# Ritmos circadianos

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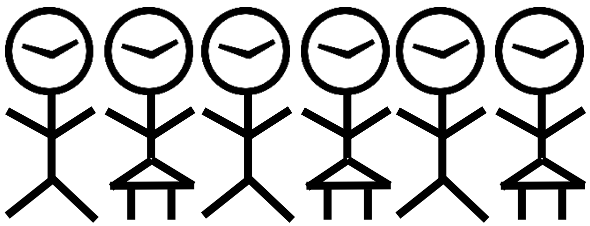
Laboratorio de Neurociencias

GARMIN
安 愛 智 信 力 和 氣 福 平 靜 喜 壽
HAPPY NEW YEAR!
TOSHIBA
12:08
REGULATOR

TIEMPO

al final, todo se trata de estimar el tiempo…



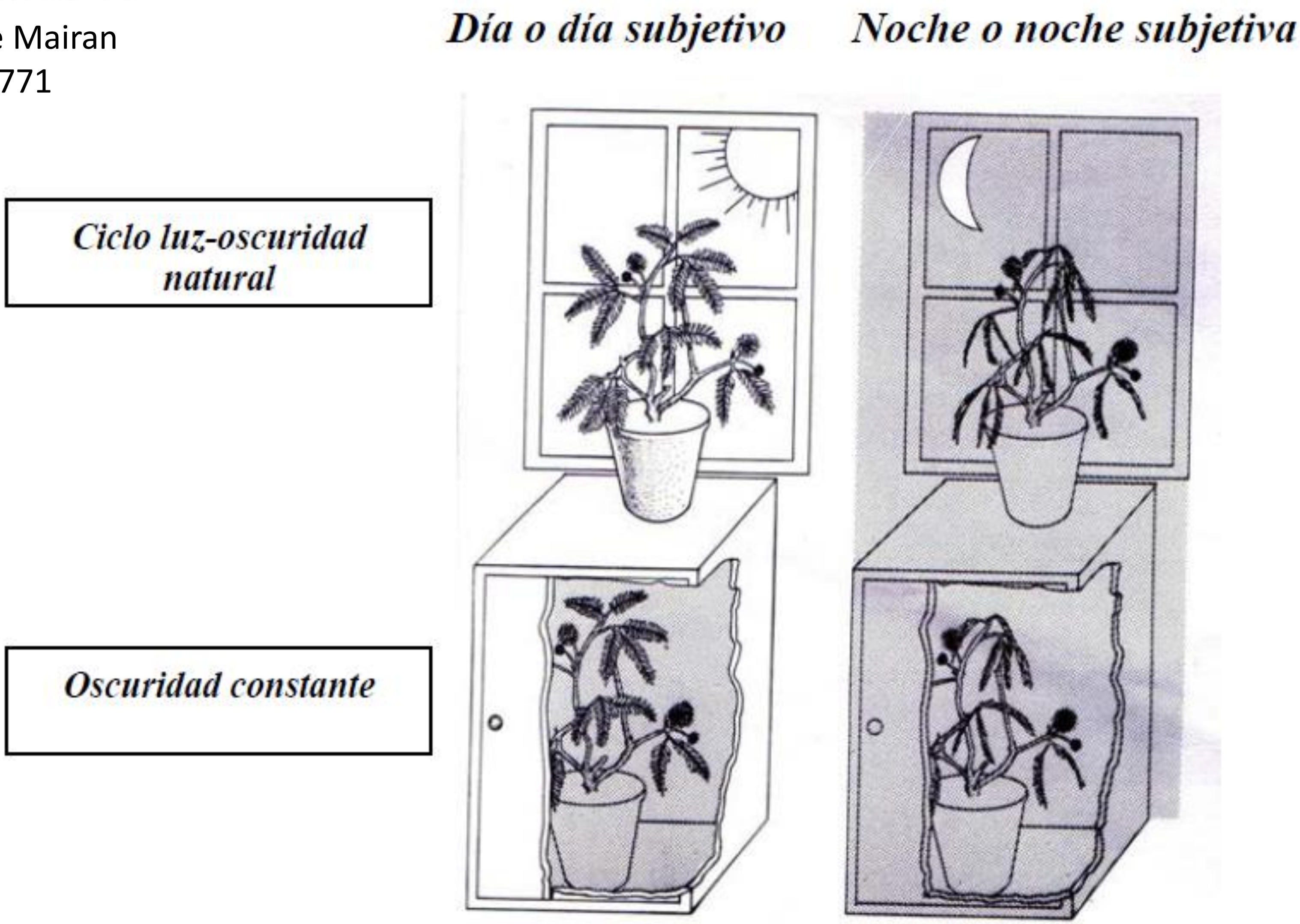
El tiempo está en todos lados, hasta dentro nuestro… somos en definitiva un reloj que va caminando… Diego Golombek

# RITMOS CIRCADIANOS – PRIMER REGISTRO

Jean Jacques Dourtous de Mairan
1678-1771

# RITMOS CIRCADIANOS – PRIMER REGISTRO

Dourtous de Mairan
1678-1771



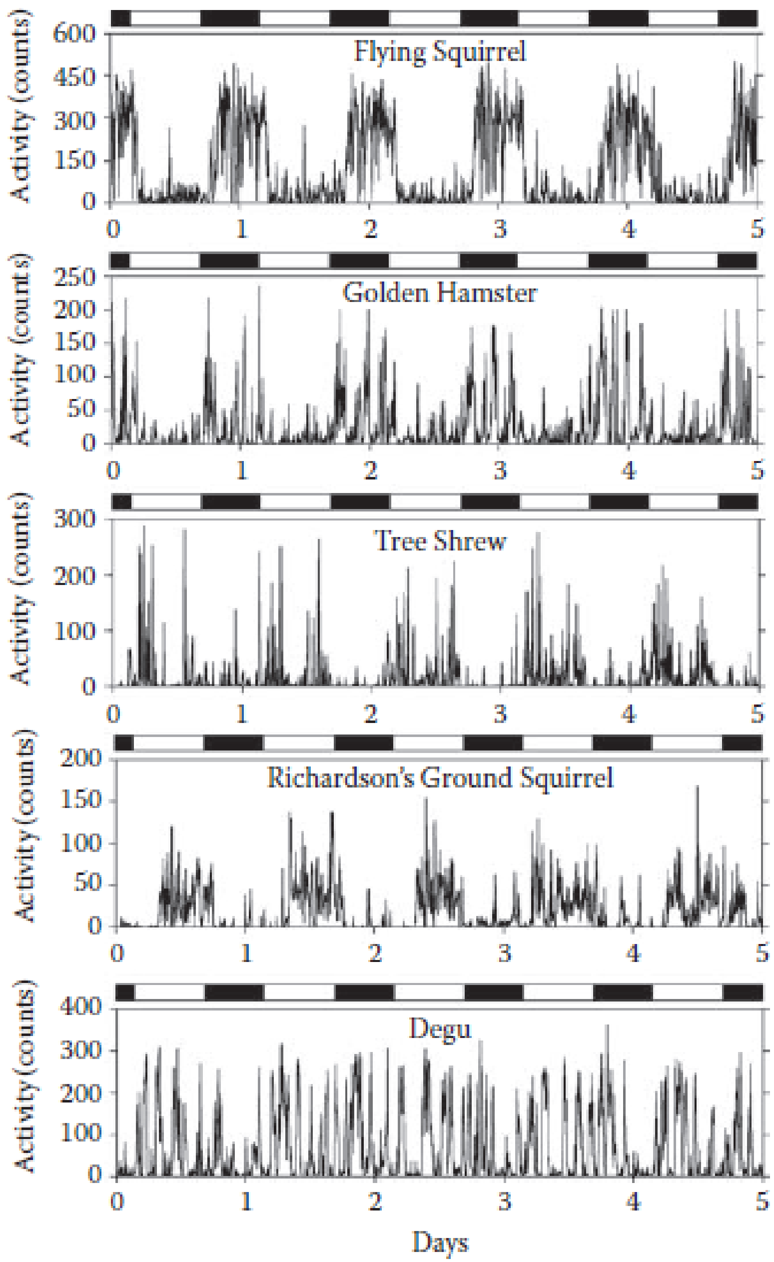
# RITMOS CIRCADIANOS - REQUISITOS

- Período ≈ 24 horas (19-28)
- Sincronizado por variables ambientales
- Endógeno

Franz Halberg, 1959

Jünger Aschoff

# RITMOS CIRCADIANOS - REQUISITOS



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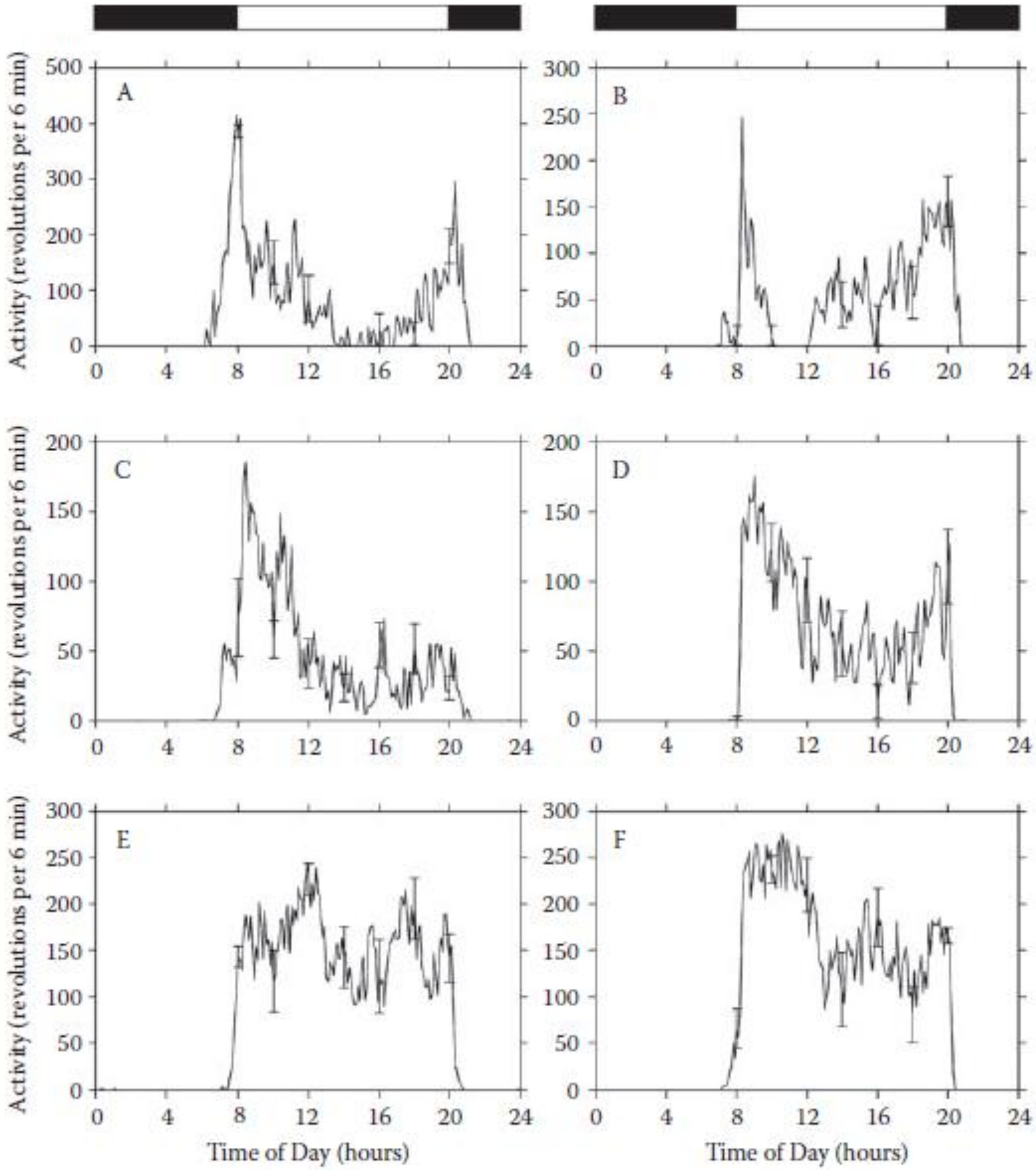


rata del Nilo

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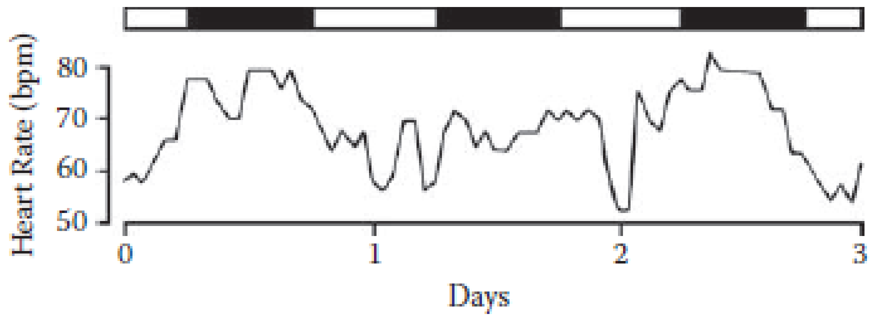
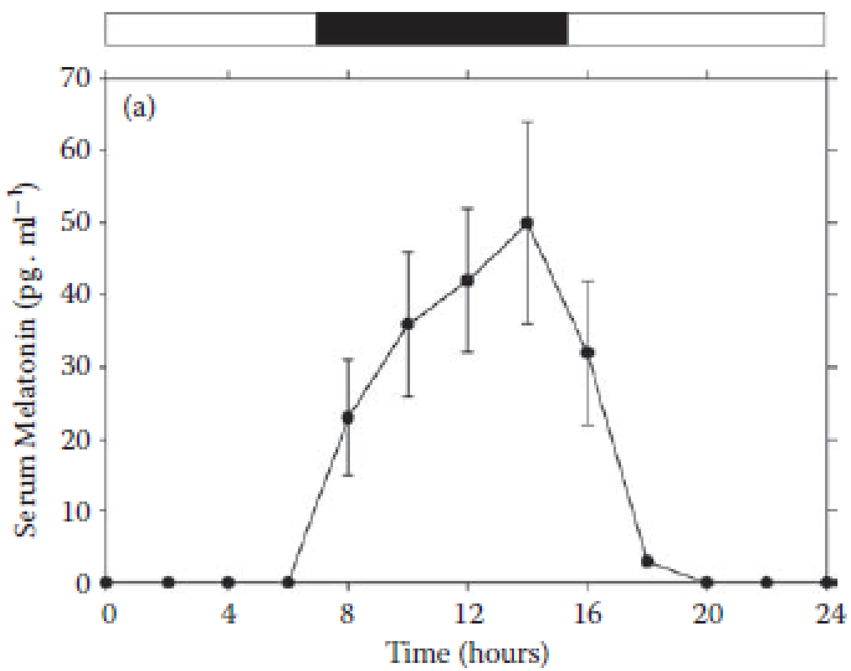



perro




cabra

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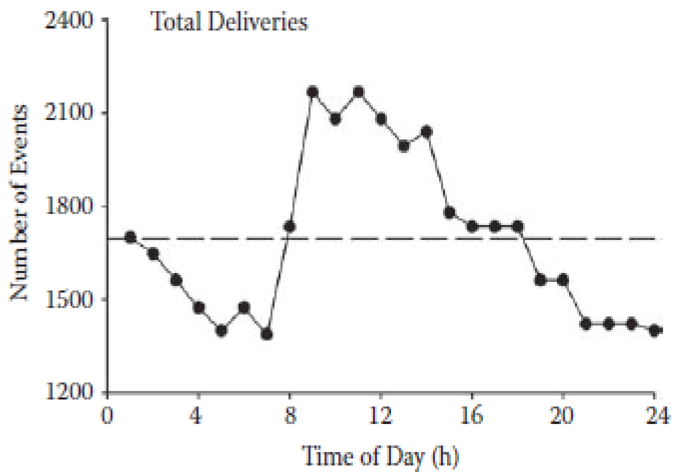
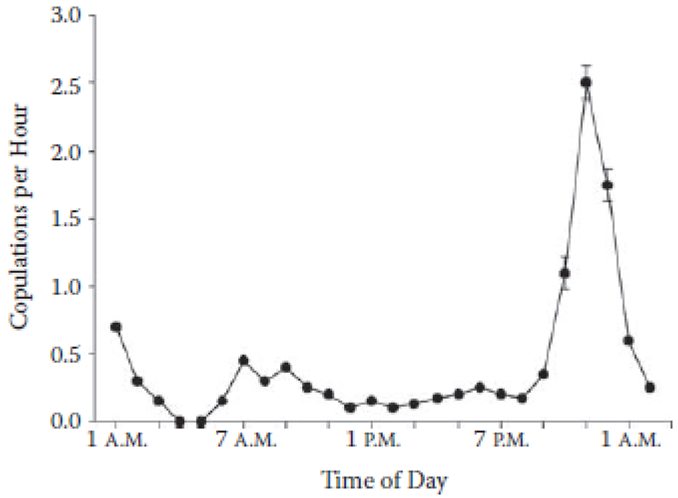
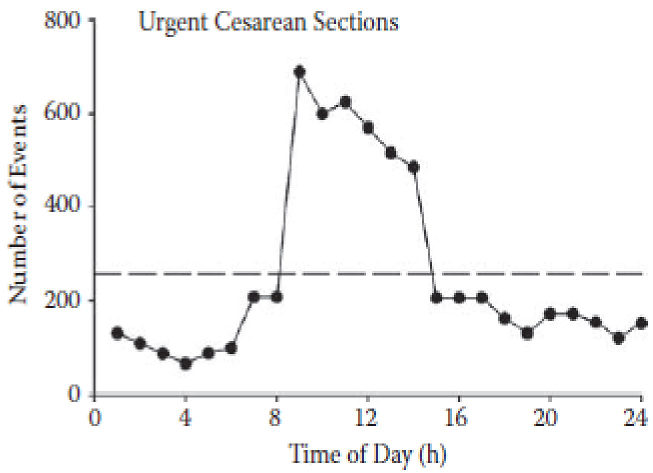
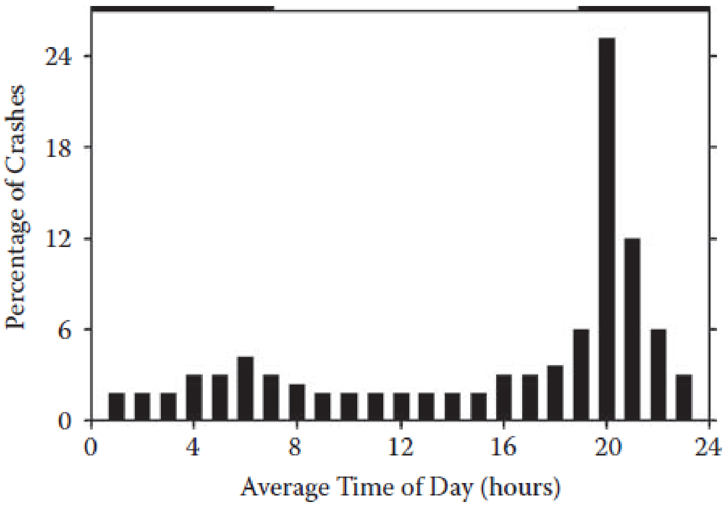


