Welcome to...

MCB 135
Introductory Systems Biology

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Developmental biologists study babies.

Neuroscientists study brains.

What do systems biologists study?

Systems biologists share an approach rather than a research topic.

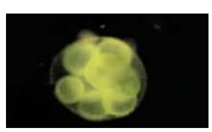
Today's outline

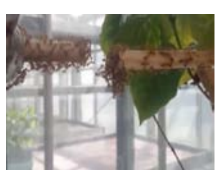
- What is systems biology?
  - The problem at hand
  - The systems approach and its alternatives
  - Example from the Game of Life
  - Brief history of the field
- Course outline
- Course logistics

Shopping? The videotaped lecture will be available online.

Emergent behavior: a property of the whole not found in any of the parts

Emergent behavior is what makes life interesting





Life is Complicated

E. coli – 1 fL cell contains:

- 1 genome (5 million base pairs, 4400 genes)
- 200,000 RNA molecules
- 3 million protein molecules
- 20 million lipid molecules
- 60 million ions
- 20 billion water molecules

Your body has ~10 trillion human cells…and 100 trillion more from microorganisms on and within it!

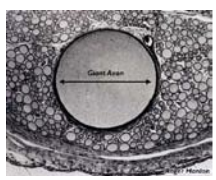
To understand emergent behavior, start by reducing the problem

Reduction works in biology, too!

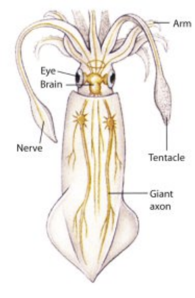
Alan Hodgkin

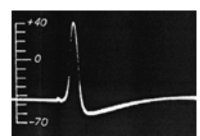
Andrew Huxley

Hodgkin-Huxley & Squid Giant Axon



Hodgkin-Huxley & Squid Giant Axon

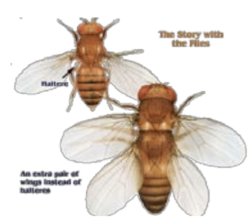




After finding a minimal system, you could…

Start removing parts and see what breaks

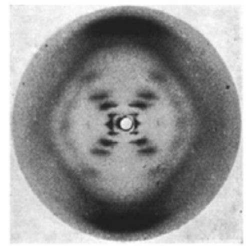
Loss-of-function mutants and knockouts: the workhorses of molecular and cellular biology



After finding a minimal system, you could…

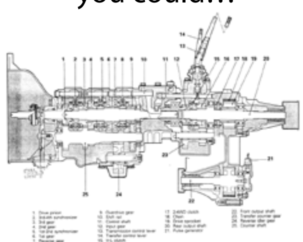
Study each part in isolation

Techniques from biochemistry and structural biology often study "single parts"



The crystal structure of DNA suggested the mechanism of its replication (later confirmed by Meselson and Stahl)

After finding a minimal system, you could…



Study the interactions between parts

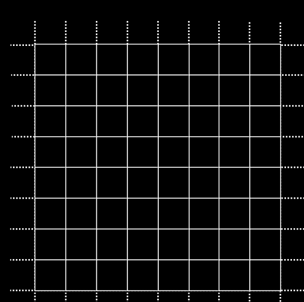
A field-neutral example: Conway's Game of Life

The Rules of Life

Played on an infinite 2D grid

Most squares are "dead" (dark)

A few squares are "alive" (light)



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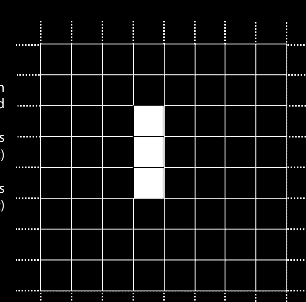
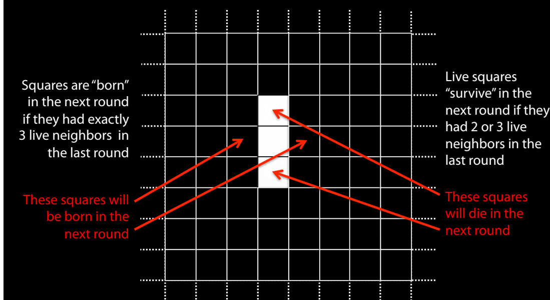


Played in rounds

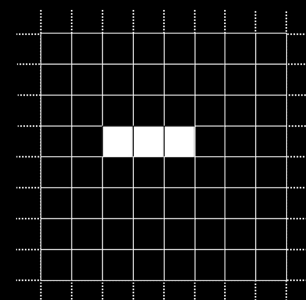
Rules tell us when a square will die or come to life

