The Origin of Biopotentials

- A biopotential is an electric voltage caused by a current flow of ions through biological tissue.
- The study of biopotentials is fundamental to the understanding of the medical instrumentation.
- It is the bioelectric phenomena at the cellular level.
- Bioelectric sources in the body are:
  - Pripheral nervous system,
  - Brain,
  - Heart
  - Active skeletal muscle
  - Retina
- Recordings of bioelectric phenomena
  - Electroneurogram (ENG)
  - Electroencephalogram (EEG)
  - Electrocardiogram (ECG)
  - Electromyogram (EMG)
  - Electroretinogram (ERG)

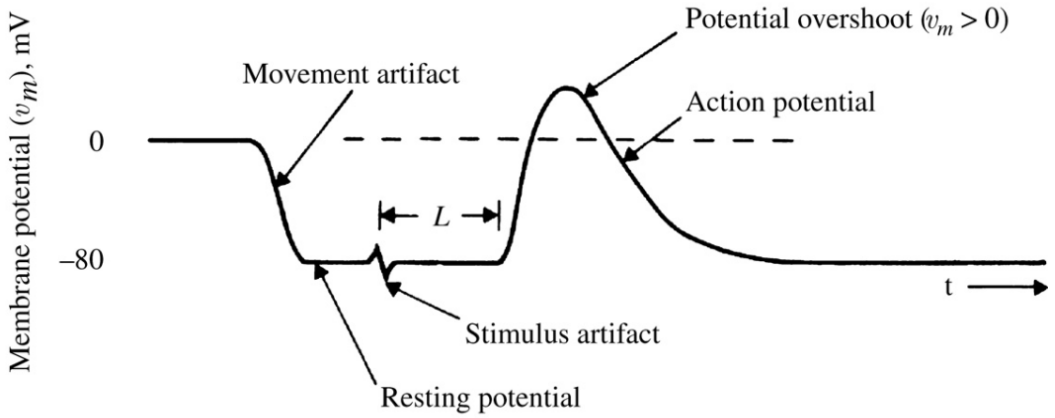
Electrical Activity of Excitable Cells

- Bioelectric potentials are produced as a result of electrochemical activity of a certain class of cells, known as excitable cells that are components of nervous or muscular tissue.

- Electrically they exhibit a resting potential and, when appropriately stimulated, an action potential.

Electrical Activity of Excitable Cells

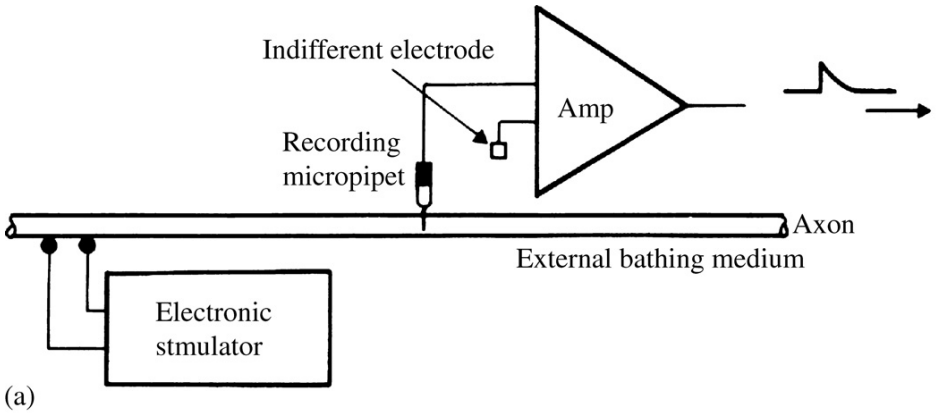
- A typical electrical recording from a single nerve fiber is shown in the Figure given below, including the dc offset potential (resting potential) that occurs upon penetration of the membrane.
- It also shows the transient disturbance of membrane potential (the action potential) when an adequate stimulus is given.



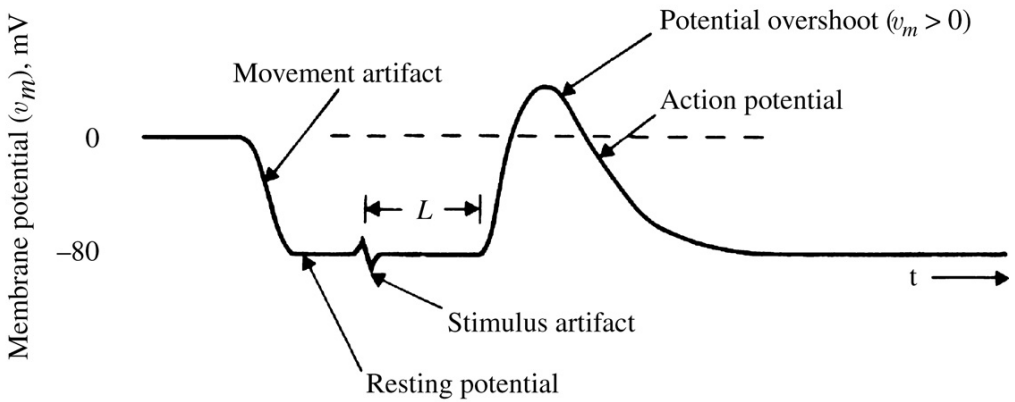
- The individual excitable cell maintains a steady electrical potential difference between its internal and external environments.
- This resting potential of the internal medium lies in the range -40 to -90 mV, relative to the external medium.

Electrical Activity of Excitable Cells (cont.)

- To measurement changes in membrane potential, an electronic stimulator supplies a brief pulse of current to the axon, strong enough to excite the axon.
- A recording of this activity is made by a penetrating micropipette.
- A short time later, an electrical stimulus is delivered to the axon; its field effect is recorded instantaneously as the stimulus artifact.



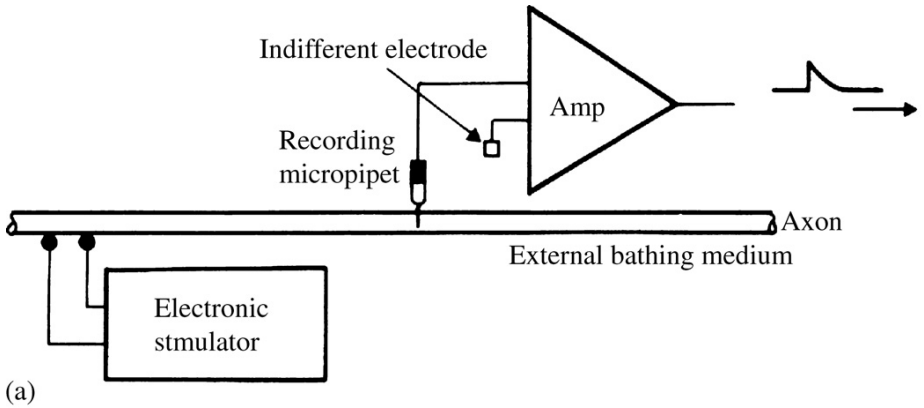
(a)



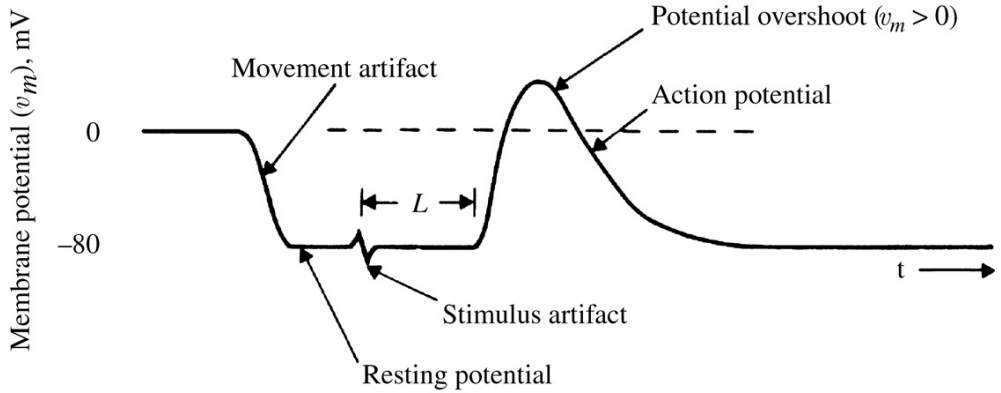
(b)

Electrical Activity of Excitable Cells (cont.)

