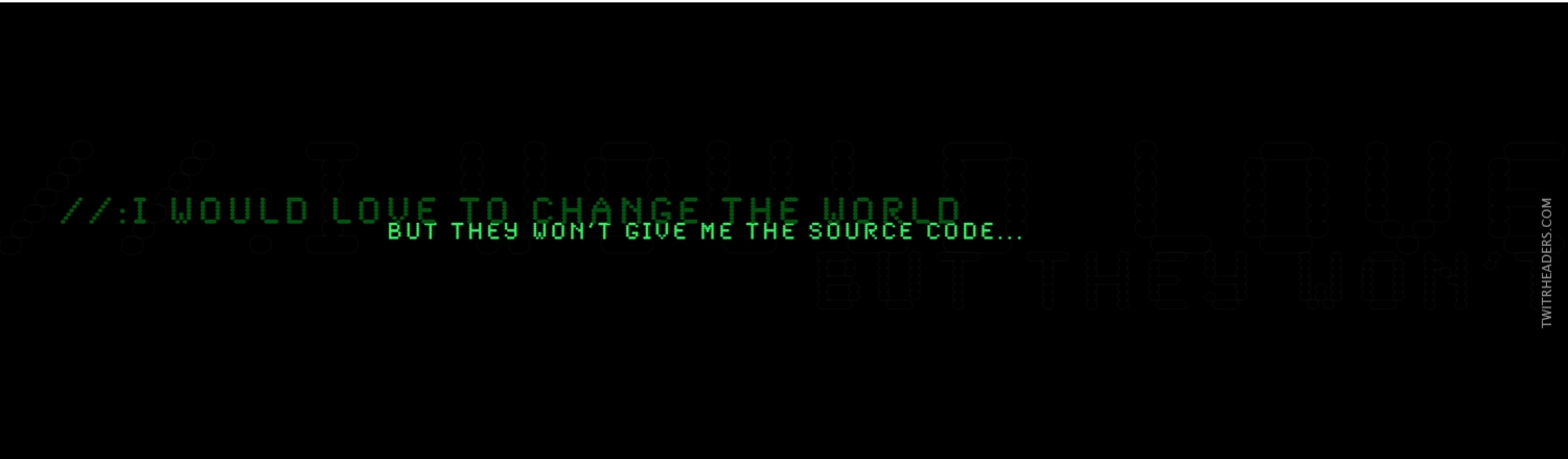
Applied Neuroscience

Columbia Science Honors Program

Fall 2016

Informatics in Neuroscience



//: SHP Applied Neuroscience Members, we will miss you dearly

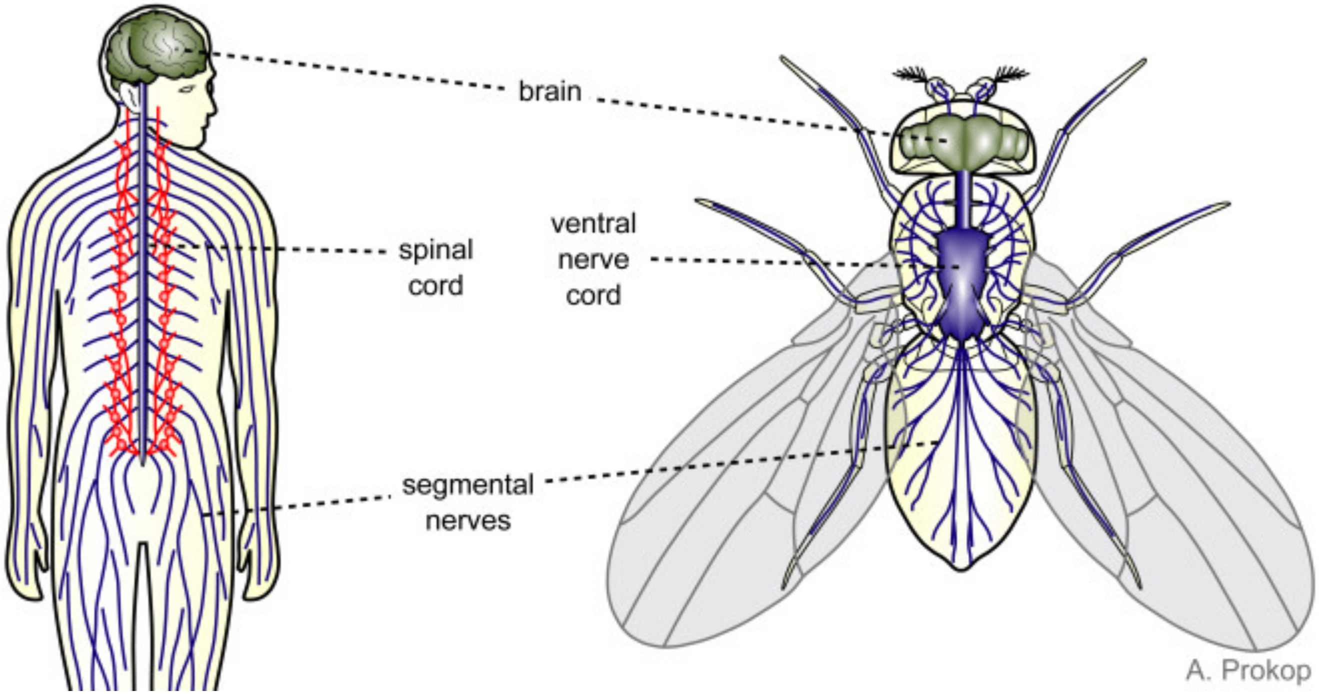
Informatics in Neuroscience

Objective: The Divide between Computation and Cognition

Agenda:

1. Fruit Fly Brain
    - *Overview*
    - *Guest Lecture by Professor Aurel Lazar*
2. Big Data in Neuroscience
    - *Connectomics*
    - *BRAIN Initiative*
    - *Allen Institute of Brain Sciences*
3. Fundamentals of Artificial Intelligence
    - *Defining Intelligence*

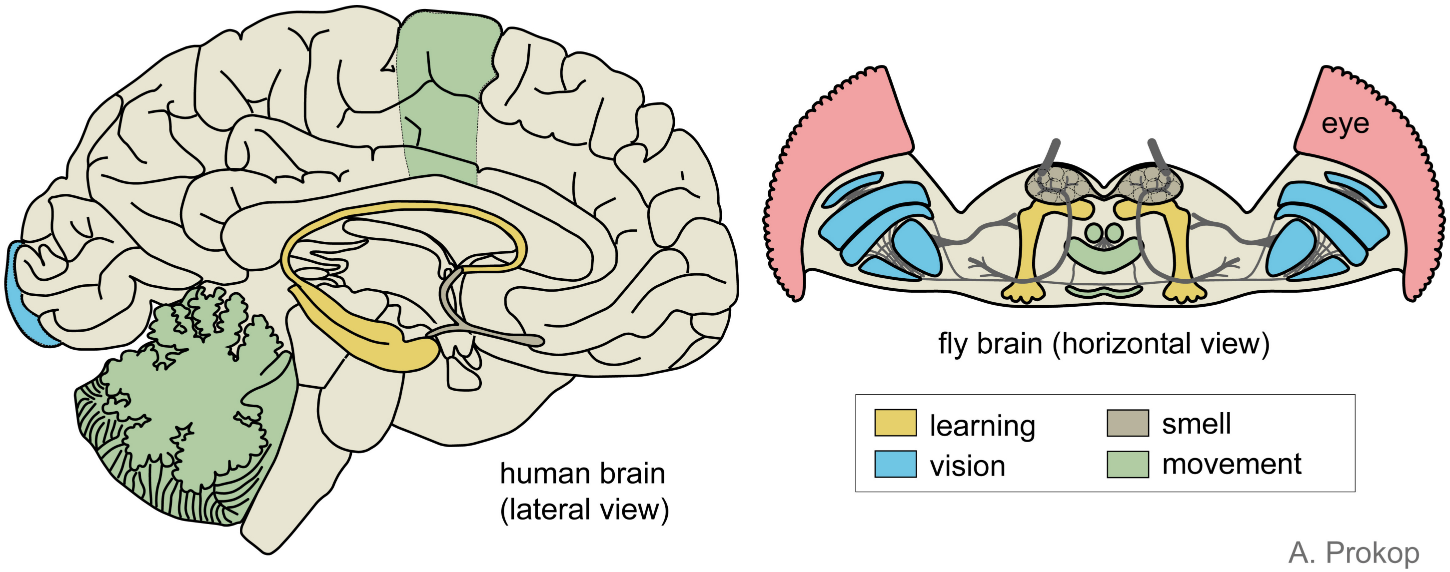
Human vs. fly nervous system



Both humans and flies have
1) Motor neurons: conduct info from CNS to muscles + glands
2) Sensory neurons: conduct info from sensory organs to CNS

They both subdivide the CNS into the brain and spinal/ventral nerve cord. Nerve cells have the same genes to allow them to form synapses and fire action potentials.

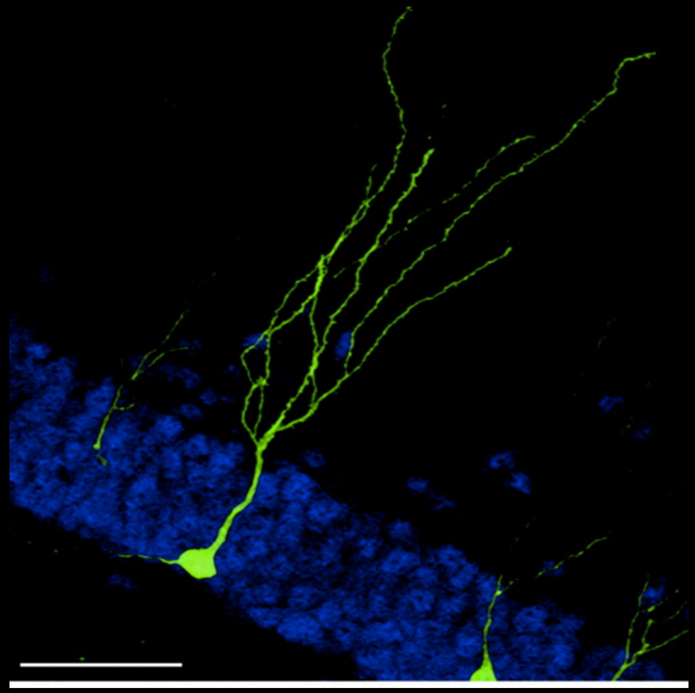
Human vs. fly nervous system

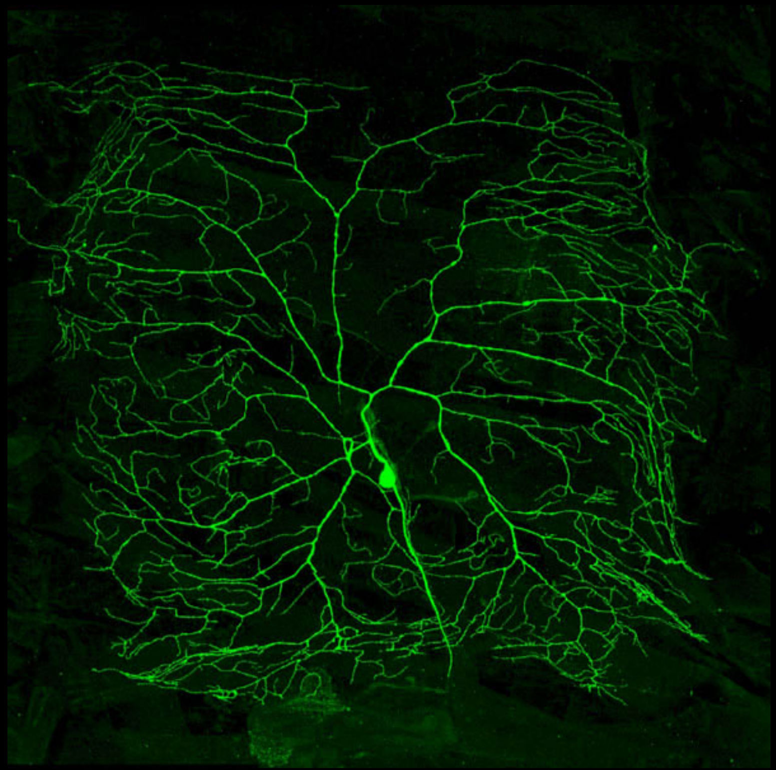


Brains of flies and humans are both highly specialized and subdivided into functional centers for:

