Midterm – example solutions

These are solutions from some of your exams. These are very often not the best ones, but all of them were right to some extent. The objective of this is to guide you, and help you judge your efforts and results in Neural Engineering.

1. **(a)** Compare shank, sieve, and needle probes. Describe their advantages and disadvantages with your own words. Cite at least one application of each. **(b)** Discuss in which *in vitro* systems a sieve probe would be useful. Be creative. (I'm looking for a system in which nobody has ever used a sieve probe yet.)

I would like to use sieve probes to study the mechanism of neural plasticity. There is already an in-vitro neurobiological system interconnected to an artificial sensory motor device.

Each sieve will not only have a circular electrode site as outer rings but the inside of the sieve can be incorporated with multiple recording sites. We can use multi vertically aligned nanotubes as electrodes so that we can have both recording as well as stimulating sites on it. These multiple recording/stimulating sites in the sieve will be coated with polylysine so that neurons will grow on that specific area. The dimension of the sieve is such that single units of neural chain can grow through it.

This should be implanted in a live brain tissue (keep it alive by keeping in the required environment). By filling the sieves with neurotrophic chemicals and stimulating the neural tissue where the electrode is implanted we can ensure that neurons grow through it.

This way we are not only providing a medium for the neuron and synapses to grow but as well monitor how they are growing. Once the data is collected from the various recording sites, we could map how the neurons with their synapses are growing.

Now by stimulating the live brain tissue in different ways we can observe the changes in synaptic potentials and hence observe the induced artificial synaptic plasticity. We could also stimulate individual neuronal branch and see how it affects the rest. By integrating the data we can create a statistical model for synaptic plasticity induced ~~due to~~ by stimulation. The analogy of this structure is more like a cylindrical case enclosing wires of individual neural links coming out of a specific area of neural tissue.

The drawbacks with this design are it's hard to fabricate such structures with the present technology. One way would be to grow the nanotubes on specific areas when the sieves are being fabricated. Coat the whole inner layer with polylysine and using an Atomic Force microscopy remove it from areas not required. It's going to be very expensive and painful procedure.

(b) Stem cell research is a hot topic because the extraordinary differential ability of stem cells. After necessary stimulus (agent or electromagnetic field stimulus), some kind of stem cell can develop into neuron like cells in pyramidal shape. In vitro culture stem cell, induce it into neuron like cells, try to let axon or dendrite like structure passes through holes of sieve probe. You can record the information during cell differentiation and you don't need to cut anything. Different stimulus will produce different neuron like cells, different information will be collected. This might be helpful for the research on the relationship between cell morphology and function and for the research on sieve probe itself.

One application for the sieve probe could be used in chemical sensors. Detecting a bomb, drugs, or weapons for example at the airports. The way it can be done is by using a dog's nose considering that a dog has to be either put to sleep or we have a clone used for just that purpose (cutting the nose). The sensor assembly would be made of an actual nose probably kept alive in some physiological environment. Olfactory receptor neurons usually reside on the olfactory epithelium in the nasal cavity. Those neurons can be connected to the sieve probe and to the display.

great idea
lot so great implementation (cloning). You can culture the cells.

One new "in vitro" system in which sieve probes would be useful is to create a biological camera whose individual components would be composed of the human eye. The eye could be generated in vitro (similar to Sedhora A. et al., 2003 where an in vitro generated eye was implanted into a tadpole whose both eyes were removed). This in vitro generated eye would have an optic nerve on which sieve probes would be used to connect to a computer which would have software that can interpret the signals as images (similar to the visual cortex in the brain). This biological camera could eventually be used to replace retinal implants and hopefully could be implanted into humans, with sieve probes replacing the visual pathway and the visual cortex replacing the signal processing computer.

2. Explain why different neurons may have different shapes of their action potentials. What do action potential signals depend on? Why isn't it always the same (stereotypical), independently of cells?

2. An action potential is an active response (voltage change) of the cell membrane when the depolarization exceeds threshold. The shapes of the action potentials and the level of thresholds vary from neuron to neuron and even at different time spans within one neuron. It is mainly determined by the features of the ion channels of the cell, which can be investigated by patch clamp recording. Different cells have different ion channels and there are several different ion channels within one cell. Therefore, different neurons have different shapes of action potentials. The excitation of an action potential obeys all-or-none law, which means that any stimulus that large enough to produce an action potential will cause the same size of action potential. Although the amplitude of it is independent of stimulus, other of its properties, such as latency, refractory period and the frequency of repeated firings, are not.