- The action potential proceeds along the axon with a constant conduction velocity.
- The time period L is the latent period or transmission time from stimulus to recording site.



(a)

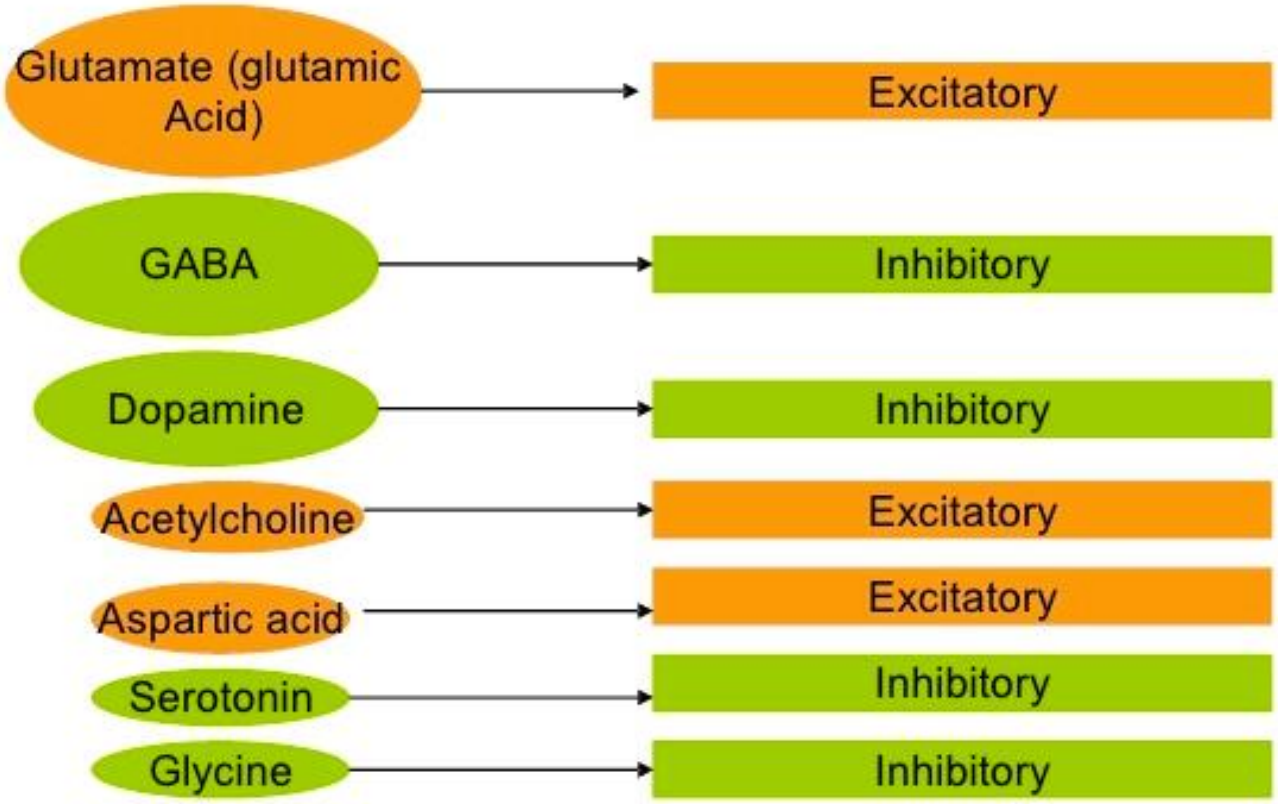


(b)

Electrical Activity of Excitable Cells (cont.)

- The particle producing electrical events in passive circuits is free electron, whereas the particle producing electrical events in biological tissue is the ion in an electrolyte solution.
- The rules governing these ionic events are:
  - Fick's law diffusion
  - Drift equation
  - Einstein relation
- A neuron can change the membrane potential of another neuron to which it is connected by releasing its neurotransmitter. Neurotransmitter interacts with receptor molecules in the postsynaptic membrane of the dendrite.
- At the post synaptic membrane neurotransmitter chemical energy is transmitted to the electrical energy (depends on the amount of neurotransmitter graded response)
- That electrical energy can be either inhibitory or exhibitory depends on the transmitted neurotransmitter.

Common natural neurotransmitters in the brain

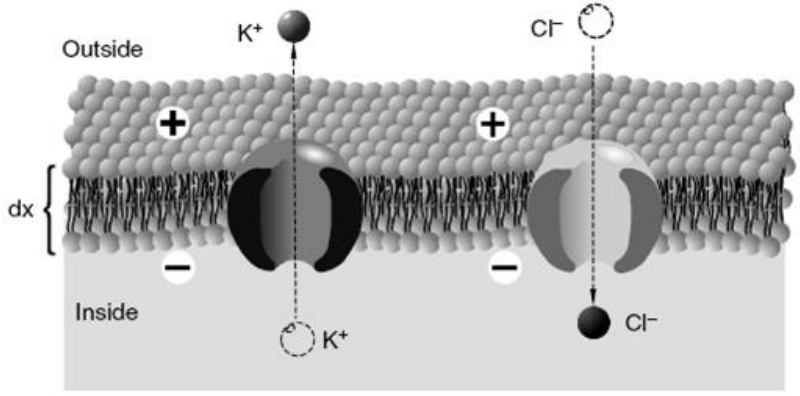


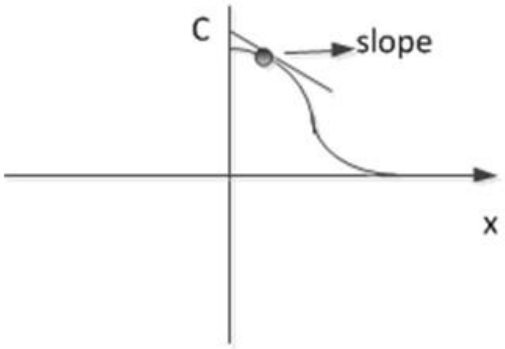
Electrical Activity of Excitable Cells (cont.)

- **Fick's Law of diffusion**
  - Molecules and particles move from a high concentration area to a low concentration area.

$$J_{diff} = -D\frac{d[C]}{dx}$$

  - J_{diff} is the flow of ions due to diffusion in A/m^2
  - [C] is the ion concentration as a function of distance (C/m^3)
  - D is the diffusion constant in m^2/s





Electrical Activity of Excitable Cells (cont.)

- **Particle Drift (Ohm's Law)**
  - Charged particles such as ions in an electric field will move under the forces of electrical attraction and repulsion. The resulting ionic flow is called the drift current.

$$J_{drift} = -\mu n[C]\frac{dv}{dx}$$

  - J_{drift} is the current density in A/m^2
  - [C] is the ion concentration as a function of distance (C/m^3)
  - v is the voltage across the membrane
  - μ is the mobility in m^2/sV
  - n is the ionic valence
    - n=1 for Na^+ and K^+
    - n=-1 for Cl^-
  - Positive ions drift down the electric field and negative ions drift up the electric field

Electrical Activity of Excitable Cells (cont.)

