Time in biology
Aion, unlimited time

Chronos, measurable time
Father time, time line: over generations
Evolution of two biological time systems:
  - circa-times, tuned to external cycles
  - physiological, internal time, lifespan

Kairos, supreme moment

Chrono-chaos: 24h society
An internal rhythm?

325 BC: Androsthenes Thasius, leaf movements (*Tamarindus indicus*)

1751 AD: Linnaeus, clock of flowers

24 hour cycles: Rhythms of day and night
Yes, rhythm independent of light and dark

1729 de Mairan leaf movements *Mimosa pudice*

Internal rhythm: 24 hour cycles
19th century: internal rhythm of about 24 hour
Time of the Day: Sun Compass

westward orientation :  

9 o’clock

12 o’clock

Starling (Sturnus vulgaris)
Pacemaker in the Supra Chiasmatic Nuclei wild type and mutant hamsters

\[ \tau = 24.5 \text{h} \]

\[ \tau = 22 \text{h} \]

Ralph & Menaker, 1988
SCN transplantation in \( \tau \)-mutant hamsters

Ralph & Menaker, 1988

wildtype vs homozygote supershort mutant

wildtype vs heterozygote short mutant

Ralph & Menaker, 1988
Clock transplantation in Silk Moth

Cecropia

- No surgery
- No brains
- Brains in ventral cavity

Pernyi

- No surgery
- Brains in ventral cavity

Exchange of brains

Truman 1971
Adult pacemaker output in vitro: neuropeptides of the SCN

Jansen et al. 1999
A molecular circadian clock: autoregulation feedback

Transcription-Translation feedback loop:

Per & Cry RNA

----> PER & CRY dimers

----> PER/CRY blocks own promoter region
But red blood cells, cyanobacteria: 3 proteins suffice

Cyano’s: three proteins KaiA, KaiB and KaiC *in vitro*; with ATP they show 24h phosphorilation cycles
Peak times (acrophases)

- Surgical death
- Inertia
- Birth
- Death
- Urine volume
- Testosterone
- Acidity urine
- Blood proteins
- Well being / Temperature
- Heart beat/ effectivity narcosis
- Body mass
- Blood pressure
- Toothache
- White blood cells
The body differs each moment of the day in physiological, cognitive and behavioural parameters.

This has major repercussions for:

Clinical practice, pharmacology, ecology, agriculture.
The circadian rhythm: freerun and entrained

**Free Run** of the Biological Clock

**Entrainment** of the Biological Clock
Entrainment: light as a major “Zeitgeber (RHT)"  

Specific “clock related” light receptors: ganglion cell, sensitive for blue light  

Light sensitive ganglion cell with melanopsin  

Rods and Cones  

Biological clock system (e.g. alertness & melatonin: very sensitive for blue light  

After Hattar et al., 2003
Entrainment via 1h light pulses

Time of day dependent shifts of the clock by light pulses

Early in the evening: *delay*

Early in the morning: *advance*

Ubiquitous Phase Response Curve
The circadian Sleep-Wake Cycle in Humans

Days in Constant Light

Sleeping

Awake

Period = 25.3 hr

Bunker studies 1960-1985, Max Planck Institute Andechs
Modern lab recording & field observations

Free run in constant conditions

Entrainment in Light-Dark cycles

acti watch
New time free human isolation facility
Sleep-wake regulation: 2 processes

S: homeostatic regulation need for sleep

C: circadiane regulation sleep awake thresholds

Borbely, 1981
Daan, Beersma, & Borbely, 1984
Chronotypes: phase of sleep

Recorded on free days, by 60000 persons in Western Europe

Chronotype (according to time of mid-sleep)
Morning vs Evening types: age dependency

Chromotype ($MSF_{sc}$, tijd rond middernacht)

- Morning
- Evening

Age (years)

Male
Female

Roenneberg et al., 2004
Specific functions of circa-rhythms:

- tuning to environment (anticipation)

