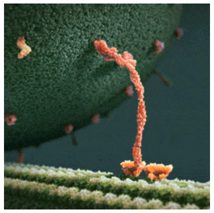
Unit 4. Life and Function

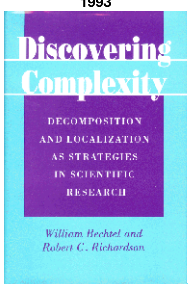
4. Bridging Mechanism and Autonomy by Means of Control



New Mechanists in Philosophy of Science

- A focus on mechanisms and mechanistic explanation is a recent development in philosophy of science

1993



2000


Thinking About Mechanisms
Peter Machamer
Lindley Darden
Carl F. Craver

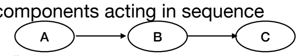
2010

Organization in Mechanisms

- The reference to decomposition captures the fact that mechanistic accounts emphasize determining the composition of a mechanism
  - its parts or entities
  - their operations or activities
- All accounts recognize that the parts of a mechanism must be properly organized for a mechanism to work
  - Insure the **productive continuity** between the different operations within the mechanism
- But there has been far less emphasis on how parts are organized

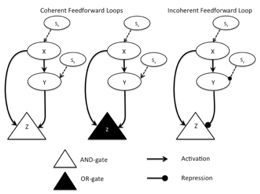
The Poverty of Thinking about Organization

- Humans tend to think of components acting in sequence
  - Assembly line

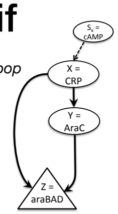


- It took 2000 years from its first known use for humans to recognize negative feedback

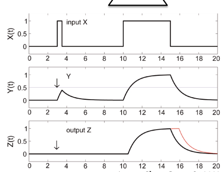
- 30 more to appreciate the power of positive feedback
- Around 2000 Alon identified motifs—small collections of units organized in ways that achieve useful effects



Analyzing the Functional Properties of a Motif



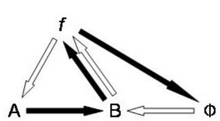
- One of the motifs Alon found through analysis of the transcription network of *E. coli* was the *coherent feedforward loop*
  - Requirement: each reaction in the pathway requires time
  - A general transcription factor X (CRP) regulates a specific transcription factor Y (AraC)
  - X and Y jointly regulate operon Z (araBAD)
  - 40 different operons are regulated in this manner
- If Z operates like an AND-gate, the coherent feedforward loop functions as a persistence detector that only begins transcription of enzymes required to metabolize arabinose when X (CRP) persists sufficiently long for Y (AraC) to be created
  - Then both X (CRP) and Y (AraC) activate operon Z



Shen-Or et al., 2002

Organization in Organisms

- The autopoietic/autonomy tradition emphasized organization in **organisms**
  - organisms are organized so as to construct/maintain themselves far from equilibrium
    - the unity of the organism consists in its being an organized system
    - the closure of efficient causation that defines the organism is a matter of organization
      - that all the activities of the organism are caused by components it built



Building a Bridge: Energy and Constraints

- For the autonomy tradition, the work done in constructing and maintaining an organism requires constraining the flow of free energy
  - constraints play a causal role in a process but are not changed as they do so
  - to maintain autonomy, they must constrain the flow of free energy to construct future constraints
- For the mechanist tradition, the parts of mechanisms can be viewed as constraints that direct the flow of free energy into the performance of the activity associated with the mechanism

Stability vs. Variability

- Both the mechanist and autonomy traditions have tended to focus on stability
  - Mechanists on stability of mechanisms—they operate whenever their start or set-up conditions arise and always in the same manner
    - Experimental protocols are designed to maintain constant operation so that the effects of manipulation can be detected
  - Autonomy theorists on the stability of an organism
    - The organism is the unity that maintains itself through time
      - Reconstructs itself each generation
      - Repairs its when damaged
    - Always to the same condition

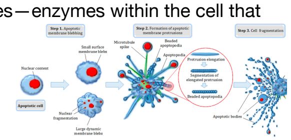
Discussion Question

How stable are you (take that in any sense you want)?

A. Very stable—day to day, week to week, month to month I am the same person
B. Pretty stable—over time I gradually change, but remain basically the same
C. Not terribly stable—I am regularly doing different things, altering who I am

Dynamic Reliance on Mechanisms

- For an organism to build, repair, and replicate itself, it must draw on different mechanisms at different times
- Consider apoptosis—programmed cell death
  - relies on a set of caspases—enzymes within the cell that degrade other proteins constituting the cell
    - serving to make the components available to other cells



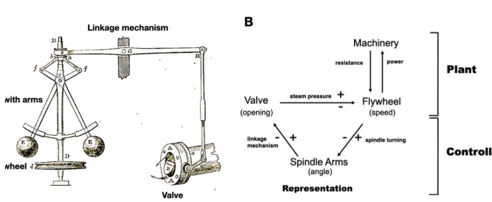
  - In you, 50-70 billion cells engage in apoptosis each day
    - Pathology results from either less or more or if the wrong cells destroy themselves