# RITMOS CIRCADIANOS - REQUISITOS

- Período ≈ 24 horas (19-28)
- Sincronizado por variables ambientales
- Endógeno

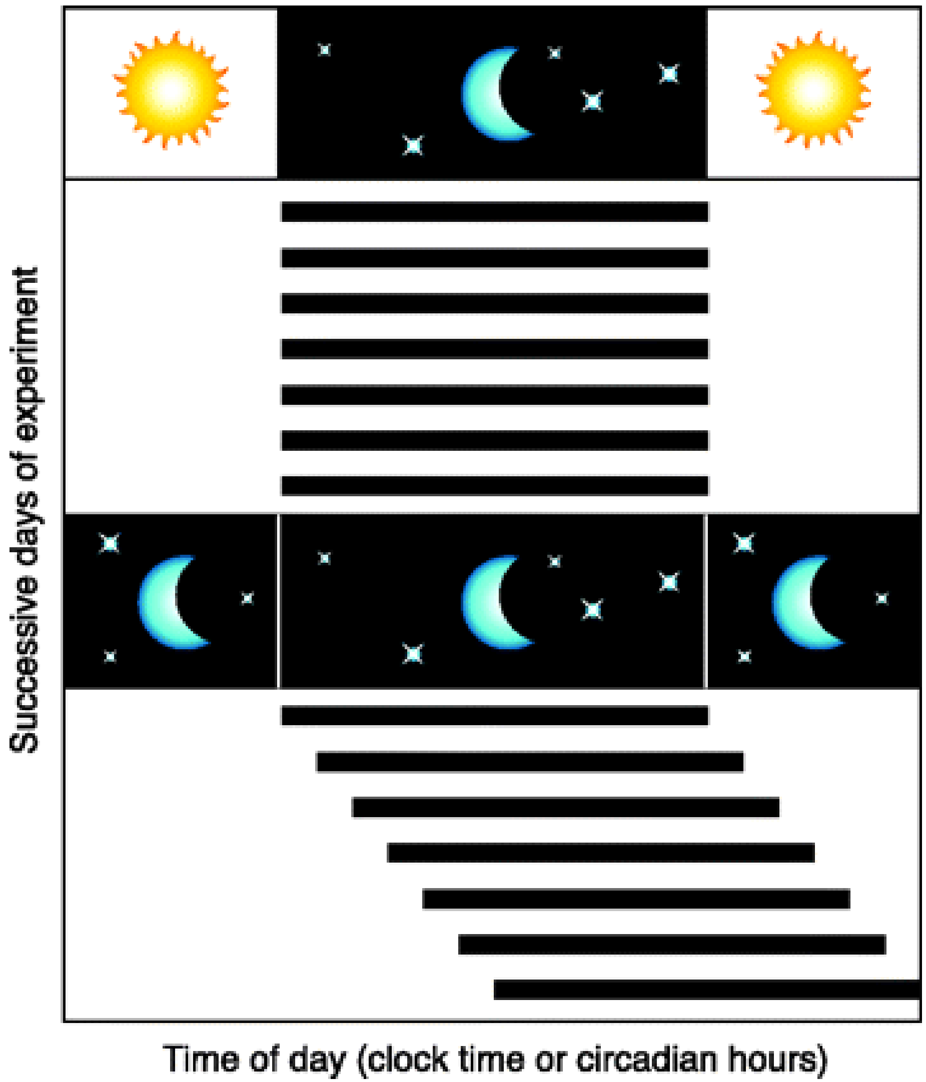
Franz Halberg, 1959

Jünger Aschoff

# RITMOS CIRCADIANOS - REQUISITOS

Sincronizado con luz

Endógeno



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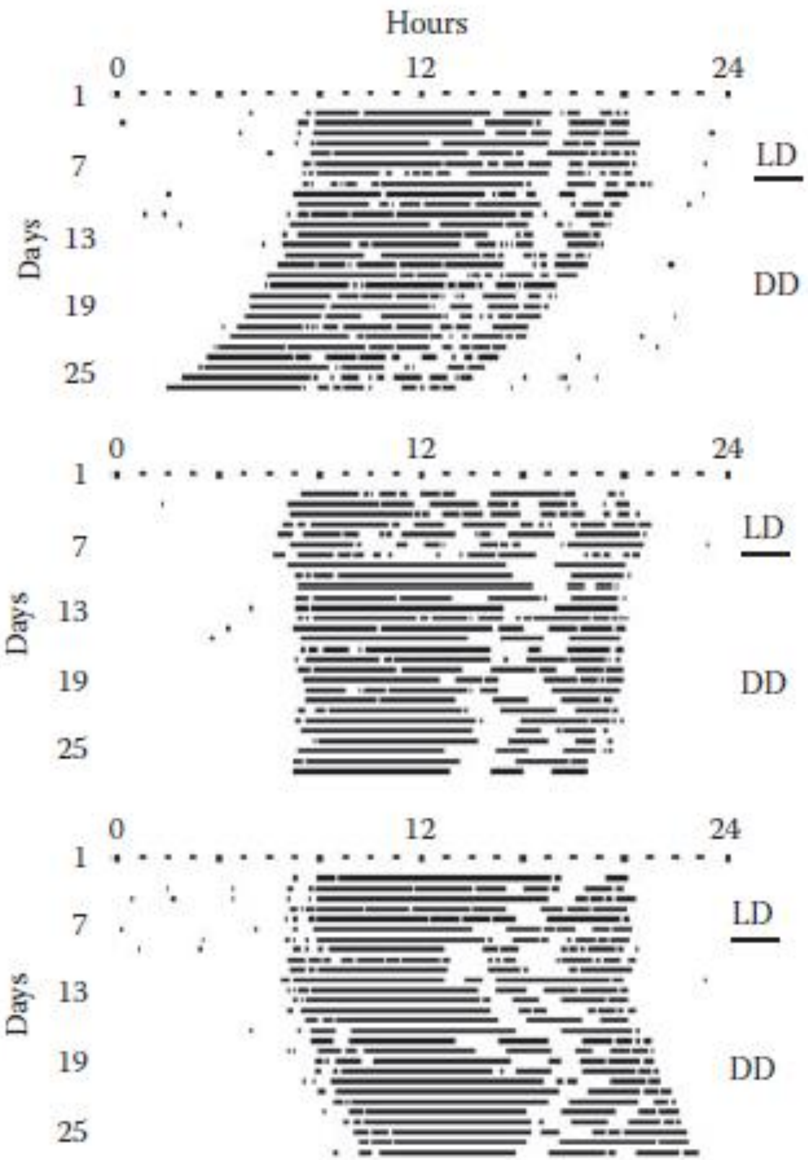
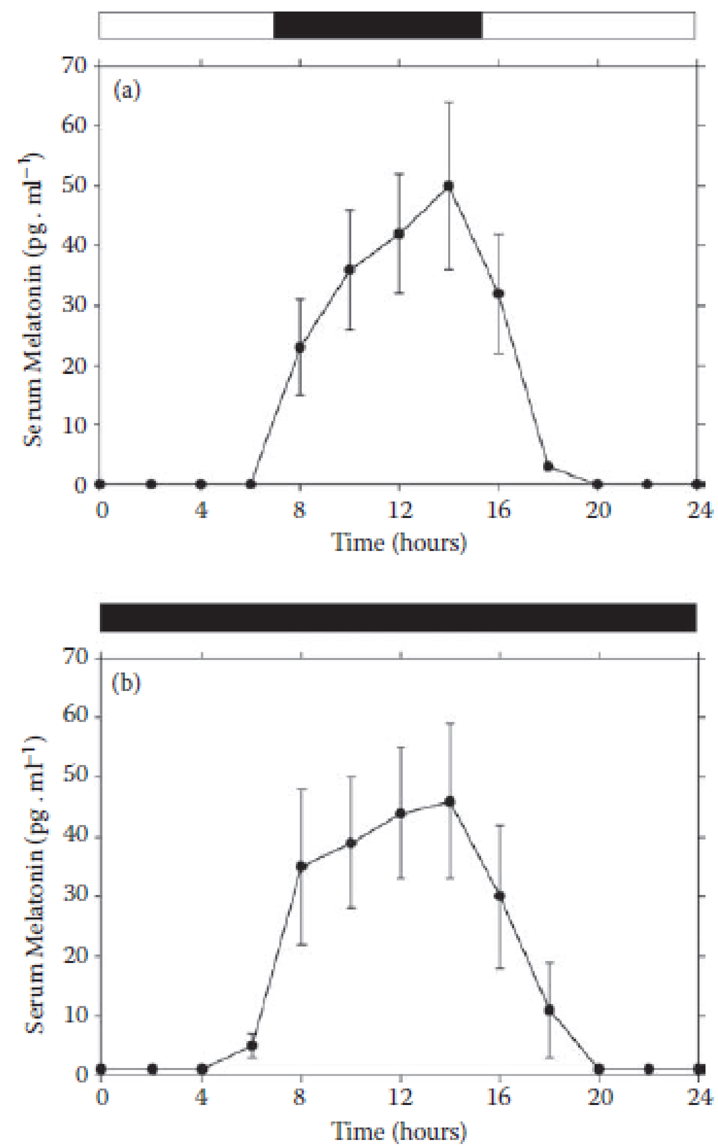
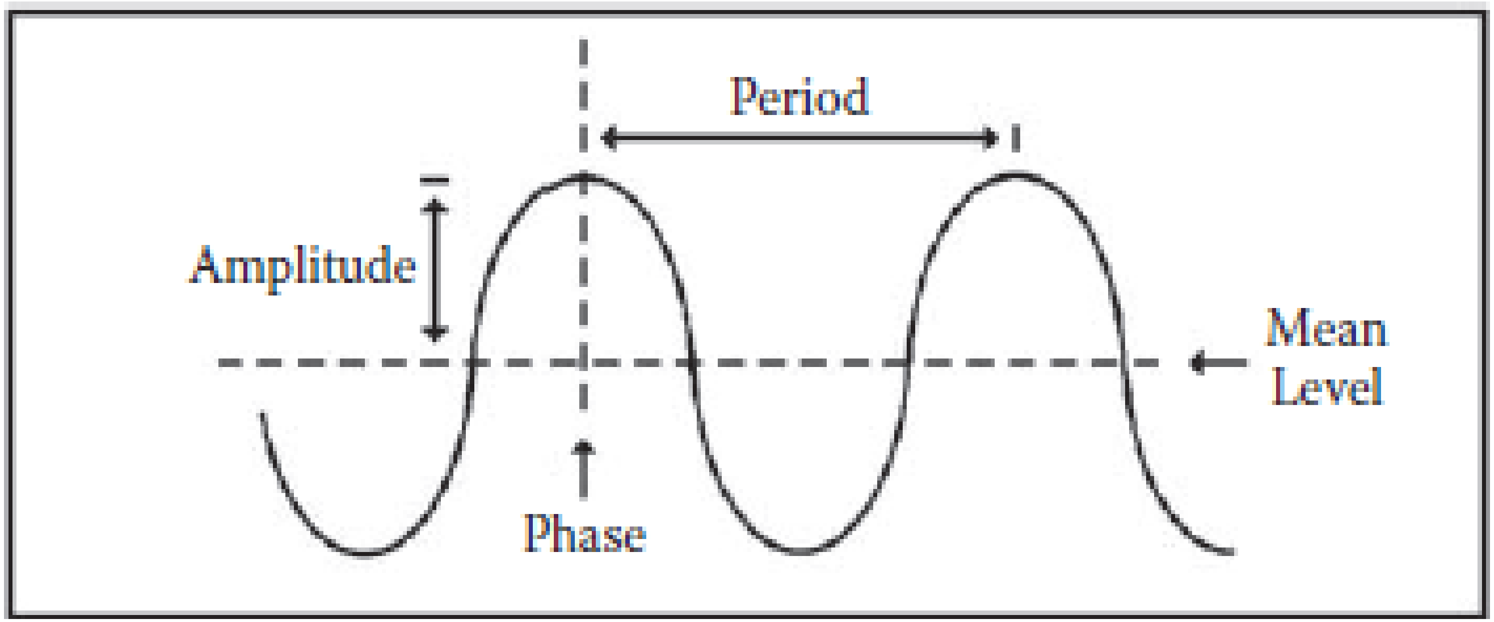


