BME205
Fundamentals of Biomedical Engineering

Michael Boyadjian

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Contents

1 Foundation of Physiology

1.1 Homoeostasis

Homoeostasis is the ability of a cell or organism to regulate its internal conditions typically using feedback systems to minimize variation and maintain health regardless of changes in external environment.

1.1.1 Body Cells

The fluid collectively contained within all body cells is known as **intercellular fluid (ICF)**. The fluid outside the cells is called **extracellular fluid (ECF)**. Extracellular fluid is made up of two components: **plasma**, the fluid component of blood; and **interstitial fluid**, which surrounds and bathes the cells

1.1.2 Body Systems

Homoeostasis is essential for the survival of each cell, and each cell, through its specialized activities, contributes as part of a body system to the maintenance of the internal environment shared by all cells. It is not a rigid, fixed state, or absolute setting, but rather a dynamic, steady state in which changes occur but are minimized by multiple dynamic equilibrium adjustment mechanisms. The following are factors that are homoeostatically regulated.

- Concentration of nutrient molecules
- Concentration of oxygen and carbon dioxide
- Concentration of waste products
- pH
- Concentration of water, salt, and other electrolytes
- Volume and pressure
- Temperature

The 11 body systems also contribute to homoeostasis in the following ways:

- The **circulatory system** transports materials, such as nutrients, oxygen, carbon dioxide, wastes, electrolytes, and hormones from one part of the body to another.
- The **digestive system** breaks down dietary food into small nutrient molecules that can be absorbed into the plasma for distribution to the body cells, and transfers water and electrolytes from the external environment to the internal environment.
- The **respiratory system** receives oxygen from the external environment and eliminates carbon dioxide from the internal environment; it is important in regulating proper pH of the internal environment by adjusting the rate of acid-forming carbon dioxide.

- The **urinary system** removes excess water, salt, acid, and other electrolytes from the plasma and eliminates them in the urine.
- The **skeletal system** provides support and protection for the soft tissues and organs. It also serves as a storage reservoir for calcium, an electrolyte whose plasma concentration must be maintained within very narrow limits.
- The **muscular system** along with the skeletal system forms the basis of movement. The system enables an individual to move toward food or away from harm.
- The **integumentary system** serves as an outer protecting barrier that prevents internal fluid from being lost from the body and foreign organisms from entering. It is also important in regulating body temperature.
- The **immune system** defends against foreign invaders and body cells that have become cancerous and paves the way for replacing injured or worn-out cells
- The **nervous system** is one of the two major regulatory systems of the body. This is especially important in detecting and initiating reactions to changes in the external environment.
- The **endocrine system** is the other major regulatory system. This is important in controlling the concentration of nutrients and, by adjusting kidney function, controlling the internal environment's volume and electrolyte composition.
- The **reproductive system** is essential for perpetuating the species. Homoeostatic mechanisms ensure that both male and female reproductive systems are optimizes to favour reproductive success.

1.1.3 Homoeostatic Control Systems

A homoeostatic control system is needed to maintain homoeostasis. This control system must be able to do three things:

1. Detect deviations from normal in the internal environment (receptor)
2. Integrate this information with any other relevant information (control centre)
3. Trigger the needed adjustments responsible for restoring this factor within the normal range (effector)

These control systems can be grouped into two classes: **intrinsic** and **extrinsic** controls. Intrinsic controls are built into or are inherent in an organ. Most factors are however maintained by extrinsic controls, regulatory mechanisms initiated outside an organ to alter the activity of the organ.

To stabilize the necessary physiological factors, homoeostatic control systems must be able to detect and make necessary adjustments to various changes bringing feedback and feedforward loops into play. **Feedback** refers to responses made after a change has been detected. **Feedforward**

describes responses made in anticipation of a change. **Disruptions** can occur when the control variable moves outside the dynamic range.

- **Negative Feedback**

  Homoeostatic control systems operate primarily on the principle of negative feedback. A change in a homoeostatically controlled factor triggers a response seeking to maintain homoeostasis by moving the factor in the opposite direction of its original change, a corrective adjustment. This is structured as the following:

- **Positive Feedback**

  The output enhances or amplifies a particular change so that the controlled factor continues to move in the direction of the initial change. This is much less frequent than negative feedback. Examples include child birth and heat stroke

2 Cell Physiology

2.1 Overview of Cell Functions

- There are around 200 different types of cells
- Similar cells will have similar features

Most cells have three common subdivisions:

- **Plasma Membrane:** Encloses the cells
- **Nucleus:** Contains the cell's genetic material
- **Cytoplasm:** Portion of the cell's interior not occupied by the nucleus but containing numerous organelles, structural proteins, transport and secretory vesicles

The following table summarizes the important structures of the cell.

Cell Part	Structure	Function
Plasma membrane	Lipid bilayer studded with proteins and small amounts of carbohydrate	Acts as selective barrier between cellular contents and extracellular fluid; controls traffic in and out of the cell
Nucleus	DNA and specialized proteins enclosed by a double-layered membrane	Acts as control centre of the cell, providing storage of genetic information; nuclear DNA provides codes for the synthesis of structural and enzymatic proteins and serves as blueprint for cell replication
Cytoplasm		
Organelles		
Endoplasmic reticulum	Extensive, continuous membranous network of fluid-filled tubules and flattened sacs, partially studded with ribosomes	Forms new cell membrane and other cell components and manufactures products for secretion
Golgi complex	Sets of stacked, flattened membranous sacs	Modifies, packages, and distributes newly synthesized proteins
Lysosomes	Membranous sacs containing hydrolytic enzymes	Serve as digestive system of the cell, destroying foreign substances and cellular debris
Centriole	Usually paired, small barrel-shaped organelles that consist of nine short triplet microtubules	Site of growth of new microtubules: both cytoplasmic transport microtubules and the microtubules that form the mitotic spindle
Peroxisomes	Membranous sacs containing oxidative enzymes	Perform detoxification activities
Mitochondria	Rod- or oval-shaped bodies enclosed by two membranes, with the inner membrane folded into cristae that project into an interior matrix	Act as energy-producing organelles; major sites of ATP production; contain enzymes for citric acid cycle and electron transport chain
Vaults	Shaped like hollow octagonal barrels	Serve as cellular trucks for transport from nucleus to cytoplasm

Cytosol: gel-like portion		
Intermediary metabolism enzymes	Dispersed within the cytosol	Facilitate intracellular reactions involving the degradation, synthesis, and transformation of small organic molecules
Ribosomes	Granules of RNA and proteins—some attached to rough endoplasmic reticulum, some free in the cytoplasm	Serve as workbenches for protein synthesis
Transport, secretory, and endocytotic vesicles	Transiently formed, membrane-enclosed products synthesized within or engulfed by the cell	Transport and/or store products being moved within, out of, or into the cell, respectively
Inclusions	Glycogen granules, fat droplets	Store excess nutrients
Cytosol: cytoskeleton portion		As an integrated whole, serves as the cell's "bone and muscle"
Microtubules	Long, slender, hollow tubes composed of secretory vesicles	Maintain asymmetric cell shapes and tubulin molecules; coordinate complex cell movements, specifically facilitating transport of secretory vesicles within cells, serving as main structural and functional component of cilia and flagella, and forming mitotic spindle during cell division
Microfilaments	Intertwined helical chains of actin molecules; microfilaments composed of myosin molecules also present in muscle cells	Play a vital role in various cellular contractile systems, including muscle contraction and amoeboid movement; serve as a mechanical stiffener for microvilli
Intermediate filaments	Irregular, threadlike proteins	Help resist mechanical stress

