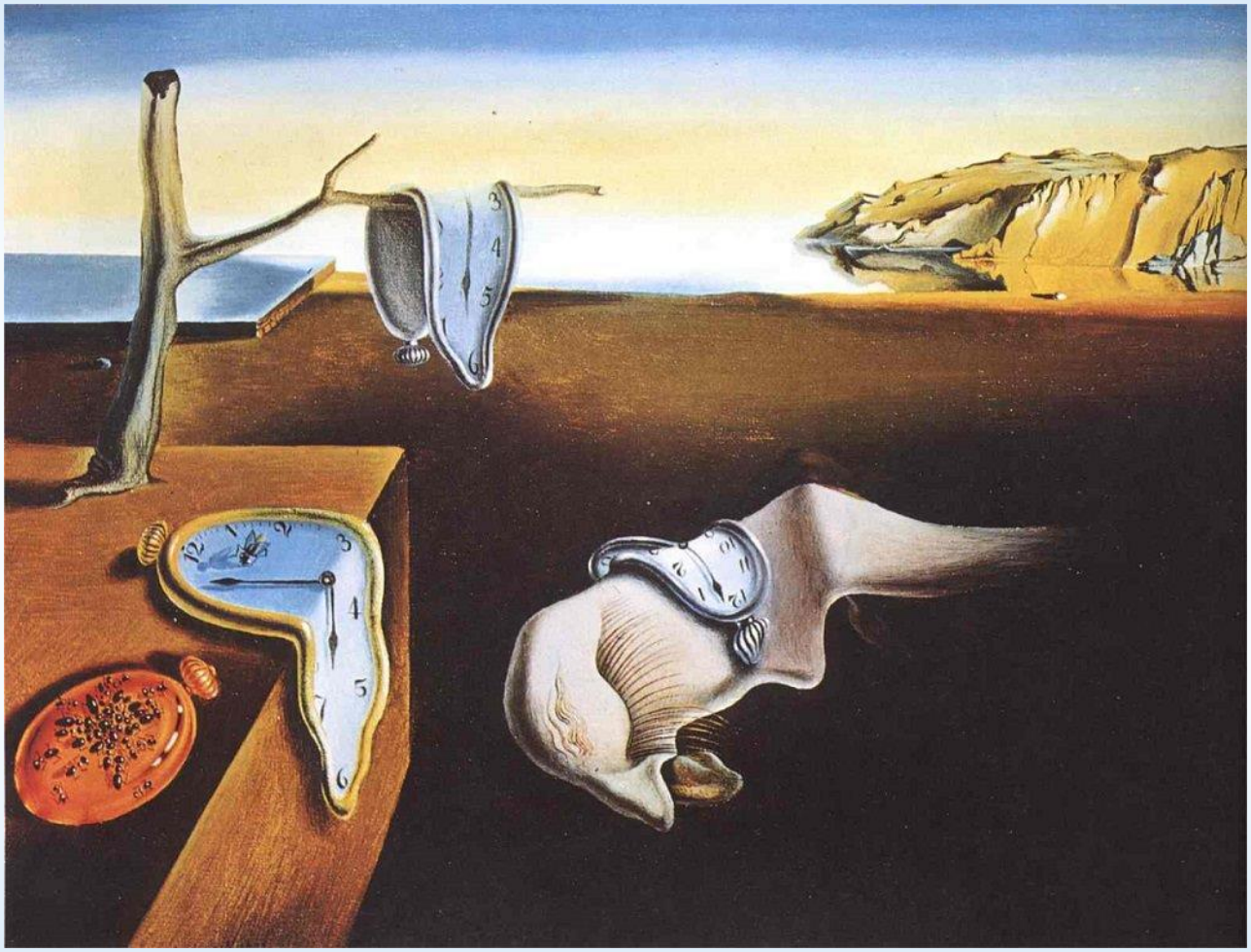
Circadian Rhythms in Physiology and Behavior



The Persistence of Memory, Salvador Dali, 1931

Homeostasis and Rhythms?

Homeostasis (Bernard, 1878): "All the vital mechanisms, however varied they may be, have but one end, that of preserving constancy in the internal environment."

A point that is not generally appreciated is that the body does not always seek constancy of its internal environment. It does not always react in ways that prevent change. On the contrary, sometimes physiological mechanisms actively promote change.

Changes in regulated levels have often initially been regarded as failures of homeostasis. Only later has the adaptive value of some of these changes been discerned. Keeping the internal environment constant is not always an overriding imperative.

Rheostasis: The Physiology of Change
N. Mrosovsky, 1990

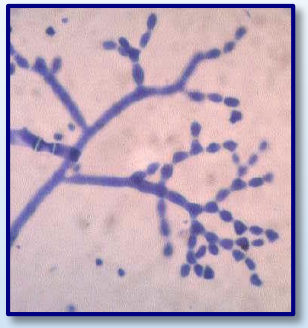
“Circadian” – About a day

Arabidopsis

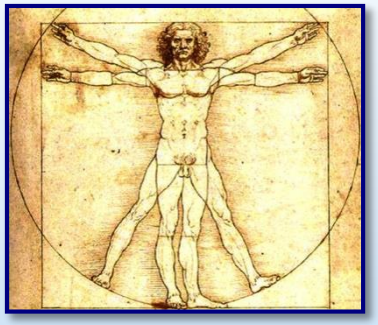
Cyanobacteria

Drosophila

Mice



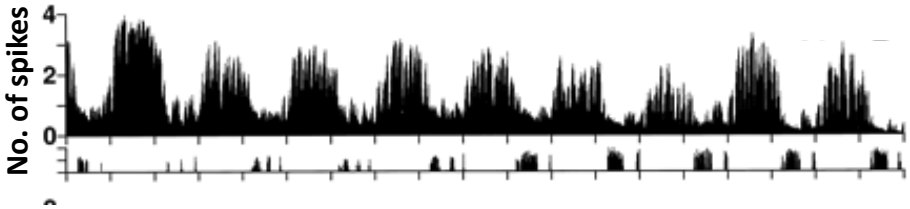
Neurospora



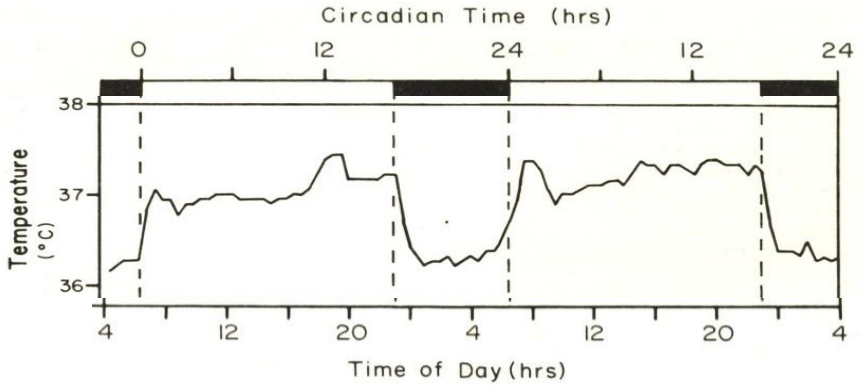
Humans

What are circadian rhythms?

The Power of Movement in Plants
Charles Darwin, 1880

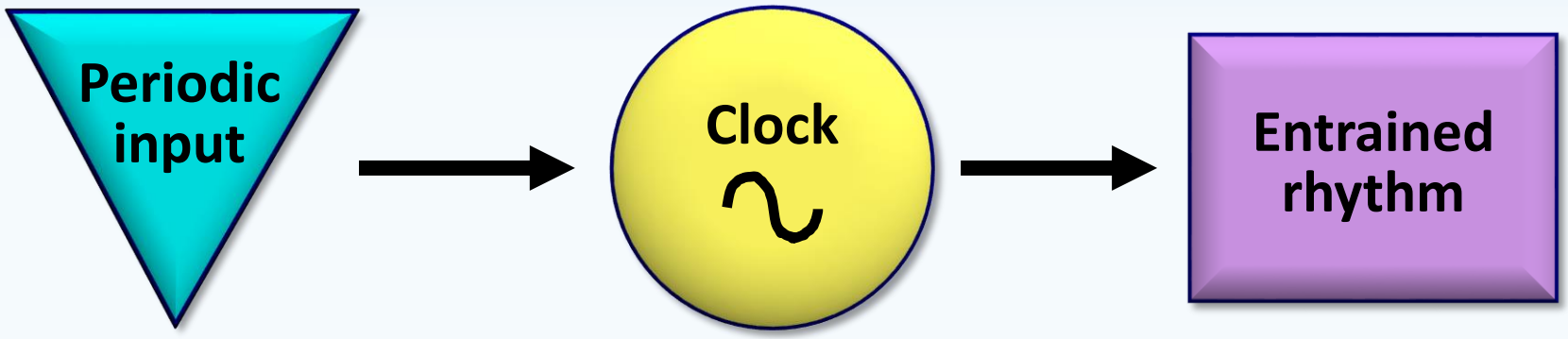


Electrical activity in hamster brain
Yamazaki *et al.*, 1998



Body temperature in humans
Moore-Ede *et al.*, 1982

Components of a circadian timing system



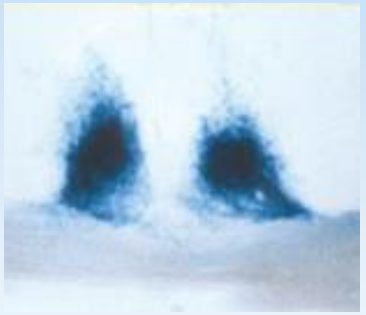
Light
Food
Temperature

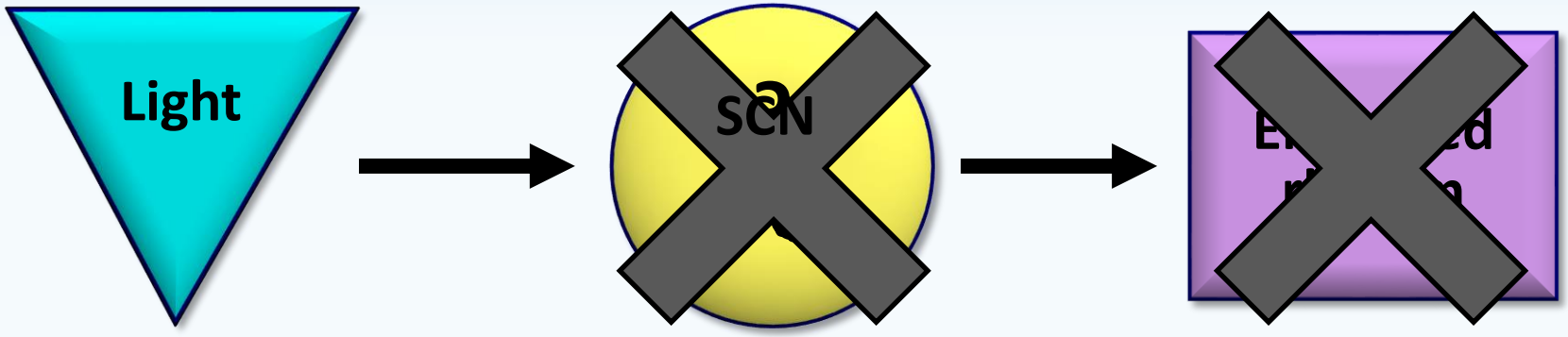
Self-sustained oscillator

Activity
Food intake
Hormones
Gene expression
Biochemistry

Pittendrigh & Bruce, 1957

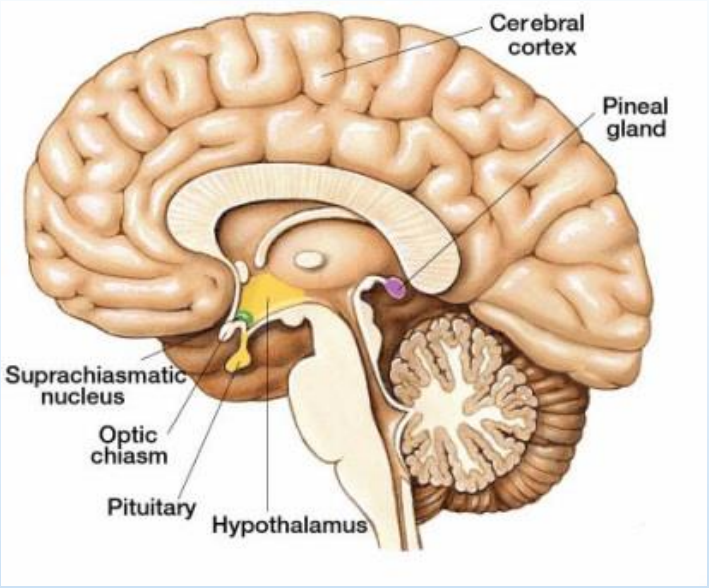
Where is “the clock?”





