CS 6824: Computing the Brain

T. M. Murali

August 23 and 25, 2016
Course Information

- Meet on Tuesdays and Thursdays, 11am–12:15pm, TORG 1080.
- Office hours: By appointment.
- Course website: [http://courses.cs.vt.edu/~cs6824/2016-fall](http://courses.cs.vt.edu/~cs6824/2016-fall). Consult this website regularly. Course schedule is subject to change.
- Papers on CiteULike: [http://www.citeulike.org/user/tmmurali/tag/2016-fall-cs6824](http://www.citeulike.org/user/tmmurali/tag/2016-fall-cs6824)
- I may use Canvas to post some lectures and some papers.
Course Pre-requisite
Course Pre-requisite
Course Pre-requisite

Course Structure

Brain Structure

Brain Cells

Brain Molecules

Papers

T. M. Murali

August 23 and 25, 2016

Computing the Brain
Course Pre-requisite

Course Structure
Brain Structure
Brain Cells
Brain Molecules
Papers

T. M. Murali
August 23 and 25, 2016
Computing the Brain
## Course Structure

Discuss recent research papers.
Course Structure

Discuss recent research papers.

▶ Lectures
Course Structure

Discuss recent research papers.

- Lectures
- Student presentations
Course Structure

Discuss recent research papers.

- Lectures
- Student presentations
- Class participation
Course Structure

Discuss recent research papers.

- Lectures
- Student presentations
- Class participation
- Assignments (3–4)
Course Structure

Discuss recent research papers.

- Lectures
- Student presentations
- Class participation
- Assignments (3–4)
- Final project (possible)
Grading

- Presentations: 35%
- Class participation: 35%
- Assignments and Final project: 30%

Class participation \neq attendance!
Grading

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- Class participation is very important.
Grading

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- Class participation ≠ attendance!
Assignments

► Typically, I will ask you to write code to replicate analysis in one or two figures in a paper we study.
► 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:

Molecular
Cellular
Anatomical

to gain insights into structure-function relations, health, and disease.
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

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- 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.

*The birth and evolution of neuroscience through cadaveric dissection, Moon K1, Filis AK, Cohen AR. Neurosurgery. 2010 Sep;67(3):799–809*
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- 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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- 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)
Andreas Vesalius (1514–1564)

- Used skillful dissection of cadavers.

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 Descendants</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Dee</td>
<td>University of Cambridge and Université Catholique de Louvain</td>
<td>1546</td>
</tr>
<tr>
<td>Gerardus Mercator</td>
<td>Université Catholique de Louvain</td>
<td>1532</td>
</tr>
<tr>
<td>Johannes Stadius</td>
<td>Université Catholique de Louvain</td>
<td>1537</td>
</tr>
<tr>
<td>Andreas Veslius</td>
<td>Università degli Studi di Padova and Université Catholique de Louvain</td>
<td>1537 105089</td>
</tr>
</tbody>
</table>

According to our current on-line database, Gemma Frisius has 4 students and 105096 descendants. We welcome any additional information.
Gerardus Mercator
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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)*
Structure to Function

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

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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.
Brodmann Areas (1909)

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.
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- 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.
- Left hemisphere: speech, language, arithmetic, analysis.
- Right hemisphere: spatial comprehension, facial recognition, emotion.

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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“The great pleasure and feeling in my right brain is more than my left brain can find the words to tell you.”
Two astonishingly different persons inhabit our heads

We are left-brained or right-brained

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 reamples, 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.
Left and Right Brains in Culture

Left Brain vs. Right: It's a Myth, Research Finds

By Christopher Wanjek  I  September 3, 2013 12:21pm ET

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

Researchers have divided the brain into discrete areas based on structure and function.

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

<table>
<thead>
<tr>
<th></th>
<th>OCCIPITAL</th>
<th>TEMORAL</th>
<th>PARIETAL</th>
<th>FRONTAL</th>
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<tbody>
<tr>
<td>F1</td>
<td>V2</td>
<td>V3</td>
<td>V4</td>
<td>V5</td>
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<td>V2</td>
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<td>V13</td>
<td>V14</td>
</tr>
</tbody>
</table>

This table is a connectivity matrix for interconnections between visual cortical areas in the macaque. Each row shows whether the area listed on the left sends inputs 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 (+) indicates a pathway that has been reported in 1 or more full-length manuscripts; small plus symbols indicates pathways identified only in abstracts or unpublished studies. Specific estimates are listed in Table 2. Dots (.) indicates a pathway, explicitly stated and found to be absent. Shading indicates pathways not carefully tested for. Question marks (?) denotes pathways whose existence is uncertain owing to conflicting reports in the literature. "WR" and "NRE" indicates unreported pathways, i.e., connections absent in the indicated direction even though the reciprocal connection has been reported. Shaded boxes along the diagonal represent intrinsic connectivity that exists within each area; these are not included among the pathways tabulated in the following table.

Brain Structure to Graphs

Neuroinformatics
June 2004, Volume 2, Issue 2, pp 145–162

The small world of the cerebral cortex

Olaf Sporns, Jonathan D. Zwi

Review Article
DOI: 10.1385/NI:2:2:145

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”)

Brain is an exception: complex cell shapes, extensive branching, and dense packing.

How many neurons in the brain? 100 billion and many more glial cells.

Golgi and Nissl stains: allowed cells to be visualised and traced under the microscope.

Cajal: catalogued many different types of nerve cells.
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Wikimedia Commons
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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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Reticular theory Nerve cells are fused to each other to form a continuous network, much like blood vessels (Golgi)

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

T. M. Murali

August 23 and 25, 2016

Computing the Brain
Cells in the Brain

Types of Brain Cells (Video, 18:54")
100s of types of neurons, differentiated by structure, function, genetics ...