> common mechanisms

<table>
<thead>
<tr>
<th>Period</th>
<th>Circa-rhythms</th>
<th>Rotation</th>
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<tbody>
<tr>
<td>24h</td>
<td>circadian</td>
<td>Earth</td>
</tr>
<tr>
<td>Year</td>
<td>circannual</td>
<td>Earth around Sun</td>
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<tr>
<td>Lunar cycle</td>
<td>circalunar</td>
<td>Moon around Earth</td>
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<tr>
<td>tides</td>
<td>circatidal</td>
<td>Moon &amp; Earth around Sun</td>
</tr>
</tbody>
</table>

General functions of internal rhythms:

- internal organization
- energy conservation

> diversity in mechanisms
- information transfer
- synchronization (internal & external)

Aschoff & Gerkema 1985
Time of Day: Once in a lifetime events

Emergence

MOSQUITO (*Clunio tsushimensis*)
Time of day: Sun Compass

Garden Warbler
(Sylvia borin)

August

October

Internal daily and seasonal program
Physiological time

Cycle length in hours

- Century
- Year
- Month
- Day
- Hour
- Minute
- Second
- mSec.

Body mass, gram

- Ultradian rhythms
- Infradian rhythms

M^0 Circadian rhythms
M^0 Circalunar rhythms
M^0 Circannual rhythms

Respiration
Heartbeat
Muscle tone

P = Physiological time

Graph showing the relationship between cycle length in hours and body mass.
External and physiological time

Cycle length in hours

- century
- year
- month
- day
- hour
- minute
- second
- mSec.

Body mass, gram

- Life Time
- M^0 Circannual rhythms
- M^0 Circalunar rhythms
- M^0 Circadian rhythms

- 1 billion breathings
- Respiration 0.28
- Heartbeat 0.27
- Muscle tone 0.21

Ultradian rhythms \(\leftrightarrow\) Infradian rhythms

- 1 billion
- Life Time

- External and physiological time

External and physiological time

**Circadian rhythms**
- Body mass, gram
- Cycle length in hours

**Ultradian rhythms**
- 10⁻¹
- 10⁻²
- 10⁻³
- 10⁻⁴
- 10⁻⁵
- 10⁻⁶
- 10⁻⁷

**Infradian rhythms**
- 1 billion breathings
- 4 billion heart beats

**Circalunar rhythms**
- Life Time

**Circannual rhythms**
- 1/4

**External and physiological time**
- 10²
- 10³
- 10⁴
- 10⁵
- 10⁶
- 10⁷

Body mass, gram

- Muscle tone 0.21
- Heartbeat 0.27
- Respiration 0.28

- 10¹
- 10²
- 10³
- 10⁴
- 10⁵
- 10⁶
- 10⁷
Circadian, Ultradian & Infradian Rhythms

- Cat: ≈100ms firing of cold receptor
- Vole: ≈2hr burst of locomotor activity
- Female rat: 5 days nestbuilding activity
- Snail: ≈5s pacemaker activity
- Mouse: ≈24hr oxygen uptake
- Human: 1yr suicides
- Lynx: 10yr fur returns

Aschoff & Gerkema 1985
LH release rhythms in ovariectomized rats

ovx rat # 1

ovx rat # 2

blood LH (ng/ml)

time (min)
Narcolepsy: Sleep and Wake Stages in 13 patients

out of bed during daytime

34 hours in bed

lights off

REM awake
SW1-4

REM - NREM cycles: Basic Rest Activity Cycle (BRAC)

Schulz 1985
Daily Activity Patterns in the Common Vole:
running wheel blocked from day 5-9

SCN independent ultradian clock
Functional in coprophagia
Functional in social synchrony
warning against predators
saving energy by huddling

Gerkema 1991
More than 900 mice genes with ultradian expression *in vitro*

A subset exhibited this *in vitro* and *in vivo*

Many related to transcriptional factors & cell cycle

Van der Veen & Gerkema 2017
Garden warbler (*Sylvia borin*)

Biebach & Gordijn, 1985
Time-place learning in mice

Running wheel: no risk

A new approach: a positive reinforcer (food reward) combined with a negative reinforcer (mild electrical stimulus)

9.00h

12.00h

15.00h
Later findings:
No role of Per genes; SCN not involved, hippocampus?
In aging loss of circadian TPA

Van der Zee et al., 2008
Mulder et al 2013-2016
Activity in constant light & darkness

