CS 4884: Computing the Brain
Computational Biology and Bioinformatics Capstone Course

T. M. Murali

January 18 and 20, 2022
This course is NOT about neural networks or deep learning.
Course Information

- Meet on Tuesdays and Thursdays, 2pm–3:15pm, MCB 110A.
- Office hours: by appointment and during class times in second half of semester.
- Course website: http://bioinformatics.cs.vt.edu/~murali/teaching/2022-spring-cs4884/. Consult this website regularly. Course schedule is subject to change.
Fundamentals of Brain Network Analysis
Alex Fornito, Andrew Zalesky, and Edward Bullmore

Fundamentals of Brain Network Analysis is a comprehensive and accessible introduction to methods for unraveling the extraordinary complexity of neuronal connectivity. From the perspective of graph theory and network science, this book introduces, motivates, and explains techniques for modeling brain networks as graphs of nodes connected by edges, and covers a diverse array of measures for quantifying their topological and spatial organization. It builds intuition for key concepts and methods by demonstrating how they can be practically applied across many different areas of neuroscience, ranging from the analysis of synaptic networks in the nematode worm to the characterization of large-scale human brain networks constructed with magnetic resonance imaging. This text is ideally suited to neuroscientists wanting to develop expertise in the rapidly developing field of neural connectomics, and to physical and computational scientists wanting to understand how these quantitative methods can be used to understand brain organization.

Key Features:
- Extensively illustrated throughout by graphical representations of key mathematical concepts and their practical applications to analyses of nervous systems
- Comprehensively covers graph theoretical analyses of structural and functional brain networks, from microscopic to macroscopic scales, using examples based on a wide variety of experimental methods in neuroscience
- Designed to inform and empower scientists at all levels of experience, and from any specialist background, wanting to use modern methods of network science to understand the organization of the brain

From the Foreword:
"This much needed primer on brain networks will become an indispensable addition to the bookshelves of all neuroscientists interested in the organization and function of nervous systems, from cellular to systems scales.

— Olaf Sporns, PhD, Distinguished Professor, Robert H. Shaffer Chair, Indiana University"
Course Pre-requisite
Course Pre-requisite
Course Pre-requisite

MY BRAIN IS OPEN

The Mathematical Journeys of

BRUCE SCHECHTER

T. M. Murali

January 18 and 20, 2022

Computing the Brain
Course Pre-requisite

MY BRAIN IS OPEN

The Mathematical Journeys of Paul Erdős

Bruce Schechter
Course Structure

- Lectures based on the textbook
Course Structure

- Lectures based on the textbook
- Assignments (2–3)
Course Structure

- Lectures based on the textbook
- Assignments (2–3)
- Final project
Course Structure

- Lectures based on the textbook
- Assignments (2–3)
- Final project
- Participation in VTURCS Research Symposium in late April.
Grading

- Assignments: 40%
- Final project: 60%
Assignments

- Typically, I will ask you to write code to replicate analysis in one or two figures in a research paper.
- These assignments may organically come about from class discussions.
- You will have about two weeks to complete assignments.
- What do you turn in?
  - Fully working code, e.g., on GitHub.
  - A short report on the results of your analysis, including the figures, discussion of difficulties you faced, how you solved them, and observations on your results.
Goals of the Course

Learn computational methods that use network/graph theory to understand the brain at three levels:

Anatomical

Cellular

Molecular

to gain insights into brain functions in health and disease.
History of the Brain: Pre-History

- Trepanation (6500 BC, Incas, Peru): drilling holes in the skull to expose *dura mater* (outermost layer of the meninges) to treat health problems.
History of the Brain: Pre-History

- Trepanation (6500 BC, Incas, Peru): drilling holes in the skull to expose *dura mater* (outermost layer of the meninges) to treat health problems.

- Egypt (c. 3000 BC): Aware of symptoms of brain damage, but considered the heart to the repository of memories.
Trepanation (6500 BC, Incas, Peru): drilling holes in the skull to expose *dura mater* (outermost layer of the meninges) to treat health problems.

Egypt (c. 3000 BC): Aware of symptoms of brain damage, but considered the heart to the repository of memories.

