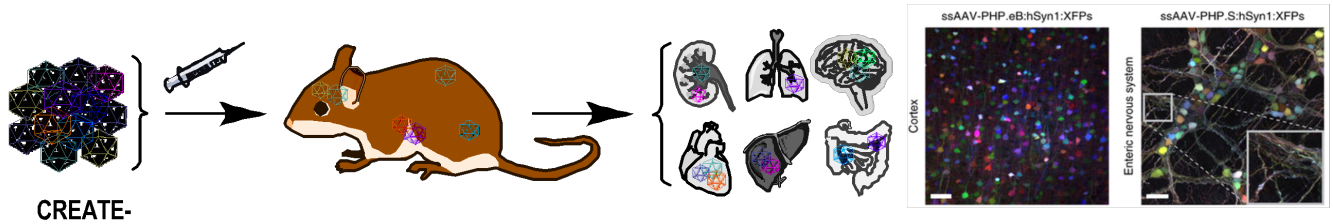
BME 499: Experimental strategies for studying neural circuits



CREATE-engineered capsids | subject with transduced cells | cleared, labeled organs | 3D imaging of color diversity

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Office Hours: TBD

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Units: 2

Semester: Spring 2023

Date - Time: Date TBD (Tuesdays or Wednesdays?) - Time TBD (7:00 – 8:50 PM ?)

Location: Lecture - TBD (MCB 204?), Lab Demos - MCB 253

Course Description

This course aims to provide students with practical knowledge and hands-on skills related to the application of advanced techniques and modern tools to the study of the mammalian brain. Specifically, students will learn how to apply optogenetics, pharmacogenetics, and tissue-clearing technologies to probing neurocircuit function and mapping neuronal pathways in rodent models. To this end, class-time will be divided between instructor-led lecture, student-led journal article presentations and in-class discussion, and hands-on laboratory modules in which students have the opportunity to directly observe and practice the techniques discussed in lecture. Students will gain direct exposure to implementing these tools and techniques in actual experiments, and they will develop a more well-rounded understanding of how to apply these various technologies to real-world applications such as disease modeling and drug discovery.

Learning Objectives

1. Understand basic information relating to the biophysical structures and circuit mechanisms that enable the generation and propagation of electrochemical signals for cell-cell communication in the central nervous system (CNS).
2. Be able to identify major brain regions and connectivity that give rise to the sensory, motor and memory-related functions of the CNS.
3. Gain exposure to key examples of nervous system dysfunction, approaches to studying this dysfunction in the laboratory setting, and the corresponding BME interventions (e.g. cochlear implants for hearing loss, retinal implants for central vision loss, bionic implants for paralysis).
4. Identify the molecular tools and experimental techniques that allow researchers to modify neuronal signaling with temporal and spatial precision in the awake-behaving subject.
5. Understand the principles that underlie light scattering and depth of penetration in tissue and other biomedically relevant materials.
6. Develop an in-depth comprehension of major experimental methods for visualizing large tissue samples abd biological specimens (i.e., through tissue-clearing and advanced microsropy techniques), for the purpose of investigating complex cellular niches or mapping the connectome.
7. Improve analytical skills, language/presentation skills through in-class presentation/discussion of journal publications and laboratory demos, as well as through the development of a final written proposal on how to test a novel research hypothesis.
8. Gain exposure to moral/ethical/philosophical issues related to studying and modifying brain function in research models and in patients
9. Encourage compassion for those with brain dysfunction/mental illness.

Course Outcomes

1. Apply course teachings to brainstorming novel neuroengineering technologies and experimental approaches for the diagnosis and treatment of neurological disease.
2. Recognize gaps in our current experimental and clinical capabilities with respect to (1) mapping the human connectome, and (2) implementing safe, noninvasive deep brain stimulation.
3. Interpret and critique data from research papers related to basic neuroscience discovery, neurological disease and their corresponding treatment in preclinical models and clinical case studies.
4. Integrate course material on brain mapping and on neural circuit control with light (i.e., optogenetics) with teachings from other BME courses on implantable electronics, brain imaging, and platforms for noninvasive brain stimulation.
5. Collaborate with classmates on experimental design and hypothesis testing.

Prerequisite(s) or Co-Requisite(s): None

Concurrent Enrollment: None

Recommended Preparation: Basic knowledge of biology or biochemistry (BISC220L or equivalent courses) and of neuroscience (BME 202 or equivalent courses).

Web page: A class website will be setup on Backboard containing information about the course: syllabus, reading handouts, homework assignments, grades, information about class activities, solutions to the homework sets, and an email directory of all students in the class. Use it as much as you find it useful. The web page can be accessed at: https://Blackboard.usc.edu.

