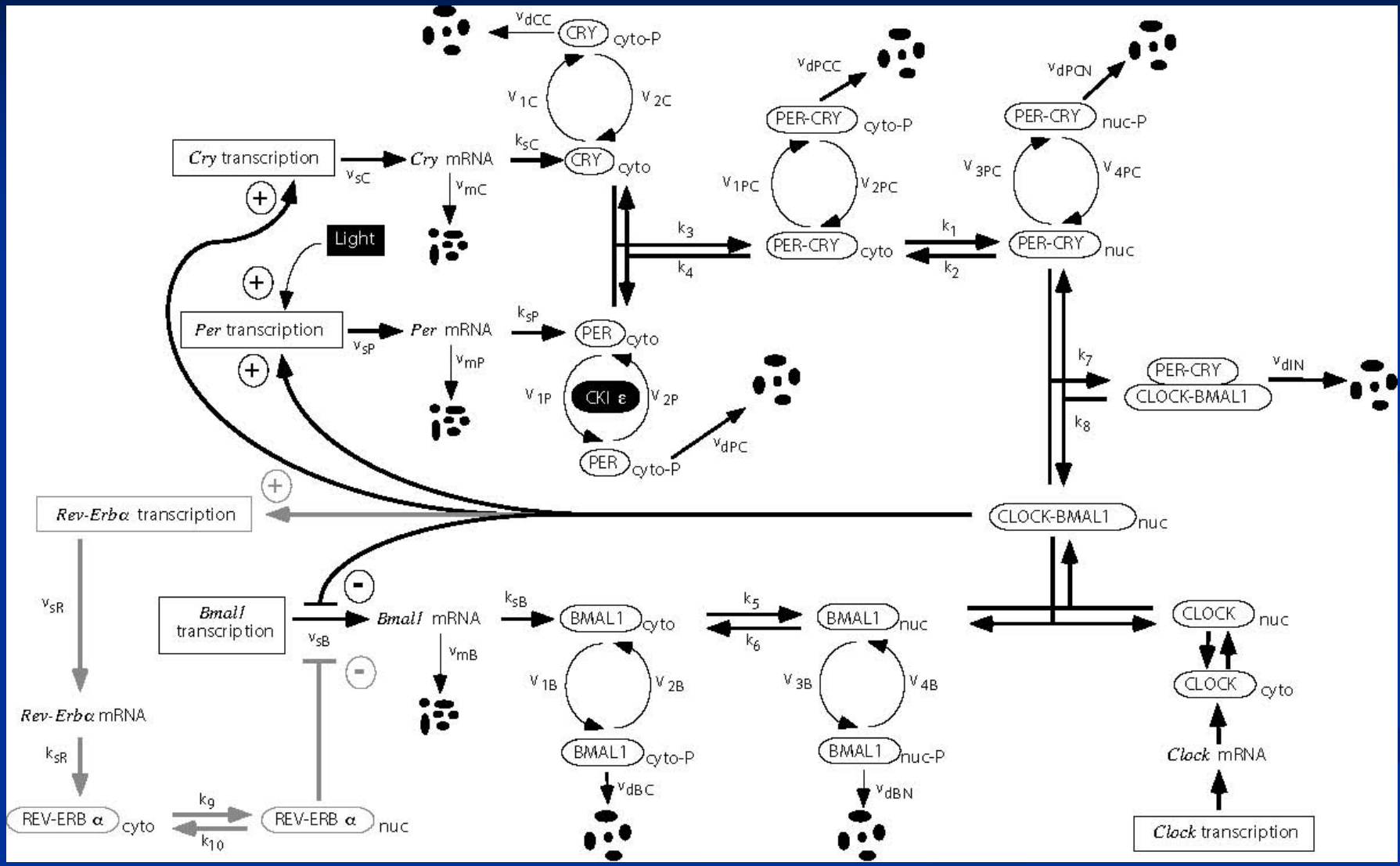
- Plants

  Roden L.C. & Carre I.A. (2001) Semin. Cell Dev. Biol. 12:305-315

OTHER MODELS

- Mouse
  - Antoch M. et al. (1997) Cell 89:4 655-667
- Mammalian
  - Leloup, J.L. & Goldbeter A. (2003) PNAS 100:12 7051-7056
  - Forger D.B. & Peskin C.S. (2003) PNAS 100:25 14806-14811
- Recently Human
  - Sancar A (2008) Nat. Struct. Mol. Biol. 15: 234-235