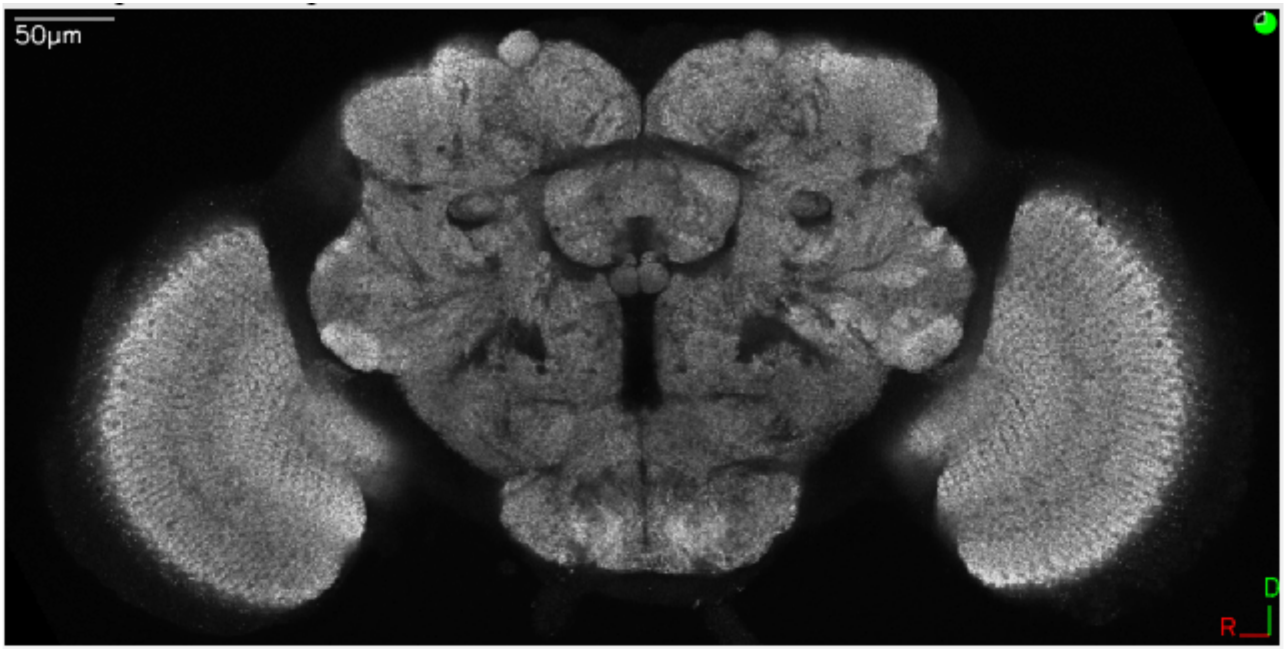
1. Vision
2. Smell
3. Motor coordination/movement
4. Learning

Which one is the fly neuron? Which is the mouse neuron?

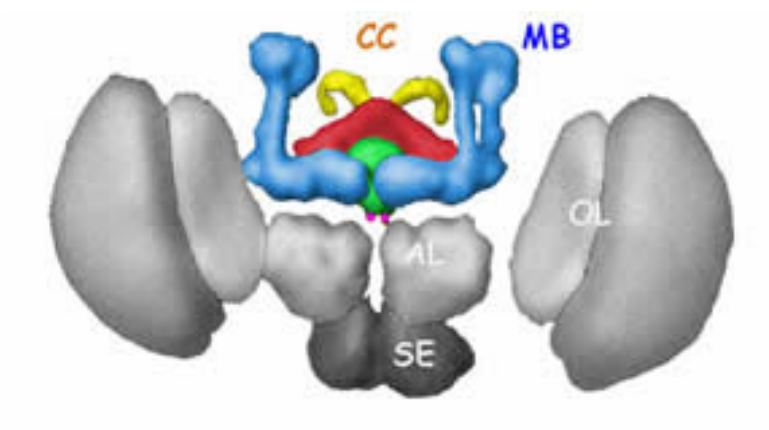




The Adult Fly Brain

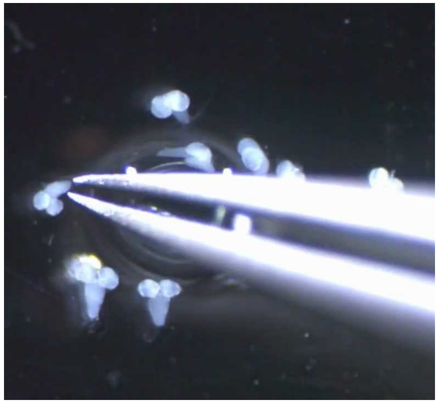


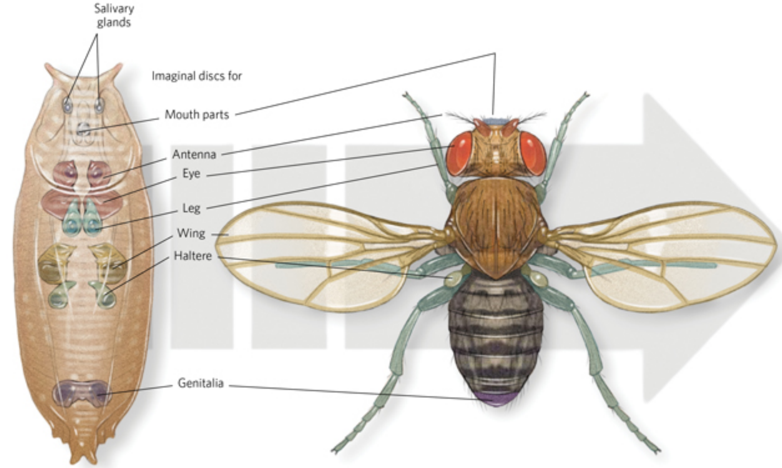
- About 250,000 neurons in *Drosophila* brain
- Approximately $1x10^7$ synapses

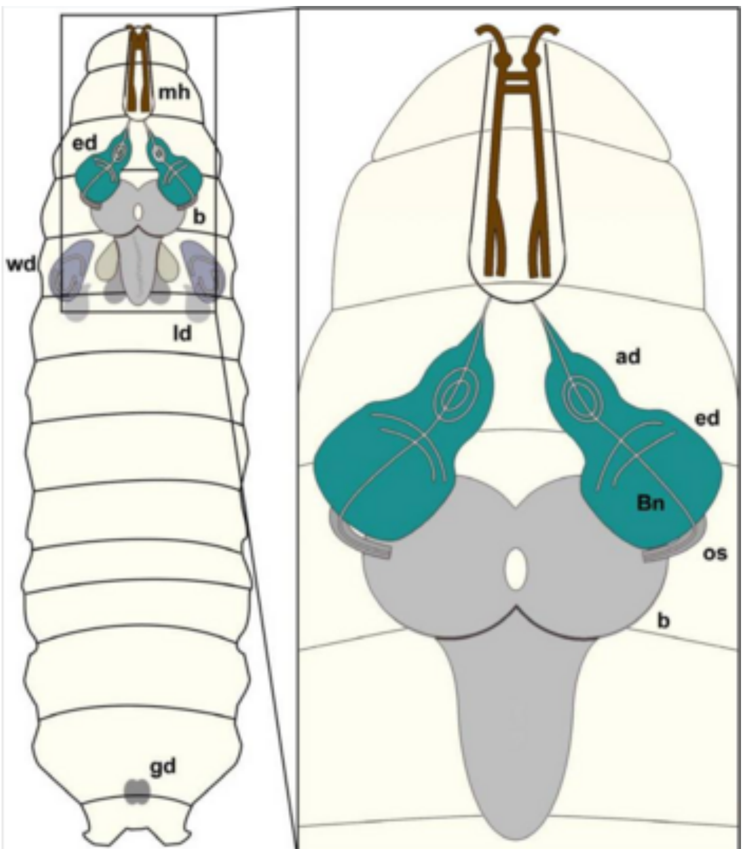


MB (mushroom bodies): olfactory learning/memory
CC (central complex): internal compass
AL (antennal lobes): olfactory bulb
SE (subesophageal ganglia): taste center
OL (optic lobes): visual system

The Larval Fly Brain



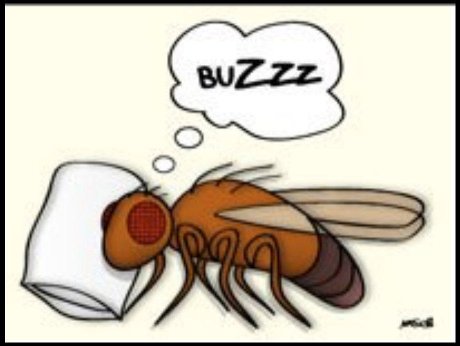




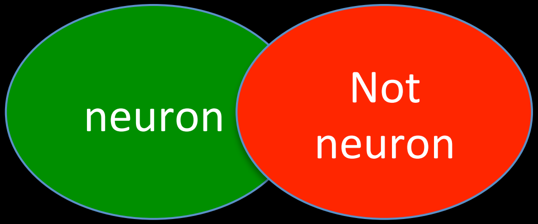
- About 10,000-15,000 neurons in larval *Drosophila* brain
- This is 10-20x less than the adult *Drosophila* brain

ed (eye imaginal discs): will form adult eyes
ad (antennal discs): will form adult antenna
os (optic stalk): connects brain to ed
Bn (Bolwig nerve): connects brain to photo receptors
b (brain): develops in adult brain

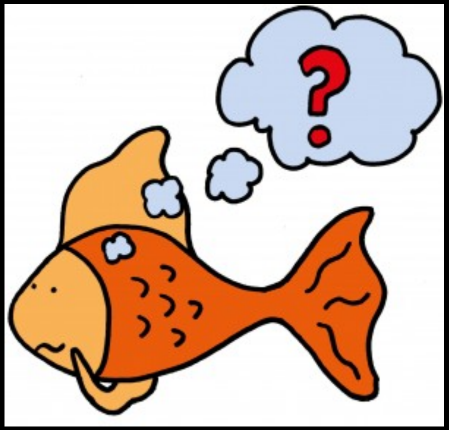
What has the fly taught us about the brain so far?