Course Notes: Copies of lecture slides, video-recorded lectures, and other class information will be posted on Blackboard (Bb) or Design2Learn (D2L) course website.

Office Hours: Time and location for office hours will be identified at the beginning of first session of the class. Students are encouraged to take advantage of office hours.

Technological Proficiency and Hardware/Software Required: None. However, if we return to remote instruction, students will be required to use an internet-enabled device with browser capabilities, such as a laptop or tablet.

Required Readings and Supplementary Materials: No assigned textbook. Required reading will consist of lecture notes, published journal articles, and assigned reading available as pdf on Bb.

Description and Assessment of Assignments:

In-class Worksheets

Throughout the semester, in-class worksheets will be assigned in order to access student comprehension of "big-picture" ideas, and/or to ensure active participaton in laboratory modules. These worksheets will take the form of a single "thought question" related to a recent journal article discussion (i.e., to be completed during the last 20 minutes of class after the JC article presentation) or a fill-in-the-blank laboratory worksheet, in which the student fills-in key information about the experimental methods in real-time during a lab demo (e.g., viral titer injection volume, opsin identity and key traits, subject parameters, chemicals and incubation times for tissue-clearing, imaging parameters on a confocal microscope, etc – akin to data that would be recorded in a daily laboratory notebook). Each worksheet must be completed during class time – to be turned in at the end of class. It is anticipated that ~8 worksheets will be assigned over the course of the semester, with the lowest 1-2 worksheet grades dropped. For this reason, NO MAKE-UP WORK WILL BE ACCEPTED for missed worksheets due to class absense.

Journal Club (JC) Presentation

Throughout the semester, each student group (1-3 students) will be responsible for leading a single journal article discussion. Presenters are expected to provide background information on the journal article (introduce the topic, explain the experimental methods, review the article findings (figures), and critique the results (holes in study, future directions of research, etc.). Student presentations (including asking/answering questions) should be < 30-40 minutes in length. Suggested journal articles are claimed on a first-come first-serve basis, via email to the professor (TA cc'd). If no one claims a given JC assignment, a student will be randomly selected approximately 5 days prior to the scheduled presentation.

In-Class Participation

Class time will often be used for in-class discussion and completion of laboratory modules. Thus, attendance for class is mandatory and will only be excused in case of an emergency, at the discretion of the instructor. If a student knows in advance that he/she/they will be absent from class for an important occasion or non-emergency situation (at the discretion of the instructor), notify the instructor by email as soon as possible (≥ 2 weeks beforehand). Except under the scenario of health/family emergency or pre-excused absence, NO MAKE-UP WORK WILL BE ACCEPTED. In the case of classes devoted to laboratory modules, in-class lab demos are arranged sequentially, in which the product of "Week A's demo" becomes the starting point of "Week B's demo"; hence, the mandatory timing of these multi-week experiments means that a single demo cannot be repeated at a later date without compromising the overall experimental progression.

The overall participation grade will be based on measures of engagement, including preparation for and participation in class discussions. Participation will be assessed over the course of the term on a 3-point scale: 0 = routinely absent from class, 1 = regularly attends class, 2 = regularly attends and actively participates in class. Students will be allowed to miss 1-2 classes (either excused or unexcused) without these absence(s) negatively impacting their overall participation grade.

Final Exam

A Final Project will be completed in lieue of a "Final Exam". Students must compose a "Specific Aims" page for an NIH grant proposal (i.e., the written Final Project, 10% grade), which will be due (Bb upload) at the end of the scheduled final exam time period. The "elevator pitch" for his/her/their Final Project (i.e., the oral Final Project, 5% grade) will be presented on the last day of class. Additional details and a rubric for grading of this final written report will be provided (please see Bb). SORRY, NO MAKE-UPS OR LATE TURN-INS WILL BE ACCEPTED – PLAN ACCORDINGLY!

Grading Breakdown:

Assessment Tool (assignments)	% of Grade
Worksheets (8 per semester)	60
JC Presentation	15
In-class Participation	10
Final Project (Oral + Written)	5+10
TOTAL	**100**

Assignment Submission and Grading Policies:

Submission guidelines

All hand-written worksheets are due at the end-of-class, for the class period during which they were assigned; all electronic worksheets are also due at the end-of-class, by upload to Bb. For all "take-home" assignments (JC presentation, Final Exam written report), a single file (e.g., a slide deck in PDF format) should be uploaded to the assignment link on the Bb site by the due date and time. Within 24 hours following an in-class JC presentation, the presenting student(s) should submit an electronic copy of their presentation (e.g., PDF of slides) to the JC presentation assignment on Bb; it is encouraged that JC presenters explicitly "write-out" the questions that they formulate for in-class discussion on these slides.

