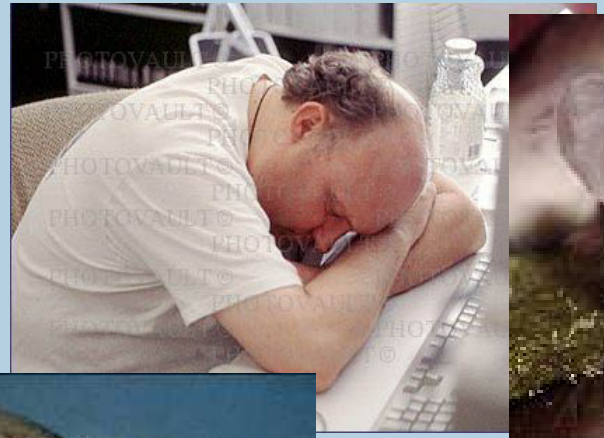
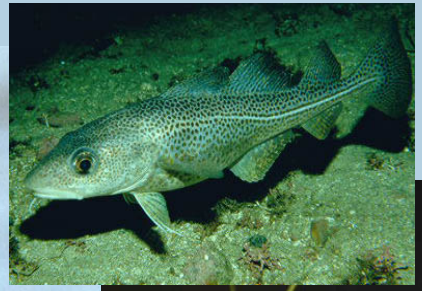
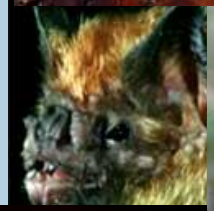


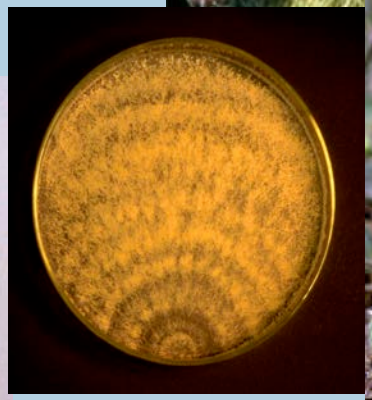


Nobelpris i fysiologi/medisin 2017:

Om Circadiane Rytmer og den Biologiske Klokken

P. Ruoff, UiS, Centre for Organelle Research





The Nobel Prize in Physiology or Medicine 2017

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Jeffrey C. Hall

Prize share: 1/3

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Michael Rosbash

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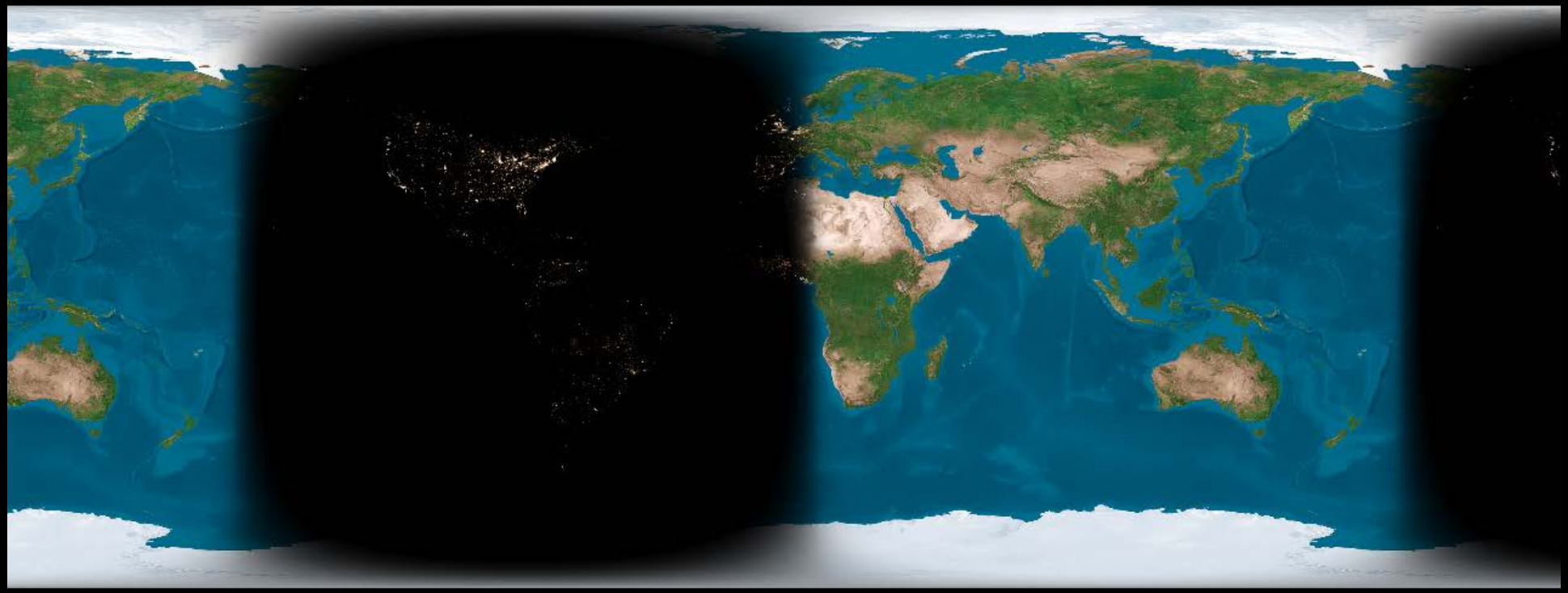
Michael W. Young

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young *"for their discoveries of molecular mechanisms controlling the circadian rhythm"*.

Nobelförsamlingen Karolinska Instituttet (2017)

solnedgang soloppgang solnedgang

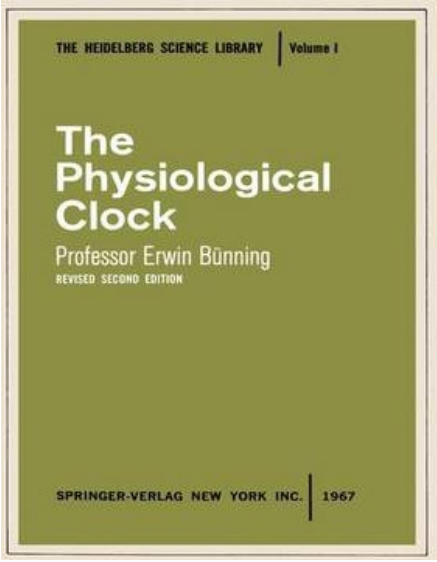


EarthDesk™

Hva er circadiane rytmer?

Gjennom evolusjonen har levevesen utviklet mekanismer som tilpasser dem til jordens natt/dag veksling.

Den fysiologiske klokken



Begrepene **fysiologisk klokke** og **circadian rytme** ble inført av **Erwin Bünning**.

Bünning var botaniker og viste allerede i 1930 årene at bladbevegelsene i planter var genetisk betinget.

I 1958 skrev han boken "*Den Fysiologiske Klokken*" som ble oversatt til mange språk og som er et milepæl innen kronobiologisk forskning.

Bünning viste at circadiane rytmer styrer **døgnperiodiske fenomener** (f. eks. søvn, bladbevegelser, åpning/lukking av blomster), men også **årsperiodiske egenskaper** (f. eks. blomsterdannelse, vinterdvale, reproduksjon, trekkoppførsel).

Linné's blomsterur

CARL von LINNÉ
(1707-1778)

"Tiger Jaw" (*Faucaria tigrinis*, South Africa, open flowers ≈ 5 pm, closes ≈ 8 pm)

Begrepet *circadian*

Hva betyr *circadian*?

circadian kommer fra latin *circa* (omtrent) og *dies* (dag).

Navnet indikerer at periodelengden av circadiane rytmer er ca. 24 timer.

Hvor finner vi circadiane rytmer?

I nesten alle eukaryotiske og noen få prokariotiske organismer (blågrønnalger).

Egenskaper av circadiane rytmer

- circadiane rytmer finnes i den enkelte celle. Siden de genereres i celler kalles dem også for **endogene** rytmer.

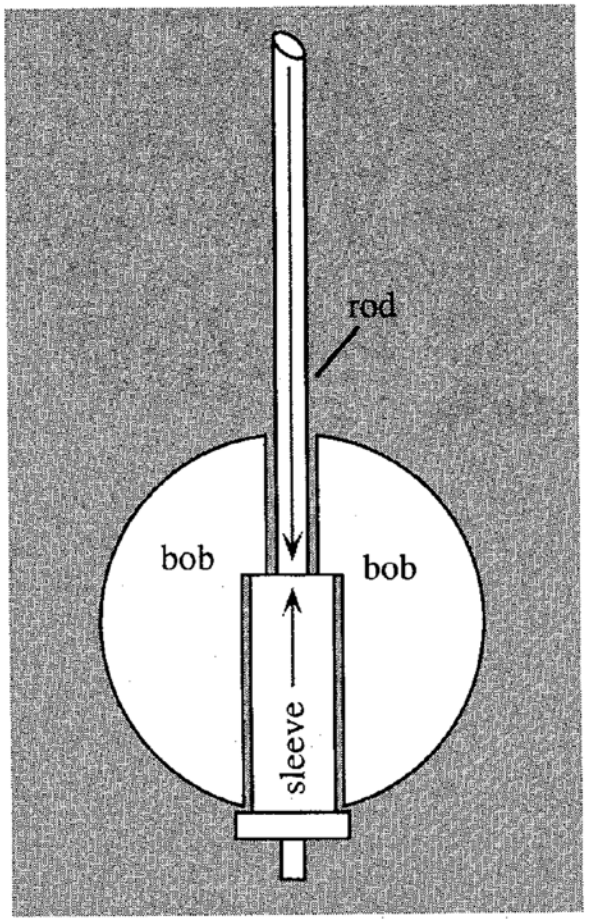
- circadiane rytmene kan **fase-skiftes** ved hjelp av forandringer i lys, temperatur, gjennom inntak av mat, alkohol, medisiner, etc.

- circadiane rytmer kan følge/tilpasse seg eksterne rytmer, f. eks. lys av/på (engelsk: **entrainment**).

- circadiane rytmer har en **homeostatisk regulering av perioden**. For eks er perioden kompensert mot ulik temperatur, pH, eller næringstilførsel ("**temperaturkompensasjon**").

Analogi: Bruk av temperaturkompensasjon i høypresisjons-pendelur

Et temperatur-kompensert pendel fra 1875. Lengde ≈ 35 cm.



