BME1500 Topics in Neuromodulation

Luka Milosevic & Taufik Valiante

Course description:

The field of Neuromodulation and its therapeutic application is experiencing unprecedented growth. Advanced therapies resulting from the convergence of machine learning, optical interfaces, electronics, mathematics, material sciences, image-guided surgery, neuroscience, and big data analyses are being rapidly developed and deployed.

The primary goal of this course is to introduce students to various neuromodulation modalities, provide students with the knowledge to be prepared for research or industrial endeavors in neuromodulation, and provide hands-on experience performing real brain data analyses.

Topics covered include interventions that are non-invasive (i.e., transcranial stimulation, functional electrical stimulation, transcutaneous spinal cord stimulation), invasive (i.e., deep brain stimulation, subcutaneous spinal cord stimulation), emerging (i.e., focused ultrasound, laser interstitial thermal therapy), and pre-clinical (i.e., optogenetics, gene therapy), in the context of movement, psychiatric, pain, and memory disorders.

Components: Lectures, interactive discussions, and research project.

Evaluation:

Course participation is mandatory. Each student will be part of a group (2-5 students) that will complete a term project. Each group will give a presentation and submit a copy of their report for grade evaluation. Final Marks will be based on Participation (20%), term project (70%), and an individually submitted project peer-review (10%).

Participation (20.0):

1) Lectures

Each student can earn 2.0 grade points per lecture. Each student will receive 0.5 points for attendance, and 1.5 points for a meaningful question or comment during the discussion period of the lectures. This point system will apply for lectures 2-11, for a maximum of 20.0 points throughout the year.

2) Student presentations

Each student will receive points for a meaningful question or comment (posed by their group) during the discussion period of each student presentation. The maximum points to be received here will be 5.0; more details to follow.

Project (70.0): please see page 5 of this document.

Peer-review (10.0): Each student will be appointed one research project final document to peer-review (1.5-page document to be submitted). The task is to write a 1-2 paragraph summary of the paper, and to highlight specific strengths and weaknesses of the work and to suggest ways to improve the work. The peer reviews will receive a mark of 0.0, 2.5, 5.0, 7.5, or 10.0 depending on completion, effort, and meaningfulness of the provided feedback.

Lectures:

NI – Non-invasive, I – Invasive, E – Emerging Technology

16:00 – 18:00	Lecture	Lecturer
1 Sep 14	Course Intro: - Intro to CRANIA & context of this course (15m) - History and present day neuromodulation (1hr) - Group Project information session (30m)	Taufik Valiante Luka Milosevic
2 (NI) Sep 21	- Transcranial stimulation (magnetic, AC, DC, ultrasound) (45m) - Project seminar session 1 (50m)	Robert Chen Project liaisons
3 (NI) Sep 28	- Functional electrical stimulation & spinal cord stimulation (45m) - Project seminar session 2 (50m)	Milos Popovic Project liaisons
4 (NI/I) Oct 5	- Vagal, sacral, hypoglossal nerve stimulation (1.5hr)	Paul Yoo
5(I) Oct 12	Deep brain stimulation for movement disorders: - clinical (45m) - mechanistic (45m)	Alfonso Fasano Luka Milosevic
6 (I) Oct 19	Neuromodulation for epilepsy: - epilepsy monitoring and neuromodulation (45m) - childhood epilepsy and other indications (45m)	Taufik Valiante George Ibrahim
7 (I) Oct 26	Intracranial approaches for memory: - memory and memory problems (45m) - neuromodulation for memory (45m)	Kathrine Duncan Taufik Valiante
8 (I) Nov 2	Pain: - brain (45m) - spine (45m)	Mojgan Hodaie Anuj Bhatia
9 (I) Nov 9	Psychiatric disorders (1.5hr)	Clement Hamani & Peter Giacobbe
10 (E) Nov 16	Emerging clinical technology: - focus ultrasound (45m) - laser interstitial thermal therapy, drug delivery (pumps, BBB) (45m)	Nir Lipsman Suneil Kalia
11 (E) Nov 23	Emerging pre-clinical technology: - optogenetics (45m) - gene therapy, tissue regeneration (45m)	Joyce Poon Cindi Morshead
12 Nov 30	Student Presentations (1.5hr)	
13 Dec 7	Student Presentations (1.5hr)	