India (c. 400 BC): Charaka described symptoms and treatments of epilepsy.
Ancient Greece

- Study of the brain was not based on dissection.
- Hippocrates (460–379 BC): Brain is the organ of sensation and intelligence.
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- Aristotle (384–322 BC): Heart is the center of intellect.
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The birth and evolution of neuroscience through cadaveric dissection, Moon K1, Filis AK, Cohen AR. Neurosurgery. 2010 Sep;67(3):799–809
Ancient Greece

- Study of the brain was not based on dissection.
- Hippocrates (460–379 BC): Brain is the organ of sensation and intelligence.
- Aristotle (384–322 BC): Heart is the center of intellect. Brain is a radiator for cooling blood. Larger brains ⇒ humans are more rational.
- Herophilus (c. 325–255 BC):
  - Father of neuroanatomy, first dissector in the Western tradition.
  - Discovered ventricles, distinguished between cerebrum and cerebellum.

*The birth and evolution of neuroscience through cadaveric dissection, Moon K1, Filis AK, Cohen AR. Neurosurgery. 2010 Sep;67(3):799–809*
Galen (130–200 AD)

- Theories dominated Western and Byzantine medicine till the 16th century.
- Used animal dissections.
- Structure-Function: cerebellum (hard) receives sensations and cerebrum (soft) stores memories.
- The brain is the location of the mind.
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- Theories dominated Western and Byzantine medicine till the 16th century.
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- Structure-Function: cerebellum (hard) receives sensations and cerebrum (soft) stores memories.
- The brain is the location of the mind.
- Brain controls senses and motor functions by movement of fluids to and from ventricles through nerves (which are hollow, cf. arteries).
The Next 1300 Years

- Dark Ages in Europe.
- Arabs copied Galen’s text among others.
- Islamic surgeon Abu al-Qasim al-Zahrawi (1000 AD) described several treatments for neurological disorders.
Renaissance (14th–16th Centuries)

- Increased recognition of need for dissection to acquire new knowledge about the body’s internal organs.
- Printing press (1439 AD) circulated Galen’s works.
- Renaissance and Reformation of the Church promoted fresh thinking.
- Dissection resulted in detailed anatomical drawings.
Leonardo da Vinci (1452–1519)
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Leonardo da Vinci (1452–1519)
Andreas Vesalius (1514–1564)

- Used skillful dissection of cadavers.
Andreas Vesalius (1514–1564)

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- *De humani corporis fabrica*: Documented and corrected 200 errors by Galen.
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Contemporaries and Descendants of Vesalius

Mathematics Genealogy Project

Gemma (Jemme Reinerszoon) Frisius

<table>
<thead>
<tr>
<th>Name</th>
<th>School</th>
<th>Year</th>
<th>Descendants</th>
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<tbody>
<tr>
<td>John Dee</td>
<td>University of Cambridge and</td>
<td>1546</td>
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<td></td>
<td>Université Catholique de Louvain</td>
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<td>Gerardus Mercator</td>
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<td>Johannes Stadius</td>
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<td>Università degli Studi di Padova and Université Catholique de Louvain</td>
<td>1537</td>
<td>105089</td>
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</table>

According to our current on-line database, Gemma Frisius has 4 students and 105096 descendants. We welcome any additional information.
Gerardus Mercator
Gerardus Mercator
**White Matter and Grey Matter (17th–18th centuries)**

**White matter**  Generic term for “stuff” that appears white in freshly dissected brain.

**Grey matter**  Generic term for “stuff” that appears grey in a freshly dissected brain.
White Matter and Grey Matter (17th–18th centuries)

**White matter**  Generic term for “stuff” that appears white in freshly dissected brain.

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He [Hercule Poirot] tapped his forehead. 'These little grey cells. It is 'up to them.'

(Agatha Christie)
Broca’s area (1861): production of speech and language
Structure to Function

- Broca’s area (1861): production of speech and language
Structure to Function

- Broca’s area (1861): production of speech and language
- Wernicke’s area (1874): comprehension of spoken and written word
Brodmann Areas (1909)

Based on the cytoarchitectural organization of neurons Brodmann observed in the cerebral cortex using Nissl staining.
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Based on the cytoarchitectural organization of neurons Brodmann observed in the cerebral cortex using Nissl staining.
Left and Right Brains (1960s)

- If the two hemispheres of the brain are separated by severing the corpus callosum,
  - information transfer between the hemispheres ceases,
  - an individual has two functionally different brains.

Roger Sperry received the Nobel Prize in 1981.
"The great pleasure and feeling in my right brain is more than my left brain can find the words to tell you."
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- Right hemisphere: spatial comprehension, facial recognition, emotion.

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T. M. Murali January 18 and 20, 2022 Computing the Brain
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Two astonishingly different persons inhabit our heads

By Maya Pines

Two very different persons inhabit our heads, residing in the left and right hemispheres of our brains, the twin shells that cover the central brain stem. One of them is verbal, analytic, dominant. The other is artistic but mute, and still almost totally mysterious.