Uhrenmuseum, Vienna, Østerrike

Fotoperiodisitet

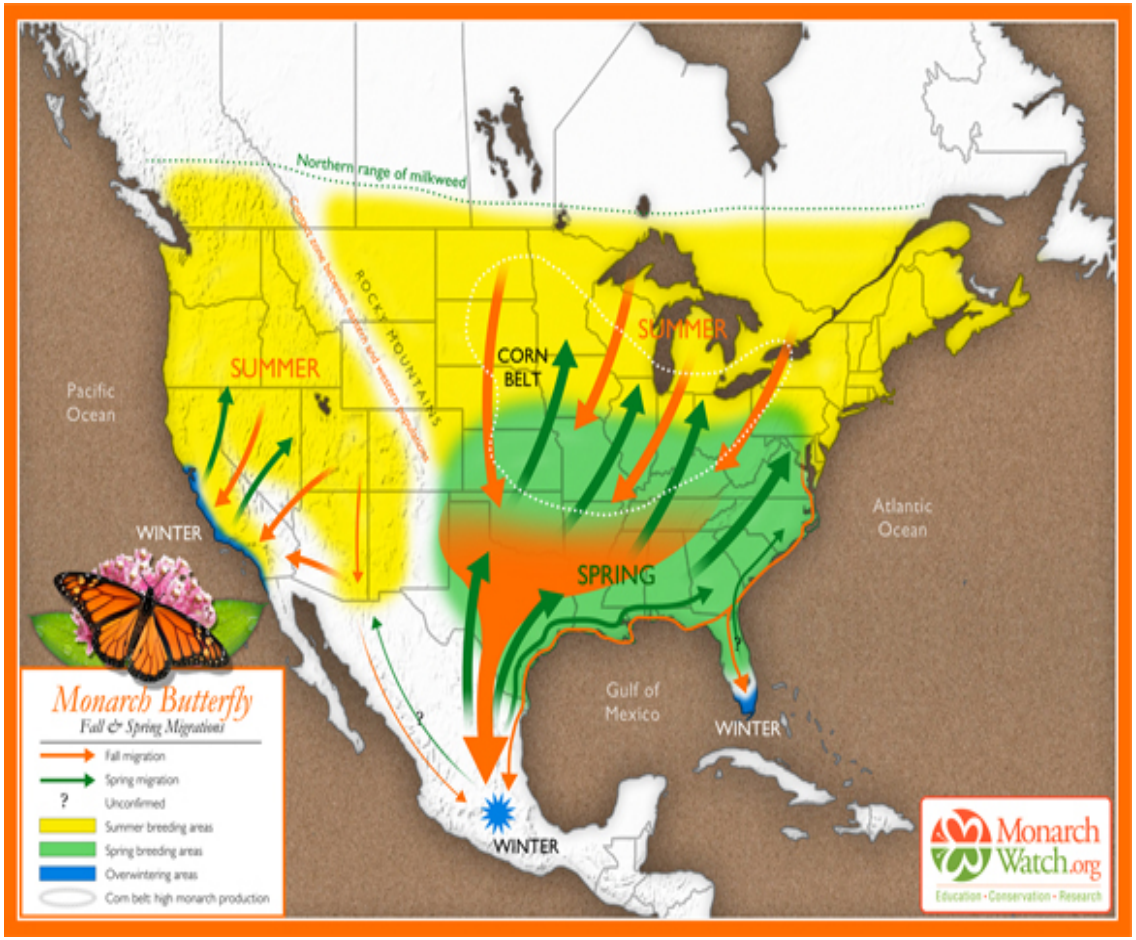
Fotoperiodisitet beskriver hvordan organismer reagerer på **daglengde** og tilpasser seg **årstider**. Både planter og dyr viser fotoperiodisitet.

Eksempler

Dyr: forandring av farge i pels/fjær, vinterdvale, trekkoppførsel om våren/høsten.

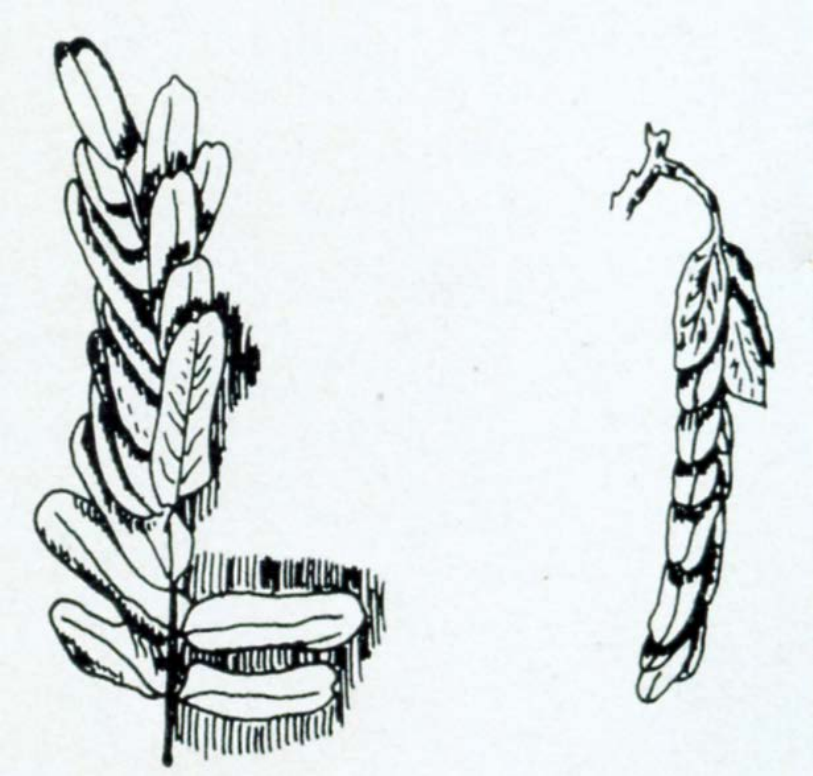
Planter: trær mister blader om høsten, blomsterdannelse om våren/ sommer, noen planter visner om høsten men kommer opp igjen om våren.

Photoperiodicity: Butterfly Migration



With 400 miles left to fly, these monarchs were resting at roost in Saltillo, Coahuila on October 18th

Historikk - 400 BC:
Androsthenes (fra Thasus) beskriver that planter ”sover”



day night

17 Mar 2016 08:31:59

Den franske astronomen De Mairan finner in 1729 at bladbevegelsene i *Mimosa* planter fortsetter i mørke

Credit: National Library of Medicine

DES SCIENCES. 35

OBSERVATION BOTANIQUE.

ON ſçait que la Senſitive eſt *héliotrope*, c'eſt-à-dire que ſes rameaux & ſes feüilles ſe dirigent toûjours vers le côté d'où vient la plus grande lumiére, & l'on ſçait de plus qu'à cette propriété qui lui eſt commune avec d'autres Plantes, elle en joint une qui lui eſt plus particuliére, elle eſt Senſitive à l'égard du Soleil ou du jour, ſes feüilles & leurs pédicules ſe replient & ſe contractent vers le coucher du Soleil, de la même maniére dont cela ſe fait quand on touche la Plante, ou qu'on l'agite. Mais M. de Mairan a obſervé qu'il n'eſt point néceſſaire pour ce phénoméne qu'elle ſoit au Soleil ou au grand air, il eſt ſeulement un peu moins marqué lorſqu'on la tient toûjours enfermée dans un lieu obſcur, elle s'épanoüit encore très-ſenſiblement pendant le jour, & ſe replie ou ſe reſſerre régulièrement le ſoir pour toute la nuit. L'expérience a été faite ſur la fin de l'Eté, & bien répétée. La Senſitive ſent donc le Soleil ſans le voir en aucune maniére; & cela paroît avoir rapport à cette malheureuſe delicateſſe d'un grand nombre de Malades, qui s'apperçoivent dans leurs Lits de la différence du jour & de la nuit.

Il ſeroit curieux d'éprouver ſi d'autres Plantes, dont les feüilles ou les fleurs s'ouvrent le jour, & ſe ferment la nuit, conſerveroient comme la Senſitive cette propriété dans des lieux obſcurs; ſi on pourroit faire par art, par des fourneaux plus ou moins chauds, un jour & une nuit qu'elles ſentiſſent; ſi on pourroit renverſer par là l'ordre des phénomenes du vrai jour & de la vraye nuit, &c. Mais les occupations ordinaires de M. Mairan ne lui ont pas permis de pouſſer les expériences juſque-là, & il ſe contente d'une ſimple invitation aux Botaniſtes & aux Phiſiciens, qui pourront eux-mêmes avoir d'autres choſes à ſuivre. La marche de la véritable Phiſique, qui eſt l'Expérimentale, ne peut être que fort lente.

E ij

EvoCam
Dec 5, 2012 12:14:02 PM

Flashing and glow circadian rhythms in *Gonyaulax polyedra*

(von der Heyde *et al*. (1992) JBR 115-123)

