Mechanisms and Delineating Circadian Phenomena

...a rose is not necessarily and unqualifiedly a rose… it is a very different biochemical system at noon and at midnight.
— Colin Pittendrigh, 1965.

Deductive-Nomological vs. Mechanistic Explanations

Under the influence of paradigmatic examples in physics, in the 1950s Carl Hempel advanced an account of explanation in terms of laws known as the Deductive-Nomological (DN) model

Laws (e.g., Boyle-Charles gas law)
Initial conditions
∴Description of phenomenon to be explained (e.g., increase in temperature of gas)

Laws: true universal generalizations with counter-factual import
Specify what would happen if initial conditions were satisfied

Problem: there aren't many examples of such laws in biology, but lots of explanations
These offer accounts of mechanisms claimed to produce the phenomenon

Conceptions of Mechanism

Machamer, Darden, and Craver [MDC] (2000)
"Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions"

Bechtel and Abrahamsen (2005, cf. Bechtel and Richardson, 1993):
"A mechanism is a structure performing a function in virtue of its component parts, component operations, and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena"

Besides the incidental differences in vocabulary, the major difference involves the last phrase of MDC—imposing an order from start to termination conditions

Clicker Question

Machamer, Darden, and Craver emphasize that their account of mechanism is dualistic. What are the two components

- Minds and brains
- Organic and inorganic
- Entities and activities
- Organized and unorganized

Features of Mechanistic Explanations

Dualism of Entities and Activities

- Activities (operations) are the producers of changes
  - Types of causings
- Entities (parts) are the things that engage in activities

Organization: “Entities often must be appropriately located, structured, and oriented, and the activities in which they engage must have a temporal order, rate, and duration”

- Productive continuity: operations must link entities into a continuous network

Contrasts with Nomological Account

Both nomological and mechanistic explanations can be concerned with causal phenomena—something happens which brings about something else

- Nomological explanations focus on the regularity in the change itself
- Critical feature of mechanistic accounts is that they focus on the system in which change is occurring and ask what is going on inside to produce its behavior

Nomological explanations emphasize linguistic representations and logic

- Logic is the glue that relates laws to actual cases

Mechanistic explanations focus on the entities and activities

- What are the operations performed that together bring about the effect?

Mentally Imagining Mechanisms

An example in Machamer, Darden, and Craver:

> In the mechanism of chemical neurotransmission, a presynaptic neuron transmits a signal to a post-synaptic neuron by releasing neurotransmitter molecules that diffuse across the synaptic cleft, bind to receptors, and so depolarize the post-synaptic cell

The account has the form of a narrative—relating a sequence of happenings

Each of these occurs at a place and in a relative time order

This narration invites one to visually imagine the events and to see them happening in a connected fashion

> As one might imagine the activities in a human-made device or actors on a stage

Visualizing Mechanisms

Often mechanisms are explicitly presented visually in diagrams

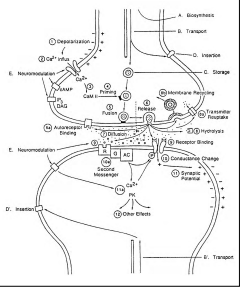
Iconic shapes or text labels are used to designate parts

Arrows are used to indicate activities such as transport of substances or reactions

> Sometimes arrows are labeled with text

In this case the sequence of steps is noted with numbers

> But a viewer does not have to follow the sequence



Hierarchy of Mechanisms

The entities (parts) of a mechanism may themselves be mechanisms

> One explains how they perform the activity (operation) in virtue of the parts and operations within them
>
> Important to note that there is now a new explanatory goal—explain the operation within the previous mechanism

Explanatory hierarchies bottom out in activities left unexplained

> In molecular biology: geomechanical activities (e.g., opening), electro-chemical (attracting), energetic (diffusion), electro-magnetic (conduction of charge)
>
> If one wants an explanation of these, typically one turns to a different science

Delineating the Phenomenon

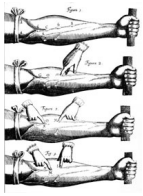
An important first step in mechanistic explanation is specifying exactly what the phenomenon is
- What happens and under what conditions does it happen
  - People have vivid memories of how they learned of major events such as the 9/11 attacks
  - Bees signal the location of food through a “dance”
  - DNA is transcribed into mRNA, which is translated into a protein

Phenomena are not just reports of data one has collected but regularities represented as having occurred in the world

Often it is important to characterize phenomena quantitatively
- It is the detailed behavior that the mechanism must explain

Phenomena and Experiments

Although some phenomena are easily identified by anyone, many require experiments to discover and characterize them
- Recall Harvey—he had to demonstrate that blood circulates
  - Only then did it make sense to explain what made it circulate—how the muscles and valves of the heart, organized in the right way, served to circulate the blood
- To demonstrate that it circulates, experimentation was required



Goal: to determine what happens and what are the factors that affect its happening

The Phenomenon (a?) of Circadian Rhythms

Endogenously generated rhythms of approximately 24 hours (circa [about] + dies [day])
- In fact, the variability is seen as crucial—if the rhythms were under exogenous (environmental) control, their period should be exactly one day

Entrainable by cues to the time in the environment (Zeitgebers)
- Daylight, temperature, feeding, etc.