Circadian rhythms



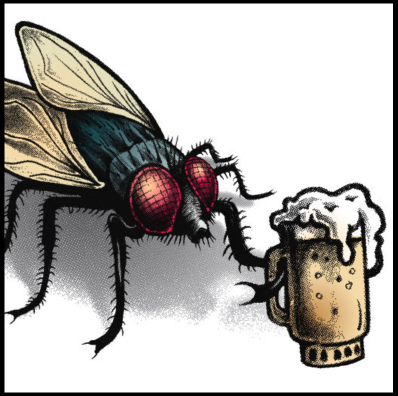
Neurodevelopment



Learning and memory

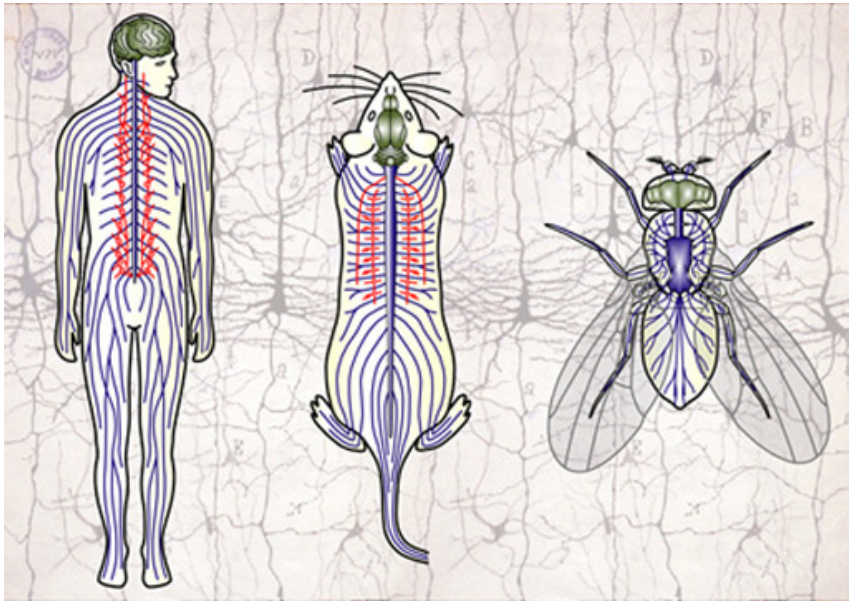
Aggression

Temperature sensing

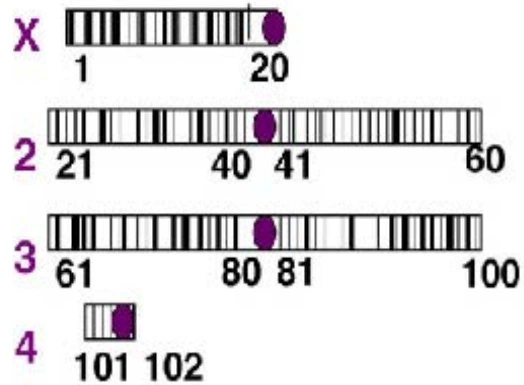


Alcohol consumption

Why work with flies?



Powerful Genetics and Biochemistry
Drosophila has four chromosomes.
Positions can be identified like a bar-code.

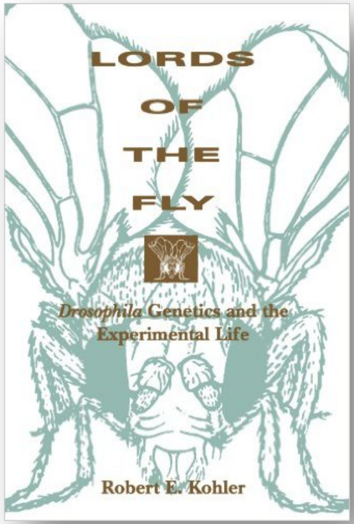


- 14,000 genes in fly, half of 30,000 genes in human
- Biological pathways are conserved from humans to flies
- 70% of human disease genes have fly homologs
- Less genetic redundancy in flies

Lords of the Fly

Calvin Blackman Bridges, 1927.
Photo courtesy of Cold Spring Harbor Laboratory Archives.

Alfred Henry Sturtevant
Photo courtesy of Cold Spring Harbor Laboratory Archives.

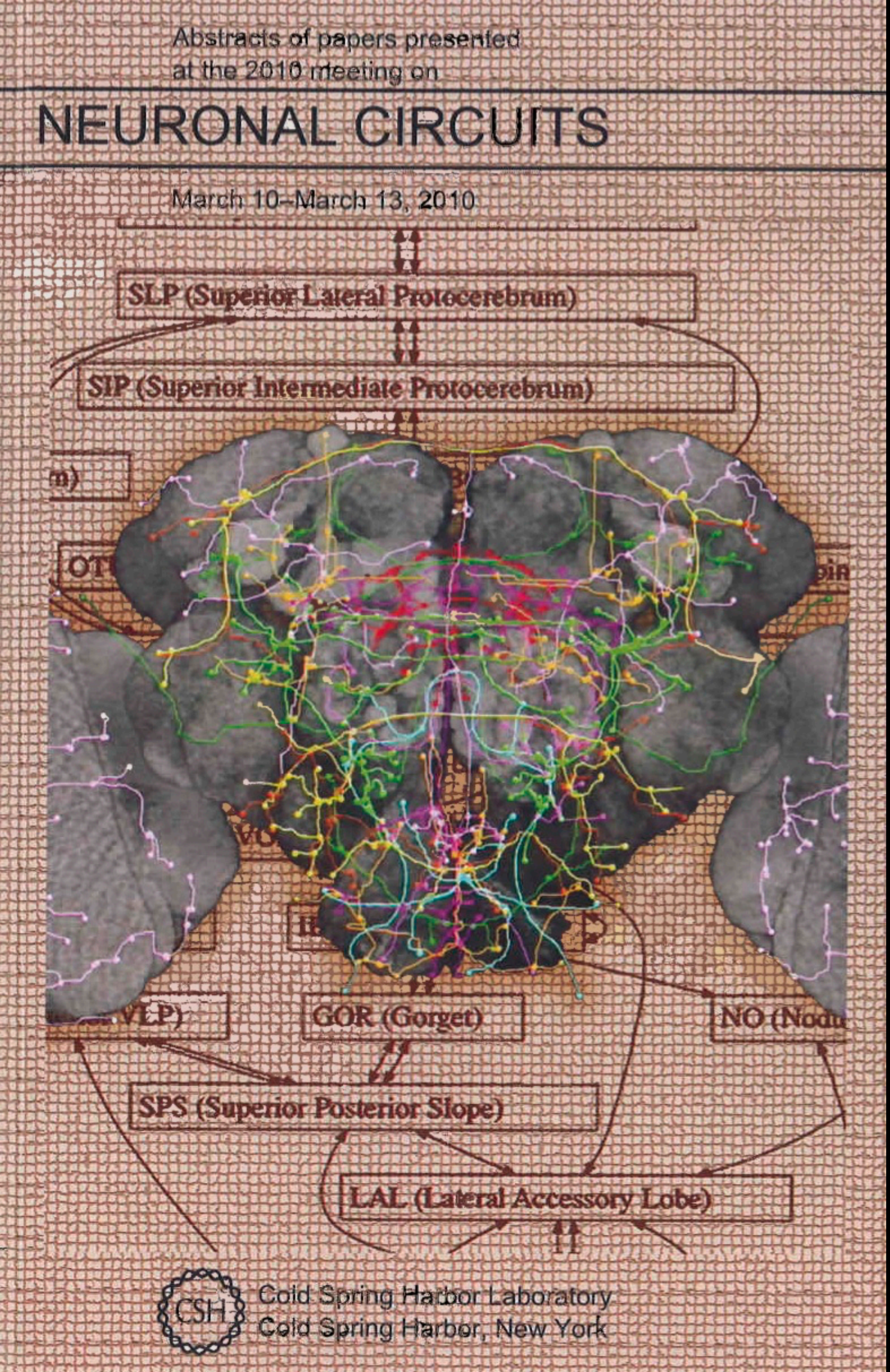


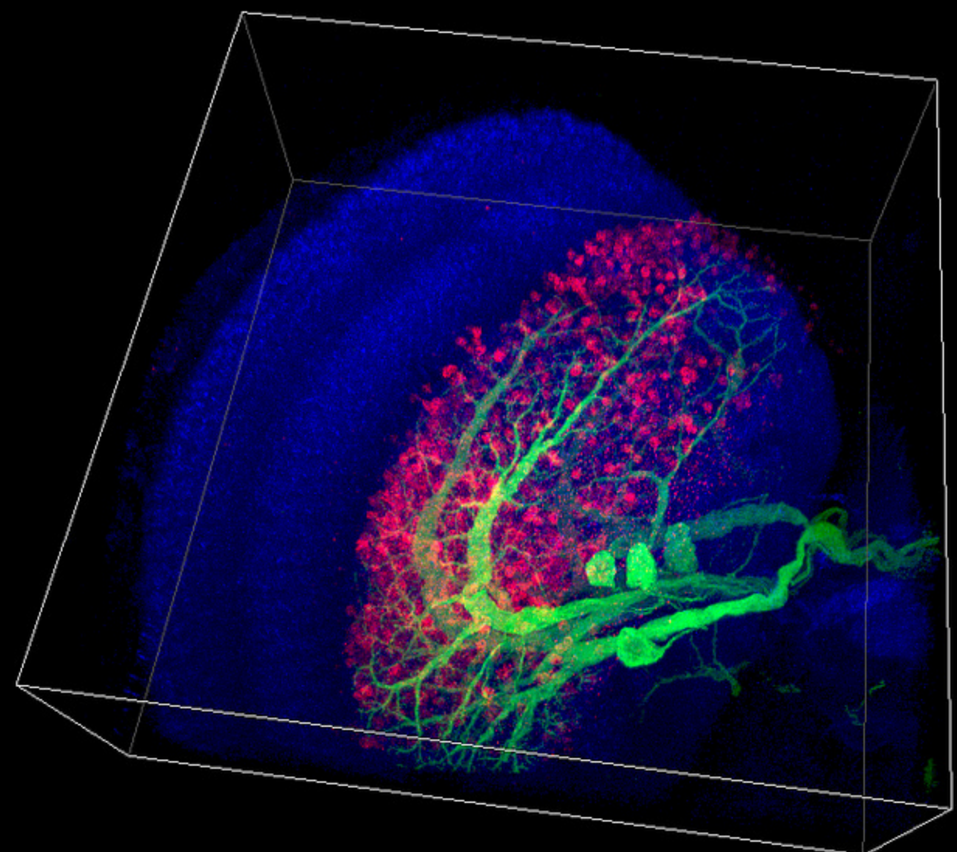
Thomas Hunt Morgan is credited for discovering the role of chromosomes in heredity.