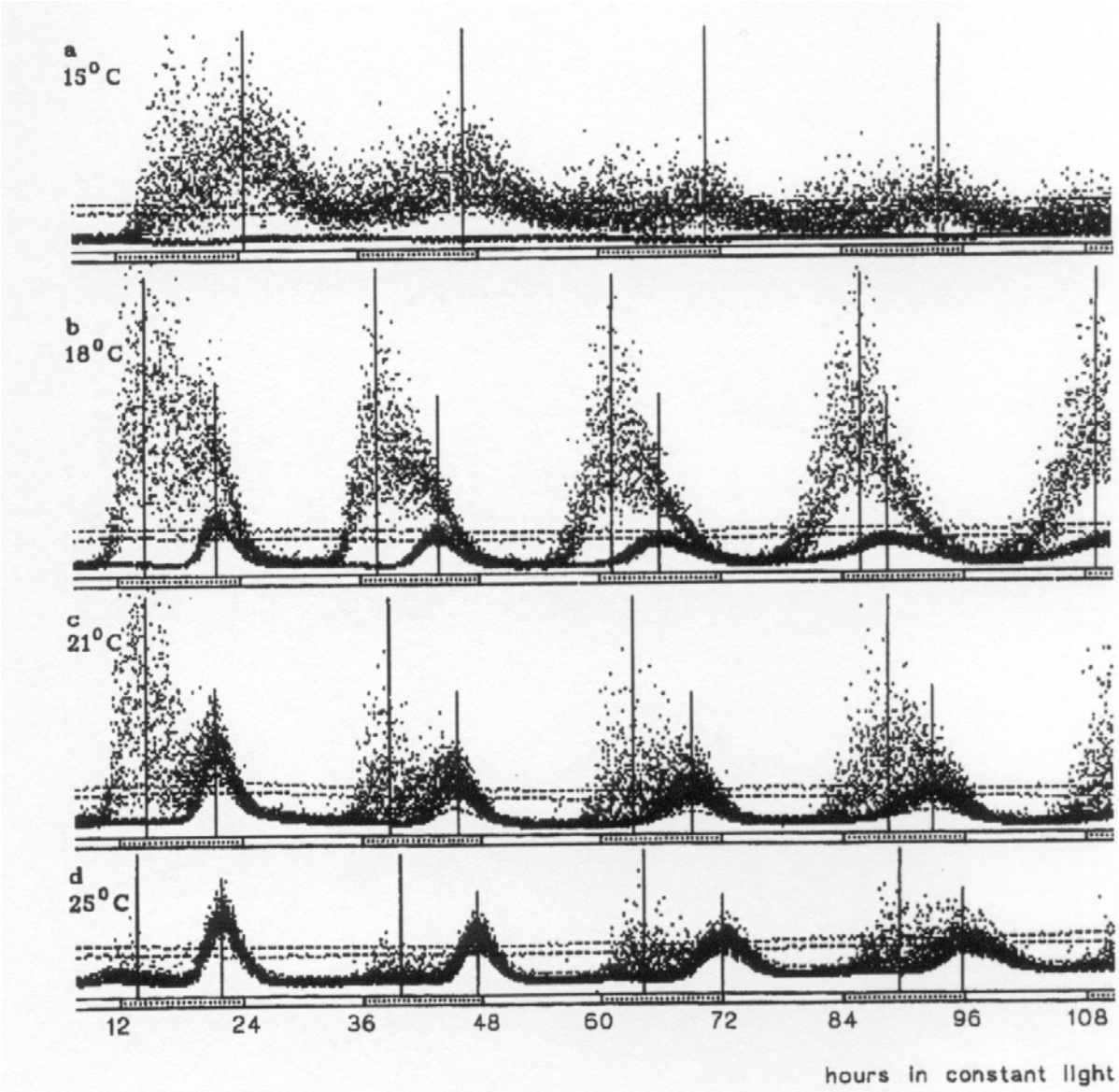
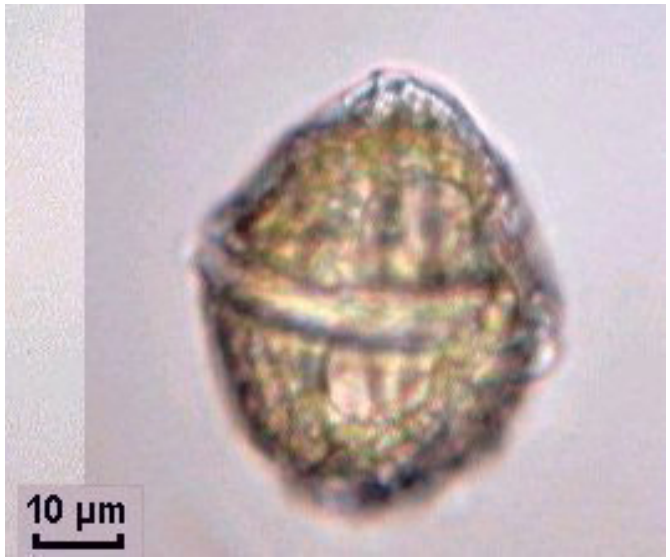


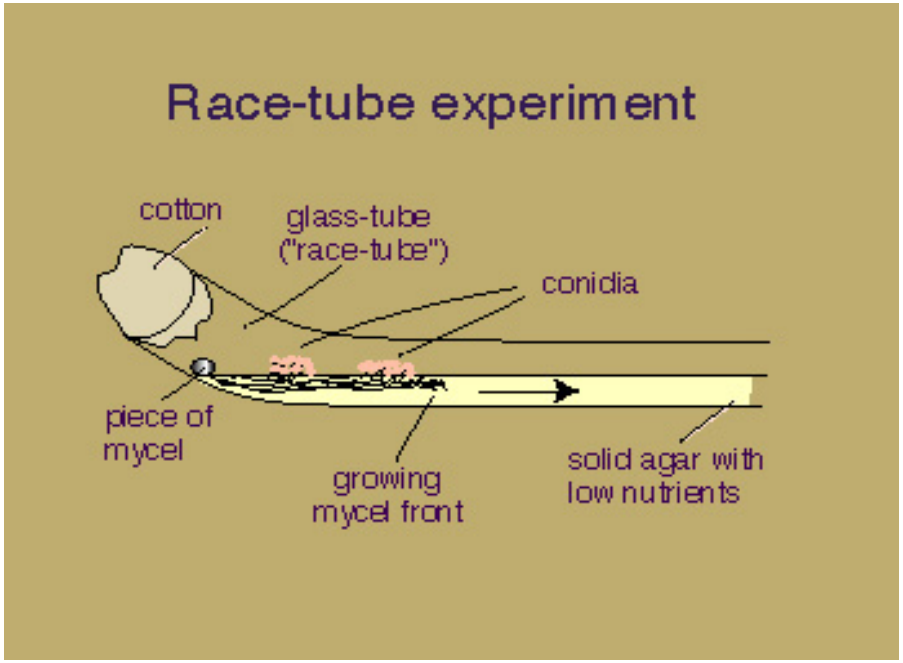
FIGURE 2. Bioluminescence rhythms at different termperatures (dim LL 1000 lux). Vertical lines indicate circadian glow and flashing maxima fitted by eye; for other details, see Figure 1.

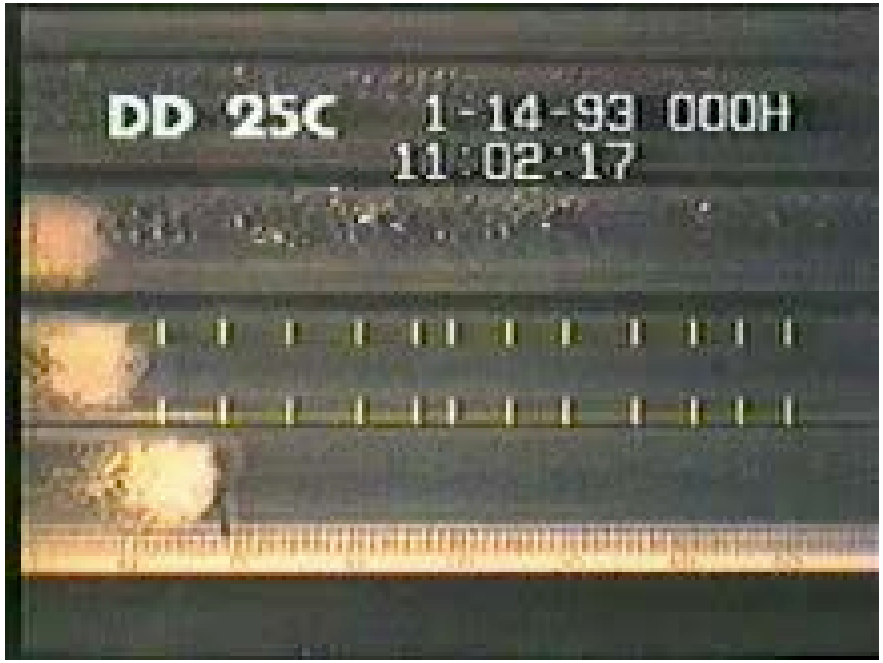
With increasing temperature flashing and glow rhythms change their amplitudes in opposite directions.



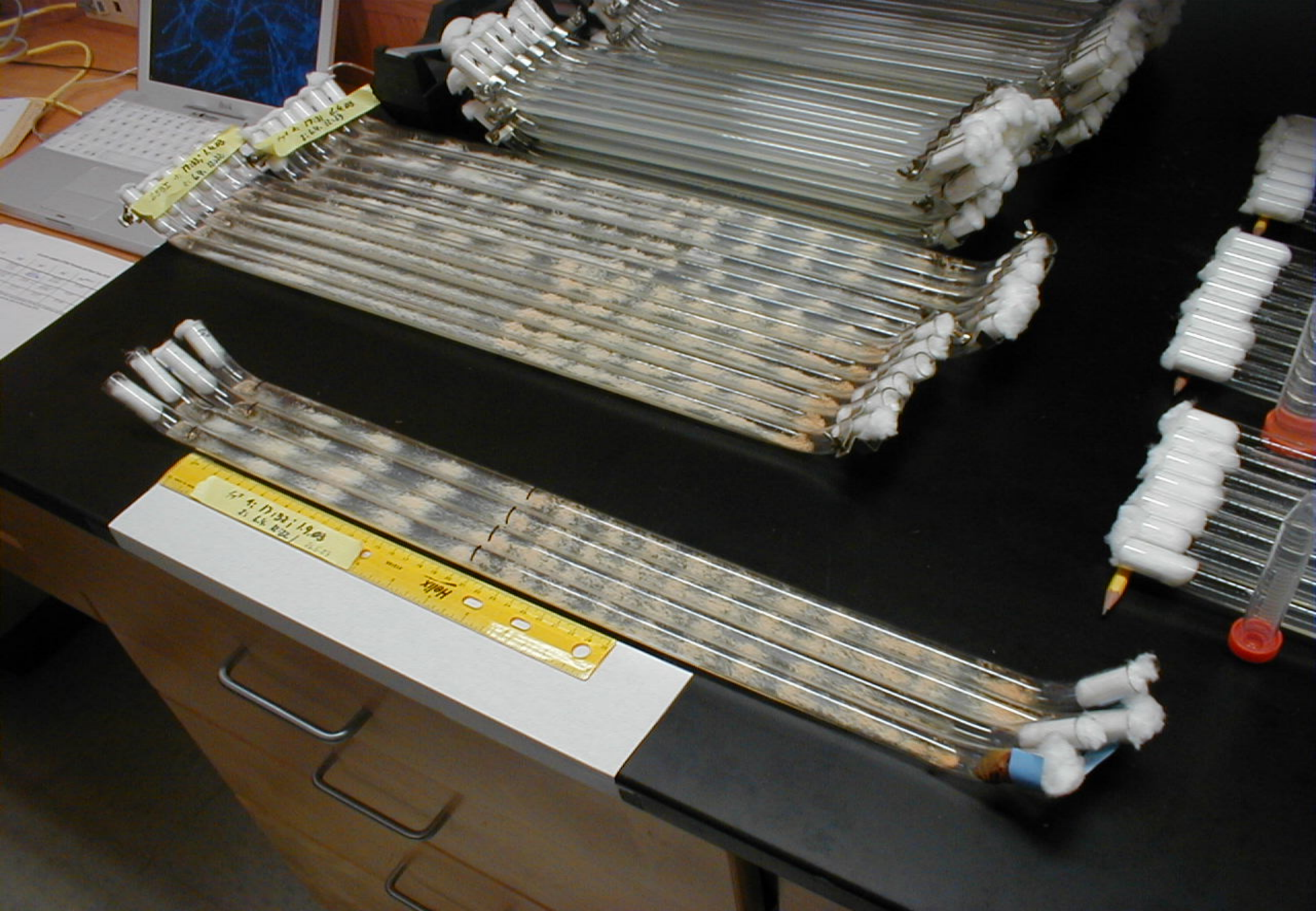
Gonyaulax polyedra

Neurospora crassa's circadiane rytme





Jason C. Thoen and Van Gooch:
"Time Lapse Video Showing an Internal Circadian Clock in Mold (*Neurospora*) Growth"



