Introduction to Physiology: The Human Body

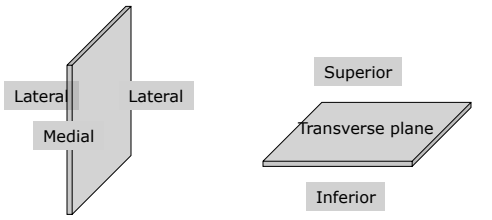
Adapted From:

Textbook Of Medical Physiology, 11th Ed.
Arthur C. Guyton, John E. Hall
Chapter 1

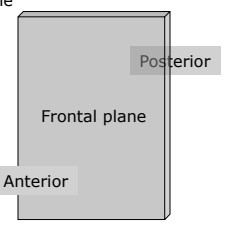
John P. Fisher

Organization of the Body

Anatomical Directions

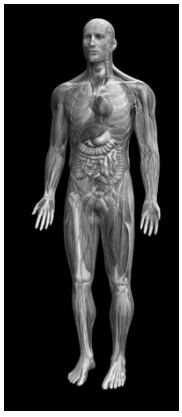


Sagittal plane



Superior

Anterior



Posterior

Inferior

Organization of the Body

Anatomical Directions

- Left — To the left of the body
- Right — To the right of the body
- Lateral — Toward the side, away from the midsagittal plane
- Medial — Toward the midsagittal plane, away from the side
- Anterior — Toward the front of the body
- Posterior — Toward the back (rear) of the body
- Superior — Toward the top of the body
- Inferior — Toward the bottom of the body

Organization of the Body

Anatomical Directions

- Dorsal — Along or toward the vertebral surface of the body
- Ventral — Along or toward the belly surface of the body
- Caudal — Toward the tail
- Cephalad — Toward the head
- Proximal — Toward the trunk
- Distal — Away from the trunk
- Visceral — Toward an internal organ
- Parietal — Toward the wall

Organization of the Body

Structural Hierarchy

- Atoms: oxygen, carbon, hydrogen
- Molecules: water, sugar, peptides
- Macromolecules: proteins, polysaccharides
- Organelles: compartments within cell that cannot survive in isolation
- Cells: structural and functional unit of organisms
- Tissues: organization of cells with a common function
- Organs: structures composed of at least 2 tissues
- Organ Systems: organs operating to accomplish a common function

Physiology

Definition

- Study of the characteristics and mechanisms of the human body
- Cells are the basic unit of life within the human body
- Approximately 100 trillion cells make up the typical human, each specially adapted to perform one or a few particular functions
  - 25 trillion red blood cells act to transport oxygen from the lungs to all tissues in the body
- All cells have some basic commonalities
  - Oxygen reacts with carbohydrates, fat, and protein to release energy
  - Nutrient consumption and energy production mechanisms are similar
  - Nearly all cells have the ability to reproduce additional, similar cells

Physiology

Extracellular and Intracellular Fluids

- Approximately 60% of the human body is fluid
  - An aqueous solution containing ions, small molecules, proteins, sugars, and macromolecules
- Two thirds of the fluid is retained within cells – *Intracellular*
  - Intracellular fluid contains large amounts of potassium, magnesium, and phosphate ions
- One third of the fluid is outside cells – *Extracellular*
  - As all cells exist within a similarly constituted extracellular fluid, this space is sometimes referred to as the internal environment or the milieu interieur
  - Extracellular fluid contains large amounts of sodium, chloride, and bicarbonate ions as well as nutrients including oxygen, glucose, fatty acids, and amino acids

Homeostatic Mechanisms

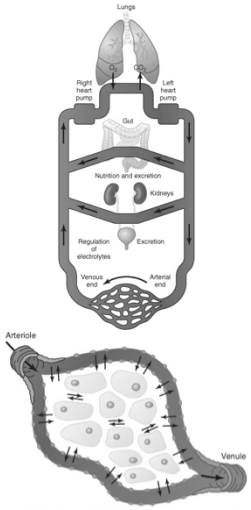
Homeostasis

- Homeostasis describes the active maintenance of an equilibrium state despite external disturbances
- Homeostasis can be considered in regards to a cell, tissue, organ, biological system, or environmental system
- In physiology, homeostasis implies the maintenance of nearly constant conditions in the internal environment
  - Actively maintained by organs and tissues
    - Lungs provide oxygen consumed by cells, and remove carbon dioxide produced by cells
    - Kidneys regulate ion concentrations by augmenting waste composition

Homeostatic Mechanisms

Homeostasis

- Extracellular fluid is constantly in motion, transported in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls
- Blood movement through the circulatory system
  - 1 circuit per minute at rest
  - 6 circuits per minute during activity
- Fluid movement between blood capillaries and cells
  - *Few cells are located more than 50 microns away from a capillary*



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Organ Systems

Nutrient Supply Systems

- Respiratory System
  - Blood is concentrated with oxygen which is transported through the alveoli in the lungs
  - Oxygen diffuses through the alveolar membrane (0.4 - 2.0 μm), a porous membrane that facilitates diffusion
- Gastrointestinal System
  - Nutrients, including carbohydrates, fatty acids, and amino acids, are absorbed from ingested food, through the walls of the gastrointestinal tract, and into the extracellular fluid of circulating blood
- Hepatic System
  - The liver acts to chemically modify ingested, but difficult to absorb, nutrients into usable forms - other bodily tissues help modify these nutrients or store them until their future use
- Musculoskeletal System
  - Provides structure and movement that allows the gathering of nutrients as well as protection from adverse surroundings

Organ Systems

Waste Removal Systems

- Respiratory System
  - Carbon dioxide is released from the blood stream and into the lung alveoli, where it is then ultimately expired into the atmosphere
- Kidney System
  - Allows for the removal of waste substances
    - Urea and uric acid
    - Excess ions and water
  - Filtration occurs in the kidney by first absorbing large quantities of plasma, and then returning to the blood those substances that are of nutritional value (glucose, amino acids, water, and ions), while excess nutrients or waste products are left behind and ultimately excreted in the urine