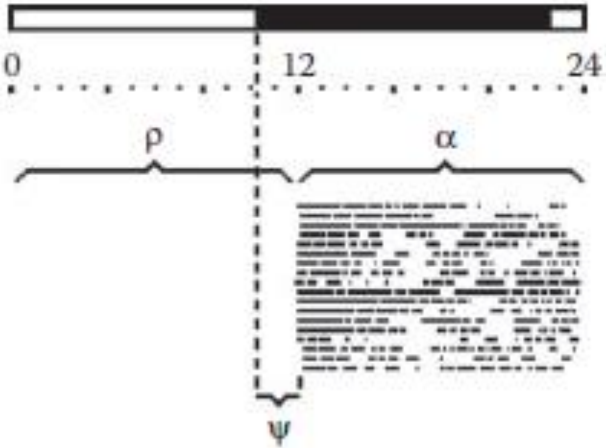

rata del Nilo



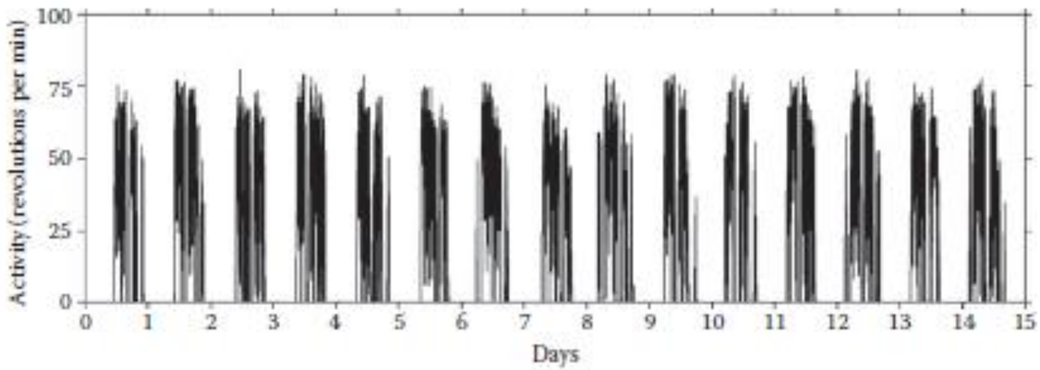

cabra

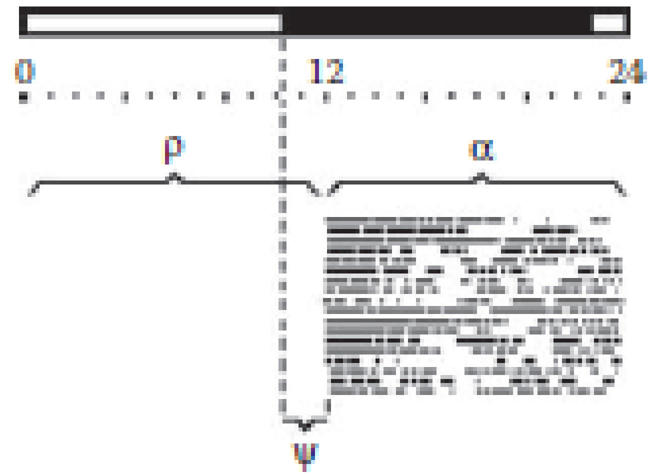
# RITMOS CIRCADIANOS - ANALISIS

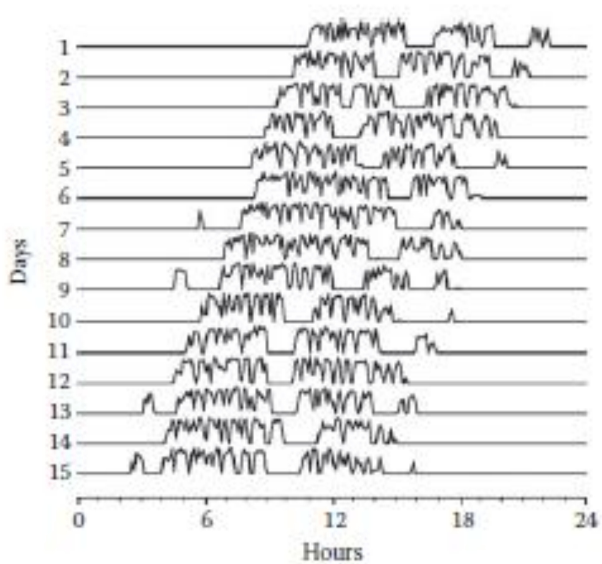


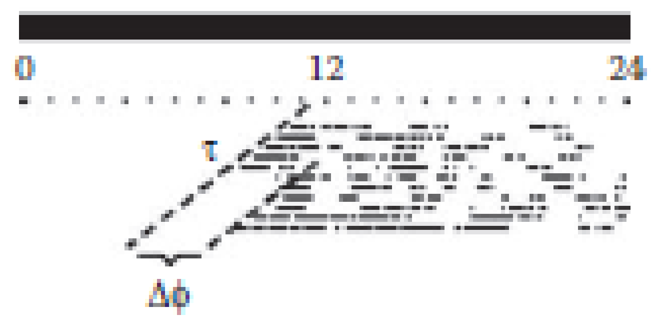



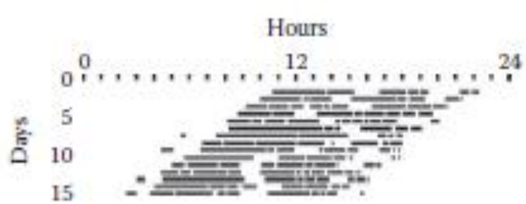
# RITMOS CIRCADIANOS - ANALISIS



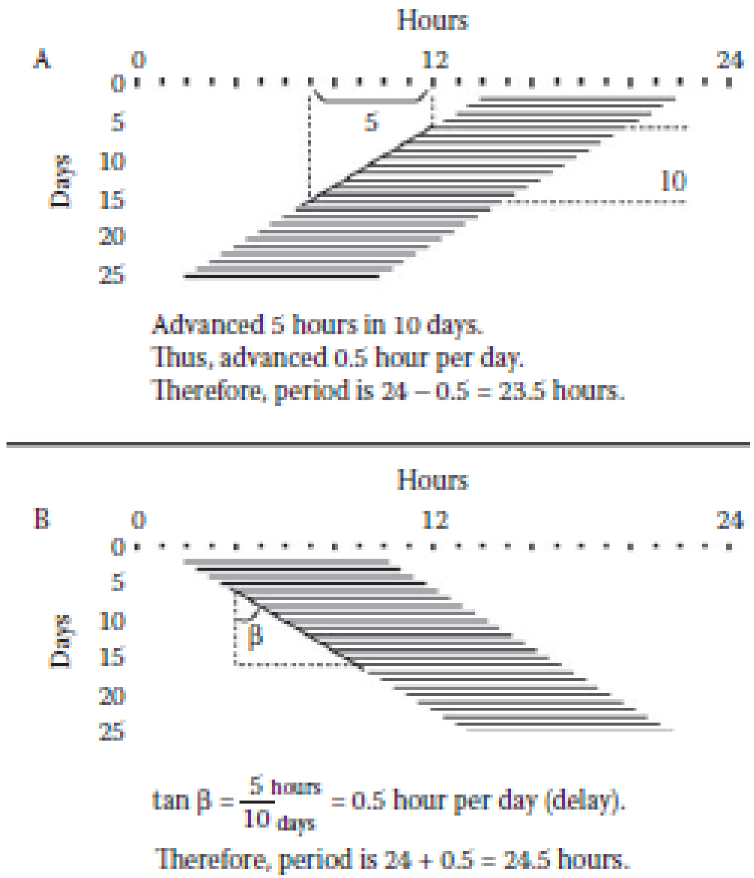



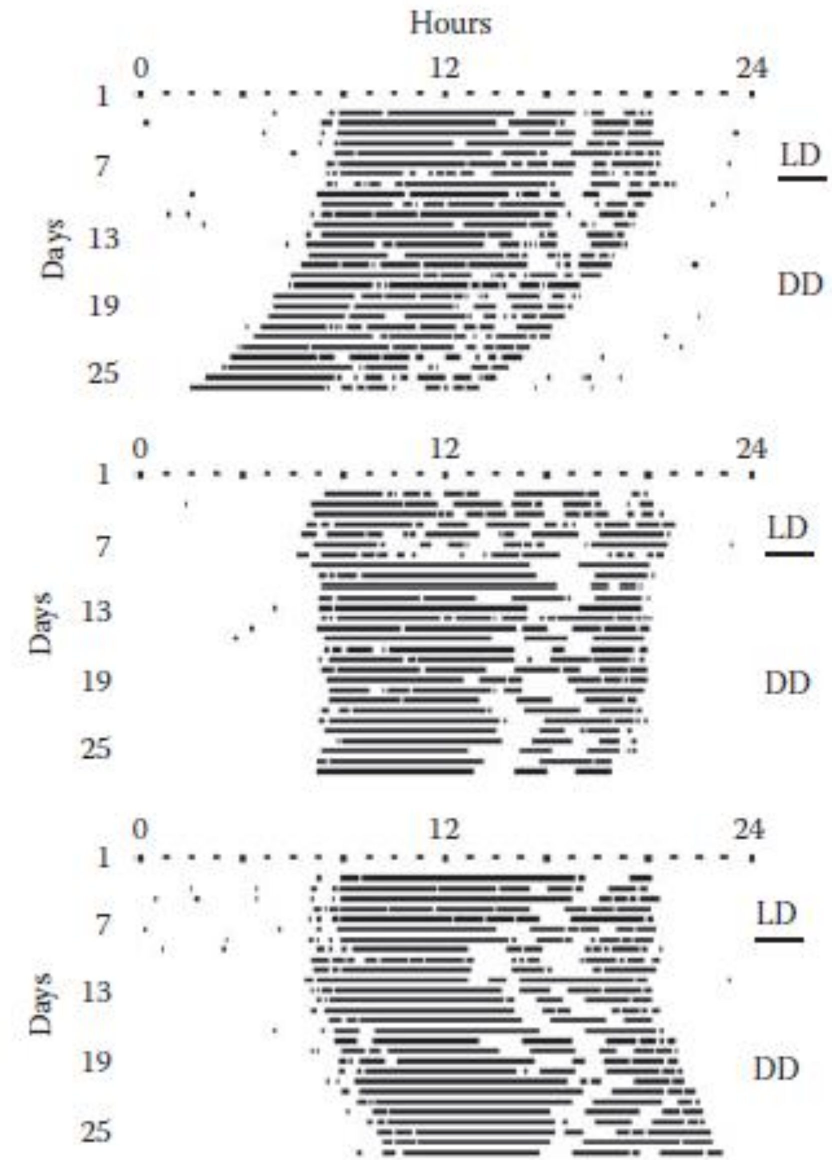

- Construcción Actograma

Maynard Johnson, 1926

- Desvío de Fase

# RITMOS CIRCADIANOS - ANALISIS

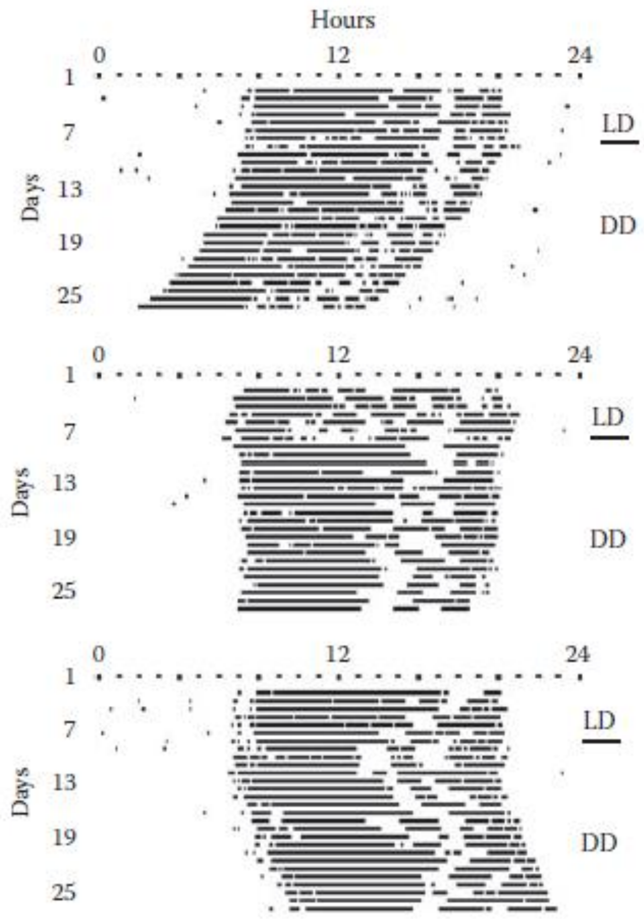



rata del Nilo

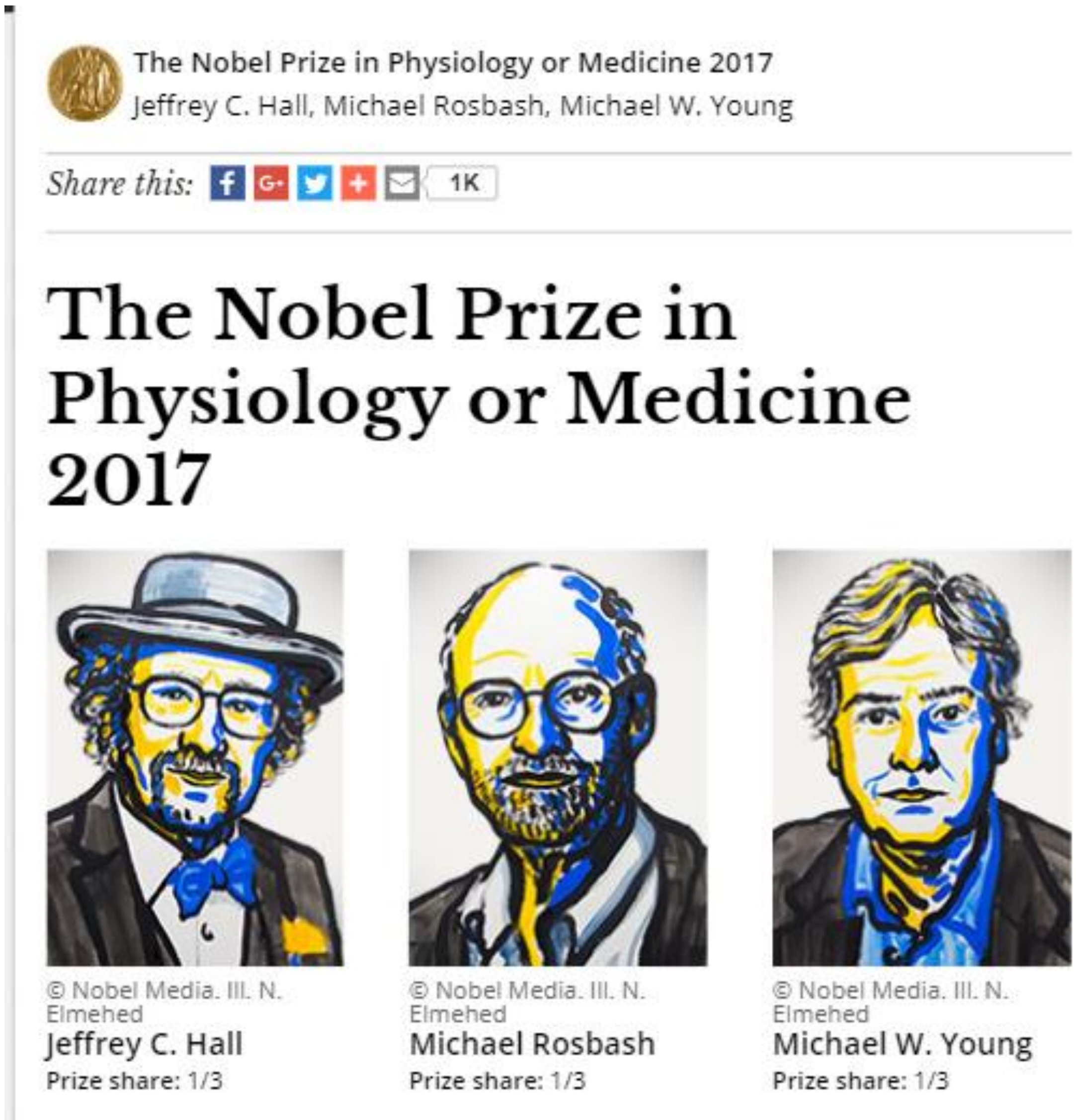
# RITMOS CIRCADIANOS

Permanencia de ritmo en curso libre → Existencia de RELOJ




Diferentes períodos entre individuos → Influencia de GENES

# RITMOS CIRCADIANOS




Diferentes períodos entre individuos → Influencia de GENES

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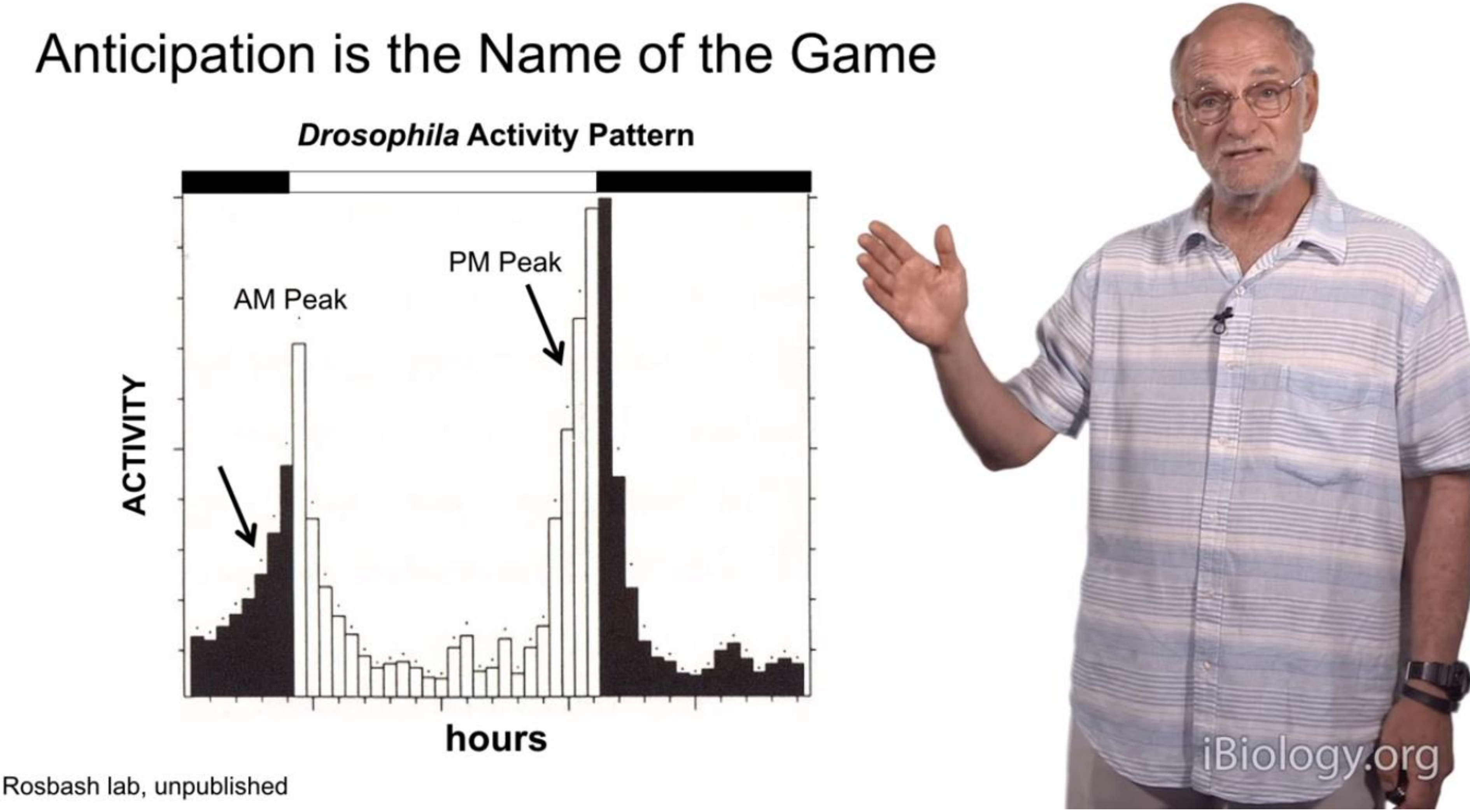


