Explanations in Neuroscience 1 Discoveries and Mechanistic Explanation

The Desire to Explain

- Science is not just interested in determining what happens but to
  - predict what will happen
  - explain what happens
- The tire on your bicycle is flat. You want to know why
  - did someone let the air out?
  - is there a leak?
- Someone tells you: there is no explanation. Tires sometimes lose all their air.
  - Satisfied?

The "Received" Philosophy of Science

- Deductive-nomological model of explanation (as articulated in the mid-20th century)
  - Explanation involves deriving a statement of the phenomenon to be explained from laws and statements of initial conditions:

    Laws (Newton's force law: *f=ma*)

    Initial conditions (object of a given mass is acted upon by a specific force)

    ∴Phenomenon to be explained (Object will experience a specific acceleration)
- Hypothetical-deductive method
  - The scientific enterprise is grounded in observations
  - Scientists propose hypotheses (laws) to explain observations
  - They evaluate these on the basis of predictions made from them
    - If the predictions turn out false, reject the hypothesis (maybe!)
    - If they turn out true, the hypothesis is supported/confirmed (maybe!)

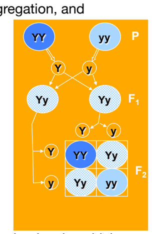
Clicker Question

Which of the following is not a explicit feature of a covering-law or deductive-nomological explanation?

A. Laws
B. Initial conditions
C. Causal interactions of parts
D. Phenomenon to be explained

Biology and Mechanistic Explanation

- Unlike physicists, biologists (including neuroscientists) seldom appeal to laws (except laws of chemistry and physics, as appropriate)
- Apparent counter example: Mendel's laws of dominance, segregation, and independent assortment
  - None of which are true (there are exceptions to each)
- What Mendel did offer was a sketch of a mechanism of inheritance
  - He posited factors, a process through which they are inherited, and a account of how they related to traits
  - He had no evidence for the mechanism other than that it gave the right answers to inheritance patterns in peas
  - But in the 20th century Mendel's factors were named *genes*, their location on chromosomes established, their composition out of DNA was determined, and the mechanism by which they are expressed in proteins discovered



Characterizations of Mechanisms

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

Clicker Question

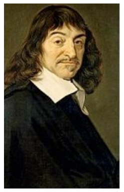
Which of the following represents a way in which mechanistic explanations are different from D-N explanations

A. They don't explicitly refer to laws
B. They attempt to account for why events happen
C. They can be presented in language
D. They must be tested

Mechanistic Versus Nomological Explanations

- Both nomological and mechanistic explanations can be concerned with causal phenomena—something happens which brings about something else
  - Nomological explanations focus on the regularity (law) characterizing the change itself and do not specifically identify causes
    - And don't respect temporal order (you can explain what was true in the past given what is true today and laws)
  - 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—specific causes
    - Laws are not central to mechanistic accounts (they may be invoked to characterize operations, but they need not be)
- Mechanistic explanations are not presented as logical arguments
  - Whereas in D-N explanations logic is the "glue" that links laws and initial conditions to phenomena being explained, in mechanistic explanations scientists model (mentally, physically, or computationally) how the parts and operations produce the phenomenon

Descartes: The Origins of the Mechanical Philosophy



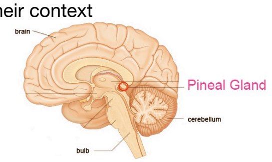
- "I have described this earth and indeed the whole universe as if it were a machine: I have considered only the various shapes and movements of its parts" (Principia IV 188).
- All action in the physical universe due to shape and motion of bits of physical matter that push and pull against each other
  - No vacuum
  - No action at a distance
- Nerve transmission and brain activity purely mechanical (albeit influenced by the mind in humans)

Descartes: Human Bodies are Machines

- For Descartes, any behaviors we share with animals are the products of mechanisms
  - Perception
  - Memory
  - Emotion
  - Action
- "… the reception of light, sounds, odors, tastes, warmth, and other like qualities into the exterior organs of sensation; the impression of the corresponding ideas upon a common sensorium and on the imagination; the retention or imprint of these ideas in the Memory; the internal movements of the Appetites and Passions; and finally, the external motions of all the members of the body … I wish that you would consider all of these as following altogether naturally in this Machine from the disposition of its organs alone, neither more nor less than do the movements of a clock or other automaton from that of its counterweight and wheels …."