Learning objectives:

	Lecture Title	Learning Outcome
1	History and present day neuromodulation (1hr)	Learn about the impact of neurodegenerative diseases on society and gain broad overview & understanding of the history and present day Neuromodulation treatments.
2 (NI)	Transcranial stimulation (magnetic, AC, DC) (45m)	Learn and understand the principles of different modalities for transcranial stimulation (magnetic, alternating current, direct current, ultrasound). This lecture will cover theoretical principles, prognostic uses (ex. studying cortico-spinal excitability), as well as clinical (ex. treatment resistant depression) and experimental (ex. Parkinson's disease) applications.
3 (NI)	Functional electrical stimulation and spinal cord stimulation (45m)	Learn about the application of transcutaneous electrical stimulation for activation of muscles and the spinal cord. Topics will include rehabilitative functional electrical stimulation (FES) paradigms for spinal cord injury and stroke, and experimental brain-machine-interfaces (BMI) and neuroprothetses in the context of brain or spinal cord injury.
4 (NI/I)	Vagal, sacral, hypoglossal nerve stimulation (1.5hr)	Students will learn about the basic principles of electrical nerve stimulation and recording and how to apply knowledge of neuromodulation technology to clinical applications. As an example, vagal nerve stimulation has been applied in epilepsy, migraine and cluster headache, depression, and tinnitus.
5(I)	Deep brain stimulation for movement disorders: - clinical (45m) - mechanistic (45m)	Learn about established (i.e. FDA-approved) clinical indications for deep brain stimulation (DBS). The first hour will include an overview of DBS indications and their clinical success. The second hour will include a summary of basal ganglia circuitry and pathophysiological changes that occur in Parkinson's disease and dystonia, as well as mechanisms by which DBS may work to ameliorate symptoms.
6 (I)	Neuromodulation for epilepsy: - epilepsy monitoring and neuromodulation (45m) - childhood epilepsy and other indications (45m)	The first hour of this lecture will provide an overview of pathophysiological aspects of epilepsy and therapeutic applications of brain stimulation for seizure reduction. This lecture will also introduce to the research field of intracranial human brain recordings in the epilepsy monitoring context. The second hour of this lecture will speak about neuromodulatory approaches for childhood epilepsy and other disorders such as dystonia and self-injurious behaviour.
7 (I)	Intracranial approaches for memory: - memory and memory problems (45m) - neuromodulation for memory (45m)	In the first hour, students will learn about the different types of memory, the brain's memory circuits (ex. circuit of Papez), and how disorders of memory may arise. The second hour will discuss experimental applications of brain stimulation to augment memory. This lecture will also discuss research opportunities for studying intracranial substrates of human memory.

8 (I)	Pain: - brain (45m) - spine (45m)	Students will learn about how the brain perceives pain and mechanisms that may incite chronic neuropathic pain syndromes. Moreover, they will learn about invasive neuromodulatory approaches for pain resolution, including stimulation of the brain and spine.
9 (E)	Psychiatric conditions (1.5hr)	This lecture will briefly introduce students to the brain's stress, mood, arousal, and reward systems, and will discuss where things may go awry in psychiatric conditions such as obsessive-compulsive disorder, post-traumatic stress disorder, treatment-resistant depression, eating disorders, addiction. Students will also learn about different experimental applications of invasive neuromodulation (i.e. DBS) for these disorders.
10 (E)	Emerging clinical technology: - focus ultrasound (45m) - laser interstitial thermal therapy, drug delivery (pumps, BBB) (45m)	Therapeutic ablation (destruction) of brain tissue is an established surgical approach that has been applied for decades in various contexts. However, recent technological advances have incited new methods for alternate forms of lesions bypassing the need for open surgical procedures. In the first hour, students will learn about the non-invasive lesioning technique of focused ultrasound (e.g. essential tremor, Parkinson's disease, epilepsy). Additionally, they will learn about methods for targeted drug delivery that bypass the blood-brain barrier. In the second hour students will learn about novel therapy delivery techniques used for various functional disorders of the brain.
11 (E)	Emerging pre-clinical technology: - optogenetics (45m) - gene therapy, tissue regeneration (45m)	In the first hour, students will learn about the discovery and mechanisms of optogenetics (viral transfection and optical "stimulation") and be exposed to recent scientific breakthroughs made possible by this technology. In the second hour, students will learn about how electrical stimulation can be used to repair damaged or diseased tissue. They will learn about ongoing investigations on stem cell activation through electrical stimulation and on combining DBS and gene therapies for spatiotemporal control of gene expression in the brain.
12	Student Presentations (1.5hr)	Learn to work collaboratively with team members and communicate effectively through oral presentations and discussions.
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Course Project:

The purpose of the project is to simulate a collaborative academic research experience. Students will work in groups of 2-5 to write a "short format" academic paper (max. 2500 words and two figures). This will involve (1) conducting a literature review on a relevant topic (see project options below), which can be used to formulate the ***Introduction*** section (and inevitably parts of the Discussion section); (2) analyzing a sample human brain dataset and writing an appropriate ***Methods*** section, generating ***Figures*** *and figure legends*, and writing a ***Results*** section; (3) interpreting the results and writing a relevant ***Discussion*** section; (4) choosing one delegate to present the paper in the form of a simulated ***Conference Presentation*** of up to 12 min + 8 min for questions and discussion.

Project Milestones:

(1) *Voting on desired project topics* – each student will rank projects from 1-4 and submit their preferences before Lecture 2 – this voting will be used to formulate the groups. Those who fail to submit preferences will be assigned a project randomly. Project Topics are outlined on pages 6 & 7 of this document.
(2) *First meeting with "Project Lead"* – this will be a meeting with an Instructor, TA, or Researcher delegated as the Primary Investigator (PI) – this will occur at some point after Lecture 3 but before Lecture 5, outside of lecture hours, and will serve as a kick-off meeting to get the groups going on the right track.
(3) *Literature Review* – max. 1500 words and 25 references – to be submitted by Lecture 4. This will not be graded, but Instructors will provide feedback on important literature that may have been overlooked.
(4) *Analysis (Methods, Figure, and Results)* – to be submitted by Lecture 7 (optional). Not graded; but Instructors will again provide feedback.
(5) *Second meeting with "Project Lead"* – this will serve as a feedback meeting for the Analysis component and will take place between Lectures 7 & 8.
(6) *Optional adhoc meeting with "Project Lead"* – students may call one additional adhoc meeting with their "PI" at any time after Lecture 2 (optional).
(7) *Final paper* – due by Lecture 10. This will be worth 55.0 grade points.
(8) *Peer Review* – due by Lecture 11. This will be worth 10.0 grade points.
(9) *Conference talk* – will take place during Lectures 11 & 12. This will be worth 15.0 grade points.

Students may distribute workloads as they see fit. Each group will be required to submit a breakdown of each of the authors' contributions to the work at the end of the semester.

Project Topics:

Project 1 – Movement and stimulation-related modulation of cortical oscillations

Modality: electroencephalography (EEG)

Patient population: Parkinson's disease

Increased power in the beta frequency (13-30Hz) oscillations are a hallmark of Parkinson's disease. Moreover, beta waves are associated isotonic muscle contractions and are suppressed prior to and during movement. This dataset comprises of EEG recordings acquired from patients with Parkinson's disease, during passive movements of the upper limb (during which parkinsonian rigidity is present); with and without the application of deep brain stimulation.

Relevant paper(s):

Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, Schneider GH, Brown P. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Experimental neurology. 2009 Feb 1;215(2):380-7.

De Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Ostrem JL, Galifianakis NB, Starr PA. Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. Proceedings of the national academy of sciences. 2013 Mar 19;110(12):4780-5.

Project 2 – Basal ganglia circuit activations elicited by deep brain stimulation

Modality: subcortical microelectrode recordings (stimulus-evoked potentials in STN and SNr)

Patient population: Parkinson's disease

The mechanisms of action of deep brain stimulation (DBS) have been historically understudied. It is however becoming apparent that the effects of DBS differ on a structure-to-structure basis and depend upon the applied stimulation settings. These intraoperative data were acquired during microstimulation of the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) in patients with Parkinson's disease. Students will expect to characterize stimulation site- and frequency-specific changes to brain activity.