Diferentes períodos entre individuos → Influencia de GENES

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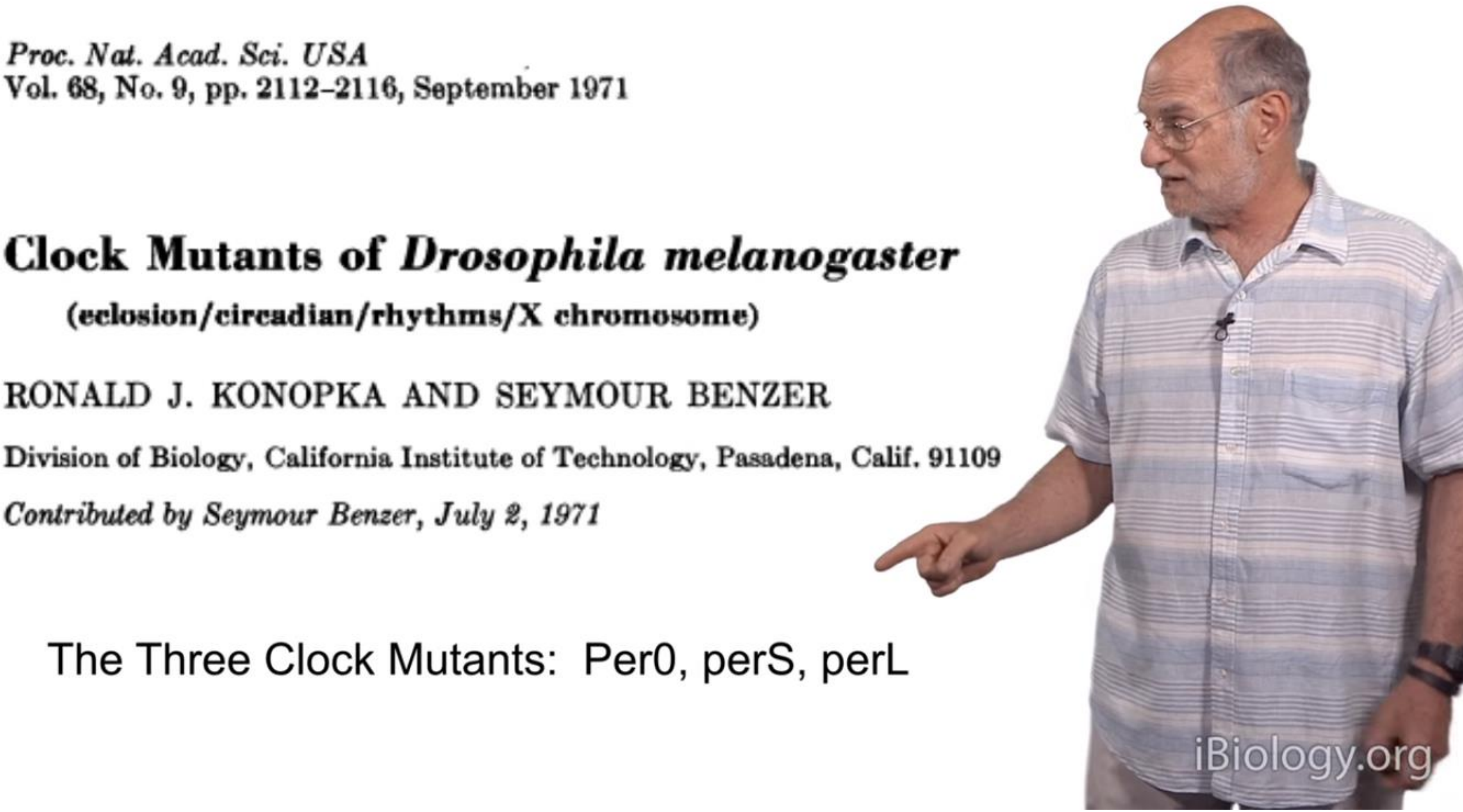


Diferentes períodos entre individuos → Influencia de GENES

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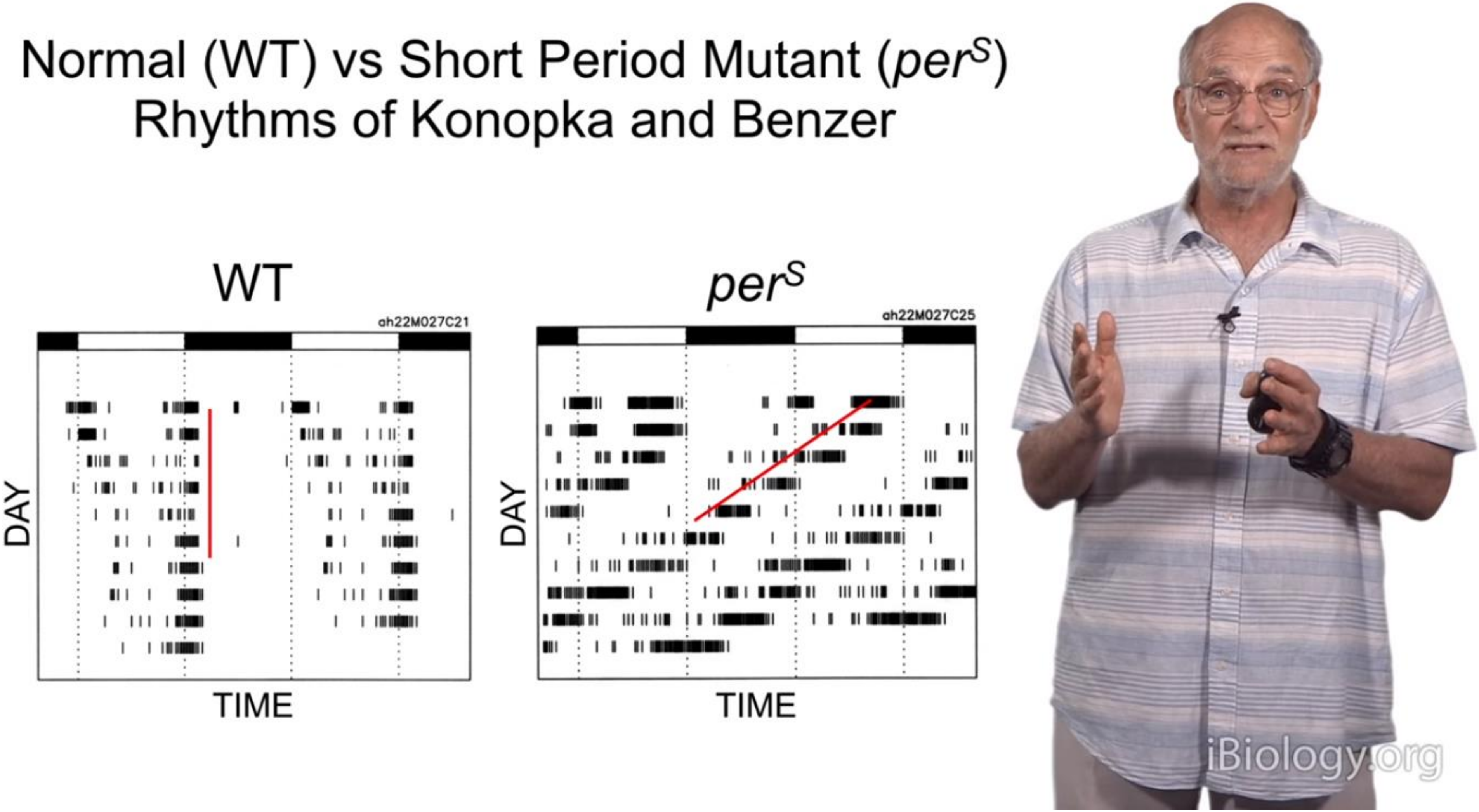


Diferentes períodos entre individuos → Influencia de GENES

# RITMOS CIRCADIANOS

Cell, Vol. 38, 701-710, October 1984, Copyright © 1984 by MIT 0092-8674/84/100701-10 $02.00/0

## Molecular Analysis of the *period* Locus in Drosophila melanogaster and Identification of a Transcript Involved in Biological Rhythms

**Pranhitha Reddy,* William A. Zehring,† David A. Wheeler,† Vincent Pirrotta,‡ Christopher Hadfield,‡ Jeffrey C. Hall,† and Michael Rosbash†**
*Department of Biochemistry
Brandeis University
Waltham, Massachusetts 02254
†Department of Biology
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Waltham, Massachusetts 02254
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Postfach 10.2209
D-6900 Heidelberg, Federal Republic of Germany

**letters to nature**

*Nature* **312**, 752 - 754 (20 December 1984); doi:10.1038/312752a0

## Restoration of circadian behavioural rhythms by gene transfer in *Drosophila*

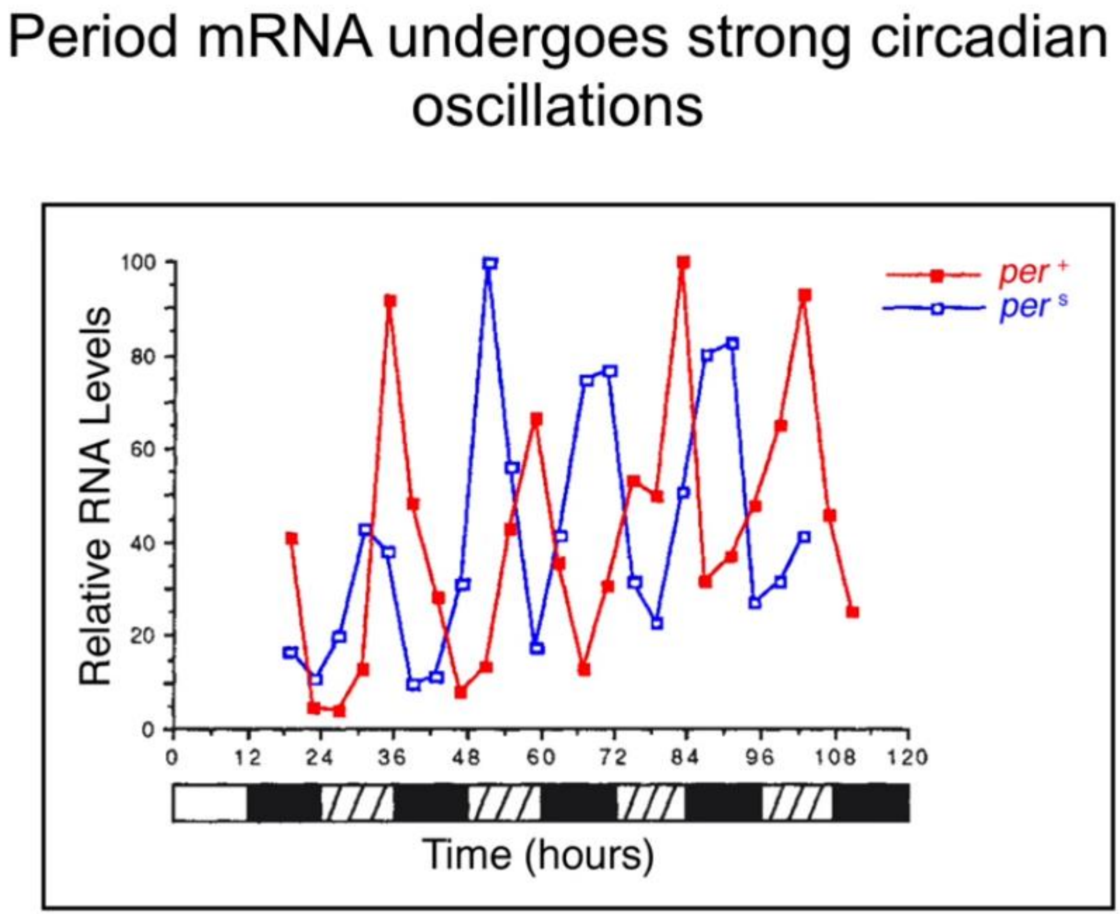
THADDEUS A. BARGIELLO, F. ROB JACKSON & MICHAEL W. YOUNG

The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

**The *per* locus of *Drosophila melanogaster* has a fundamental role in the construction or maintenance of a biological clock. Three classes of *per* mutations have been identified: *per* $^{l}$ mutants have circadian behavioural rhythms with a 29-h rather than a 24-h period, *per* $^{s}$ mutants have short-period rhythms of 19 h, and *per* $^{0}$ mutants have no detectable circadian rhythms[1–4]. Each of these mutations has a corresponding influence on the 55-s periodicity of male courtship song[5]. Long-and short-period circadian rhythm phenotypes can also be obtained by altering the dosage of the wild-type gene[4]: for example, females carrying only one dose of this X-linked gene have circadian rhythms with periodicities about 1 h longer than those carrying two doses. In a previous report[6], cloned DNA was used to localize several chromosomal rearrangement breakpoints that alter *per* locus function. The rearrangements all affected a 7-kilobase (kb) interval that encodes a 4.5-kb poly(A)$^{+}$ RNA. We report here that when a 7.1-kb fragment from a *per* $^{+}$ fly, including the sequences encoding the 4.5-kb transcript, is introduced into the genome of a *per* $^{0}$ (arrhythmic) fly by P element-mediated transformation, circadian rhythmicity of behaviour such as eclosion and locomotor activity is restored. The transforming DNA complements *per* locus deletions and is transcribed, forming a single 4.5-kb poly(A)$^{+}$ RNA comparableto that produced by wild-type flies.**