Descartes: Mind-Body Dualism

- But Descartes could not conceive how thought or language could be generated mechanically
  - We have an unlimited capacity for generating new sentences and new thoughts
  - Which are appropriate to their context
- Res cogitans: thinking thing
  - Which affects the physical body at the pineal gland

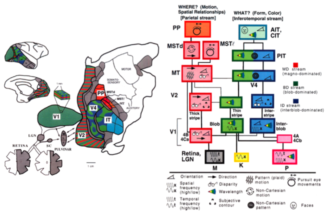


The Legacy of Descartes in Biology

- Descartes speculated about mechanisms. He did not engage in empirical inquiry
- But he inspired the mechanist mindset: If you want to figure out how something works, take it apart
  - Find out what its components are (parts/entities)
  - Determine what they do (operations/activities)
  - Figure out how they are organized
- Test of whether you have really understood: Can you put the mechanism back together?
  - From the parts that were isolated
  - From new parts
  - In a computational simulation

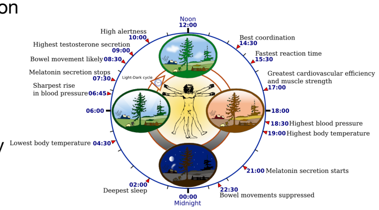
Decomposing the Visual System

- Since the pioneering work in the 19th century, many different brain regions have been found that process information about where things are and what they are
  - Two relatively independent processing streams



Discovering How An Organism Knows Time of Day

- Organisms function differently at different times of day
- Why would it be useful for organisms to vary their activities across a 24-hour period?



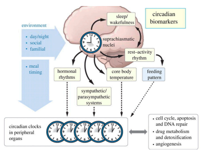
- Since one can open one's eyes and see the world, why have an internal mechanism keep track of time?

The Phenomenon of Circadian Rhythms

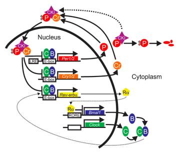
- Oscillations of approximately 24 hours that
  - Are generated endogenously
  - Are entrainable to local day-night conditions
  - Are temperature compensated
- These oscillations regulate a wide range of biological activities in a very broad range of organisms (bacteria, fungi, plants, and animals)

Circadian Rhythms in Mammals

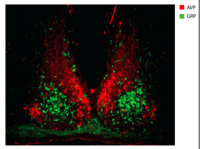
- Circuits in almost all cells have the capacity to generate circadian rhythms
  - but individual cells have slightly different periods
- Neurons in the suprachiasmatic nucleus send a synchronizing signal to circadian oscillators in the rest of the cells of the body
- Rhythms generated by intracellular feedback loops in which proteins suppress their own transcription
- Synchrony within and between neurons in the SCN results from VIP and AVP released by different populations of neurons



Scully et al., 2011

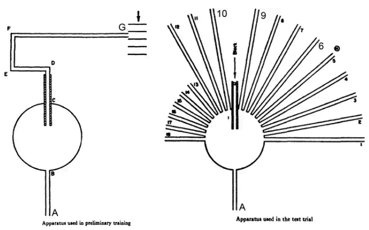


Lowrey & Takahashi, 2004


Welsh DK, et al. 2010.
Annu. Rev. Physiol. 72:551–77

Discovering that Organisms Have Spatial (Cognitive) Maps

- Working with rats in the 1940s, Edward Tolman demonstrated navigational capacities that suggested they possessed a map of their environment



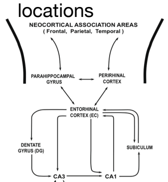
Apparatus used in preliminary training

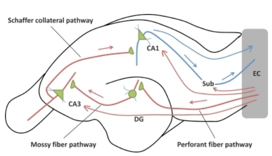
Apparatus used in the test trial

(From E. C. Tolman, B. F. Ritchie and D. Kalish, Studies in spatial learning. I. Orientation and short-cut. *J. exp. Psychol.*, 1946, 36, p. 17.)

Finding the mechanism and taking it apart

- Lesion studies revealed that the ability to navigate with a cognitive map depended on the hippocampus
- The hippocampus has a distinctive architecture, with different regions with distinctive cell types organized as a loop
- Strategy: record from neurons while animals is in different locations

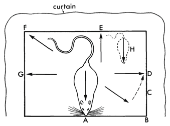


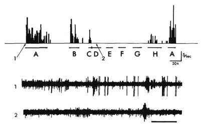


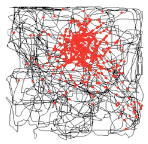
Zhang et al., 2011

Finding Parts: Place Cells

- Recording from neurons in the CA1 and CA3 regions of the hippocampus in the 1970s, John O'Keefe discovered cells that generated action potentials when rats were in one location in their environment
  - Characterized the hippocampus as embodying a "cognitive map"







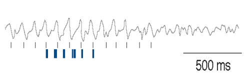
Discussion Question

How much could you learn from the firing of a given place cell when you are in a given location?