Organ Systems

Regulatory Systems

- Nervous System
  - Contains three major constituents
    - Sensory input system: detects the state of the body and surrounding environment
      - Touch, sight, hearing
    - Central nervous system: stores information, generates thoughts, and determines reactions in response to the sensory input system
      - Composed of the brain and spinal cord
    - Motor output portion: allows for the generation of actions based upon the signals provided by the central nervous system
      - Motor neurons which drive muscle actions
  - Autonomic System
    - Operates at a subconscious level to control the function of internal organs, including heart, gastrointestinal tract, and glandular secretions
- Hormonal System
  - Eight major endocrine glands secrete hormones that are transported throughout the body to help regulate cellular function

Organ Systems

Reproductive System

- Provides a mechanism to maintain the overall population of the species, thus allowing for population homeostasis

Control Systems

Maintaining Homeostasis

- The maintenance of homeostasis requires the activity of a number of different control systems
  - React to the surrounding environment
  - Initiate actions to maintain cell, tissue, organ, and organ system function

Control Systems

Regulation of Fluid Oxygen and Carbon Dioxide Concentration

- As O_2 is a major nutrient and CO_2 a major waste product, mechanisms must be in place so that O_2 concentration does not fall too low, nor CO_2 concentration rise too high
- Hemoglobin, the functional protein in red blood cells, combines with O_2 in the lungs and releases O_2 in tissues
  - Since hemoglobin has a high affinity for O_2, it will not release O_2 in highly oxygenated tissues, but only in those tissue which establishes a large gradient in O_2 concentration
- High CO_2 concentrations are regulated by the respiratory system
  - High CO_2 causes an excitation of the respiratory system, causes increases in tidal volume and an increase in respiratory rate
  - Thus CO_2 is expired more quickly, reducing CO_2 concentration in the lungs

Control Systems

Regulation of Arterial Pressure

- Baroreceptor system as an example of arterial pressure control
- Nerve receptors, called baroreceptors, exist in the bifurcation region of the carotid arteries in the neck and in the arch of the aorta
  - *Baroreceptors detect changes in stretch of the arterial wall*
- When arterial pressure increases, the arterial wall stretches, baroreceptors sense the stretch and send nerve impulses to the medulla of the brain
- Transmitted impulses inhibit the vasomotor center, which then slows the excitation of the sympathetic nervous system stimulation of the heart and arterial system
  - Decrease in heart rate and dilation of the arterial system
- Changes in both the heart rate and arterial resistance allow a reduction in arterial pressure
- The converse stimulation, a decrease in arterial pressure, can also stimulate the same pathway to promote the maintenance of arterial pressure

Control Systems

Regulation of Extracellular Environment

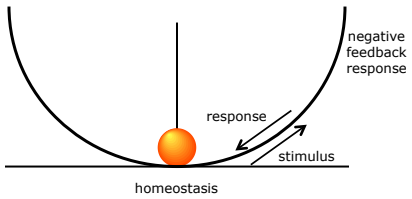
	Normal Value	Normal Range	Short Term Non-Lethal Limit	Unit
Oxygen	40	35 - 45	10 - 1000	mmHg
Carbon Dioxide	40	35 - 45	5 - 80	mmHg
Sodium Ion	142	138 - 146	115 - 175	mmol/L
Potassium Ion	4.2	3.8 - 5.0	1.5 - 9.0	mmol/L
Calcium Ion	1.2	1.0 - 1.4	0.5 - 2.0	mmol/L
Chloride Ion	108	103 - 112	70 - 130	mmol/L
Bicarbonate Ion	28	24 - 32	8 - 45	mmol/L
Glucose	85	75 - 95	20 - 1500	mmol/L
Temperature	37.0	36.7 - 37.1	18.3 - 43.3	°C
[H+]	7.4	7.3 - 7.5	6.9 - 8.0	pH

- Normal ranges are small, typically caused by illness
- Death can occur by persistent, larger deviations
  - Temperature, acidity, potassium, calcium, and glucose

Control Systems

Negative Feedback Systems

- Most control systems of the body act by negative feedback
  - A stimulus causes a reaction that opposes the acting stimulus
    - Increased CO_2 causes increased pulmonary ventilation, which decreases CO_2
    - Decreased arterial pressure activates the baroreceptor system which acts increase heart rate and arterial constriction, which increases arterial pressure
- The negative feedback system acts to maintain homeostasis



Control Systems

Gain of Control Systems

- The gain of a control system is a parameter which describes the degree of effectiveness with which a control system can maintain constant conditions
  - Gain = Correction / Error

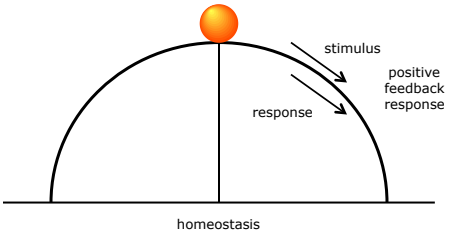
- Example
- In a normal person with a functioning baroreceptor control system, a defined stimulus causes arterial pressure to increase from 100 mmHg to 125 mmHg
  - Error is +25 mmHg - *if the baroreceptor system provided perfect control, there would be no change in arterial pressure*
- A person with a non-functioning baroreceptor control system, the same stimulus causes arterial pressure to increase from 100 mmHg to 175 mmHg
  - Difference from the normal response is 50 mmHg
  - Thus, the baroreceptor system provides a correction of -50 mmHg
- Gain = -50 mmHg / +25 mmHg = -2
  - The baroreceptor system *reduces* the effect of the stimulus *by two thirds*

Control Systems of the Body

Positive Feedback

- In a positive feedback control system, a stimulus causes a responses that promotes the stimulus

- In general, positive feedback systems lead to instability and therefore are not utilized as often as negative feedback systems