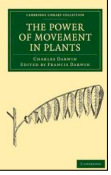
Temperature compensated—rhythms have nearly the same period at different temperatures
- Typically biochemical reactions are temperature sensitive—faster at higher temperatures

Clicker Question

Which of the following exhibit circadian rhymicity?

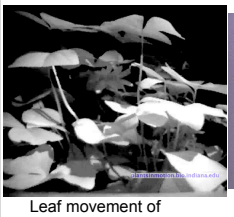
- The orientation of leafs of plants
- The body temperature of humans
- Spore formation in fungi
- Human perception of pain
- All of the above

De Mairan's Mimosa Experiment



- In 1729 de Mairan, a French astronomer, not only noted the regular opening and closing of the leaves of a mimosa plant
  - To determine whether this was just a response to sunlight, confined the plant to darkness
  - Its leaves still opened and closed on a daily cycle
- Investigation taken up 150 years later by Darwin who developed instrument for measuring leaf movements, and quantified and graphed the results

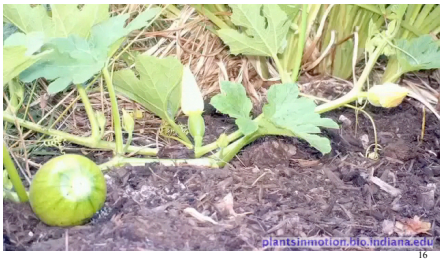
Sleep Activity of Plants



Leaf movement of Oxalis plant under 12L:12D

Bean living in constant dim light—behavior result of endogenous clock

Growth Activity of Pumpkins



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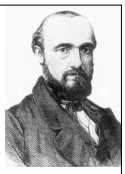
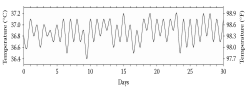
First Clues to Circadian Rhythms in Humans



In 1868 Carl Reinhold August Wunderlich conducted a study of body temperature involving more than 25,000 individuals

- Recorded temperature several times during the day
- Between 2 AM and 8 AM, mean temperature was 36.2°C / 97.2° F
- Between 4 PM and 9 PM, mean temperature was 37.5° C / 99.5° F
- Mean of over 1 million reports: 37°C / 98.6°F



Representing Oscillations

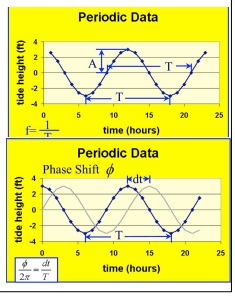
A common way of representing circadian or other oscillations is by placing time on the x-axis and the variable measured on the y-axis

The distance between two troughs is the period (τ) of oscillation

- Freq=1/period

The difference between the mean value and the maximum is the amplitude

Two oscillations with the same wave-form but shifted in time are phase-shifted



Clicker Question

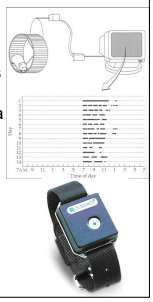
What happens to circadian rhythmicity exhibited in the activity patterns of organisms when no light or other time cues are available

- Rhythms shorten into the ultradian range
- Rhythms are maintained at approximately 24 hours
- Rhythms lengthen into the infradian range
- Rhythmicity is lost since it depends on light cues

Recording Circadian Behavior: Actograms

Researchers have developed techniques to make manifest the pattern of circadian behavior in animals

- Record each time a behavior occurs and show it as a hash mark across a 24 (or 48 hour) line
- Or number of behaviors within a time bin by height of line



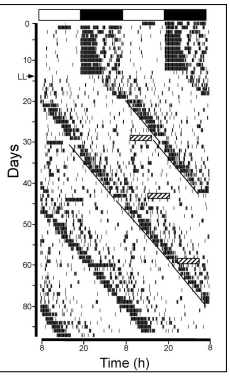
Typical Plotting

Indicate light pattern by black and white (sometimes grey) bars

Uses indicators such as arrows to indicate change (here from LD to LL

Show each day twice, first on the right of one line and again on the left of the next

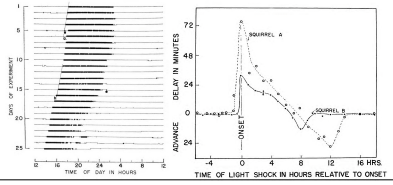
- This allows for deciphering patterns of change in both active and inactive phases



Entrainment and Phase Response Curves

The change in circadian rhythms in response to Zeitgebers depends upon the time at which they are administered

Phase response curve shows how much advance or delay results from a light pulse

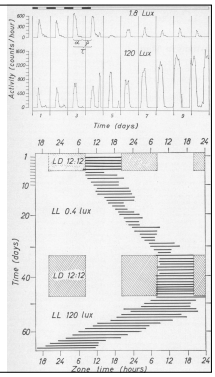


Oscillations are Endogenous

Free running: behavior in the absence of time cues (Zeitgebers)