   Neurons in different part of nervous system are diverse, in their morphology, electrical and biochemical properties. Action potentials of them also vary in shape and size. This kind of diversity accommodates the function diversity of them.

Cells in different regions of the nervous system are diverse in their morphology and in their electrical and biochemical properties. The action potential can vary in shape and size in different neurons. The pattern of action potential firing is also very diverse in different neurons, which reflects differences in membrane ion channels. Neurons have to control a variety of different behaviors and physiological functions, so it is actually not surprising that not all action potentials are the same. For instance, some neurons control rapid reflexes while others control slower behaviors such as breathing.

The action potential is the signal that carries messages over long distances along axons in the nervous system. The generation of an action potential depends on several factors. The relative permeability of the cell membrane to sodium and potassium is what controls the membrane potential. The ionic permeability of the plasma membrane of excitable cells is not fixed, and a large, transient increase in sodium permeability is the basis for the generation of the action potential.

There are several major characteristics of action potentials that are affected by the underlying ionic permeability changes. Action potentials are triggered by depolarization, or a reduction in membrane potential. A threshold of depolarization must be reached in order to trigger an action potential, typically about 10-20 mV. Action potentials are all-or-none events, meaning that once a stimulus is strong enough to reach threshold, the amplitude is independent of the strength of the stimulus. If depolarization is above threshold, the event will go to completion, but if the depolarization is below threshold, no action potential will occur. Some action potentials travel faster than others. At the peak of an action potential, the membrane potential reverses its sign, causing the inside of the cell to become positive for a short time. Then, the action potential repolarizes toward the normal resting potential. After a neuron fires an action potential, there is a small period of time in which another action potential cannot be triggered, called the absolute refractory period.

Different neurons exhibit different patterns of action potential firing because of differences in membrane ion channels. Some neurons are normally silent, with their membrane potential staying at the resting potential unless the firing of the action potentials is triggered by an external stimulus. Once the stimulus is no longer present, they return to their nonfiring state. Many other neurons have more complex electrical activity, and often fire action potentials in regular patterns without external stimuli.

Also, the electrical properties of a neuron are not fixed. Instead, they are modulated by input from the environment, including hormones released, chemical and electrical signals from other neurons to which the neuron is connected, and sensory information from the outside world. This modulation by the environment allows the organism to adapt its behavior in a constantly changing environment.

3. You are designing a generic implantable neural prosthesis. You have to consider the four principles of brain function (principles emerged in the early 20th century as a consequence of new neuronal recording techniques). What would you change in your design to account for principles 3 and 4 (synaptic plasticity and theory of cell assemblies)?

In the early twentieth century, recording from the nervous system resulted in the emergence of several principles of brain function. These four principles are: coordinated patterns of activity, theory of mass action, synaptic plasticity, and theory of cell assemblies (information representation is stochastic, redundant, related to function not to anatomy). In the design of a generic implantable neural prosthesis, in order to account of principles three and four (synaptic plasticity and the theory of cell assemblies), some changes would need to be made.

For principle three, the Hebbian rule suggests that simultaneous activity between a presynaptic cell and a postsynaptic cell would increase the strength of the synapse and make this pathway more likely to respond to future stimuli. To account for this in a generic implantable neural prosthesis, a neural network that takes into account the four key properties that characterize a Hebbian synapse, and such a neural network should be incorporated into the device. First, there should be a time-dependent mechanism because modifications in a Hebbian synapse depend on the exact time of occurrence of the presynaptic and postsynaptic signals. Second, local mechanism should be taken into account. By nature, a synapse is the site of transmission where the information signals are in spatiotemporal connection. The Hebbian synapse uses this information to produce a local synaptic modification that is input specific. Third, there should be an interactive mechanism. The change that occurs in a Hebbian synapse depends on signals from both sides of the synapse. Fourth, conjuctional or correlational mechanism should be taken into account. The presynaptic and postsynaptic signals are correlated over time, and this correlation is the basis of learning. In mathematical terms, there is a synaptic weight of a neuron with presynaptic and postsynaptic signals. At each time step, the synaptic weight would be adjusted.