Control Systems of the Body

Positive Feedback

- Positive feedback systems do occur in the body
  - Blood clotting
    - A rupture in a blood vessel initiates a clot formation, and enzyme activation within the clot causes other enzymes in the blood to clot
    - The cycle continues until the vessel in plugged and bleeding stops
  - Uterine contractions in childbirth
  - Sodium ion flux in nerve signal propagation
- Typically, positive feedback control systems work within a larger negative feedback control system
  - For example, the blood clotting cycle works within the maintenance of blood volume negative feedback cycle

Control Systems of the Body

Adaptive Control

- Many of the control systems developed to maintain homeostasis are not simple negative feedback systems, but more complex communicating networks
- Adaptive control systems change their response each time a stimulus is presented until the proper response is determined
  - Some body movements require rapid responses that cannot wait for signal transmission to the central nervous system and the subsequent response
    - Sensory nerve signals from the moving parts transmit signals to the brain as to whether the movement was properly completed
    - If not, the brain sends signals so that the next response is altered
    - This continues until the proper response is obtained

Introduction to Physiology: The Cell

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Chapter 2

John P. Fisher

Eucaryotic Cells

- Procaryotic cells, which are primarily bacteria, consist of a single compartment containing DNA, RNA, proteins, and small molecules encapsulated by a plasma membrane, which is enclosed by a cell wall
- Eucaryotic cells, including fungus, plant cells, and animal cells, have a nucleus containing DNA and enclosed by a plasma membrane. Additionally, the cytoplasm contains many organelles also enclosed by a plasma membrane

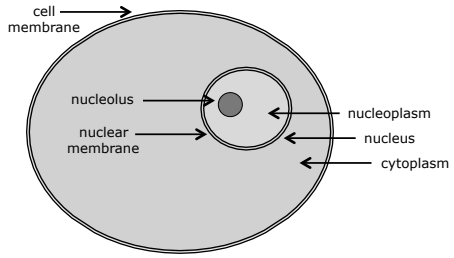
	Procaryotes	Eucaryotes
Organisms	Bacteria	Fungus, plant cells, animal cells
Cell Size	1 – 10 microns	5 – 100 microns
Metabolism	Anaerobic or aerobic	Aerobic
Organelles	Few or none	Nucleus, mitochondria, endoplasmic reticulum
DNA	Circular in cytoplasm	Linear within nuclear envelope
RNA / Proteins	Synthesized in cytoplasm	RNA syn. in nucleus, proteins syn. in cytoplasm
Cytoplasm	No cytoskeleton	Cytoskeleton and membrane functions
Organization	Unicellular	Multicellular with many different cell types

Alberts et al., Molecular Biology of the Cell

Organization of the Cell

Eucaryotic cells

- The two major parts of the cell are the nucleus, consisting of the nucleolus, nucleoplasm, and surrounding nuclear membrane, and the cytoplasm
- The substances of the cell are referred to as the protoplasm
  - Water
  - Ions
  - Proteins
  - Lipids
  - Carbohydrates



Organization of the Cell

Protoplasm

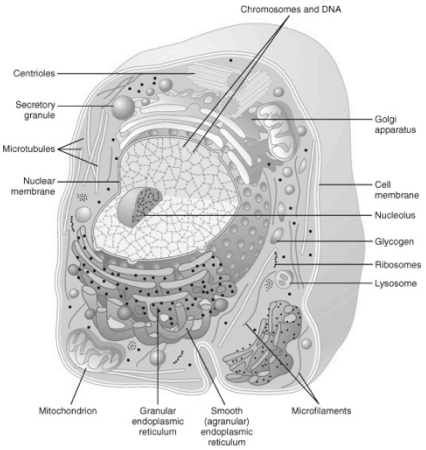
- Water
  - Comprises 70 – 85% of cell mass, with the exception of adipocytes, and contains dissolved molecules, suspended particulates, and membranes
- Ions
  - Significant within cell: Potassium, magnesium, phosphate, sulfate, bicarbonate
  - Less significant within cell: Sodium, chloride, and calcium
- Proteins
  - Compose 10 – 20% of the cell mass
  - Structural proteins include filaments and microtubules (polymeric proteins)
  - Globular proteins (mostly enzymes) are individual, soluble molecules that catalyze actions required for cellular function

Organization of the Cell

Protoplasm

- Lipids
  - Molecules that are hydrophobic / "fat soluble" / lipophilic
  - Phospholipids and cholesterol are the most significant (2% of cell mass)
    - Form cell membranes and intracellular membrane barriers
  - Triglycerides are the fat stored by adipocytes as an energy source
- Carbohydrates
  - Lesser in content, comprising 1 – 6% of cell mass, depending upon cell type
  - Dissolved glucose is readily available in extracellular fluid
  - An insoluble glucose polymer, glycogen, is found intracellularly

Eucaryotic Cell



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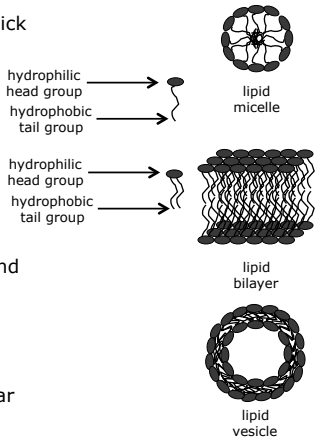
Eucaryotic Cell

Cell Membrane

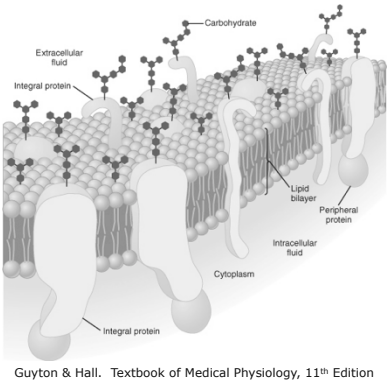
- Thin, elastic structure approximately 7.5 – 10 nm thick
- Composed of proteins and lipids
  - 55% proteins
  - 25% phospholipids
  - 13% cholesterol
  - 4% other lipids
  - 3% carbohydrates
- Basic structure is a lipid bilayer
  - Composed of two opposing layers of lipids
  - Hydrophilic head adjacent to the extracellular and intracellular water
    - Hydrophilic head is made up of phosphates
  - Hydrophobic (lipophilic) tail pointed inwards
    - Hydrophobic tail is made up of fatty acids
- Interspersed within the lipid bilayer are large globular proteins