Relevant paper(s):

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Fasano A, Popovic MR, Hutchison WD. Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. Brain. 2018 Jan 1;141(1):177-90.

Ozturk M, Viswanathan A, Sheth SA, Ince NF. Electroceutically induced subthalamic high-frequency oscillations and evoked compound activity may explain the mechanism of therapeutic stimulation in Parkinson's disease. Communications biology. 2021 Mar 23;4(1):1-4.

Project 3 & 4 – Structural and functional networks activated by deep brain stimulation

Modality: structural (MRI) functional (fMRI) and diffusion (dMRI) magnetic resonance imaging

Patient population: (3) Parkinson's disease & (4) major depressive disorder

Deep brain stimulation (DBS) not only effects neural activity locally, but also engages brain-wide networks. By localizing the position of the implanted DBS electrode on a structural MRI, the "volume of tissue activated" can be modelled, and structural and functional network engagement can be interrogated on group level. These types of analyses can be done in an open-source software called Lead-DBS, using patient-specific imaging and standard connectomic atlases.

Relevant paper(s):

Horn A, Li N, Dembek TA, Kappel A, Boulay C, Ewert S, Tietze A, Husch A, Perera T, Neumann WJ, Reisert M. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. Neuroimage. 2019 Jan 1;184:293-316.

Elias GJ, Boutet A, Joel SE, Germann J, Gwun D, Neudorfer C, Gramer RM, Algarni M, Paramanandam V, Prasad S, Beyn ME. Probabilistic mapping of deep brain stimulation: insights from 15 years of therapy. Annals of Neurology. 2021 Mar;89(3):426-43.

Project 5 & 6 – Neuronal cell-typing and classification using human single-neuron recordings

Modality: microelectrode recordings (single-neuron)

Patient population: (5) Parkinson's disease (basal ganglia) & (6) epilepsy (mesial temporal lobe)

Intracranial single-neuron recordings can be acquired from patients during awake neurosurgery for Parkinson's disease, a procedure which involves the delineation of neural structures based on characteristic neuronal behaviour (i.e. spike firing rates and patterns). This procedure is used to inform surgical intervention location, but also allows researchers to learn about the behaviour of neurons within the brain's motor circuits. Intracranial single-neuron recordings can also be acquired within the epilepsy monitoring unit. Clinically, these recordings are used for seizure onset localization, but can also be used for to learn about the behaviour of neurons within the brain's mnemonic structures. These datasets will allow students to use different techniques (e.g. machine learning) to discretize structures from one another based on neuronal behaviour.

Relevant paper(s):

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1998 Oct;44(4):622-8.

Lee EK, Balasubramanian H, Tsolias A, Anakwe SU, Medalla M, Shenoy KV, Chandrasekaran C. Non-linear dimensionality reduction on extracellular waveforms reveals cell type diversity in premotor cortex. Elife. 2021 Aug 6;10:e67490.

Project 7 – Pathophysiological thalamic activity related to tremor

Modality: subcortical microelectrode recordings (single-neuron) and limb accelerometry

Patient population: essential tremor

Tremor is defined by involuntary rhythmic muscle contractions that can occur in one or more body parts. Essential tremor (ET) is characterized by cerebellar pathology, which leads to characteristic tremor-related brain oscillations (3-6Hz) that are highly congruent with limb tremor. This dataset includes simultaneously acquired local field potential (LFP) and single-neuron recordings form the (cerebellar-receiving) thalamic ventral intermediate nucleus, as well as accelerometry during postural tremor. Students will be expected to characterize relationships between these central and peripheral signals and their modulation by deep brain stimulation.

Relevant paper(s):

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain. 2018 Jul 1;141(7):2142-55.

Scherer M, Steiner LA, Kalia SK, Hodaie M, Kuehn AA, Lozano AM, Hutchison WD, Milosevic L. Single-neuron bursts encode pathological oscillations in Parkinson's disease and essential tremor. bioRxiv. 2022 Jan 1.