- **Einstein's relationship**
  - Two physical constants, mobility μ and diffusion coefficient D are related to each other:

$$\frac{D}{\mu} = \frac{kT}{q}$$

  - T is the absolute temperature in degrees Kelvin
  - k is the Boltzmann's constant (k=1.38x10-23 J/K)
  - μ is the mobility
  - D is the diffusion constant in m^2/s
  - Q is the magnitude of the electric charge ($1.602x10^2$ C)

The Resting State

- The cell membrane is a very thin (7 to 15 nm) lipoprotein complex that is essentially impermeable to intracellular protein and other organic anions (A^-)

- The membrane in the resting state is only slightly permeable to Na^+ and rather freely permeable to K^+ and Cl^-. The permeability of the resting membrane to potassium ion (P_K) is approximately 50 to 100 times larger than its permeability to sodium ion (P_{Na}).

- Typically, the K^+ concentration of the internal medium is 140mmol/liter, whereas that of the external medium is 2.5 mmol/liter.

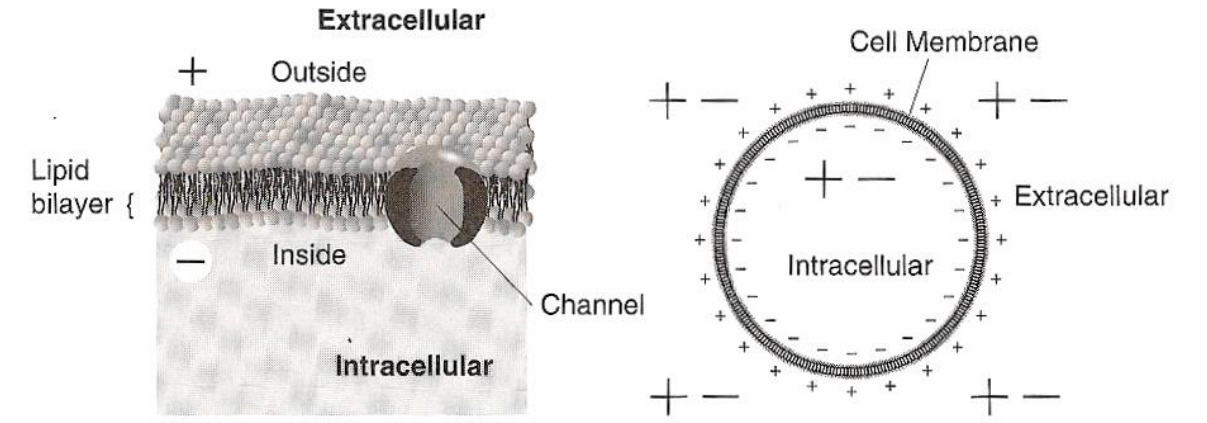
- The concentration difference creates a diffusion gradient that is directed outward across the membrane.

The Resting State (cont.)

- The movement of the K^+ along this diffusion gradient (while the nondiffusible anion component stays within the cell) is in such a direction as to make the interior of the cell more negative relative to the external medium (that is, positive charge is removed from the interior).

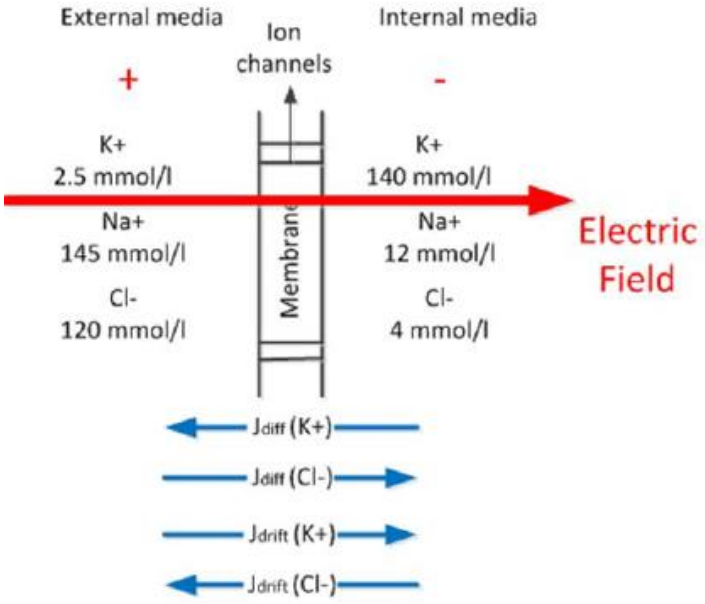
- Consequently, a transmembrane potential difference is established.

- Electrically the membrane can be described as a leaky capacitor, since it is comprised of a thin dielectric material that acts as a charge seperator, and has transmembrane ion channels of different types some of which allow a leakage flow of ions across the membrane at rest.



The Resting State (cont.)

- The electric field supported by the membrane capacitor at rest is directed inward from positive to negative across the membrane.
- It tends to inhibit the outward flow of positively charged ions (such a K^+), as well as the inward flow of negatively charged ions (such as Cl^-).
- Thus the diffusional and electrical forces acting across the membrane are opposed to one another, and a balance is ultimately achieved.



- The membrane potential at which such an equilibrium occurs (considering K^+ to be the main ionic species involved in the resting state; that is, $P_K \gg P_{Na}$) is called the equilibrium potential for the K^+ (E_K).

The Resting State (cont.)

- It is measured in volts and is calculated from the Nernst equation,

$$E = \frac{RT}{nF} ln \frac{[K]_o}{[K]_i} = 2.3026 \frac{RT}{nF} log_{10} \frac{[K]_o}{[K]_i}$$

$$E = \frac{kT}{q} ln \frac{[K]_o}{[K]_i} = 2.3026 \frac{kT}{q} log_{10} \frac{[K]_o}{[K]_i}$$

  - n is the valence electrons of K^+ (n=1 for K^+ and Na^+)
  - $[K]_i$ is the intracellular concentration of K^+ in moles per liter
  - $[K]_o$ is the extracellular concentration of K^+ in moles per liter
  - R is the universal gas constant ($R=8.314472 JK^{-1}mol^{-1}$)
  - T is absolute temperature in K
  - F is the Fraday constant ($F=9.6855399 \times 10^4 Cmol^{-1}$)
  - k is the Boltzmann's coefficients ($k=1.38 \times 10^{-23} J/K$)
  - q is the charge ($q=1.602 \times 10^{-19} C$)
  - For T=300K (room temp), kT/q=26mV

The Resting State (cont.)

- A more accurate expression for the membrane equilibrium potential E, which accounts for the influence of other ionic species in the internal and external media was first developed by Goldman (1943) and later modified by Hodgkin and Katz (1949), who assumed a constant electric field across the membrane:

$$E = \frac{kT}{q} ln \left\{ \frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o} \right\}$$

- Here E is the equilibrium transmembrane (resting) potential when net current through the membrane is zero and P_M is the permeability coefficient of the membrane for a particular ionic species M.
- It is called the Goldman–Hodgkin–Katz (GHK) formulation.

The Resting State (cont.)

- For frog skeletal muscle, typical values for the intracellular and extracellular concentrations of the major ion species (in millimoles per liter) are as follows.