Measuring human circadian rhythms

Humans live in isolated areas, with no contact/clues about the external environment.

Their activity rhythms and other rhythms are monitored.

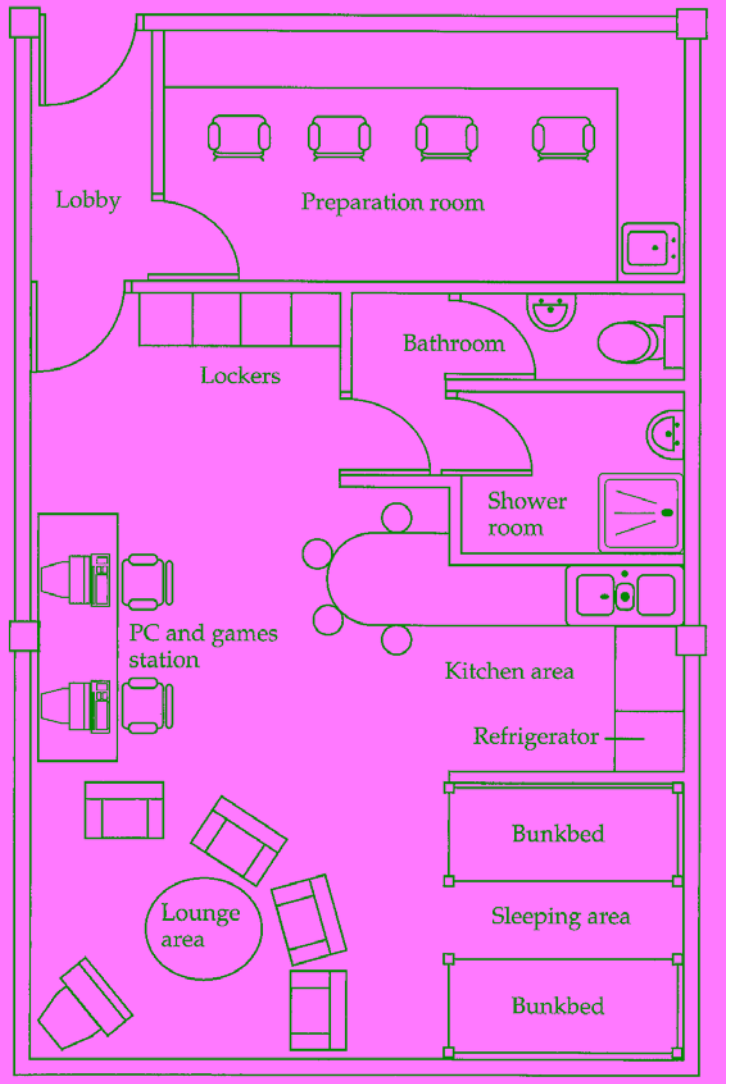
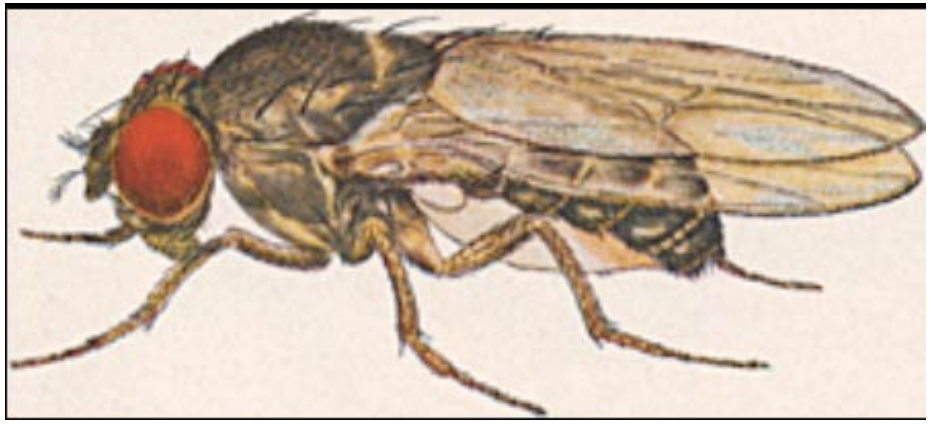


FIGURE 9.7 Plan of the human circadian isolation unit at Liverpool John Moores University. The unit provides areas for sleeping, cooking, relaxing, and studying. An LD cycle is programmed with artificial light, and the whole facility is sound attenuated to reduce any time cues. Monitoring equipment is stationed in an adjacent room. (Courtesy of J. Waterhouse.)

Free-running activity rhythms in humans is generally larger than 24 h (≈25-26h)

Perioden etter 1953
Utvikling av modellorganismer



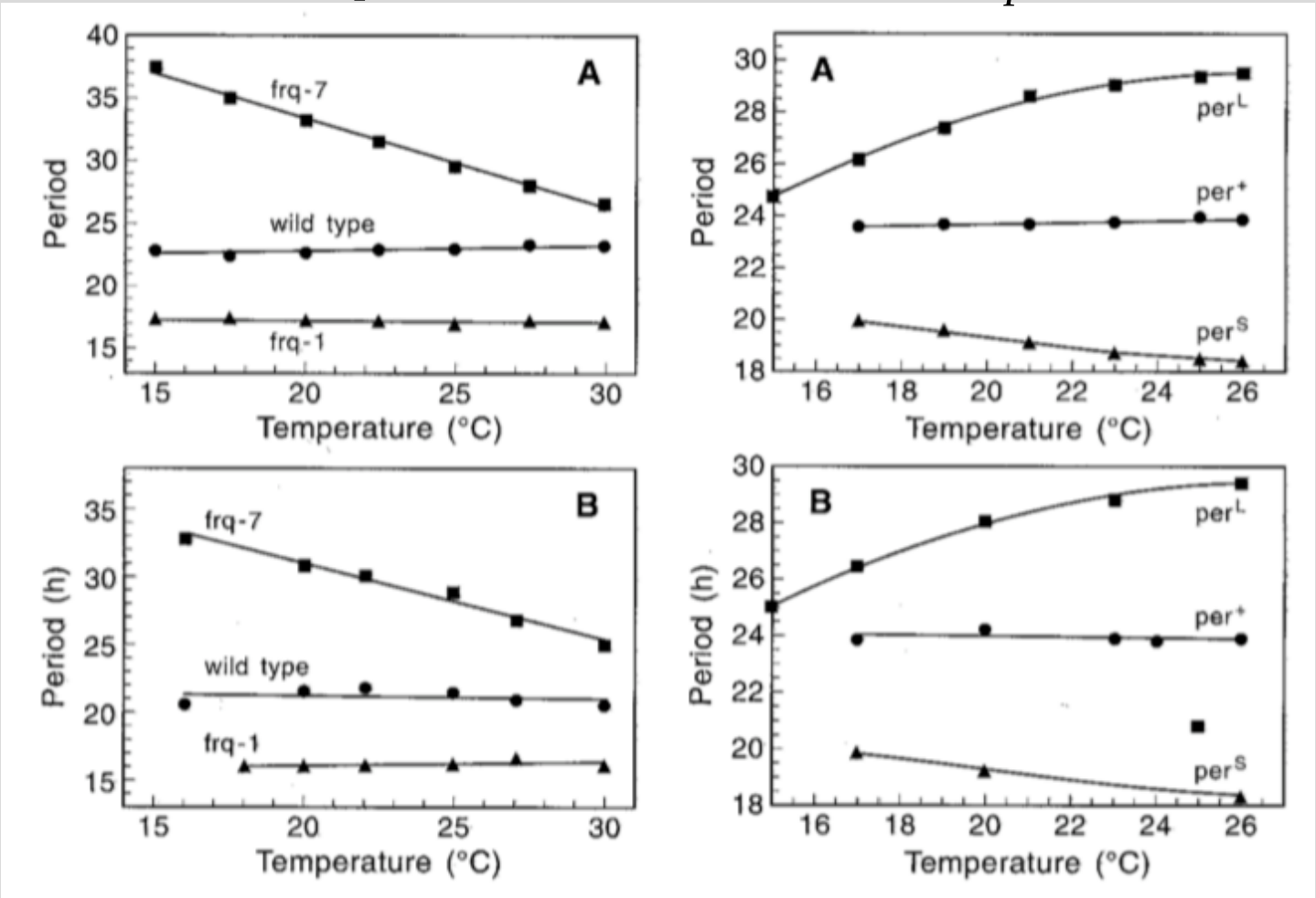
2-4 mm

1971: Ron Konopka finner klokkemutanter i *Drosophila*

1973: Jerry F. Feldman beskriver klokkemutanter i *N. crassa.*

Temperaturkompensasjon i circadiane klokkemutanter for genene *frequency* (*Neurospora*) og *period* (*Drosophila*)