2.2 Cellular Metabolism

- **Intermediary metabolism** refers collectively to the large set of of chemical reactions inside the cell that involve degradation, synthesis, and transformation of of small organic molecules, such as sugars, amino acids, and fatty acids.
- **Anabolic** processes favour the synthesis of molecules
- **Catabolic** processes favour the breakdown of complex molecules to simple ones
- Source of energy for body is stored in carbon bonds in food
- The body converts the bonds into high energy **adenosine triphosphate (ATP)** bonds

2.2.1 ATP Production

There are 3 chemical pathways for ATP production:

- Substrate Level Phosphorylation
- Anarobic Glycolosis
- Aerobic Glycolosis

Follow 4 steps:

1. Glycolosis

2. Decarboxylation of Pyruvate
3. Tricarboxylic Acid Cycle
4. Electron Transport Chain (ETC)

Ideally, 1 glucose would produce 38 ATP

- Assumes no energy is required in process
- ETC runs at 100 % efficiency

ATP is then used for the following:

- Synthesis of New Energy Compounds
- Membrane Transport
- Mechanical Work

2.3 Plasma Membrane

The survival of every cell depends on the maintenance of intracellular contents unique for that cell type. This difference in composition is maintained by by the plasma membrane, an extremely thin layer of lipids and proteins that forms the outer boundary of every cell and encloses the intracellular contents. The plasma membrane plays an active role in determining cell composition by selectively permitting specific cells to pass between the cell and its environment. It also maintains differences in ion concentrations between a cell's interior and exterior.

2.3.1 Structure and Composition

The plasma membrane consists of mostly lipids, proteins, and some carbohydrates.

- **Phospholipids:** Have a polar, elecrically charged head, negatively charged phosphate group, and two fatty acid tails
  - **Hydrophillic:** Water loving polar end; interacts with water molecules
  - **Hydrophobic:** Water fearing non-polar end; does not mix with water
- **Lipid Bilayer:** Formed by phospholipids
  - Cholesterol helps to stabilize the bilayer
  - Membrane proteins are attached / inserted into the bilayer
  - Fluid nature, but structural integrity; flexible to still be able to change shape
  - Known as the fluid mosaic model

  - Has three important functions:
    1. Forms basic structure of the membrane; "picket around a fence"
    2. Hydrophobic barrier serves as a barrier to passage of water-soluble substances between the ICF and ECF; helps maintain different mixtures and concentrations of solutes inside the cell
    3. Responsible for fluidity of membrane

- **Membrane Proteins:** Various membrane proteins have different functions
  - **Water Filled Pathways / Channels**
    * Water soluble substances small enough can pass through without contact with hydrophobic interior
    * Selectively attract / repel ions
    * Adapt shape in response to control mechanisms
  - **Carrier Molecules**
    * Transfer specific substances across that are unable to cross on their own
  - **Docking Marker Acceptors**
    * Bind with secretory vesicles
    * When stimulatory signals trigger fusion with IC membrane it opens up
  - **Membrane Bound Enzymes**
    * Control specific cell reactions
  - **Receptor Sites**
    * Bind with things in cell environment that triggers events
  - **Cell Adhesion Molecules**
    * Protrude from surface to form loops / hooks to grip to each other / connect tissues
  - **Other**
    * Important for self recognition

- **Self Recognition**
  - Unique combinations of sugar chains projected from surface membrane serve as identity markers
  - Surface markers define boundaries to tissue growth; cancer ignores this

2.4 Cell-to-Cell Adhesions

Plasma membranes participate in cell-to-cell adhesions. Cells are held together by 3 different means:

- Extracellular Matrix
- Cell Adhesion
- Specialized Cell Junctions

2.4.1 Biological Glue (Extracellular Matrix)

- Holds together cells as a meschwork of fibrous proteins embedded in gel like water substances composed of complex carbohydrates
- Gel provides a pathway for diffusion of nutrients, wastes, and other soluble traffic between blood and tissue
- There are three main protein fibres
  - **Collagen:** Cable like structures that provide tensile strength; scurvy weakens this
  - **Elastin:** Rubber like protein which can expand and contract; commonly found in lungs
  - **Fibronectin:** Promotes adhesion; holds cells in position
- ECM is secreted by local cells, most by fibroplasts
- Specialized composition; different, depending on cells
- Helps regulate behaviour and functions of cells (only circulating blood cells are designed to function without connecting to ECM)

2.4.2 Cell Junctions

- **Desmosomes**
  - Act like spot rivets, anchoring adjacent non-touching cells
  - Consists of two components
    - A pair of dense, button-like cytoplasmic thickenings known as plaque, located on the inner surface of each of the two adjacent cells
    - Strong glycoprotein filaments con- taining cadherins (a type of CAM) that extend across the space between the two cells and attach to the plaque on both side
  - Most common in heart , uterus, skin that requires stretching
- **Tight Junctions**
  - Cells make direct contact and bind together sealing passageway between the two cells
  - Found primarily at sites of epithelial tissue, like digestive tracts
  - Impermeability prevents material from passing between two cells; prevents undesirable leaks
  - "Kiss" sites where membrane is fused
- **Gap Junctions**
  - Gap in between cells by small tunnels formed by connexons
  - Connexons formed by 6 proteins arranged in hollow-like structure

- Used as communicating junctions
- Allow small water soluble particles to pass, but not large ones
- Abundant in cardiac and smooth muscle
- Helps transmit electrical signals and small signalling molecules

2.5 Overview Membrane Transport

Anything that passes between a cell and the surrounding extracellular fluid must be able to penetrate the plasma membrane Permeability refers to whether a substance can cross the membrane. The plasma membrane is **selectively permeable** as it permits some substances but restricts others. Two factors decide whether substances are permitted:

1. Relative Solubility of the Particle in Lipid
2. Size of the Particle

2.6 Unassisted Membrane Transport

Molecules (or ions) that can penetrate the plasma membrane on their own are passively driven across the membrane by two forces: diffusion down a concentration gradient and/or movement along an electrical gradient.