Species	Intracellular	Extracellular
Na^+	12	145
K^+	155	4
Cl^-	4	120

- Assuming room temperature (20 C) and typical values of permeability coefficient for frog skeletal muscle (P_{Na}= $2x10^{-8}$ cm/s, P_K=$2x10^{-6}$ cm/s, and P_{Cl}=$4x10^{-6}$ cm/s), calculate the equilibrium resting potential for this membrane,using the Goldman equation.

- Solution:

$$E = \frac{kT}{q} ln \left\{ \frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o} \right\}$$

$$E = 0.02524 ln \left\{ \frac{P_K[4]_o + P_{Na}[145]_o + P_{Cl}[4]_i}{P_K[155]_i + P_{Na}[12]_i + P_{Cl}[120]_o} \right\}$$

$$E = -85{,}3mV$$

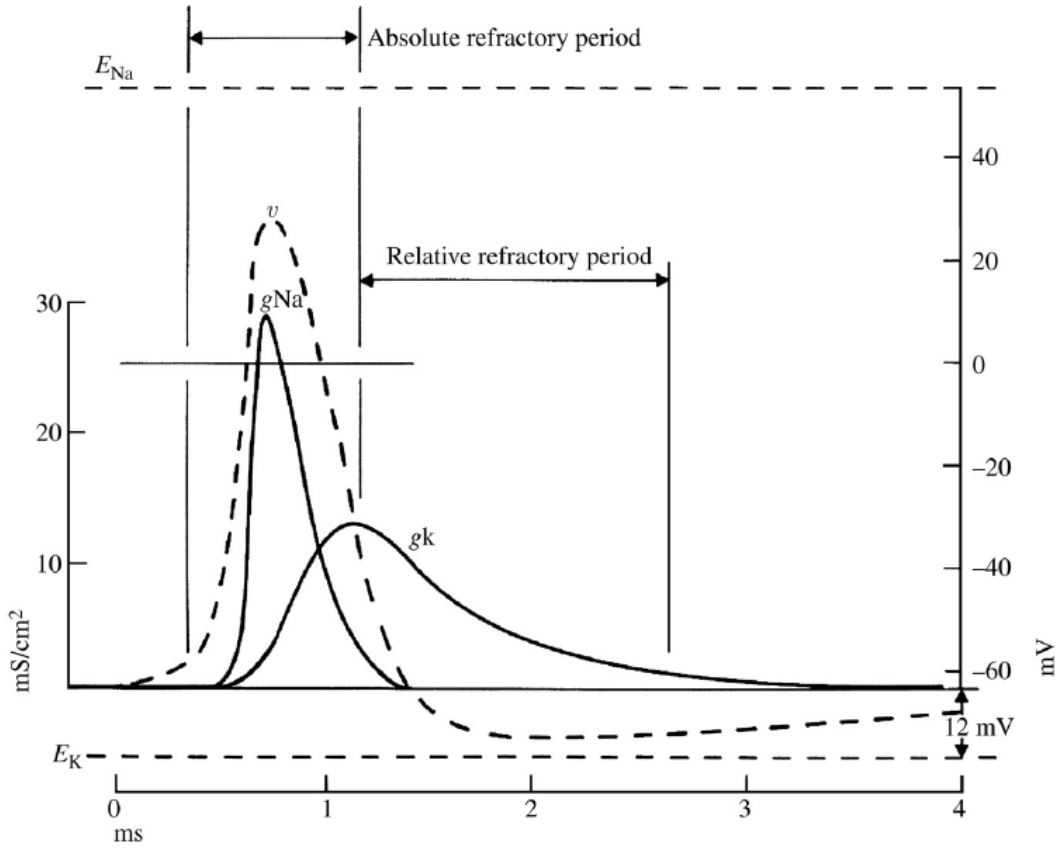
- which is close to typical measured values for the resting membrane potential in frog skeletal muscle.

The Resting State (cont.)

- Maintaining the steady-state ionic imbalance between the internal and external media of the cell requires continuous active transport of ionic species against their electrochemical gradients.
- The active transport mechanism is referred to as the sodium–potassium pump.
- It actively transports Na^+ out of the cell and K^+ into the cell in the ratio 3 Na^+ : 2 K^+.
- The associated pump current i_{NaK} is a net outward current that tends to increase the negativity of the intracellular potential.
- Thus, **the factors influencing the flow of ions across the membrane are**
  - (1) diffusion gradients,
  - (2) the inwardly directed electric field,
  - (3) membrane structure (availability of pores)
  - (4) active transport of ions against an established electrochemical gradient.

The Active State

- Another property of an excitable cell is its ability to conduct an action potential when adequately stimulated.



- υ is the membrane potential.
- g_{Na} is the membrane ionic conductance for Na^+.
- g_K is the membrane ionic conductance for K^+.
- **Absolute refractory period**: membrane can not respond to any stimulus
- **Relative refractory period**: membrane can respond to intense stimulus.

The Active State (cont.)

- The stimulus: Depolarize the cell membrane that is sufficiently exceed its threshold potential and thereby elicit an all-or-none action potential, which

  - travels in an unattenuated fashion,
  - at a constant conduction velocity (0.5 m/s to 120 m/s)
  - lasts approximately 1 to 5 ms along the membrane.

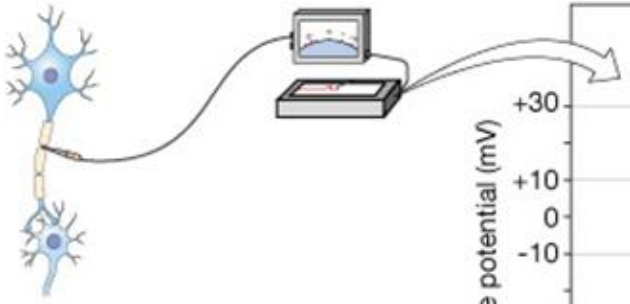
- Because of the steady resting potential, the cell membrane is said to be **polarized.**

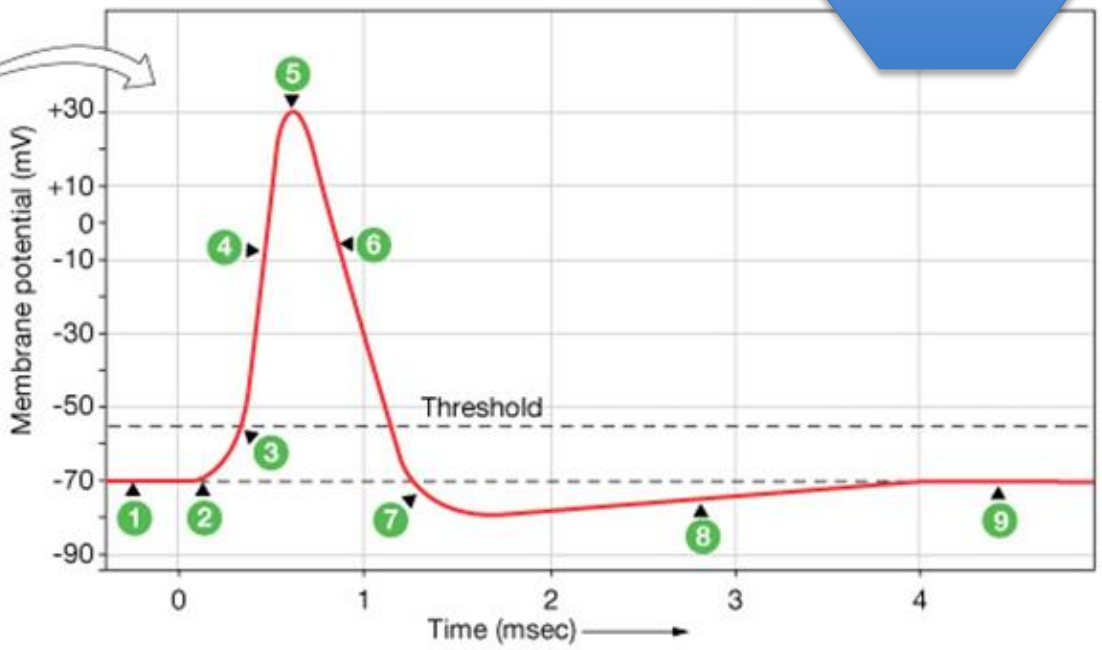
- Increasing the magnitude of cell polarization by making inside the cell less negative is said to be **depolarization.**