This nonspeaking side of the human brain—the right hemisphere—is now the focus of intensive research by brain scientists. This sudden surge of interest is probably no accident at a time when Yoga, Arica, Tibetan exercises and other nonverbal disciplines are enjoying such a vogue. Some re-

ample, those concerned with vision—to find their way through a tangle of other nerve fibers, even when obstacles are placed in their path, and somehow connect with the appropriate cells so as to reach specific terminals in the visual cortex. Next, he began to study visual perception and memory. He wanted to find out what happened when an animal learned certain discriminations that involved the visual cortex—when it learned, for instance, to push a panel marked with a circle rather than a square. Where in its brain was that knowledge stored?

He put the question to a young graduate student, suggesting that he investigate how cats that between a circle and a square, knowing that the information they acquired would go to only one hemisphere. When he switched their eye patches to cover their trained eyes, however, the cats performed just as well as before. Their memory of this skill was intact. This meant either that the knowledge was stored in the central brain stem, well below the twin hemispheres, or that the knowledge acquired by one hemisphere had somehow been transmitted to the other.

“Obviously the corpus callosum was the next thing to test,” recalls Dr. Myers. “But from the available evidence, cutting it would have no effect. If the surgery is properly done, the animals are
Left and Right Brains in Culture
Left and Right Brains in Culture

Are You More Right-Brained Or Left-Brained?

Research says it doesn't exist, but let's see where your personality falls.

Erin La Rosa
BuzzFeed Staff

Section A

Check off all that apply:

☐ 1. You're better with faces than names.
The idea that one side of the brain is dominant is a myth, researchers say.

Credit: Human brain image via Shutterstock
Parts of the Brain (Now)

The Brain: Structure and Function (Video, 13:55)
Automated Parcellation of the Human Brain

A multi-modal parcellation of human cerebral cortex


Affiliations | Contributions | Corresponding authors

Nature 536, 171–178 (11 August 2016) | doi:10.1038/nature18933
Received 12 November 2015 | Accepted 15 June 2016 | Published online 20 July 2016

Human brain mapped in unprecedented detail

Nearly 100 previously unidentified brain areas revealed by examination of the cerebral cortex.

Linda Geddes

20 July 2016

(Video, 2")
### Brain Structure to Graphs

Table 3
Matrix of connections in visual cortex

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</table>

This table is a connectivity matrix for interconnects between visual cortical areas in the macaque. Each row shows whether the area listed on the left sends axons to the areas listed along the top. Conversely, each column shows whether the area listed on the top receives inputs from the areas listed along the left. Large plus symbols (+) indicate a pathway that has been reported in 1 or more full-length manuscripts; small plus symbols indicate pathways identified only in abstracts or unpublished studies. Specific citations are listed in Table 5. Dot (.) indicates pathways explicitly tested and found to be absent. Blanks indicate pathways not carefully tested for. Question marks (?) denote pathways whose existence is uncertain owing to conflicting reports in the literature. "RR" and "NRT" indicate nonretinal pathways, i.e., connections absent in the indicated direction even though the reciprocal connection has been reported. Stacked boxes along the diagonal represent intrinsic circuitry that exists within each area, those not included among the pathways tabulated in the following table.

Brain Structure to Graphs

The small world of the cerebral cortex

Olaf Sporns, Jonathan D. Zwi

Review Article

Cite this article as:

Cells in the Brain (Late 19th and early 20th Century)

*Cell theory*: Cell is the fundamental unit of all living organisms (Video, 1:40")
Cells in the Brain (Late 19th and early 20th Century)

*Cell theory:* Cell is the fundamental unit of all living organisms (Video, 1:40")

- Brain is an exception: complex cell shapes, extensive branching, and dense packing.
Cells in the Brain (Late 19th and early 20th Century)

*Cell theory:* Cell is the fundamental unit of all living organisms  (Video, 1:40”)

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- How many neurons in the brain?
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- Cajal: catalogued many different types of nerve cells.
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Reticular Theory vs. Neuron Doctrine

- “Neuron” coined by Waldeyer in 1891.
- In 1896, Rudolph Albert von Kolliker coined the term “axon” to describe the long slender cables that transmit signals away from cell bodies.
- In 1889, William His used “dendrites” to name the thin branching fibers that ferry signals toward the cell body.
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**Neuron doctrine**  Nerve cells are discrete entities that communicate by specialised contacts (Cajal and Sherrington)
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- Both Golgi and Cajal received the Nobel prize in Physiology or Medicine in 1906.
Cells in the Brain

Ferris Jabr, Scientific American, May 14, 2012
Cells in the Brain

Types of Brain Cells (Video, 18:54")
Types of Neurons

- 100s of types of neurons, differentiated by structure, function, genetics ...
- neuromorpho.org: archive of digitally reconstructed neurons.