He mentored these three intellectually gifted students:

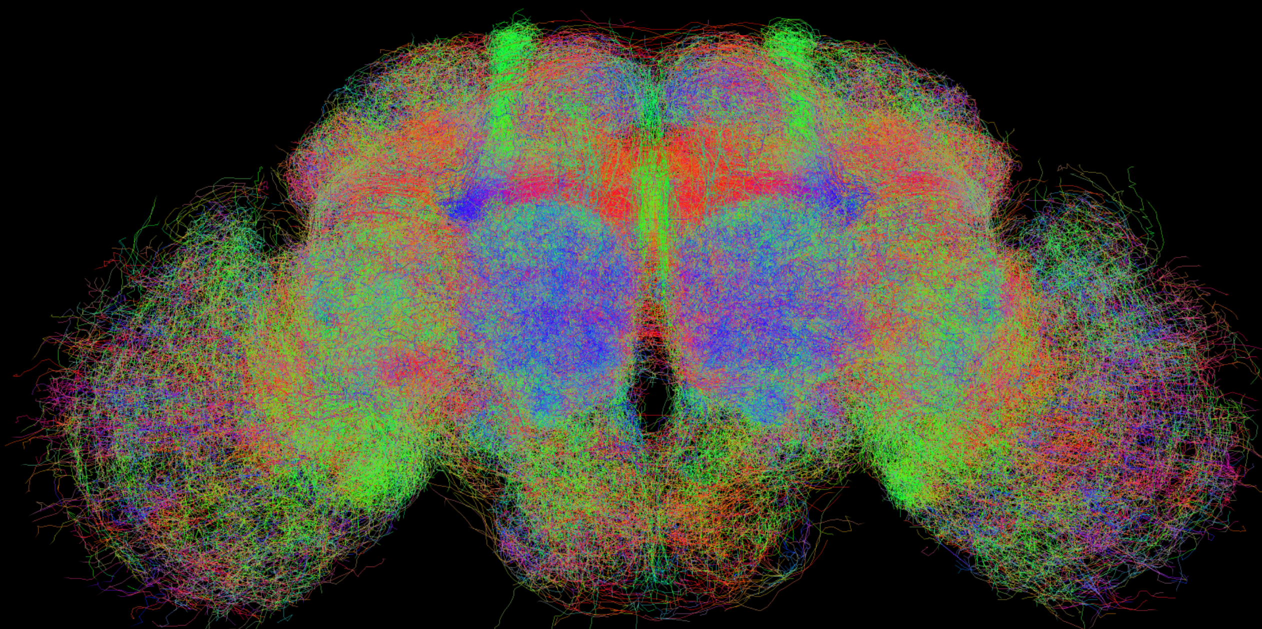
1. **Calvin Bridges**: improved techniques and equipment in *Drosophila* research
2. **Alfred Sturtevant**: principle of genetic mapping *(the frequency of crossing-over between two genes could help determine their proximity on a linear genetic map)*
3. **Hermann Muller**: discovered the production of mutations by X-ray irradiation

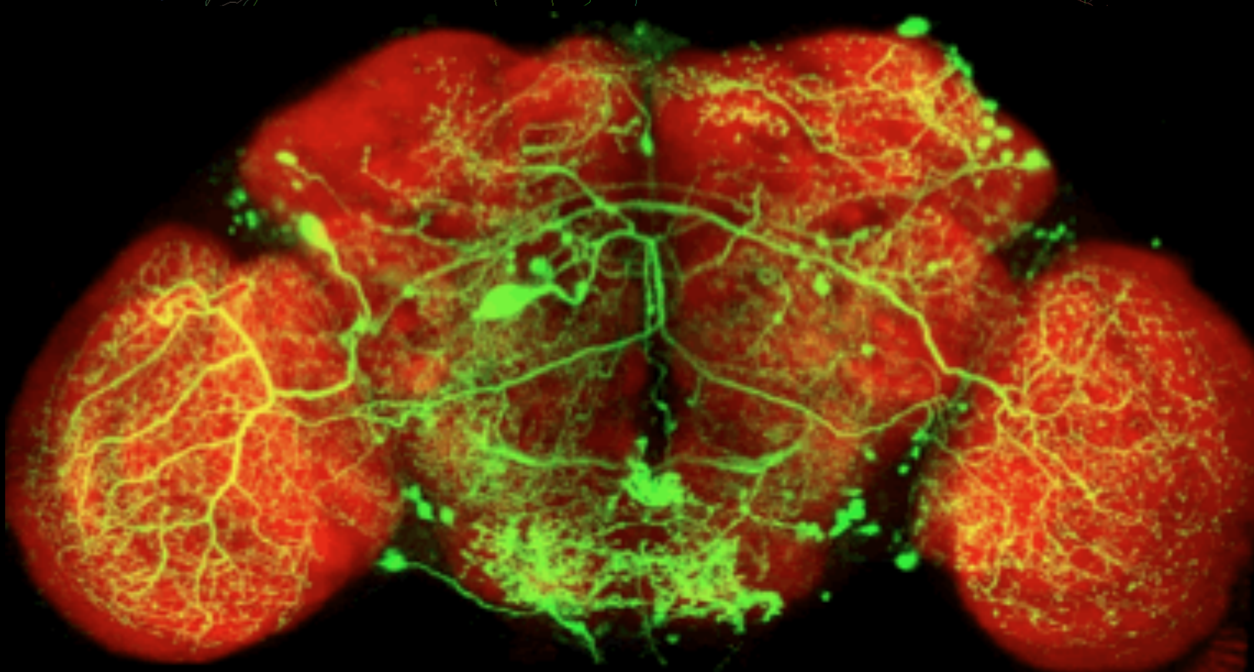
Drosophila Neural Circuits





Guest Lecture





Introduction to the Digital Fruit Fly Brain

Professor Aurel Lazar
Department of Electrical Engineering

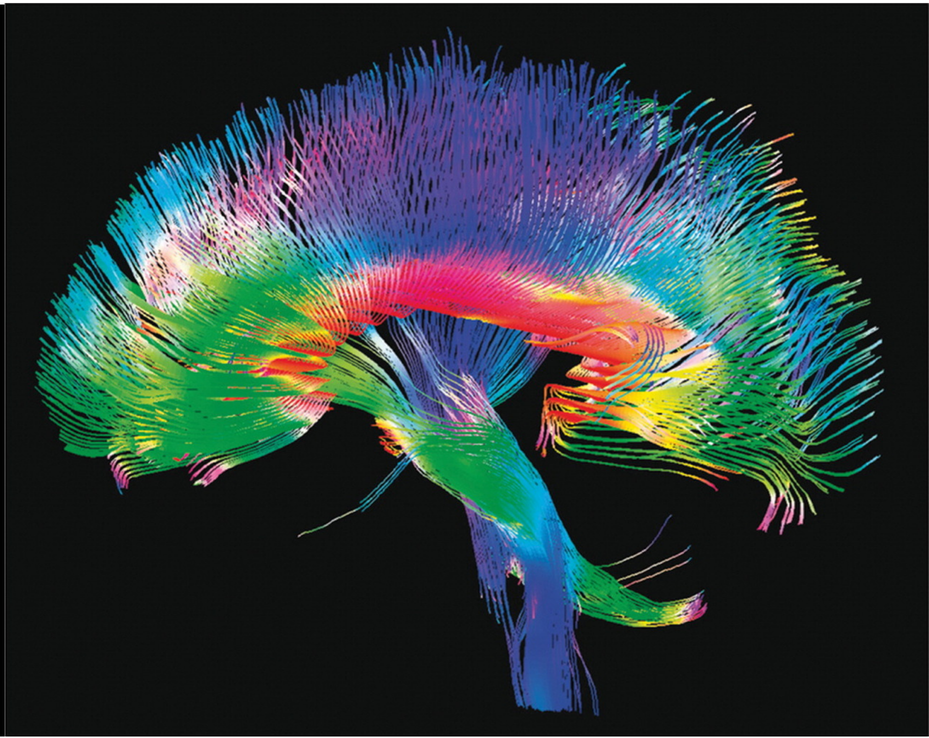
Columbia University
IN THE CITY OF NEW YORK

Connectomics

Comprehensive maps of connections within an organism’s nervous system is called the **connectome**.

The field of science that deals with the assembly, mapping and analysis of data on neural connections is called **connectomics**.

This term was first suggested in 2005 by Dr. Olaf Sporns and Dr. Patric Hagmann.

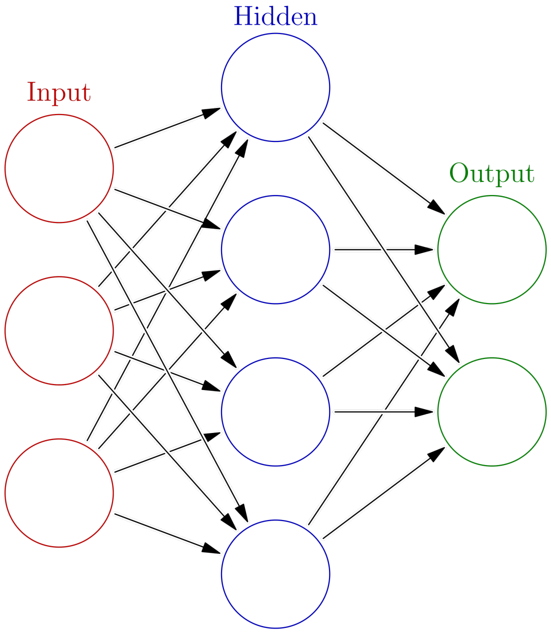


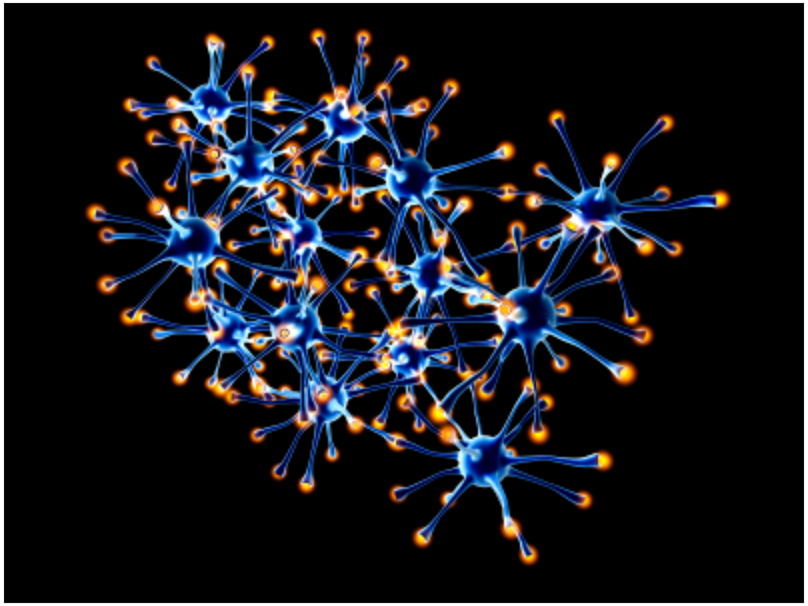
Structural connectivity as a basis for function

The function of a neural network is critically dependent upon its interconnections.

A lot of effort and time has gone into understanding the structure and function of neural networks. We currently do not have a full map of the network connectivity of the brain of any species.

The only notable exception to this is the nematode *C. elegans.*





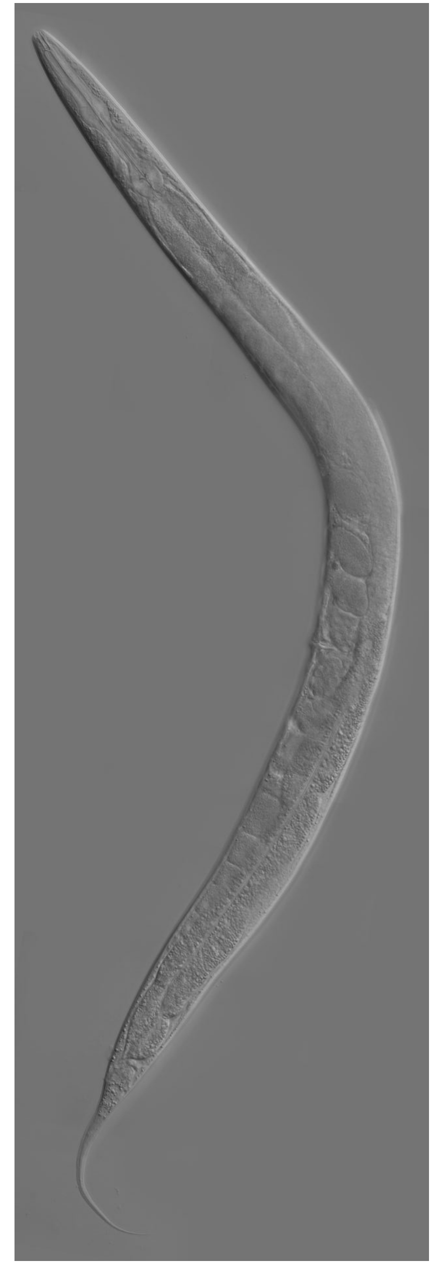
C. elegans

Caenorhabditis elegans (*C. elegans)* is a transparent nematode commonly used in neuroscience research.

They have a simple nervous system: 302 neurons and 7000 synapses.