- **Passive Diffusion of Particles**
  - Molecules are always in constant motion; more likely to distribute
  - Spreading is called **diffusion**; difference in concentration is called **concentration gradient**
  - Steady state is dynamic equilibrium
- **Passive Diffusion of Ions**
  - Cations move towards negatively charged areas
  - Anions move toward positively charges areas
  - Electrical gradient promotes movement of ions
  - Electrochemical gradient is combination of electrical / concentration gradient
- **Osmosis**
  - Water readily permeates membrane
  - Water moves from low concentration of solute to high concentration through semi-permeable membrane
  - Water moves down its own gradient
  - Three types of Osmosis

    - **Penetrating Solute:**
        - Solute moves down concentration gradient, water balances volumes
        - Ceases when solute concentration balanced
    - **Non-Penetrating Solute:**
        - Water moves to higher concentration until solute concentration balanced
        - Ending volumes change
    - **Pure Water with Non-Penetrating**
        - Water moves until hydrostatic pressure balances osmotic pressure
        - Osmotic pressure is monitored to balance ECF and ICF
  - **Tonicity:** The effect a solution has on cell volume
    - **Isotonic:** Same concentration of non-penetrating solutes as normal body cells
    - **Hypotonic:** Below-normal concentration of nonpenetrating solutes
    - **Hypertonic:** Above-normal concentration of nonpenetrating solute

2.7 Assisted Membrane Transport

For large, poorly lipid-soluble particles, they require deliberate transportation of essential nutrients (e.g. glucose, amino acids, etc.)

- **Carrier Mediated Transport:**
  - Span the membrane, can flip flop to bring things in or back out
  - Three important characteristics to determine material and amount to be transferred:
    1. **Specificity**
        - Carrier proteins are geared to transport specific substances
    2. **Saturation**
        - Limited number of carrier bonding sites
        - There is a transport maximum (T_m)
        - Rate of transport is directly related to concentration until T_m is reached
    3. **Competition**
        - Different closely related compounds compete for same carrier
- **Active of Passive Transport:**
  - **Facilitated Diffusion**
    - Glucose into cell; not polar, thus not lipid soluble
    - High concentration causes net to go inwards, as passengers more likely to bind on the outside
  - **Active Transport**
    - Involves protein carrier and usually ATP as energy source

    - ATP is required to modify affinity for bonding
    - **Phosphorylation** causes binding site to have greater affinity for passengers on low concentration side
    - Carrier flips, dephosphorylates, and passenger is released
    - Frequently called "pumps"
    - Na^+ - K^+ pump plays important roles
        - Establishes Na^+ and K^+ concentration gradients across the plasma membrane of all cells
        - Helps regulate cell volume by controlling the concentra- tions of solutes inside the cell
        - Energy used to run the Na^+ - K^+ pump also indirectly serves as the energy source for the cotransport of glucose and amino acids across intestinal and kidney cells
  - **Secondary Active Transport**
    - Glucose transported from lumens of intestines and kidneys are different than glucose facilitated diffusion
    - Instead it relies on cotransport luminal carriers
    - Carriers have one site for Na^+ and one for K^+
    - When Na^+ is binded, affinity for glucose is increased
    - Types of transport
        - **Primary:** Energy is directly expended
        - **Secondary:** Doesn't use energy directly, second hand energy of an ion concentration gradient

- **Vesicular Transport**
  - For larger molecules, requires energy expenditure to form vesicle and movement within
  - **Endocytosis:** Transport into the cell
    - Once inside, endocytosis vesicles will either fuse with lysosomes to degrade and release contents into ICF or travel across the cell and release by exocytosis
    - There are three types:
        1. **Pinocytosis**
            - Small droplet of ECF is internalized, a pouch is formed by membrane deforming coat proteins
            - Dynamin is a specialized protein to cut the endocycotic vesicle from the membrane
        2. **Receptor Mediated Endocytosis**
            - Highly selective process that allows cells to import needed cells
            - Triggered by a protein / binding of a specific molecule

        - Some viruses, such as HIV and flu virus take advantage of this
      3. **Phagocytosis**
        - Much less common, large multimolecular particles are internalized
        - Lysosomes fuse with this internalized vesicle where they safely attack stuff
  - **Exocytosis:** Transport out of the cell
    * Opposite of exocytosis
    * Vesicle fuses with the membrane, opens up and releases its content into exterior
    * Materialized packages for transport by the endoplasmic reticulum and golgi complex are externalized by exocytosis
    * Provides mechanism for secreting large polar molecules that are unable to cross membrane, contents are specific and released only on receipt of appropriate signals
    * Allows cells to add channels, carriers, receptors to membrane

- **Secretory Vesicles**
  - Products of golgi apparatus collected at dilated edges of sacs, which pinches them off
  - Each surface protein marker serves as a specific docking marker
  - Secretory vesicles bud off golgi vesicles and fuse only with the membrane to prevent damage to the organelles
  - Contents never come into contact with cytosol

2.8 Selective Permeability of the Membrane

2.8.1 Separation of Charges

- **Membrane Potential:** Difference in electrical potential cause by difference in number of cations / anions between ECF and ICF
  - Can be harnessed to do work
  - When this changes, movement across current
  - $V = I/R$; R determined by intrinsic properties of membrane

2.8.2 Concentration / Permeability of Ions

- Excitable tissues produce rapid transient changes in membrane potential serving as electrical signals
- Resting membrane potential is when membrane is not transmitting signals
- Ions affecting membrane potentials (Na^+, K^+) and ions
- Na^+ more in the ECF, K^+ more in ICF

- Knowing percentages of each type of ion allows us to analyse the effects of K^+ alone, Na^+ alone, and both together
- Electrical gradient for cations are always toward the negative side

1. **Effect of Movement of K^+**
    - ICF > ECF, therefore concentration favours outside the cell
    - As K^+ leaves, ICF becomes negatively charged by cations that are unstable to leave, establishing membrane potential
    - Two forces opposing each other, creating **equilibrium potential**
    - More K^+ in ICF but it would stop moving out
    - $E_{K^+} = -90mV$; negative means inside is -90 to the outside
    - Equilibrium potential an be calculated with Nernst Equation

$$E = 6I \log \frac{C_o}{C_i} = 6\frac{RT}{zF} \log \frac{C_{ECF}}{C_{ICF}}$$

2. **Effect of Na^+ Alone**
    - Buildup of Na^+ inside concentration gradient, negative Cl^- outside
    - Electrical gradient balances concentration gradient
    - $E_{Na^+} = 60mV$
3. **Concurrent Na^+ and K^+**
    - K^+ greater effect because greater permeability; general rule for all ions
    - Na^+ neutralizes part of its effects
    - $-20mV$ is typical resting potential

- Chloride Movement at Resting
    - High concentration in ECF, anion, resting potential at -70 mV
    - Membrane potential drives Cl^- movement alone so no pumps exist, permeability allows it to diffuse at equilibrium
    - Electrochemical gradient outwards balances inward concentration gradient

2.8.3 Depolarization and Hyperpolarization

- **Polarization:** Neurons typically at -70 mV; either charges positively would be polarized
- **Depolarization:** Movement in positive direction, or upward on recording device
- **Repolarization:** Return to resting potential
- **Hyperpolarization:** Membrane is more polarized than resting potential, moves even further from $0V$ becoming more negative

