NBL 355-655 Module 8 Review Q&A

1. *Why do neurons propagate/conduct AP along the axon? When the AP is said to “travel” down an axon, what is actually traveling and what does that affect?*

Neurons propagate/conduct APs along the axon so that the axon presynaptic region can become depolarized and can participate in/initiate synaptic transmission. Propagation/conduction of the action potential ensures that the presynaptic terminus undergoes a large depolarization that will produce synaptic transmission and communication with the target cells. What really travels/moves are the Na+ and K+ ions inside the axon, which are the Na+ and K+ currents.

1. *What factors determine the movement of ions across the axonal membrane and within the axoplasm? What are the two currents in the axon?*

The factors that affect the movement of ions are chemical diffusion and coulomb forces, which together underlie the DF-electrochemical gradient. The two currents are the transmembrane current (through ion channels) and the axial current (in the axoplasm). The axial current depends on the diameter of the axon while the transmembrane current depends on the presence of ion channels and whether the membrane is myelinated.

1. *Describe the mechanisms of continuous AP conduction.*

In continuous conduction, the AP activates VGNa+ channels in the adjacent membrane region, Na+ flows into the axon (the transmembrane current) and that Na+ diffuses in the axon (the axial current). Since VGNa+ channels are located all along the axon, the Na+ needs to travel only a short distance in the axon, and as it does, it depolarizes the adjacent membrane potential, and thus activates the adjacent VG Na+ channels. There is sequential activation of the VG Na+ channels all along the entire length of the axon. This involves the transmembrane Na+ current followed by a small axial Na+ current, followed by a transmembrane Na+ current and so on. In a similar manner, VG K+ channels are located all along the axonal membrane where they repolarize the AP, producing an outward K+ current at every membrane along the axon. In continuous conduction, the AP is regenerated at every membrane region along the axon.

1. *What are the two mechanisms that axons use to increase the rate of AP conduction? What types of neurons require an increased rate of AP conduction?*

The two mechanisms that increase the rate of AP conduction are increasing the diameter of an axon, and myelination. The types of neurons that need an increased rate of AP conduction are neurons with long axons. These include both somatic and autonomic lower motor neurons and sensory neurons (whose axons are located in the PNS in nerves), and in the CNS the projection/principal neurons that need to send their signals over long distances. Projection/principal neurons extend their axon outside of one CNS region where its cell body is located, and make synapses with target neurons in another region of the CNS.

1. *What are the myelinating cells in the CNS and PNS? In addition to myelination, what else do myelinating cells provide?*

Myelinating cells in the CNS are oligodendrocytes. Myelinating cells in the PNS are Schwann cells. In addition to affecting the speed and efficiency of the action potential, myelinating cells also provide trophic (survival) support to the axons they myelinate.

1. *What are the Nodes of Ranvier (NoR)? What happens at the NoR and why? Why are the NoR spaced the distance apart that they are?*

Nodes of Ranvier are small gaps in the myelinated axon that are the regions of theaxonal plasma membrane that are not myelinated. The Na+/K+ ATPase, leak channels, VGNa+ channels and VGK+ channels are all localized to the Nodes of Ranvier. As these are the regions where there is no myelin membrane, this is where Na+ and K+ ions cross the membrane to establish the RMP, and to regenerate the AP (depolarize or repolarize the membrane potential). The Nodes are spaced at the distance they are so that they are far enough to favor the axial current, but close enough so the membrane potential doesn’t decay below threshold before it reaches the adjacent Node of Ranvier.

*7. Describe the mechanisms of saltatory AP conduction. How are continuous and saltatory conduction similar, how are they different?*

In saltatory conduction, which occurs in a myelinated axon, the AP is regenerated only at the Nodes of Ranvier, because those are the only regions of the axonal membrane where the VG channels are located and where the channels have access to the extracellular fluid. At the Node, an AP is generated by activation of VG Na+ channels, and produces the Na+ current as Na+ flows across the membrane (a transmembrane current). Those Na+ ions then move along the axon (the axial Na+ current), which depolarizes the membrane potential. There are no VG channels in the myelinated segments. There are also no leak channels or pumps in the myelinated segments. In addition, the myelin covers the axonal membrane so there is also no extracellular fluid around the axonal membrane. This also means that as the axial current is moving along the axon, the ions can’t flow back across the membrane (through leak channels or transporters), and so no current is lost across the membrane. The axial current flows passively along the axon and as it does, it depolarizes the adjacent membrane within the myelinated segment. Some Na+ ions do diffuse into the axoplasm, and so some current is lost with distance from the Node and time. However, by the time the current has spread to the adjacent Node, it is still large enough that it will depolarize the membrane potential above threshold (-55 mV) so that it will activate the VG channels at the next Node, which regenerates the AP. Therefore, the AP is regenerated only at the Nodes. Between the Nodes in the myelinated segments, there is only passive movement of current. In a similar manner, VG K+ channels are located only at the Nodes, so the repolarization of the AP occurs only at the Nodes as well.

Similarities: Both types of conduction are similar in that they both produce an action potential (a large depolarization followed by repolarization and hyperpolarization) where they are produced. They both involve the opening and closing of the voltage gated Na+ and voltage gated K+ channels. They are both initiated at the initial segment and travel along the axon in one direction to the presynaptic terminus. They both are required to depolarize the presynaptic region to initiate synaptic transmission.

Differences: In an unmyelinated axon, conduction is continuous since the VGNa+ and VGK+ channels are located all along the length of the axon. These channels produce a transmembrane inward Na+ current followed by a transmembrane outward K+ current. Continuous conduction doesn’t require much axial current, just enough to depolarize the adjacent VG channels. So the rate is slower (1-10 m/sec) because it takes time to open the VG channels, for the Na+ ions to flow in and then move to activate the adjacent VG channels.

In saltatory conduction, the VG Na+ and VGK+ channels are located only at the Nodes of Ranvier (the unmyelinated regions). Thus the transmembrane Na+ and K+ currents are produced only at the Nodes. In the myelinated segments, more of the Na+ and K+ currents travel along the axon (axial currents). Saltatory conduction is much faster (20-100 m/sec) because it relies more on the axial current, which is must faster than the transmembrane current (since the transmembrane current requires more time to open the VG channels and Na+ to flow in etc). The axial current can involve more movement of charges by Coulomb forces, which is faster than chemical diffusion. In addition, in myelinated axons there is also an internodal potential, which adds to the membrane potential and increases the electrochemical gradient. Saltatory conduction is more efficient because it requires fewer total VG channels (since they are localized at only the Nodes) and less energy is required to produce the resting membrane potential (which occurs at the Nodes and then spreads passively).

*8. In myelinated axons, VGNa+ and VGK+ channels are located only at the NoR. In addition, myelination increases the membrane resistance (Rm), enhancing axial/internal current because ions don’t move back across the membrane by channels and transporters. How/why do both of these factors affect the speed and efficiency of AP propagation along a myelinated axon?*

See discussion above. Increasing the Rm will decrease the transmembrane current. In myelinated axons, the transmembrane current occurs only at the Nodes. By increasing the membrane resistance in the myelinated segments, it prevents ions from crossing back across the membrane as easily. This means that more ions move within the axoplasm since they are not lost across the membrane, and this enhances the axial current in the axoplasm. The axial current is faster than the transmembrane current since it doesn’t require the opening of ion channels and also, the axial current can involve the movement of charges by Coulomb forces, which is faster than chemical diffusion. This increases the speed of depolarization along the axon. As mentioned above, it also enhances the efficiency since the channels and the active transporters only need to be present at the Nodes (so it requires fewer of these).

*9. What mechanism ensures that the AP moves in only one direction down the axon?*

The inactivation of the VG Na+ channels ensures the unidirectional conduction of the AP. Once they are activated/opened, the VG Na+ channels close and inactivate. Hence, even though the downstream segment of the axon mediates a Na+ current and is depolarized, the upstream VG Na+ channels can’t open again because they are inactivated. They require repolarization of the AP back to the RMP (through the function of the VG K+ channels) to return to the closed-active state, where they can then be opened again and produce another AP. However, by the time this happens (repolarizing back to RMP and the VG Na+ channels returning to the open-active state), the Na+ current and depolarization of the downstream AP is too far away (and thus will have already passively decayed) to have any effect on the upstream VG Na+ channels.

*10. If the myelin membrane is damaged or lost, as occurs in the demyelinating disorder multiple sclerosis (MS), how could this affect AP conduction? How could it affect synaptic transmission? How could it affect axons?*

If the myelin membrane is damaged or lost, as in MS, the action potentials could stop completely (AP conduction would be stopped). This could prevent the AP signal from reaching the end of the presynaptic region, and thus prevent synaptic transmission. This is what happens in MS, and some of the most vulnerable axons are long axons in the spinal cord that control motor neurons that innervate muscles in the legs, and the optic nerve involved in transmission in the visual system. (Only CNS axons are demyelinated in MS.) Demyelination can also be detrimental to the health of the axon because oligodendrocytes, which provide myelin, also provide trophic (survival) support to the axons they myelinate. Without trophic support, the axon could degenerate. As we learned earlier, once CNS axons degenerate, they can’t regenerate in the CNS, leading to an irreversible loss of axons.

*11. Why is AP conduction significantly faster in a myelinated axon? Why is the axial current so fast?*

AP conduction is faster in a myelinated axon because myelination favors the axial current over the transmembrane current. The axial current moves so fast because of the Coulombic interactions, in which ions are attracted to or repulsed by nearby ions. This facilitates the movement of an ionic charge rapidly through the axoplasm (which has a theoretical speed equal to the speed of light), which is much faster than the rate of the chemical diffusion of ions in solution.

12. *What does the frequency and duration of APs depend on? What is the neural code?*

In the simplest systems, the frequency and duration of the train of APs depends on the magnitude and duration of the summed graded potentials (inputs from synapses) in the neuron. The neural code refers to how information is encoded in APs (frequency, timing, pattern, and/or number- or some other aspect) and then decoded at the synapse in synaptic transmission.

From Wikipedia: The link between stimulus and response can be studied from two opposite points of view. Neural encoding refers to the map from stimulus to response. The main focus is to understand how neurons respond to a wide variety of stimuli, and to construct models that attempt to predict responses to other stimuli. Neural decoding refers to the reverse map, from response to stimulus, and the challenge is to reconstruct a stimulus, or certain aspects of that stimulus, from the spike sequences it evokes.

**Hypothesized coding schemes** (The basic definitions of rate coding, temporal coding, and population coding will be on the quiz.)

A sequence, or 'train', of spikes may contain information based on different coding schemes. In motor neurons, for example, the strength at which an innervated muscle is contracted depends solely on the 'firing rate', the average number of spikes per unit time (a 'rate code'). At the other end, a complex 'temporal code' is based on the precise timing of single spikes. They may be locked to an external stimulus such as in the visual and auditory system or be generated intrinsically by the neural circuitry. Whether neurons use rate coding or temporal coding is a topic of intense debate within the neuroscience community, even though there is no clear definition of what these terms mean.

**Rate coding**

The rate coding model of neuronal firing communication states that as the intensity of a stimulus increases, the frequency or rate of action potentials, or "spike firing", increases. Rate coding is sometimes called frequency coding. Rate coding is a traditional coding scheme, assuming that most, if not all, information about the stimulus is contained in the firing rate of the neuron. In most sensory systems, the firing rate increases, generally non-linearly, with increasing stimulus intensity. Any information possibly encoded in the temporal structure of the spike train is ignored. Consequently, rate coding is inefficient but highly robust with respect to the ISI 'noise'. In rate coding, learning is based on activity-dependent synaptic weight modifications. Rate coding was originally shown by ED Adrian and Y Zotterman in 1926. In this simple experiment different weights were hung from a muscle. As the weight of the stimulus increased, the number of spikes recorded from sensory nerves innervating the muscle also increased.

**Spike-count rate**

The spike-count rate, also referred to as temporal average, is obtained by counting the number of spikes that appear during a trial and dividing by the duration of trial. The length T of the time window is set by the experimenter and depends on the type of neuron recorded from and to the stimulus. In practice, to get sensible averages, several spikes should occur within the time window. Typical values are T = 100 ms or T = 500 ms, but the duration may also be longer or shorter. Despite its shortcomings, the concept of a spike-count rate code is widely used not only in experiments, but also in models of neural networks. It has led to the idea that a neuron transforms information about a single input variable (the stimulus strength) into a single continuous output variable (the firing rate). There is a growing body of evidence that in Purkinje neurons, at least, information is not simply encoded in firing but also in the timing and duration of non-firing, quiescent periods.

**Time-dependent firing rate**

The time-dependent firing rate is defined as the average number of spikes (averaged over trials) appearing during a short interval between times t and t+Δt, divided by the duration of the interval. It works for stationary as well as for time-dependent stimuli. To experimentally measure the time-dependent firing rate, the experimenter records from a neuron while stimulating with some input sequence. The number of occurrences of spikes nK(t;t+Δt) summed over all repetitions of the experiment divided by the number K of repetitions is a measure of the typical activity of the neuron between time t and t+Δt. A further division by the interval length Δt yields time-dependent firing rate r(t) of the neuron, which is equivalent to the spike density of PSTH. The time-dependent firing rate coding relies on the implicit assumption that there are always populations of neurons.