Project 8 – Eye-movement related modulation of hippocampal activity

Modality: subcortical microelectrode recordings (local field potentials and event-related potentials)

Patient population: epilepsy

Eye movements are closely related to a variety of memory processes. Since the hippocampus is known to be the hub of declarative memory processes, investigating the interaction between eye movements and hippocampal activity is critical. Event related potentials (ERPs) are often used to characterize neural responses to a particular event (such as the start or stop of an eye movement). The spectral properties of these ERPs can provide insights into potential mechanisms that generate neural responses. This dataset includes recordings from the human hippocampus, along with concurrently recorded eye movement timings. Students will be expected to characterize the eye-movement related ERPs in the human hippocampus (in the time and frequency domain).

Relevant paper(s):

Katz CN, Patel K, Talakoub O, Groppe D, Hoffman K, Valiante TA. Differential Generation of Saccade, Fixation, and Image-Onset Event-Related Potentials in the Human Mesial Temporal Lobe. Cerebral Cortex. 2020 Oct;30(10):5502-16.

Katz CN, Schjetnan AG, Patel K, Barkley V, Hoffman KL, Kalia SK, Duncan KD, Valiante TA. A corollary discharge mediates saccade-related inhibition of single units in mnemonic structures of the human brain. Current Biology. 2022 Jul 1.

Inclusivity:

You belong here. The University of Toronto commits to all students, faculty and staff that you can learn, work and create in a welcoming, respectful and inclusive environment. In this class, we embrace the broadest range of people and encourage their diverse perspectives. This team environment is how we will innovate and improve our collective academic success. You can read the evidence for this approach here.

We expect each of us to take responsibility for the impact that our language, actions and interactions have on others. Engineering denounces discrimination, harassment and unwelcoming behaviour in all its forms. You have rights under the Ontario Human Rights Code. If you experience or witness any form of harassment or discrimination, including but not limited to, acts of racism, sexism, Islamophobia, anti-Semitism, homophobia, transphobia, ableism and ageism, please tell someone so we can intervene. Engineering takes these reports extremely seriously. You can disclose incidents of discrimination or harassment to our Assistant Dean, Diversity, Inclusion and Professionalism through email or through a disclosure form. You can also talk to anyone you feel comfortable approaching, including your professor or TA, an academic advisor, the Engineering Equity Diversity & Inclusion Action Group, any staff member or a U of T Equity Office.

You are not alone. Here you can find a list of clubs and groups that support people who identify in many diverse ways. Working together, we can all achieve our full potential.

Accommodations:

The University of Toronto supports accommodations for students with diverse learning needs, which may be associated with mental health conditions, learning disabilities, autism spectrum, ADHD, mobility impairments, functional/fine motor impairments, concussion or head injury, blindness and low vision, chronic health conditions, addictions, deafness and hearing loss, communication disorders and/or temporary disabilities, such as fractures and severe sprains, or recovery from an operation.

If you have a learning need requiring an accommodation the University of Toronto recommends that students register as soon as possible with Accessibility Services at https://studentlife.utoronto.ca/service/accessibility-services-registration-and-documentation-requirements/.

Phone: 416-978-8060
Email: accessibility.services@utoronto.ca

Mental Health:

As a university student, you may experience a range of health and/or mental health challenges that could result in significant barriers to achieving your personal and academic goals. Please note, the University of Toronto and the Faculty of Applied Science & Engineering offer a wide range of free and confidential services that could assist you during these times.

As a U of T Engineering student, you have a First- Year Advisor, a Departmental Undergraduate Advisor or a Departmental Graduate Administrator who can support you by advising on personal matters that impact your academics. Other resources that you may find helpful are listed on the U of T Engineering Mental Health & Wellness webpage, and a small selection are also included here:

- Accessibility Services & the On-Location Advisor

- Graduate Engineering Council of Students' Mental Wellness Commission
- Health & Wellness and the On-Location Health & Wellness Engineering Counsellor
- Inclusion & Transition Advisor
- U of T Engineering's Learning Strategist and Academic Success
- U of T Engineering's Mental Health Programs Officer
- My Student Support Program (MySSP)
- Registrar's Office
- SKULE Mental Wellness
- Scholarships & Financial Aid Office & Advisor

If you find yourself feeling distressed and in need of more immediate support resources, consider reaching out to the counsellors at My Student Support Program (MySSP) or visiting U of T Engineering's Urgent Support – Talk to Someone Right Now webpage.