Stephan & Zucker, 1972
Moore & Eichler, 1972

Locomotor activity
Drinking
Corticosterone
Food intake

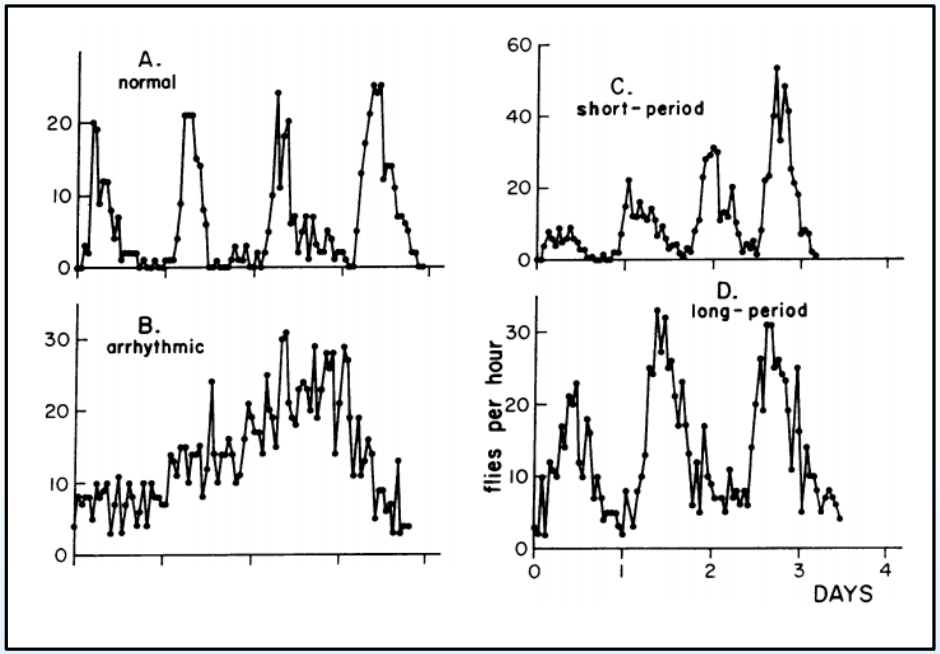


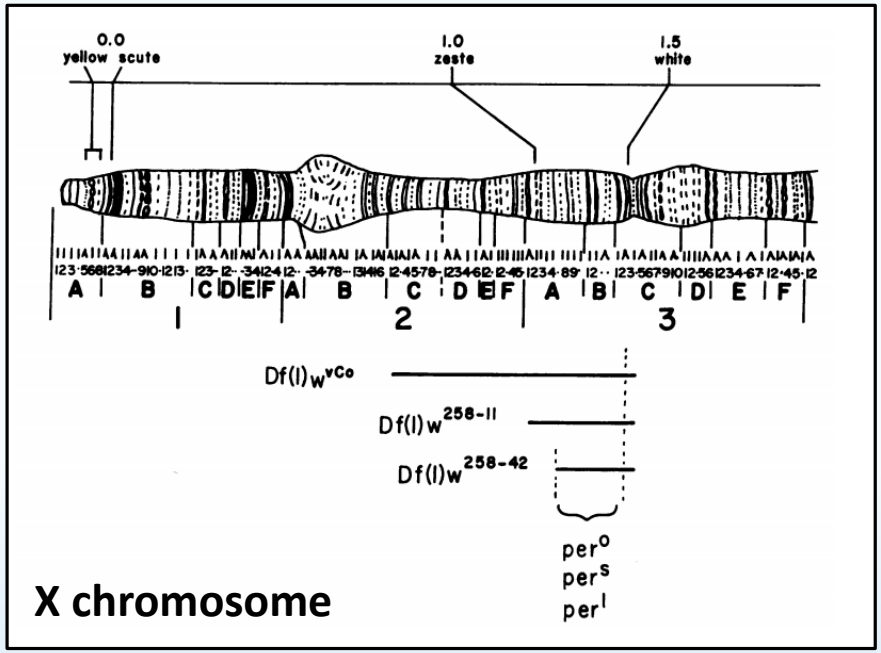
Do genes underlie the clock timekeeping mechanism?

What is the timekeeping mechanism of the clock?

Mutant Screening: Drosophila

Drosophila + EMS





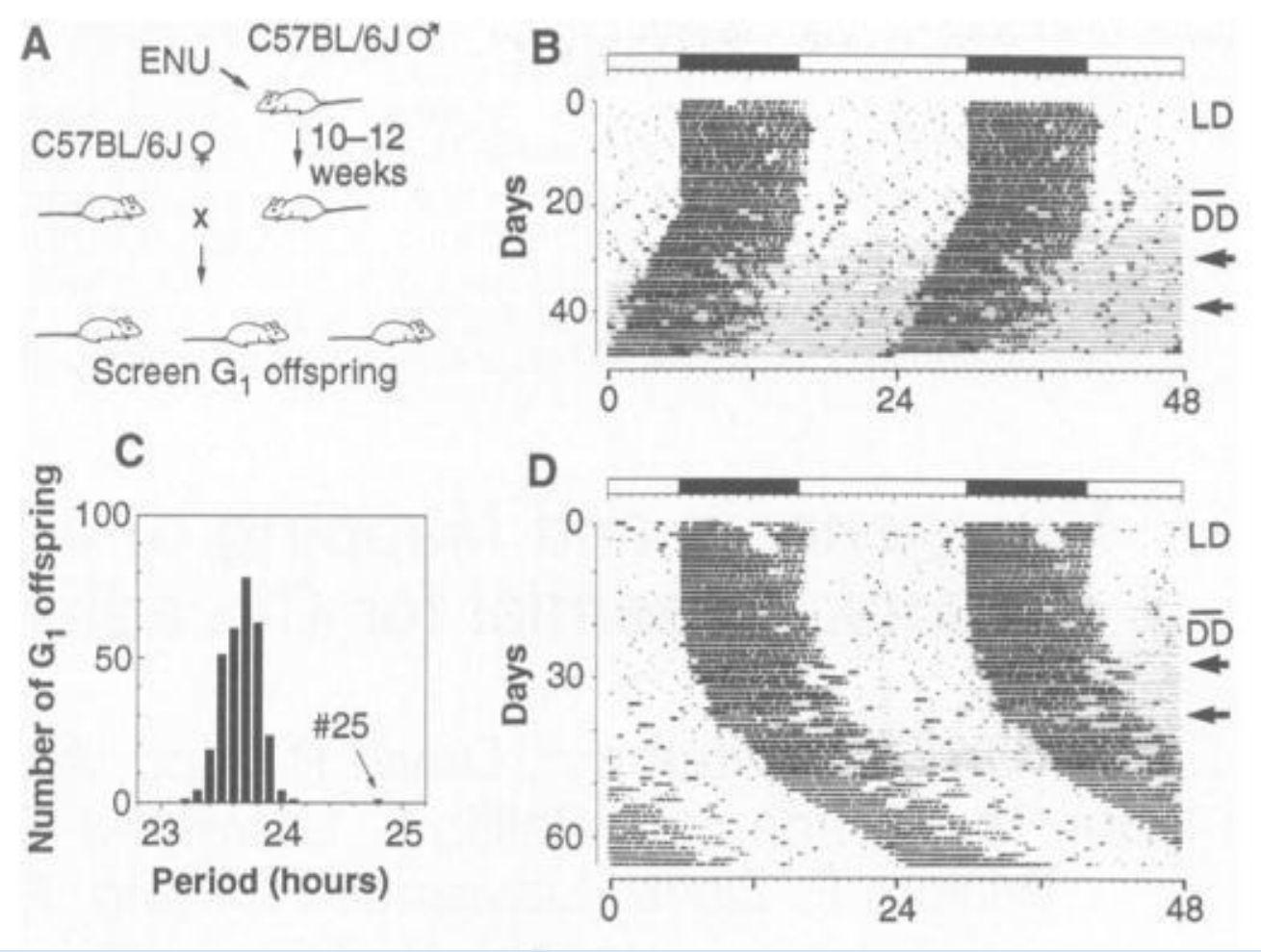
3 of 2000 were circadian mutants

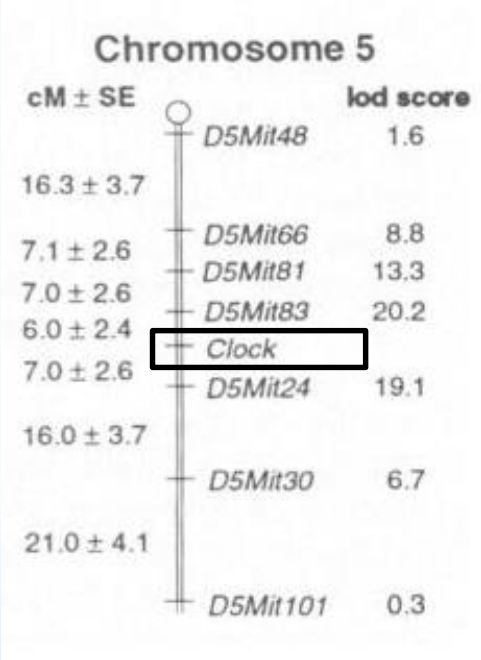
Konopka & Benzer, 1971

(1990: Drosophila *period* cloned by Rosbash, Hall, and Young)

What is the timekeeping mechanism of the clock?