The Rules of Life



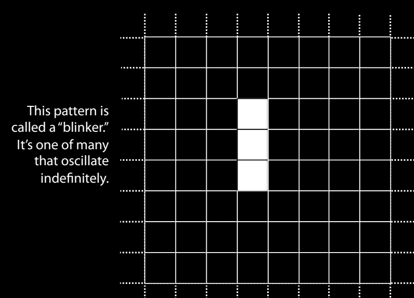
Round one

The Rules of Life



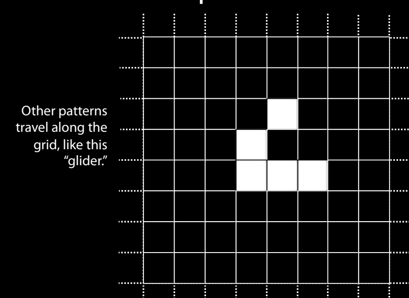
Round two

The Rules of Life

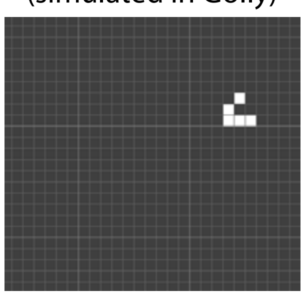


Round three

These simple rules produce complex behaviors



Glider motion (simulated in Golly)



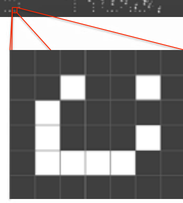
Understanding emergent behaviors in GoL: the dot matrix printer

In a sense, you already understand how the printer works: you know the initial pattern and the rules for its changes with time.

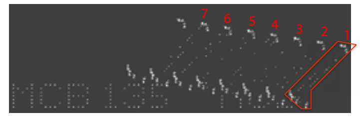
An alternative explanation of how the dot matrix printer works

There are seven vertical rows of "dots" in the message.

Each "dot" is a spaceship (similar to a glider, but it moves straight)

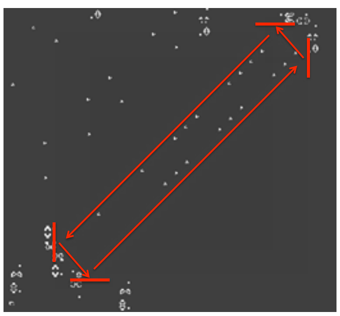


An alternative explanation of how the dot matrix printer works



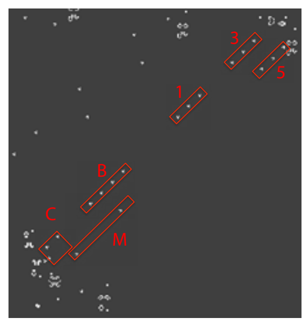
There are seven similar printing units, each of which is responsible for generating the spaceship pattern in one row.

An alternative explanation of how the dot matrix printer works



Within each printing unit, gliders travel around an infinite loop, bouncing off of reflectors.

An alternative explanation of how the dot matrix printer works



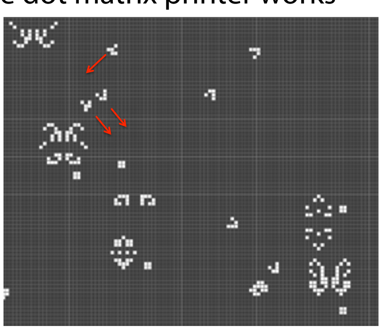
Within each printing unit, gliders travel around an infinite loop, bouncing off of reflectors.

This is the "memory tape" for when dots should be printed.

M C B 1 3 5

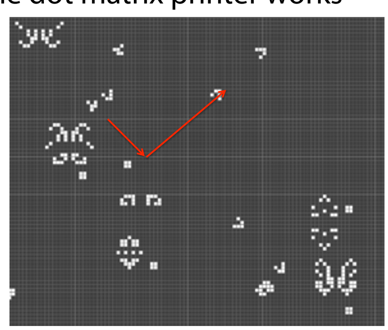
An alternative explanation of how the dot matrix printer works

A duplicator in one corner makes a copy of each passing glider



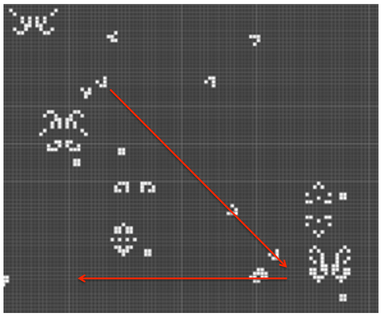
An alternative explanation of how the dot matrix printer works

The original glider stays in the loop



An alternative explanation of how the dot matrix printer works

The copy heads towards a "converter" that turns gliders into spaceships

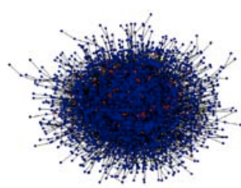


Take-home lessons

- In Life, emergent behaviors can be explained with multiple levels of abstraction
- A complete understanding of the rules may not be necessary or even helpful for explaining some phenomena
- Focusing on interactions between appropriately-chosen parts (a *systems approach*) can give a clear understanding

This is common sense: why does it need its own field?