A DYNAMIC NETWORK MODEL



Leloup, J.L. & Goldbeter A. (2003) PNAS 100:12 7051-7056

$$\frac{dM_P}{dt} = v_{sP}\frac{B_N^n}{K_{AP}^n + B_N^n} - v_{mP}\frac{M_P}{K_{mP} + M_P} - k_{dmp}M_P$$

MODEL

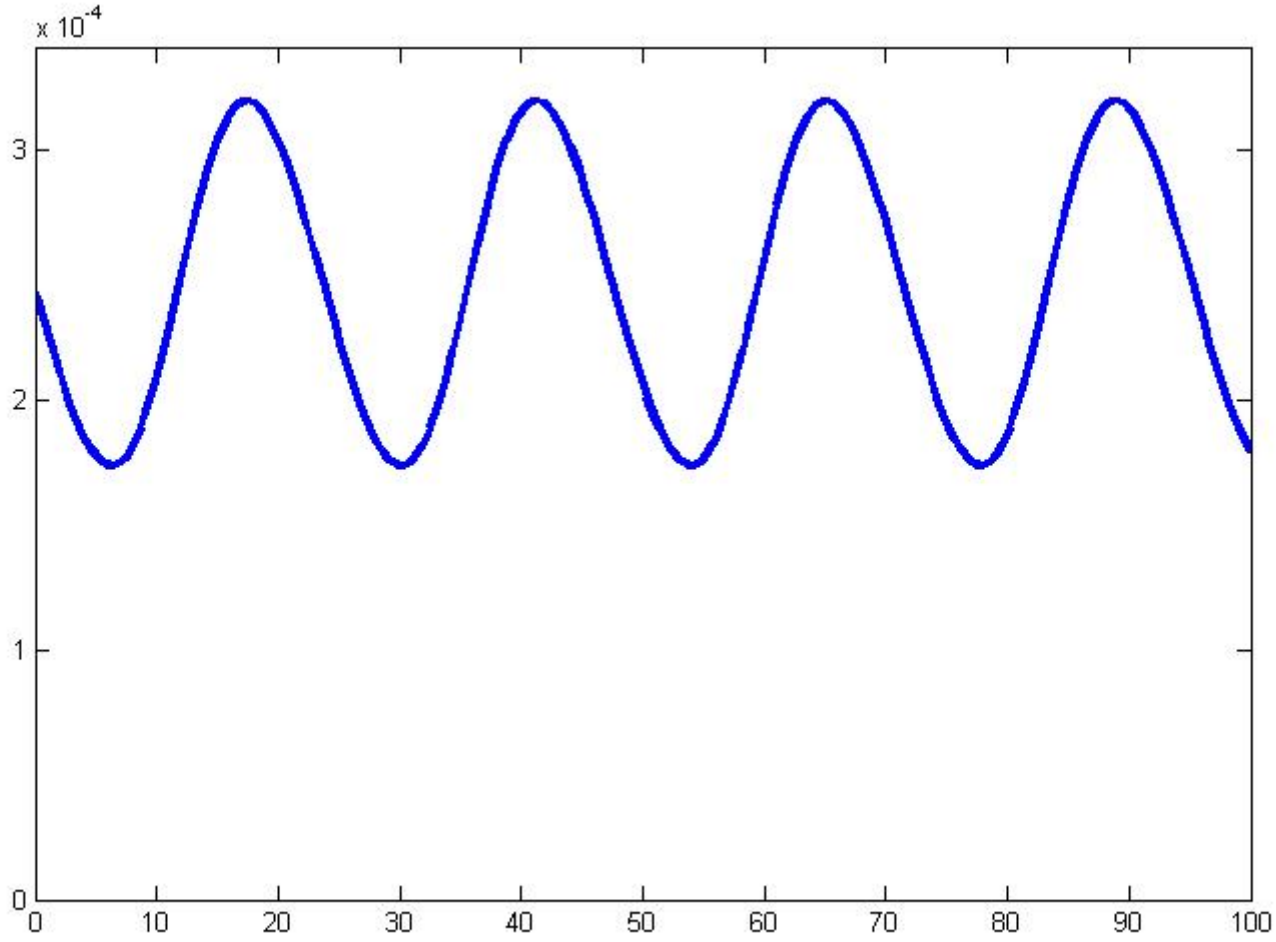
- Model by
  - Forger D.B. & Peskin C.S. (2003) PNAS 100:25 14806-14811