Welcome to NeuroLex, the Neuroscience Lexicon.
A dynamic lexicon of 34,533 neuroscience terms, including 754 neurons and 1303 parts of the nervous system supported by The Neuroscience Information Framework and the International Neuroinformatics Coordinating Facility
Types of Neurons

Princeton researchers crowdsource brain mapping with gamers, discover six new neuron types

Liz Fuller-Wright, Office of Communications
May 17, 2018 11 a.m.
White Matter and Grey Matter (17th–18th centuries)

**White matter** Generic term for “stuff” that appears white in freshly dissected brain.

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White matter  Generic term for “stuff” a collection of axons, which appear white in freshly dissected brain.

Grey matter  Generic term for “stuff” a collection of neuronal cell bodies, which appear grey in a freshly dissected brain.
Brain Structure to Graphs

- Diffusion tensor imaging.
- Tracking white matter (axon) bundles to connect voxels.
- Massive graphs: 15M nodes, 50M edges.
Research on largest network of cortical neurons to date published in Nature

Robust network of connections between neurons performing similar tasks shows fundamentals of how brain circuits are wired

March 28, 2016 | Download PDF

Even the simplest networks of neurons in the brain are composed of millions of connections, and examining these vast networks is critical to understanding how the brain works. An international team of researchers, led by R. Clay Reid, Wei Chung Allen Lee and Vincent Bonin from the Allen Institute for Brain Science, Harvard Medical School and Neuro-Electronics Research Flanders (NERF), respectively, has published the largest network to date of connections between neurons in the cortex, where high-level processing occurs, and have revealed several crucial elements of how networks in the brain are organized. The results are published this week in the journal Nature.

Cellular Communication: Neuron Firing

Neuron, YouTube, 11:20"
Otto Loewi (1873–1961)

- Galvani showed that electric stimulation of sciatic nerve causes muscles in frog legs to twitch (1780).
- How do nerves communicate with muscles: electricity or chemicals?

Later identified as acetylcholine, which had been discovered in 1914 by Sir Henry Dale. The first neurotransmitter. Loewi and Dale received the Nobel Prize in 1936.
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Neurotransmitters

(A) LIFE CYCLE OF NEUROTRANSMITTER

1. Neurotransmitter is synthesized in cell body or in terminal
2. Neurotransmitter is packaged into vesicles
3. Neurotransmitter is released when vesicles fuse
4. Neurotransmitter binds to and activates postsynaptic receptors
5. Neurotransmitter diffuses away and is metabolized and/or transported back into terminal
Neurotransmitters

(B) SMALL-MOLECULE TRANSMITTERS
1. Synthesis of enzymes in cell body
2. Slow axonal transport of enzymes
3. Synthesis and packaging of neurotransmitter
4. Release and diffusion of neurotransmitter
5. Transport of precursors into terminal

(C) PEPTIDE TRANSMITTERS
1. Synthesis of neurotransmitter precursors and enzymes
2. Transport of enzymes and pre-peptide precursors down microtubule tracks
3. Enzymes modify pre-peptides to produce peptide neurotransmitter
4. Neurotransmitter diffuses away and is degraded by proteolytic enzymes
Neurotransmitters
# Neurotransmitters

## TABLE 47-1

<table>
<thead>
<tr>
<th>NEUROTRANSMITTER</th>
<th>PHYSIOLOGIC EFFECTS</th>
<th>RELATIONSHIP TO MENTAL DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Sleep/wake cycle. Signals muscles to become active.</td>
<td>Decreased in Alzheimer’s and Parkinson’s diseases.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Controls complex movements, cognition, motivation, and pleasure. Regulates emotional responses.</td>
<td>Increased in schizophrenia and mania. Decreased in depression and Parkinson’s.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Affects attention, learning, memory, and regulation of mood, sleep, and wakefulness.</td>
<td>Decreased in depression. Increased in schizophrenia, mania, and anxiety.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Affects sleep and wakefulness, especially falling asleep. Affects mood and thought processes.</td>
<td>Probably plays a role in thought disorders of schizophrenia. Decreased in depression. Possibly decreased in anxiety and obsessive-compulsive disorder.</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid (GABA)</td>
<td>Amino acid that modulates other neurotransmitters.</td>
<td>Decreased in anxiety and schizophrenia.</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease

Mechanisms and secrets of Alzheimer’s disease: exploring the brain, Video, 6:26”
Rita Levi-Montalcini (1909–2012)

- M.D. at University of Turin (1936).
- Lost her job due to laws barring Jews (1938).
- Secret lab in bedroom to study nerve growth in chicken embryos (WWII).