- Finding interactions between biological parts is hard (but getting easier)
- Important phenomena are occurring at levels from single molecules to populations
- Understanding systems with many parts requires simulation and/or analysis



Human Protein Interaction Network

One field by many names

- Von Bertalanffy's General Systems Theory
- Norbert Wiener's Cybernetics
- "New Cybernetics"
- Systeomics
- Systems Biology

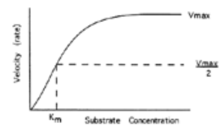
… now has departments at many schools (but few undergraduate programs)

What We'll Cover in MCB 135

What can living things do?

- What are the parts in biological systems?
- Do systems built from organic parts have inherent limitations?
- Can they compute anything a general computer can, i.e. are they Turing complete?

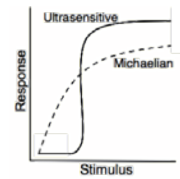
Enzymes and Biochemical Modeling

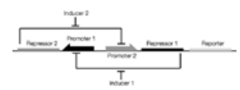


- How can we model biochemical networks?
- What is an enzyme?
- Why does non-linearity in enzyme kinetics make some behaviors hard?
- What's the work-around?

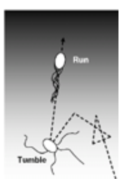
Switch-like behaviors

- When do living things need to make "yes-or-no" decisions?
- How can they do this when variables like concentration are (virtually) continuous?
- Do we understand well enough to engineer this behavior?



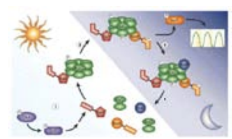


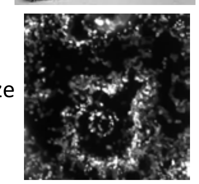
Homeostasis and Control Theory



- When is constancy needed?
- What types of feedback can be used to correct deviations from a desired state?
- What can go wrong?

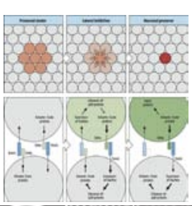
Cycles and Clocks





- Why and how do living things track time?
- How do organisms synchronize with the environment and each other?

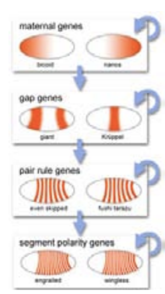
Variation and Noise



- When do deterministic, high copy number assumptions fail?
- How should we model systems in this regime?
- Can random variation be exploited to break symmetry?

Shaping the Body

- How do organisms self-assemble from single cells?
- What are morphogens?
- Why are these processes robust to variation in temperature, size, and gene expression?



Engineering Biological Systems

- When is it easier to engineer vs. evolve a new type of biological system?
- What are the prediction and implementation challenges?
- How does biology inform and inspire other forms of engineering?

Course Logistics

Is systems biology for you?

- Systems biology uses abstraction: a rounded biology education is not required
- The math and computer skills needed depend on the problem at hand
- Prominent systems biologists studied many disciplines as undergrads: life sciences, physics, applied math, engineering, computer science…

Simulation

- New to programming?
  - Adam Cohen and other science faculty run an evening MATLAB boot camp starting next week
  - Ingalls (and Ogata, on reserve) contain primers on working with MATLAB
- Prefer a different language?
  - If we can read and compile your code, we'll accept it (but please, no unusual libraries or packages)
  - In particular Perl, Python, C[++], & Java are fine

Students in MCB 135 are expected to:

- Complete weekly problem sets
  - Collaboration encouraged
- Participate in weekly paper discussions
  - …and lead discussion of one paper
- Prepare a two-page research proposal
  - Final version due during exam period
  - Opportunities for feedback on drafts

Still interested?

- Locate/buy the textbooks
  - Ingalls *Mathematical Modeling in Systems Biology*
  - Alon. *An Introduction to Systems Biology*
- Submit discussion section time preferences
  - Link on course website
- Check out the (optional) problem set zero
  - Not graded, but may help you brush up on MATLAB and/or programming

Next Time:
Logic and Computability