Diferentes períodos entre individuos → Influencia de GENES

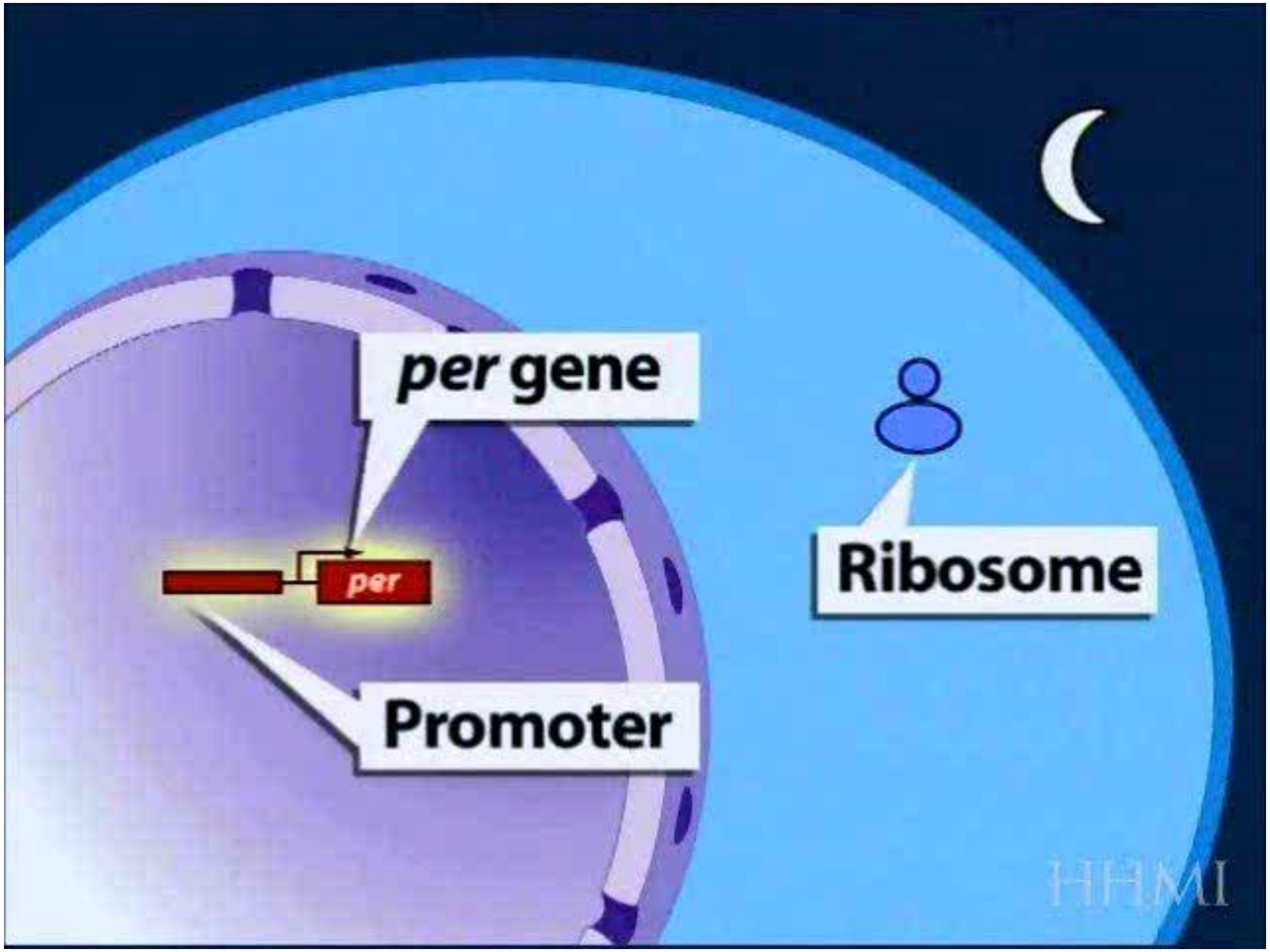
# RITMOS CIRCADIANOS




Original Figure in Hardin et al., 1990


Diferentes períodos entre individuos → Influencia de GENES

# RITMOS CIRCADIANOS

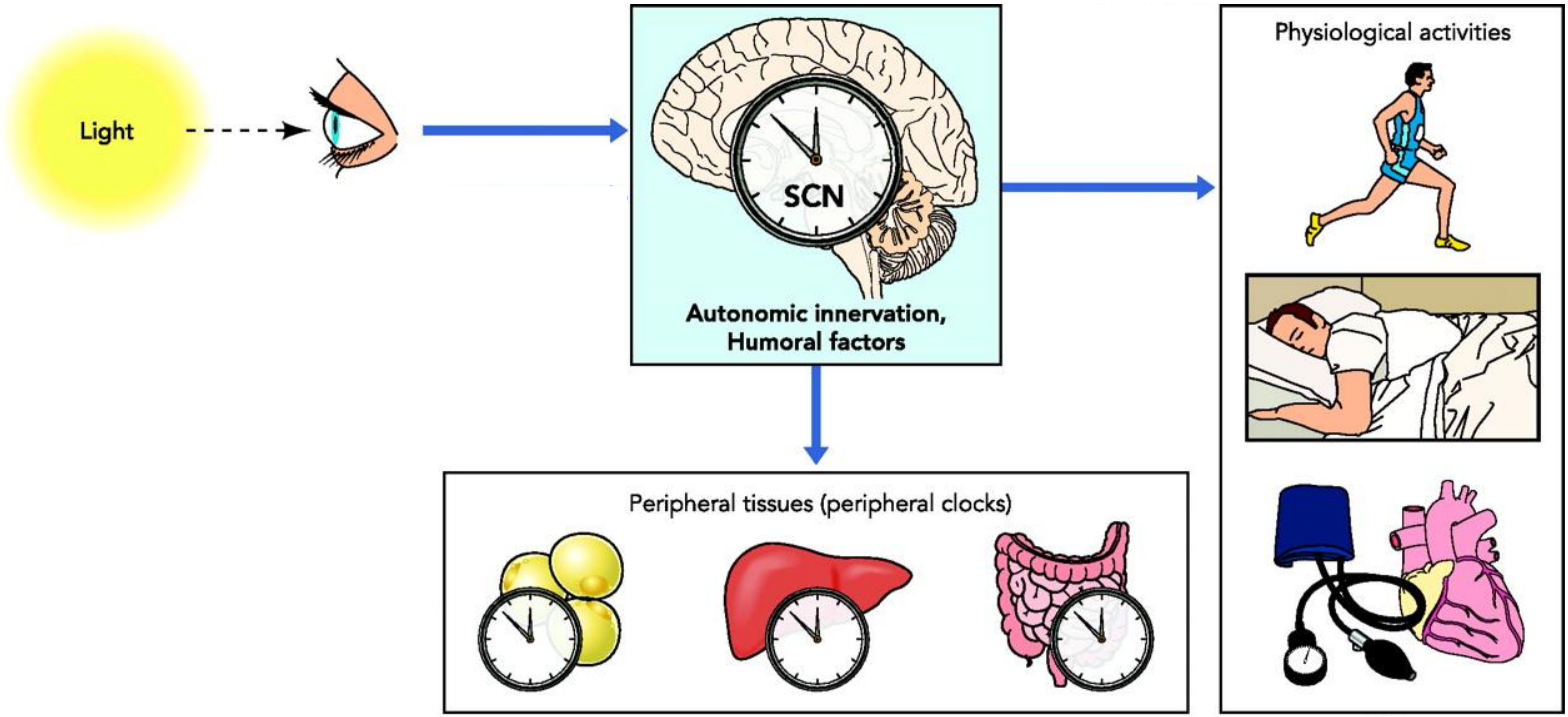



Diferentes períodos entre individuos → Influencia de GENES

# RITMOS CIRCADIANOS – SISTEMA CIRCADIANO

"…El tiempo entra por los ojos. Eso lo sabe cualquiera.

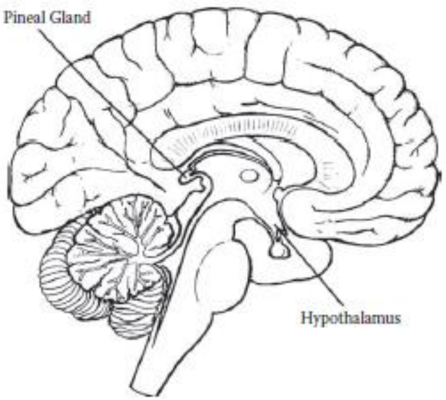
Julio Cortázar, 1952

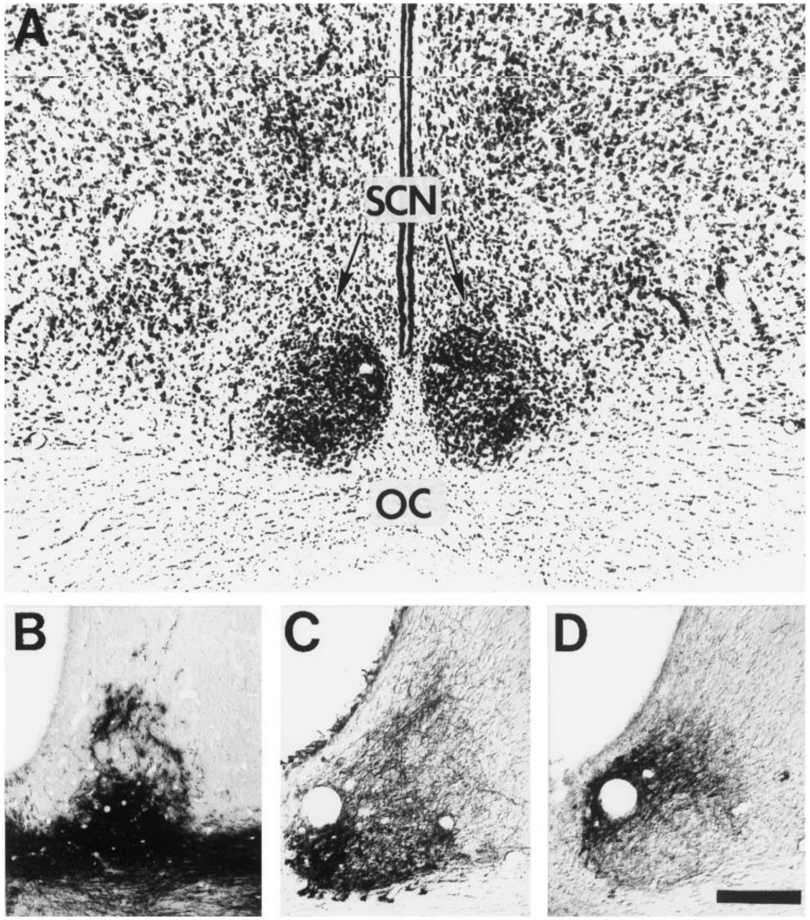


# RITMOS CIRCADIANOS – SISTEMA CIRCADIANO

## marcapaso

## Núcleo supraquiasmático hipotálamo anterior



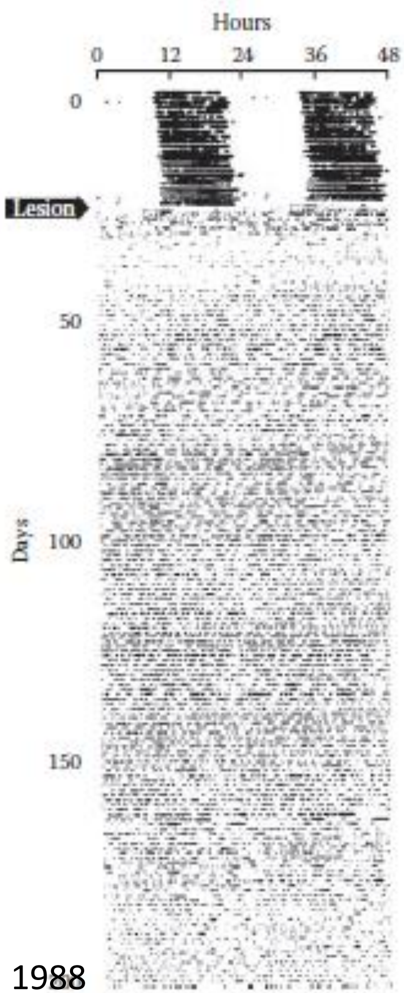

Tracto retínulo-hipotalámico

# RITMOS CIRCADIANOS – SISTEMA CIRCADIANO

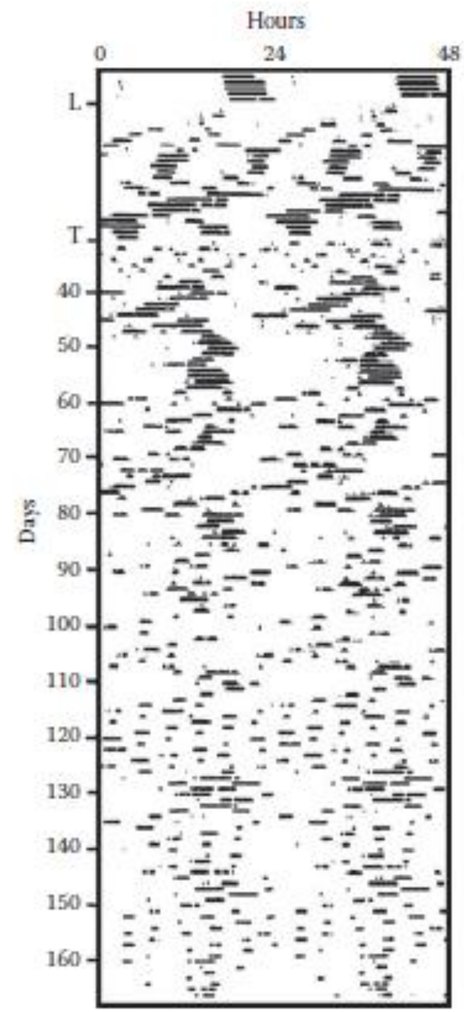
## marcapaso

## Núcleo supraquiasmático hipotálamo anterior

Ardilla




Sato & Kawamura, 1988



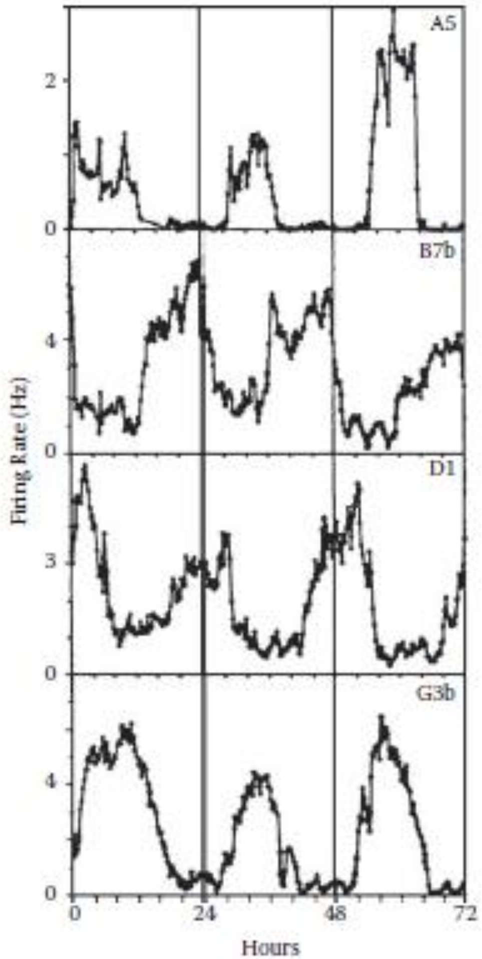

Hamster

Vogelbaum & Menaker, 1992

# RITMOS CIRCADIANOS – SISTEMA CIRCADIANO

## marcapaso

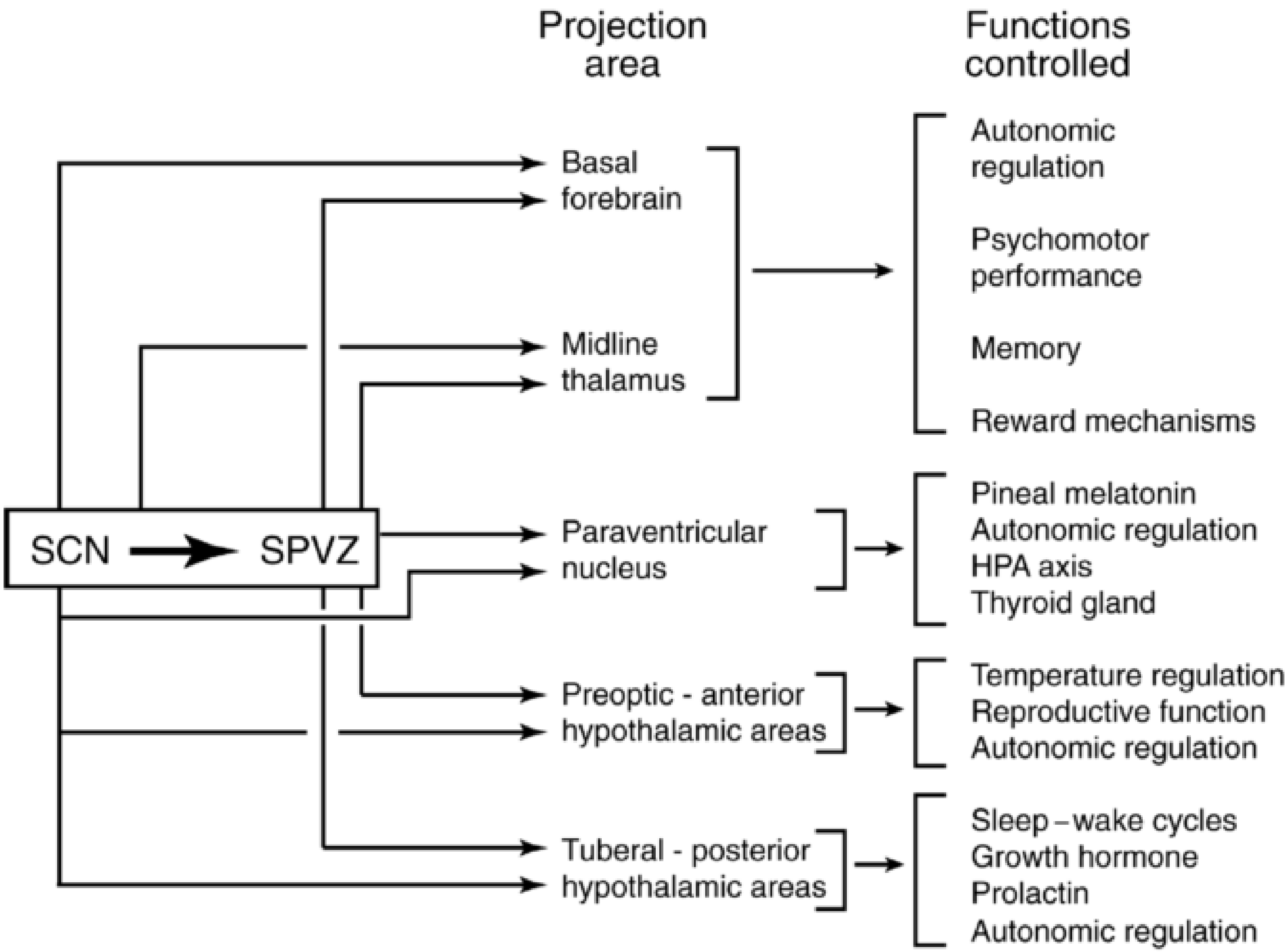
Núcleo supraquiasmático hipotálamo anterior