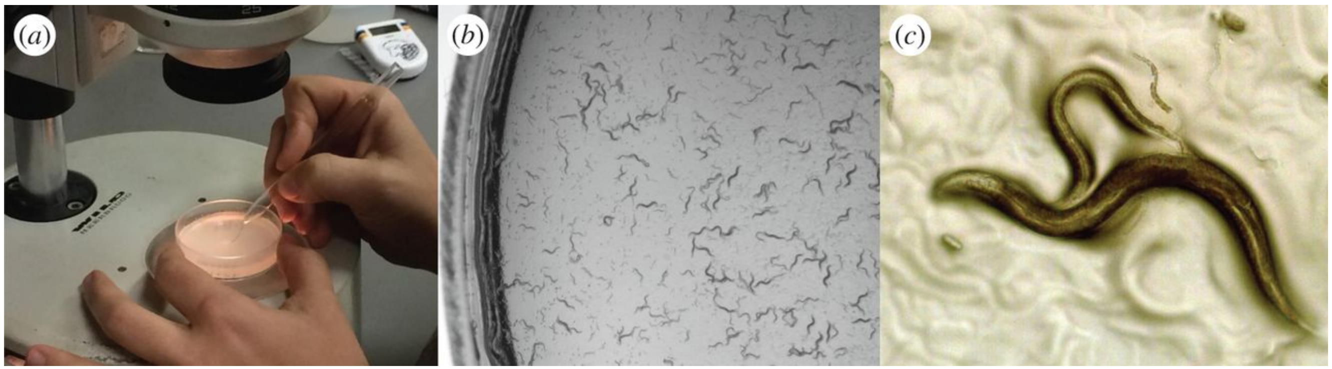
Advantages of using *C. elegans* in research:

- Acts as a model for neuronal development and function
- Powerful genetic studies can be conducted
- Small
- Completely sequenced genome
- Can be frozen and preserved
- Invariant cell lineage



History of the *C. elegans* connectome

In the 1970s, Sydney Brenner and his colleagues began preserving *C. elegans* in agar and osmium fixative, sliced up their bodies and imaged the cells using an electron microscope.



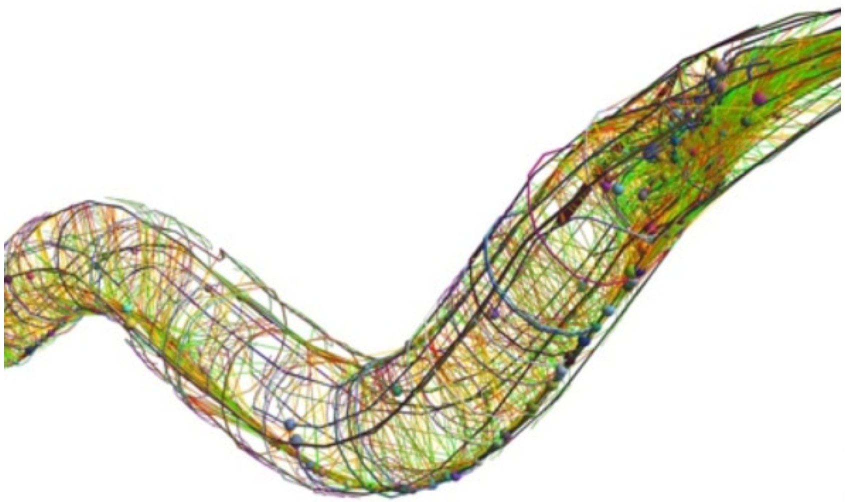
Sydney Brenner

In 1986, they published a near complete draft of the wiring diagram of the *C. elegans* nervous system.

More than 20 years later, Dmitri Chklovskii at Janelia Farm Research Campus published a more comprehensive version.

Dmitri Chklovskii

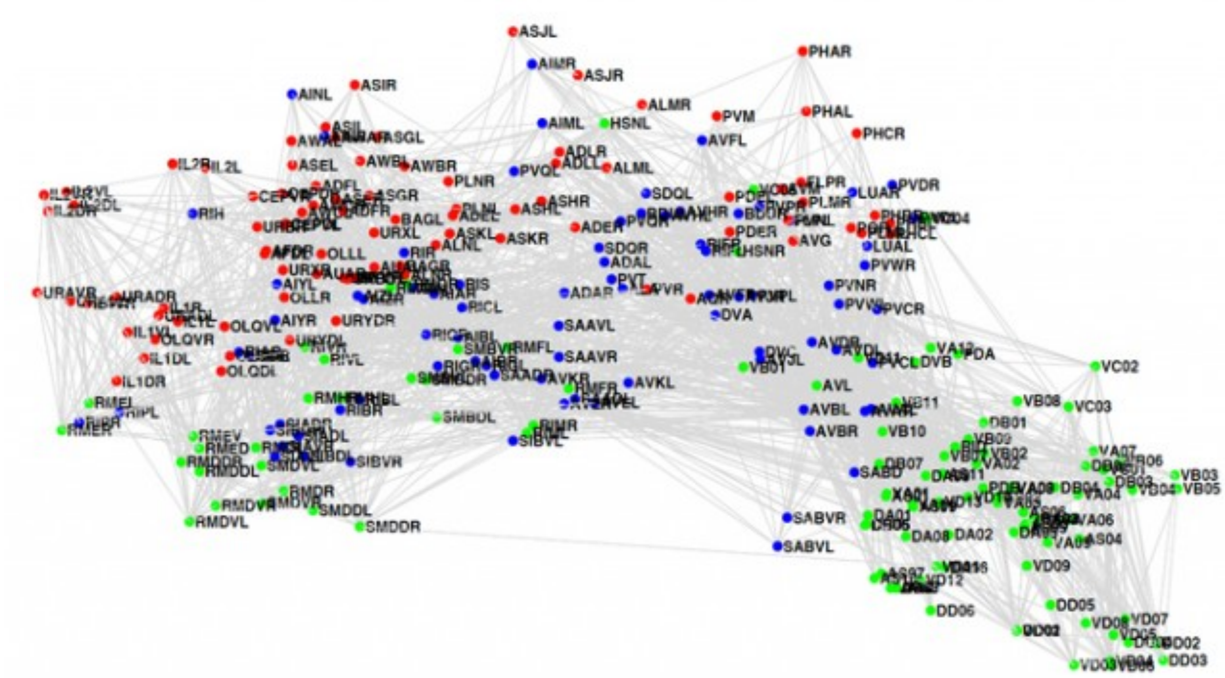
The *C. elegans* connectome



Obtaining this connectome was tedious:

- Took dozen years of man power
- Every neuron was individually identified, its precise location determined, and its projections to other neurons traced
- All of this was done by hand

Was it worth it?



The debate over connectomics

C. Elegans is the only organism with a complete connectome.

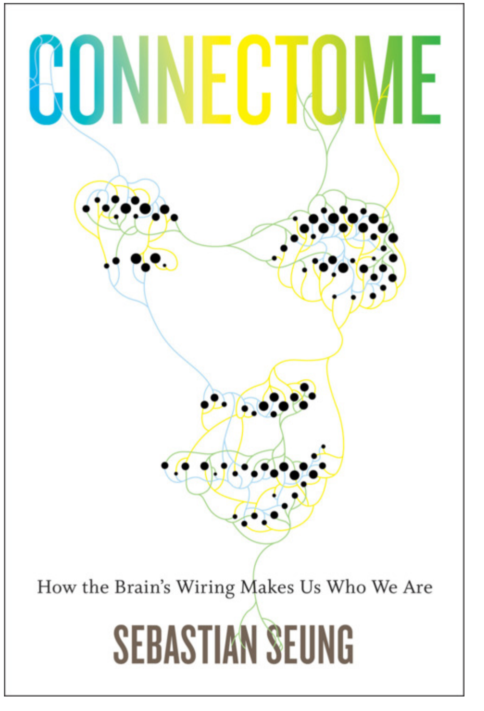
Researchers are working on connectomes for the fruit fly and the mouse.

Some neuroscientists want to create a connectome for the entire human brain.

Arguably, the most famous proponent for connectomics is Sebastian Seung (MIT).

He's a computational neuroscientist who wants to do a similar experiment to Sydney Brenner's but will use advanced imaging and AI to handle the huge amount of data a mouse brain will generate.

Sebastian Seung



Sebastian Seung: I am my connectome (TEDGlobal 2010)

Watch the full video here: http://www.ted.com/talks/sebastian_seung?
utm_source=tedcomshare&utm_medium=referral&utm_campaign=tedspread

The debate over connectomics

Other neuroscientists think that connectomics at such a large scale (human brain: 86 billion neurons and 100 trillion synapses) is not a good use of neuroscience resources.

They think that it would take too long and we wouldn't know how to interpret it.

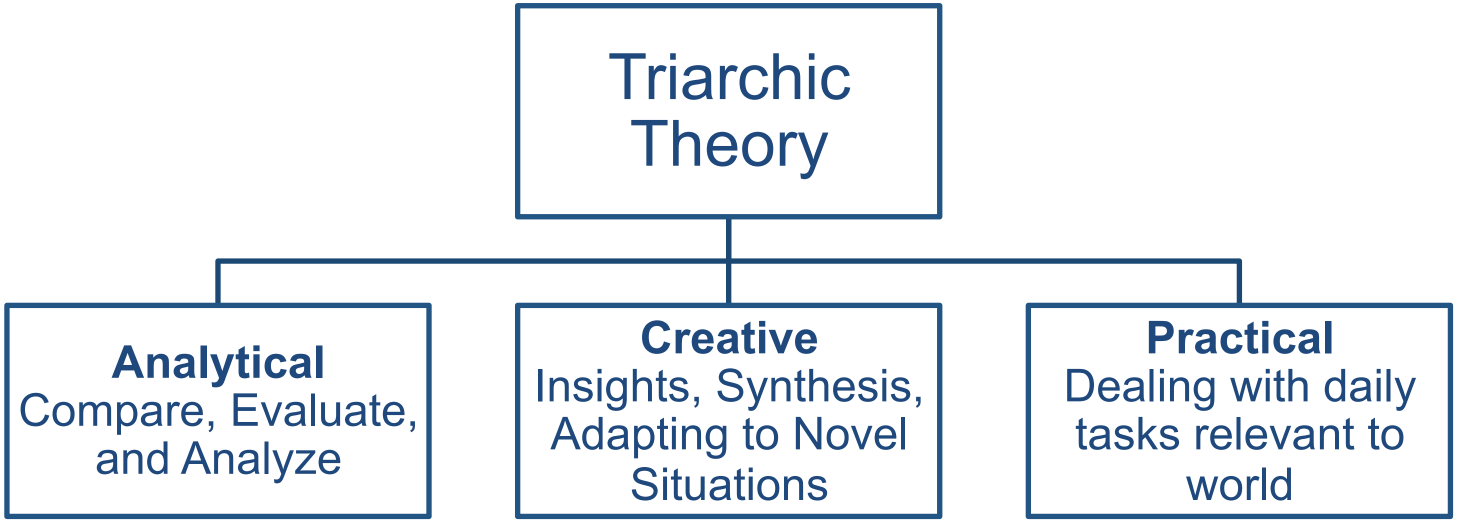
Some people don't think the *C. elegans* connectome has provided many insights into worm's behavior.

A connectome does not reveal how neurons behave in real time and does not reveal how neurons regulate one another's behavior.

"It's like a road map that tells you where cars can drive, but does not tell you when or where cars are actually driving." – Oliver Hobert, Columbia University

So, do you think connectome research is worth funding?

Intelligent Behavior



According to Sternberg, the above three abilities work together to create intelligence behavior. Other ideas include:

- Intelligence is not fixed but develops over time.
- Intelligence means to adapt by using your strengths in addition to improving your weaknesses.
- Intelligence involves more than adapting to one's environment. It also involves modifying the environment.