2.8.4 Electrical Signals and Ion Movement

- Net inward = positive, then depolarized, upward deflection
- Net outward = negative, then hyperpolarized, downwards deflection
- **Leak Channels:** Open all the time, unregulated leakage of chosen ions
- **Gated Channels:** Can alternately be closed or opened; closing results from 3-D configuration
  - Voltage
  - Chemical
  - Mechanical
  - Thermal

There are two types of potential

- **Graded Potential:** Short distance
- **Action Potential:** Long distance

2.9 Action Potentials

Action potentials are brief, rapid, large changes in membrane potential where potential actually reverses (inside becomes more positive). It involves only a portion of the total excitable cell membrane. They also do not decrease in strength across the cell membrane

2.9.1 Reversal of Membrane Potential

- Graded potential changes can initiate an action potential before the graded change dies off
- Graded potential by electrical / chemical means depolarizes areas where action potentials can take place
- Process
  1. Triggering event causes the membrane to depolarize from resting -70 mV until it reaches threshold potential
  2. Threshold potential between -50 and -55 mV is where explosive depolarization takes place
  3. Membrane re-polarizes dropping back to resting
  4. Brief hyper-polarization at end of phase
- An action potential lasts 1 ms, between 0 to +30 mV is called overshoot

- **Voltage Gated Membrane Channel**
- Na^+
  - Small distortions in channel shape induced by changes can cause them to flip to another conformation
  - Consists of activation gate (opens/closes like a door) and inactivation gate (ball and chain sequence of amino acids guarding channel)
  - Membrane potential determines conformation
- K^+
  - Also has 3 conformations
  - Consists of 4 individual subunits
  - Rather than distinct activation and in activation gates
  - Instead electrical fields change conformation of the subunits, which determines if K^+ can flow through
- **Changes in Permeability and Ion Movement During an Action Potential**
  - At -70 mV all voltage gatedNa^+ and K^+ channels are closed but capable of opening
  - When action potential begins depolarizing towards threshols, voltage gated Na^+ opens
  - Na^+ becomes 600 than more permeable to Na^+ than K^+, attempt to drive Na^+ equilibrium of +60 mV
  - When gate opens, conformation allows inactivation fate to slowly bind
  - Remains inactivated until membrane potential is resting
  - As Na^+ inactivation begins, a spin of K^+ begins; K^+ opens delay after initial depolarization to threshold
    1. Rapid opening of Na^+ activation gates,Na^+ enters for positive peak
    2. Slow closing of inactivation gates to prevent further Na^+ from entering
    3. Slow opening of K^+ gates helping to restore peak to resting potential
  - AS voltage returns to normal Na^+ and K^+ channels close
  - Slow closing of K^+ gates cause more K^+ to leave than necessary causing hyper-polarization

2.9.2 Restoration of Concentration

- Na^+ - K^+ pump restore ions to original concentration
- Only 1 of 100000 K^+ ions leave cell during action potential; Na^+ moves more
- Still there is more K^+ in ICF than Na^+ in ECF
- Na^+ - K^+ crucial to maintain gradients long term

2.9.3 Propagation of Action Potential

- Mechanisms exist to conduct / spread action potential
- Neurons consist of
  - Cell body
  - Dendrites - up to 400000
  - Axon

2.9.4 Conduction via Nerve Fibre

- When action potential at axon hillcock, impulse automatically conducted throughout nerve without further stimulation
- There are two methods of conduction
- **Contiguous conduction**
  - Spread of action down membrane of the length of axon
  - Must spread to depolarized area which have reached threshold, accomplished by local current flow
  - Flow of opposite charges attract opening Na^+ gates at inactive areas
  - Propagation is non-decremental

2.9.5 One-Way Propagation

- Oscillations are prevented by **refractory period** (makes it forward only)
  - New events cannot occur in regions that have just undergone an action potential
  - Two part refractory period
    1. **Absolute Refractory Period:** Period which membrane is completely unresponsive to further change; must reset to resting potential
    2. **Relative Refractory Period:** Time where a triggering event considerably stronger is necessary to generate action potential
  - By the time refractory period occurs, action potential has already propagated thus preventing backwards flow

2.9.6 All-or-None Fashion

- If any part is depolarized to threshold, action potential is relayed in an undiminished fashion
- Stronger event does not generate a potential
- If event does not reach threshold, nothing happens

2.9.7 Strength of Stimulus and Frequency of Action Potentials

- To differentiate between stimuli, frequency of action potentials vary
- Larger potential generates greater number of action potentials
- Strength also affects number of neurons reading threshold, increasing total info sent
- Speed of action potential depends on if fibre is myelinated and its diameter

2.9.8 Myelination and Speed of Conduction

- Covered with myelins
  - 80 % lipid, 20 % protein
  - Act as an insulator preventing leakage because ions cannot permeate barrier
  - Not actively part of cell but wrap themselves around
- Myelin types
  - Brain, Spinal Cord
- Nodes of Ranvier run between myelin sheets, only here can action potential spread
  - Separated by space
  - Conducts around 50x faster
  - Conserves energy

2.9.9 Fibre Diameter and Velocity of Action Potential

- Increase diameter decreases resistance
- Types and Speeds
  - Skeletal - large; travel at 127 m/s
  - Digestive - small; travel at 0.7 m/s
- of myelinated increased efficiency and need for enormous fibres does not exist

2.10 Graded Potentials

Graded potentials are local changes in membrane potential that occur in varying grades or degrees of magnitude or strength.

- **Triggering Events**
  - Caused by specific triggering events that cause gated ion channels to open in a specialized region of the cell membrane

- Most commonly Na^+ gated channels open allowing Na^+ to travel down concentration gradient
- Results in depolarization towards positive Na^+ equilibrium
- Magnitude related to strength of event

- **Graded Potentials and Passive Currents**
  - When it occurs locally in an nerve, only excited membrane is called; active area more positive than rest area
  - Flow of ions is called current, positive on ECF goes toward Na^+ gate; moves away in ICf
  - Active areas spread in all directions to inactive areas
  - Amount of current that flows between two areas depend on difference in potential and on resistance; body lipids have high resistances; ICF and ECF have low resistances

- **Graded Potentials and Current Loss**
  - Current is lost through open channels on the membrane
  - The signal is decremental, decreases from initial site until it is not a graded potential
  - Limited signalling distance
  - Useful for
    * Post synaptic potentials
    * Receptor potentials
    * End plate potentials
    * Pacemaker potentials
    * Slow wave potentials
  - Excitable cells usually only produce one of these signals

2.11 Synapses and Neuronal Integration

- When action reaches axon terminals, they release a chemical messenger
- Neurons terminate at three different locations
  1. **Muscle:** Neuron **innervates the muscles**
  2. **Gland:** Tells it to secrete
  3. **Another Neuron:** Convey electrical message
- Junction between two neurons is called a synapse

2.11.1 Synapses

- Usually between an axon terminal of one neuron and dendrite of another
- Pre-synaptic neuron conducts action potential towards synapse ending with a synaptic knob
- Synaptic knob contains synaptic vesicles, which store chemical neuromessenger
- Action between pre and post neuron is called synaptic cleft
- Pre and post don't touch, excitation occurs by chemical means, moves in 1 direction