- Lessening the magnitude of cell polarization by making inside the cell more negative is said to be **hyperpolarization.**

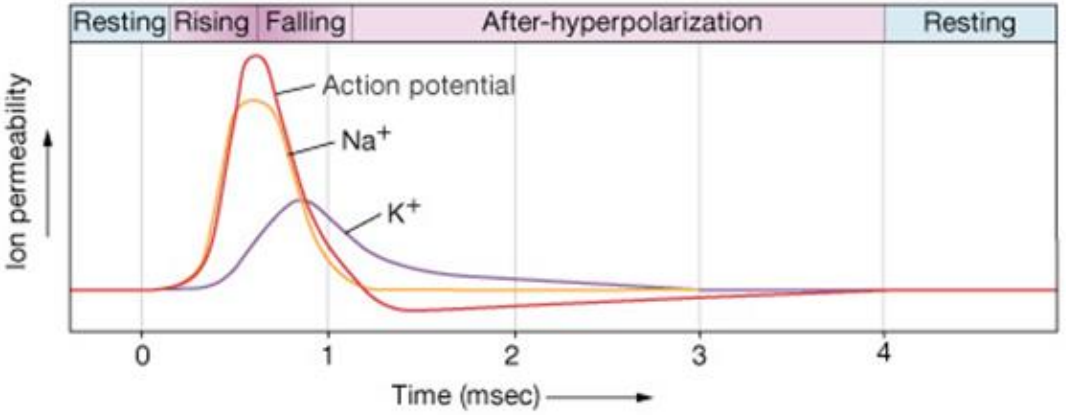
The Active State (cont.)

Watch video 3.1





1. Resting membrane potential
2. Depolarizing stimulus
3. Membrane depolarizes to threshold. Voltage-gated Na^+ channels open and Na^+ enters cell. Voltage-gated K^+ channels begin to open slowly.
4. Rapid Na^+ entry depolarizes cell.
5. Na^+ channels close and slower K^+ channels open.
6. K^+ moves from cell to extracellular fluid.
7. K^+ channels remain open and additional K^+ leaves cell, hyperpolarizing it.
8. Voltage-gated K^+ channels close, some K^+ enters cell through leak channels.
9. Cell returns to resting ion permeability and resting membrane potential.



Equivalent Circuit Model for the Cell Membrane

- The Goldman equation is limited because it cannot be used to determine how rapidly the membrane potential changes in response to a change in permeability.

- It is inconvenient for determining the magnitude of the individual Na^+, K^+, and CI^- currents.

- This information can be obtained with a simple mathematical model derived from electrical circuits. Within this model, called **an equivalent circuit**, all of the important functional properties of the neuron are represented by an electrical circuit consisting only of

  - conductors or resistors (representing the ion channels),
  - batteries (representing the concentration gradients of relevant ions)
  - capacitors (the ability of the membrane to store charge)

- **Equivalent circuits provide us with an intuitive understanding as well as a quantitative description of how current flow due to the movement of ions generates signals in nerve cells**

Equivalent Circuit Model for the Cell Membrane (cont.)

- The nerve cell has three types of passive electrical characteristics:
  - Electromotive force
  - Resistance
  - Capacitance

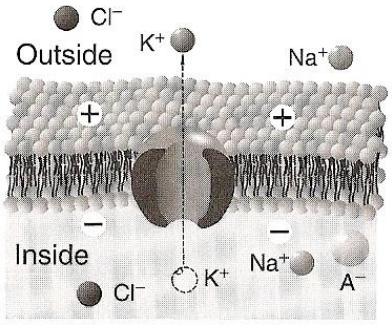
- The nerve membrane is a lipid bilayer that pierced by a variety of different types of ion channels, where each channel is charaterized as being passive (always open) or active (gates that can be opened).

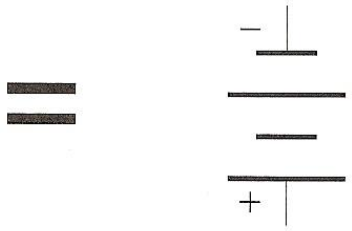
- Each ion channel is characterized by its selectivity.

- In addition, there is the active Na-K pump that maintains V_m across the cell membrane

Equivalent Circuit Model for the Cell Membrane (cont.)

- **Electromotive force properties:**
  - The three major ions K^+, Na^+, and Cl^- are differentially distributed across the cell membrane at rest through passive ion channels.
  - This seperation of charge exists across the membrane results in a voltage potential V_m as described by the Goldman Equation.
  - The Nernst potential for K^+ is the electrical potential difference across the channel and easily modeled as a battery.





$$E_K = 26 \ln \frac{[K^+]_o}{[K^+]_i} mV$$

  - The same model is applied for Na^+ and Cl^- with values equal to the Nernst potentials for each.

Equivalent Circuit Model for the Cell Membrane (cont.)

- **Resistive properties:**
  - In addition to the electromotive force, each channel also has resistance; that is, it resists the movement of electrical charge through the channel.
  - The term conductance G which is the ease with which the ions move through the membrane, is typically used to represent resistance.
  - Since the conductances (channels) are in parallel, the total conductance is the total number of channels (N) times the conductance for each channel (*G '):*

$$G = N \times G'$$

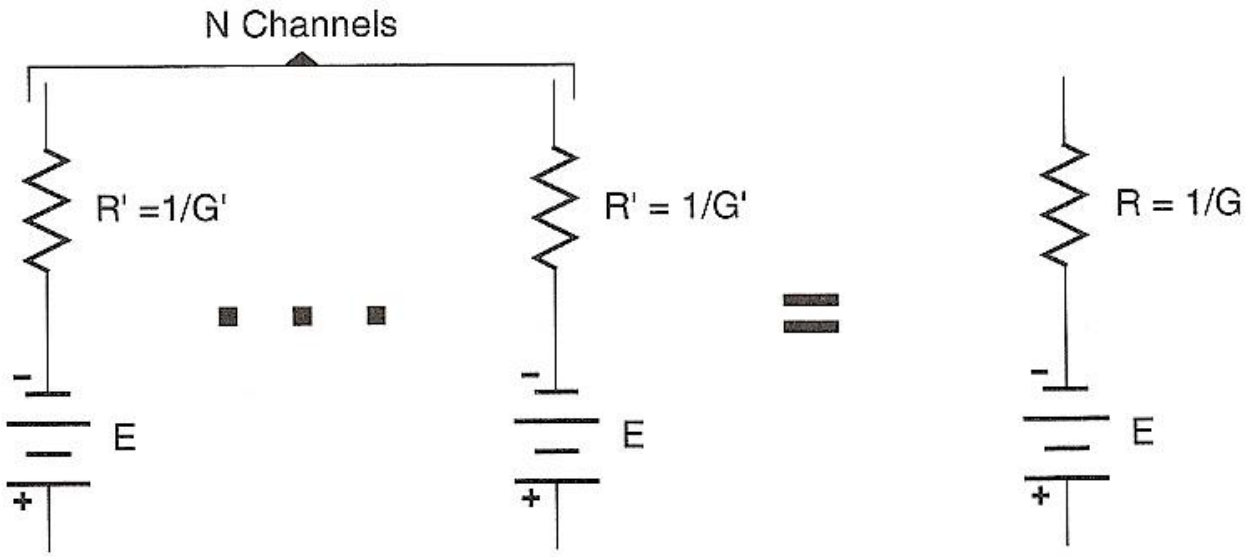
  - It is usually more convenient to write the conductance as resistance

$$R = \frac{1}{G}$$

measured in ohms (Ω).

