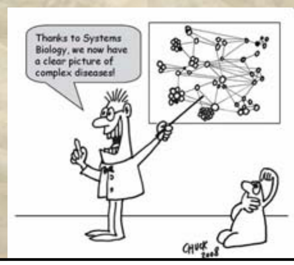
Living Mechanisms as Complex Systems



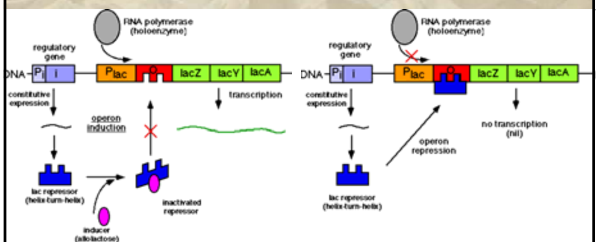
The Traditional Mechanistic Perspective

- Decompose the organism into parts and operations
  - Understand each on its own
  - Link the whole together (sequentially, linearly)
- Applied to genetics
  - For each trait this is gene (or maybe a few) which has its effect independently of the rest

Control Genes: The Lac Operon

- In 1900, F. Dienert discovered that the enzymes needed for galactose metabolism were found in yeast only when the yeast used galactose as a carbon source
  - the presence of galactose had called forth or *induced* the specific enzymes (e.g., β-galactosidase) necessary to metabolize galactose
- Joshua Lederberg developed three mutant strains (*lac*Z$^-$, *lac*Y$^-$, and *lac*A$^-$) that each lacked an enzyme needed to metabolize lactose and these were all mapped to the same region on the chromosome
  - This suggested the induction occurred at the level of the chromosome
- Lederberg produced a different mutant (*lacI*$^-$) which always produced the enzymes, and it was located nearby

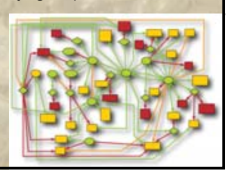
Basics of the Lac Operon: Jacob and Monod (1961)



- When lactose is available, inducer binds to repressor and stops it from binding to the promoter; lac genes are transcribed
- When lactose is absent, repressor binds to the promoter, and lac genes are not transcribed

Gene Regulation Meets Rube Goldberg

- Transcription Regulation: modify the ability of RNA polymerase to initiate transcription: general transcription factors, inhibitors, promoters, enhancers
- Chromatin remodeling, either by modifying histones around which DNA winds (preventing unwinding and hence expression) or by adding methyl groups to the DNA, reducing transcription. Heritable for several generations
- Post-transcriptional Regulation: capping, splicing, or adding Poly(A) Tail to mRNA
- Gene regulatory networks: must be treated as systems



Recall the Vitalists' Objection to Mechanism

- Mechanistic accounts were too simple to capture the phenomena found in living systems
- Bichat: Life as the sum of the forces that resist death
  - Ordinary mechanisms seem to be subject to death—decompose in the normal course of ongoing activity
  - Living systems maintain themselves in the face of such processes

Translating the Vitalists' Concern to the Molecular View of Life

- For the most part, living organisms stand out against their environments as enduring structured entities
  - Also true of individual cells, the fundamental living units
- Living organisms, including cells, are not just passive systems but active ones
  - Metabolic systems: changing chemical compounds into other chemical compounds
  - Doing things that alter their environments in ways that help maintain themselves
- Focal issue: how do living systems maintain themselves as such active systems?

Weber's Characterization of Life

- "It will be argued below that living systems may be defined as open systems maintained in steady-states, far-from-equilibrium, due to matter-energy flows in which informed (genetically) autocatalytic cycles extract energy, build complex internal structures, allowing growth even as they create greater entropy in their environments."

Frederic Gowland Hopkins' Vision for Biochemistry

A living cell is "not a mass of matter composed of a congregation of like molecules, but a highly differentiated system: the cell, in the modern phraseology of physical chemistry, is a system of co-existing phases of different constitutions" (Hopkins 1913 [1949] p. 151)

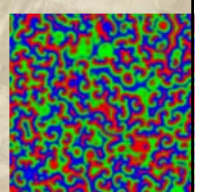
"It is important to remember that changes in any one of these constituent phases ... must affect the equilibrium of the whole cell-system, and because of this necessary equilibrium-relation it is difficult to say that any one of the constituent phases ... is less essential than any other to the "life" of the cell ... Certain of the phases may be separated, mechanically or otherwise, as when we squeeze out the cell juices, and find that chemical processes still go on in them; but "life", as we instinctively define it, is a property of the cell as a whole, because it depends upon the organisation of processes, upon the equilibrium displayed by the totality of the co-existing phases."