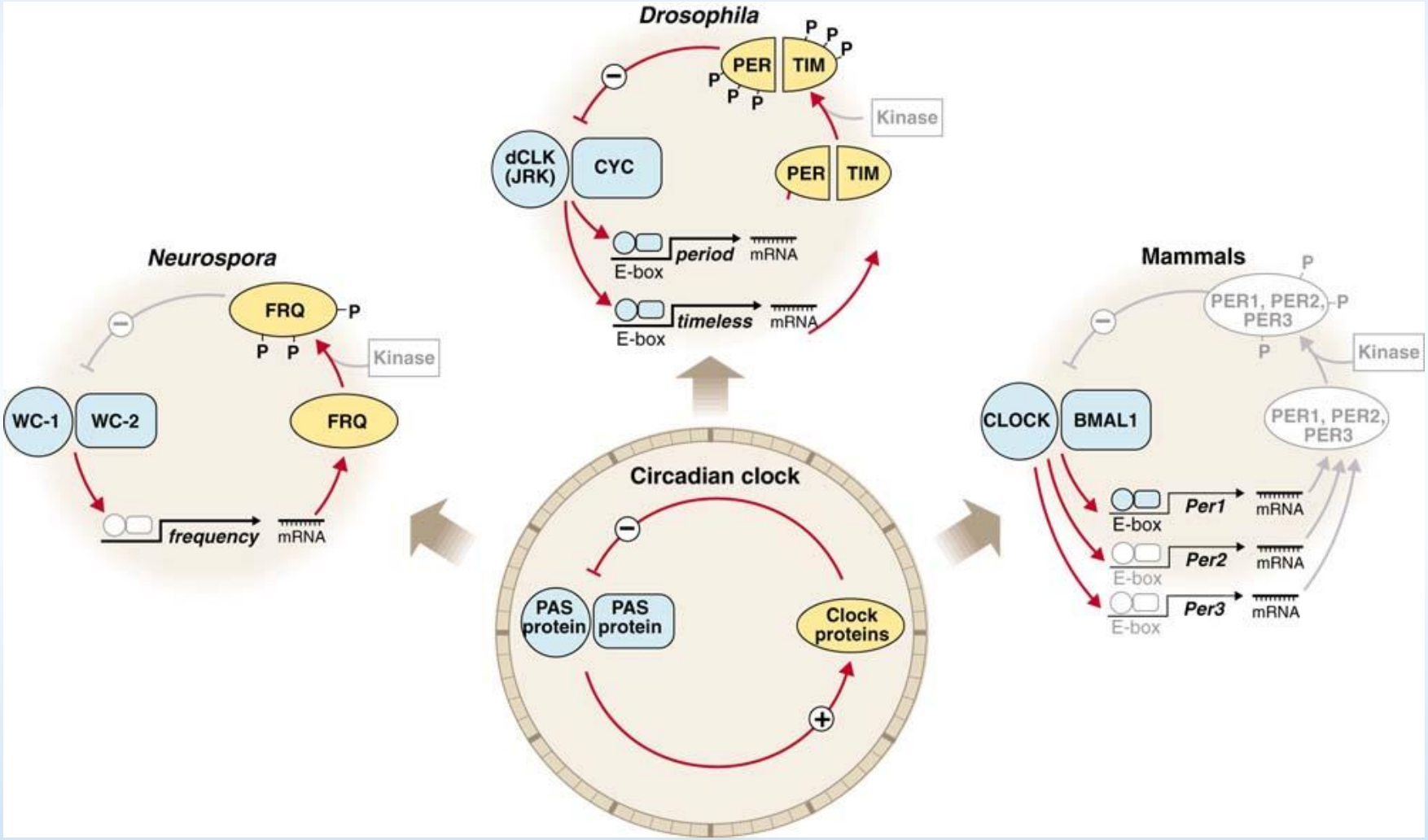
Mutant Screening: Mice





Vitaterna et al…Takahashi, 1994

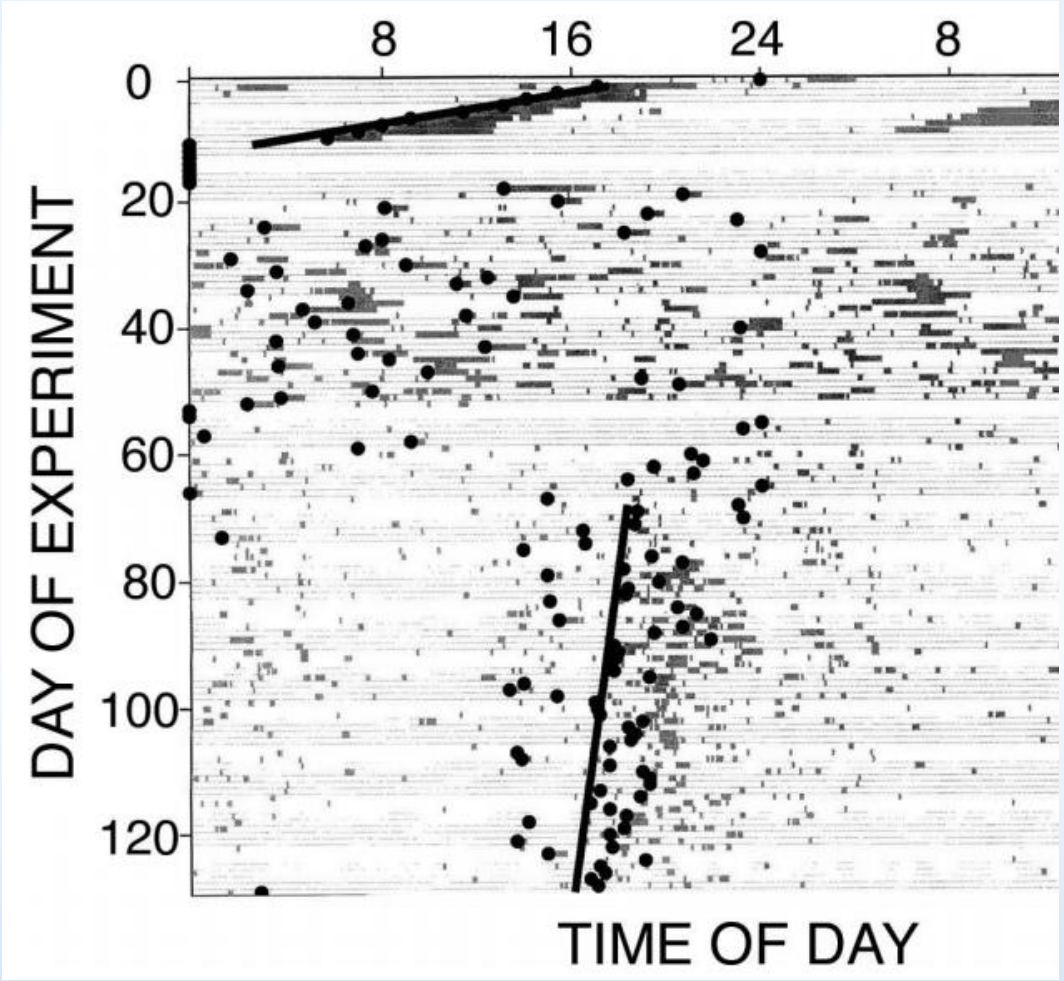
Circadian timekeeping: Feedback loops of transcription and translation



http://www.sciencemag.org/content/vol280/issue5369/images/large/1548-1-full.jpeg

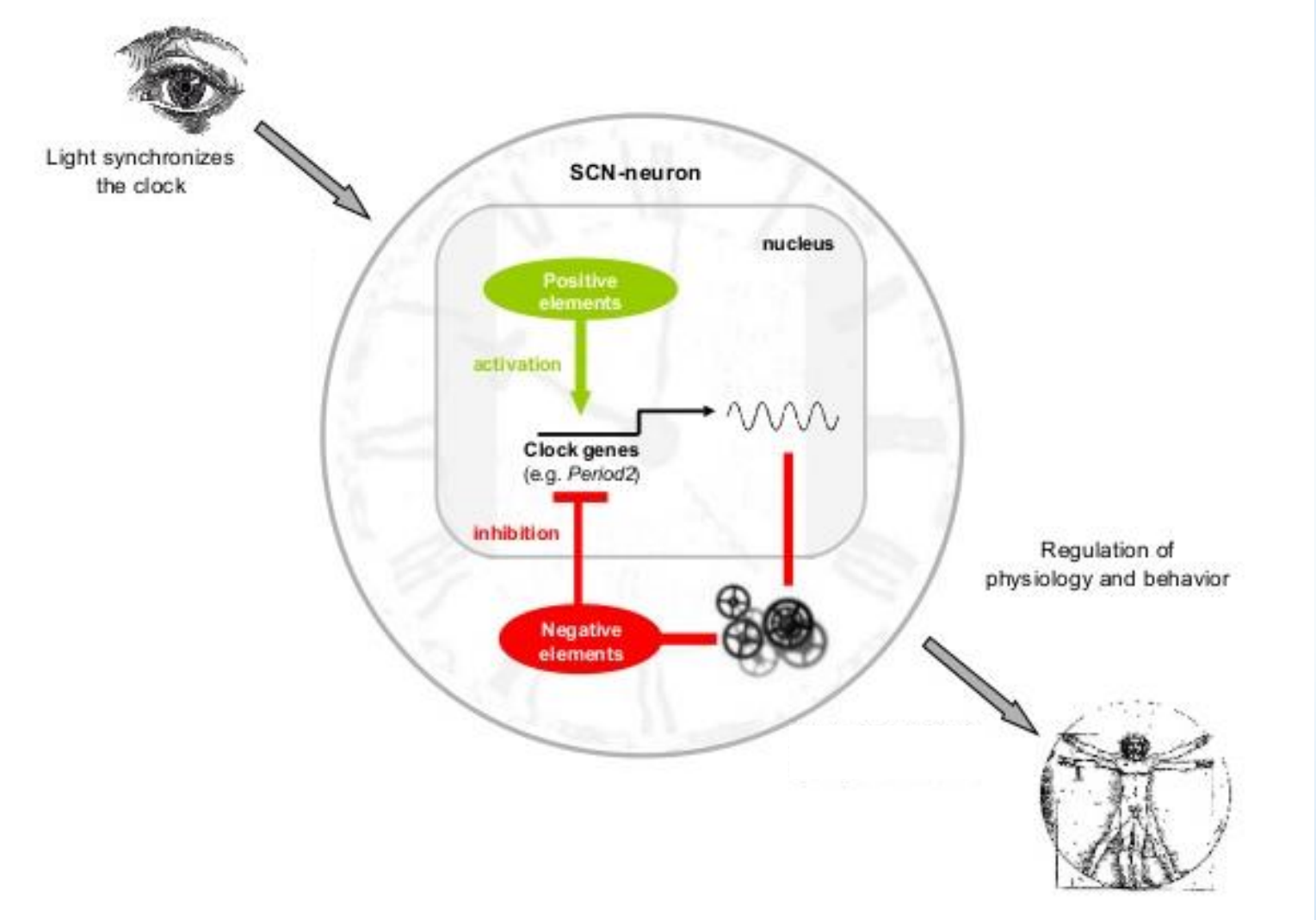
Genes encode circadian behavior

SCN transplant studies



Martin Ralph & Mike Menaker 1989

Input → Genes → Behavior



Too simple?

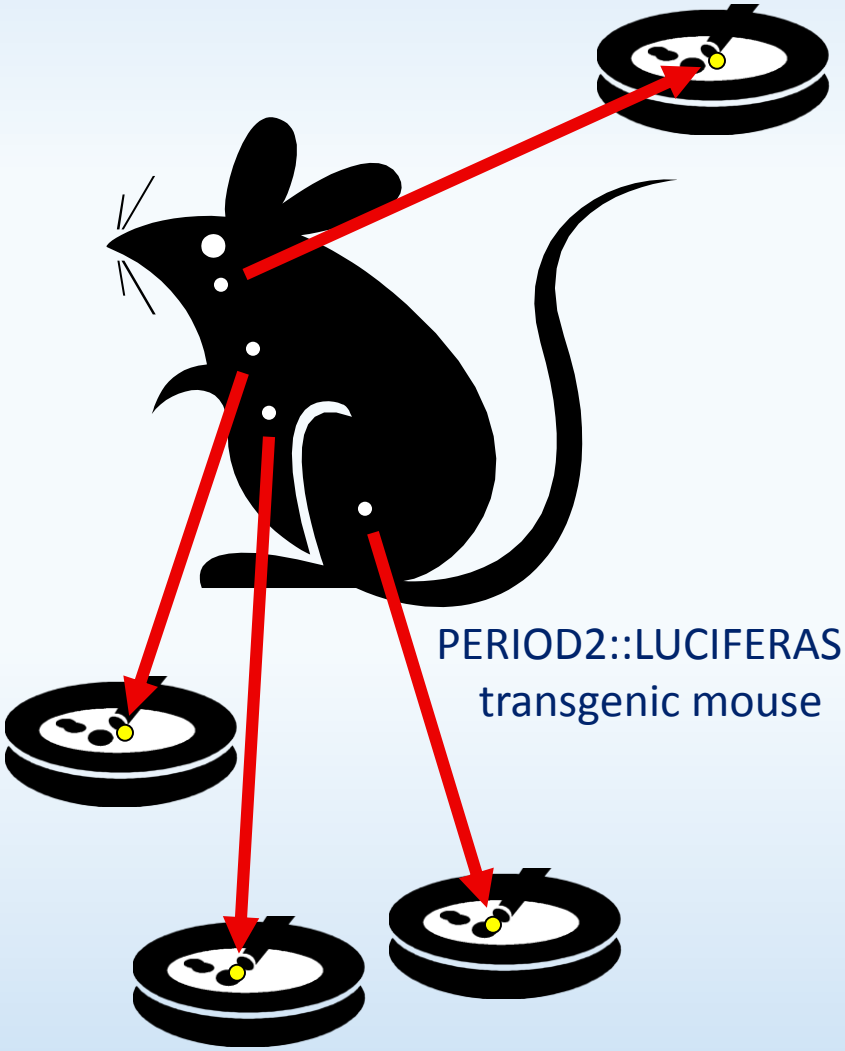
Is the SCN the only endogenous clock?