$$\frac{dx}{dt} = f(x)$$

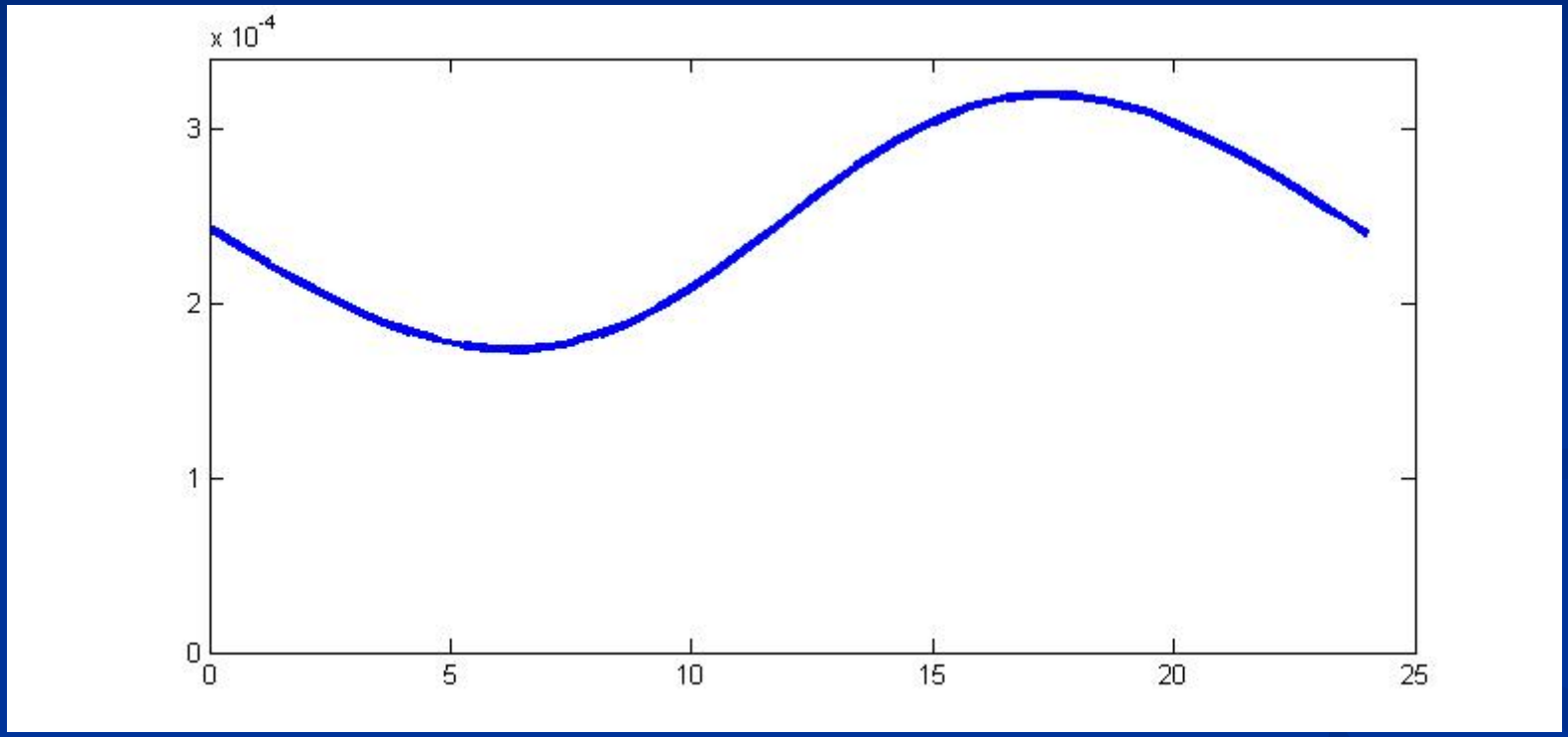
$$x_i = \sum_j \sum_{k \in V_{ij}} \nu_{jk} x_j - \sum_j \sum_{k \in V_{ji}} \nu_{jk} x_j$$