For principle four, individual neurons do not convey information by themselves, but instead work together as assemblies of activity to represent information. In order to take this into account for the implantable neural prosthesis, an area of (motor) cortex that will control the prosthesis should be recorded from/used for the prosthesis. For example, if the prosthesis was an artificial finger, more than one neuron would be used to control it. The prosthesis might consist of an array of electrodes that stimulate the motor cortex that would cause the prosthetic finger to move. The prosthesis would also consist of an electrode driver, a controller, a coil interface, and the transmitter data modulator. The output from the Hebbian synapses would be sent to a computer where the neural network would be used to update the synaptic weights in accordance with the mathematical model for synaptic plasticity. As learning occurs, the assembly of neurons involved would become more coordinated in moving the prosthetic finger, and the movement would become more realistic and control would be faster.

4. In the paper IEEE TBE 2006, vol. 53, n. 4, 726-737, why were the authors expecting extracellular signals to be better when the surface area of the electrodes was small? (in page 730, it reads: "*Rather unexpectedly, the quality of the unit recordings was not significantly poorer when the electrode surface areas were larger, although the microelectrodes with the large exposed tips tended to record multiple, rather than single, neuronal units.*") Attempt to give a technical explanation. However, please in the end write a "bottom line" sentence, explaining it in lay terms. No need to be creative.

Because the lower readings, peaks, of the electrodes with lower surface area are smaller, they are more selective. The larger peaks from the electrodes with greater surface area have a main peak but also carry larger ripple peaks in one reading, these ripple peaks come from nearby neurons firing. The ripples from the small electrodes are much smaller to the main peak and can be almost ignored.

Larger surface electrodes retrieve signals from multiple neurons which lead to larger unselective plots of multiple peaks while smaller surface area electrodes are more precise and selective in reading individual cell activity.

The expectation of smaller surface area electrodes to have better signals is because the size has an impact on recording signal quality. Smaller surface area offers higher spatial resolution, higher amplitude and better discrimination between units. The impedance is also higher on smaller surface areas which means that the current will be lower. The bottom line is that spatial resolution. That is the ability to sharply and clearly define the extent or shape of features. It describes how close two features can be and still be resolved as unique.

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5. Pick one researcher (author) whose work is directly related to your final project. The author should be a senior person in the field you are researching. After scanning some of his/her papers, write two to three paragraphs describing his/her research interests and his/her main contribution to Neural Engineering. Finally, discuss the impact of his/her work on society.

Miguel A.L. Nicolelis, MD, PhD , is currently working in the Department of Neurobiology at Duke University Medical Center. In 1984, he received his MD from the University of Sao Paolo Medical School in Brazil. He then received his PhD from the Department of Physiology from the Institute of Biomedical Science at the University of Sao Paolo in Brazil. He then did his postdoctoral fellow at Hahnemann University in the Department of Physiology and Biophysics. His current position is Professor of Neurobiology Biomedical Engineering and Psychological and Brain Sciences and he is also the co-director for the Center for Neuroengineering.

Dr. Nicolelis' research focuses on several areas, including neural ensemble recordings in behaving animals, distributed processing of tactile information, sensory plasticity, thalamocortical function, neuroprosthetic design, brain machine interface, conditional motor learning, and gustatory processing by ensembles of neurons. The current focus of his lab/research is to understand the general computational principles involved in the dynamic interactions between populations of cortical and subcortical neurons that mediate tactile perception. He has helped contribute to the development of new electrophysiological techniques, including recording long-term simultaneous extracellular activity of up to 128 single neurons distributed across multiple levels of somatosensory and motor pathways in behaving animals. In conjunction with electrophysiological techniques, his work uses multivariate statistics, computer graphics, and neural network models. By using all of these methods, he is able to analyze the spatiotemporal structure of neuronal ensemble activity and its correlation with different aspects of exploratory tactile behaviors. This work is important because a large part of the mammalian brain is devoted to the active exploration of the surrounding environment. This exploration uses large assemblies of neurons that are distributed across multiple levels of parallel sensory pathways.