- Birds in constant dim or bright light
- Period (τ) varies from 24 hours

"These two facts, the undamped continuation of the rhythm and the deviation of the period from 24 hours, allow only one plausible explanation: that this rhythm is not imposed on the organism by the environment but is truly endogenous" Aschoff



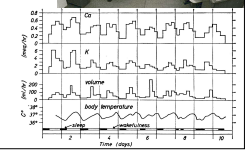
Aschoff's Cave Experiment

Volunteers spent several days/weeks in an underground bunker from WWII where they had no indication of external time

They chose when to have lights on, when to eat, etc.

Their bodily functions were regularly monitored

Their pattern of activity varied somewhat from 24 hours

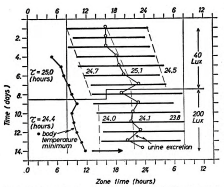


Effect of Brightness of Light

Since light is a Zeitgeber, individuals might be resetting their own clocks as a result of their activities

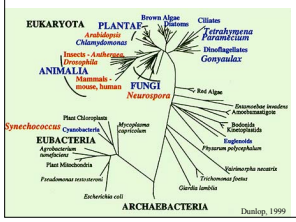
Since subjects would not agree to no light, the best alternative was to leave light under their control but vary its brightness

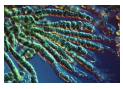
With brighter light, their rhythms were closer to 24 hours



The Phenomenon is Found in Many Species

The major limit in studying circadian rhythms in different species is finding one or more behaviors whose periodic changes can be monitored

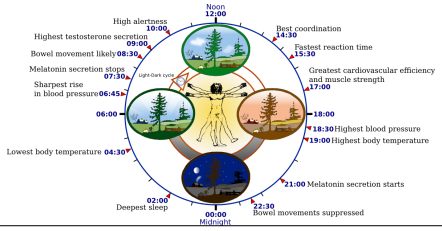




Circadian Rhythms Regulate Many Activities of Life

This is just a small sample

More recently it has been possible to measure gene expression across the day



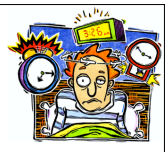
The Importance of Preparing in Advance

- Importance of plants spreading their leaves and orienting to the sun before sunlight arrives
  - Linnaeus designed a flower clock of species that open and close at different times of day
- Adjusting eyes to light (for fish it can take 20 minutes, plenty of time to become someone's meal)
  - Horseshoe crab: for 350 millions years it has changed its receptivity to light 1,000,000 fold over the course of the day

Abnormal Sleep Patterns

- Familial advanced sleep phase syndrome
  - Screen of patients within a family revealed involvement of CK1δ, which phosphorylates PER2
    - Mouse studies showed that Ser662Gly mutation in *Per2* results in shortening of period, mimicking sleep shift
- Delayed sleep phase syndrome
  - Gene polymorphism studies have linked it to *Per3* and *Clock*
- Both disorders involve
  - Irregular patterns of sleep
  - Failure to entrain sleep patterns

Jet Lag



As a result of crossing multiple time zones, an individual's endogenous sense of time may be several hours different than the local day-night cycle

- Sleep, body temperature, hormones, digestive enzymes may all be produced at inappropriate times, resulting in fatigue, insomnia, headaches, depression
- Depending on number of time zones crossed, several days may be required to recover from jet lag
- Eastbound travel is usually more disruptive than westbound travel

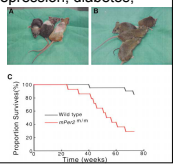
Shift-work/Jet Lag and Cancer

Epidemiological studies show disruption of circadian rhythms (due to shift work or regular time zone change) is associated with a variety of cancers—level of risk proportional to cumulative exposure to circadian stressor

- Breast cancer
- Prostrate cancer
- Non-Hodgkin's lymphoma
- Also associated with sleep disorders, depression, diabetes, cardiovascular problems and obesity

Linkage is likely to be the disruption of the cell cycle, leading to abnormal and unregulated growth (tumorigenesis)

- First study: Fu et al. (2002) identified abnormal DNA damage response after γ-radiation in *Per2* null mutant



Rhythms on Different Time Scales

- Ultradian: milliseconds to hours
  - Action potentials in neurons
  - Heart beats
  - 90 minute sleep cycles (from stage I to REM)
- Circadian: circa (approximately) + dies (day)
- Infradian
  - Estrous cycles (28 days in humans)
  - Annual cycles of migration, hibernation
  - Multi-year cycles (cycads that emerge from larvae 13 or 17 years after eggs were laid)

Many Fields of Biology Contributed to Understanding Circadian Rhythms

Center for Chronobiology at UCSD involves

- Cell and molecular biologists
- Experimental psychologists
- Psychiatrists
- Sleep researchers
- Cancer researchers
- Biological engineers

and even a philosopher