On Intelligence

Intelligence: [1]capacity to learn and solve problems
[2]ability to adapt to different contexts

Nature, Nurture, or Both?

Is intelligence genetic? Acquired? A combination of both?

Fluid Intelligence: ability to reason and use information *(peaks in 20s)*

Crystallized Intelligence: acquired skill and learned knowledge *(continues to increase into old age)*

Emotional Intelligence: capacity to reason about emotions *(to assess and generate emotions so as to assist thought)*

Social Intelligence: knowledge of social matters and insight into traits of others

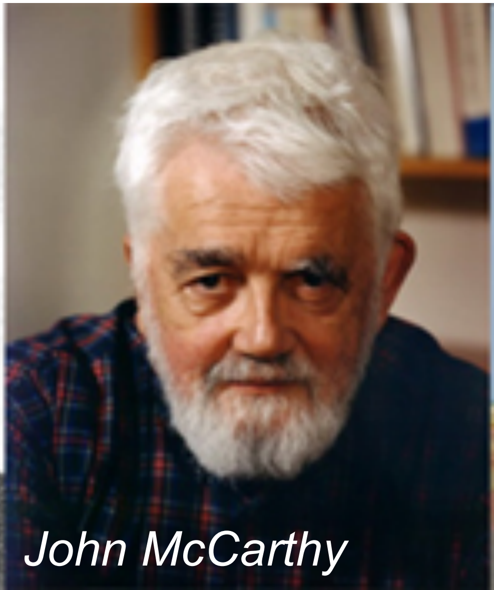
Artificial Intelligence: "*the computational part of the ability to achieve goals in the world*" *(John McCarthy, Stanford)*

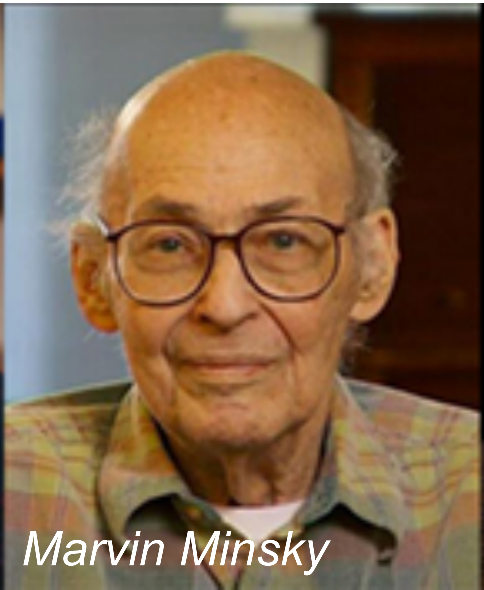
iWonder: Artificial Intelligence

Artificial Intelligence has four perspectives that can be represented by two dimensions:

1. Thinking v. Acting
2. Human v. Rational

	Human-Like Intelligence	Ideal Intelligence/ Pure Rationality
Thought	**2. Thinking Humanly**	**3. Thinking Rationally**
Behavior	**1. Acting Humanly**	**4. Acting Rationally**



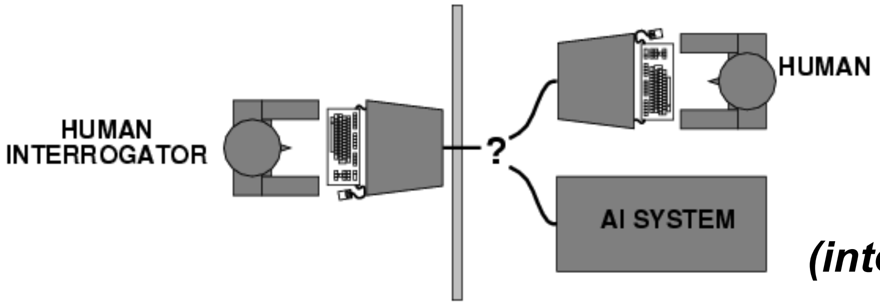


1. Acting Humanly: Turing Test

	Human-Like Intelligence	Ideal Intelligence/ Pure Rationality
Thought	2. Thinking Humanly	3. Thinking Rationally
Behavior	**1. Acting Humanly**	4. Acting Rationally

"Can machines think? Can machines behave intelligently?"

Operational Test for Intelligent Behavior: The Imitation Game



AI system passes if interrogator cannot tell which one is the machine.

(interaction via written questions)

No computer vision or robotics or physical presence required!

In 1950, Alan Turing predicted that a machine may have a 30% chance of fooling a lay person for 5 minutes by 2000.

This was achieved by Siri (Apple).

However, we have not truly passed the Turing test. Even if we did, how useful is it? *Deception appears **required** and **allowed**.*

2. Thinking Humanly: Modeling Cognition

	Human-Like Intelligence	Ideal Intelligence/ Pure Rationality
Thought	**2. Thinking Humanly**	3. Thinking Rationally
Behavior	1. Acting Humanly	4. Acting Rationally

Requires scientific theories of ***internal activities of the brain***

1. **Cognitive Science (Top-Down)** computer models based on experimental techniques in psychology

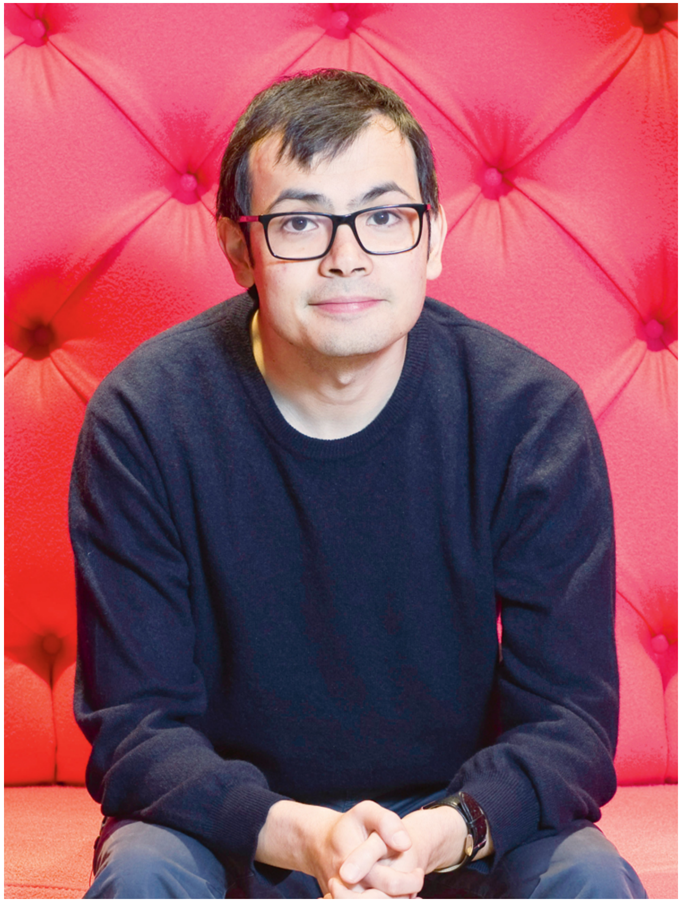
   i.e. predicting and testing behavior of human subjects

2. **Cognitive Neuroscience (Bottom-Up)** direct identification from neurological data

   i.e. neural networks and deep learning

Is the brain a good model for machine intelligence?

Demis Hassabis: Model the Brain's Algorithms



Natural v. Artificial Intelligence

Idea: Brain structure can inspire new computer algorithms and architectures.

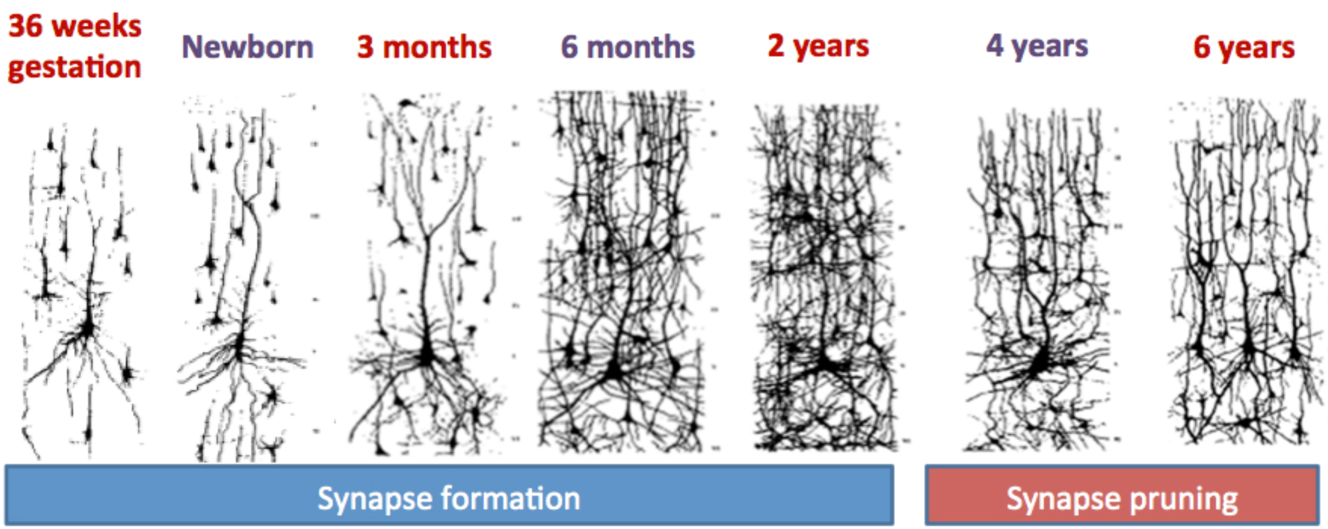
- *grid cells for navigation*
- *hierarchical cell layers for vision processing*

To advance AI:

- *What representations and processes does the brain use to portray the world around us?*
- *How is conceptual knowledge acquired?*
- *What is consciousness?*
- *What are dreams?*

> *"We're building systems that are able to reconfigure themselves in new ways that we haven't preprogrammed. I don't know if you'd call that writing itself. It's more like how the brain works."*

Brain-Based Algorithms: Hierarchy



When the brain reaches adulthood, it has 50-60% less synaptic connections that it had at its peak in childhood.
Note how computer networks are distinct.

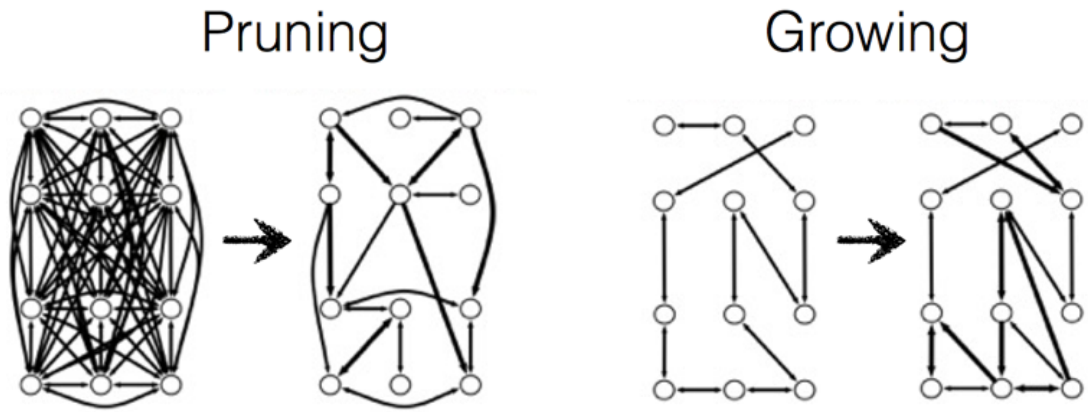
Hierarchy evolves not because it produces more efficient networks, but instead because hierarchically wired networks have fewer connections.