Light
Food
Temperature

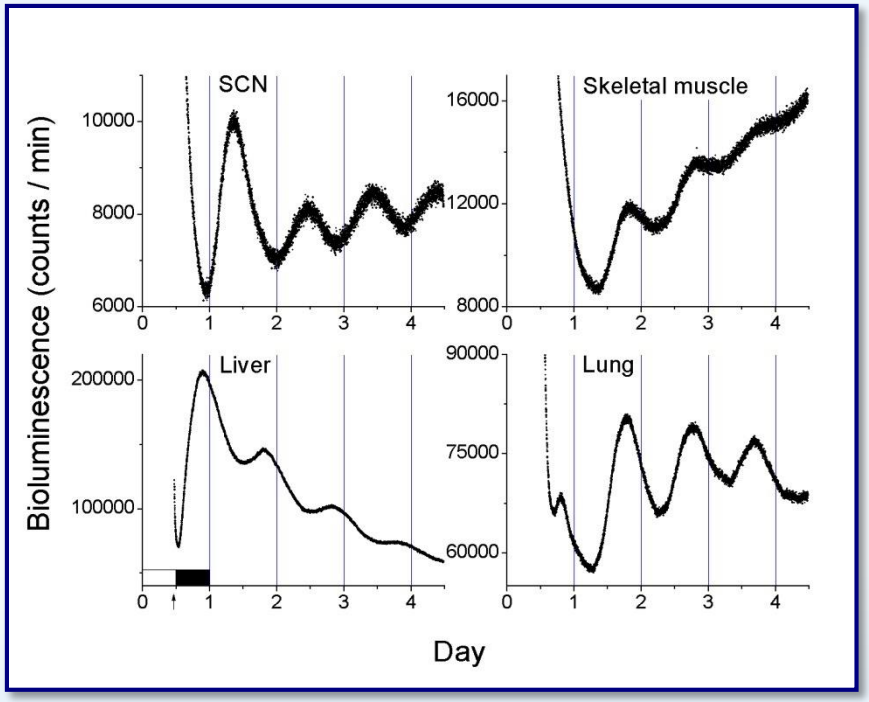
Self-sustained oscillators?

Activity
Food intake
Hormones
Gene expression
Biochemistry

Circadian reporter animals reveal the multi-oscillator network in mammals



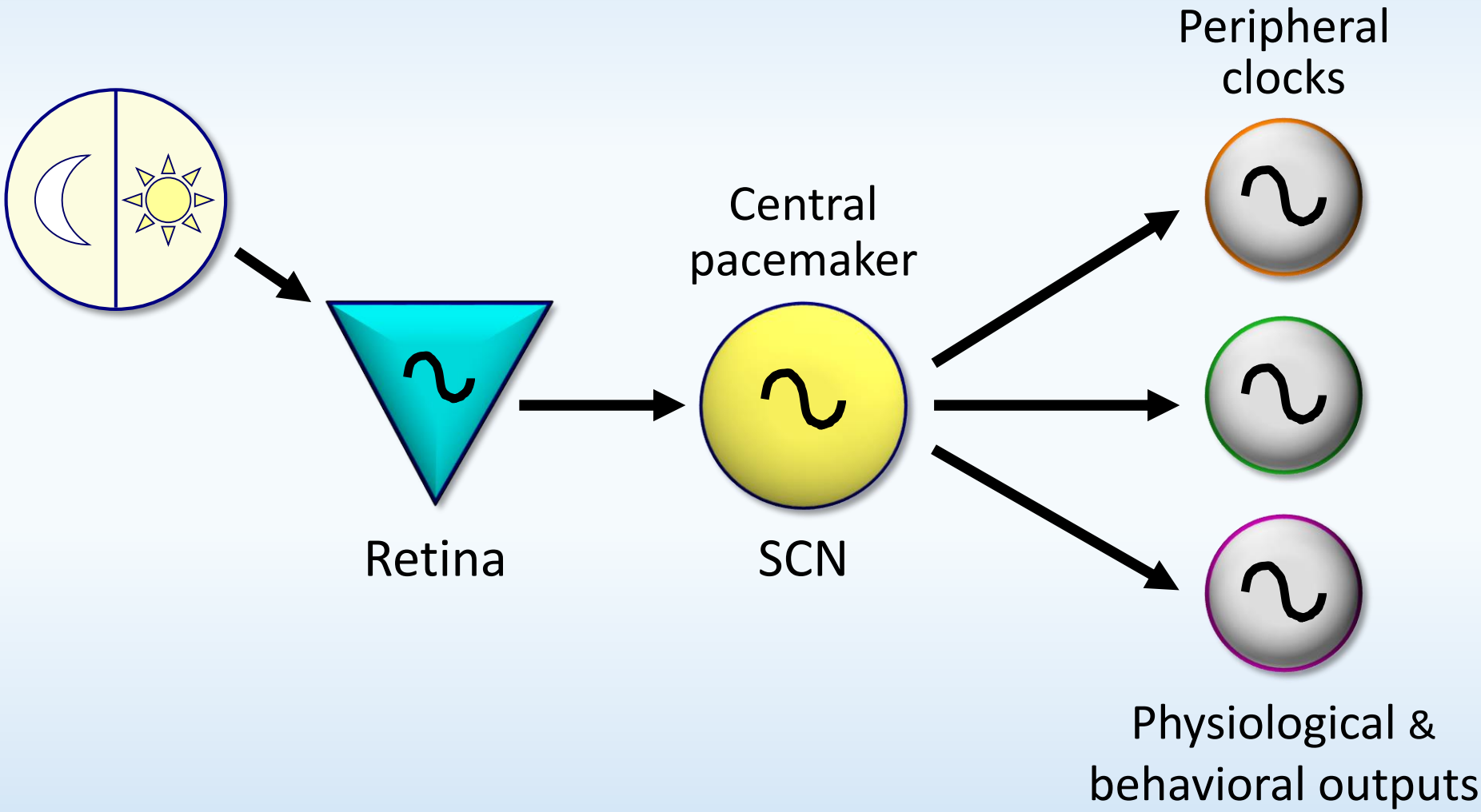
PERIOD2::LUCIFERASE
transgenic mouse



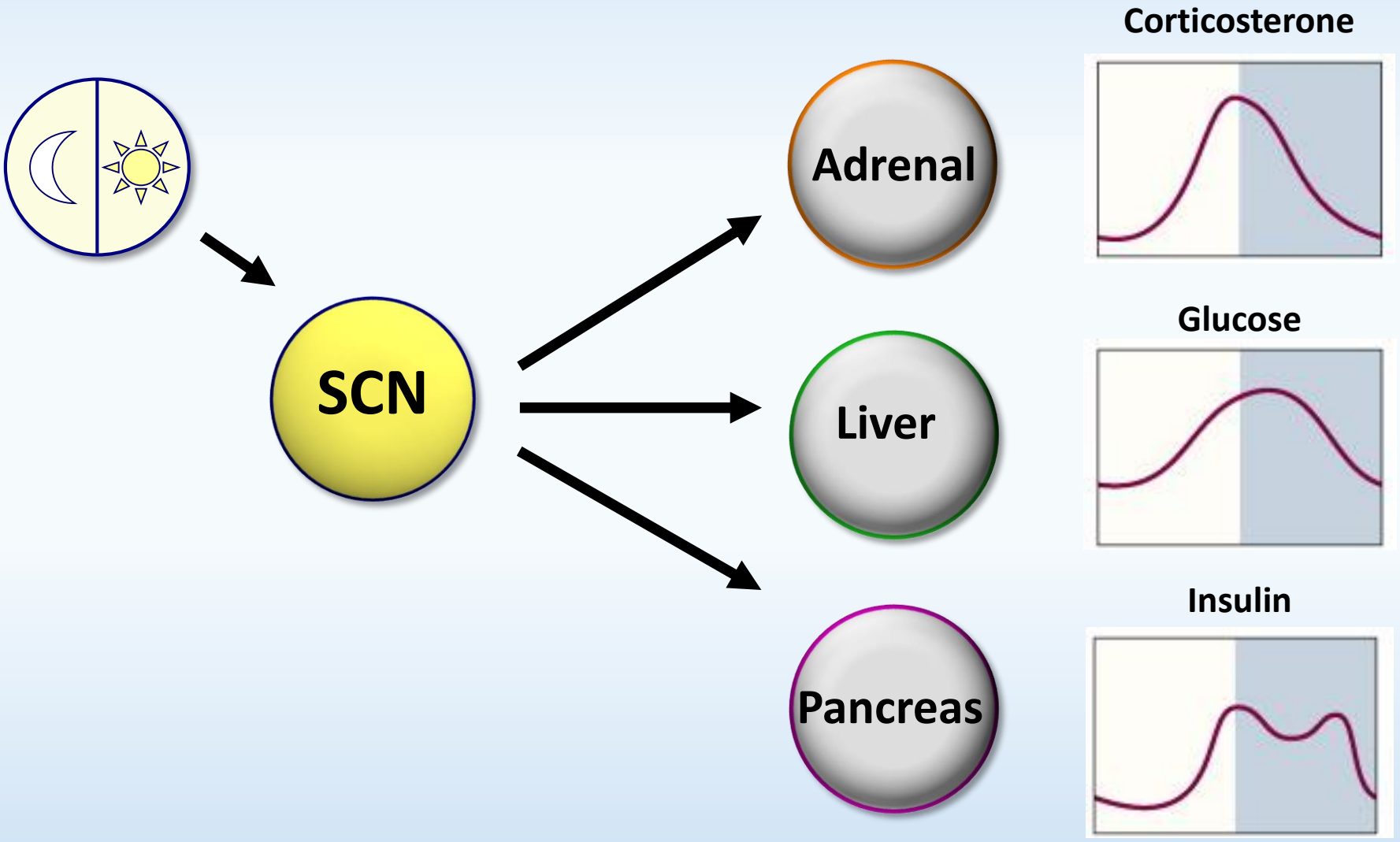
Real-time monitoring of
bioluminescence in *ex vivo* tissues

(Yamazaki *et al.* Menaker, 2000; Yoo *et al.* Takahashi, 2004)

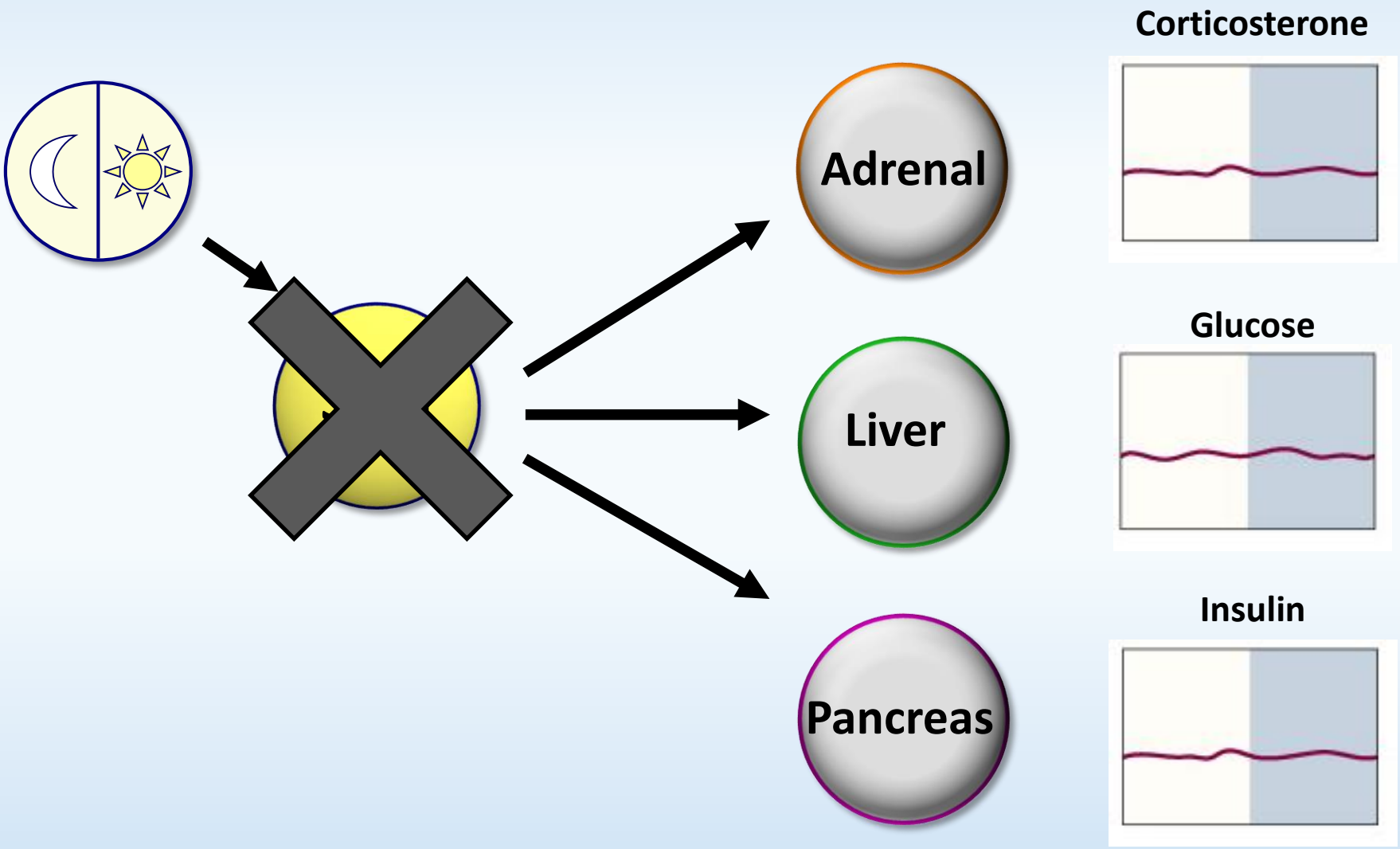
The mammalian circadian system: An orchestra of clocks



