Biology and the New Mechanistic Philosophy of Science

Traditional Nomological Accounts

- For much of the 20th Century, philosophy of science embraced a nomological perspective on explanation
  - Laws, like Newton's force laws, were taken as the core of explanations
- The Deductive-Nomological Model

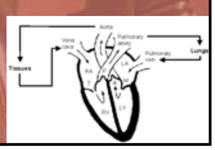
  Laws of a given science

  Initial Conditions

  ∴ (Statement of) the phenomenon to be explained
- PROBLEM: There are few laws distinctive to biology, including neuroscience
  - Those that appear are applications from physics and chemistry (e.g., Ohm's Law)

The Mechanist Alternative

- Even without advancing laws, life scientists are very much in the business of producing explanations
  - These typically describe the **mechanism** responsible for the phenomenon
- "Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions." (Machamer, Darden, & Craver, 2000)
- A mechanism is a structure performing a function in virtue of its **component parts, component operations,** and their **organization** (Bechtel, 2006, Bechtel & Abrahamsen, 2005)



The Centrality of Decomposition

Finding a mechanism requires taking a system apart

Two types of decomposition:

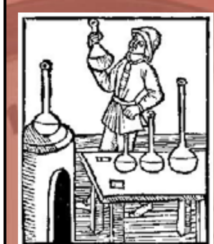
- **Functional**: differentiating the operations that are performed
- **Structural**: differentiating the parts that perform the operations

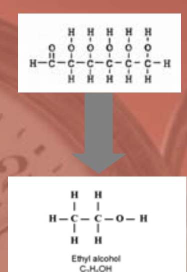
Either can lead in the process of developing explanations, but ultimately they come together

- **Localization**: relating component operations to component parts

Sometimes You Need to Figure out Operations without Knowing the Parts

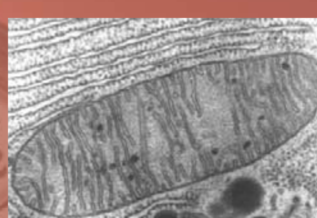
- What are the operations in fermentation?



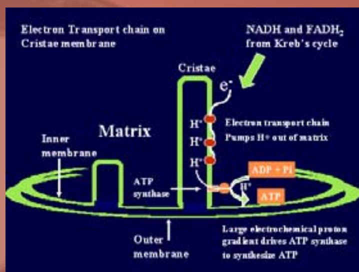


Structural decomposition independent of functional decomposition

On the basis of electron micrographs, George Palade identified the crystae of the mitochondria before their function in ATP synthesis was determined.



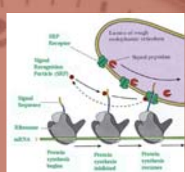
Integrating Structural and Functional Decomposition: electron transport and oxidative phosphorylation



A. Centrality of Pictures and Diagrams

In the traditional view, pictures and diagrams are at best crutches for feeble intellects

- Comparable to relying on figures to understand geometry
- Linguistic representation is primary



But a mechanism, with multiple parts interacting in multiple ways, is best portrayed in figures and diagrams

- Language is used to provide commentary on the diagram (directions for performing simulations)

B. Simulation, not logic, as the glue of explanation

Simulation: using models to step through the operations performed in the real system

- physical models
- computer models—including animation simulators
- models in one's head

When done in the head, imagine the parts and then transform the images

C. Models of Mechanisms are often Gappy

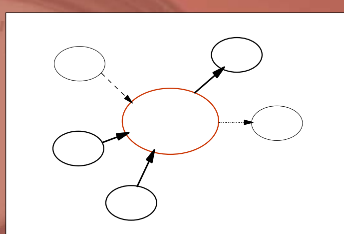
Only some of the components and some of the operations are specified
- What is specified is not sufficient to produce the behavior of the real system
  - Some of the critical operations are not even anticipated in the early models
  - Some of the operations performed by multiple parts are combined into one part
  - Machamer, Darden and Craver: sketches and schmea

These gaps are often revealed when researchers try to re-synthesize the system from what the model says are the operative components

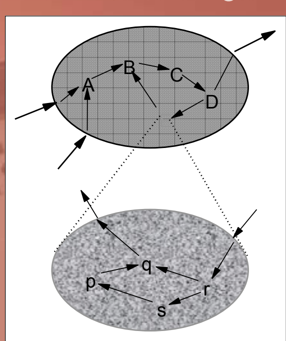
Subsequent development of the model involves filling in the missing steps

D. Reconceptualizing Unity of Science as Integrating Mechanisms

Horizontal Integration: One mechanism interacts with other mechanisms



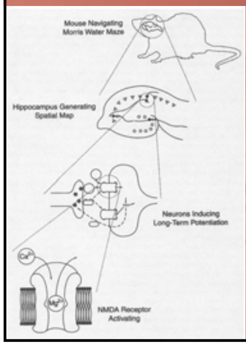
Vertical Integration or Reduction



The behavior of a part of a mechanism is (in part) explained by
- decomposing it structurally and functionally

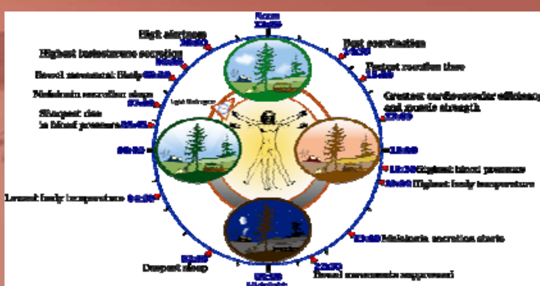
View mechanism as a nest hierarchy of components within components