Eucaryotic Cell

Cell Membrane

- The membrane has selective barrier properties
  - Water soluble molecules are excluded
    - Ions, glucose, and urea are excluded
  - Fat soluble molecules are permitted
    - Oxygen, carbon dioxide, and alcohol can pass though the membrane easily
- The membrane is not static, but fluid – allowing *lipid molecules and proteins to move within the two dimensional surface of the cell*
- Cholesterol contains a highly fat soluble core, thus storing the molecule in the lipid bilayer
  - Cholesterol augments the permeability and fluidity of the bilayer



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Eucaryotic Cell

Cell Membrane Proteins

- The membrane contains many globular proteins, most of which are glycoproteins
  - Integral proteins protrude both side of the lipid bilayer
  - Peripheral proteins exist only on one side
    - Typically attached to integral proteins and act to regulate their function
- Many integral proteins provide structural channels
  - Allow for the selective transport of water soluble molecules, especially ions
  - Transport may be actively facilitated by carrier proteins, or passively allowed by pores or channels
- Other integral proteins acts as receptors for water soluble chemicals
  - Interaction of the cell surface bound receptor with specific ligands cause the protein to undergo a conformation change that enzymatically activates an intracellular portion of the protein
  - Second messengers in the cytoplasm then relay this activated state onto other participants within the cell

Eucaryotic Cell

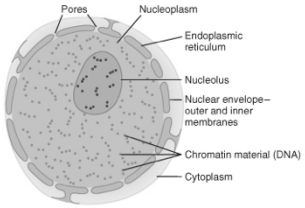
Cell Membrane Carbohydrates

- Membrane carbohydrates generally occur in combination with proteins or lipids, in the form of glycoproteins or glycolipids
  - Most integral proteins are glyoproteins
  - On tenth of the membrane lipids are glycolipids
  - Proteoglycans, carbohydrates with protein cores, are also present
- The entire surface of the cell therefore has a loose carbohydrate coat called glycocalyx
  - Typically have a net negative charge that repels other negatively charged objects, including other cells, at moderate distances
  - Glycocalyx is "sticky" allowing close contact (attachment) between cells
  - Acts as receptors substances for hormones
  - Augment immune responses

Eucaryotic Cell

Nucleus

- The nucleus is the container of DNA in eukaryotic cells
- DNA condenses into chromosomes
  - Humans have $6x10^9$ nucleotide pairs organized into 46 chromosomes, 2 of which are sex chromosomes
  - The 46 chromosome molecules vary in size from $50x10^6$ to $250x10^6$ nucleotide pairs
  - Humans, and all diploid organisms, have two copies of each chromosome (maternal and paternal) except for the sex chromosomes, thus humans have 24 different chromosomes



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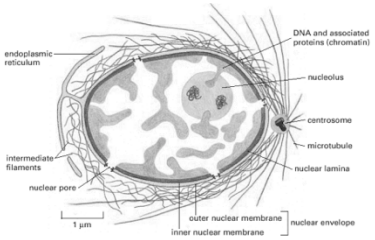
Eucaryotic Cell

Nucleus

- The nucleus is enveloped by a nuclear membrane, which consists of two lipid bilayers
- The outer membrane is continuous with the ER, and the space within the two lipid bilayers of the nuclear membrane is continuous with the space within the ER

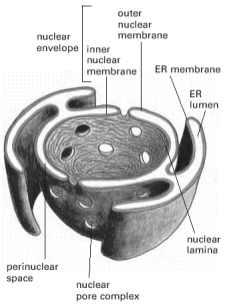


Alberts et al.,
Molecular Biology of the Cell

Eucaryotic Cell

Nuclear Membrane

- Several thousand nuclear pores penetrate both membranes
  - Pores consist of protein complexes > 100 nm in diameter, but with an effective pore size of about 9 nm
  - Molecules < 44 kDa can pass through the pore, molecules < 15 kDa pass into the nucleus extremely rapidly
- Most nuclei contain one or highly staining structures called the nucleoli
  - Is not defined by a lipid membrane
  - Contains large amounts of RNA and proteins, similar to those found in ribosomes

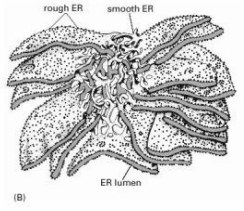


Alberts et al.,
Molecular Biology of the Cell

Eucaryotic Cell

Endoplasmic Reticulum

- Interconnected tubular and flat vesicular structures, with extremely high surface area made up of a protein laden lipid bilayer membrane
  - Up to 30 - 40 times the surface area of the cell membrane
- The space within the tubules and vesicles is filled with endoplasmic matrix
  - Space is continuous with the space within the nuclear membrane
- Functions in protein synthesis, as some substances enter the ER
- Functions in metabolism, as the surface is covered metabolic proteins

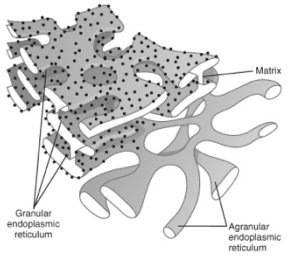


Alberts et al.
Molecular Biology of the Cell

Eucaryotic Cell

Endoplasmic Reticulum

- Granular endoplasmic reticulum has a surface packed with attached ribosomes
  - Ribosomes, formed from RNA and proteins, are responsible for synthesizing new proteins
- Smooth endoplasmic reticulum (SER) has no attached ribosomes
  - SER functions in the synthesis of lipid substances as well as other enzymatic processes of the cell