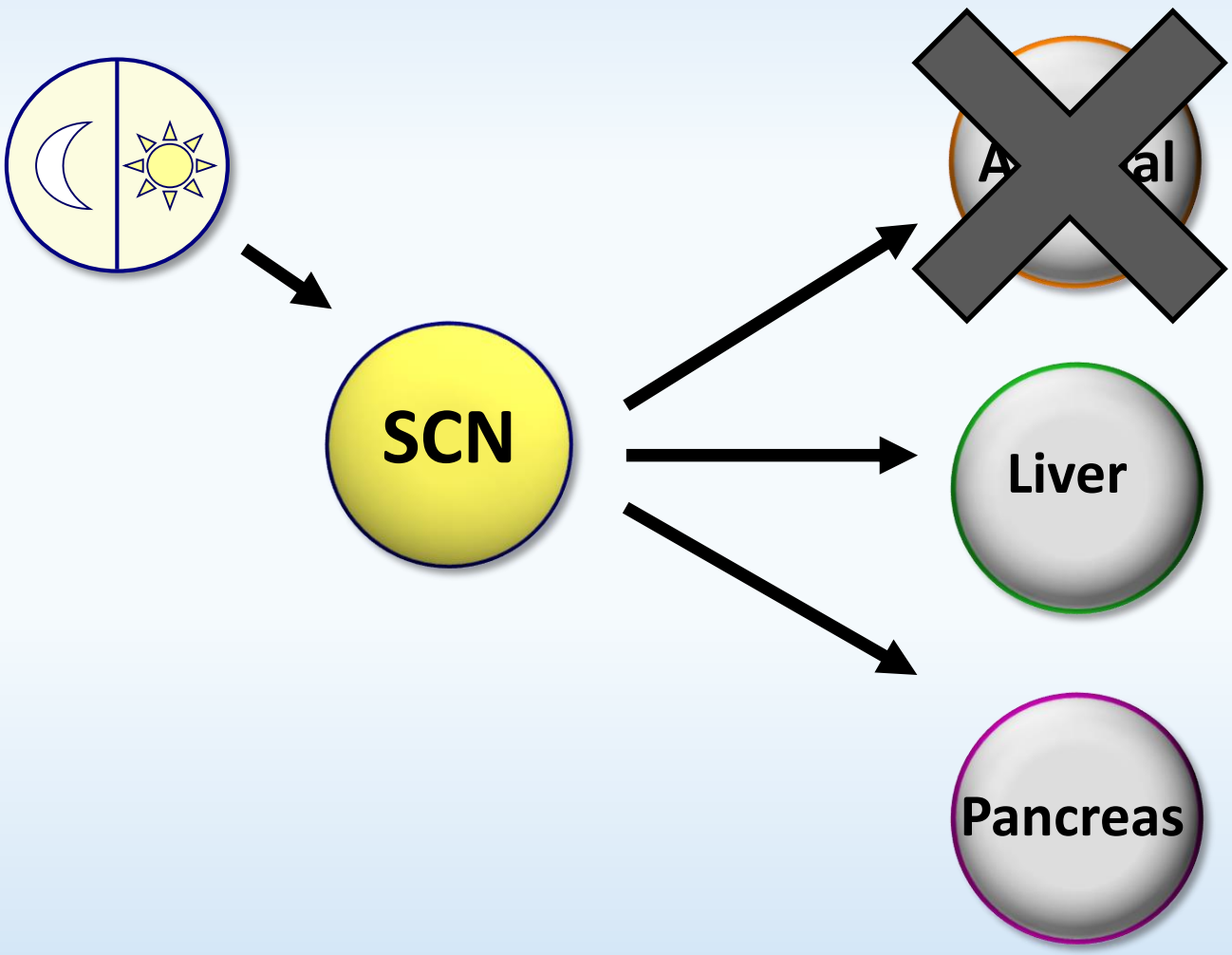
An orchestra of rhythms in rats

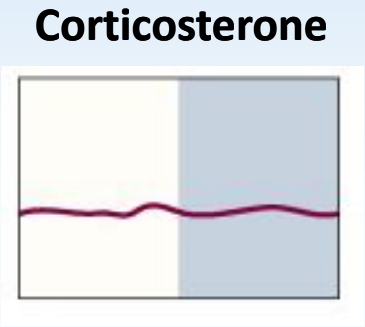


Rhythms are abolished by SCN lesion



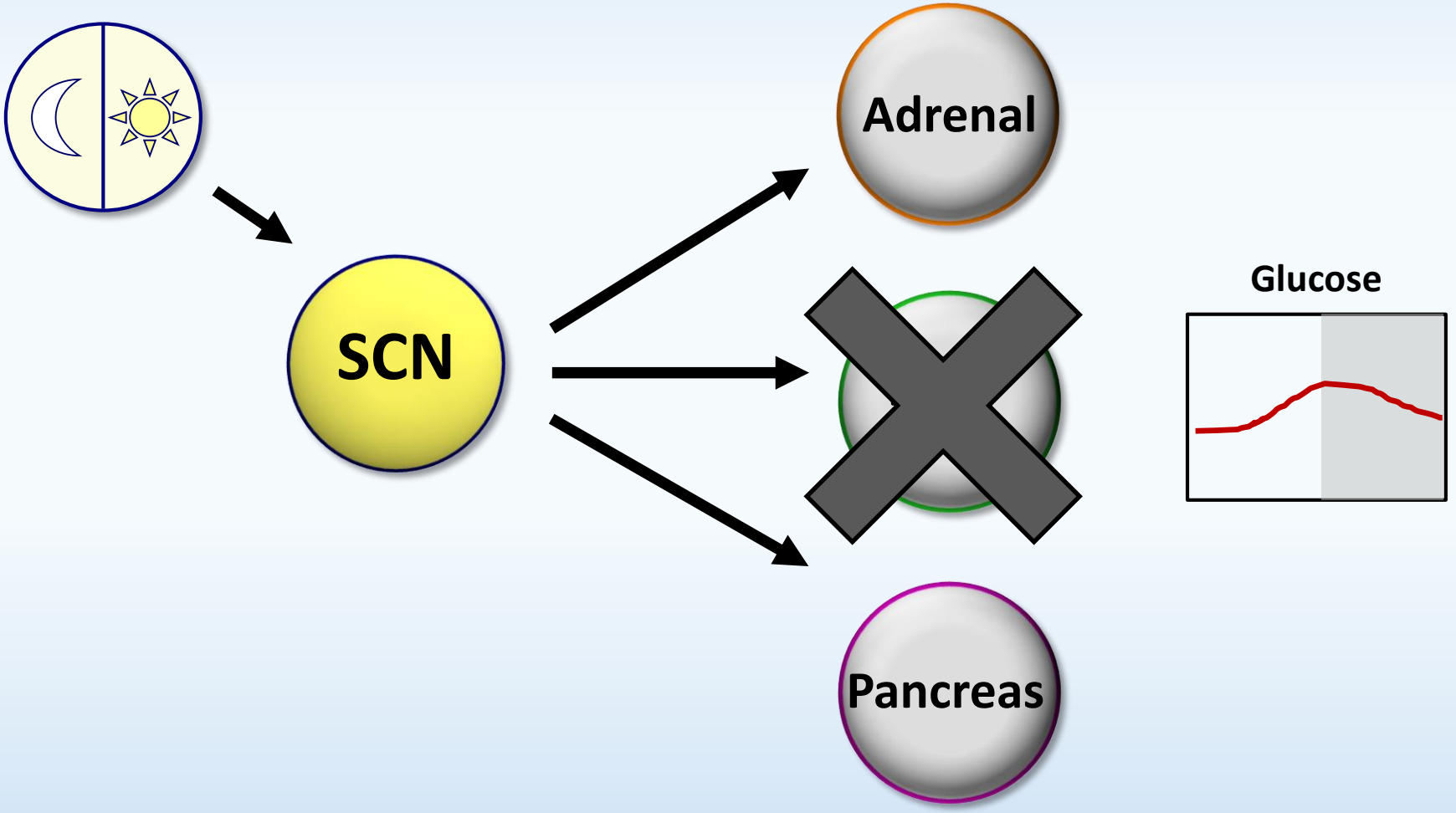
Peripheral clocks are required for normal function