Dr. Nicolelis' main contribution to the field of neural engineering is the control of a robotic arm by the brain. This was done in a monkey model. His research in brain machine interfaces has made major contributions to the field of neuroengineering, and has even been recognized by MIT's Magazine of Information Technology as one of the major emerging technologies that will change the world. Obviously, the impact of his work on society is great. Currently at Duke, the development of a custom VLSI "neurochip" is underway that will decodes brain signals and might eventually be useful in the restoration of motor function for patients who are paralyzed or have neurological deficits. Therefore, this work will help improve the quality of life for many people.

6. After considering the side effects of stimulation in the brain, in particular with implants in STN and GPi, as described below, suggest a solution to deal with the problem, either *a priori* (for example, modifying the implant), or *a posteriori* (keep the implant the same, deal with at least one of the side effects).

[The text quoted below is from the journal **Neuron**, vol. 52, 197-204, October 5th, 2006, "*Deep brain stimulation for neurologic and neuropsychiatric disorders*", a review by T. Wichmann and M.R. DeLong]

The precise mechanism of the action of high frequency stimulation is yet unknown.

The electric field induced by DBS is dependent on the

1. Electrode contact geometry,
2. Distribution of cathodes and anodes and
3. Biophysical properties of the tissue medium.

One of the reasons for unknown DBS modulation mechanisms and extent of current spread are due to the inhomogeneous and anisotropic tissue conductivities nature of the Brain.

The side effects induced by DBS depend on the exact location of the stimulation electrode, the choice of stimulation parameters and type, position and orientation of various neural elements subjected to stimuli.

In the paper they say that, "side effects are likely caused by inadvertent stimulation of limbic circuit element in portions of nearby zone incerta, ventral STN or SNR". However, this has not only been reported with stimulation of unintended targets but also reported with well-placed electrodes within the motor regions STN and Globus Pallidum.

Stimulation and lesions produce similar behavioral response. Therefore, DBS acts by inactivating/blocking the local cells. ~~Although~~, stimulation of ~~a~~ structures composed of mainly cell bodies such as nuclei or ganglia results in inhibition, but stimulation of fiber bundles results in excitation. (Benabid, et. al. 2000)

A recent

Recent study (McIntyre, 2006) has shown that we can control the volume of tissue activation through the electrode geometry. They also say that it would be beneficial if we can have relatively large contact while optimizing VTA (Volume tissue activation) aspect ratio for a given target area.

The traditional DBS electrodes used are same for different anatomical regions and are also limited to a minimum diameter.

Keeping all the above things in mind my suggestion would be to make changes in the present implant system to negate these effects.

The First thing would be to reduce the size of the electrode diameter yet keep its charging capacity efficient enough. I would deposit CNT on the active area of electrode, perpendicular to the electrode axis and later deposit Iridium oxide. The advantage of doing so is that CNT's not only have high aspect ratios, they also will increase the surface contact area and Iridium Oxide will provide for high charge capacity at high frequency stimulation. The next step would be to compute volume and area of tissue this structure would affect, using the help of the available computational models. I would insert recording electrodes in the areas where I know it might affect the other neural elements. These recording electrodes would have another outer covering above the active area, which will have small nano-pore pumps made of CNT's. Nano-pumps made of CNT's can be opened if sound waves are passed on its surface. These nano-pumps could be used to selectively deliver chemicals at cellular level. The electrode area that's jutting out of the scalp can have a provision through which the medicines can be injected into the brain via nano pipettes connected to the nano-pumps. Once the stimulation is initiated, the recording electrodes would sense the activity and provide a feedback to the medicine unit. The necessary medication will be diffused into the necessary neural element to activate or inactivate it as long as the simulation persists.

The medicinal unit could be made as a refillable unit and with capabilities of indicating when it needs to be refilled. The number of recording electrodes would depend on what major side effects we need to counteract to have a better-improved life.

the other problem is that the stimulation would also affect the drug itself

Initially I wanted to suggest a single electrode that could stimulate and inject medicine if the patient observes side effects. I assumed that the medicine would flow to the affected area but I think that's not how medicines diffuse. We need to deliver it to the specific region. Another draw back I observed with a single electrode was that somebody had to administer the medicine be it the patient or the doctor always. Hence, I rooted out the first idea.

By controlling the electrode geometry I will be able to see that the current field is limited to my region of interest, thus reducing the effects it causes to nearby neural systems. The nano-pumps are created to inhibit neural fibers and axon excitation nearby cells.