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Eucaryotic Cell

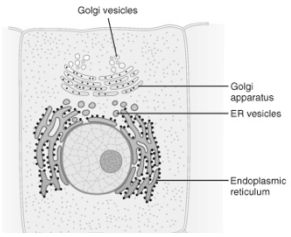
Functions of the Endoplasmic Reticulum

- Protein Formation
  - Proteins are formed by the granular endoplasmic reticulum
  - Proteins are formed by ribosomes, where they are extruded by ribosomes through the walls of the endoplasmic reticulum to the interior of endoplasmic vesicles and tubules, known as the endoplasmic matrix
  - Enzymes in the endoplasmic matrix rapidly reconfigure the proteins by conjugation with carbohydrate molecules (glycosylation) as well as crosslinking, folding, and cleaving
  - Free proteins (not glycoproteins) are formed in the cytosol by ribosomes not bound to the endoplasmic reticulum
- Lipid Formation
  - Lipids, especially phospholipids and cholesterol, are formed by the smooth endoplasmic reticulum
  - These molecules generally are incorporated into the wall of the endoplasmic reticulum, so that the organelle is continually increasing in size
  - Endoplasmic reticulum vesicles break away from the SER and mostly migrate to the Golgi apparatus

Eucaryotic Cell

Golgi Apparatus

- Composed of four or more stacked layers of thin, flat enclosed vesicles lying near the nucleus
- Prominent in secretory cells where it is located on the side of the cell from which secretory substances are released
- Golgi apparatus functions with the ER, where transport vesicles bud off the ER and diffuse to the Golgi apparatus – the Golgi apparatus processes ER vesicles to form lysosomes, secretory vesicles, or other cytoplasmic components



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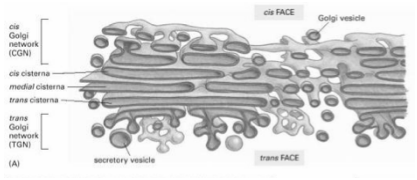
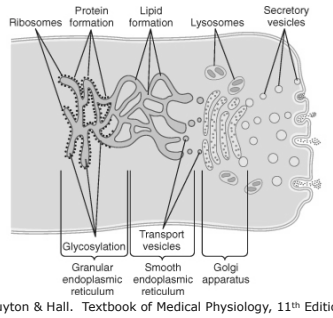


Alberts et al., Molecular Biology of the Cell

Eucaryotic Cell

Functions of the Golgi Apparatus

- Involved in the formation of some large saccharide polymers bound with a small amount of protein, such as hyaluronic acid and chondroitin sulfate
- Vesicle formation
  - Vesicles from the ER, containing newly synthesized proteins, fuse with the proximal portion of the Golgi, releasing their proteins into the vesicular space
  - The Golgi glycosylates and concentrates the proteins as they move distally
  - Finally vesicles, containing functional proteins, bud off the Golgi and diffuse throughout the cell
  - Time Line: Nutrient amino acids are taken up and synthesized into proteins in the granular ER in 3-5 min, present in the Golgi in 20 min, and secreted from the cell in 1 -2 hr



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Eucaryotic Cell

Vesicles: Lysosomes

- Small, 250 – 750 nm in diameter
- Surrounded by a lipid bilayer
- Filled with 5 to 9 nm granules
  - Granules are aggregates of hydrolases
  - Provide an intracellular digestive system
  - Digests damaged cellular structures, food particles that have been ingested by the cell, and unwanted matter (bacteria)

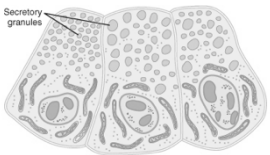
Eucaryotic Cell

Vesicles: Peroxisomes

- Similar to lysosomes, except
  - Formed from the SER or self replication - not from the Golgi apparatus
  - Contain oxidases, rather than hydrolases
    - Combine oxygen with hydrogen ions to for hydrogen peroxide (H_2O_2)
    - Hydrogen peroxide, in conjucntion with catalase, oxidizes many substances that may be cytotoxic

Vesicles: Secretory Vesicles

- Almost all secretory substances are formed from the ER-Golgi apparatus system and then released from the Golgi into the cytoplasm in the form of storage vesicles known as secretory vesicles or secretory granules



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Eucaryotic Cell

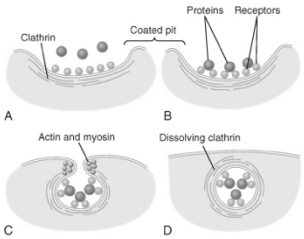
Endocytosis

- Most substances pass through the cell membrane by diffusion and active transport
- Very large particles enter the cell by endocytosis
- Two forms of endocytosis exist: pinocytosis and phagocytosis

Eucaryotic Cell

Endocytosis: Pinocytosis

- Ingestion of extremely small vesicles (100 - 200 nm) that contain extracellular fluid
- Occurs continually at the cell membrane
- Mechanism
  - Target protein binds to receptors, concentrated in coated pits
  - Clathrin molecules, intracellular to the receptors, initiate an invagination process utilizing actin and myosin contractile filaments
  - Finally, a pinocytic vesicle buds off into the cytoplasm of the cell
- Consumes ATP and requires extracellular calcium ions



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Eucaryotic Cell

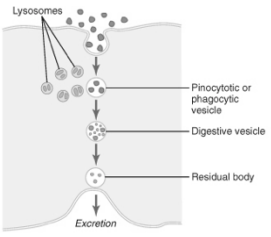
Endocytosis: Phagocytosis

- Largely similar, though it involves the consumption of large particles (rather than molecules) and utilizes a separate system of receptor and signaling proteins
- Occurs only in a few cells
  - Tissue macrophages and white blood cells
- Initiated by particulate binding on the cell surface
  - In the immune response, particulates are typically covered by antibodies and the antibodies initiate cell surface binding
    - The intermediation of antibodies is called opsonization

Eucaryotic Cell

Endocytosis: Cell Digestion

- The entry of nutrients or particles into the cell by pinocytosis or phagocytosis is followed by an accumulation as well as attachment of lysosomes
- Lysosomes release hydrolases into the vesicle, forming a digestive vesicle
- The hydrolytic products (amino acids, glucose, phosphates) then diffuse through the membrane of the vesicle into the cytoplasm of the cell
- The remaining byproducts are not digestible and are excreted by the vesicle out of the cell by a process known as exocytosis – essentially the opposite of endocytosis