Equivalent Circuit Model for the Cell Membrane (cont.)

- An equivalent circuit for the channels for a single ion is given as a resistor series with a battery.



Equivalent Circuit Model for the Cell Membrane (cont.)

- **For Example**; An equivalent circuit for K^+ channels:

- Each K^+ channel can be represented as a resistor or conductor of ionic current with a single-channel conductance of G'_K (remember, conductance (G) = 1/resistance).

- If there were no K^+ concentration gradient, the current through the K^+ channel would be given by Ohm's law:

$$i_K = G'_K \times V_m.$$

- However, there is normally a K^+ concentration gradient and there will be a chemical force driving K^+ across the membrane. In the equivalent circuit this chemical force is represented by a battery, whose electromotive force is given by the Nernst potential for K^+, E_K.

- From the Nernst equation, we also know that the equilibrium potential for K^+ is negative.

- Thus, the K^+ current that flows solely because of its concentration gradient is given by

$$i_K = -G'_K \times E_K$$

Equivalent Circuit Model for the Cell Membrane (cont.)

- For a real neuron that has both a membrane voltage and K^+ concentration gradient, the net K^+ current is given by the sum of the currents due to the electrical and chemical driving forces:

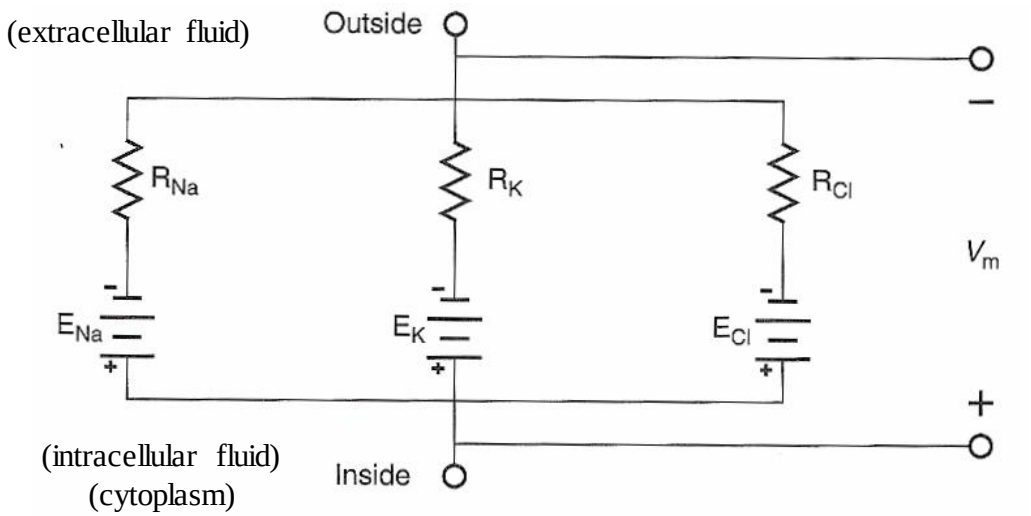
$$i_K = (G'_K \times V_m) - (G'_K \times E_K) = G'_K (V_m - E_K)$$

- The term $V_m - E_K$ is called *the electrochemical driving force*.
- It determines the direction of ionic current flow and (along with the conductance) the magnitude of current flow.
- This equation is a modified form of Ohm's law that takes into account that ionic current flow through a membrane is determined not only by the voltage across the membrane but also by the ionic concentration gradients.

What are the i_{Na} and i_{Cl} ?

Equivalent Circuit Model for the Cell Membrane (cont.)

- Equivalent circuit for three ions:



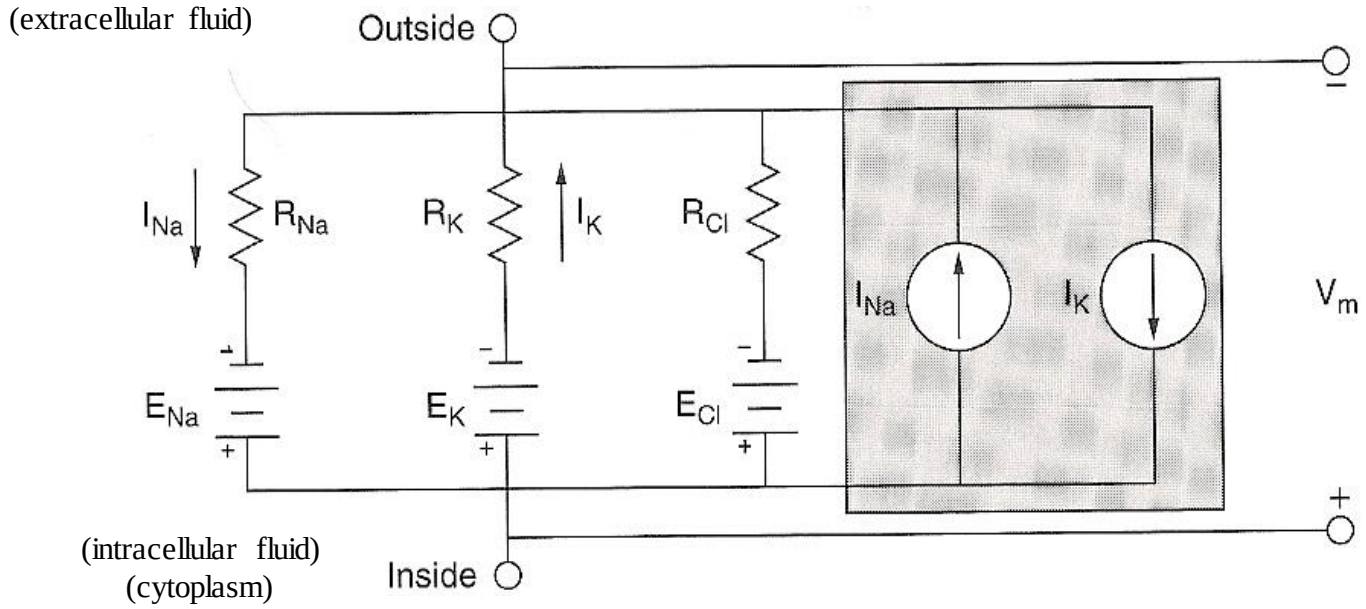
$$Vm = \frac{G_K E_K + G_{Na} E_{Na} + G_{Cl} E_{Cl}}{G_K + G_{Na} + G_{Cl}}$$?

or

$$Vm = \frac{R_{Na} R_{Cl} E_K + R_K R_{Cl} E_{Na} + R_K R_{Na} E_{Cl}}{R_{Na} R_{Cl} + R_K R_{Cl} + R_K R_{Na}}$$

Equivalent Circuit Model for the Cell Membrane (cont.)