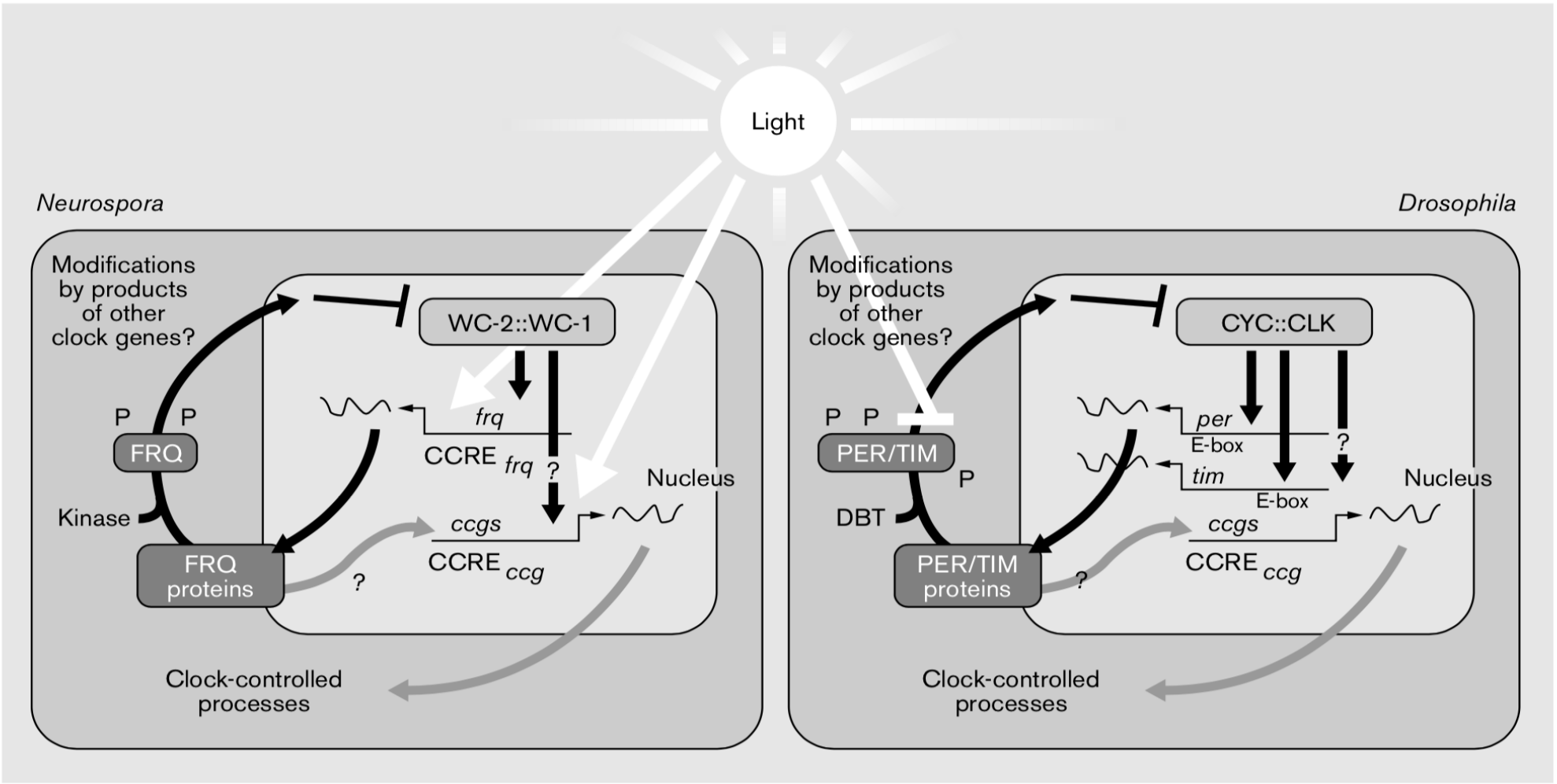
Neuropora *Drosophila*



Ruoff et al. (1996)

Gardner & Feldman 1981 Konopka et al. 1989

Molekylære Mechanismer: Transcriptional-Translational Negative Feedback loops

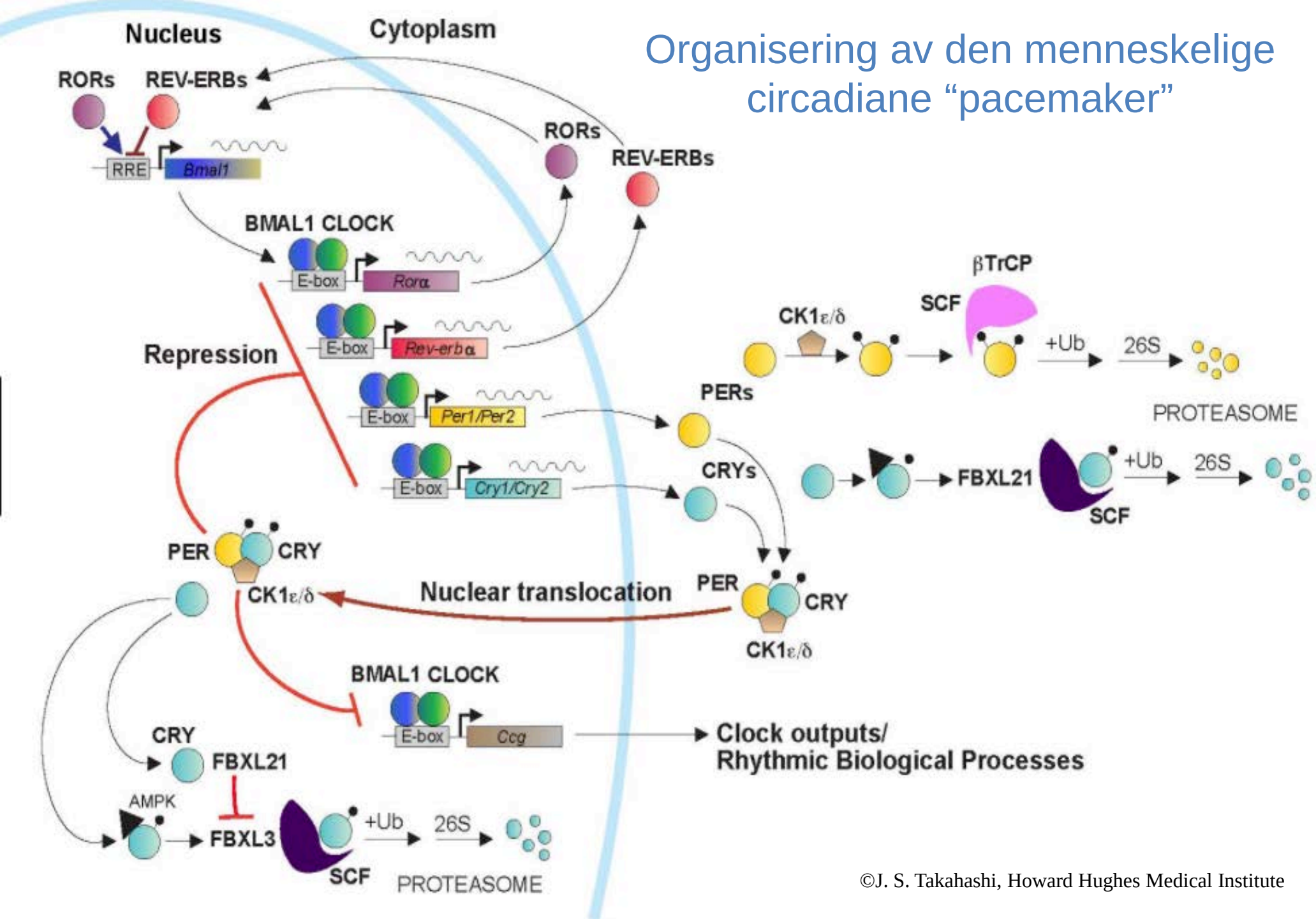


Dunlap (1996)

Current Opinion in Genetics & Development

Michael Roshbash forklarer den negative feedback organisering i *Drosophila*

Organisering av den menneskelige circadiane “pacemaker”



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Advanced Sleep-Phase Syndrome

RESEARCH NEWS

JANUARY 12, 2001

First Human Circadian Rhythm Gene Identified

Researchers exploring the genetic basis of a rare syndrome that causes people to fall asleep and awaken earlier than normal have pinpointed the first human gene that controls circadian rhythm. The finding establishes a link between the human circadian system and that of animal models such as *Drosophila*, mice and hamsters, say the researchers. It also raises the possibility of treating jet lag, as well as sleep problems in adolescents, the elderly and shift workers.

A research team that included Howard Hughes Medical Institute investigator Louis J. Ptacek reported that a mutation in a gene called h*Per*2 is responsible for familial advanced sleep-phase syndrome (FASPS) in members of a Utah family. This syndrome typically causes sleep onset around 7 p.m., and spontaneous awakening around 2 a.m., in affected family members. The research was published online by the journal *Science* on January 12, 2001. The article will also appear in print in a future issue of *Science*.