Late Policy for Assignments

Late assignments will only be accepted in cases of extremely extenuating circumstances (e.g., family or health emergency; accompanied by note); under non-emergency scenarios (e.g., sports, conference travel, interviews, etc.), permission should be obtained from the instructor 2 weeks before the deadline; any make-up work is assigned at the discretion of the instructor. Otherwise, late submissions (even if it is by a minute) will not accepted, and will result in zero points received for that assignment. Students are responsible for allowing sufficient time for turning in assignments (e.g., including uploading files to Bb). We recommend starting early and not leaving submission to the last minute. The cutoff time for all submissions is the last minute of class (i.e., for Worksheets) or the last minute of the scheduled final exam period for Bb upload of the written report.

To reiterate, except for family or medical emergencies, there will be no make-ups for in-class assignments (e.g., class participation, worksheets) or assignment due-dates. Planned absenses (e.g., sports, conference travel, interviews, etc) must be communicated to the instructor at least two weeks in advance in order to arrange for make-up work; the creation and content of make-up work is at the sole discretion of the instructor. Lab demos cannot be repeated.

Homework & Academic Integrity Policy:

Academic Integrity
Students are expected completely understand everything that they submit as their own. It is anticipated and expected that students consult one another for clarification of concepts, advice, to compare a final numerical solution to a worksheet problem, etc. It is not acceptable to show someone else your written work (i.e., a short answer response, or the written work to arrive at a numerical solution), even if it is easier than explaining a concept verbally. You may use whatever materials you find on the web, in other texts, or other sources to assist in preparing your homework, put you may not plagarize these materials. Copying/transcribing the work prepared by another student and other forms of plagiarizing are strictly prohibited. Violations of this policy will result in an *automatic F* in the class and filing of an academic misconduct report to the Office of Student Conduct. All students are expected to adhere to the USC standards of Academic Integrity (http://www.usc.edu/student-affairs/SJACS/docs/AcademicIntegrityOverview.pdf and http://www.usc.edu/student-affairs/SJACS/docs/GradIntegrity.pdf).

Grading Timeline
Worksheet grades are provided within one week of their completion. Journal Club presentations will be graded after all students have presented; students may discuss their performance and approximate grade at any point during the semester with the instructor during office hours or by individual appointment.

Regrade Policy
All regrading requests are due within one week of their return. The requester must email Prof. Treweek about this regrade, providing a clear explanation for the regrade and attaching the original graded assignment.

Grading Scale
Final letter grades are not assigned based on absolute percentage values, but they are curved to generate a reasonable grade distribution. Students can expect their final grades to loosely align with the following scale:

A	95-100
A-	90-94
B+	87-89
B	83-86
B-	80-82
C+	77-79
C	73-76
C-	70-72
D+	67-69
D	63-66
D-	60-62
F	59 and below

Additional Course Policies:

Technology Policy
During class, devices should only be used to participate in activities guided by the instructor or for note-taking. Use of devices for other purposes (email, web-surfing, social media, A/V-recording) is not permitted, wherein any non-academic use of such devices that distracts the instructor or students will result in no credit for in-class work for the day. Photographing or audio/video-recording of lecture material and/or slides is strictly prohibited, as is uploading course content to third-party sites for viewing and/or distribution.

Communication Policies
To promote independence and critical thinking, students are encouraged to work through the following process for obtaining answers to course-related questions before contacting the instructor. First, consult the course syllabus and Bb message board. If you do not find the answer you need, consult a classmate or post your question to Bb. After you have exhausted these methods, email the instructor, cc'ing the TA (if applicable) and including the course number and your name in the subject line. The instructor (and/or TA)

will reply to emails within 48 hours on weekdays, or within 72 hours over weekends and holidays. The instructor does not respond to last-minute questions during the 24 hours before an assignment is due.

Rules about computers (ipads, smart phones, etc) in class

Computers will frequently be used in class for activities or to access class-related information. Computers are not to be used for email or web surfing during class time, unless by explicit permission from the instructor or TA. If you are seen using your device for anything besides in-class work, you will be asked to put it away for the remainder of the session; any in-class work (i.e., worksheet) will receive a zero for that day. If it happens a second time, your overall participation score will be impacted. Photographing or video-recording of lecture material/slides is strictly prohibited.