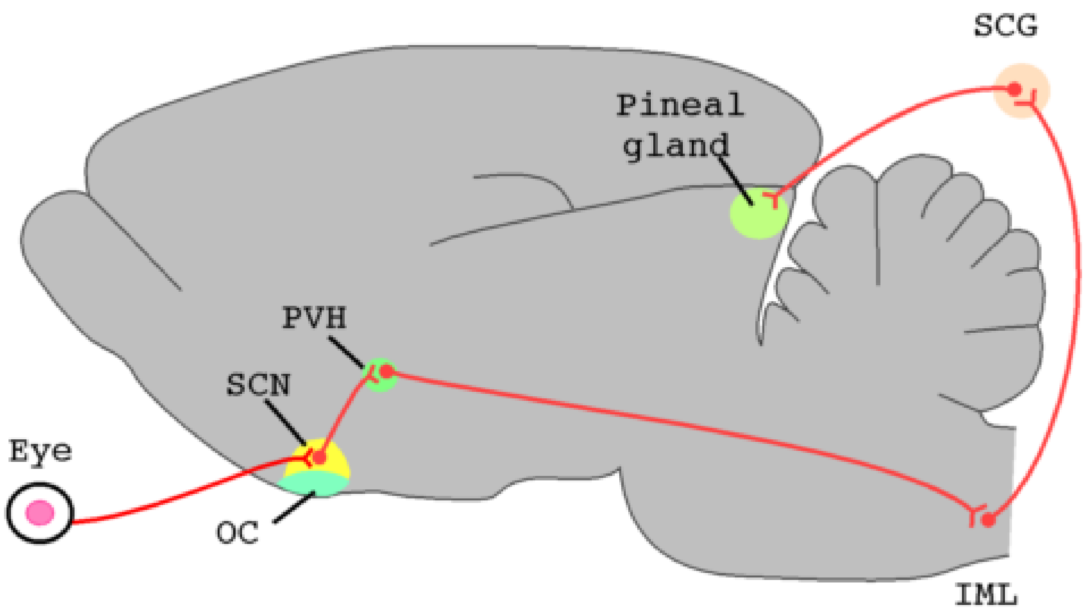

Reppert lab, 1995

# RITMOS CIRCADIANOS – SISTEMA CIRCADIANO

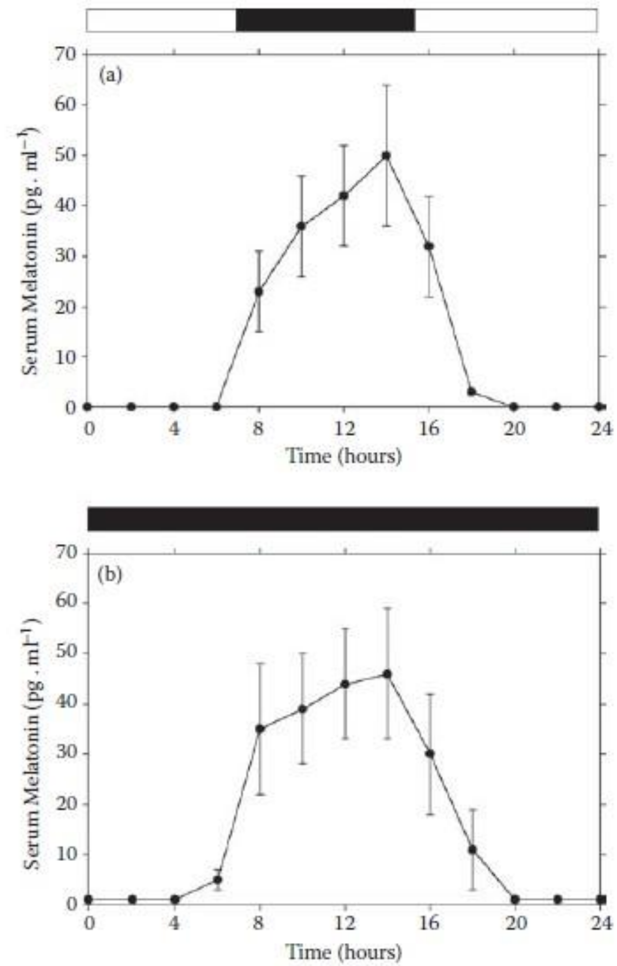
## efectores



# RITMOS CIRCADIANOS – Sincronizado por Luz

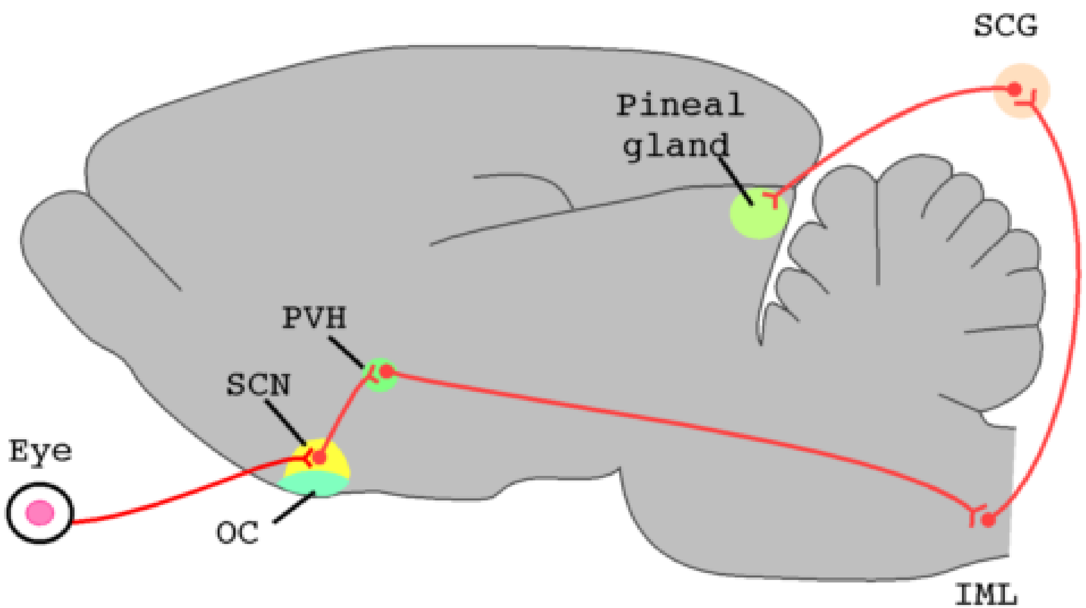



melatonina

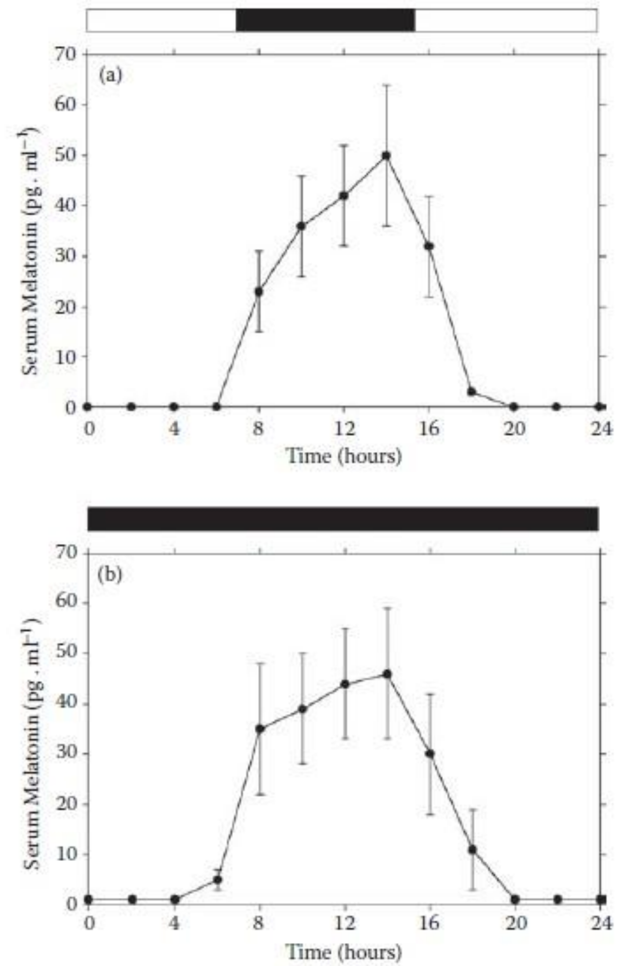


# RITMOS CIRCADIANOS – Sincronizado por Luz

Permanencia de ritmo en curso libre → melatonina circadiana




melatonina




Diferencias según duración noche → melatonina estacional

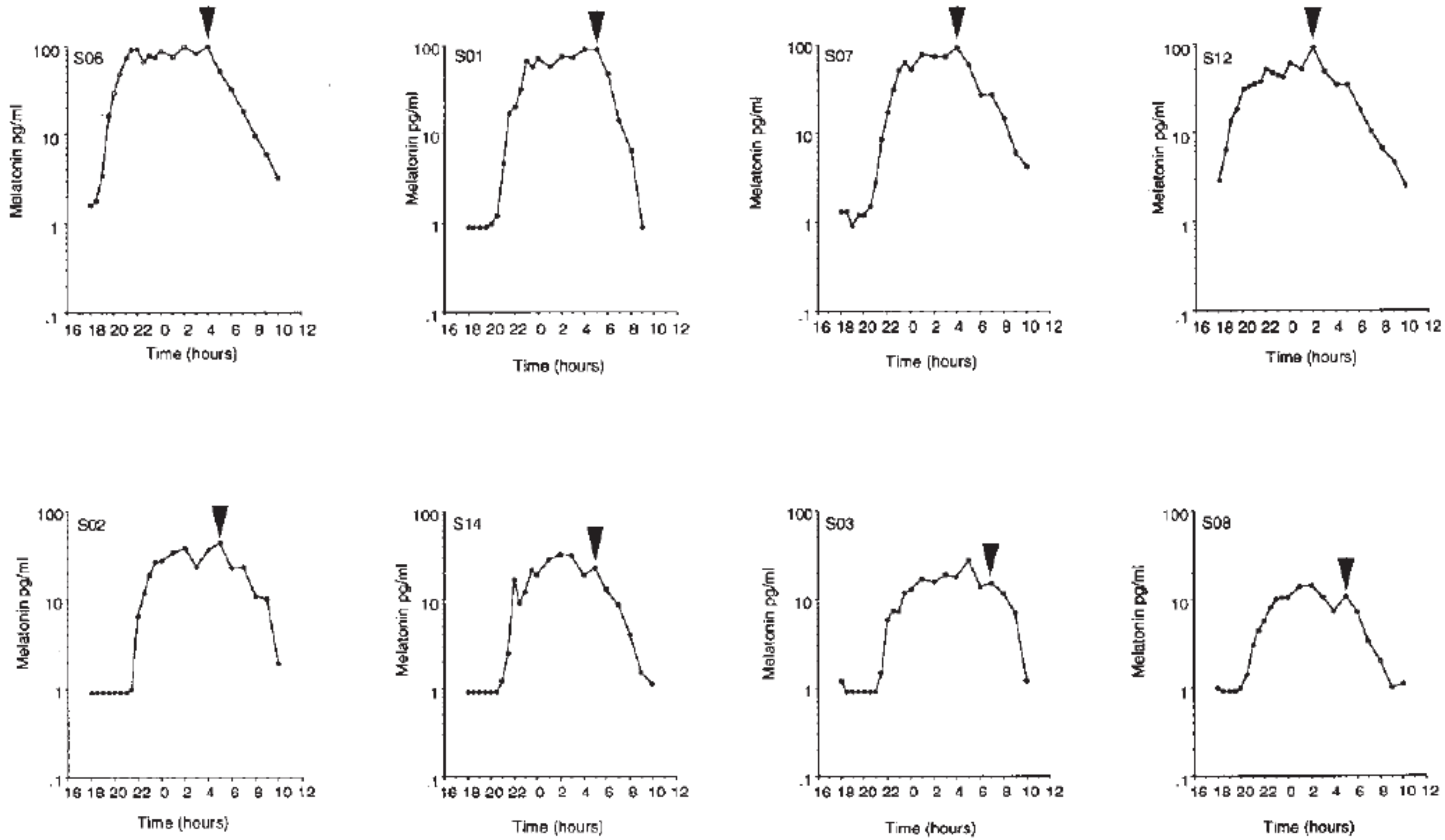
# DIM LIGHT MELATONIN ONSET

Procedures for Dim Light Melatonin Onset (DLMO) measurements in saliva

1. During the saliva collection period consumption of bananas, alcoholic beverages, or coffee are prohibited.
2. During the time of collection the subject must remain in dim light (10 lx) from 1 h prior to scheduled saliva collection. Curtains in the room must remain closed. Watching TV is permitted.
3. Fifteen minutes before every collection of saliva the subject must rinse his mouth with water.
4. Eating is permitted after saliva collection (except for the food described at “1”).
5. Subjects must not brush their teeth during the saliva collection period.
6. Nighttime saliva collection must only be done under dim light conditions.
7. Physical activities during the collection period are to be avoided as much as possible.

Lewy et al J Biol Rhythms 1999

# DIM LIGHT MELATONIN ONSET




Lewy et al J Biol Rhythms 1999

PERSPECTIVE

# Casting light on sleep deficiency

The use of electric lights at night is disrupting the sleep of more and more people, says **Charles Czeisler**.

There are many reasons why people get insufficient sleep in our 24/7 society, from early starts at work or school, or long commutes, to caffeine-rich food and drink. But the precipitating factor is an often unappreciated, technological breakthrough: the electric light. Without it, few people would use caffeine to stay awake at night. And light affects our circadian rhythms more powerfully than any drug.

Just as the ear has two functions (hearing and balance), so too does the eye. First, rods and cones enable sight; and second, intrinsically photosensitive retinal ganglion cells (ipRGCs) containing the photopigment melanopsin enable pupillary light responses, photic resetting of the circadian clock, and other sightless visual responses. Artificial light striking the retina between dusk and dawn exerts other physiological effects through sightless vision. It inhibits sleep-promoting neurons and activates arousal-promoting orexin neurons in the hypothalamus, and suppresses the nightly release of the soporific hormone melatonin. These factors reduce sleepiness, increase alertness and interfere with our sleep.

**TECHNOLOGY HAS DECOUPLED US FROM THE 24-HOUR DAY TO WHICH OUR BODIES EVOLVED.**

Paradoxically, the daily peak of waking energy driven by the brain's master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus occurs not at the start but near the end of our usual waking day, providing us with a 'second wind' that keeps us going as the day wears on. Before the widespread use of electric light, people probably experienced that second wind in the mid-afternoon, keeping them going until night fell. But light exposure after sunset signals 'daytime' to the SCN, shifting the clock later, postponing the second wind and delaying the onset of melatonin secretion. As a result, many people are still checking e-mail, doing homework or watching TV at midnight, with hardly a clue that it is the middle of the solar night. Technology has effectively decoupled us from the natural 24-hour day to which our bodies evolved, driving us to go to bed later. And we use caffeine in the morning to rise as early as we ever did, putting the squeeze on sleep.

The more we light up our lives, the less we seem to sleep. As the cost of generating light has plummeted by two orders of magnitude over the past century, its consumption has increased accordingly. Between 1950 and 2000, for example, as the cost of light production fell sixfold, UK per capita light consumption rose fourfold. This increasing light consumption has paralleled the rise in sleep deficiency.

Today, 30% of all employed US adults and 44% of night workers report averaging less than 6 hours sleep per night[1], whereas 50 years ago less than 3% of the US adult population slept so little. Worldwide, children are sleeping about 1.2 hours less on school nights than a century ago[2]. Most of us also sleep at different times during the week than at weekends and holidays, inducing 'social jetlag', which further disrupts circadian rhythms (see 'Stepping out of time', page S10).