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VERSIÓN EN ESPAÑOL

HHMI INVESTIGATOR

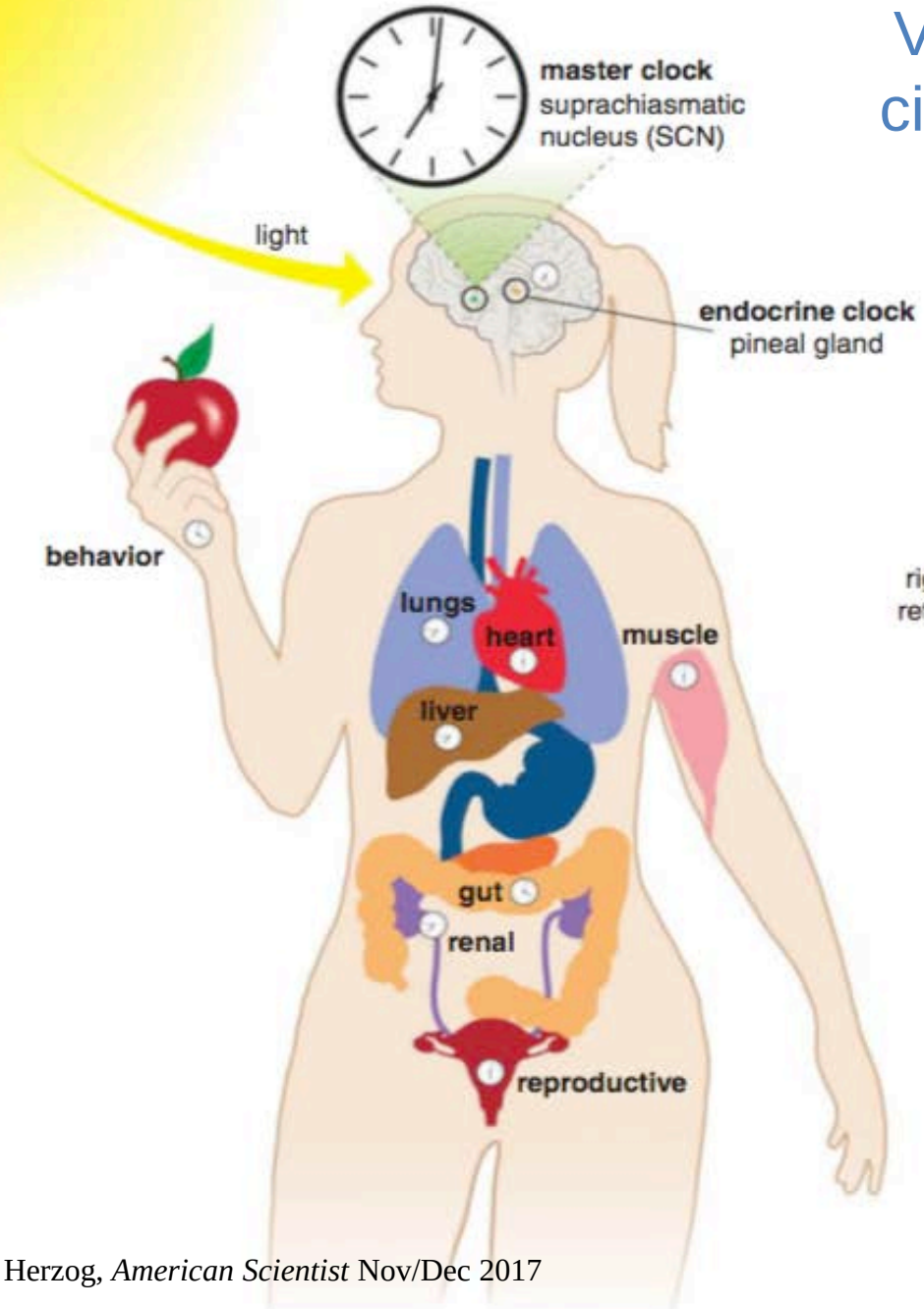
Louis J. Ptacek

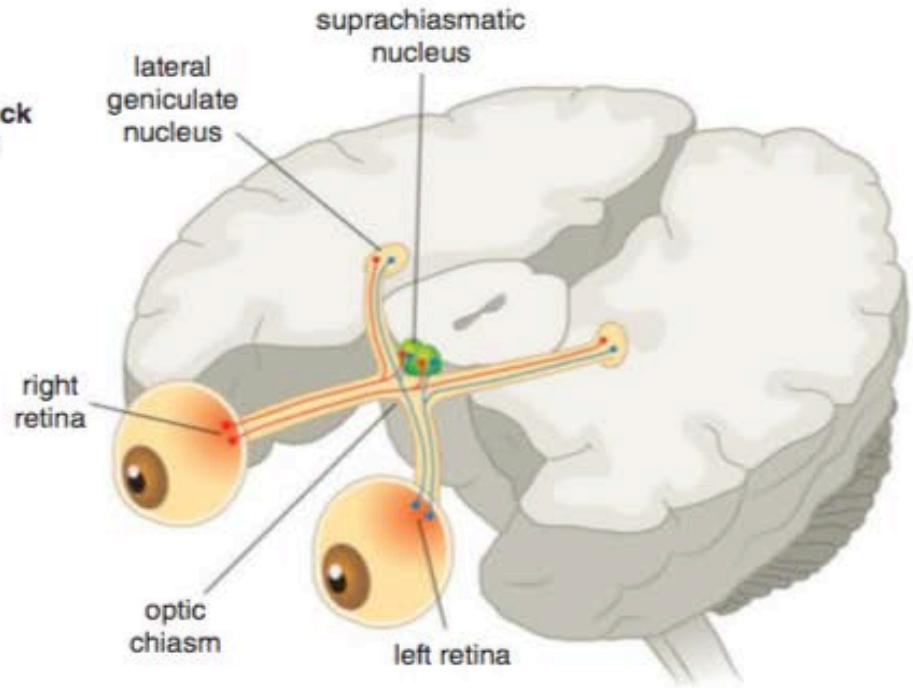
ABSTRACT:

Understanding Brain Function Through Study of Inherited Traits in Humans

RELATED LINKS

Vekselvirkning mellom de ulike circadiane oscillatorer i kroppen

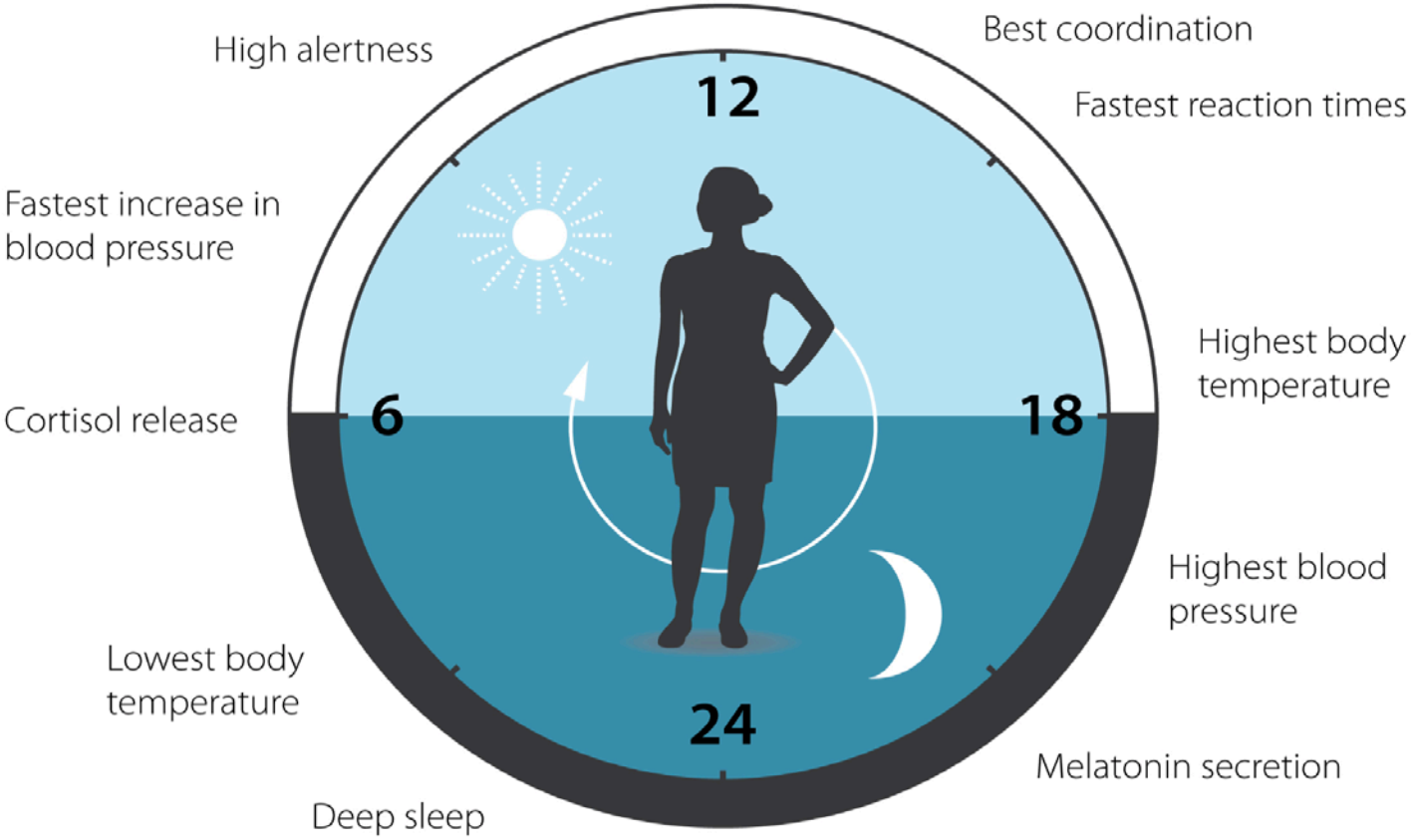




A master clock in the brain, the *suprachiasmatic nucleus* (SCN), helps keep the schedule for clocks in tissues throughout the body (*left*). The strongest signal for setting this master clock is light. Specialized nerve cells for light detection in the retina connect the eyes to the SCN, which is a pair of bilateral nuclei sitting on top of the crossing of the optic nerves at the base of the brain within the hypothalamus.

Webb & Herzog, *American Scientist* Nov/Dec 2017

Innflytelse av den circadiane klokken på menneskelig fysiologi



Nobelförsamlingen Karolinska Instituttet (2017)

On the whole, society is working more and sleeping less, increasing the risk for depression and anxiety issues.

Webb & Herzog, *American Scientist* Nov/Dec 2017

Nobel Prizes and Laureates
Medicine Prizes 2017

▼ About the Nobel Prize in Physiology or Medicine 2017
Summary
Prize Announcement
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Award Ceremony Video
Award Ceremony Speech

▶ Jeffrey C. Hall
▶ Michael Rosbash
▶ Michael W. Young

All Nobel Prizes in Physiology or Medicine
All Nobel Prizes in 2017

The Nobel Prize in Physiology or Medicine 2017
Jeffrey C. Hall, Michael Rosbash, Michael W. Young

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The Nobel Prize in Physiology or Medicine 2017

Photo: Brian Summers
Jeffrey C. Hall
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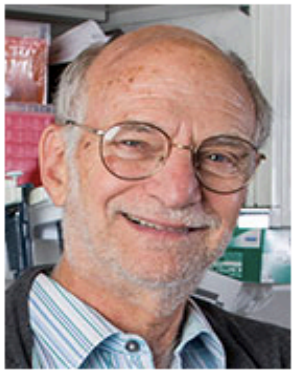
Photo: Scott Eisen, HHMI
Michael Rosbash
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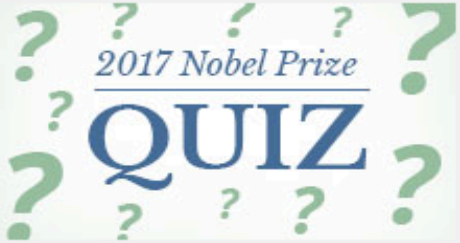
The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young *"for their discoveries of molecular mechanisms controlling the circadian rhythm"*.