Erwin Schrödinger: *What is Life?*

- The entropy problem: How could order be maintained in the face of the 2^{nd} Law of Thermodynamics
  - Problem 1: how could genes retain their structure in the face of mutation?
  - Problem 2: how could metabolism enable organisms to maintain themselves in a non-equilibrium state
    - Negentropy: Organisms route energy through themselves in a manner that builds structure (reduces entropy) and increases entropy outside of the self

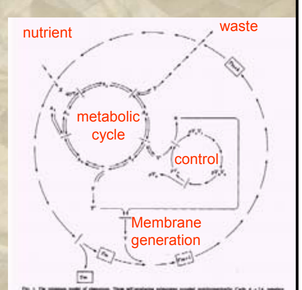
Belousov-Zhabotinsky Reaction

- In the mid-1950s Boris Belousov discovered a reaction that generated an oscillation in concentrations of cerium(IV) and cerium(III) ions in a mixture of potassium bromate, cerium(IV) sulfate, propanedioic acid and citric acid in dilute sulfuric acid when a heat source was provided
- Response: that is impossible: you are claiming perpetual motion!
- Rediscovered by Anatol Zhabotinsky in 1960s but still no uptake
- Later came to be seen as a model of self-organization in auto-catalytic systems in non-equilibrium conditions



Tibor Gánti's Chemoton

- The Hungarian chemist Tibor Gánti posed the question: what is the simplest chemical system exhibiting the features of life?
- Required a metabolic cycle that both extracted matter and energy and used it to rebuild itself
- Also need to build a containment vesicle
- And possess a way of controlling its own activities



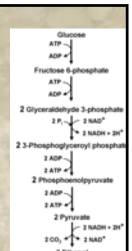
Varela: Autopoietic Mechanisms

- Following a related line of thinking, Chilean biologist Francisco Varela (together with Humberto Maturana) introduced the notion of autopoiesis—self construction
- "An autopoietic system is organized (defined as a unity) as a network of processes of production (transformation and destruction) of components that produces the components that: (1) through their interactions and transformations continuously regenerate and realize the network of processes (relations) that produce them; and (2) constitute it (the machine) as a concrete unity in the space in which they exist by specifying the topological domain of its realization as such a network." (1979, p. 13).

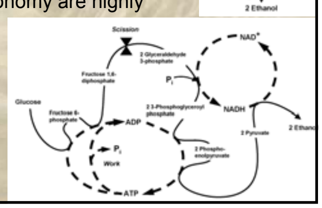
From Autopoiesis to Autonomy

- "Autopoietic machines are autonomous: that is, they subordinate all changes to the maintenance of their own organization, independently of how profoundly they may be otherwise transformed in the process. Other machines, henceforth called *allopoietic* machines, have as the product of their functioning something different from themselves" (Varela, 1979, p. 15)
- Although Varela does not emphasize it, need to pick up the entropy thread from Schrödinger
  - An autonomous system is one that recruits matter and energy from its environment and uses it to build and repair itself

The Case for Dynamic Mechanistic Explanation

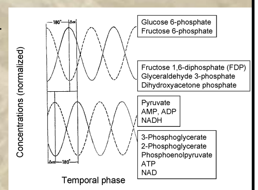


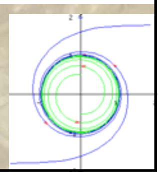
- We tend to think of mechanisms operating sequentially
  - "from start or set-up conditions to finish or termination conditions"
- But operations in biological mechanisms in systems exhibiting autonomy are highly connected to others
  - Integrated systems in which different processes, sometimes spatially remote from each other, nonetheless affect each other



The Case for Dynamic Mechanistic Explanations

- As a result of non-sequential organi-zation of non-linear operations, real biological systems often exhibit complex dynamics, such as oscilla-tions (and synchrony between different oscillations)
- Understanding how and when such complex dynamics arises requires mathematical modeling and graphical representation of the resulting behavior
- Such analysis is a natural complement of mechanistic research: “dynamical models without mechanistic grounding are empty, while mechanistic models without complex dynamics are blind”



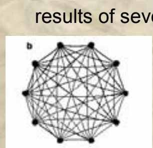


Oscillations can be Good for Organisms

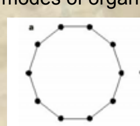
- Common perspective: organisms maintain a steady state (homeostasis)
- But regular oscillations allow organisms to maintain different regimes in which different activities can occur
- Also, enable organisms to coordinate their activities with oscillatory environments (annual, daily)
  - Daily circadian oscillations enable organisms to prepare for environmental conditions/opportunities
- Coupling of oscillations enables coordination between remote components
  - But when that coupling gets messed up (as in jet lag), many untoward consequences can arise

Small Worlds

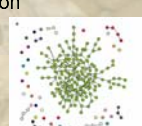
- Mathematicians in the 20th century characterized the results of several modes of organization



Totally connected
Globally coordinated

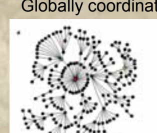


Regular lattice
Local specialization



Random
Globally coordinated

Discovery at the end of the century: small world organization; globally connected but local specialization



Small Worlds Ubiquitous in Biology

- Many biological systems—gene regulation networks, metabolic systems, neuronal networks—seem to be small worlds
- Their combined properties of local specialization and global integration may in fact explain complex diseases, etc.
- The vitalists/holists were right
  - We do need to understand the system as a whole
  - But new tools make it possible for mechanists to do this