2.11.2 Neurotransmitters / Signal

- What happens at the synapse?
    1. Action potential is propagated to axon terminal, where it opens a Ca^{2+} voltage gated channels
    2. Ca^{2+} is highly concentrated in ECF, electrical gradient is also inward, ion flows into synaptic knob through channels
    3. Ca^{2+} induces release of a neurotransmitter of some synaptic vesicles into synaptic cleft
    4. Neurotransmitter diffuses across cleft and binds with protein receptors in sub-synaptic membrane
    5. Binding triggers opening of specific ion channels on post synaptic neuron, thus changing its permeability
- Since post synaptic depends on a chemical messenger from pre-synaptic neuron, it is one way

2.12 Synapse Behaviour

- Neurons aren't constrained to one type of neurotransmitter
    - Neuroactive peptides and other neuroactive molecules can be contained in the same neuron
    - Mature neurons commonly contain one small molecule transmitter and one or more peptides
- Neurotransmitter binding changes ion permeability
- Two types of synapses
    - **Excitatory Synapses**
        * Response to neurotransmitter binding to receptor is the opening of non-specific cotton channels
        * Difference to earlier passages is the simultaneous increase of permeability for both Na^+ and K^+

    * At resting:
        · K^+: Concentration gradient favours movement outwards from post synaptic neuron
        · Na^+: Concentration and electrochemical gradient favour movement into post-synaptic neuron
    * At excitatory state:
        · K^+: Few move in
        · Na^+: Lots move in
    * Effect is that potential is closer to threshold and is more easily excitable
    * Called **excitatory post-synaptic potential**
  - **Inhibitory Synapses**
    * Binding of different released neurotransmitter increases permeability of either K^+ or Cl^- resulting in small hyper-polarization in post synaptic neuron
    * Makes neuron less likely to reach threshold
    * Said to be **inhibitory post-synaptic potential**

- EPSP and IPSP arise from chemicals unlike action potentials which result from voltage gated channels

2.12.1 Receptor Combinations

- Each synapse always releases the same neurotransmitter and its sub synaptic receptors always lead some change in permeability
- Different synapses can have different receptor behaviours to the same neurotransmitter
- Synapses can release more than one neurotransmitter at the same axon terminal

2.12.2 Neurotransmitter Removal

- EPSP / IPSP lasts as long as neurotransmitter is binded
- Once purpose is served, it can be removed by:
    1. Diffusing away from the synaptic cleft
    2. Be inactivated by specific enzymes within the sub-synaptic membrane
    3. Be taken back into axon terminals by transport mechanism in the pre-synaptic membrane

2.12.3 Grand Post Synaptic Potential

- EPSPs and IPSPs are graded potentials
- Signal is received from many pre-synaptic neurons

- Total potential is known as **grand post-synaptic potential** $GPSP = \sum IPSP + \sum EPSP$
- Threshold can be reached with two methods
    1. Temporal Summation
        - Summing of several EPSPs occurring together because of successive firing of a single pre-synaptic neuron
        - Amount of neurotransmitter released is directly related to frequency of pre-synaptic action potentials
    2. **Spatial Summation**
        - $EPSP_1 + EPSP_2$ reach threshold but neither alone
        - When different pre-synaptic neurons concurrently activate several excitatory inputs
- **Cancellation:** When EPSPs and IPSPs hyperpolarize and depolarize and cancel out
- **Importance of Post-Synaptic Neuronal Integration**
    - EPSP depends on all pre-synaptic inputs to decide whether or not to pass on information
    - Dendrites are primarily processors of incoming information
    - System prevents small EPSP from releasing action potentials

2.12.4 Action Potentials at Axon Hillcock

- Axon Hillcock has the lowest threshold because it has the most Na^+ channels there
- Much more responsive than dendrites or remainder of cell, which is why most action potential originates there

2.13 Neuropeptides as Neuromodulators

- Some neurons also release neuropeptides
- **Classic Neurotransmitters**
    - Small rapid acting molecules that trigger opening of specific ion channels causing EPSPs or IPSPs within milliseconds
- **Neuropeptides**
    - Larger molecules made up anywhere from 2-40 amino acids
    - Synthesized in cell body endoplasmic reticulum and golgi complex and moved to axon terminals
    - Packaged in dense-core vesicles, not synaptic vesicles
    - Undergo exocytosis by Ca^{2+} same as neurotransmitters

  - Some may function as neurotransmitters, others as neuromodulators

- **Neuromodulators**
  - Do not form EPSPs or IPSPs
  - Make long term changes subtly modulate action of synapse
  - Many have roles as hormones

2.13.1 Pre-synaptic Inhibition or Facilitation

- Another means other than neuromodulators that depresses / enhances synaptic effectiveness
- If synaptic axon terminal is innervated by another axon terminal:
  - If neurotransmitter is increased $\rightarrow$ pre-synaptic facilitation
  - If neurotransmitter is reduced $\rightarrow$ pre-synaptic inhibition
- Modulatory neuron controls this by reducing Ca^{2+} entry to the terminal

2.13.2 Drugs, Diseases, and Transmission

- **Drugs**
  - Alter biological function of the organism
  - Those that affect nervous system alter synaptic mechanisms
    * Altering synthesis / axonal transport / storage / release of a transmitter
    * Modifying neurotransmitter interaction with post-synaptic receptor
    * Influencing neurotransmitter reuptake / destruction
    * Replacing deficient neurotransmitter with substitute
- **Parkinson's Disease**
  - Deficiency of dopamine in basal nuclei
- **Synaptic Transmission**
  - **Stryclinc Toxin:** Clogs receptor sites
  - **Tetanus Toxin:** Prevents neurotransmitter release

2.13.3 Neurons

- **Convergence:** A post synaptic neuron is influenced by many cells
- **Divergence:** A pre synaptic input influences many other neurons
- Estimated 10 million neurons in the brain alone

3 Central Nervous System

3.1 Organization of the Nervous System

The nervous system is organized into the central nervous system (CNS), peripheral nervous system (PNS)

- **Central Nervous System (CNS)**
  - Brain and Spinal Cord
- **Peripheral Nervous System (PNS)**
  - Nerve fibres that carry information
  - **Afferent Division:** Carries info to CNS
  - **Efferent Division:** Carries info to effector organs
    - **Somatic Nervous System:** Nerve fibres of the motor neurons that supply the skeletal muscle
    - **Autonomic Nervous System (ANS):** Nerve fibres that innervate smooth muscle, cardiac muscle, and glands
      - Sympathetic Nervous System
      - Parasympathetic Nervous System

There are three classes of neurons that make up the nervous system:

- **Afferent Neurons**
  - At peripheral ending, a sensory receptor generates an action potential
  - No dendrites or pre-synaptic inputs
  - Propagate signals to spinal cord; typically found in PNS
- **Efferent Neurons**
  - Primarily in PNS, cell body in CNS
  - Convey signals to efferent organs
- **Interneurons**
  - Entirely in CNS, 99 % of neurons
  - Estimated 100 billion interneurons