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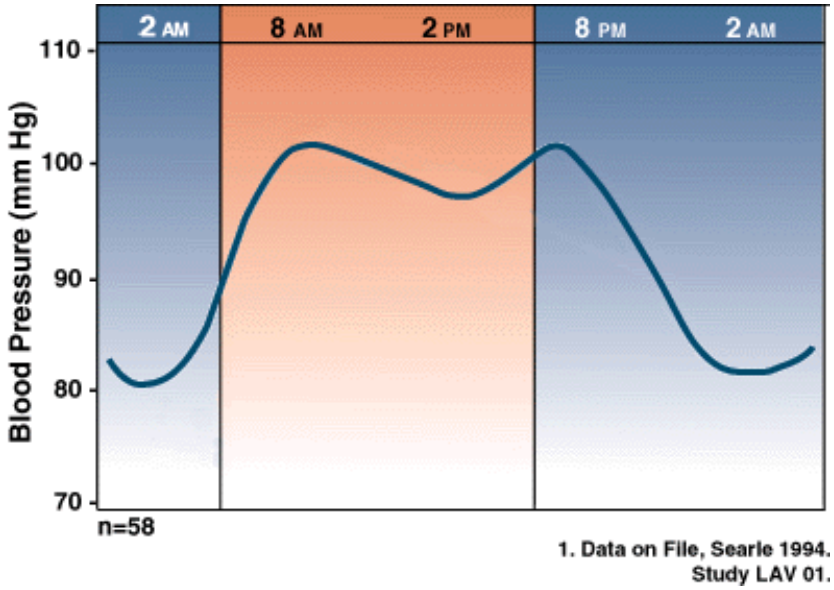
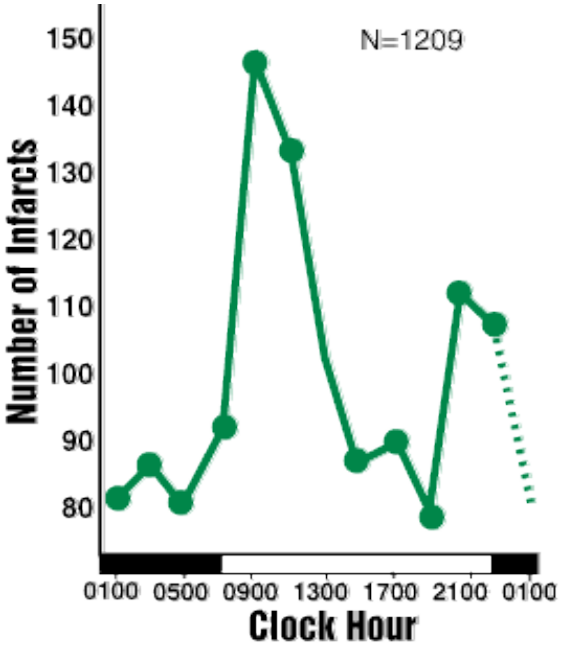
Circadian variasjon av blodtrykk / hjerteinfarkt



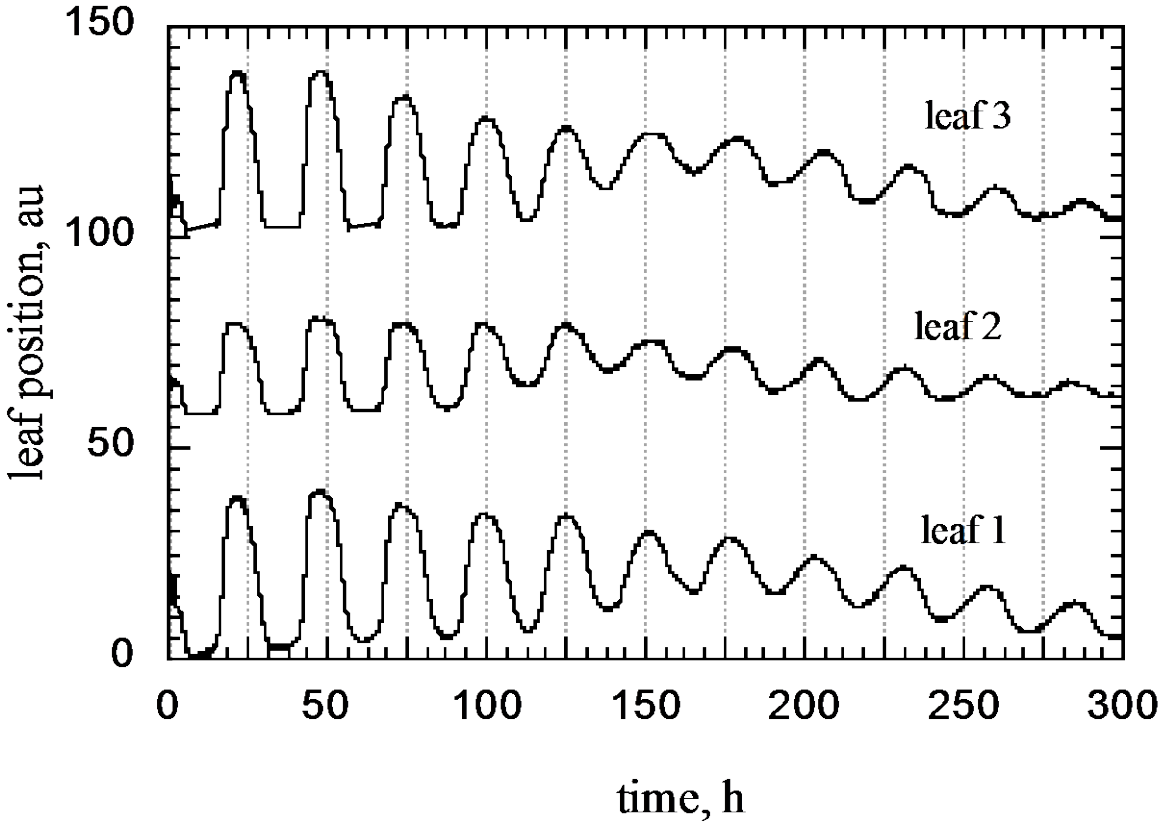
Circadian variasjon
av blodtrykk



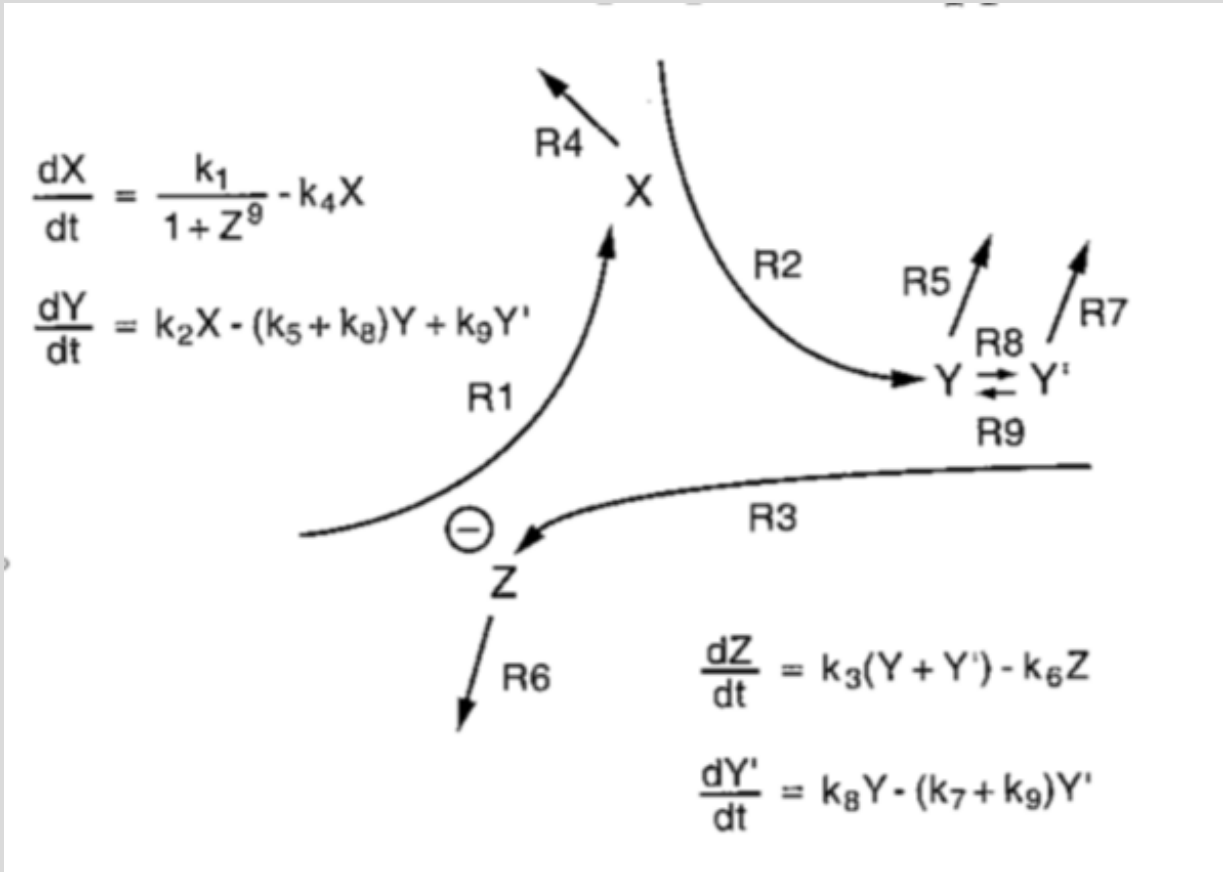
Circadian variasjon av
antall hjerteinfarkt

Oxalis bladbevegelser

(Prof. Anders Jonsson, NTH)

