9.01 Introduction to Neuroscience
Fall 2007

9.01 Problem Set 3: Learning and memory

Fall 2007
Due Friday, Dec. 7 at 12 noon.

No late submissions will be accepted.

This problem set will develop your understanding of neural network models of memory, and of the NMDA receptor. While collaboration is allowed, you are required to write up your solutions independently, as well as document the names of your collaborators. In your answers, please try to address all major points yet also be concise.

1. **The McCulloch-Pitts model neuron**. Previously we learned how action potentials and synaptic potentials are caused by the dynamics of ionic conductances. Such dynamics were modeled mathematically by Hodgkin and Huxley in their Nobel-winning 1952 paper. But much simpler models of neurons have also proved useful for studying the computational capabilities of neural networks. The first was proposed in 1943 by McCulloch and Pitts, and captures the idea that a neuron fires an action potential when a sufficiently large number of incoming excitatory synapses are activated together. McCulloch and Pitts proposed the model while working at the University of Chicago, and used it to argue that neural networks could be universal computers. Later they moved to MIT and collaborated with the neurophysiologist Jerome Lettvin and the mathematician Norbert Wiener. Pitts was an eccentric, self-taught genius who died at the untimely age of 46.

a) Suppose that a cortical neuron has a resting potential of –70 mV. If its voltage is driven to the threshold value of –50 mV, it generates an action potential. The neuron receives about 10,000 excitatory synapses. If a single synapse is activated, it produces a small change in voltage, an excitatory postsynaptic potential (EPSP) with amplitude of 0.5 mV. Let's make the approximation that the EPSPs sum approximately linearly if multiple synapses are activated simultaneously. How many synapses must be activated simultaneously in order to make the neuron fire an action potential?

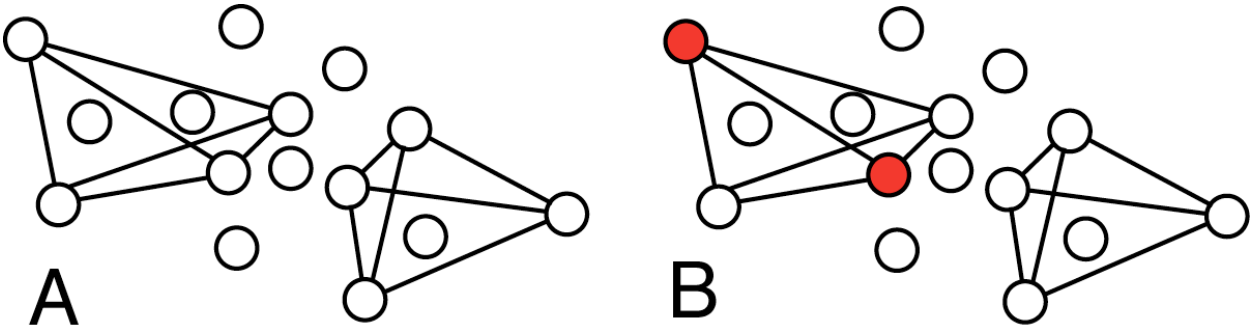
b) Let $x_1,\ldots,x_n$ be the n inputs to the neuron. Let y be its output. Both inputs and output are assumed to be binary, taking on the values 0 (inactive) or 1 (active). Then the McCulloch-Pitts model neuron is

$$y = \begin{cases} 1, & \sum_{i=1}^{n} x_i \geq \theta, \\ 0, & \text{otherwise} \end{cases}$$

The neuron becomes active (y=1) when the number of active inputs is greater than or equal to the integer-valued threshold θ.[1] If we want to model the cortical neuron of part (a), how would we set the parameters θ and n?

[1] Note that gradations in firing rate among active neurons are ignored for simplicity. The full McCulloch-Pitts model also includes inhibitory synapses, but only excitatory synapses are considered here.

2. **Pattern completion by a Hebbian cell assembly**. In class we discussed the CA3-specific NR1 knockout mouse that was generated in the Tonegawa lab. If the knockout mouse learned the Morris water maze with multiple visual cues present, but was tested after some cues were removed, then its performance was significantly worse than that of a normal mouse. It was proposed that this was due to defective performance of the hippocampal CA3 network at "pattern completion." Let's try to understand the phenomenon of pattern completion in a network of McCulloch-Pitts model neurons. Pattern completion is the Hebbian conception of how a memory can be retrieved from synaptic connections.



a) Figure A shows a lot of neurons, symbolized by circles. There are two cell assemblies, each containing four neurons. A line symbolizes two excitatory synapses between a pair of neurons, one in each direction. Describe what activity patterns could have previously created the cell assemblies through Hebbian synaptic plasticity. This is the Hebbian conception of how memories are stored in synaptic connections. Before the cell assemblies were created, you can assume that there were very weak synapses between all pairs of neurons. Such weak synapses are not drawn in Figure A; only the strong ones are shown.

b) In Figure B, two neurons in one cell assembly have become active (symbolized by red). (They were activated by synaptic inputs from some sensory source, which are not shown). Suppose that all neurons are described by the McCulloch-Pitts model with a threshold of $\theta=2$. Will pattern completion occur, i.e., will the whole cell assembly become active? Explain your answer.

c) Suppose that the threshold is $\theta=3$. Will pattern completion occur in Figure B? Explain your answer.

d) Now consider a more general case. Suppose that all cell assemblies contain n neurons, and all neurons have the same threshold θ. Suppose that k neurons of a cell assembly are activated by sensory input. Characterize the conditions under which pattern completion occurs.

3. **Voltage dependence of the NMDA receptor**. At glutamate synapses, AMPA and NMDA receptor types are typically colocalized. The conductance of the NMDA receptor depends on voltage; the channel is blocked by magnesium unless the membrane is depolarized. The fraction of receptors that are *not* blocked by magnesium is given by

$$B(V) = \frac{1}{1 + 0.33\exp(-0.06V)}$$

a) Graph this function from $V = -100$ mV to 0 mV.

b) Suppose that you could magically clamp the voltage of a neuron at any value that you like. Suppose also that you could measure the change in the conductance of the neuron due to stimulation of an incoming glutamate synapse. (Both of these can be accomplished by using the voltage clamp method to record from a neuron in a brain slice preparation.) You measure the conductance change while the brain slice is bathed in three different solutions,

i) Saline solution plus CNQX
ii) Saline solution plus CNQX plus AP5
iii) Saline solution plus CNQX minus magnesium

and while the neuron is held at two different voltages, –70 mV and 0 mV. The saline solution mimics the extracellular milieu *in vivo*. CNQX is an AMPA receptor antagonist. AP5 is an NMDA receptor antagonist.

The three solutions and two voltages make for a total of six different conditions. In each condition, you measure a conductance change. Suppose that the amplitude of the conductance change with solution (iii) and 0 mV is denoted by the value 1, and all other amplitudes are measured relative to that. Now calculate all five of the other amplitudes.