3.2 Central Nervous System

The central nervous system has many important roles and functions:

- Subconsciously regulate your internal environment by neural movements
- Experience emotions
- Voluntary control movement
- Perceive / be conscious of yourself and surroundings
- Thought and memory

The system is grouped as follows

- Brain stem
- Cerebellum
- Forebrain
  - Diencephalon
    - Hypothalamus
    - Thalamus
  - Cerebrum
    - Basal Ganglia
    - Cerebral Cortex

3.3 Protection of CNS

- **Glial Cells**
  - 90 % of cells in CNS, only half the volume of the brain
  - Do not initiate or conduct nerve impulses; communicate with neurons and between themselves via chemicals
  - Glue as they are CNS connective tissue and support neurons physically and metabolically
  - Four major types:
    - **Astrocytes**
      - Main connective tissue of cells; hold neurons together
      - Scaffolding around neurons during fetal brain development
      - Responsible for establishing brain-blood barrier
      - Brain injuries and neural scar formation
      - Neurotransmitter activity

        - Maintain proper ECF ion concentration in brain
        - Enhance synapse formation and strengthen synapse impulse transmission
    - **Oligodendrocytes**
        - Form insulating myelin sheaths around axons
    - **Microglia**
        - Immune cells in the CNS; wispy with loing branches that extend outwards
        - Can cause neurodegenerative diseases if too overzealous
    - **Epindymal**
        - Like internal CNS cavities (brain and spinal cord)
        - Contribute to cerebrospinal fluid formation

- **Protection of CNS**
    - Skull and vertabral column
    - Meninges
        - Protective / nourishing membranes between bone and tissue
        - 3 membranes
            - Dura Mater
            - Arachnoid Mater
            - Pia Mater
    - Cerebrospinal fluid
        - Acts as a cushion for the brain
    - Blood-brain barrier
        - Highly sensitive membrane of endothelial cells; material exchange only through capillary walls

3.4 Spinal Cord

- Long slender cylinder of nerve tissue protected by the vertebral column
    - **Vertebral Canal**
        - **Paired Spinal Nerves:** Emerge from spinal cord between the protrusions of adjacent successive vertebrae
        - **Cauda Equina:** The paired nerve roots that descend far below end of the spinal cord
    - **Spinal Cord White Matter**
        - Surrounds butterfly shaped gray matter
    - **Spinal Cord Gray Matter**

        * **Dorsal Horn:** Carrying cell bodies of inter neurons and terminals of afferent neurons
        * **Lateral Horn:** Cell bodies of automatic efferent nerve fibres
        * **Ventral Horn:** Cell bodies of somatic efferent neurons
    - **Spinal Nerves**
        * Connect with each side of a spinal cord via dorsal and ventral root
    - **Peripheral Nervous System**
        * Made of 31 spinal nerves and 12 cranial nerves

- **Reflexes**
    - Basic reflexes
    - Acquired reflexes
    - Stretch reflexes
    - Withdrawal reflexes

3.5 Brain Stem

All fibres must pass through stem if headed toward higher brain centres. Its functions include

1. Origin of most of cranial nerves
2. Control heart/blood circulation, respiration, and digestion
3. Regulates muscle reflexes for balance and posture
4. Reticular formation
5. Governs sleep

3.6 Thalamus and Hypothalamus

Two divisions of the diencephalon

- **Thalamus**
    - Relay station and synaptic integrating centre for preliminary sensory processing before these inputs go to the cortex
- **Hypothalamus**
    - Collection of specific nuclei and fibres underneath the thalamus
    - Integrating centre for homeostatis functions and is an important link between autonomic nervous system and the endocrine system

3.7 Cerebral Cortex

Largest portion of brain, which is divided into two halves - left and right brain

- **Gray and White Matter in Cortex**
  - Thin outer layer of gray matter
  - Thick center core of white matter
  - Gray matter integrates input info and starts output info and the white matter transmits these signals throughout the cortex because each area of the cortex may process different info that needs to be integrated together
- **Layers and Columns**
  - Organized into 6 layers based on cell types within
  - Layers organized into columns; neurons in each column function as a team
- **Lobes**
  - **Occipital:** Initial visual processing
  - **Temporal:** Initial sound processing
  - **Parietal:** Receiving and processing sensory input
  - **Frontal:** 3 main functions
    - Voluntary motion
    - Speaking
    - Elaboration of thought
- **Neuroplasticity and Regeneration of Brain Tissue**
  - Brain has a degree of plasticity
  - Higher plasticity in developmental years
  - When area of brain is damaged, neuron connections can change
  - Generation of new brain cells has also been proposed

4 Peripheral Nervous System

4.1 Afferent Division

- Afferent neurons (sensory or receptor neurons) carry nerve impulses from receptors or sense organs toward the CNS
- Structure such that they have a long dendrite, short axon, and smooth rounded cell body

4.1.1 Fight or Flight Response

Physiological adjustments to the stress associated with the afferent division of the PNS are as follows:

1. Afferent division provides information (sound, sight, and smell) to the CNS about the external environment that influences conscious activity (e.g. decision making)
2. Arousal occurs, which adjusts efferent output (e.g. heart rate)
3. Turn to the direction of the sounds
4. Eyes accommodate to provide clear, crisp image
5. Pupils dilate to provide more light
6. Decision to fight or flee most likely based on ability to judge distance; this requires cognitive processing and good eye sight

4.1.2 Somatosensation

- Somatosensory system consists of receptors and processing centres that integrate and create sensory modalities
- Modality determined by which sensory neuron is activated and where stimulus terminates in the brain
- Primary somatosensory area located in the parietal lobes of the cerebral cortex
- System reacts to diverse stimuli through four types of receptors found throughout the body
  - Thermoreceptors
  - Mechanoreceptors
  - Photoreceptors
  - Chemoreceptors
- Sensory information is transmitted in the form of an action potential via afferents through spinal tracts to the brain

4.1.3 Sensation: Internal and External

- Afferent information about the internal environment never reaches levels of conscious awareness, but the input is essential for determining efferent output to maintain homeostasis
- The **visceral afferent** is the incoming pathway for information derived from the internal viscera
- Afferent input from receptors located on the body surface or in the muscles / joints does reach conscious awareness; known as sensory afferent
- Can either be characterized as **somatic sensation** arising from the body surface or **special senses** such as vision, hearing, taste, smell, and equilibrium

4.1.4 Perception

- **Perception** is the conscious interpretation of the external world as created by the brain from a pattern of nerve impulses delivered to it from sensory receptors
- Humans have receptors that only detect a limited number of existing energy forms
- Information channels to our brains are not high-fidelity recorders
- Cerebral cortex further manipulates data to extract significant features