- neuromorpho.org: archive of digitally reconstructed neurons.
- neurolex.org

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

We Just Discovered 6 New Kinds of Brain Cells

The map of the human brain gets a little more complete.

Daniel Berger, Xiaolong Jiang, Fabian Sinz, Xaq Pitkow, Andreas Tolias

By William Herkowitz  Nov 26, 2015
White Matter and Grey Matter (17th–18th centuries)

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**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?
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- How do nerves communicate with muscles: electricity or chemicals?
- Loewi settled this question through his discovery of *vagusstoff* (1921).

Later identified as acetylcholine, which had been discovered in 1914 by Sir Henry Dale. The first neurotransmitter.

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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

Transporter
Precursor
Neurotransmitter molecules
Ca²⁺
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.</td>
<td>Increased in schizophrenia and mania.</td>
</tr>
<tr>
<td></td>
<td>Regulates emotional responses.</td>
<td>Decreased in depression and Parkinson’s.</td>
</tr>
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<td>Norepinephrine</td>
<td>Affects attention, learning, memory, and regulation of mood, sleep, and wakefulness.</td>
<td>Decreased in depression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased in depression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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).
- 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.
- Received Nobel prize (with Stanley Cohen, 1986).
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Neurotrophins

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

[Diagram showing interactions between neurotrophins and their signaling pathways]
Neurotrophins

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

Decreased synthesis and/or transport
- Decreased neurotrophin
- Decreased pro-neurotrophin

Amyloid-β
- Excitotoxicity
- Cytokines
- Chemotherapy
- Ischaemia
- Trauma, and so on

Decreased proteolytic conversion
- Decreased neurotrophin
- Decreased pro-neurotrophin

Increased synthesis, decreased degradation

Rett syndrome
- Pro-survival signalling
  - AKT
  - NF-κB
  - ERK, and so on

Huntington’s disease
- Altered synaptic function
- Decreased neurite integrity
- Demyelination
- Decreased survival

Alzheimer’s disease
- Sprouting
- Pruning

Ageing
- Pain
- Epilepsy

Status epilepticus

Activated microglia

Astrocytes

T. M. Murali
August 23 and 25, 2016
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.

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

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.

www.barbellmedicine.com

T. M. Murali August 23 and 25, 2016 Computing the Brain
Network is Complex

Motility Circuits

Cytostasis and Differentiation Circuits

Proliferation Circuits

Viability Circuits

proteases → adjacent cells → extracellular matrix

E-cadherin → integrins

Apc → b-catenin → TCF4

p16 → cyclin D → pRb → E2F

Smads

hallmark capabilities

changes in gene expression

DNA-damage sensor

p53

p21

tumor-suppressor genes

T. M. Murali

August 23 and 25, 2016

Computing the Brain
Network is Complex
Network is Complex but Very Poorly Understood
Paper Presentations

- Each student is responsible for presenting for two lectures (total of 150 minutes).
- Ideally, each presentation given by one student but you are welcome to work in larger groups to read, understand, and discuss papers.
- Each student and I mutually decide upon one–two papers.
- Division of time for each paper: present for 90 minutes and expect 60 minutes of questions and discussion during the presentation. Be prepared for some discussions to take over your presentation.
- Some papers will require two full classes, i.e., a total of 150 minutes, including time for questions.
- You can pair up with another student to present two papers over four lectures.
- Prepare your presentation well in advance. Practise multiple times.
- Please give me PDF copies of slides (no Microsoft PowerPoint) to post on the course web page.
Selecting Papers

- List of papers to be presented is available on course web site.
- If you like a paper already assigned to another student, you are welcome to ask that student or me if you can join him/her.
- Sometimes presenting a paper may require reading and presenting earlier papers, e.g., Aditya Pratapa is presenting ”An introduction to diffusion tensor image analysis” as a prelude to ”Rich-Club Organization of the Human Connectome”.
- I will be happy to consider papers that you have come across and think are suitable for the course.
- Let me know a list of three papers you want to present by Friday, September 16.
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- **Let me know a list of three papers you want to present by Friday, September 16.**
- Send me a detailed list of reading notes of the type I created for the first two papers.
  - I will edit and post them on the class web page as a guide to your fellow students.
  - These notes will help you (the presenter) as well by helping you outline the structure of your presentation.
Suggestions on Reading Papers

- Form reading groups to discuss papers. There can even be a single reading group for the entire class.

- Be sceptical and critical: even papers in Nature, Science, or PNAS have errors or invalid thinking. In fact, we will study some papers that systematically catalogue errors.

- Study each paper in terms of its figures:
  - Digest the content of each figure.
  - Understand the analysis performed to generate each figure.
  - Figure out the algorithm or the idea used to generate each figure.
  - If necessary, read a cited paper that describes the method in detail.
  - Try to understand the biological experiment underlying the data.

- Discuss aspects you do not understand with Murali or with students with complementary expertise.

- Read supplementary information. Often has details about the assumptions, the techniques, and the results.
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Suggestions on Presenting Papers

- Give an overall introduction to the main goal of the paper.
- Describe any innovation in the paper.
- Present meat of the paper in terms of the figures in it.
  - Discuss each panel or group of related panels separately.
  - Make sure each panel is enlarged enough to be visible.
  - Make slides for the approach used to generate the panel, i.e., do not just show the figure and speak about the underlying method.
  - Make extra figures to illustrate your points.
- Discuss with me or use your judgment to decide which figures in the paper you should discuss in your presentation.
  - Your reading notes should be clear about what your fellow students should read.
- Feel free to use good videos to explain concepts that are unfamiliar to you.