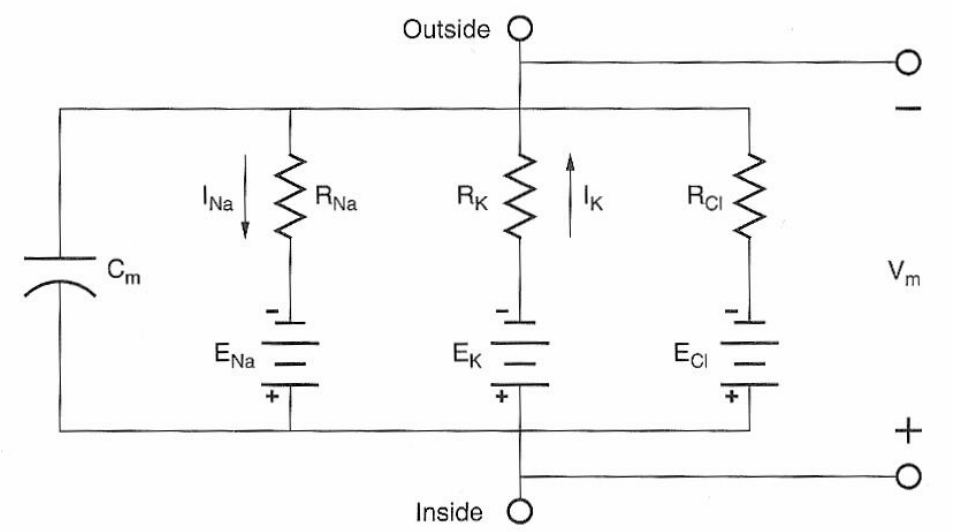
- Na-K Pump



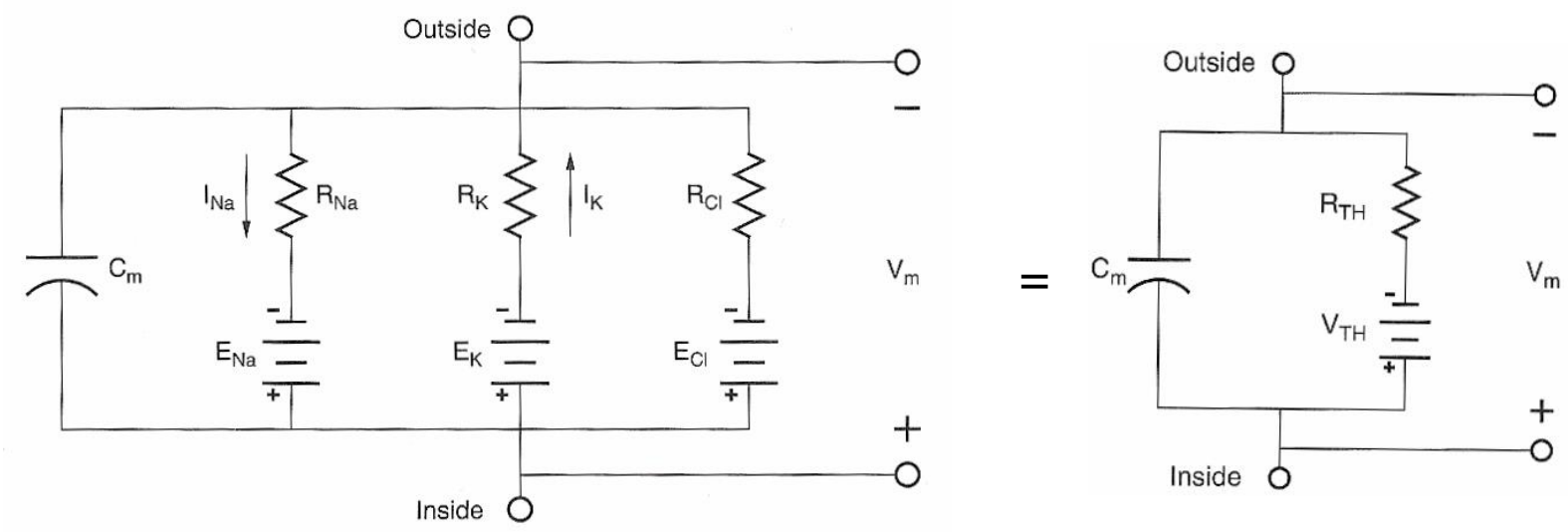
Equivalent Circuit Model for the Cell Membrane (cont.)

- **Capacitive properties:**

  - Capacitance occurs whenever electrical conductors are separated by an insulating material.
  - In the neuron, the cytoplasm and extracellular fluid are the electrical conductors and the lipid bilayer of the membrane is the insulating metarial.
  - Capacitance of a neuron membrane is approximately 1μF/cm2 .
  - Membrane capacitance implies that ions do not move through the membrane except through ion channels.



Equivalent Circuit Model for the Cell Membrane (cont.)



$$V_{th} = \frac{R_{Na}R_{Cl}E_K + R_K R_{Cl}E_{Na} + R_K R_{Na}E_{Cl}}{R_{Na}R_{Cl} + R_K R_{Cl} + R_K R_{Na}}$$

$$R_{th} = \frac{1}{\frac{1}{R_K} + \frac{1}{R_{Na}} + \frac{1}{R_{Cl}}}$$

- The time constant for the membrane circuit model is

$$\tau = R_{th} \times C_m$$

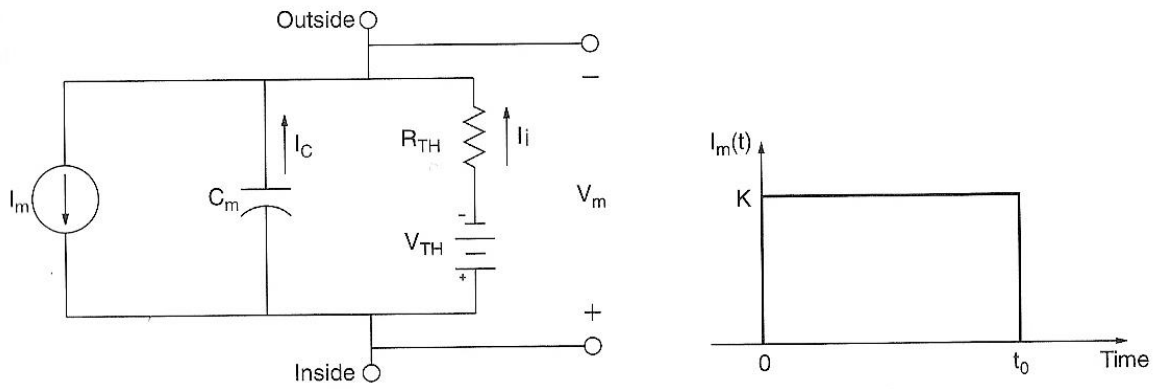
- The range for τ is from 1 to 20ms in a typical neuron.

- At steady state, the capacitor acts as an open circuit and

$$V_{th} = V_m$$

Equivalent Circuit Model for the Cell Membrane (cont.)

- **Example:**
  - Compute the change in Vm due to a current pulse through the cell membrane.



  - The membrane potential V_m due to a current pulse I_m with amplitude K and duration t_0 applied at $t=0$, is found by applying Kirchhoff's current law at the cytoplasm, yielding

$$-I_m + I_i + I_C = 0$$

$$-I_m + \frac{V_m - V_{th}}{R_{th}} + C_m \frac{dV_m}{d_t} = 0$$

Equivalent Circuit Model for the Cell Membrane (cont.)

$$-I_m + \frac{V_m - V_{th}}{R_{th}} + C_m \frac{dV_m}{d_t} = 0$$

- The laplace transform of the node equation is

$$-I_m(s) + \frac{V_m(s)}{R_{th}} - \frac{V_{th}}{sR_{th}} + sC_m V_m(s) - C_m V_m(0^+) = 0$$

where $V_m(0^+)=V_{th}$

- The laplace transform of the current pulse is

$$I_m(s) = \frac{K}{s}\left(1 - e^{-t_0 s}\right)$$

- Substituting $I_m(s)$ into the node equation and rearranging terms yields

$$V_m(s) = KR_{th}\left(\frac{1}{s} - \frac{1}{s + \frac{1}{C_m R_{th}}}\right)\left(1 - e^{-t_0 s}\right) + \frac{V_{th}}{s}$$

Equivalent Circuit Model for the Cell Membrane (cont.)