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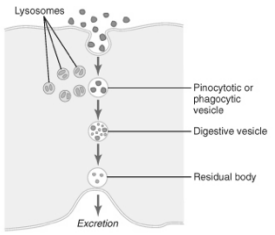
Eucaryotic Cell

Endocytosis: Cell Digestion

- Digestive processes are utilized to reduce a tissues size
  - Uterus after pregnancy
  - Skeletal muscles after inactivity
- Digestive processes are also used to eliminate a portion or entire cell after damage
  - Lysosomes rupture in response to damage, releasing hydrolases into the cytoplasm of the damaged cell (autolysis)



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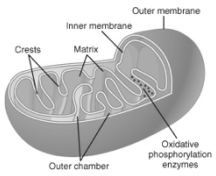
Eucaryotic Cell

Mitochondria

- Powerhouse of the cell, extracting energy from nutrients and oxygen
- Present in all portions of the cytoplasm, varying in number from less than 100 to 1000s, depending upon cell type
- Enveloped by two lipid bilayers – an outer membrane and an inner membrane
- Oxidative enzymes within and on the inner membrane *oxidize nutrients to form carbon dioxide and water as well as energy in the form of adenosine triphosphate* (ATP)
  - ATP then provides energy throughout the cell by phosphate based reactions
- Mitochondria contain their own DNA and are self replicative, forming additional mitochondria as the energy needs of the cell increase



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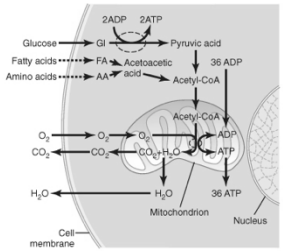
Eucaryotic Cell

Functions of the Mitochondria

- Extraction of energy from nutrients
  - Sources of nutrients are oxygen, carbohydrates, fats, and proteins
    - Carbohydrates are converted to glucose
    - Fats are converted to fatty acids
    - Proteins are converted to amino acids
  - These broken down nutrients can then be absorbed by the cell
  - Nutrients are reacted with oxygen under the influence of various enzymes (oxidative reactions) to produce energy
  - Oxidative reactions occur within the mitochondrion



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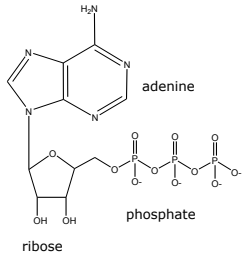
Eucaryotic Cell

Functions of the Mitochondria

- Energy released is captured in the form of the nucleotide adenosine triphosphate (ATP)
  - Nitrogenous base adenine
  - Pentose sugar ribose
  - Three phosphate radicals
    - Last two phosphates are held by a high energy phosphate bond
    - Each of these bonds contains about 12 Kcal per mol of ATP
- When ATP releases energy, it releases a phosphate group and becomes adenosine diphosphate (ADP)
- When energy is stored by the cell, it does so by reconstituting ATP from ADP

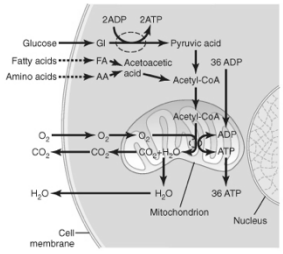


Adenosine Triphosphate (ATP)

Eucaryotic Cell

Functions of the Mitochondria

- Glycolysis
  - Glucose enters the cell cytoplasm and then is converted to pyruvic acid by glycolysis
  - As a product of this reaction, ADP is converted to ATP
  - However, glycolysis accounts for only 5 percent of the cell's energy needs
- Citric Acid Cycle
  - Pyruvic acid, from all nutrients, is converted into acetyl-CoA in the mitochondrion
  - As a byproduct, hydrogen atoms are released
  - These hydrogen atoms bind with dissolved oxygen, releasing energy that converts ADP to ATP
  - This mitochondrial process forms the major portion of ATP



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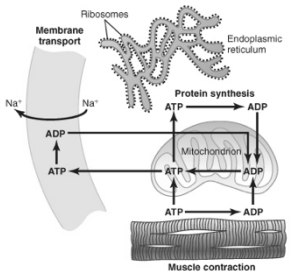
Eucaryotic Cell

Functions of the Mitochondria

- ATP is utilized in three general classed of cellular functions
  - Membrane transport of substances
    - Sodium, potassium, calcium magnesium, phosphate, cholride urate and hydrogen ions
  - Synthesis of chemical compounds
    - Proteins, phospholipids, cholesterol, purines, pyrimidines
    - Can reach up to 75% of ATP utilization
  - Mechanical work
    - Muscle fiber contraction, ciliary motion



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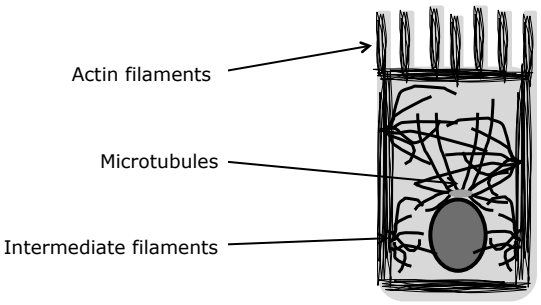
Eucaryotic Cell

Cytoskeleton

- The cytoskeleton is formed primarily by three protein filaments: actin microfilaments, microtubulues, and intermediate filaments



Epithelial Cell

Eucaryotic Cell

Cytoskeleton: Actin Filaments

- Most abundant protein *within* cells (5% of total cell proteins)
- Each actin molecule (G actin) is 375 amino acids long, with 1 ATP
- Soluble monomer molecule spontaneously assembles into filaments on the addition of salt
  - ATP is required and regulates polymerization
- Actin filaments consist of two stranded helical polymers of G actin
- Flexible structures, with a diameter of 5 – 9 nm
- Approximately half of actin is in monomer form and half is in filament form
- The polymerization and depolymerization of actin is constantly occurring, providing cell surface protrusions such as lamellipodia and microspikes
- Polymerization of actin can be regulated by extracellular signaling molecules which bind cell surface receptors
- Highly concentrated in the cortex, just beneath the plasma membrane