Nested Hierarchy of Rat Spatial Memory

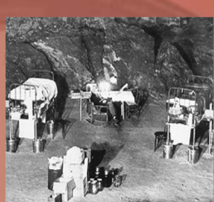


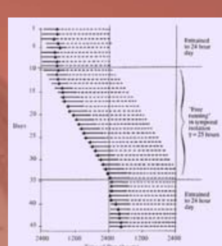
- Behavior of spatial learning exhibited by whole rat
- Removal of the hippocampus eliminates capacity to learn
  - Hippocampus plays critical role in the mechanism of spatial memory
- Acquiring new memory involves changes in synapse—long term potentiation
- LTP is accomplished by building new NMDA receptors
- Here explanation “bottoms out”

Circadian Phenomena



Demonstrating that the Rhythms are Endogenous

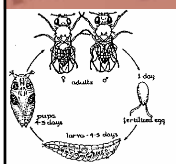




Circadian Rhythms Exhibited by Many Organisms

- Leaf unfolding in *Mimosa*

- Nitrogen fixation in *Cyanobacteria*

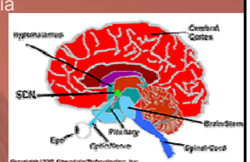


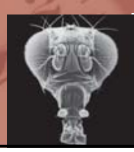
- Eclosion in *Drosophila*

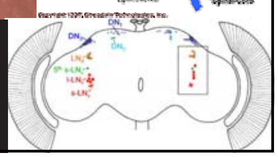
- Running wheel activity in mice

Decomposing the Circadian System - I

- In mammals the primary clock is the suprachiasmic nucleus (SCN), composed of 8-10,000 neurons in each hemisphere
  - SCN lesions produce arrhythmia
  - SCN transplants restore rhythms
  - SCN able to maintain rhythms
- In *Drosophila*, select cells in lateral brain areas maintain rhythms

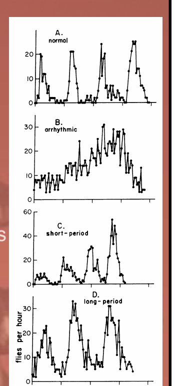






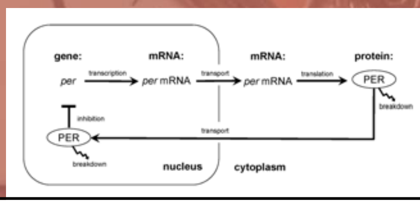
Decomposing the Circadian System - II

- Ronald Konopka and Seymour Benzer (1971) isolated first clock gene (*period*) by "testing fly lines, each of which contained a mutagenized sex (X) chromosome, for aberrant eclosion."
  - Found three lines
    - *per*^{0}: arrhythmic
    - *per*^{S}: shortened cycling times: ~19 hrs
    - *per*^{L}: extended cycling times: ~28 hrs
- *per is* expressed in many cells of the body, including prothoracic gland, antenna, proboscis, Malphigian tubules, ovaries, testis, and gut
- Sun et al. (1997): mouse homologs of *per*: *Per1, Per2, Per3*



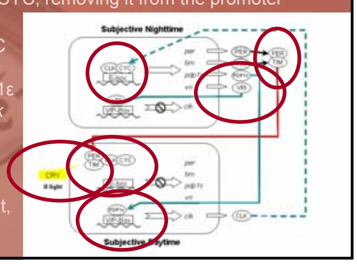
A First Explanation Based on Gene Transcription and Translation

- With the advent of cloning, it became possible to measure concentrations of *per* mRNA and PER
  - Both oscillated, with PER lagging behind *per* mRNA
- Hardin et al. (1990) proposed a feedback loop mechanism for circadian oscillations in *Drosophila*



At Least Two Feedback Loops—Not Just One

- PER operates by forming a dimer with TIM (PER:TIM)
- Second dimer (CLK:CYC) binds to and activates promoter regions on both *per* and *tim* genes
- PER:TIM binds to CLK:CYC, removing it from the promoter regions on *per* and *tim*
- Second cycle: CLK:CYC binds to the promoter region *pdp1ε*, and PDP1ε binds to promoter on *clk*
  - Creating a positive feedback loop
- Another protein, CRY, breaks down TIM in light, explaining entrainment

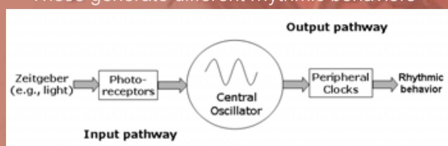


Networks within SCN

- About 30% of the 10,000 neurons in each hemisphere keep time endogenously
  - The agreement among individual neurons is low (S.D. = 1.2 hours)
- Synchronization seems to be accomplished by a peptide that is released by a subset of core SCN cells
  - As a result, neurons in the core oscillate in synchrony
- Those in the shell are also affected by the peptide and synchronize, but out ahead of those in the core
- Phenomena such as jet lag largely due to challenges of resynchronizing SCN oscillators after a perturbation

Traditional View of SCN Function

- SCN receives inputs from sensory systems (e.g., photoreceptors) that serve as Zeitgebers to maintain synchronization with the environment
- SCN sends signals to peripheral clocks in bodily organs (liver, lungs, etc.) that are slaves to the SCN
  - These generate different rhythmic behaviors



Emerging Interactive View of Circadian System

- SCN modulates the retina which provides its input
  - It partly selects is input
- Melanopsin, the key mammalian photoreceptor, is affected by peripheral oscillators regulated by the SCN
- Peripheral oscillators can function autonomously from SCN
  - And may feedback on the operation of the oscillators in the SCN