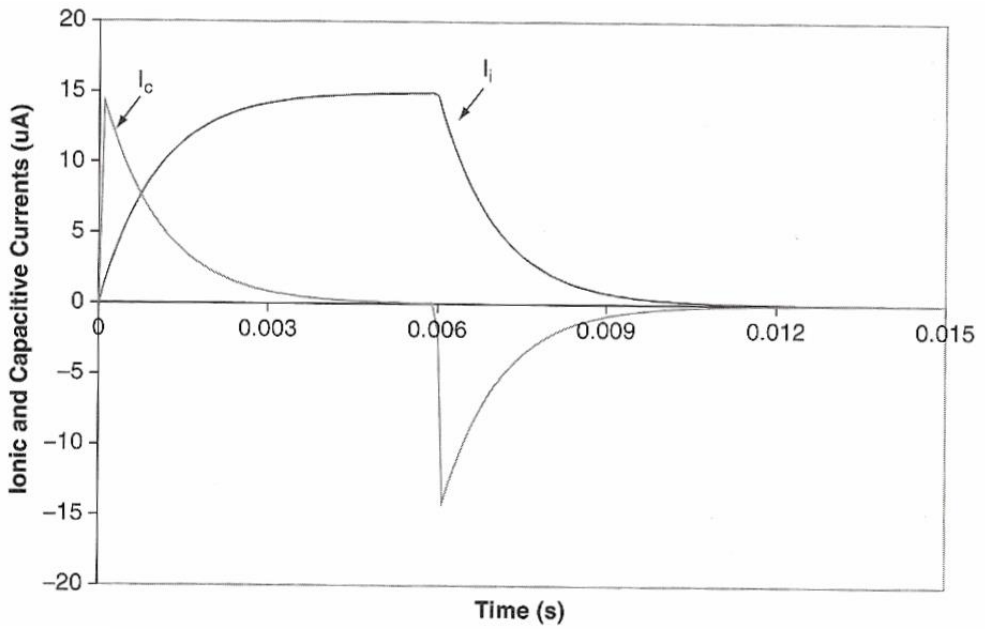
- Transforming back into the time domain yields the solution

$$V_m(t) = V_{th} + R_{th}K\left(1 - e^{\frac{t}{R_{th}C_m}}\right)u(t) - R_{th}K\left(1 - e^{\frac{t-t_0}{R_{th}C_m}}\right)u(t-t_0)$$

- The ionic current I_i and capacitive current I_c

$$I_i = \frac{V_{th} - V_m}{R_{th}}$$

$$I_c = C_m \frac{dV_m}{dt}$$



Functional Organization of the Peripheral Nervous System

- The spinal nervous system is functionally organized on the basis of what is commonly called the reflex arc. The components of this arc are as follows:
  - A sense organ, consisting of many individual sense receptors that respond preferentially to an environmental stimulus of a particular kind, such as pressure, temperature, touch, or pain. (e.g. receptor)
  - A sensory nerve, containing many individual nerve fibers that perform the task of transmitting information (encoded in the form of action potential (frequency) from a peripheral sense receptor to other cells lying within the central system (brain and spinal cord). (Transfer info from receptor to CNS)

Functional Organization of the Peripheral Nervous System (Cont.)

- The CNS, which serves as a central integrating station. Here information is evaluated, and, if warranted, a "motor" decision is implemented. That is, action potentials are initiated in motor-nerve fibers associated with the motor-nerve trunk. (information processing station)
- A motor nerve, serving as a communication link between the CNS and peripheral muscle. (transfer information from CNS to effector organ)
- The effector organ, which consists, for example, of skeletal muscle fibers that contract (shorten) in response to the driving stimuli (action potentials) conducted by motor-nerve fibers. (i.e. muscles)

Functional Organization of the Peripheral Nervous System (Cont.)

- The simplest example of the behaviour of the reflex arc: knee-jerk reflex

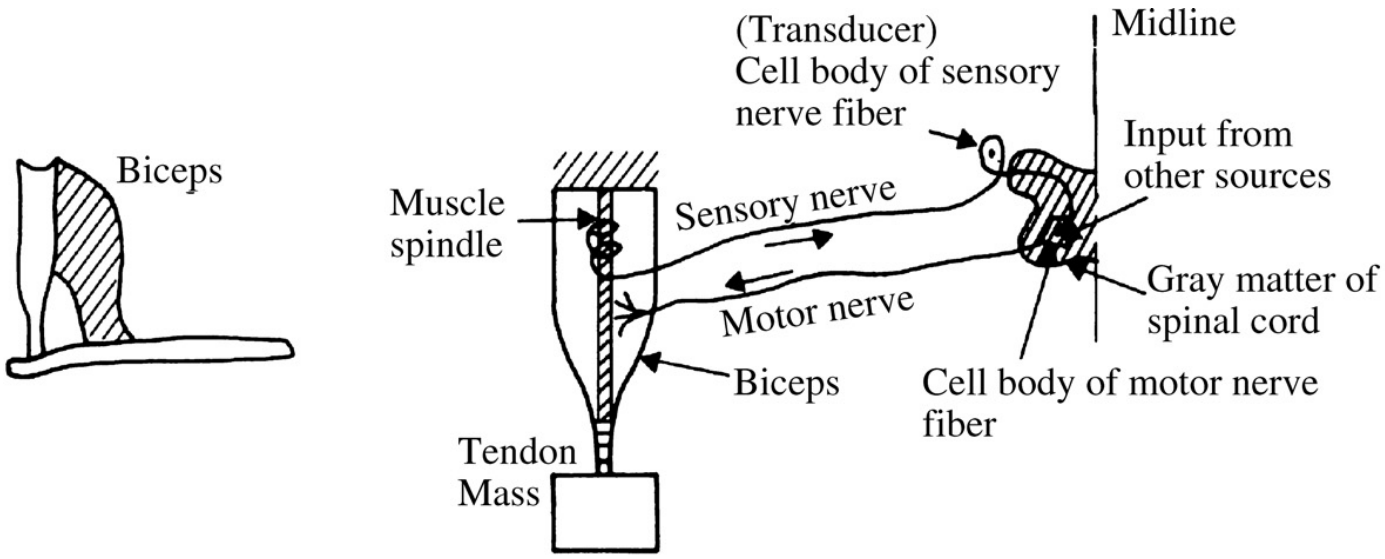


Figure 4.6 : Schematic diagram of a muscle-length control system for a peripheral muscle (biceps)(a) anatomical diagram of limb system, showing interconnections

- The initial stimulus to the muscle was a stretch.
- The response was a contraction of the muscle.

Functional Organization of the Peripheral Nervous System (Cont.)

- Junctional Transmission:
- Communication links in reflex arc:
  - intercommunication between neurons (neuro–neuro junctions) called synapses,
  - communications links between neurons and muscle fibers called neuromuscular junctions.
- These occur at small, specialized regions of the muscle fiber referred to as an endplate regions.
- The junctional transmission process in each of these cases is electrochemical in nature.

Neuromuscular junction