Course Schedule: A Weekly Breakdown

Week	Type	Topic covered
1	Lecture	Course structure, assignments, grading and class policies Introduction to neurobiology and neuroanatomy Rodent models for neurological disease and drug discovery
2	Lecture	Neurotransmitter Systems, and Neuronal Signaling Rodent models for neurological disease and drug discovery
3	Lecture	Optogenetics and chemogenetics: background and experimental design Strategies for transgene delivery
4	Lab	Surgical techniques – direct brain injection of viral vectors, implantation of indwelling devices
5	JC Lecture	JC #1: Optogenetic deconstruction of neural circuits Genetically-encoded sensors: visualizing circuit activity *in vivo*
6	JC Lecture	JC #2: Noninvasive neuromodulation for disease treatment Multiplexed optical and electrical neuronal recording strategies
7	Lab demo	Optogenetic and chemogenetic modulation in the awake-behaving mouse
8	Lecture	Visualizing complex cellular niches and long-range neural circuits: tissue clearing Theory and methods for enhancing the optical transparency of large specimens
9	Lab demo	CLARITY vs iDISCO vs CUBIC tissue-clearing, part 1
10	Lab demo Lecture	CLARITY vs iDISCO vs CUBIC tissue-clearing, part 2 Intersectional-genetic and labeling strategies for dissecting neuronal circuits
11	Lab demo Lecture	CLARITY vs iDISCO vs CUBIC tissue-clearing, part 3 Considerations for high-resolution imaging of large tissue specimens
12	Lab demo	Imaging cleared tissues; data visualization strategies
13	JC	JC#3: Tissue-clearing for systems neuroscience JC#4: Circuit-tracing, Mapping the connectome (big data)
14	Discussion	Advanced topics in experiment design: considerations for imaging the *very small* (super-resolution, ExM) or *very large* (long WD objectives, uDISCO); Clinical limitations of optogenetics and chemogenetics, and alternatives for neuromodulation
15		**Final project (oral due)**
FINAL		**Final project (written due)**

Statement on Academic Conduct and Support Systems

Academic Conduct:

Plagiarism – presenting someone else's ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in SCampus in Part B, Section 11, "Behavior Violating University Standards" policy.usc.edu/scampus-part-b. Other forms of academic dishonesty are equally unacceptable. See additional information in SCampus and university policies on scientific misconduct, policy.usc.edu/scientific-misconduct.

Support Systems:

Counseling and Mental Health - (213) 740-9355 – 24/7 on call
studenthealth.usc.edu/counseling
Free and confidential mental health treatment for students, including short-term psychotherapy, group counseling, stress fitness workshops, and crisis intervention.

National Suicide Prevention Lifeline - 1 (800) 273-8255 – 24/7 on call
suicidepreventionlifeline.org
Free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week.

Relationship and Sexual Violence Prevention and Services (RSVP) - (213) 740-9355(WELL), press "0" after hours – 24/7 on call
studenthealth.usc.edu/sexual-assault
Free and confidential therapy services, workshops, and training for situations related to gender-based harm.

Office of Equity and Diversity (OED)- (213) 740-5086 | Title IX – (213) 821-8298
equity.usc.edu, titleix.usc.edu
Information about how to get help or help someone affected by harassment or discrimination, rights of protected classes, reporting options, and additional resources for students, faculty, staff, visitors, and applicants. The university prohibits discrimination or harassment based on the following *protected characteristics*: race, color, national origin, ancestry, religion, sex, gender, gender identity, gender expression, sexual orientation, age, physical disability, medical condition, mental disability, marital status, pregnancy, veteran status, genetic information, and any other characteristic which may be specified in applicable laws and governmental regulations. The university also prohibits sexual assault, non-consensual sexual contact, sexual misconduct, intimate partner violence, stalking, malicious dissuasion, retaliation, and violation of interim measures.

Reporting Incidents of Bias or Harassment - (213) 740-5086 or (213) 821-8298
usc-advocate.symplicity.com/care_report
Avenue to report incidents of bias, hate crimes, and microaggressions to the Office of Equity and Diversity |Title IX for appropriate investigation, supportive measures, and response.

The Office of Disability Services and Programs - (213) 740-0776
dsp.usc.edu
Support and accommodations for students with disabilities. Services include assistance in providing readers/notetakers/interpreters, special accommodations for test taking needs, assistance with architectural barriers, assistive technology, and support for individual needs.

USC Support and Advocacy - (213) 821-4710
uscsa.usc.edu
Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity at USC - (213) 740-2101
diversity.usc.edu
Information on events, programs and training, the Provost's Diversity and Inclusion Council, Diversity Liaisons for each academic school, chronology, participation, and various resources for students.

USC Emergency - UPC: (213) 740-4321, HSC: (323) 442-1000 – 24/7 on call
dps.usc.edu, emergency.usc.edu
Emergency assistance and avenue to report a crime. Latest updates regarding safety, including ways in which instruction will be continued if an officially declared emergency makes travel to campus infeasible.

USC Department of Public Safety - UPC: (213) 740-6000, HSC: (323) 442-120 – 24/7 on call
dps.usc.edu
Non-emergency assistance or information.