- Connections in biological networks are costly:
  need to be built, housed, maintained
- For the same reason, human-made systems such as the Internet and road systems are also hierarchical.

In addition to hierarchy, important design principles include:

- **Regularity:** decomposition of a large system into simple units
- **Modularity:** each unit can be designed independently of each other

Brain-Based Algorithms



"Engineered networks are built by adding connections rather than removing them. You would think that developing a network using a pruning process would be wasteful. However, this can prove beneficial." Ziv Bar-Joseph, CMU

When it comes to developing efficient, robust networks, the brain may often know best. Why is network topology important?

Biology: structure is to function

Computer Science: production of efficient interconnected systems

What are the advantages of a brain-based algorithm created with pruning?

- Direct flow information
- Multiple paths for information to reach same endpoint

minimizes risk of network failure

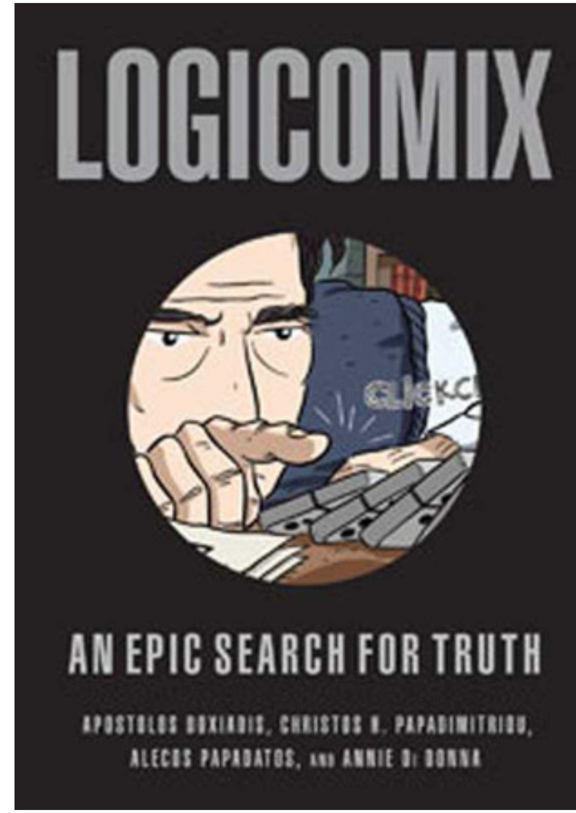
Deep learning is bring perception (hearing and vision) within reach.

SALK INSTITUTE

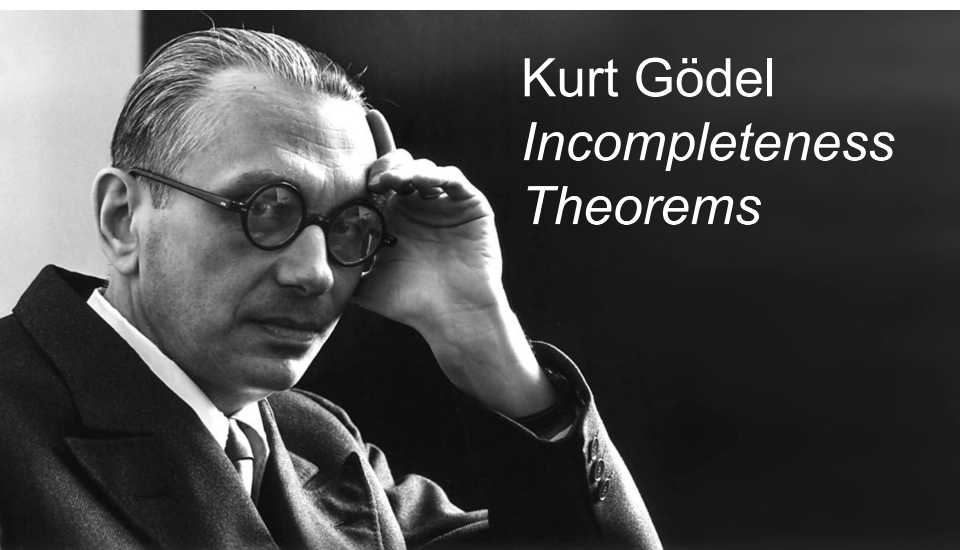
Carnegie Mellon University

3. Thinking Rationally: Laws of Thought

	Human-Like Intelligence	Ideal Intelligence/ Pure Rationality
Thought	2. Thinking Humanly	**3. Thinking Rationally**
Behavior	1. Acting Humanly	4. Acting Rationally



Greek schools have developed various forms of ***logic:*** *notation and rules of derivation for thought*
Idea: Inference derives new information from stored facts.



No **formal system extending basic arithmetic** can be used to prove its own consistency.
Idea: Knowing a computer model does not imply absolute control over the results. There is uncertainty.

On Rationality

"The arithmetic seems correct yet I find myself haunted by the idea that the basic axioms on which the arithmetic is based might give rise to contradictions which would then invalidate these computations."

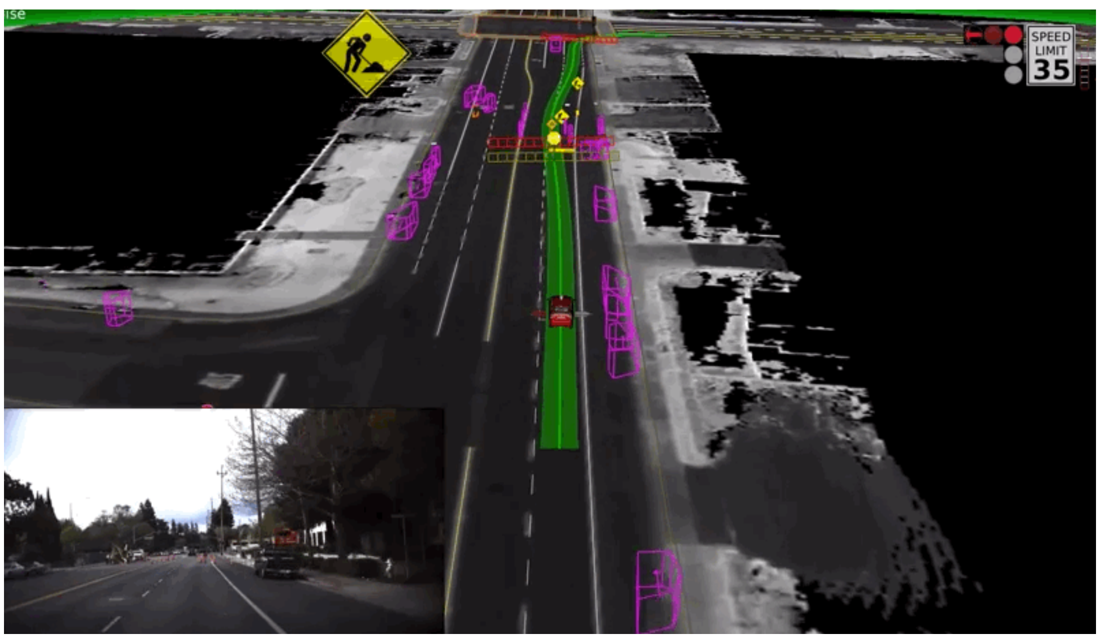
Limitations of logic include:

- Intelligent behavior is often not mediated by logical deliberation
- Logical representations of intelligence are non-trivial *(Bayesian networks and graphical models)*
- Seems to require some connection to "acting in the world" *(We feel the need and desire to affect our environment)*

4. Acting Rationally: Rational Agents

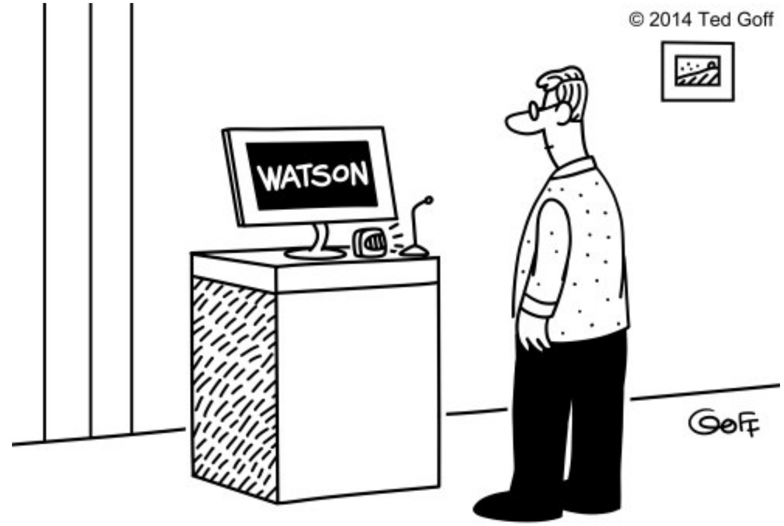
	Human-Like Intelligence	Ideal Intelligence/ Pure Rationality
Thought	2. Thinking Humanly	3. Thinking Rationally
Behavior	1. Acting Humanly	**4. Acting Rationally**

An **agent** is an entity that *perceives and acts in the world.*
i.e. an autonomous system
Example: Self-Driving Car by Google

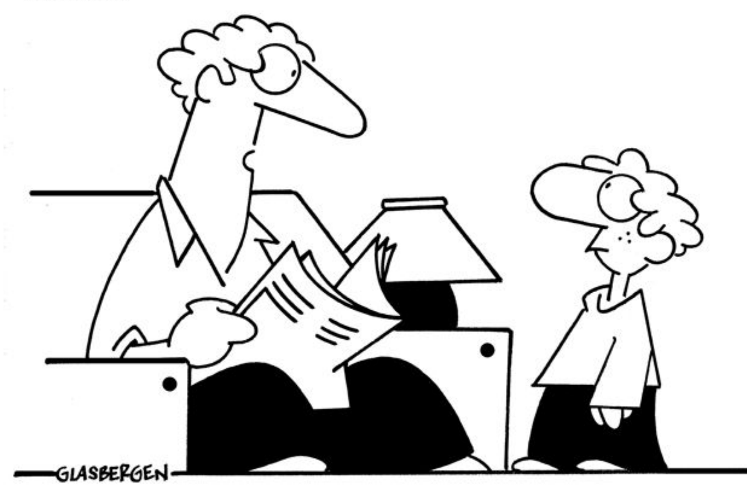


Caveat: Computational limitations may make perfect rationality unachievable.

Building Intelligent Agents



"Go ahead and think that I'm not really thinking. I thought you would think that."



"Artificial intelligence is when you get a college degree, but you're still stupid when you graduate."

I. Building exact models of human cognition
II. Developing methods to match or exceed human performance in certain domains, possibly by very different means.

Artificial intelligence focuses on the latter using neural networks.