The US Institute of Medicine estimates that between 50 million and 70 million people in the United States suffer adverse health and safety consequences from sleep disorders and sleep deficiency[3], including greater risk of obesity, diabetes, heart disease, depression and stroke. The obesity boom has triggered a parallel epidemic of obstructive sleep apnoea, which disrupts sleep (see 'Heavy sleepers', page S8). Children become hyperactive rather than sleepy when they don't get enough sleep, and have difficulty focusing attention, so sleep deficiency may be mistaken for attention-deficit hyperactivity disorder (ADHD), an increasingly common condition now diagnosed in 19% of US boys of high-school age. Some 40% of people in the United States report that their sleep is often insufficient, with 25% reporting difficulty concentrating owing to fatigue. The WHO has even added night-shift work to its list of known and probable carcinogens. And the death toll from driving while tired is second only to that caused by drink driving.

The number of people with sleep deficiency seems destined to rise. With 19% of electricity consumption worldwide devoted to producing light, many governments are phasing out traditional incandescent light bulbs[4]. Energy efficient solid-state light-emitting diodes (LEDs) are now widely used in televisions and computer screens, laptops, tablets and hand-held devices, and will drive a further increase in per capita light consumption.

Solid-state white light is typically rich in blue light, and the colour composition matters. The ipRGCs are most sensitive to short-wavelength (blue and blue–green) light, so night-time exposure to LEDs is typically more disruptive to circadian rhythms, melatonin secretion and sleep than incandescent lighting.

But solid-state lighting could also provide some solutions. A solid-state white-light fixture can comprise multicoloured LEDs, so it is relatively easy to control not only the light intensity, but also the colour composition. The adverse effects of night-time light on sleep and circadian rhythms can be reduced by replacing blue-enriched light with red- or orange-enriched white light after sunset. Unfortunately, existing uses of this new-found colour control have tended to be wrong-headed: some airlines, for example, suffuse aircraft cabins with monochromatic blue light at night, the optimal colour for suppressing melatonin and disrupting sleep.

Sleep is essential to our physical and mental wellbeing, so it is vital that we learn more about the impact of light consumption and other ways our 24/7 society affects sleep, circadian rhythms and health. We must then use this knowledge to develop behavioural and technical interventions to mitigate these ill effects. It is time to reassess the early assurances of Thomas Edison that using electric light "is in no way harmful to health, nor does it affect the soundness of sleep". ■

**Charles A. Czeisler** *is from the Division of Sleep Medicine, Harvard Medical School, and Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, in Boston, Massachusetts.*
*charles_czeisler@hms.harvard.edu*

1. Luckhaupt, S. E. *Morb. Mort. Wkly Rep.* **61**, 281–285 (2012).
2. Matricciani, L., Olds, T. & Petkov, J. *Sleep Med. Rev.* **16**, 203–211( 2012).
3. Colten, H. R & Altevogt, B. M. (eds) *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem* (National Academies Press, 2006).
4. National Research Council *Assessment of Advanced Solid State Lighting* (National Academies Press, Washington, DC, 2013).

The author declares a conflict of interest: go.nature.com/ygtirj

# VOLUNTARIOS UNIVERSIDAD COLORADO, AMAZONAS, USA

## Luz Natural versus Luz Artificial

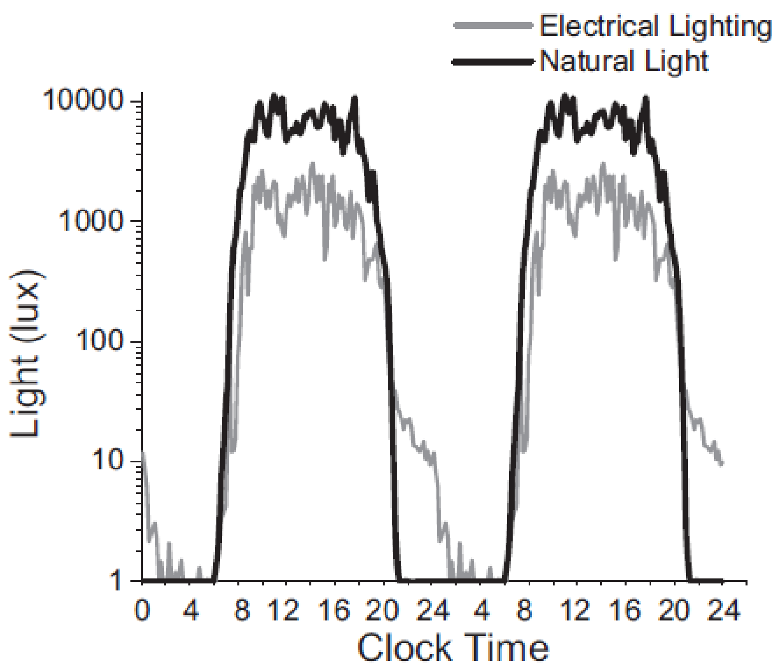
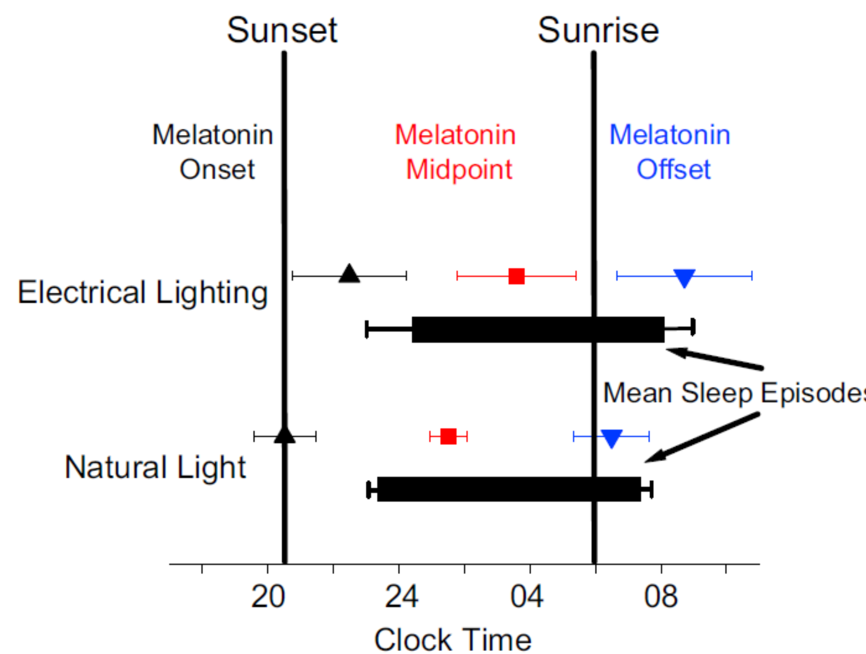



Figure 2. Light Exposure

Average light exposure (lux) plotted on a log scale during the week of exposure to electrical lighting in the constructed environment and exposure to the natural light-dark cycle while camping. Data are double plotted so that light levels across midnight (24 hr local clock time) can be more easily observed. For reference, 1 lux is equivalent to the light exposure received by the eye when gazing at a candle 1 m away, moonlight is ~0.1 lux, typical indoor lighting is ~200 lux, sunrise or sunset is ~10,000 lux, and a bright blue midday sky is >100,000 lux. See also Figure S3 and Table S1.




Wright et al Curr Biol 2013

# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS


**Montevideo**
marzo 2016

Comienzo semestre

L:O 12:12

**BCAA**
enero 2016

EVIIA II

L:O 20:4

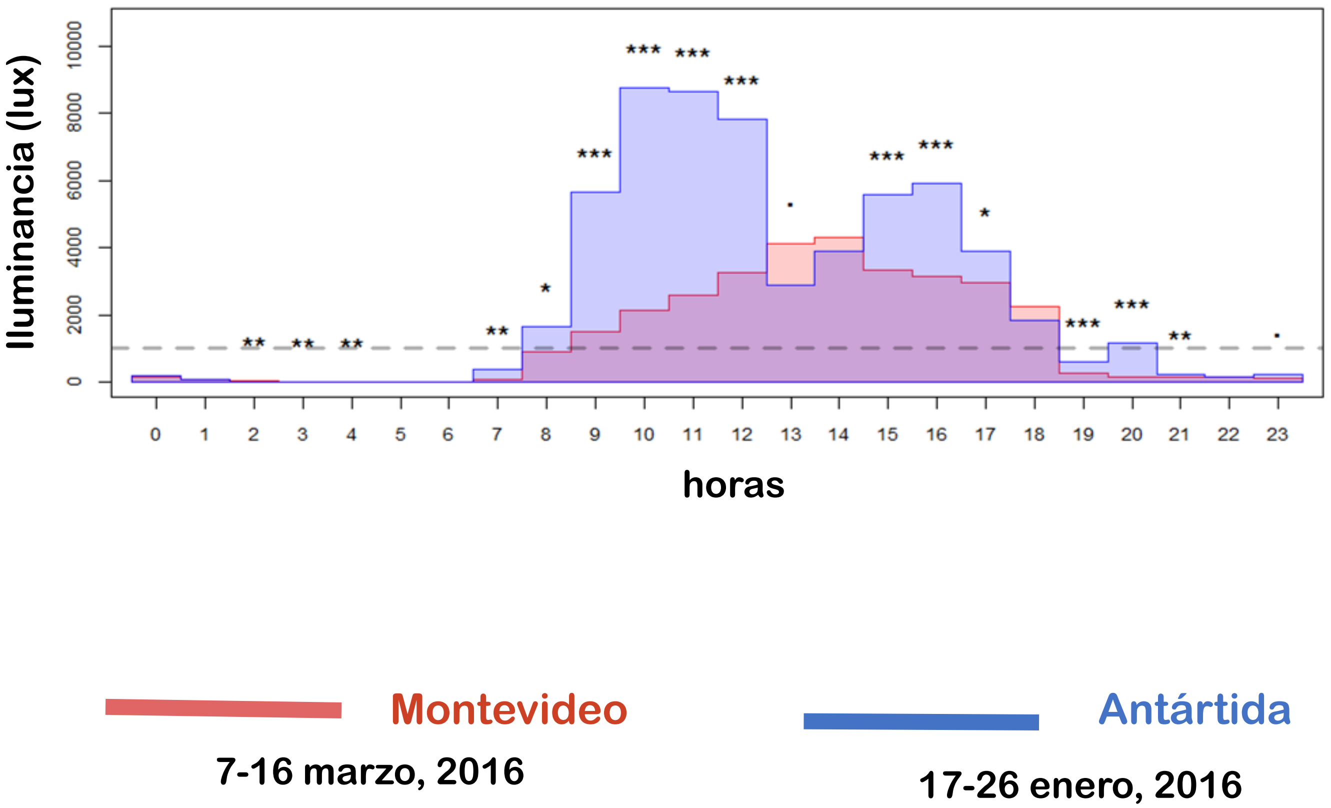
EVIIA
Facultad de Ciencias

# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS

## Aumento Incidencia Luz Natural

### Impacto Antártico: Exposición a la luz

**Data loggers (HOBO)– incidencia de luz**
**Actimetría (n=14) – exposición real a la luz**




Silva et al unpubl

# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS

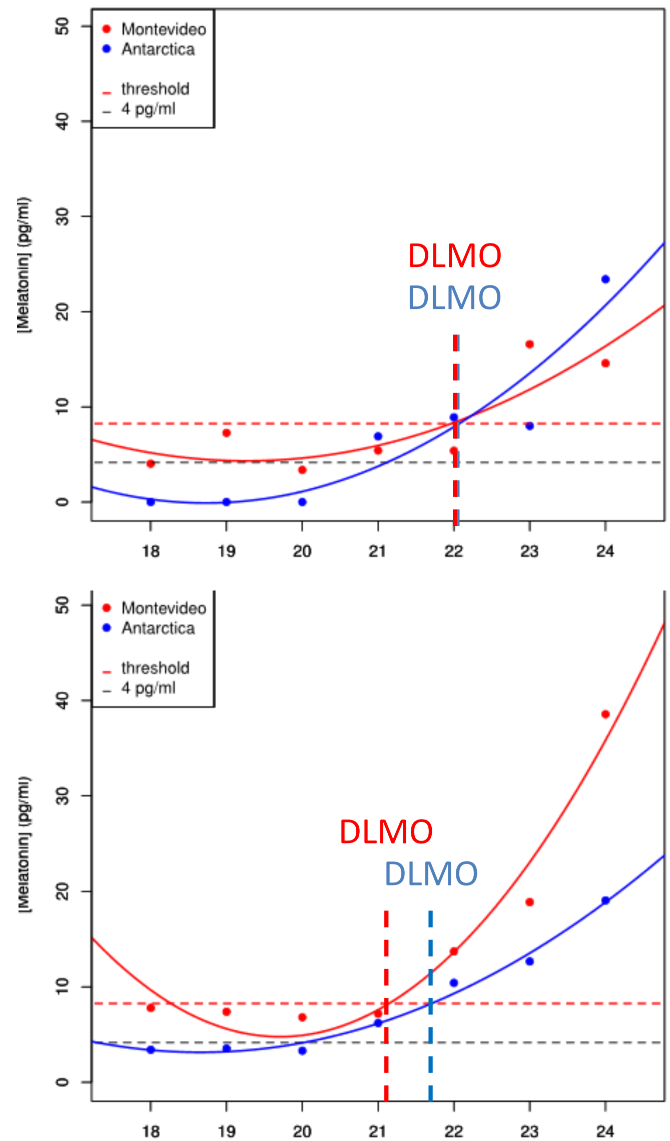
## Aumento Incidencia Luz Natural

Impacto Antártico: MELATONINA - DLMO

# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS

## Aumento Incidencia Luz Natural

### Impacto Antártico: MELATONINA - DLMO

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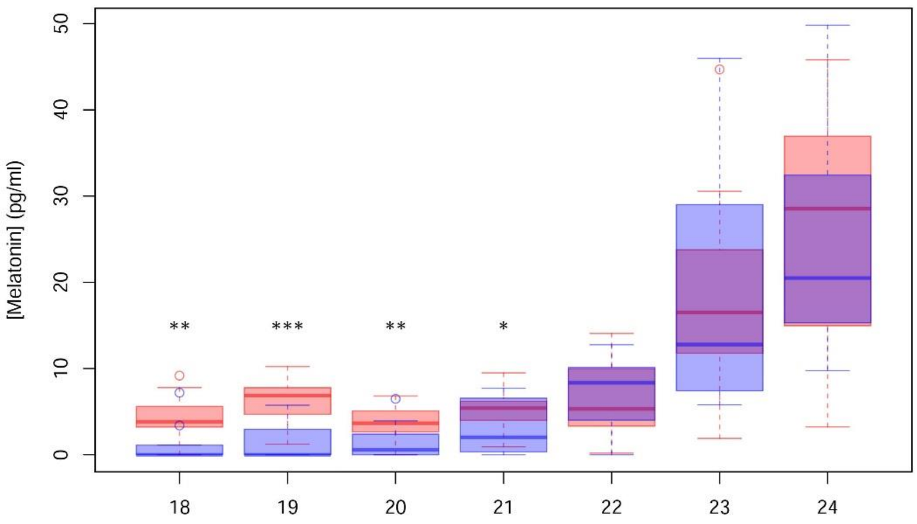
# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS

## Aumento Incidencia Luz Natural

### Impacto Antártico: MELATONINA - DLMO

## Melatonina




*Wilcoxon matched-pairs test, n=12, * p<0.05; ** p<0.01; *** p<0.001*

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# POBLACIÓN ESTUDIANTES UNIVERSITARIOS URUGUAYOS

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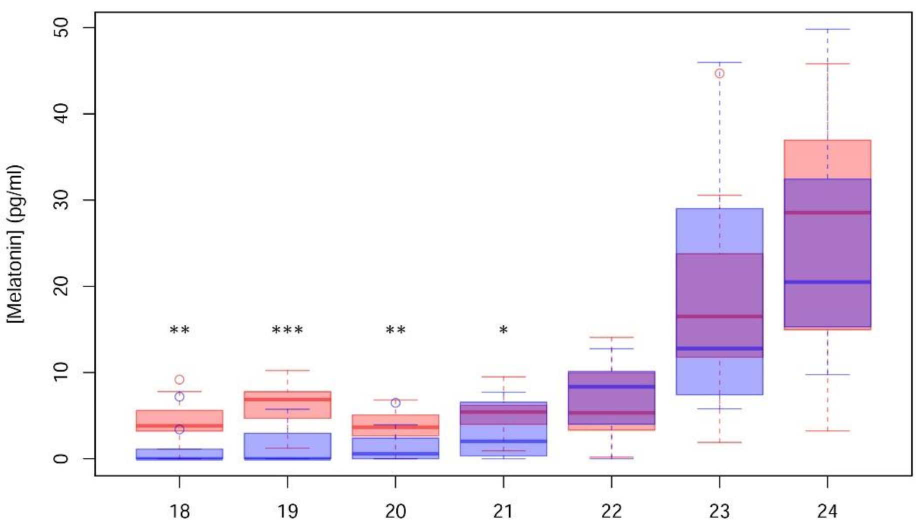
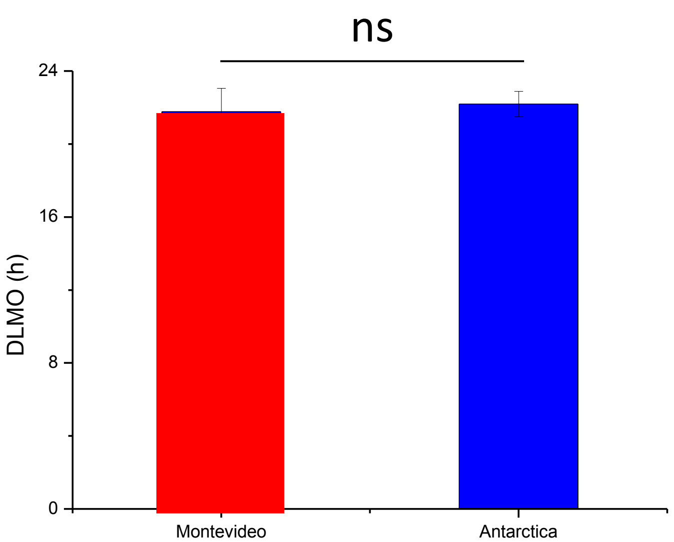
### Impacto Antártico: MELATONINA - DLMO

Melatonina




DLMO




*Wilcoxon matched-pairs test, n=12, * p<0.05; ** p<0.01; *** p<0.001*

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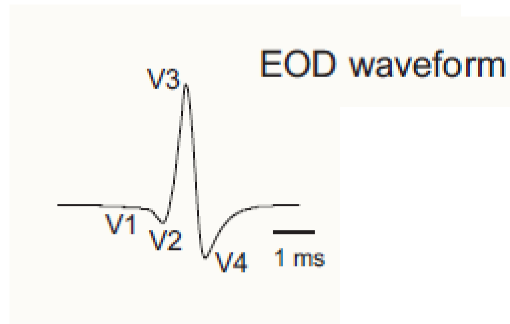
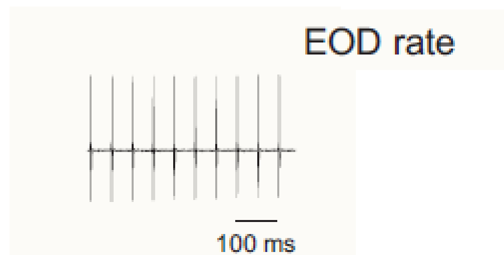
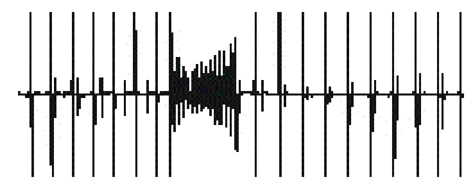
# ¿LA LUZ ES EL ÚNICO SINCRONIZADOR?

## *Gymnotus omarorum*

- Territorial
- Agresivo
- Reproductor estacional

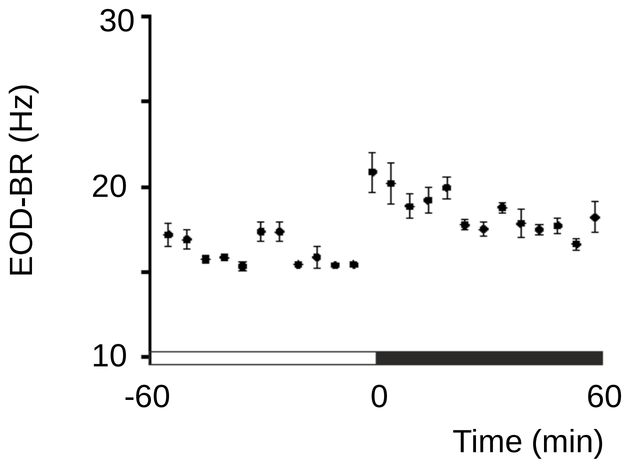


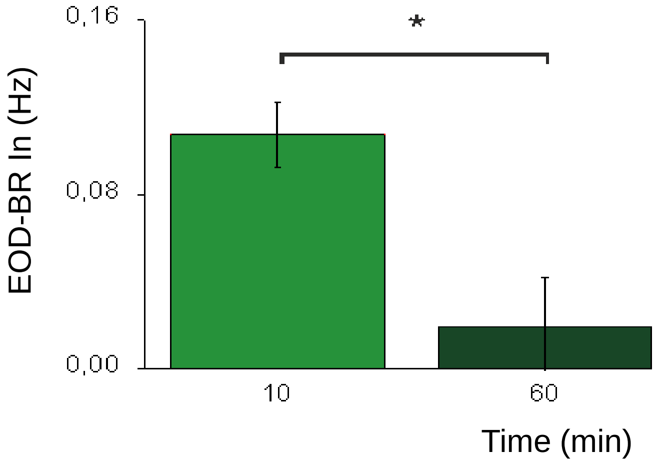



# ¿LA LUZ ES EL ÚNICO SINCRONIZADOR?

## *Gymnotus omarorum* aislado en laboratorio




Migliaro & Silva, 2016

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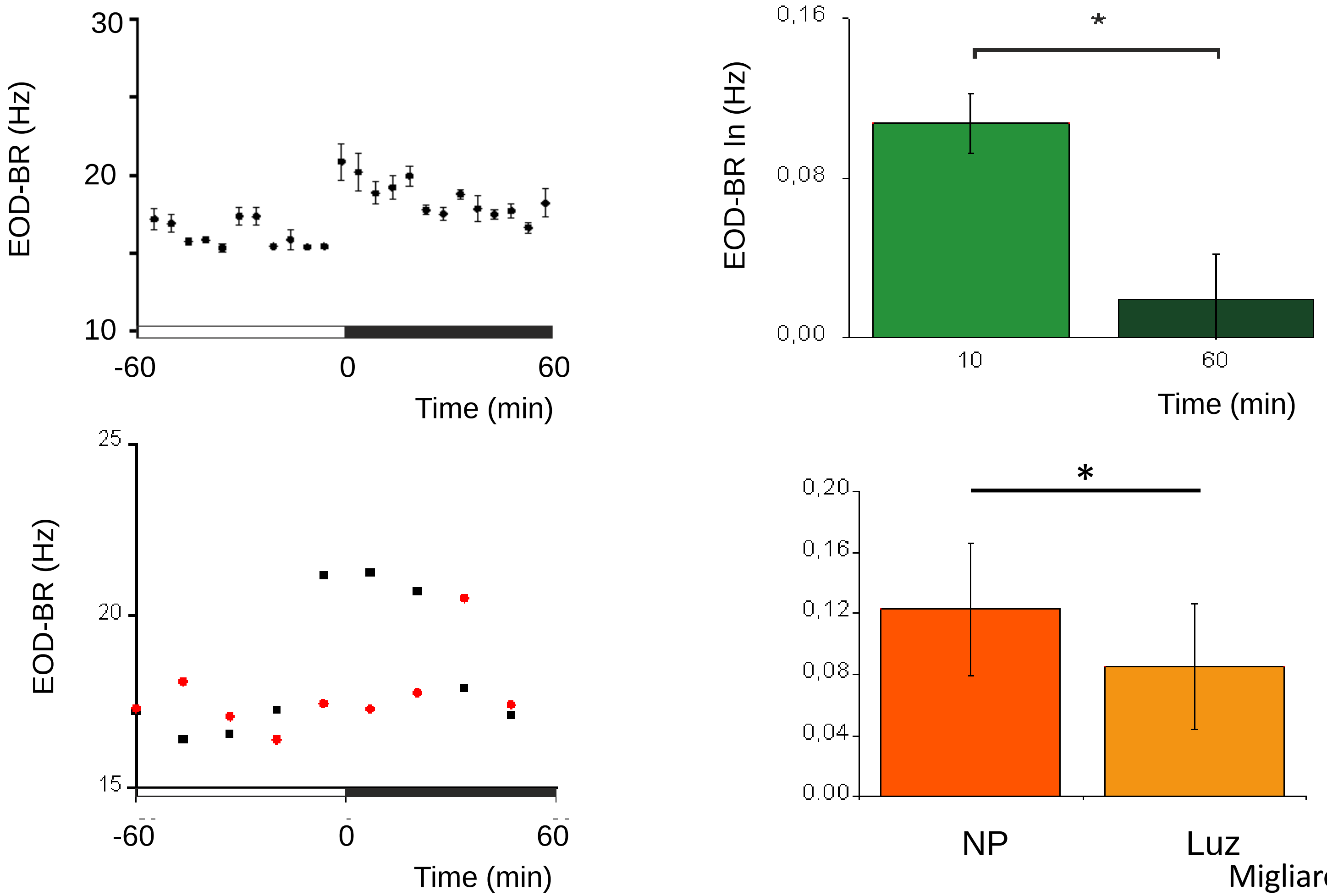
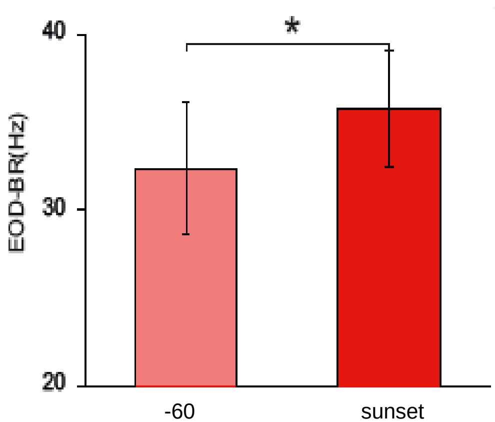
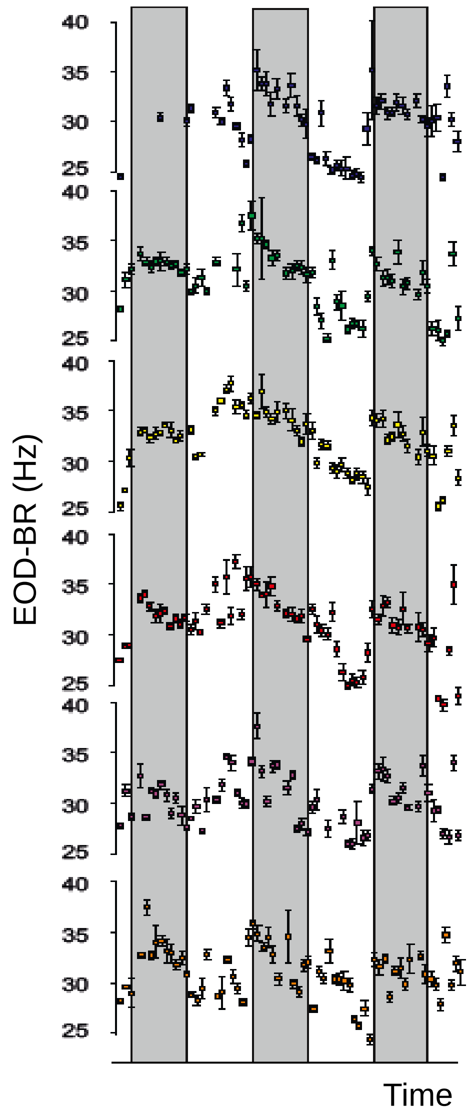


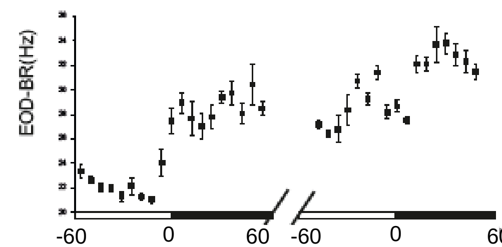

Migliaro & Silva, 2016

# ¿LA LUZ ES EL ÚNICO SINCRONIZADOR?

## *Gymnotus omarorum* en su entorno natural





Migliaro et al, unpubl

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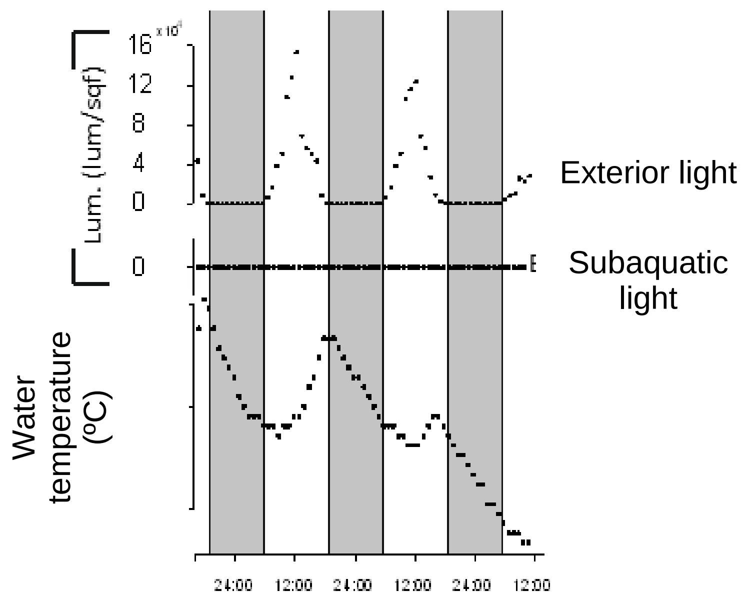


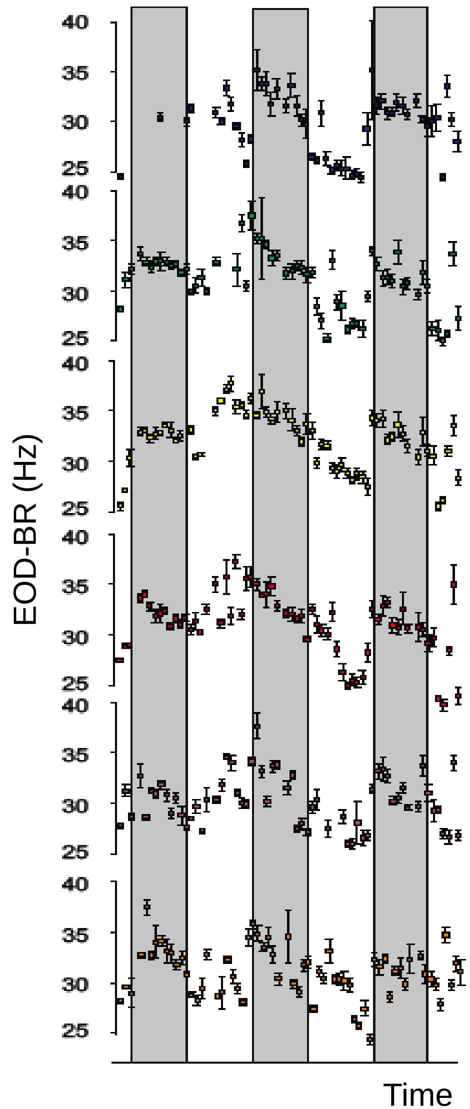


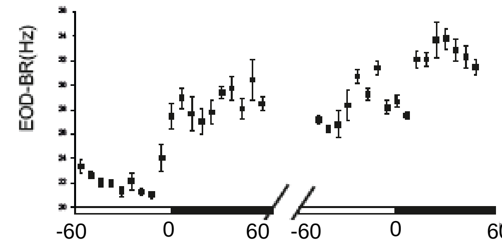



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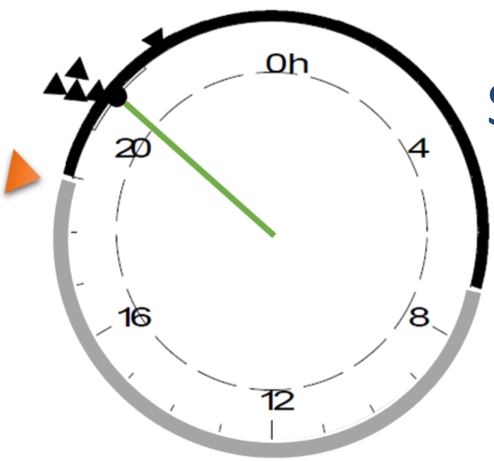
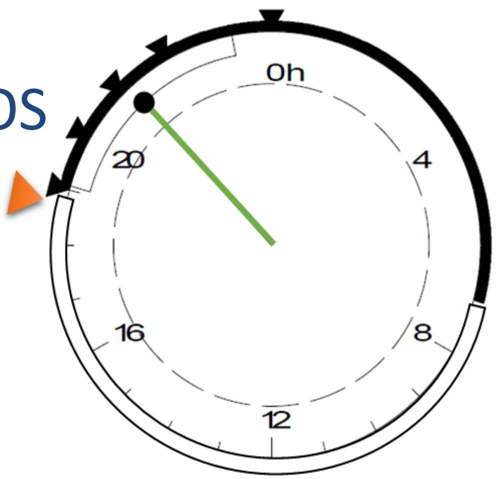



SINCRONIZADORES ALTERNATIVOS

Temperatura?
Contexto social?

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