[Image of Rita Levi-Montalcini]
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- Secret lab in bedroom to study nerve growth in chicken embryos (WWII).
- Received one-semester research fellowship at WUSTL (1946).
- Isolated nerve growth factor (NGF) by observing that cancerous tissues caused extremely rapid growth of nerve cells in chicken embryos (1952). *First growth factor discovered.*

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T. M. Murali
January 18 and 20, 2022

Computing the Brain
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- Isolated nerve growth factor (NGF) by observing that cancerous tissues caused extremely rapid growth of nerve cells in chicken embryos (1952). *First growth factor discovered.*
- Received Nobel prize (with Stanley Cohen, 1986).
Neurotrophins

Family of proteins that induce the survival, development, and function of neurons.
Neurotrophins

Changes in neurotrophin levels or in the ratio of pro-neurotrophin to mature neurotrophin can cause and/or contribute to numerous diseases.
Cellular Communication: Hunger Response

Produced by adipose (fat) tissue, **leptin** suppresses appetite as its level increases. When body fat decreases, leptin levels fall, and appetite increases.

SECRETED BY THE STOMACH WALL, **ghrelin** is one of the signals that triggers feelings of hunger as mealtimes approach. In dieters who lose weight, ghrelin levels increase, which may be one reason it’s so hard to stay on a diet.

A rise in blood sugar level after a meal stimulates the pancreas to secrete **insulin** (see Figure 41.3). In addition to its other functions, insulin suppresses appetite by acting on the brain.

The hormone **PYY**, secreted by the small intestine after meals, acts as an appetite suppressant that counters the appetite stimulant ghrelin.
Cellular Response to External Signals

A Cell is Like

Motility Circuits
- proteases
- adjacent cells
- E-cadherin
- integrins
- extracellular matrix
- Apc
- b-catenin
- TCF4

Cytostasis and Differentiation Circuits
- anti-growth factors
- p16
- cyclin D
- pRb
- Smads
- p21
- DNA-damage sensor
- p53

Proliferation Circuits
- growth factors
- receptor tyrosine kinases
- Ras
- Myc

Viability Circuits
- survival factors
- cytokines
- abnormality sensor
- Bcl-2
- death factors

changes in gene expression
Hallmark capabilities
A Cell is Like

YOU DON'T GET TO
500 MILLION FRIENDS
WITHOUT MAKING
A FEW ENEMIES
A Cell is Like

facebook

Motility Circuits
- proteases
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Cytostasis and Differentiation Circuits
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Proliferation Circuits
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- Myc
- cytokines

Facebook helps you connect and share with the people in your life.
Network is Complex

Motility Circuits
- Proteases
- Adjacent cells
- E-cadherin
- Integrins
- B-catenin
- TCF4

Cytostasis and Differentiation Circuits
- Anti-growth factors
- Smads
- P16
- Cyclin D
- pRb
- E2F
- p21
- DNA-damage sensor
- p53

Proliferation Circuits
- Growth factors
- Tyrosine kinases
- Receptor
- Ras
- Myc

Viability Circuits
- Survival factors
- Cytokines
- Abnormality sensor
- Bcl-2
- Death factors

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Computing the Brain
Network is Complex
Network is Complex but Very Poorly Understood
Early Brain Graphs

Large-scale human network for language (Lichtheim, 1885)
Early Brain Graphs

Neuronal network for psychoanalysis (Freud, 1891, 1895)
Early Brain Graphs

Hub-and-spoke model of spatial attention (Mesulam, 1990)
Dawn of Connectomics

Macaque visual cortex (Felleman and van Essen, 1991)
Dawn of Connectomics

Tract-tracing in the macaque visual cortex (Felleman and van Essen, 1991)
Dawn of Connectomics

Wiring diagram of macaque connectome (Felleman and van Essen, 1991)
Dawn of Connectomics

Topological representation of macaque connectome (Young, 1992)
Functional connectivity network from functional MRI data
Human Connectomics

Modular organisation of network
Human Connectomics

Connectivity network from diffusion MRI data
Human Connectomics

Topological layout of network
Human Connectomics

Anatomical layout of network