A. It just says "you are here"
B. By knowing how that place cell is connected to other place cells, you could know where you are in an environment
C. If you also knew what place cells had fired recently, you could identify your route
D. Other

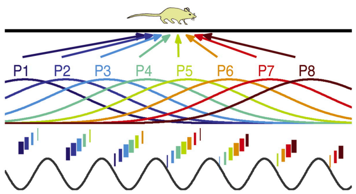
EEG Oscillations and Representations

- In the 1990s researchers determined that place cell firing occurred in relation to background theta rhythms and this provided information that goes beyond mere firing rates
  - When the rat first enters the place field, a place cell fires a burst around the trough of the theta cycle
  - As the rat moves through the place field, firing advances with respect to the theta cycle (here, 6 firing cycles to 5 theta cycles)



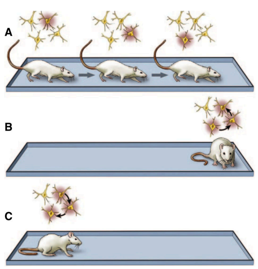
Knowing where one has been and where one is going

- In the cycles after an animal enters a place field, the corresponding place cell advances in the theta oscillation
  - and the place cell for the new location occurs after it
  - providing a trace of where the animal has been and where it is going



Replay and Preplay

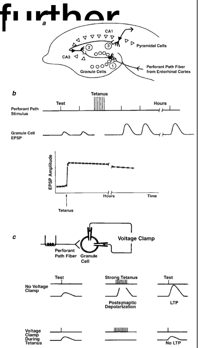
- When the rodent travels along a path, successive place cells are activated
- If it pauses at the end of the path, the sequence of firing is replayed in reverse
- If it is stopped before traveling along the path, the place cells fire in the same order as when the rodent is allowed to travel down the path



Buckner, 2010

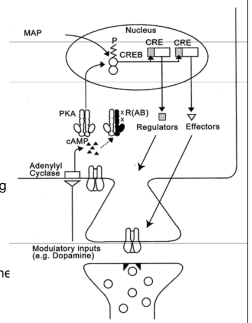
How do maps form? Decomposing yet further

- Animals form different maps (different activity pattern of place cells) for different environments
- To learn a new map, changes need to be made in how neurons respond to each other
- The discovery of long-term potentiation in cells in the hippocampus provided a candidate mechanism
  - Electric stimulation of neurons results in increase lasting for hours/days/weeks in excitatory post-synaptic potentials (EPSPs) to inputs on axons that synapse there
  - Ongoing theta (5-7 Hz) oscillations linked to LTP
    - They involve inputs on interneurons that project to the same synapse as the excitatory projection representing the stimulus and together provide the equivalent of the tetanus



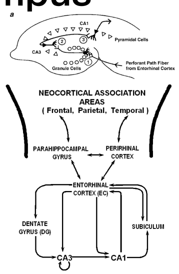
What explains LTP? Going down another level

- LTP itself is a cellular phenomenon involving changes in synapses
- Molecular processes in LTP have been identified
  - Dopamine from the interneurons primes adenylyl cyclase, which catalyzes the reaction from ATP to cAMP
  - cAMP binds to regulatory subunits of protein kinase A (PKA)
  - PKA turns off inhibition of phosophorylated calcium-calmodulin kinase II (CaMKII), allowing it both
    - to bind to AMPA receptors so as to move them to the synapse and
    - to bind with cyclic AMP response element binding protein (CREB), which turns on gene expression needed to build new synapses



From LTP Back to the Whole Hippocampus

- To learn new memories, it is essential
  - To recognize when a stimulus is another instance of one that has already been learned
    - Requires recurrent connections so as to have a network with attractors
  - To learn to respond differently to a different stimulus, one must differentiate the new inputs from the previous ones
    - Requires sparse coding that separates the inputs
- Different parts of the hippocampus appear suited for these different tasks
  - The Dentate Gyrus provides sparse coding
  - The CA3 fields have large number of recurrent projections that generate attractors
- Rolls recomposed this network in a computational simulatio exhibit the desired behavior
  - This moves up from the molecules to the organized network in the hippocampus



Decomposition and Recomposition

- To discover the parts and operations within a mechanism researchers ***decompose*** it
  - Adopt strategies to reveal the parts and what they are doing
    - Researchers must be creative in designing ways to reveal parts and operations
    - In the case of the visual system, it took 150 years to identify the main brain areas and determine what some of them do
- But individual parts don't by themselves produce the phenomenon to be explained
  - Researchers must develop ways to ***recompose*** the mechanism
    - Mentally in their heads
    - In diagrams
    - Physically in scale models
    - Computationally using mathematical simulations

Mentally Simulating Mechanisms

- An early 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
- Understanding such narratives becomes challenging when multiple activities are occurring at once or where operations thought of as later feed back to modify operations thought of as earlier
- Computational models provide a way of understanding what would happen as the mechanism operates