Multiple Sclerosis

Two critical structural properties determining action potential conduction velocity are axonal diameter and myelination. Experiments using squid giant nerve fibers allowed for the derivation of an equation (**Equation 1**) relating conduction velocity to the electrical parameters of the nerve: [d (axon diameter), ρ (resistivity of neuron interior), C (membrane capacitance per area), and R* (unit area resistance of membrane during excitation)].

$$v = \sqrt{\frac{d}{8\rho C^2 R^*}}$$

Equation 1

Myelinated axons exhibit clustering of Na^+ channels, allowing for saltatory conduction required for appropriate neuron function. Typical measurements of human axon characteristics are shown below (**Table 1**).

Table 1. (* denotes a per unit length value)

Physical Property	Myelinated Axon	Demyelinated Axon
Radius of Axon	4×10^{-6} m	4×10^{-6} m
Resistance*	6.4×10^{9} Ω/m	6.4×10^{9} Ω/m
Capacitance*	9×10^{-10} F/m	4×10^{-7} F/m
Conductivity*	2×10^{-7} $Ω^{-1}$/m	2×10^{-4} $Ω^{-1}$/m

Multiple Sclerosis (MS) is a disease where progressive demyelination diminishes neuron function through disrupting saltatory conduction, a process that neurologically sensitizes MS patients to temperature increases. However, interventions that produce a transient reduction in serum calcium ions improve conduction rates in MS patients.

To investigate the impact of temperature on nerve function, conduction velocities of isolated ulnar nerves were measured from three different subject groups of mice. The data were averaged and fitted to a linear regression model (**Fig. 1**). Blocking temperature, denoted as "X," is defined as the temperature where conduction was no longer detected.

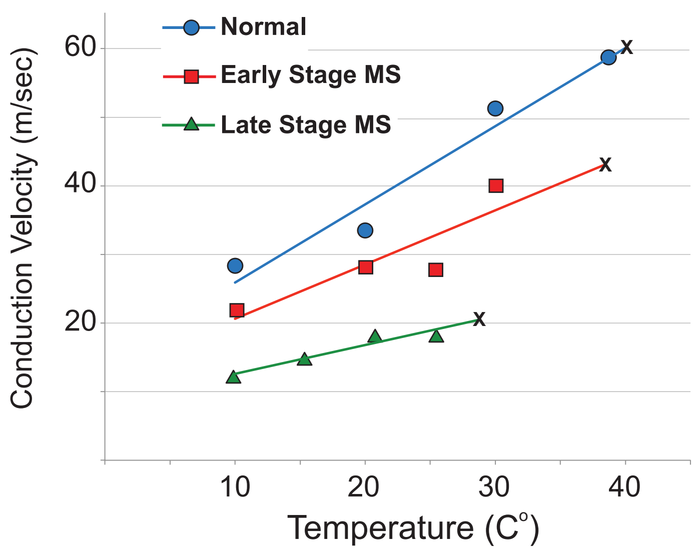
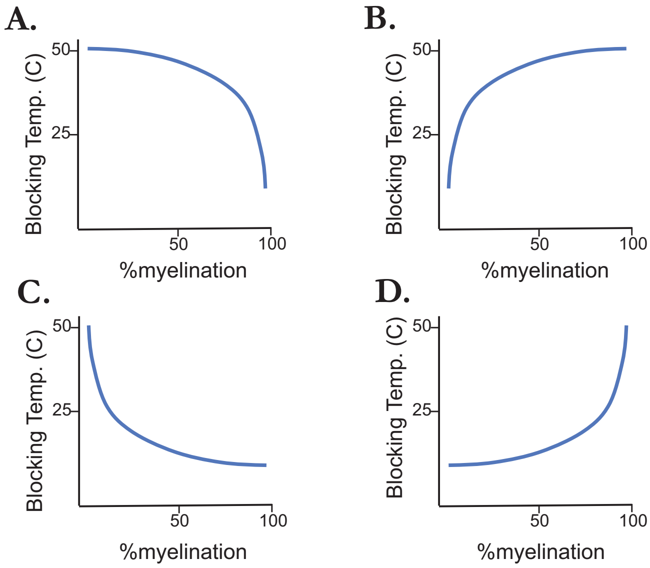


Figure 1. Measurement of conduction velocity as a function of temperature. Control rodents were healthy (Normal) whereas the other two experimental groups exhibited mild (Early stage) or severe (Late stage) MS symptoms.

1) **Which of the following graphs represents the relationship between myelination and blocking temperature?**



2) **Calculate the amount of energy required to recharge a demyelinated axon following depolarization?**

A. 2×10^{-9} J/m

B. 2×10^{9} J/m

C. 8×10^{-9} J/m

D. 8×10^{9} J/m

3) **All of the following statements comparing myelinated and demyelinated axons are true except:**

A. Myelinated axons have higher conduction velocity than demyelinated axons.

B. Demyelinated axons undergo conduction block at a higher temperature than myelinated axons.

C. Ion transport in myelinated axons occurs over a greater temperature range than demyelinated axons.

D. Ion transport in demyelinated axons occurs over a smaller temperature range than myelinated axons.

4) **If the axon radius is changed to ¼ its initial amount, the resulting conduction velocity would:**

A. increase by 2-fold.

B. decrease by 2-fold.

C. increase by 16-fold.

D. decrease by 16-fold.

5) **What is the amount of power required to recharge an axon if energy expended per action potential is 2×10^{-9} J/m and the length of an action potential is 10^{-2} seconds?**

A. 5×10^{-11} W/m

B. 2×10^{-9} W/m

C. 2×10^{-7} W/m

D. 5×10^{-7} W/m

6) **Which is the most likely outcome if MS patients were treated with a calcitonin antagonist?**

A. Decreased conduction velocity

B. Re-myelination of motor neurons

C. Increased conduction velocity

D. Cannot be determined

7) **Calculate the number of Na^+ ions that cross a demyelinated axon during a neuronal action potential:**

A. 2×10^{-11}/m

B. 4×10^{-8}/m

C. 4×10^{8}/m

D. 2×10^{11}/m

Annotations.

1) B 2) A 3) B 4) B 5) C 6) D 7) D

	Foundation 3: Neurobiology-A			Foundation 4: Motion-A Electrochem.-C		
	A			A	C	
Concepts				4	2,5	
Reasoning	6				7	
Research						
Data	3				1	

Big Picture. This passage emphasized the basic foundational concepts of physics including electrical transmission, power/energy, and velocity. These topics were all woven together in the context of Multiple Sclerosis (MS), a prevalent and degenerative neurological disease.

No background knowledge of MS was required and the passage provided you with only limited factual details regarding the disease. However, it was important to note that patients with MS have diminished conduction velocity and sensitivity of conduction to temperature as well as the vague comment about calcium reduction being beneficial. These points were all that you needed to get a grasp of the data that was presented in Figure 1. Notice that the graph was not overly intuitive as it incorporated several points at once. You should have realized that as MS progresses: (1) the overall conduction velocities were reduced; (2) conduction velocities existed over a more limited temperature range; (3) blocking temperatures were lower as a function of disease progression. What was not as obvious was that disease progression also correlates with degree of myelination (i.e. decreased myelination occurs with disease progression).

Finally, you needed to be able to work with both the formula for conduction velocity (which was probably new to you) and the table of values for myelinated versus demyelinated axons.

1) **B.** For this question you had to analyze the data presented in Figure 1 and then apply the findings to the series of graphs that were presented in the question stem. However, the problem was that Figure 1 did not directly give you a relationship between percentage of myelination and blocking temperature, but it did actually provide you with enough information to get an accurate idea of what the relationship between myelination and temperature are. First of all, appreciate from the passage that normal axons should be near 100% myelinated. In contrast, early stage MS patients would have a lower percentage of myelinated axons and later stage patients would exhibit even lower percentages of myelination. Moreover, the "X" on the graphs denoted the blocking temperature so you should have identified that there is a reduction in blocking temperature as the degree of myelination decreased. This **ruled out choices A and C**. Next, you had to realize the difference between answer choices B and D. In choice B, the blocking temperature is reduced with decreasing percentage of myelination but does so gradually at first and then accelerates downward. Answer choice D presents the opposite scenario as there is a significant decrease initially and then it gradually levels off. When inspecting Figure 1 for the trend that the blocking temperature exhibited, you will notice that it is reduced gradually at first and then accelerates downward (**Fig. 2**). This makes **choice B correct**.

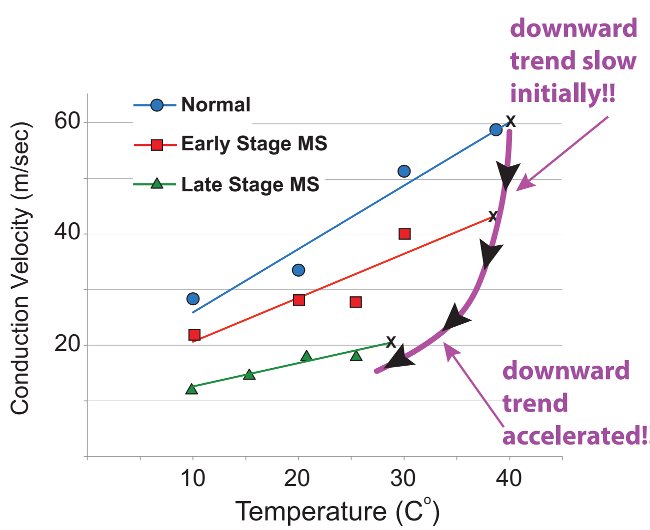


Figure 2. Accelerating downward trend of blocking temperature as an axon becomes progressively demyelinated.

2) **A. 2×10^{-9} J/m.** The amount of energy required to recharge a demyelinated axon following depolarization is equal to the amount of potential energy (PE) the axon has in the resting state. In other words, you needed to use one of the electrical potential energy formulas to arrive at the correct answer. The capacitance (C) of a demyelinated axon is provided in the passage but the voltage change (V) during an action potential is not. This should be outside knowledge that you had walking into the exam. Recall that resting membrane potential is -70mV, which then changes to +35mV during an action potential. This gives a voltage change of about 100mV or 1×10^{-1} volts. This was the "missing value" to plug into the equation as shown below (**Fig. 3**).

$$PE = \frac{1}{2}CV^2$$

From table

$$PE = \frac{1}{2}(4 \times 10^{-7}\ \frac{F}{m})(1 \times 10^{-1}\ V)^2$$

From...your brain

$$PE = (2 \times 10^{-7})(1 \times 10^{-2})\frac{J}{m}$$

$$PE = 2 \times 10^{-9}\ \frac{J}{m}$$

Figure 3. Calculations to determine the amount of energy required to recharge a demyelinated axon.

3) **B. Demyelinated axons undergo conduction block at a higher temperature than myelinated axons.** While not directly referenced in the question stem, you needed to inspect the results presented in Table 1 and Figure 1 in order to correctly answer this question. Among the most straightforward results was the fact that normal (myelinated) axons had higher conducting velocities than early/late stage MS axons (demyelinated) making **choice A incorrect** (because it's a supported conclusion). Also, you should have noted that the regression lines presented in Figure 1 represent the temperature range that conduction velocity can be measured. The lines became progressively shorter as the axon became demyelinated. This result supported both **choices C and D so they were also incorrect**. The results in Figure 1 do not support the conclusion that demyelinated axons undergo conduction block at higher temperatures but, in fact, support the opposite conclusion. This makes **choice B correct**.

4) **B. decrease by 2-fold.** This was a "formula-management" question where you had to handle a novel mathematical relationship and make a conclusion. First, isolate the two variables in the question stem to determine that conduction velocity is proportional to the square root of the axon diameter (**Fig. 4** and **Equation 1**). The same relationship is true for the radius, since changes in diameter and radius are directly proportional to one another. If the diameter decreases, note that the velocity must also decrease **ruling out choices A and C**. From there, the square root of four is two so **choice B is correct**.

$$v = \sqrt{\frac{d}{8\rho C^2 R^*}}$$

Formula provided by passage

$$v \propto \sqrt{d}$$

velocity is proportional to diameter (therefore radius)

$$v \propto \sqrt{\frac{d}{4}}$$

diameter is reduced by 4-fold

$$v \downarrow 2$$

Figure 4. Relationship between conduction velocity and diameter (i.e. radius).

5) **C. 2×10^{-7} W/m.** This question is as straightforward as it looked so don't overthink it. You did not need to get any of the values from Table 1 because the question stem provided you with all that you needed. You were looking to calculate the power per unit distance (P) so the standard equation applied (P = W/t where W = work per unit distance and t = time) and then you just "plugged and chugged" (**Fig. 5**).

$$P = \frac{W}{t} \qquad P = \frac{2 \times 10^{-9}\ J/m}{10^{-2}\ secs} \qquad P = 2 \times 10^{-7}\ \frac{W}{m}$$

Figure 5. Calculations to determine power.

6) D. Cannot be determined. This question was entirely dependent on the phrase, "Interventions that produce a transient reduction in calcium ions improve conduction rates in MS patients." Moreover, you had to understand that if a patient is treated with a calcitonin antagonist, they would experience an increase in serum calcium levels. The natural inclination would be that this should worsen their condition, but be very careful here. A graphical representation of the logic you needed to understand this point is shown below (**Fig. 6**). As you can see, the statement informs you that reductions in calcium improve conduction rates but that statement tells you nothing about increases in calcium levels. Therefore, you cannot anticipate the outcome of increasing calcium levels on conduction rates making **choice D correct**. This type of question gets at the heart of interpreting data and, more specifically, not over-interpreting observations to the point of extrapolating outcomes.

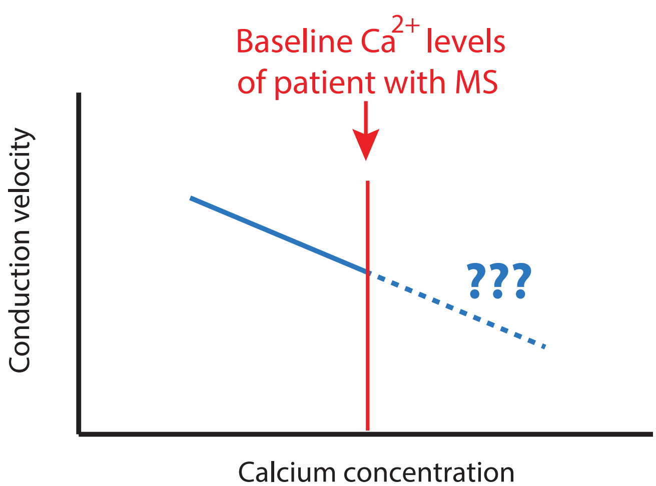


Figure 6. The provided relationship of reduced calcium levels improving conduction velocity does not state that increasing calcium concentration will reduce conduction velocity.

7) D. 2×10^{11}/m. This was a two-part physics problem in that you had to the answer to the first calculation to plug into the second formula. There was some relatedness between this question and question 2 in that you had to "bring to the table" that 0.1V is the change in potential during an action potential. First, determine the amount of charge crossing a membrane, which used a standard formula that related charge (Q) to capacitance (C) and voltage (V) (**Fig. 7**). Notice that the numerical answer to this first equation was **choice B but this is not the correct answer** because the question stem is asking for particle number. You had to plug the charge value into another equation, which relates quantized charge to number of charged particles (n) where each particle has an elementary charge (e) (**Fig. 7**). From there, you could arrive at the correct answer.

$$Q = CV$$

Note that capacitance is per unit length (from Table 1)

$$Q = (4 \times 10^{-7}\,\frac{F}{m})(0.1V)$$ ← estimated voltage change during AP

$$Q = 4 \times 10^{-8}\,\frac{C}{m}$$ ← charge per unit length of demyelingated axon during AP

$$Q = ne$$ ← alternative formula to related particle number

$$n = \frac{Q}{e} = \frac{(4 \times 10^{-8}\,\frac{C}{m})}{(1.6 \times 10^{-19}\,C/\text{particle})}$$

$$n = 2 \times 10^{11}\ \text{particles/m}$$

You need to memorize this number!

Figure 7. Calculating the number of particles crossing an axonal membrane during an AP.