Towards Gaining Control: Identifying Flexible Constraints

- Many constraints are fixed—at least during the period in which the mechanism is being used, they don't change
- Others are flexible—they can take on different states as the mechanism operates
  - Depending on the state they are in, the mechanism works differently
- Flexible constraints create the possibility that what the mechanism does on an occasion is controlled by something else
  - which might itself be a mechanism

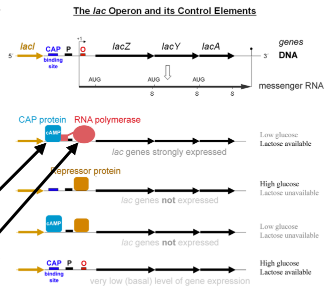
Control Mechanisms

- Like other mechanisms, control mechanisms perform work by constraining flows of free energy, but with two additional features
  - the work they perform is on flexible constraints of other mechanisms
  - their work is determined by measurements they make
    - the constraints in them are set as a result of the conditions to which they are responsive



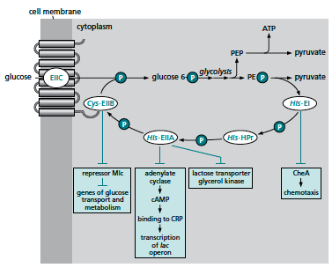
Example: The Lac Operon

- One of the first regulatory mechanisms to be discovered
- Bacteria such as *E. coli* can metabolize a host of sugars, including both glucose (preferred) and lactose
- The genes for metabolizing lactose are only expressed when glucose is in short supply and lactose is available



Measuring Glucose Levels

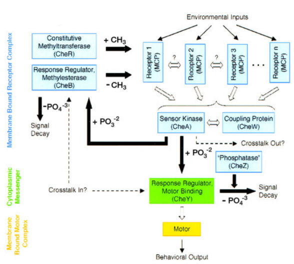
- To measure glucose levels, *E. coli* rely on an elaborate mechanism that is designed to transport glucose into the cell
  - That mechanism relies on phosphate procured in the process of glycolysis and adding it to a new molecule to be transported into the cell
  - When there is no glucose on which to offload the phosphate, it triggers the synthesis of cAMP, which can then bind to the CAP



Marks et al., 2017

Controlling Movement

- To procure glucose or lactose, the bacterium must detect where it is
- To do this is relies on a motor connected to flagellum
  - when it rotates counterclockwise, the motor drives the bacterium forward
  - when it rotates clockwise, it allows the bacterium to tumble
- This motor is controlled by receptor proteins that phosphorylates the motor when nutrients are increasing
  - increase is detected by constantly resetting the receptors based on what they are currently detecting

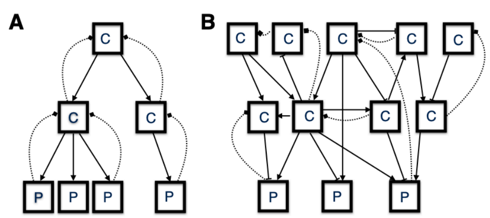


Clicker Question

Which feature is characteristic of a hierarchy rather than a heterarchy

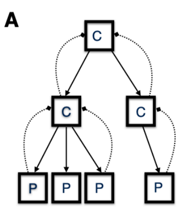
A. Individual mechanisms are often controlled by multiple independent controllers
B. There is a top level controller overseeing all the other controllers
C. There is no strict layering of controllers—controllers can be added to act on any other component

Hierarchy vs. Heterarchy



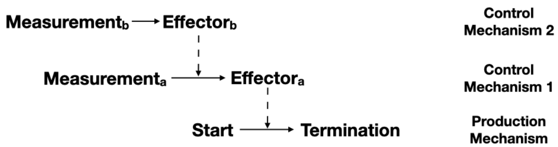
Hierarchy

- In a hierarchy, each component, except the one at the top, is subordinate to those above it
  - subordinate components supply information to the component above it
  - and execute the commands given to them by their superior
- Many social organizations employ (at least in theory) a hierarchical organization
  - businesses
  - military
  - governments
  - universities



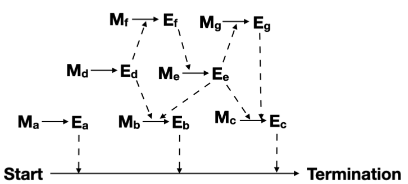
Multiple Control Mechanisms

- One control mechanism can operate on another, suggesting a hierarchy



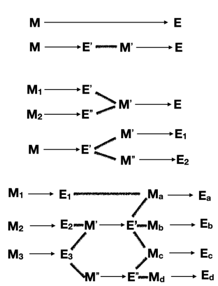
The Breakdown of Hierarchy

- Multiple different control mechanisms can operate independently on the same controlled mechanism
  - It is the controlled mechanism that determines a response to multiple controllers
- A control mechanism can operate on multiple other control mechanisms



Signaling Within Control

- The measurement component of a control mechanism can
  - directly act on the effector
  - or via intermediates
    - signals produced by one component may be responded to by another
- One component can respond to or produce multiple signals
- Control components can be added opportunistically, resulting in networks of control processes
  - Without requiring a hierarchy



Who Would Design A Heterarchical Control Network?