4.2 Receptor Physiology

- A **stimulus** is a change detectable by the body that meets a minimum threshold; they exist in a variety of energy forms, such as heat, light, sound, pressure, and chemical changes
- **Transduction** converts mechanical or chemical simulations into an electrical signal through changes in ion permeability at controlled ion channels
- Four basic properties help CNS differentiate incoming stimuli from PNS: *modality*, *intensity*, *location*, *duration*

4.2.1 Adequate Stimuli and Threshold

- Each receptor type is specialized to respond best to one type of energy, known as adequate stimulus
- Perceived sensation depends on the *modality* of receptor stimulated rather than type
- Minimum stimulus required is called the *threshold*
- Depending on the type of energy, receptors are categorized as follows
  - **Photoreceptors:** Responsive to visible light wavelengths

- **Mechanoreceptors:** Sensitive to mechanical energy
- **Thermoreceptors:** Sensitive to heat
- **Chemoreceptors:** Sensitive to specific chemicals

- Information detected by receptors is used for a variety of purposes
  - Control of efferent output, for both regulating motor behaviour based on external and internal stimuli and also to direct/maintain homeostasis.
  - Critical for cortical arousal and consciousness
  - Perception of the world around us.

4.2.2 Stimuli and Receptor Permeability

- Receptor can either be specialized ending of afferent neuron or separate receptor cell closely associated with peripheral ending of the neuron
- Receptor stimulation changes the membrane permeability and generally Na^+ is responsible for the depolarization of the membrane with a inward flux of Na^+
- Depolarization process is known as generator potential (for (1)) or receptor potential (for (2))
- Receptor/generator potential is a graded potential with varying duration and amplitude, depending on the strength of stimulus

4.2.3 Receptor Potentials and Action Potentials

- If a receptor/generator has enough magnitude, it can initiate an action potential in the afferent neuron membrane by opening the Na^+ channels in those regions
- The method that the Na+ channels open change depending on the receptor:
  - **Separate Receptor Cell:** Chemical messenger released diffuses across space between receptor cell from afferent neuron ending and binds with specific protein receptor sites, opening the Na+ channels
  - **Specialized Afferent Ending:** Local current flow opens voltage gated Na+ channels.
- If magnitude of the ionic flux reaches threshold, action potential produced and propagates towards CNS.
- Location of action potential for:
  - **Efferent Neuron/Interneuron:** Initiated at axon hillock located at the start of the axon next to the cell
  - **Afferent Neuron:** Initiated at peripheral end of an afferent nerve
- Intensity of the stimulus is reflected by the magnitude of the receptor potential.

- Larger receptor potential → higher frequency of action potentials generated
- Stronger stimulus → more area affected, so more receptors respond

4.2.4 Adaptation to Sustained Stimulation

Adaptation is when a receptor diminishes the extent of their depolarization despite sustained stimulus strength. This leads to a decrease in frequency of action potentials generated.

There are 2 receptor types, based on their speed of adaptation

- **Tonic Receptors:** These do not adapt or adapt very slowly. Important in situations where stimulus information needs to be maintained. (muscle stretch receptor)
- **Phasic Receptors:** Adapts rapidly to a maintained stimulus, but when that stimulus is removed the receptor responds with a slight depolarization called the off response. Important in situations where its not important to relay status quo information (touch receptors are like this, we're not continuously conscious of wearing our watch/clothes etc)

4.2.5 Labelling Somatosensory Pathways

- At the spinal cord, afferent information has two possible destinations:
  - Become part of reflex arc
  - Relayed up to the brain for further processing and possible conscious awareness
- Pathways conveying conscious somatic sensation, somatosensory pathways, are made up of chains of neurons (also called labelled lines) and connected in a specific sequence for more complex processing of sensory information
- **Labelled Lines and Location of Stimulus**
  - **First-order sensory neuron:** afferent neuron that first detects the stimulus and synapses on a second order sensory neuron
  - **Second-order Sensory Neuron:** located in spinal cord or medulla and synapses on a third order sensory neuron and so on
  - On each step, the input is further processed and specific sensory modality is projected to specific location in the cortex via specific pathways.
- **Phantom Pain**
  - Activation of a sensory pathway at any point gives rise to the same sensation produced by stimulation of the receptors in the body part itself.
  - This can cause Phantom Pain where people can feel pain in body parts that have been removed.
  - Severed endings of the afferent pathways can trigger action potentials which gets perceived at the somatosensory cortex as pain in the missing body part.

4.2.6 Aculty, Receptive Field Size, and Lateral Inhibition

- Receptive Field: each somatosensory neuron responds to stimuli in specific regions on the skin, known as the receptive field
- A smaller receptive field has a larger acuity (discriminative ability)
- Another factor influencing acuity is lateral inhibition which is when nearby areas of the receptive field get stimulated as well, inhibiting the acuity.

4.2.7 Mechanoreceptors

- Sensitive to pressure, stretch, vibration, acceleration and sound.
- There are five types of mechanoreceptors important for somatic sensation of touch
  - **Pacinian Corpuscles:** Located in skin and respond to deep pressure and touch. Very sensitive to vibration.
  - **Meissner's Corpuscles:** Phasic, tactile, myelinated responding to light touch. Rapidly adapt and concentrated on finger tips, nipples, and lips
  - **Merkel's discs:** Most sensitive to low frequency vibrations and are slow adapting. Are found in superficial layers of skin and beneath the ridges making up fingerprints.
  - **Ruffini Corpuscles:** Slow-adapting, myelinated nerve endings found in deep skin layers. Response to stretch and torque
  - **Free Nerve Endings:** Most abundant and can be found in many tissues. Specialize in touch, pressure, temperature and pain detection.

4.3 Autonomic Nervous System

- Influences smooth muscles, glands, and the heart through its two subdivisions: *sympathetic* and *parasympathetic* systems
- Systems maintain a dynamic equilibrium aimed at maintaining homoeostasis
- Includes the enteric nervous system, which influences the pancreas, liver, and gallbladder, controlling gastrointestinal motility, secretion, and blood flow
- Hypothalamus, brain stem, and spinal cors are hub of the neural output

4.3.1 Autonomic Nerve Pathways

- Each autonomic nerve pathway extending from the CNS to an innervated organ is a two-neuron chain.
- Axon of the first neuron, **preganglionic fibre**, synapses with cell body of the second neuron

- Axon of second neuron, **postganglionic fibre** innervates the effector organ
- Parasympathetic preganglionic fibres arise from the cranial (brain) and sacral (lower spinal cord) areas of the CNS. These fibres are longer than sympathetic preganglionic fibres because they do not end until they reach terminal ganglia that lie in or near the effector organs.