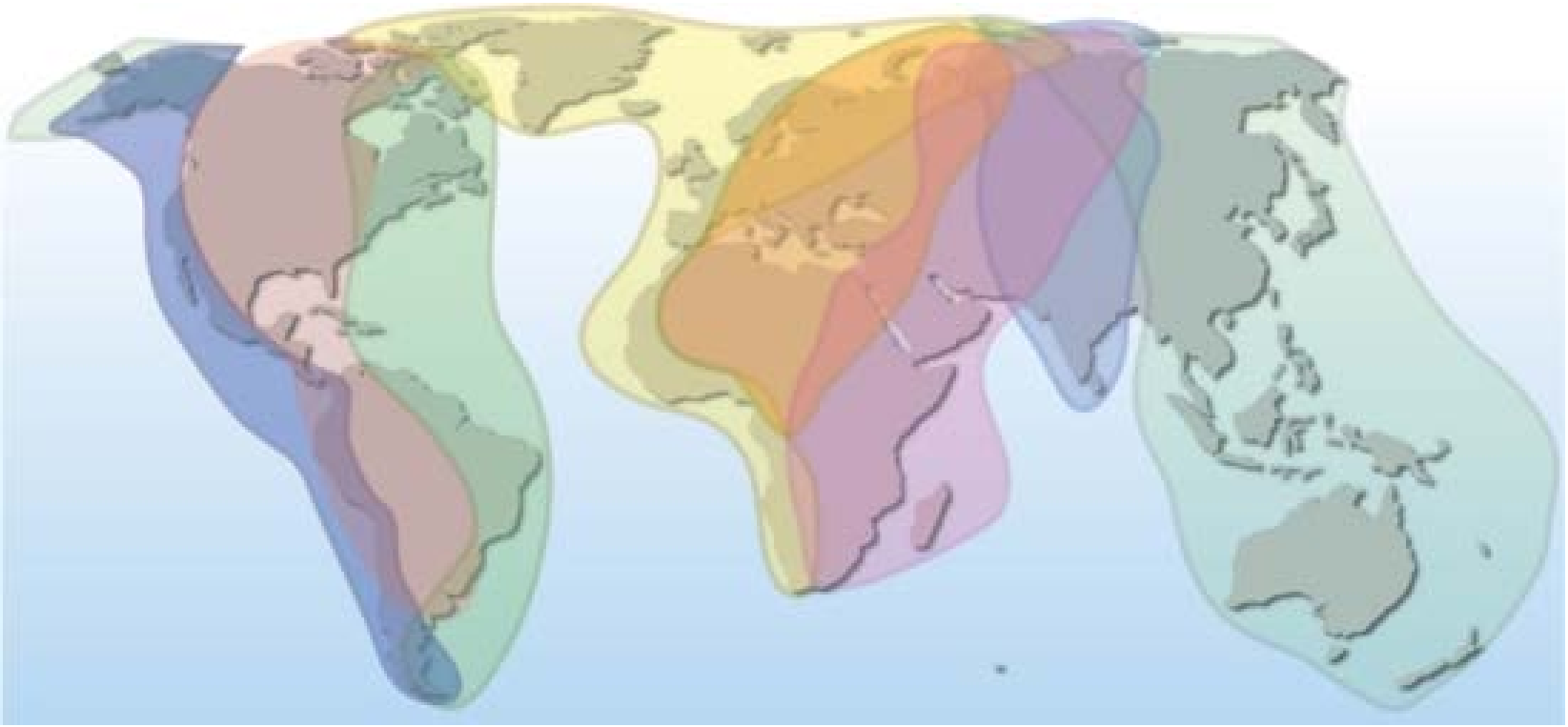


Goodwin's Negative Feedback Oscillator from 1963 is able to explain temperature compensation in *Neurospora* og *Drosophila*



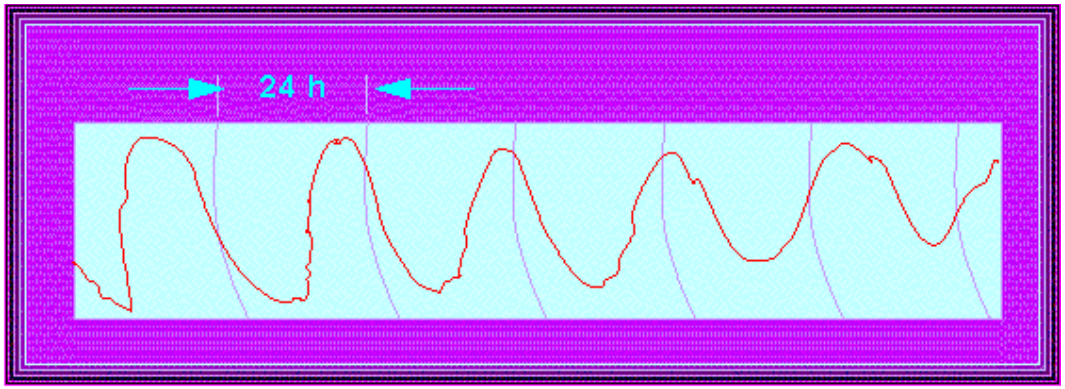
Ruoff et al. (1996)

Seasonal adaptation of organism (photoperiodicity): Major global bird migration routes to the Arctic

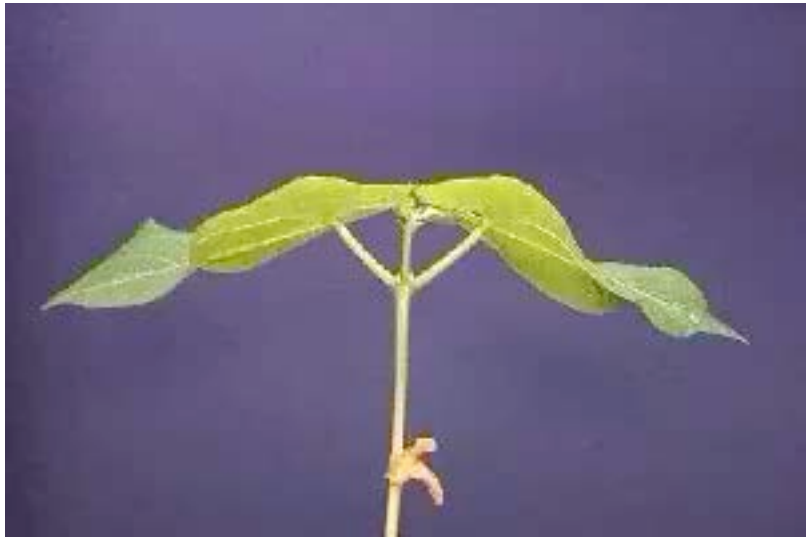


Major global bird migration routes to the Arctic. No other place on Earth receives so many migratory species.

Leaf movements under free-running conditions



***Phaseolus coccineus*. Opptak av bladbevegelse i en bønneplante (fra E. BÜNNING and M. TAZAWA, 1957).**

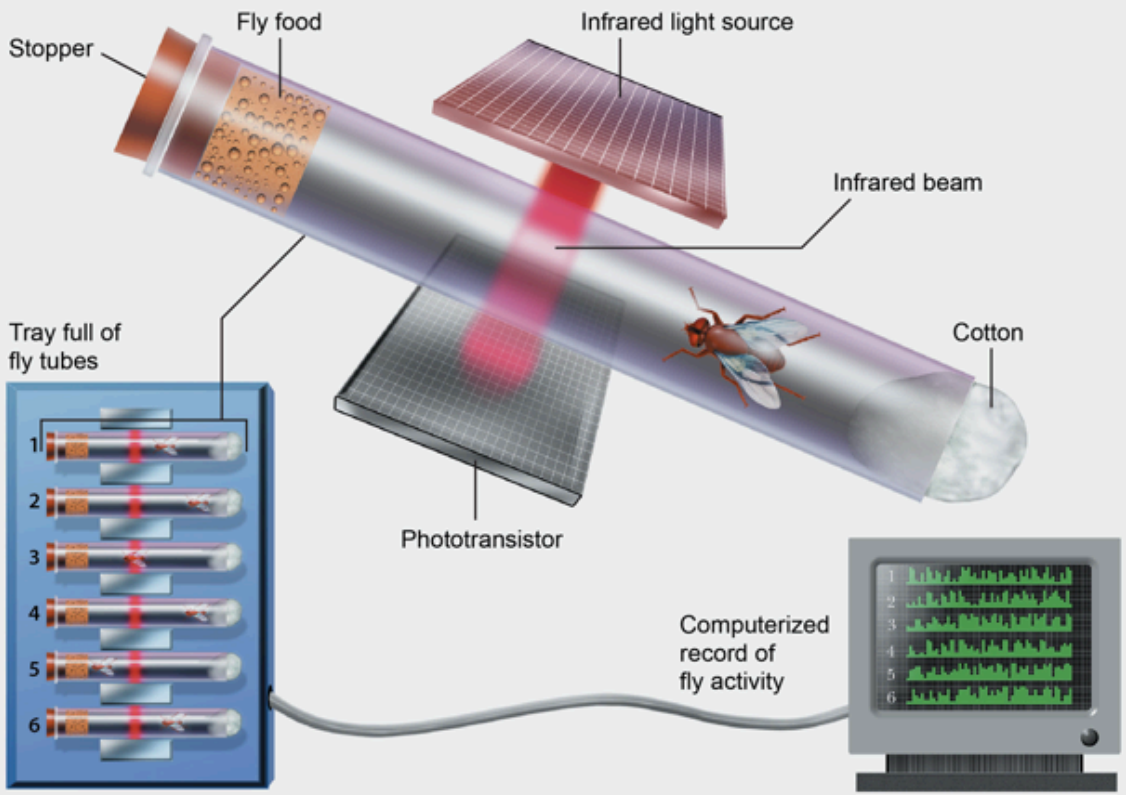


Opptak av bladbevegelse av en bønneplante (Roger P. Hangarter, Indiana University).

Monitoring the Circadian Rhythms of Flies

An Apparatus to Track Fly Activity

To identify genes that play a role in the day-night activity cycle of flies, researchers expose fruit flies to mutation-causing chemicals that affect the genes of their offspring. When they become adults, each of the offspring is placed into a small glass tube. The tubes have fly food at one end and cotton at the other end to let in air. The fly tubes are placed into special trays equipped with infrared lights and detectors. Fruit flies normally rest at night and are active during the day. The trays, which are connected to a computer, monitor each fly's movements by recording how many times it passes through an infrared beam. Analyzing thousands of mutant flies in this manner eventually yields some with abnormal circadian rhythms. —*M.W.Y.*



M. Young, Scientific American
March 1, 2000