Eucaryotic Cell

Cytoskeleton: Microtubules

- Long hollow cylinders made of the protein tubulin
- Outer diameter of approximately 25 nm
- Stiff structures that usually have one end anchored in the microtubule organizing center (centrosome) and the other end free in the cytoplasm
- More rigid than actin
- Highly dynamic structures that alternately grow and shrink by the addition and loss of tubulin subunits
- Motor proteins move along microtubules to carry specific membrane bounded organelles to desired locations in the cell
  - Kinesins move toward the + end (cytoplasm) of the microtubule
  - Dyneins move toward the – end (centrosome) of the microtubule

Eucaryotic Cell

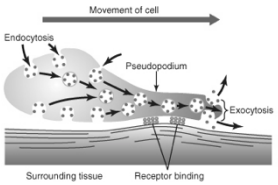
Cytoskeleton: Intermediate Filaments

- Rope like fibers with a diameter of approximately 10 nm
- Resist tensional forces
- Monomers of different intermediate filaments differ in amino acid sequence and molecular weight
- All contain a dimer-forming, extended coiled coil structure
  - Monomer pairs to form coiled coil dimer
  - Coiled coil dimers align to form filaments
- Major Types of Intermediate Filaments
  - Nuclear Lamins — Found in nuclear lamina
  - Vimentinlike Proteins — Found in mesenchymal cells
  - Keratins — Found in epithelial cells
  - Neuronal I.F. — Found in neurons

Eucaryotic Cell

Locomotion of Cells

- Ameboid movement
  - Movement of entire cell relative to the surroundings, involving
    - Continual formation of new cell membrane at the pseudopodium
    - Receptor mediated attachment
    - Force generation, perhaps by actin polymerization
- Ciliary Movement
  - Whip-like movement of cilia (small hairs) on the surface of cells
  - In humans, it occurs only in the respiratory airways and fallopian tubes
  - Requires ATP, calcium, and magnesium



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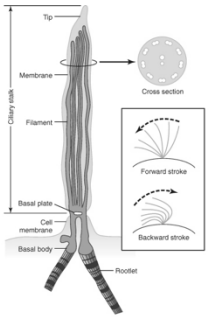

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Genetic Control of Cell Functions

Adapted From:

Textbook Of Medical Physiology, 11th Ed.
Arthur C. Guyton, John E. Hall
Chapter 3

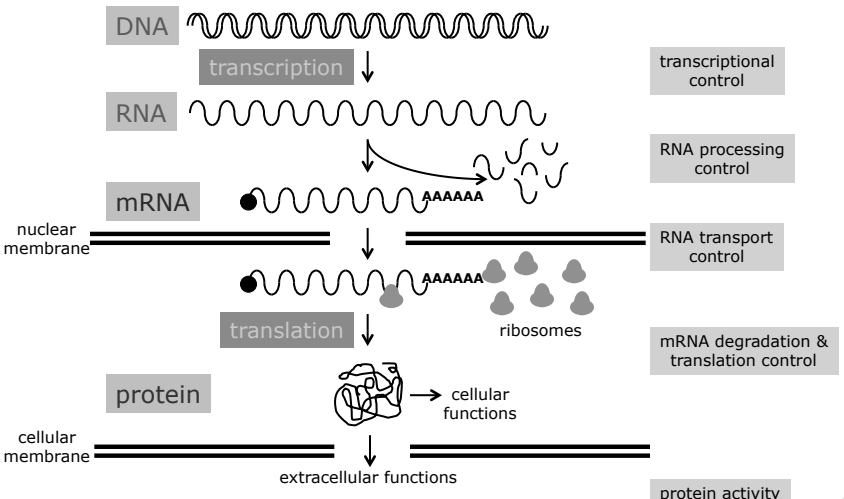
John P. Fisher

Cell Function

What do cells do?

- The predominate task of a cell is to synthesize compounds, and largely proteins
- Cells are classified by the proteins they synthesize
  - Osteoblasts synthesize proteins that makeup the organic phase of bone
  - Macrophages synthesize proteins that assist in fighting foreign bodies
- A cell's phenotype is often described by its protein expression
- In principle, all the cells of an organism have the same genetic information, but what differs between cells is the proteins they synthesize

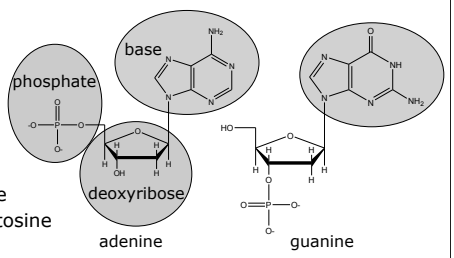
Cell Function

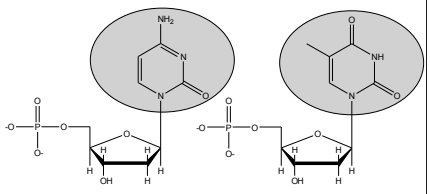


Genes in the Cell Nucleus

Deoxyribonucleic Acid

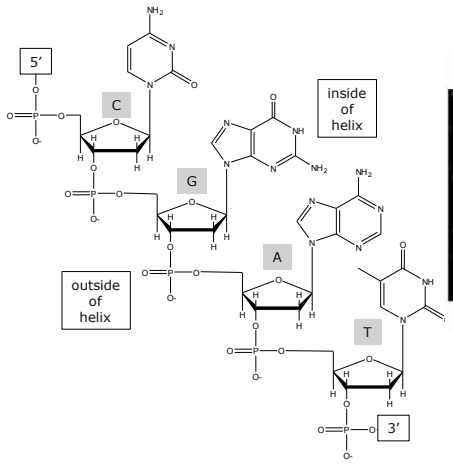
- Long, double stranded, helical molecule
  - Genes are linearly encoded along DNA
- DNA Components
  - Phosphoric acid
  - Deoxyribose
  - One of four nitrogenous bases
    - Purines: A, Adenine and G, Guanine
    - Pyrimidines: T, Thymine and C, Cytosine
- Nomenclature
  - Base
  - Deoxyribonucleoside
    - Base + Sugar
  - Deoxyribonucleotide
    - Base + Sugar + Phosphate