Artificial Intelligence Research

Problem solving, planning, and search:
Generic problem solving architecture based on ideas from cognitive science

Knowledge Representation:
To store and manipulate information (logic)

Automated reasoning/ Inference:
To use stored information to answer questions and draw new conclusions

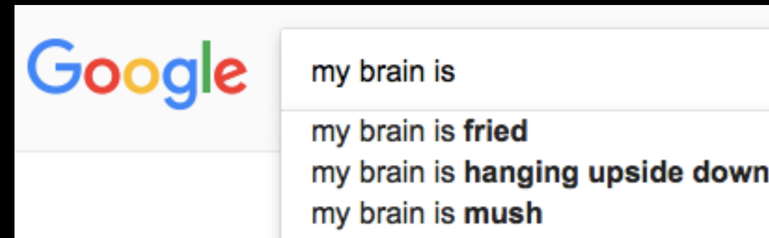
Machine Learning:
Intelligence from data; to adapt to new circumstances and to detect and extrapolate patterns

Natural Language Processing:
To communicate with the machine

Computer Vision:
Processing visual information

Robotics:
Autonomy, manipulate, full integration of AI capabilities

The Age of the Brain: Obama's BRAIN Initiative

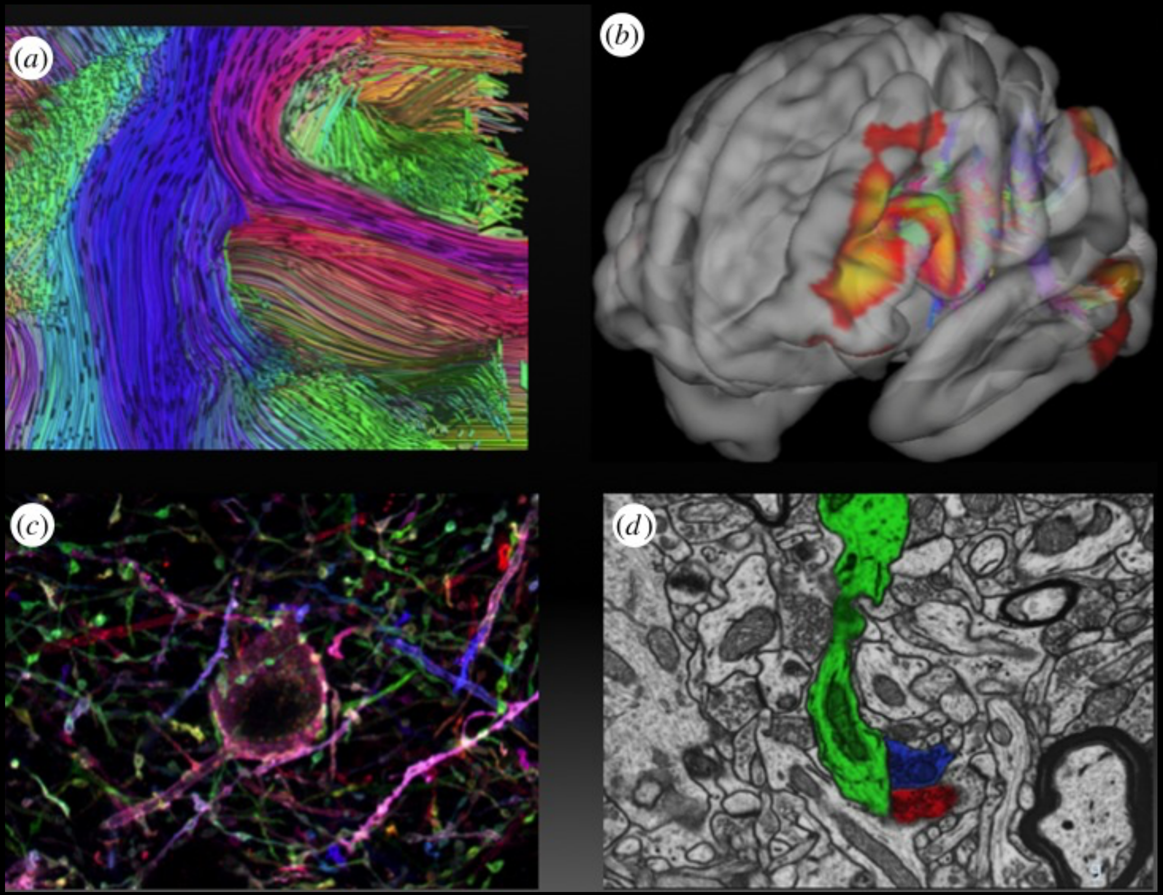


Public:
DARPA: 50 million
NIH: 40 million
NSF: 20 million

Private:
The Allen Brain Institute: 60 million
HHMI: 30 million
Salk Institute: 28 million
Kavli Foundation: 4 million

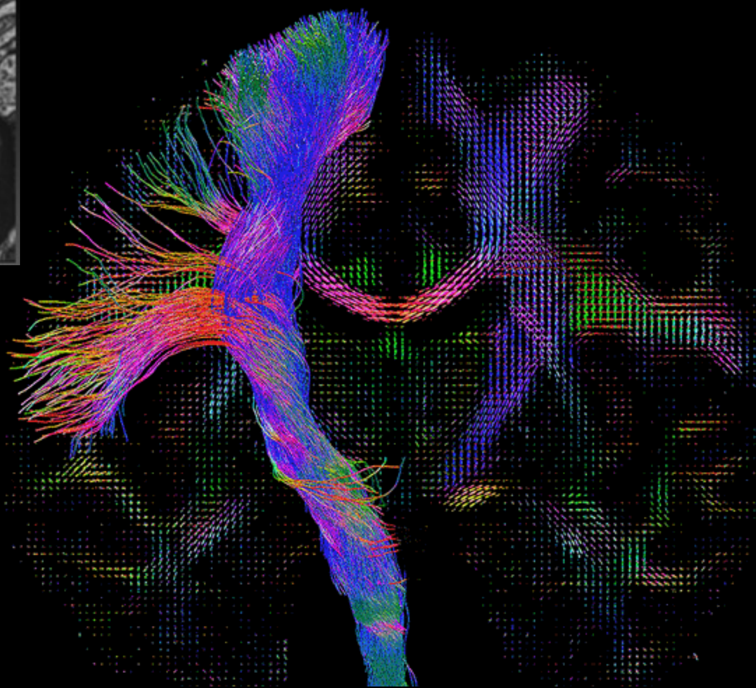
1. Generate a census of cell types
2. Create structural maps of the brain
3. Develop new large-scale network recording capabilities
4. Develop a suite of tools for circuit manipulation
5. Link neuronal activity to behavior
6. Integrate theory, modeling, statistics, and computation with experimentation
7. Delineate mechanisms underlying human imaging technologies
8. Create mechanisms to enable collection of human data
9. Disseminate data and training

The Age of the Brain: Obama's BRAIN Initiative



On left: Spatial scales of structural analysis

(a) Macro-connectomics
(b) fMRI
(c) Meso-connectomics
(d) Dense electron microscopic reconstructions



On right: One side of the cortico-spinal tract (the pathway responsible for voluntary movement) connecting the brain to the spinal cord, superimposed onto ***Fiber Orientation Distributions (FODs)***

Allen Institute for Brain Science

Seattle-based private, non-profit medical research organization.

“Our mission is to accelerate the understanding of how the human brain works in health and disease. Using a big science approach, we generate useful public resources, drive technological and analytical advances, and discover fundamental brain properties through integration of experiments, modeling and theory.”

Their vision:

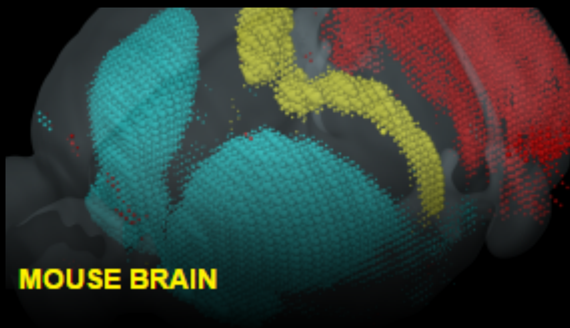
- Deciphering how information is coded and processed in the brain
- Unraveling the codes within cells that govern their identity and function
- Characterizing and cataloguing the wide variety of cells that constitute the brain

ALLEN INSTITUTE *for*
BRAIN SCIENCE

Allen Brain Atlas

Several online public resources exploring the nervous system.

ALLEN BRAIN ATLAS
DATA PORTAL



Mouse Brain Atlas: 3D map of gene expression in the mouse brain, including more than 21,000 genes at the cellular level

ALLEN SPINAL CORD ATLAS

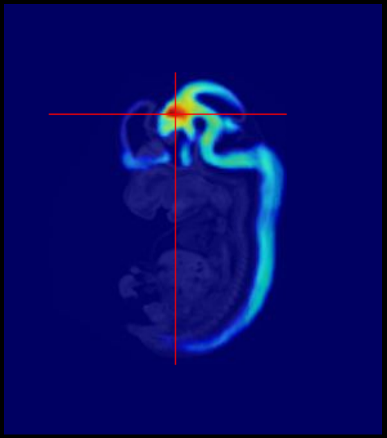
Spinal Cord Atlas: genome-wide map showing where each gene is expressed in the mouse spinal cord.

Interesting fact: this atlas helped researchers at UBC discover a new class of cells in the spinal cord that behave like stem cells!

Allen Brain Atlas

Several online public resources exploring the nervous system.

ALLEN BRAIN ATLAS
DATA PORTAL



<u>Developing Mouse Brain Atlas</u>: highly detailed map of gene activity in the mouse brain, at different points across development.

<u>Human Brain Atlas</u>: highly comprehensive atlas integrates many types of data (MRI, DTI, histology and gene expression data). One of the newest projects – had a feature in *Nature* in 2012.

What does some of the automation look like?

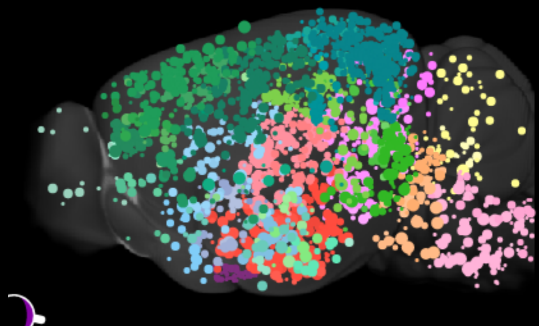
ALLEN HUMAN BRAIN
REFERENCE ATLAS

Allen Brain Atlas

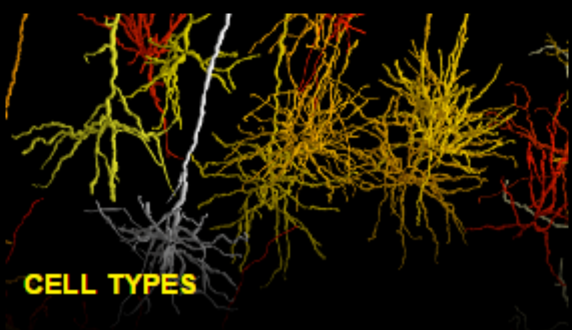
Several online public resources exploring the nervous system.

ALLEN BRAIN ATLAS

DATA PORTAL



Mouse Brain Connectivity Atlas: first transition from gene expression to neural circuitry. It is a 3D, high resolution map of neural connections in the mouse brain (connectomics!).



Cell Type Database: useful for scientists wanting to observe, measure and sort cells into types (kind of like the periodic table sorting chemical elements). First release of data had > 240 cells in the mouse brain.

Allen Brain Atlas

Several online public resources exploring the nervous system.

ALLEN BRAIN ATLAS
DATA PORTAL

NIH Blueprint NHP Atlas

Non-Human Primate (NHP) Atlas: contains information about gene expression, neuroanatomical data and informatics tools for the developing rhesus macaque monkey brain.

AGING, DEMENTIA and TBI STUDY

Aging, Dementia and Traumatic Brain Injury Study: detailed neuropathologic, molecular and trascriptomic characterization of brain in control and traumatic brain injury patients.

Bonus slide: what would it be like to work in a place like this?

(while it doesn't seem like you can intern here as a college student, take a look at the Janelia Farm Undergraduate Scholars program if you're interested in working at a private neuroscience research institute during the summer!)

Next Time

Computational Models of Psychiatric Disorders

On right: Three stages of a seizure

Guest Lecture by
Evan Schaffer and Sean Escola

Final Class of Fall Semester: