The Action Potential

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** If this is not printed in color, it is suggested you color code the ion channels and ions as you go through this topic. Ions channels and ions should be color coded as follows:
Red: Sodium ion channels and sodium ions
Blue: Potassium ion channels and potassium ions

Page 1. Introduction

- Neurons communicate over long distances by generating and sending an electrical signal called a nerve impulse, or action potential.

Page 2. Goals

- To understand that rapid changes in permeability of the neuronal membrane produce the action potential.
- To recognize that altering voltage-gated ion channels changes membrane permeability.
- To understand the movement of sodium and potassium ions during the action potential.
- To examine refractory periods.
- To learn about conduction velocity.

Page 3. The Action Potential: An Overview

- The action potential is a large change in membrane potential from a resting value of about -70 millivolts to a peak of about +30 millivolts, and back to -70 millivolts again.
- The action potential results from a rapid change in the permeability of the neuronal membrane to sodium and potassium. The permeability changes as voltage-gated ion channels open and close.
- In the following pages we will study step-by-step the changes that occur as an action potential is generated and then propagated down the axon.

Page 4. The Action Potential Begins at the Axon Hillock

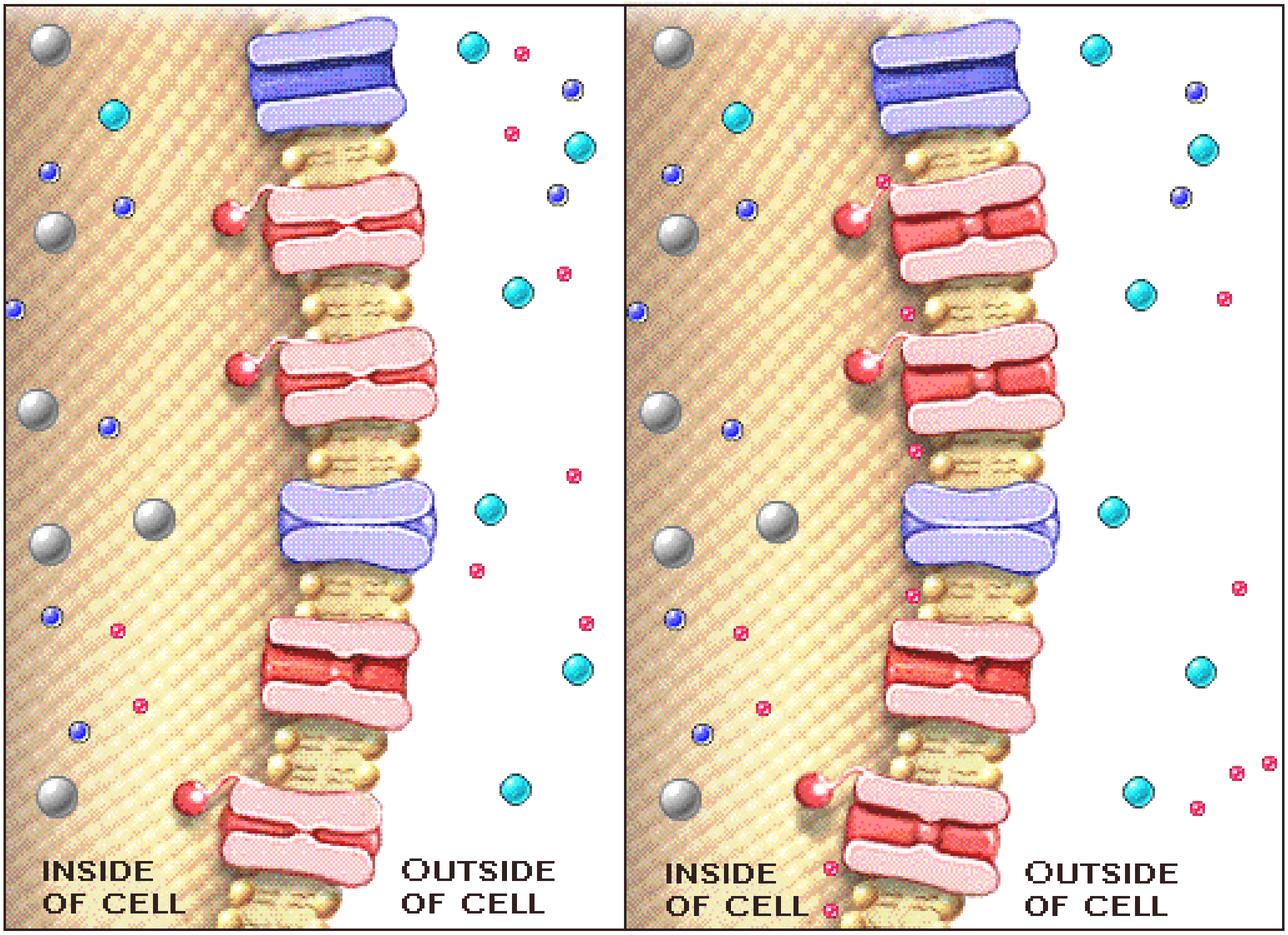
- The action potential is generated at the axon hillock, where the density of voltage-gated sodium channels is greatest.
- The action potential begins when signals from the dendrites and cell body reach the axon hillock and cause the membrane potential there to become more positive, a process called depolarization.
- These local signals travel for only a short distance and are very different from action potentials. We will study them in a separate module that covers synapse.

Page 5. During Depolarization Sodium Moves into the Neuron

- As the axon hillock depolarizes, voltage-gated channels for sodium open rapidly, increasing membrane permeability to sodium.
- Sodium moves down its electrochemical gradient into the cell.
- On the diagram on the top of the next page, color code the ion channels. Label the ion channels as follows from top to bottom:
    - Potassium passive channel.
    - Sodium voltage-gated channel.
    - Sodium voltage-gated channel.
    - Potassium voltage-gated channel.
    - Sodium passive channel.
    - Sodium voltage-gated channel.
- Describe what happens to the sodium voltage-gated channel when the membrane is depolarized:

____

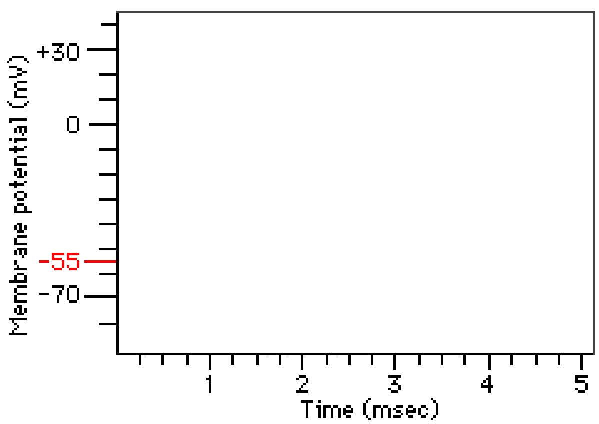
____



Page 6. Threshold

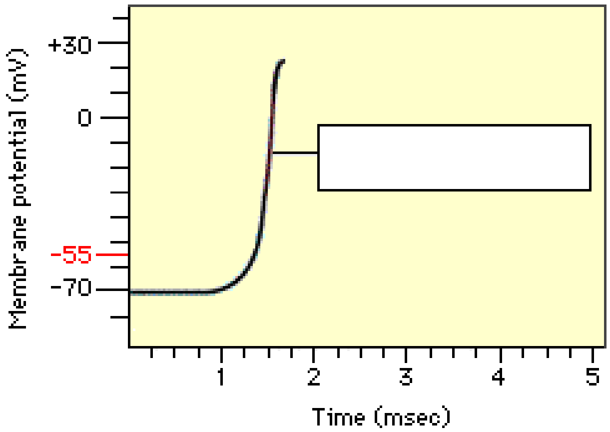
- If the stimulus to the axon hillock is great enough, the neuron depolarizes by about 15 millivolts and reaches a trigger point called threshold.
- At threshold, an action potential is generated. Weak stimuli that do not reach threshold do not produce an action potential. Thus we say that the action potential is an all-or-none event.
- Action potentials always have the same amplitude and the same duration.
- At -55 millivolts the membrane is depolarized to threshold, and an action potential is generated.
- Threshold is a special membrane potential where the process of depolarization becomes regenerative, that is, where a positive feedback loop is established.

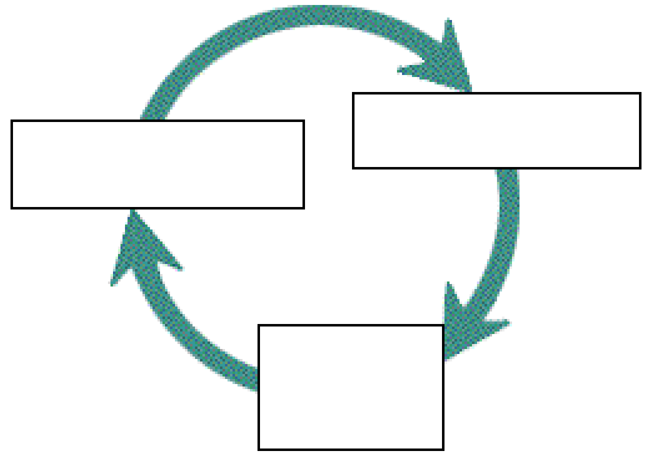
- Record the membrane potential as you work through this page:



Page 7. An Action Potential is Generated When a Positive Feedback Loop is Established

- When, and only when, a neuron reaches threshold, a positive feedback loop is established.
- At threshold, depolarization opens more voltage-gated sodium channels.
- This causes more sodium to flow into the cell, which in turn causes the cell to depolarize further and opens still more voltage-gated sodium channels.
- This positive feedback loop produces the rising phase of the action potential.
- Label this diagram:





Page 8. Interrupting the Positive Feedback Loop: Voltage-Gated Sodium Channels Inactivate

- The rising phase of the action potential ends when the positive feedback loop is interrupted.
- Two processes break the loop:
  1. the inactivation of the voltage-gated sodium channels.
  2. the opening of the voltage-gated potassium channels.

- The voltage-gated sodium channels have two gates:
  1. A voltage-sensitive gate opens as the cell is depolarized.
  2. A second, time-sensitive inactivation gate stops the movement of sodium through the channel after the channel has been open for a fixed time.

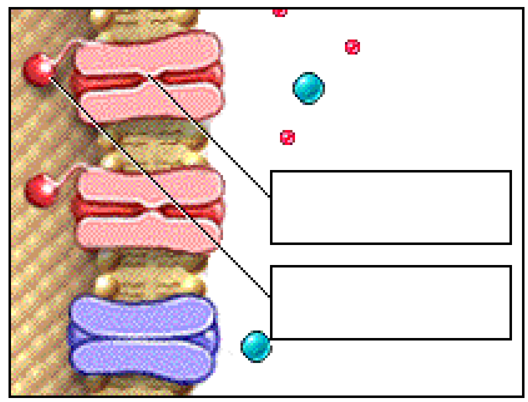
- At the resting membrane potential, the voltage sensitive gate is closed.

- As the neuron is depolarized, the voltage-sensitive gate opens.

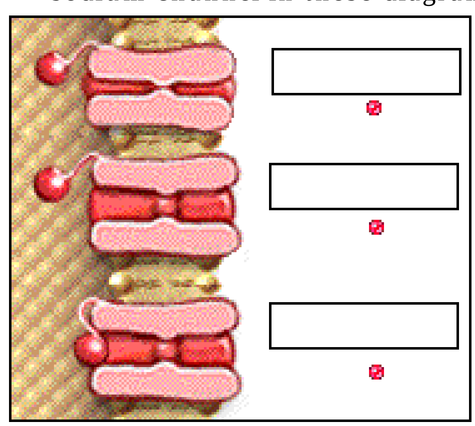
- At a fixed time after the channel opens, it inactivates.

- At the peak of the action potential, voltage-gated sodium channels begin to inactivate. As they inactivate, the inward flow of sodium decreases, and the positive feedback loop is interrupted.

- Label the two gates on the voltage-gated sodium channel:



- Label the state of the gates on the voltage-gated sodium channel in these diagrams:



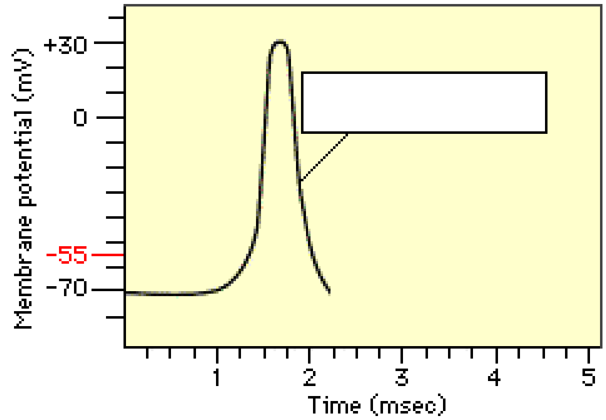
Page 9. Interrupting the Positive Feedback Loop: Voltage-Gated Sodium Channels Open

- We've looked at the sodium channels. Now let's see what happens to the potassium channels.
- The voltage-gated potassium channels respond slowly to depolarization. They begin to open only about the time that the action potential reaches its peak.
- You've seen that potassium moves out of the cell as voltage-gated potassium channels open. As potassium moves out, depolarization ends, and the positive feedback loop is broken.
- Both the inactivation of sodium channels and the opening of potassium channels interrupt the positive feedback loop. This ends the rising phase of the action potential.

Page 10. Repolarization

- You have seen potassium leaving the cell as voltage-gated potassium channels opened.
- With less sodium moving into the cell and more potassium moving out, the membrane potential becomes more negative, moving toward its resting value.
- This process is called repolarization.

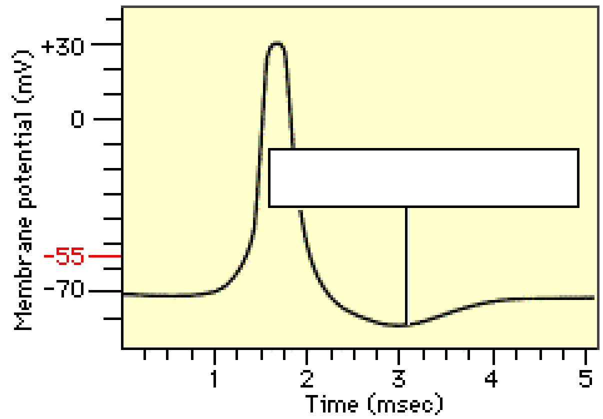
• Label this graph:



Page 11. Hyperpolarization

- In many neurons, the slow voltage-gated potassium channels remain open after the cell has repolarized. Potassium continues to move out of the cell, causing the membrane potential to become more negative than the resting membrane potential.
- This process is called hyperpolarization.
- By the end of the hyperpolarization, all the potassium channels are closed.

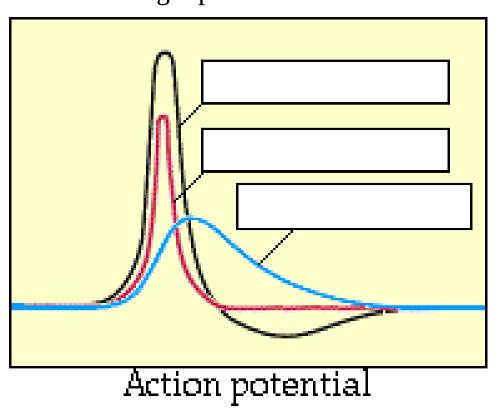
• Label this graph:



Page 12. The Opening and Closing of Channels Changes Neuronal Permeability During the Action Potential

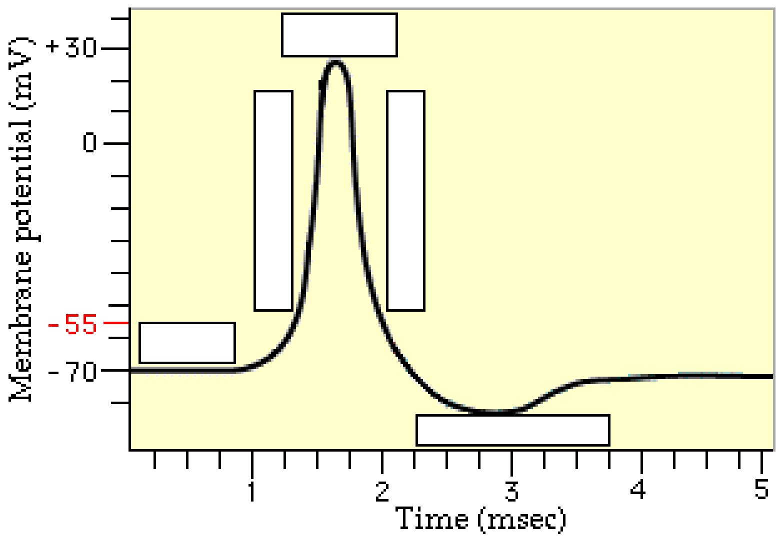
- As you have just learned, the opening and closing of voltage-gated channels changes the cell's permeability to sodium and potassium during the action potential.
- Sodium permeability increases rapidly during the rising phase of the action potential.
- Sodium permeability decreases rapidly during repolarization.
- Potassium permeability is greatest during repolarization.
- Potassium permeability is decreasing slowly during hyperpolarization.
- Now let's see the simultaneous changes in sodium and potassium permeability during the action potential.
- The rapid increase in sodium permeability is responsible for the rising phase of the action potential.
- The rapid decrease in sodium permeability and simultaneous increase in potassium permeability is responsible for the repolarization of the cell.
- The slow decline in potassium permeability is responsible for the hyperpolarization.

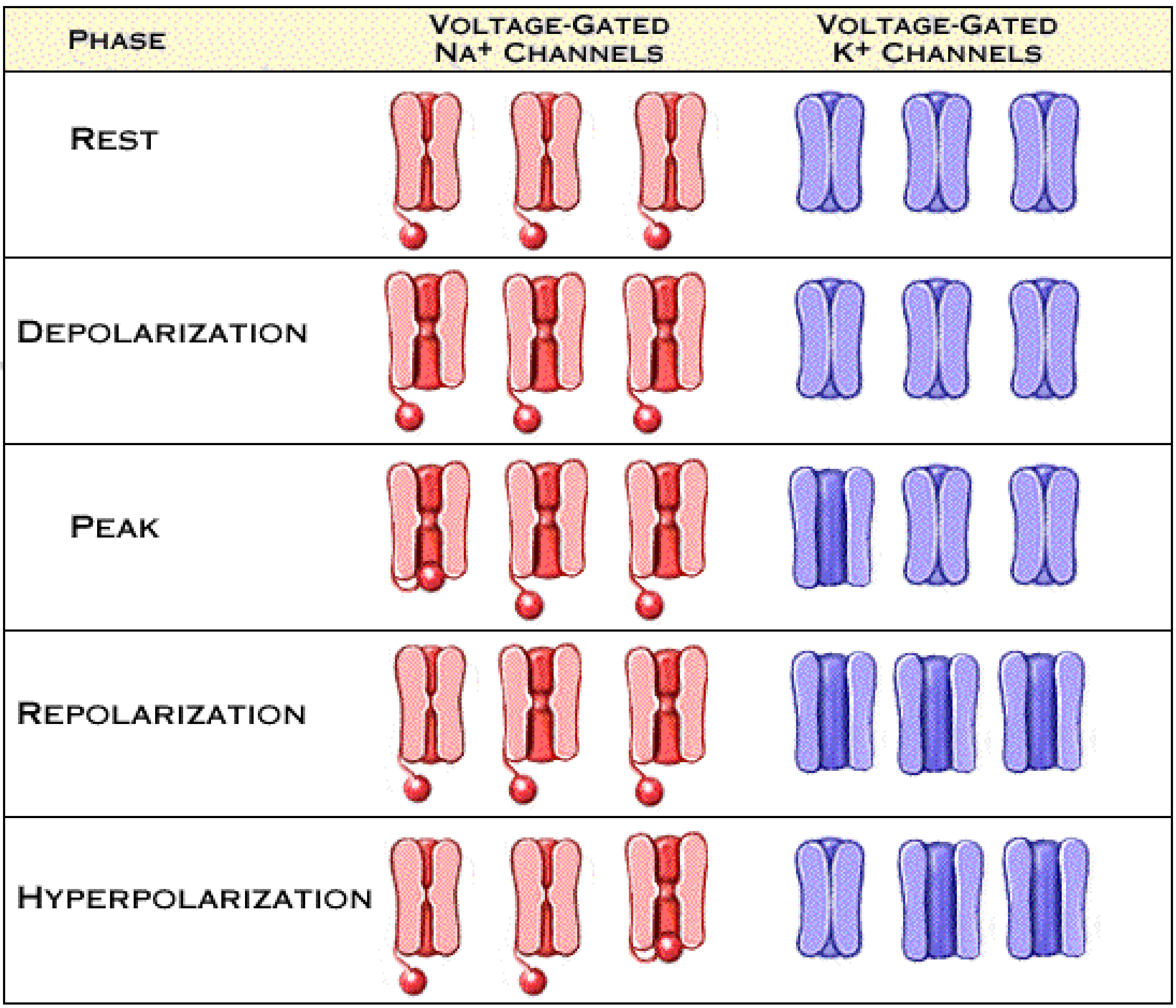
• Label this graph:



Page 13. Ion Channel Activity During the Action Potential: A Summary

- During an action potential, voltage-gated sodium channels first open rapidly, then inactivate, then reset to the closed state. Voltage-gated potassium channels open and close more slowly.
- Label the parts of this graph:





- **Rest.** Voltage-gated sodium and potassium channels are closed when the neuron is at rest.
- **Depolarization.** Voltage-gated sodium channels open rapidly, resulting in movement of sodium into the cell. This causes depolarization.
- **Initiation of Repolarization.** Voltage-gated sodium channels begin to inactivate and voltage-gated potassium channels begin to open. This initiates repolarization.

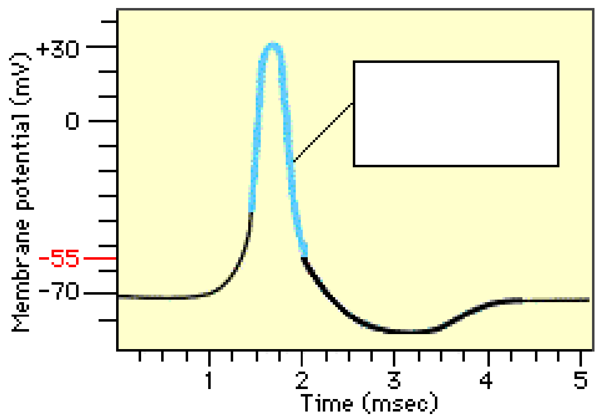
- **Repolarization.** Voltage-gated sodium channels continue to inactivate, then reset to the closed state. Potassium channels continue to open. This results in a net movement of positive charge out of the cell, repolarizing the cell.
- **Hyperpolarization.** Some voltage-gated potassium channels remain open, resulting in movement of potassium out of the cell. This hyperpolarizes the cell.
- We've seen that sodium moves into the neuron and potassium moves out during an action potential. However, the amount of sodium and potassium that moves across the membrane during the action potential is very small compared to the bulk concentration of sodium and potassium. Therefore, the concentration gradient for each ion remains essentially unchanged.

** Now is a good time to go to quiz questions 1, 2, 5, 6, 7, and 8:
- Click the Quiz button on the left side of the screen.
- Work through questions 1 and 2.
- After answering question 2, click on the scrolling page list at the top of the screen and choose "5. Threshold Experiment".
- Work through questions 5, 6, 7, and 8.
- After answering question 8, click the Back to Topic button on the left side of the screen.
- To get back to where you left off, click on the scrolling page list at the top of the screen and choose "14. The Absolute Refractory Period".

Page 14. The Absolute Refractory Period

- Just after the neuron has generated an action potential, it cannot generate another one. Many sodium channels are inactive and will not open, no matter what voltage is applied to the membrane. Most potassium channels are open. This period is called the absolute refractory period.
- The neuron cannot generate an action potential because sodium cannot move in through inactive channels and because potassium continues to move out through open voltage-gated channels.
- A neuron cannot generate an action potential during the absolute refractory period.

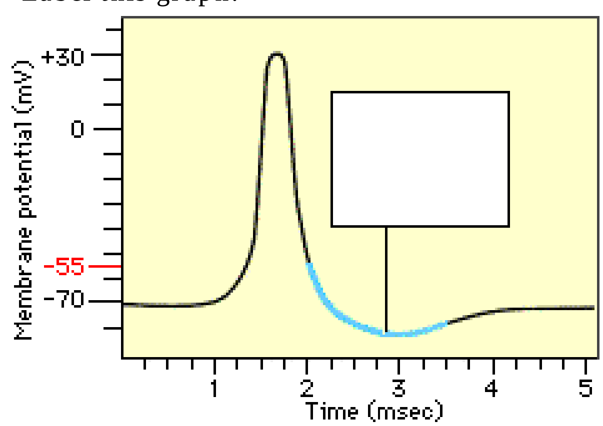
- Label this graph:



Page 15. The Relative Refractory Period

- Immediately after the absolute refractory period, the cell can generate an action potential, but only if it is depolarized to a value more positive than normal threshold. This is true because some sodium channels are still inactive and some potassium channels are still open. This is called the relative refractory period.
- The cell has to be depolarized to a more positive membrane potential than normal threshold to open enough sodium channels to begin the positive feedback loop.
- The lengths of the absolute and relative refractory periods are important because they determine how fast neurons can generate action potentials.

- Label this graph:



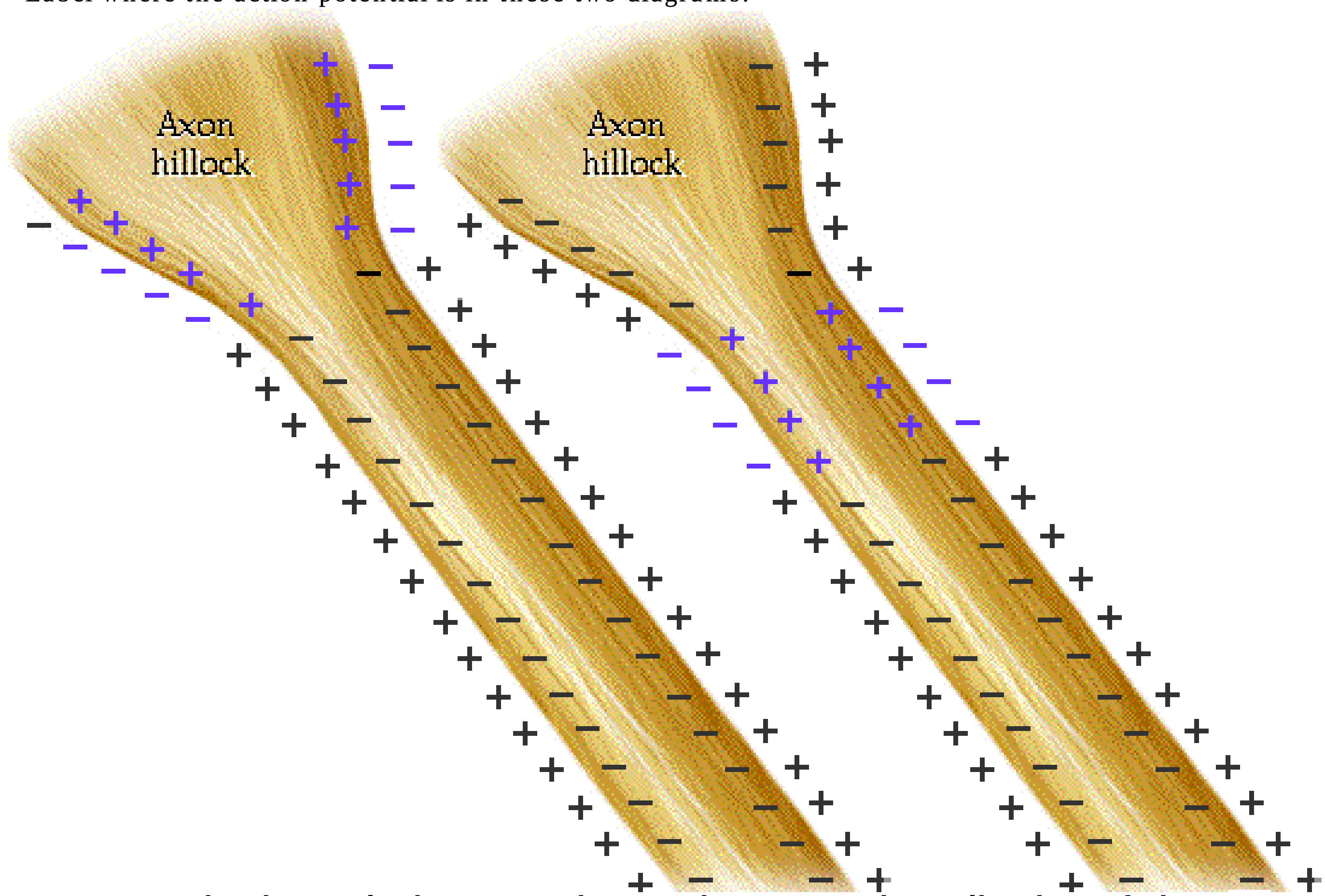
** Now is a good time to go to quiz question 4:
- Click the Quiz button on the left side of the screen.
- Click on the scrolling page list at the top of the screen and choose "4. Stimulation of the Action Potential".
- After answering question 4, click the Back to Topic button on the left side of the screen.
- To get back to where you left off, click on the scrolling page list at the top of the screen and choose "16. The Action Potential is Propagated Along the Axon".

Page 16. The Action Potential is Propagated Along the Axon

- After an action potential is generated at the axon hillock, it is propagated down the axon.

• Positive charge flows along the axon, depolarizing adjacent areas of membrane, which reach threshold and generate an action potential. The action potential thus moves along the axon as a wave of depolarization traveling away from the cell body.

• Label where the action potential is in these two diagrams:



Page 17. Conduction Velocity Depends on Diameter and Myelination of the Axon

• Conduction velocity is the speed with which an action potential is propagated.
• Conduction velocity depends on two things:
  1. The diameter of the axon.
     • As the axon diameter increases, the internal resistance to the flow of charge decreases and the action potential travels faster.
  2. How well the axon is insulated with myelin.
     • Recall that myelinated axons have areas of insulation interrupted by areas of bare axon called nodes of Ranvier.
     • In a myelinated axon, charge flows across the membrane only at the nodes, so an action potential is generated only at the nodes. The action potential appears to jump along the axon. This type of propagation is called saltatory conduction.
     • A myelinated axon typically conducts action potentials faster than an unmyelinated axon of the same diameter.
• More speed is gained by insulating an axon with myelin than by increasing the axon diameter.

Page 18. Summary

• The action potential is an all-or-none event that can travel for long distances because it is a regenerative electrical signal.
• When the axon hillock is depolarized to threshold, an action potential is generated. Voltage-gated channels open, thereby increasing permeability of the neuron first to sodium and then to potassium.
• As sodium moves rapidly into the neuron, it produces the rising phase of the action potential.
• As the inward movement of sodium slows and the outward movement of potassium increases, the membrane repolarizes.
• Immediately after an action potential, the neuron cannot generate another action potential during the absolute refractory period. During the relative refractory period it can generate another action potential only if stronger stimuli arrive at the axon hillock.

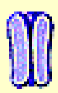
• The diameter and myelination of an axon determine its conduction velocity.

** Now is a good time to go to quiz question 3:
- Click the Quiz button on the left side of the screen.
- Click on the scrolling page list at the top of the screen and choose "3. Conduction Velocity".

Notes on Quiz Questions:

Quiz Question #1: The Positive Feedback Loop
- This question asks you to identify the events that interrupt the positive feedback loop of depolarization.

Quiz Question #2: Ion Channels during Depolarization
- This question asks you to characterize the voltage gates involved in the action potential. You may predict the correct answer on this chart as you proceed:

Ion channel	Gate	Resting membrane potential	Depolarization	When?
Na^+ 	Voltage	Open or Closed	Opens or Closes	Early or Late
Na^+ 	Time-sensitive inactivation	Open or Closed	Opens or Closes	Early or Late
K^+ 	Voltage	Open or Closed	Opens or Closes	Early or Late

Quiz Question #3: Conduction Velocity
- This question asks you to predict the problem with action potential conduction in a patient with Multiple Sclerosis.

Quiz Question #4: Stimulation of the Action Potential
- This question demonstrates the absolute refractory period.

Quiz Question #5: Threshold Experiment
- This question allows you to determine the resting membrane potential and threshold for two different neurons.

** Note: This question has several different parts to it.

Quiz Question #6: Phases of the Action Potential
- This question asks you to define depolarization, repolarization and hyperpolarization.

Quiz Question #7: Ion Channel Activity: A Summary
- This question asks you to label the parts of an action potential graph and associate the state of the sodium and potassium voltage-gated ion channels at each part of the graph.

Quiz Question #8: Action Potential Express
- This question asks you to list the sequence of events that occur in an action potential.

Study Questions on the Action Potential:

1. (Page 1.) What is another name for an action potential?
2. (Page 3.) What does an action potential consist of?
3. (Page 4.) Where is the action potential generated?
4. (Page 4.) What causes an axon potential to occur at the axon hillock?
5. (Page 5.) What happens to ion channels when the membrane depolarizes at the axon hillock?
6. (Page 6.) How much does the axon hillock have to depolarize to reach threshold?
7. (Page 6.) What happens at threshold?

8. (Page 6.) What happens if there is a weak stimulus at the axon hillock and threshold is not reached?

9. (Page 6.) Do action potentials always have the same amplitude and the same duration?

10. (Page 6.) Threshold is a special membrane potential where the process of depolarization becomes regenerative. What does this mean?

11. (Page 7.) What happens to sodium voltage-gated channels at threshold?

12. (Page 7.) Explain how the positive feedback loop maintains the rising phase of the action potential.

13. (Page 8.) Label the diagrams on page 8.

14. (Page 8, 9.) The rising phase of the action potential ends when the positive feedback loop is interrupted. What two processes break the loop?

15. (Page 8.) What are the names of the two gates on the voltage-gated sodium channels?

16. (Page 8.) When does the voltage-sensitive gate open?

17. (Page 8.) What is the function of the time-sensitive inactivation gate?

18. (Page 8.) What happens to the voltage gated sodium channels at the peak of the action potential?

19. (Page 9.) When do the voltage-gated potassium channels open?

20. (Page 9.) What happens when the voltage-gated potassium channels open and the potassium moves out of the cell?

21. (Page 10.) When does repolarization occur? What happens to the membrane potential?

22. (Page 11.) What is hyperpolarization?

23. (Page 11.) Why does hyperpolarization occur?

24. (Page 12.) Label the graph on p. 12.

25. (Page 12.) During the action potential, when does sodium permeability increase rapidly?
a. during repolarization b. during the rising phase of the action potential
c. during hyperpolarization d. during repolarization

26. (Page 12.) During the action potential, when does sodium permeability decrease rapidly?
a. during repolarization b. during the rising phase of the action potential
c. during hyperpolarization d. during repolarization

27. (Page 12.) During the action potential, when is potassium permeability the greatest?
a. during repolarization b. during the rising phase of the action potential
c. during hyperpolarization d. during repolarization

28. (Page 12.) During the action potential, when does potassium permeability decrease slowly?
a. during repolarization b. during the rising phase of the action potential
c. during hyperpolarization d. during repolarization

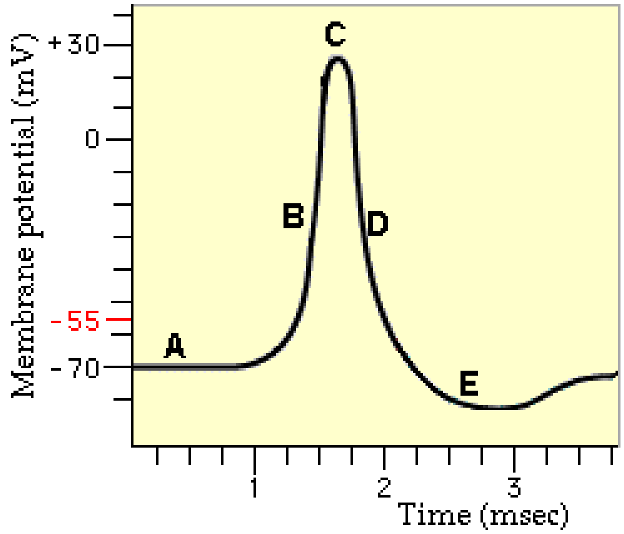
29. (Page 12.) The rapid increase in sodium permeability is responsible for _____.
a. the repolarization of the cell
b. the hyperpolarization
c. the rising phase of the action potential

30. (Page 12.) The rapid decrease in sodium permeability and simultaneous increase in potassium permeability is responsible for _____.
a. the repolarization of the cell
b. the hyperpolarization
c. the rising phase of the action potential

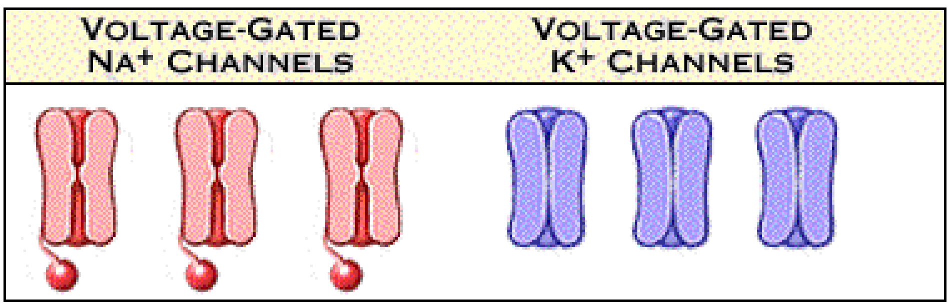
31. (Page 12.) The slow decline in potassium permeability is responsible for _____.
a. the repolarization of the cell
b. the hyperpolarization
c. the rising phase of the action potential

32. (Page 13.) Which part of the graph to the right corresponds to the following:
    hyperpolarization
    depolarization
    rest
    initiation of repolarization
    repolarization

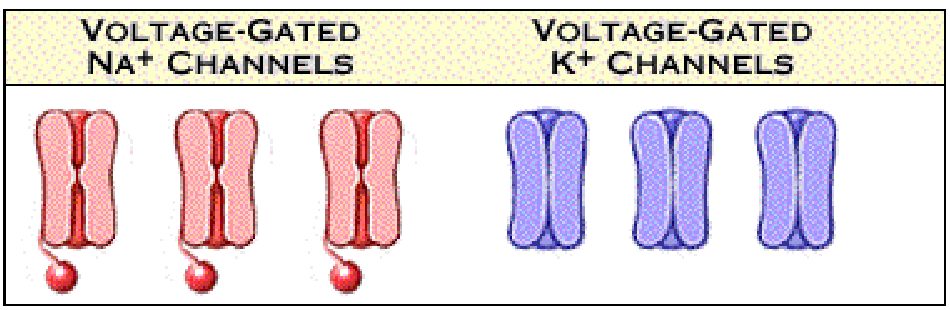
33. (Page 13.) Which part of the graph to the right corresponds to:
    A time when voltage-gated sodium channels are inactivated, then reset to the closed state. Potassium channels continue to open.
    A time when voltage-gated sodium and potassium channels are closed.
    A time when voltage-gated sodium channels begin to inactivate and voltage-gated potassium channels begin to open.
    A time when some voltage-gated potassium channels remain open, resulting in movement of potassium out of the cell.
    A time when voltage-gated sodium channels open rapidly, resulting in movement of sodium into the cell.



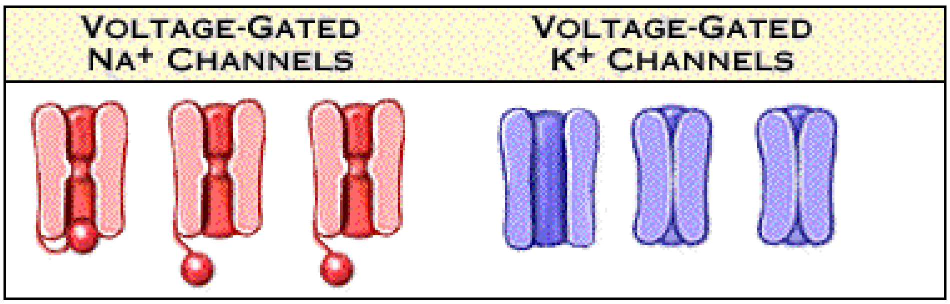
34. (Page 13.) Which phase of the action potential does the diagram below best correspond to?
    a. rest b. depolarization c. peak d. repolarization e. hyperpolarization



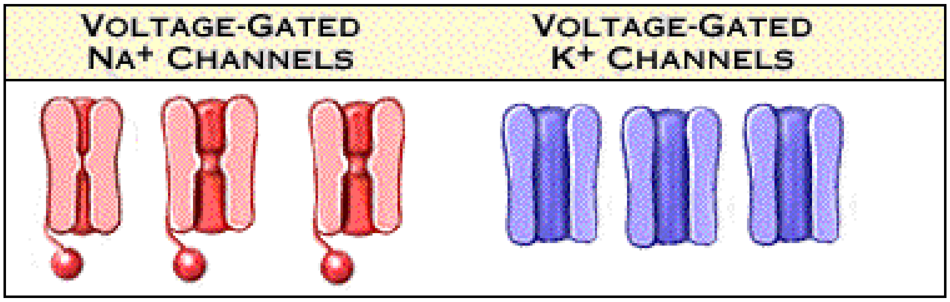
35. (Page 13.) Which phase of the action potential does the diagram below best correspond to?
    a. rest b. depolarization c. peak d. repolarization e. hyperpolarization



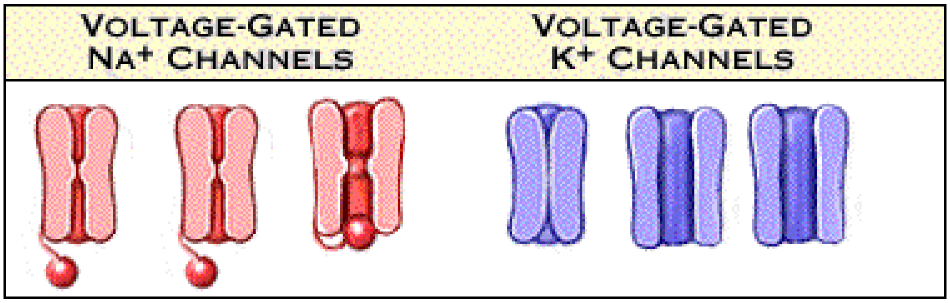
36. (Page 13.) Which phase of the action potential does the diagram below best correspond to?
    a. rest b. depolarization c. peak d. repolarization e. hyperpolarization



37. (Page 13.) Which phase of the action potential does the diagram below best correspond to?
a. rest b. depolarization c. peak d. repolarization e. hyperpolarization



38. (Page 13.) Which phase of the action potential does the diagram below best correspond to?
a. rest b. depolarization c. peak d. repolarization e. hyperpolarization



39. (Page 14.) What is the absolute refractory period?

40. (Page 14.) Why can't a neuron generate another action potential during the absolute refractory period?

41. (Page 15.) What is the relative refractory period?

42. (Page 15.) Why is it more difficult for a neuron to generate another action potential during the relative refractory period?

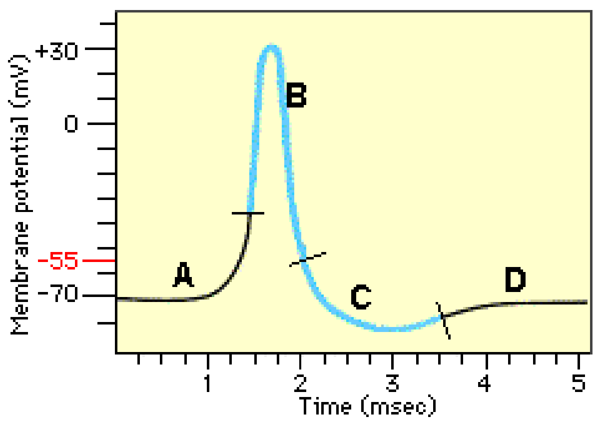
43. (Page 14, 15.) What letter on this graph to the right corresponds to the absolute refractory period?

44. (Page 14, 15.) What letter on this graph to the right corresponds to the relative refractory period?

45. (Page 16.) What happens after an action potential is generated at the axon hillock?

46. (Page 16.) How is an action potential propagated down the axon?

47. (Page 17.) What is conduction velocity?



48. (Page 17.) What two factors does conduction velocity depend on?

49. (Page 17.) What is the effect of axon diameter on conduction velocity?

50. (Page 17.) What is the effect of myelin on conduction velocity?

51. (Page 17.) Why do myelinated axons conduct action potentials faster than non myelinated axons?

52. (Summary) Fill out the chart associated with quiz question #2.

Answers to Study Questions on the Action Potential:

1. A nerve impulse.
2. A large change in membrane potential from a resting value of about -70 millivolts to a peak of about +30 millivolts, and back to -70 millivolts again.
3. At the axon hillock.
4. When signals from the dendrites and cell body reach the axon hillock and cause the membrane potential there to become more positive, a process called depolarization.

5. Voltage-gated channels for sodium open rapidly, allowing sodium to move down its electrochemical gradient into the cell.
6. By about 15 millivolts. So depolarization occurs when the membrane potential at the axon hillock goes from -70 mV to -55 mV.
7. An action potential is generated.
8. Then an action potential is not generated.
9. Yes.
10. At threshold a positive feedback loop is established.
11. At threshold, depolarization opens more voltage-gated sodium channels.
12. When depolarization opens voltage-gated sodium channels, this causes more sodium to flow into the cell, which in turn causes the cell to depolarize further and opens still more voltage-gated sodium channels.
13. From top to bottom: Voltage-sensitive gate, Time-sensitive gate, Closed, Open, Inactivated
14. (1) The inactivation of the voltage-gated sodium channels. (2) The opening of the voltage-gated potassium channels.
15. (1) A voltage-sensitive gate. (2) A time-sensitive inactivation gate.
16. As the cell is depolarized.
17. It stops the movement of sodium through the channel after the channel has been open for a fixed time.
18. They begin to inactivate, the inward flow of sodium decreases, and the positive feedback loop is interrupted.
19. They begin to open only about the time that the action potential reaches its peak.
20. Depolarization ends, and the positive feedback loop is broken.
21. Less sodium moving into the cell and more potassium moving out, the membrane potential becomes more negative, moving toward its resting value.
22. When the membrane potential becomes more negative than the resting membrane potential.
23. The slow voltage-gated potassium channels remain open after the cell has repolarized, potassium continues to move out of the cell, causing the membrane potential to become more negative than the resting membrane potential.
24. From top to bottom: Action potential, Sodium permeability, Potassium permeability
25. b
26. d
27. a
28. c
29. c
30. a
31. b
32. Hyperpolarization: E, depolarization: B, rest: A, initiation of repolarization: C, repolarization: D
33. A time when voltage-gated sodium channels are inactivated, then reset to the closed state. Potassium channels continue to open: D
    A time when voltage-gated sodium and potassium channels are closed: A
    A time when voltage-gated sodium channels begin to inactivate and voltage-gated potassium channels begin to open: C
    A time when some voltage-gated potassium channels remain open, resulting in movement of potassium out of the cell: E
    A time when voltage-gated sodium channels open rapidly, resulting in movement of sodium into the cell: B
34. c
35. e
36. a
37. d
38. b
39. A period of time after a neuron has generated an action potential where the cell cannot generate another action potential.
40. Because sodium channels are inactivated and it cannot move in through inactive channels. Also potassium continues to move out through open voltage-gated channels.
41. A period of time after a neuron has generated an action potential where the cell can generate an action potential, but only if it is depolarized to a value more positive than normal threshold.
42. Some sodium channels are still inactive and some potassium channels are still open. The cell has to be depolarized to a more positive membrane potential than normal threshold to open enough sodium channels to begin the positive feedback loop.
43. B
44. C
45. It is propagated down the axon.

46. Positive charge flows along the axon, depolarizing adjacent areas of membrane, which reach threshold and generate an action potential. The action potential thus moves along the axon as a wave of depolarization traveling away from the cell body.
47. The speed with which an action potential is propagated.
48. The diameter of the axon and how well the axon is insulated with myelin.
49. As the axon diameter increases, the internal resistance to the flow of charge decreases and the action potential travels faster.
50. A myelinated axon typically conducts action potentials faster than an unmyelinated axon of the same diameter.
51. Myelinated axons have areas of insulation interrupted by areas of bare axon called nodes of Ranvier. In a myelinated axon, charge flows across the membrane only at the nodes, so an action potential is generated only at the nodes. The action potential appears to jump along the axon in a process called saltatory conduction.
52.

Ion channel	Gate	Resting membrane potential	Depolarization	When?
Na^+ 	Voltage	Closed	Opens	Early
Na^+ 	Time-sensitive inactivation	Open	Closes	Late
K^+ 	Voltage	Closed	Opens	Late