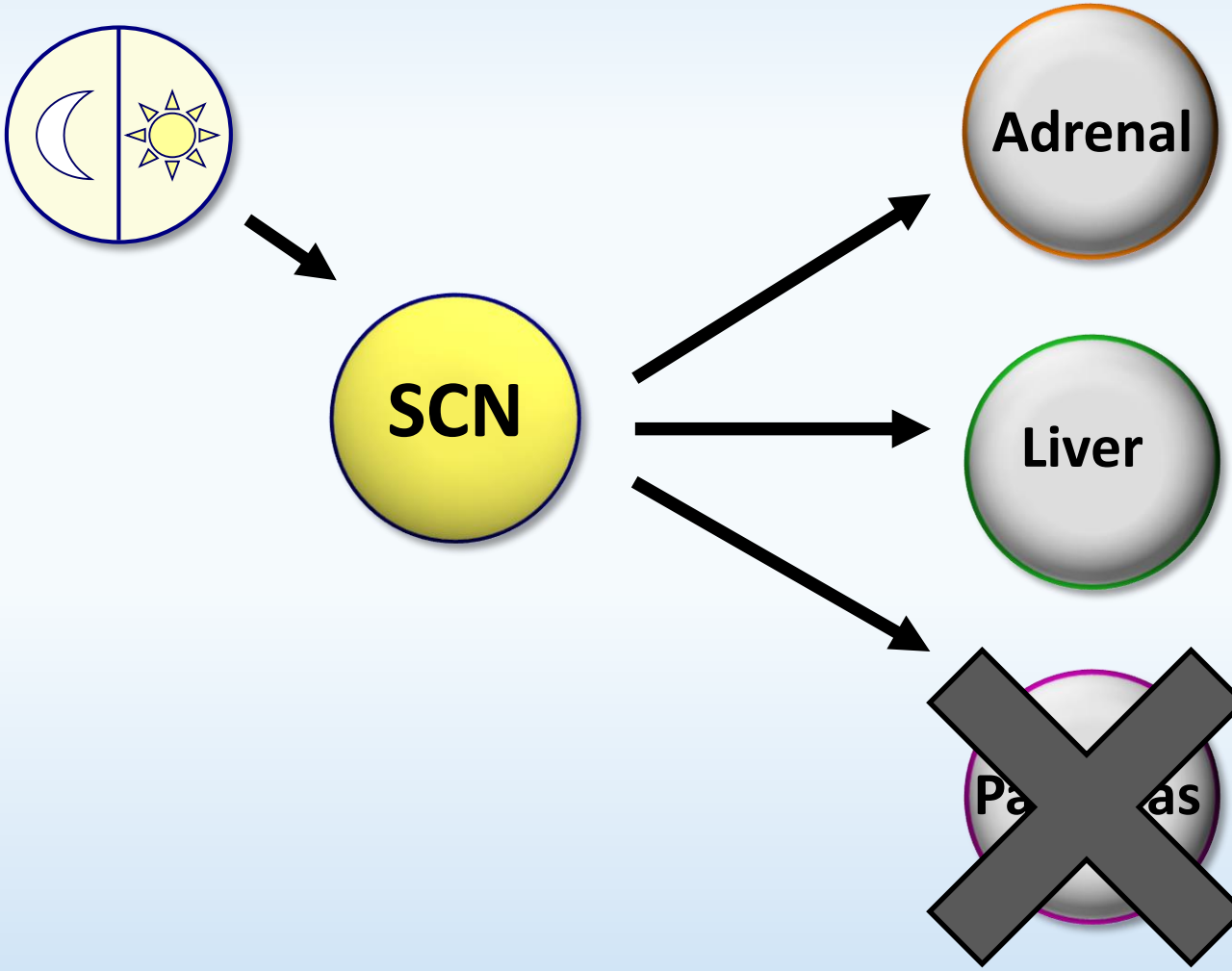
Son et al 2008

Peripheral clocks are required for normal function



Lamia et al 2008

Peripheral clocks are required for normal function

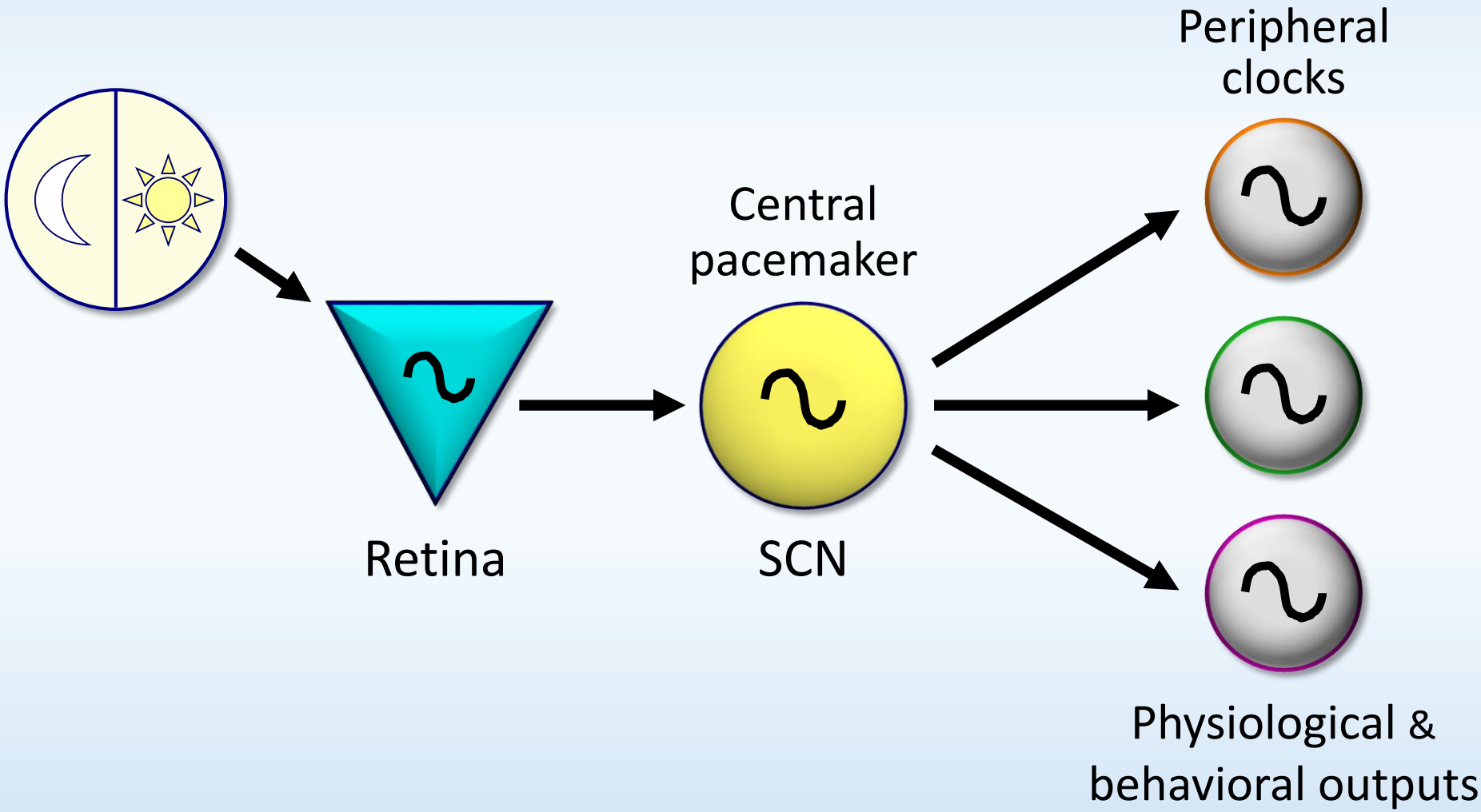


Insulin

Rhythm ND, but mice are diabetic

Marcheva et al 2008

The mammalian circadian system: An orchestra of clocks



Desynchronized rhythms: Impact of shift work on health

Increased mortality risk

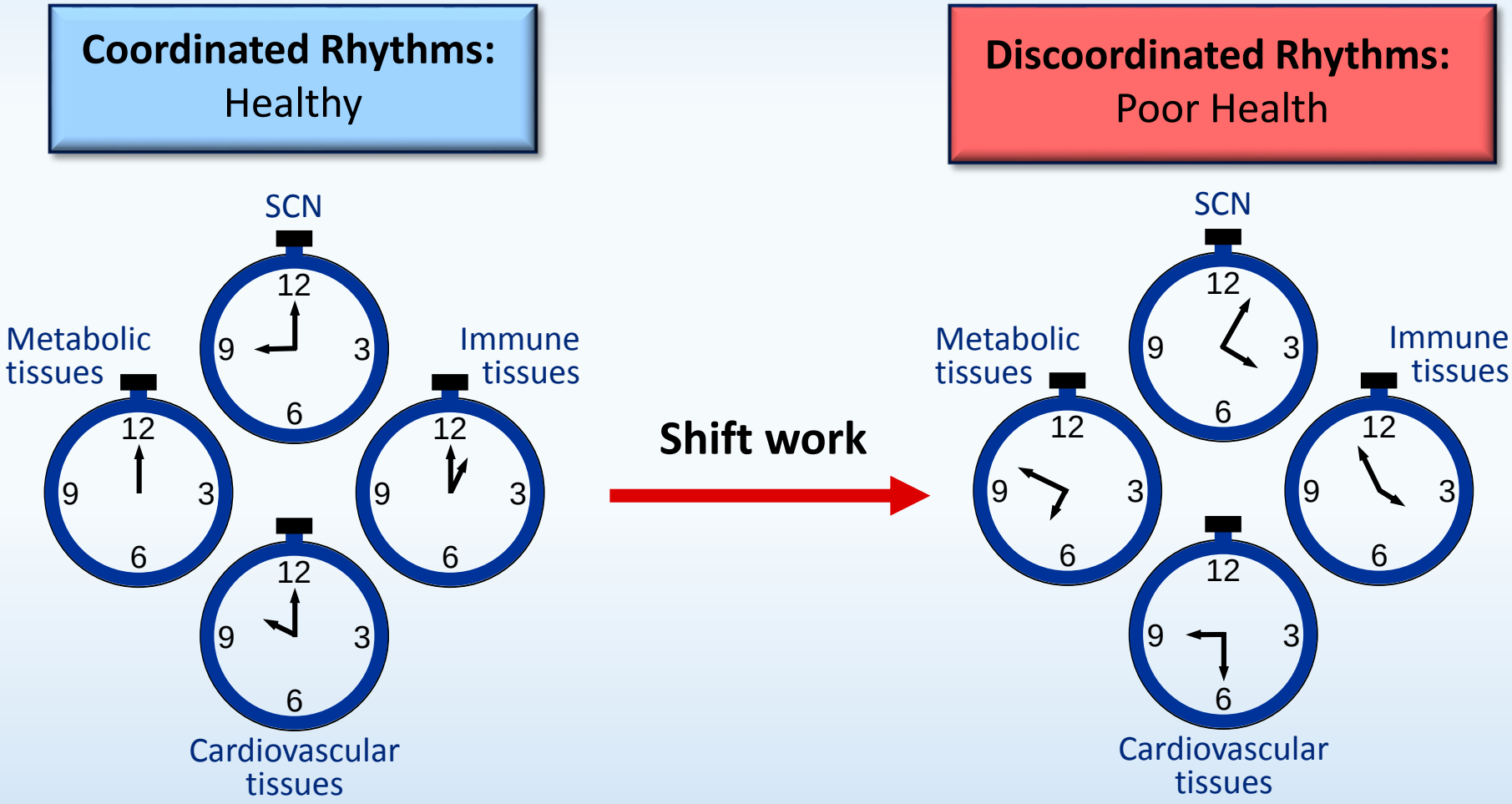
Increased cancer

Learning & memory deficits

Gastrointestinal disorders

Obesity & metabolic syndrome

Circadian misalignment confers poor health



BIO 425: Consequences of Circadian Rhythm Disruption

Tuesdays 12-1pm

Do circadian rhythms increase fitness?

White-tailed antelope ground squirrel

Semi-fossorial, diurnal, travels extensively (240m) among the brush in the desert

Captured and taken to lab: activity monitoring, SCN lesion

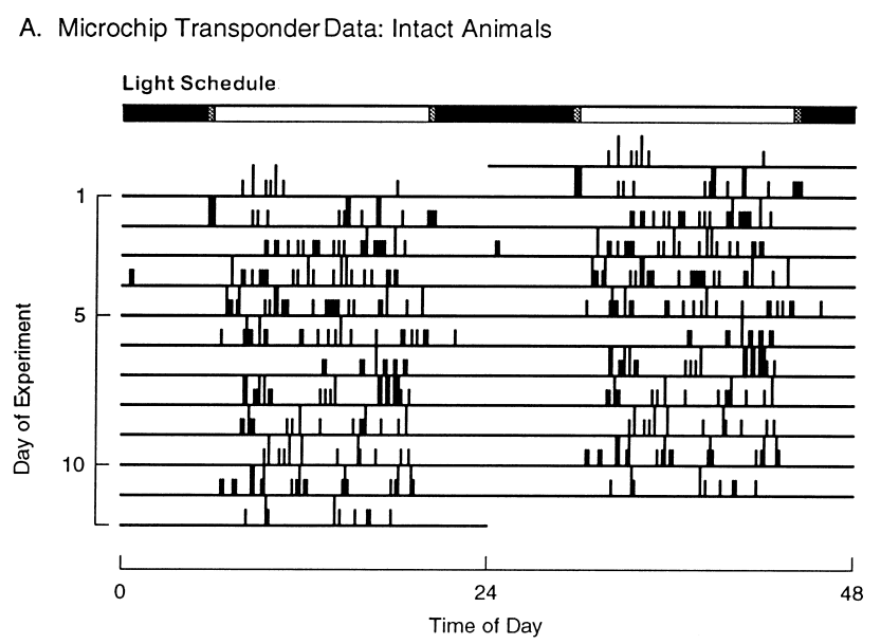
April: taken to Desert Research Station (all in CA)