4.3.2 Parasympathetic and Sympathetic Postganglionic Fibres

- Both pre-ganglionic fibres release the same neurotransmitter, **acetylcholine (ACh)**, but the post-ganglionic endings of the two systems release different ones.
- Parasympathetic postganglionic fibres release acetylcholine; they're called **cholinergic fibres**
- Sympathetic postganglionic fibres release noradrenaline; they're called **adrenergic fibres**

4.3.3 Innervations of Visceral Organs

- Afferent information coming from the viscera (internal organs) usually does not reach the conscious level.
- Most visceral organs are innervated by both sympathetic and parasympathetic nerve fibres
- Usually both systems are partially active such that some level of action potential activity exists in both the sympathetic and the parasympathetic fibres supplying a particular organ - called **tonic** activity.
- **Sympathetic dominance** to a particular organ exists when the sympathetic fibres' rate of firing to that organ increases above tonic level, coupled with a simultaneous decrease below tonic level in the parasympathetic fibres' frequency of action potentials to the same organ.
- Sympathetic Dominance - *fight or flight*
- Parasympathetic Dominance - *rest and digest*
- The two divisions are reciprocally controlled - increased activity in one decreases activity in another, except in a few cases
  - Innervated blood vessels receive only sympathetic nerve fibres
  - Sweat glands are innervated by only sympathetic nerves
  - Salivary glands are innervated by both but are not antagonistic

4.3.4 Adrenal Medulla

- An adrenal gland lies above both kidneys on each side
- They are endocrine glands with an outer *adrenal cortex* and inner *adrenal medulla*

- **Adrenal medulla** is a modified sympathetic ganglion that does not give rise to postganglionic fibres; it secretes hormones into the blood
- 20 percent of the adrenal medullary hormone output is norepinephrine, and the remaining 80 percent is the closely related substance epinephrine (adrenaline)

4.3.5 Different Receptor Types

- **Cholinergic Receptors**
  - Nicotonic: Activated by nicotine; found on the postganglionic cell bodies in all autonomic ganglia.
  - Muscarinic: Activated by the mushroom poison muscarine
- **Adrenergic Receptors**
- **Autonomic Agonists and Antagonists**

4.3.6 Control of Autonomic Activities

- The spinal cord integrates some autonomic reflexes, such as urination, defecation, and erection, but all these spinal reflexes are subject to control by higher levels of consciousness.
- The medulla within the brain stem is most directly responsible for autonomic output, and includes centres for control- ling cardiovascular, respiratory, and digestive activity via the autonomic system.
- The hypothalamus plays an important role in integrating the autonomic, somatic, and endocrine responses that automatically accompany various emotional and behavioural states. For example, the increased heart rate, blood pressure, and respiratory activity associated with anger or fear are brought about by the hypothalamus acting through the medulla.
- The pre frontal association cortex can also influence autonomic output through its involvement with emotional expression characteristic of the individual's personality. An example is blushing when embarrassed, which is caused by dilation of blood vessels supplying the skin of the cheeks. Such responses are mediated through hypothalamic medullary pathways.

4.4 Somatic Nervous System

4.4.1 Motor Neurons and Skeletal Muscle

- Skeletal muscle is innervated by **motor neurons**, the axons which constitute the somatic nervous system
- Axon of a motor neuron is continuous from its origin in the CNS to its ending on skeletal muscle

- Motor neurons can only stimulate skeletal muscle, and not inhibit it, unlike the autonomic fibres and their effector organs

4.4.2 Motor Neurons: The Final Common Pathway

- Considered the **final common pathway**, because the only way any other parts of the nervous system can influence skeletal muscle activity is by acting on these motor neurons.
- Level of activity and subsequent output to skeletal muscle fibred depends on the relative balance of EPSPs and IPSPs brought about by its presynaptic inputs originating from these diverse sites in the brain
- The somatic system is under voluntary control, but much of the skeletal muscle activity involving posture, balance, and stereotypical movements is subconsciously controlled.

4.5 Neuromuscular Junction

4.5.1 Linkage of Motor Neurons and Skeletal Muscle Fibres

- An action potential in a motor neuron is rapidly propagated from the cell body within the CNS to the skeletal muscle along the large myelinated axon
- Axon divides into many terminal branches as it approached a muscle
- Axon terminals form a special junction - **neuromuscular junction**

4.5.2 Acetylcholine

- Nerve and muscle cells do not actually come into direct contact at neuromuscular junction
- Synaptic cleft is too large to permit electrical transmission of an impulse; action potential cannot jump that far
- A chemical messenger, **acetylcholine**, carries the signal between the axon terminal and muscle fibre

1. An action potential in a motor neuron is propagated to the axon terminal (terminal button).
2. Local action potential triggers the opening of voltage-gated Ca^{2+} channels and the subsequent entry of Ca^{2+} into the terminal button.
3. Ca^{2+} triggers the release of ACh by exocytosis from a portion of the vesicles.
4. ACh diffuses across the space separating the nerve and muscle cells and binds with receptor channels specific for it on the motor end plate of the muscle cell membrane.
5. this binding brings about the opening of these nonspecific cation channels, leading to a relatively large movement of Na^{+} into the muscle cell compared to a smaller movement of K^{+} outward.

6. The result is an end-plate potential. Local current flow occurs between the depolarized end plate and the adjacent membrane.
7. This local current flow opens voltage-gated Na^+ channels in the adjacent membrane.
8. The resultant Na^+ entry reduces the potential to threshold, initiating an action potential, which is propagated throughout the muscle fibre.
9. ACh is subsequently destroyed by acetylcholinesterase, an enzyme located on the motor end-plate membrane, terminating the muscle cell's response.

4.5.3 Acetylcholinesterase and Acetylcholine Activity

- The muscle cell's electrical response is turned off by an enzyme in the motor end-plate membrane; this enzyme is **acetylcholinesterase** (AChE), which inactivates ACh
- ACh never contributes to end-plate potential
- ACh removal ends the EPP, so the remainder of the muscle cell membrane returns to resting potential
- AChE permits the choice of allowing relaxation to take place (no more ACh released) or keeping the contraction going (more ACh released), depending on the body's momentary needs.

4.5.4 Vulnerability of the Neuromuscular Junction

- Black Widow Spider Venom Causes Explosive Release of ACh
- Botulinum Toxin Blocks Release of ACh
- Curare Blocks Action of ACh at Receptor Sites
- Organophosphates Prevent Inactivation of ACh
- Myasthenia Gravis Inactivates ACh Receptor Sites

5 Muscle Physiology

5.1 Structure of Skeletal Muscle

- Controlled contraction of muscles allow the following:
  - Purposeful movement of the whole body or parts of the body (such as walking or waving your hand)
  - Manipulation of external objects (such as driving a car or moving a piece of furniture)
  - Propulsion of contents through various hollow internal organs (such as circulation of blood or movement of a meal through the digestive tract)

  - Emptying the contents of certain organs to the external environment (such as urination or giving birth).

- Muscle tissue is the largest group in the body, accounting for half the weight
- Skeletal muscle makes up 40% in men and 32% in women

5.2 Molecular Structure of Skeletal Muscle Contraction

5.3 Skeletal Muscle Mechanics

5.4 Smooth and Cardiac Muscle

6 Cardiac Physiology

6.1 Anatomy of the Heart

6.2 Electrical Activity of the Heart

6.3 Mechanical Events of the Cardiac Cycle

6.4 Cardiac Output and its Control