- 73 ODEs (mostly linear), 2 Algebraic Equations
- 74 variables
- Solved using MATLAB

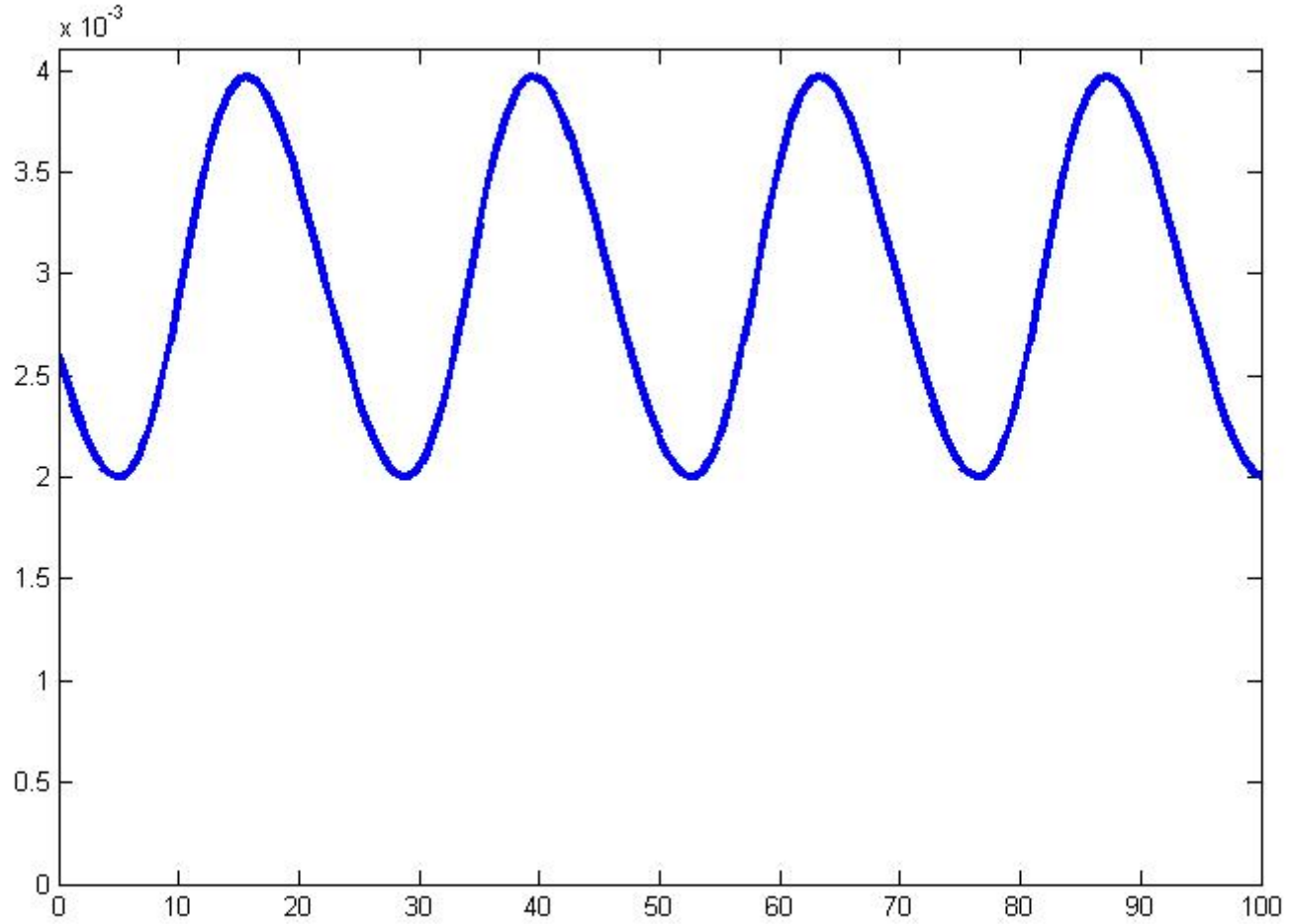
PER PROFILE – 100 hrs



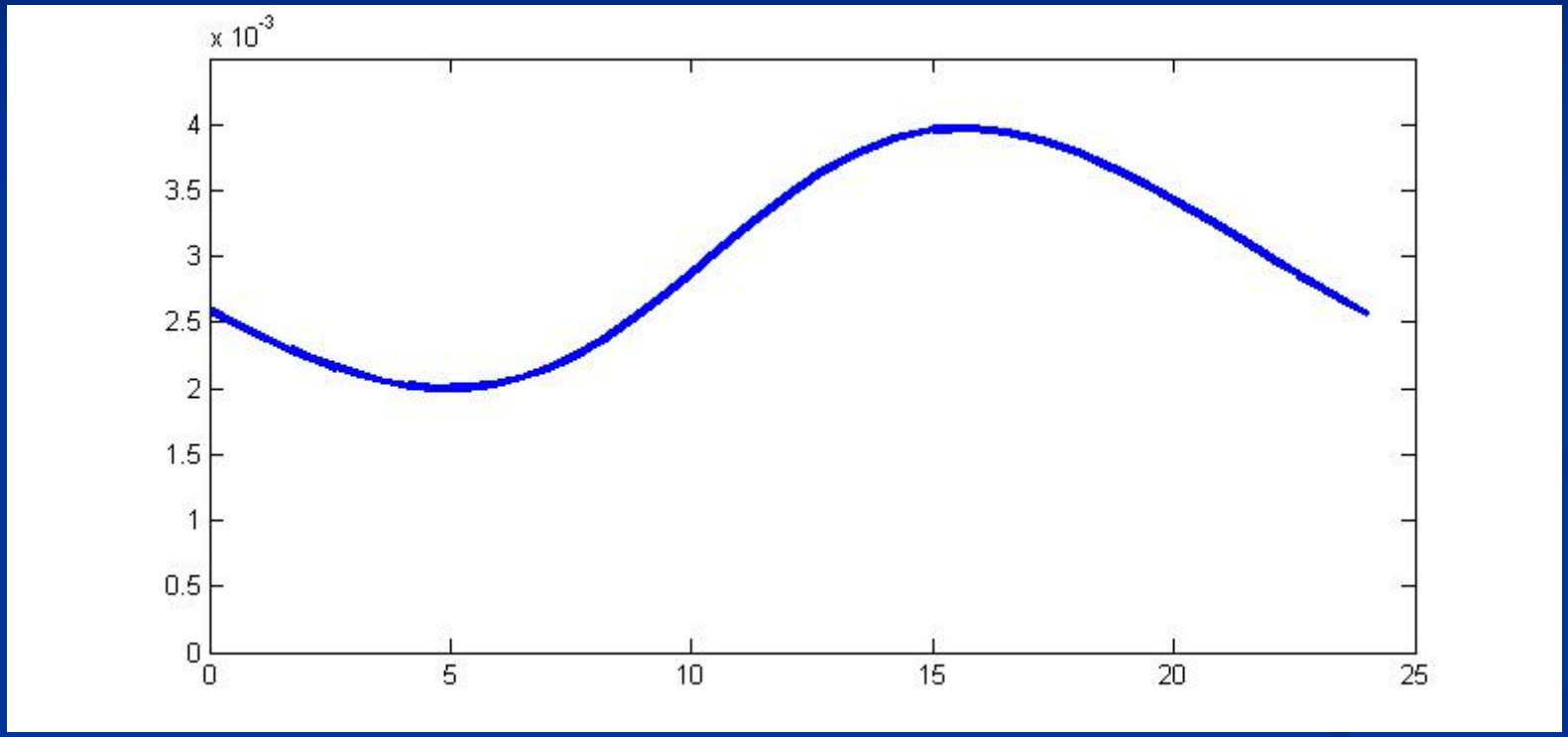
PER PROFILE – 24 hrs



CRY PROFILE – 100 hrs



CRY PROFILE – 24 hrs



OBSERVATIONS

- The dynamic model published by Forger & Peskin (2003) is reasonably accurate to capture the oscillatory behavior of mammalian circadian clock
- Need to do more parameter estimation studies for better fit

- *Introduce discrete switches to understand the effect of regulatory agents*

CONCLUSIONS

- Circadian Clock
  - A very important mechanism for humans
  - A new therapeutic target for many disease
- Dynamic Models
  - There are several available “good” models
  - Due to complexity and interaction of circadian rhythm with all biological processes, these models will continue to get larger
- Therapeutic Target
  - CRY
    - No crystal structure
    - Homology based structural model

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