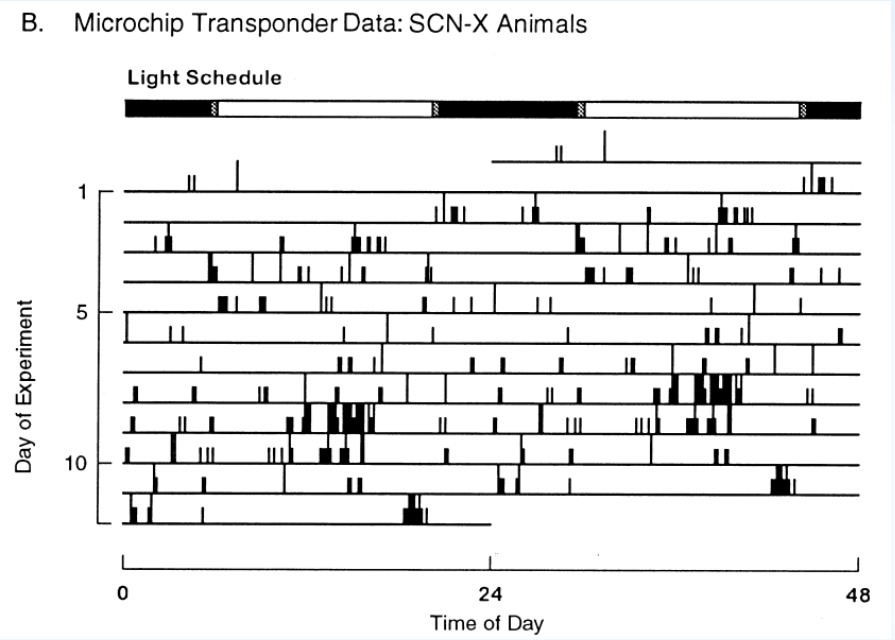
20ftx20ft enclosure central feeder/water, video cameras

10 dens (artificial burrows) were positioned at the back of the enclosure

DeCoursey et al, 1997

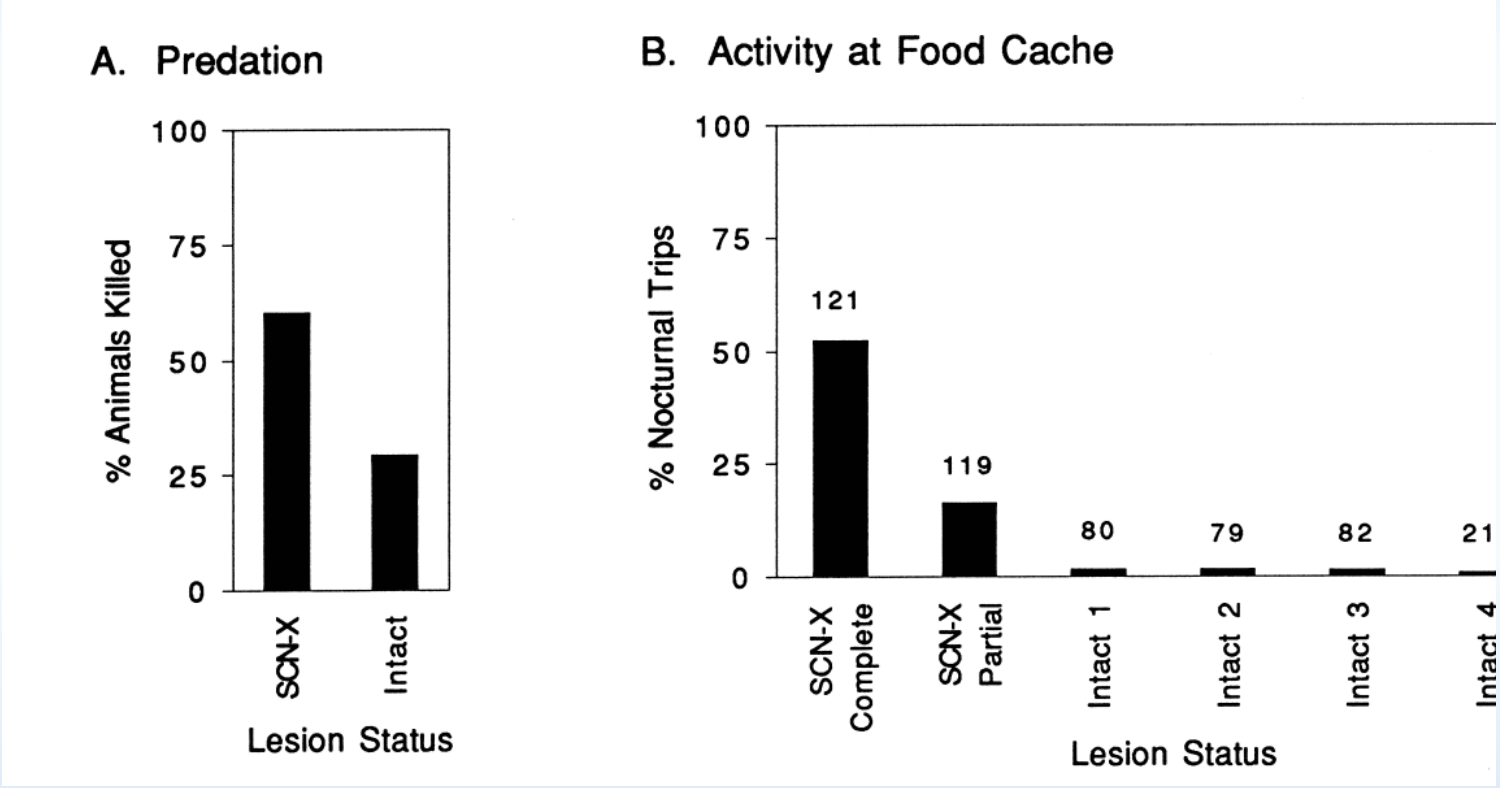
SCN-lesioned antelope squirrels have arrhythmic activity





DeCoursey et al, 1997

No significant difference between SCN-lesioned and intact animals



FERAL CAT

DeCoursey et al, 1997

Try, try again!

Eastern chipmunk

Semi-fossorial, diurnal, small territories, always return to same den

Mountain Lake Biological Station (VA), 56 trapping stations

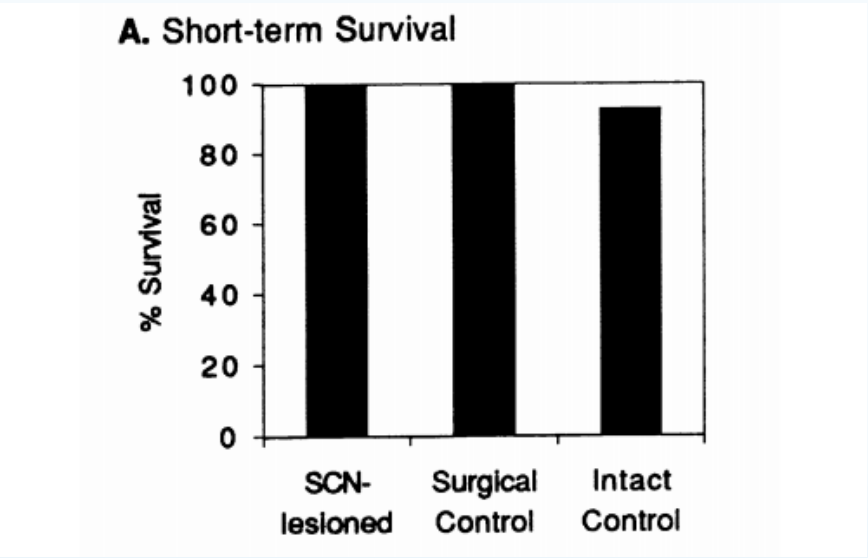
28 total trapped, fitted with colored radio telemetry collars

15 captured and taken to lab: 10 SCN-lesioned, 5 sham surgery (13 left at site)

No enclosure central, trapping area covered ~10 acres feeder/water, video cameras

DeCoursey and Krulas, 1998

Arrhythmic chipmunks had worse long-term survival



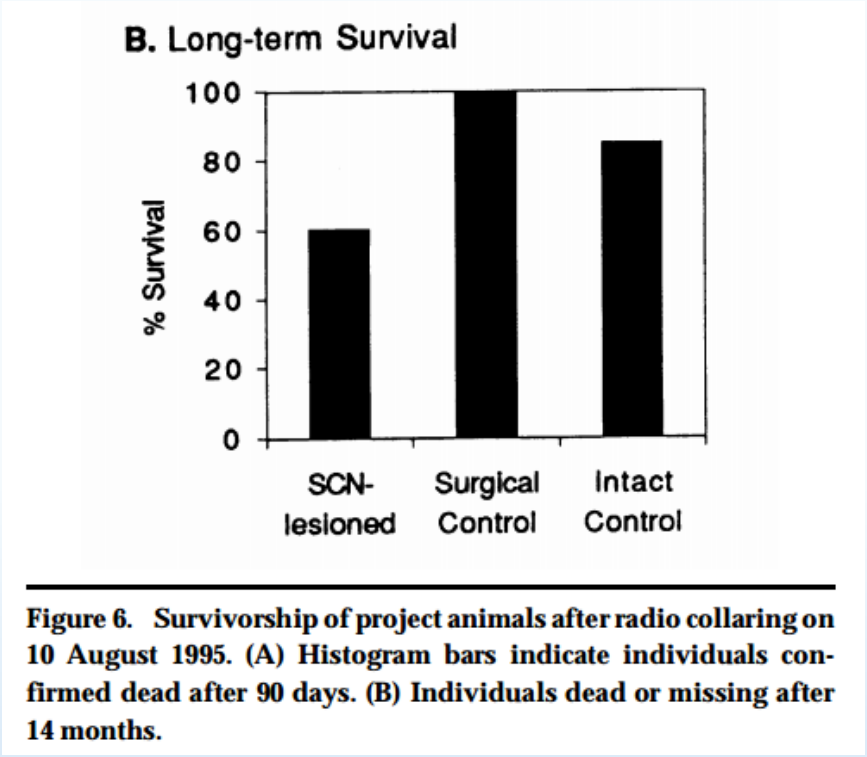


Figure 6. Survivorship of project animals after radio collaring on 10 August 1995. (A) Histogram bars indicate individuals confirmed dead after 90 days. (B) Individuals dead or missing after 14 months.

DeCoursey and Krulas, 1998

Circadian Clocks…..

- Are ubiquitous
- Impact nearly all physiology and behavior
- Are genetically encoded (timekeeping mechanism conserved)
- Improve fitness

What can we learn from animals that live in unusual conditions?

Tasmanian Glowworms

Adult flies

Larva

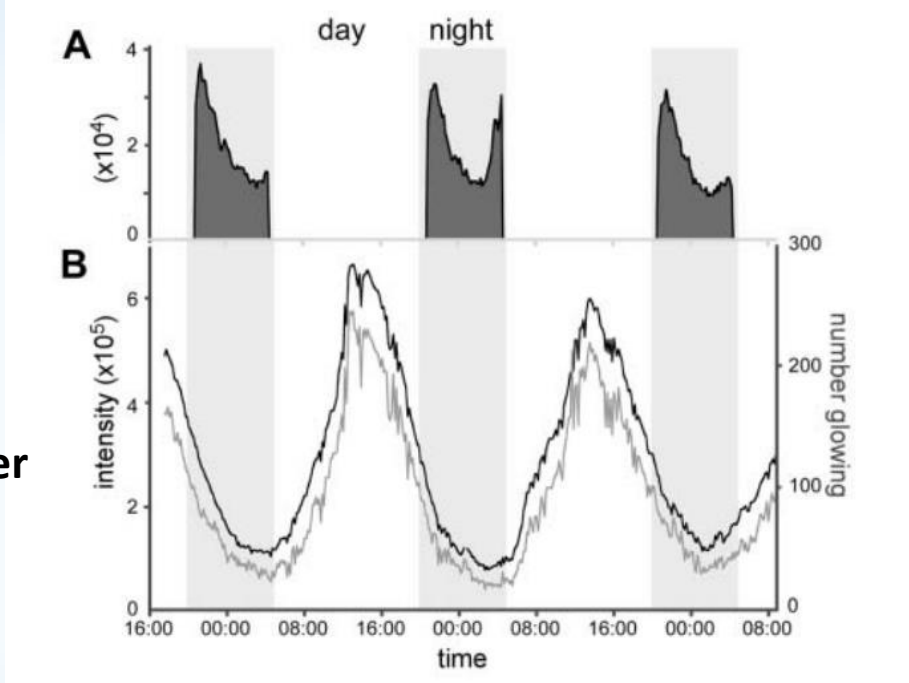
http://www.stokedforsaturday.com/2015/07/glowworms-in-motion/

David Merritt, University of Queensland

Glowworm bioluminescence is rhythmic even in the deep cave chamber

Cave mouth

Deep cave chamber



http://www.dmerritt.net.au/LabWeb/LabWeb/Analysing_Glowworm_Rhythms.html

David Merritt, 2011

Why do glowworms in the deep cave entrain (synchronize) to mid-day?

- No light (but they will synchronize to light)
- No temperature fluctuations (8°C)
- Prey availability!