- Seemingly not a rational designer who builds the control system from scratch!
- But what about the person who must intervene when the original design fails?
  - It doesn't make sense to start all over again
  - But rather, to figure out a patch that will address the problem but not alter much else
  - In computer programs, these are called *kludges*
- What about organisms?
  - Evolution is conservative
    - keep components as long as they operate reasonably well, especially if other components depend upon them
  - Evolution is opportunistic
    - If a new component, wherever in the organism it is introduced, improves performance (or doesn't much impair it), it may get retained

Won't Heterarchy Just Result in Chaos?

- It certainly can
  - and does—all organisms die, and many die early in life
    - leaving no successors with their genome
  - there are plenty of examples in which people, lacking direction, act against their own preservation/success
  - in cancer individual cells throw off the yoke of the whole organism and seek their own fortune—replicating, securing resources, defeating defense mechanisms of the rest of the organism
- But there are lots of examples of kludged systems that work reasonably well
  - the operating system on your computer has been patched (kludged) many times
  - existing organizations have undergone many changes to address problems and continue to function

Discussion Question

You and three friends are stranded on a relatively well-provisioned island. How would you organize yourselves?

A. Elect one of you as ruler
B. Each set out on your own, sometimes trading with each other
C. Divide up the tasks among yourselves, each doing what he/she is pretty good at
D. Discuss all issues on which decisions are needed together until you reach a consensus and then act on it
E. Argue and bicker among yourselves, cooperating just enough to stay alive (or not)

Evolving Heterarchical Designs

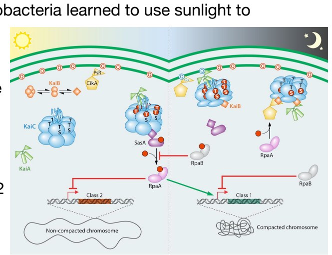
- Evolution on earth has had approximate 4 billion years to work out designs that work reasonably well
  - for nearly 3 billion years all life was single-cell
    - with short lifespans and mutations in each organism, that provided a lot of opportunities to try out many designs for a cell
    - most of that exploration involved adding or deleting control connections
      - many of which are retained in cells today (including those in multicellular organisms)
- Evolution doesn't optimize—it satisfices
  - to be maintained, the design just needs to meet the need
    - to work well enough to allow the organism to leave offspring

What Maintains Unity in an Organism?

- If no agent is maintaining order, won't the components simply go in different directions?
  - think of social organizations that break up because the individuals go their own ways and refuse to stay unified
- For a different perspective, consider a group that has to stay together to survive
    - the context in which they find themselves provides a common reference
- An organism has a boundary (which it creates) at which it interacts with the world outside
  - all components inside operate in the same (internal and external) environment
- Individual organisms often live in social networks with members of the same and other species
  - evolution has come up with communal organizations in which individuals have specific roles
- Unity arises as the different components all confront the same challenges, not from a central authority

Global Control Without Hierarchy

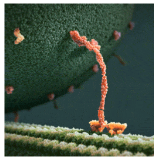
- The 24-hour cycle of light and dark on our planet sets different demands for organisms at different times of day
- Around the time that cyanobacteria learned to use sunlight to synthesize sugar and release oxygen, they evolved a circadian clock that allows them to escape the poisonous effects of oxygen
- Relying on a cycle of phosphorylation and dephosphorylation over a 24-hour period, them turn on different genes during the day and night



Cohen and Golden, 2015

Moving Cargo in Cells

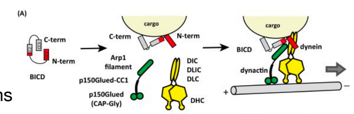
- Proteins and organelles are made at one site in a cell but need to be moved to another site to perform their function
- In the 1980s two molecular motors, kinesin and dynein, were discovered that moved cargo along microtubules
  - kinesin towards the edge of the cell
  - dynein towards the center



Animation by John Lieber

Controlling Motors

- Motors are expensive to operate
  - and left to their own will create traffic jams
- When there is no cargo to transport, both kinesin and dynein adopt a conformation in which they cannot execute motion
  - they are autoinhibiteed
- When they discovered this, researchers set out to determine what other components operate on the motor to render it operable
  - These were not viewed as parts of the motors but as control mechanisms operating on them



Hoogenraad, C. C., & Akhmanova, A. (2016)

Controlling Competing Motors

- Kinesin and dynein act to move cargo in opposite directions
  - What happens when both attach to the same cargo?
- Initial proposal—they engaged in a tug-of-war with the winner determining where the cargo went
- More recently, evidence points to a switch—TRAK2—which determine which motor is able to bind the microtubules and move the cargo