Reindeer on Svalbard: no free run

Van Oort et al., Nature, 2005
Van Oort et al., Naturwissenschaften, 2007
Wake up light, light at night
Social jetlag
Shiftwork, obesitas, sleep timing
Impact of artificial light in the morning, in the evening

Wake up lamp:
increased alertness
 clock advance

Blue light in the late evening:
Sleep impairment
 melatonin suppression

Gordijn et al 2007
Geerdink et al 2016

Sleep
Obesitas
Cognitive disfunction
Light at night:

- Disturbing seasonal, photoperiodic responses
- Impact on reproduction, immunology?
- Changes in prey-predator relations
- Unknown long term effects at the level of populations and biodiversity
Social jetlag: chronotype distributions

Mid-sleep on workdays (red)
Mid-sleep on free days- (green)

Roenneberg et al 2007
Roenneberg & Merrow 2016
Social jetlag & chronotype

Also:
> obesitas, >depression

Social Jetlag (ΔMS, h)

Chronotype (MSF_{SC}, local time)

smokers (%)
Shiftwork:

3 uur in the morning: Lyon & Leipzig
Shiftwork:

Sleep disturbance
Decreased alertness and cognitive performance
Increased prevalence of obesity, diabetes 2
Potential impact: coronary heart diseases
Long term exposure: impact on cancer not excluded
No work at night

Fast forward rotating shifts: less problems with alertness and sleep quality

Power naps potentially a good tool

and mind the chronotypes
Circadian and ultradian activity timing

Zeitgeber

Peripheral clocks

light receptor

SCN

RHT

Chronos & Kairos tell us: do not play around with time too much

m.p.gerkema@rug.nl
Vermoeidheid is ook een klokfenomeen

72 uur slaaponthouding. De vermoeidheid werd elke drie uur gescoord ten opzichte van de normale vermoeidheid (n=15)

Åkerstedt en Fröberg, 1977
<table>
<thead>
<tr>
<th>CHRONOS:</th>
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<tbody>
<tr>
<td>Internal contextual time</td>
<td>Internal physiological time:</td>
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<td>Circa rhythms and clocks</td>
<td>Ultradian rhythms and clocks</td>
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<td><strong>KAIROS:</strong> the moment</td>
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| **TPA in birds and mice** | |
| | |

| **Wake up light, light at night** | |
| **Social jetlag** | |
| **Shiftwork, obesitas, sleep timing** | |
Seasons: because the earth is tilted...

- 23.5 degree in relation to the sun
- the axis of the earth points to different directions through the year.

- March 21: One rotation on axis 23 hours 56 minutes
- June 21: One revolution around sun 365 ¼ days
- September 23: One revolution around sun 365 ¼ days
- December 21: One rotation on axis 23 hours 56 minutes
Per mutants: eclosion rhythm Drosophila

Konopka and Benzer, 1971
allocation of activity in mammals: day and night

and continuous activity: ultradian

arhythmic
Active the full 24 h day:

**Ultradian rhythms**

![Graph showing ultradian rhythms over days and time of day](image-url)
Active the full 24 h day:

Non rhythmic activity pattern
and during the full 24 h-day:

inactive, during hibernation
Impact of SCN lesion on rhythmicity in the vole

intact: circadian & ultradian rhythmicity

SCN-x: ultradian rhythmicity

Gerkema et al. 1991
Vole feeding activity with and without access to food

Gerkema & van der Leest, 1991
Effects of lengthening of $\alpha$ on subsequent $\rho$:

**homeostatic models versus clock model**

Gerkeema & van der Leest, 1991
Activity bout $\alpha'$ and subsequent $\rho'$

Gerkema & van der Leest, 1991
Activity bout $\alpha'$ and subsequent $\rho'$

Gerkema & van der Leest, 1991
Experimental setup warning against predators

Gerkema & Verhulst, 1991
Ultradian synchronization in the vole

Gerkema, 1991
Oxygen consumption of four voles separated and not separated by wire mesh.

\( \text{O}_2 \) consumption ml.g\(^{-1}\).h\(^{-1}\)

ambient temperature \( ^0\text{C} \)

Gerkema, 1992