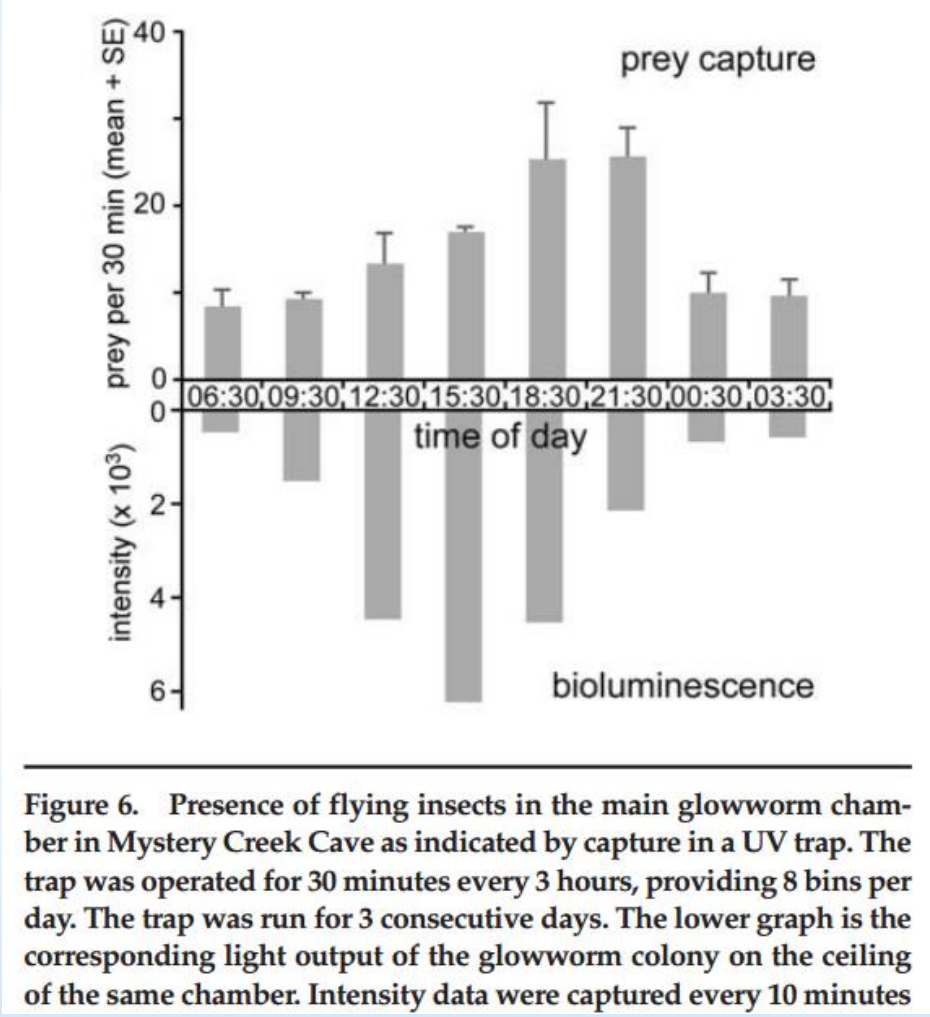


Figure 6. Presence of flying insects in the main glowworm chamber in Mystery Creek Cave as indicated by capture in a UV trap. The trap was operated for 30 minutes every 3 hours, providing 8 bins per day. The trap was run for 3 consecutive days. The lower graph is the corresponding light output of the glowworm colony on the ceiling of the same chamber. Intensity data were captured every 10 minutes

David Merritt, 2011

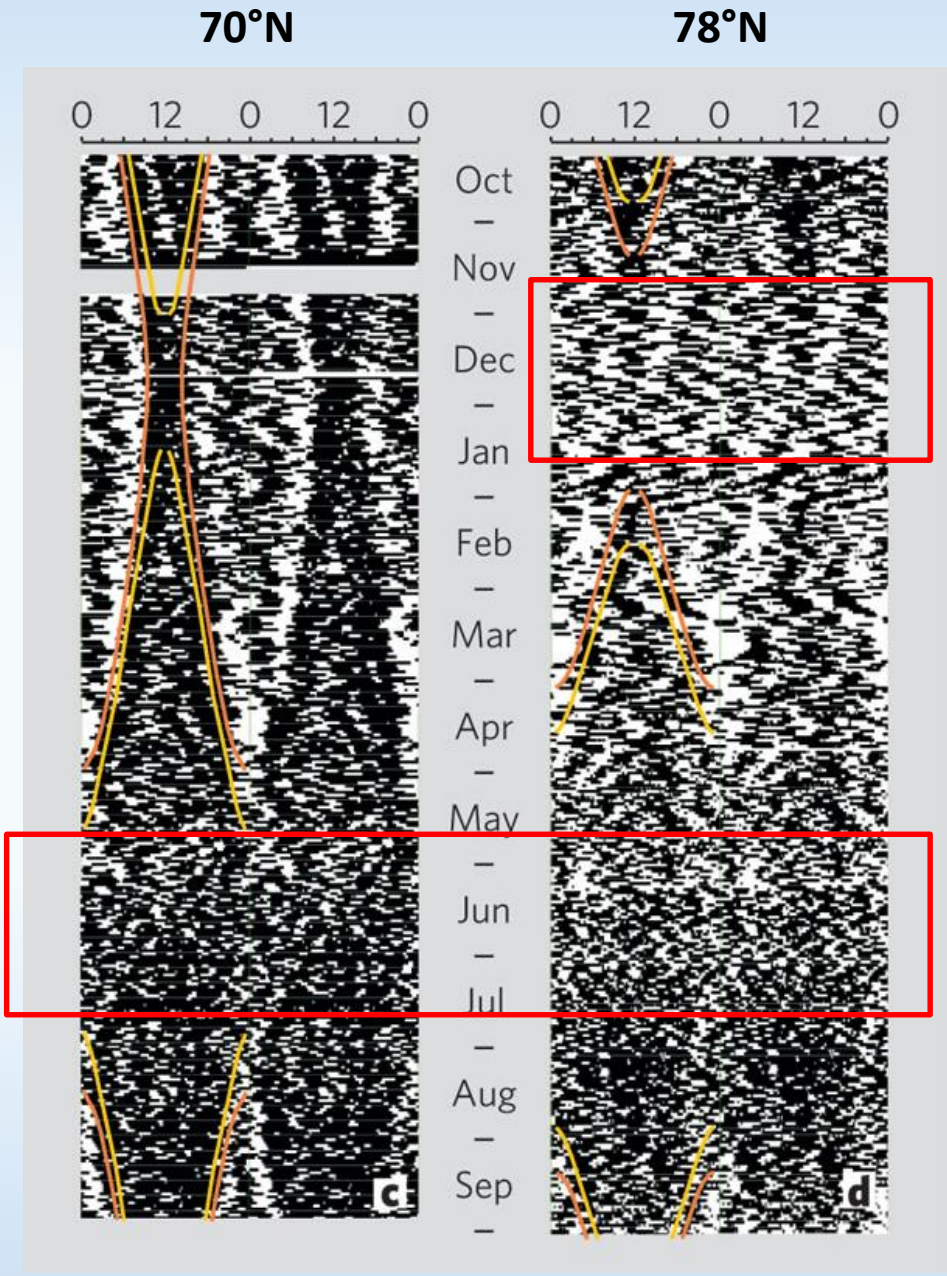
Arctic Reindeer

Polar day (constant light): April 19-Aug 23

Polar night (constant darkness): Oct 28-Feb 14

Midnight in June

Mid-day in February



van Oort et al, 2005

What is the advantage of activity around the clock (a suppressed clock)?

- Polar animals (reindeer, arctic ground squirrels, ptarmigans)
  - Food constantly available or capture transient chances to eat?

- Highly social insects in the nest (honeybees, termites)
  - Division of labor benefits the colony (workers are arrhythmic)

- Migrating birds
  - Travel long distances in short time

- Reproductive and maternal behavior (Egg-laying queen bees/ants, humans, dolphins)
  - Incredible fecundity; Newborns will die

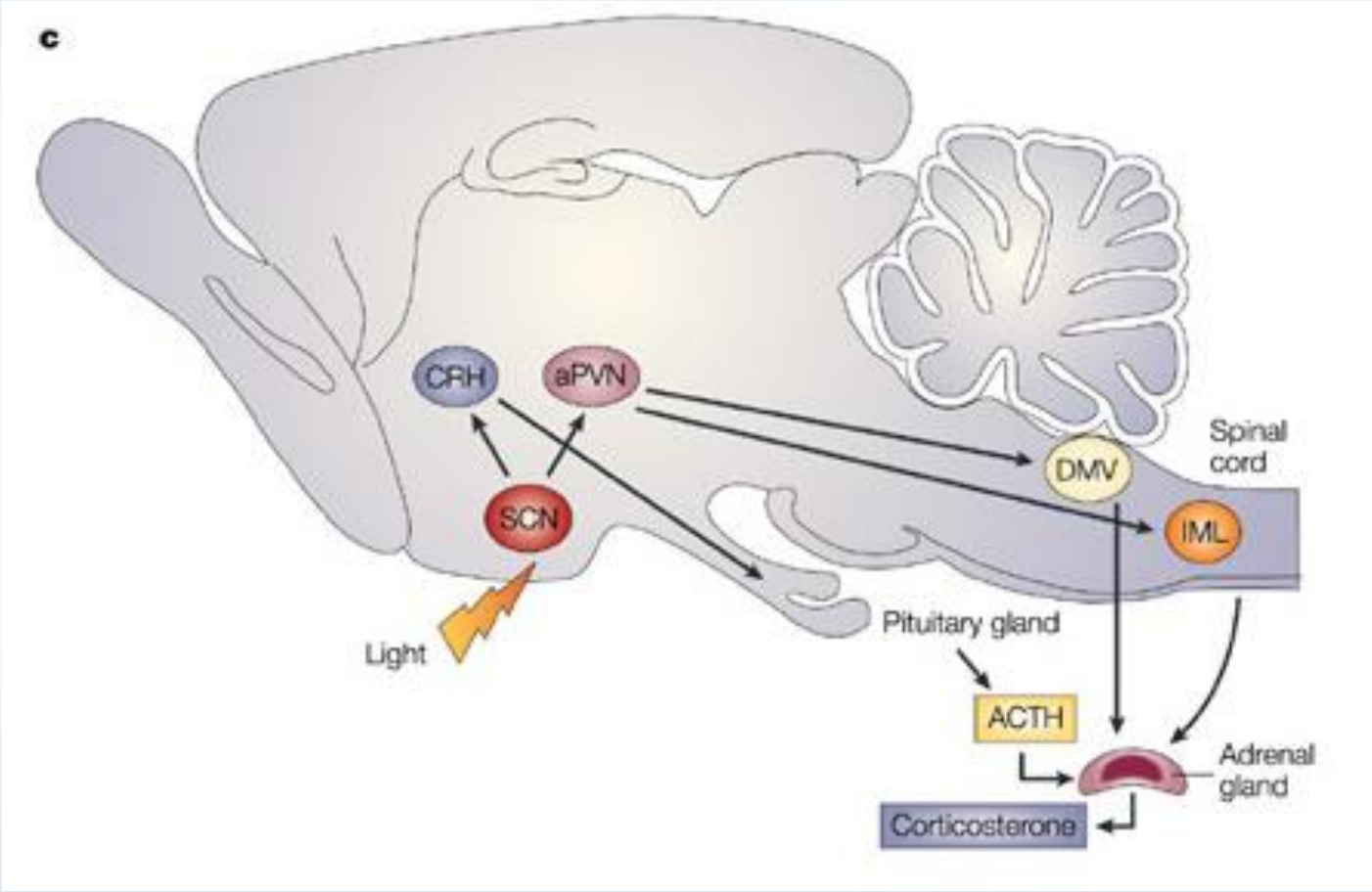
Plasticity can be advantageous

Bloch et al 2013

Circadian Clocks…..

- Are ubiquitous
- Impact nearly all physiology and behavior
- Are genetically encoded (timekeeping mechanism conserved)
- Improve fitness
- Are plastic

SCN efferents



Fu and Lee, 2003

Role of sympathetic nervous system in coordinating tissue rhythms