**Temporal coding**

When precise spike timing or high-frequency firing-rate fluctuations are found to carry information, the neural code is often identified as a temporal code. A number of studies have found that the temporal resolution of the neural code is on a millisecond time scale, indicating that precise spike timing is a significant element in neural coding. Such codes, that communicate via the time between spikes are referred to as interpulse interval codes, and have been supported by recent studies. Neurons exhibit high-frequency fluctuations of firing-rates, which could be noise or could carry information. Rate coding models suggest that these irregularities are noise, while temporal coding models suggest that they encode information. If the nervous system only used rate codes to convey information, a more consistent, regular firing rate would have been evolutionarily advantageous, and neurons would have utilized this code over other less robust options. Temporal coding supplies an alternate explanation for the “noise," suggesting that it actually encodes information and affects neural processing. Temporal codes employ those features of the spiking activity that cannot be described by the firing rate. For example, time to first spike after the stimulus onset, characteristics based on the second and higher statistical moments of the ISI probability distribution, spike randomness, or precisely timed groups of spikes (temporal patterns) are candidates for temporal codes

**Phase-of-firing code**

Phase-of-firing code is a neural coding scheme that combines the spike count code with a time reference based on oscillations. This type of code takes into account a time label for each spike according to a time reference based on phase of local ongoing oscillations at low or high frequencies. It has been shown that neurons in some cortical sensory areas encode rich naturalistic stimuli in terms of their spike times relative to the phase of ongoing network oscillatory fluctuations, rather than only in terms of their spike count. The local field potential signals reflect population (network) oscillations. The phase-of-firing code is often categorized as a temporal code although the time label used for spikes (i.e. the network oscillation phase) is a low-resolution (coarse-grained) reference for time. As a result, often only four discrete values for the phase are enough to represent all the information content in this kind of code with respect to the phase of oscillations in low frequencies. Phase-of-firing code is loosely based on the phase precession phenomena observed in place cells of the hippocampus. Another feature of this code is that neurons adhere to a preferred order of spiking between a group of sensory neurons, resulting in firing sequence. Phase code has been shown in visual cortex to involve also high-frequency oscillations.[40] Within a cycle of gamma oscillation, each neuron has its own preferred relative firing time. As a result, an entire population of neurons generates a firing sequence that has a duration of up to about 15 ms.

**Population coding**

Population coding is a method to represent stimuli by using the joint activities of a number of neurons. In population coding, each neuron has a distribution of responses over some set of inputs, and the responses of many neurons may be combined to determine some value about the inputs. From the theoretical point of view, population coding is one of a few mathematically well-formulated problems in neuroscience. It grasps the essential features of neural coding and yet is simple enough for theoretic analysis. Experimental studies have revealed that this coding paradigm is widely used in the sensor and motor areas of the brain.

**Correlation coding**

The correlation coding model of neuronal firing claims that correlations between action potentials, or "spikes", within a spike train may carry additional information above and beyond the simple timing of the spikes. Early work suggested that correlation between spike trains can only reduce, and never increase, the total mutual information present in the two spike trains about a stimulus feature However, this was later demonstrated to be incorrect. Correlation structure can increase information content if noise and signal correlations are of opposite sign. Correlations can also carry information not present in the average firing rate of two pairs of neurons. A good example of this exists in the pentobarbital-anesthetized marmoset auditory cortex, in which a pure tone causes an increase in the number of correlated spikes, but not an increase in the mean firing rate, of pairs of neurons.

**Independent-spike coding**

The independent-spike coding model of neuronal firing claims that each individual action potential, or "spike", is independent of each other spike within the spike train.

**Position coding**

A typical population code involves neurons with a Gaussian tuning curve whose means vary linearly with the stimulus intensity, meaning that the neuron responds most strongly (in terms of spikes per second) to a stimulus near the mean. The actual intensity could be recovered as the stimulus level corresponding to the mean of the neuron with the greatest response. However, the noise inherent in neural responses means that a maximum likelihood estimation function is more accurate.

**Sparse coding**

The sparse code is when each item is encoded by the strong activation of a relatively small set of neurons. For each item to be encoded, this is a different subset of all available neurons. In contrast to sensor-sparse coding, sensor-dense coding implies that all information from possible sensor locations is known. As a consequence, sparseness may be focused on temporal sparseness ("a relatively small number of time periods are active") or on the sparseness in an activated population of neurons. In this latter case, this may be defined in one time period as the number of activated neurons relative to the total number of neurons in the population. This seems to be a hallmark of neural computations since compared to traditional computers, information is massively distributed across neurons.