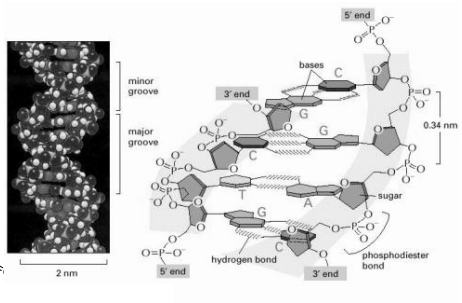




Genes in the Cell Nucleus

Deoxyribonucleic Acid





Alberts et al.,
Molecular Biology of the Cell

No. 4356 April 25, 1953 NATURE 737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹ Young, F. B., Gerard, H., and Jevons, W., *Phil. Mag.*, **40**, 169 (1920).
² Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
³ Van Arx, W. S., Woods Hole Papers in Phys. Oceanog., Meteor., **11**, 169 (1950).
⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

This figure is purely diagrammatic. The two ribbons symbolise the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

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King's College, London. One of us (J.D.W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

¹ Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
² Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
³ Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
⁴ Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
⁵ Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Cambridge Univ. Press, 1947).
⁶ Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).

Molecular Structure of Deoxypentose Nucleic Acids

Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

WHILE the biological properties of deoxypentose nucleic acid suggest a molecular structure containing great complexity, X-ray diffraction studies described here (cf. Astbury[5]) show the basic molecular configuration has great simplicity. The purpose of this communication is to describe, in a preliminary way, some of the experimental evidence for the polynucleotide chain configuration being helical, and existing in this form when in the natural state. A fuller account of the work will be published shortly.

The structure of deoxypentose nucleic acid is the same in all species (although the nitrogen base ratios alter considerably) in nucleoprotein, extracted or in cells, and in purified nucleate. The same linear group of polynucleotide chains may pack together parallel in different ways to give crystalline[1–3], semi-crystalline or paracrystalline material. In all cases the X-ray diffraction photograph consists of two regions, one determined largely by the regular spacing of nucleotides along the chain, and the other by the longer spacings of the chain configuration. The sequences of different nitrogen bases along the chain is not made visible.

Oriented paracrystalline deoxypentose nucleic acid ('structure B' in the following communication by Franklin and Gosling) gives a fibre diagram as shown in Fig. 1 (cf. ref. 4). Astbury suggested that the strong 3·4-A. reflexion corresponded to the inter-nucleotide repeat along the fibre axis. The ~ 34 A. layer lines, however, are not due to a repeat of a polynucleotide composition, but to the chain configuration repeat, which causes strong diffraction as the nucleotide chains have higher density than the interstitial water. The absence of reflexions on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

Diffraction by Helices

It may be shown[4] (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is given by the squares of Bessel functions. A uniform continuous helix gives a series of layer lines of spacing corresponding to the helix pitch, the intensity distribution along the nth layer line being proportional to the square of J_n, the nth order Bessel function. A straight line may be drawn approximately through the innermost maxima of each Bessel function and the origin. The angle this line makes with the equator is roughly equal to the angle between an element of the helix and the helix axis. If a unit repeats a times along the helix there will be a meridional reflexion (L_1) on the ath layer line. The helical configuration produces side-bands on this fundamental frequency, the effect[5] being to reproduce the intensity distribution about the origin around the new origin, on the ath layer line, corresponding to C in Fig. 2.

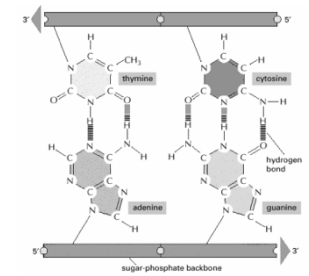
Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mass at 23 Å. diameter and remainder distributed along a radius, the mass at a given radius being proportional to the radius. About C on the tenth layer line similar functions are plotted for an outer diameter of 12 Å.

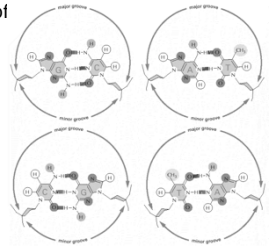
We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit or nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole diffraction pattern is modified by the form factor of the nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the helix axis, the phases of radiation scattered by the helices of different diameter passing through each point are the same. Summation of the corresponding Bessel functions gives reinforcement for the inter-

Genes in the Cell Nucleus

Deoxyribonucleic Acid

- The two strands of the DNA double helix are held together by specific hydrogen bonding between complementary bases, a purine with a pyrimidine
  - Adenine binds only with Thymine with 2 H bonds
  - Guanine binds only with Cytosine with 3 H bonds
- Due to the loose hydrogen bonding of DNA, the double helix can separate into two strands easily
- The double helix is formed by a rotational form resulting from the base bonding
  - 10 bases are included within one complete turn of the double helix
  - Major and minor grooves are created in the helix due to the unequal spacing of base pairs about the phosphate – sugar backbone



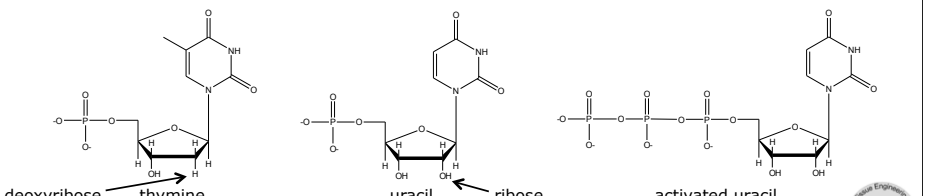


Alberts et al.,
Molecular Biology of the Cell

Transcription

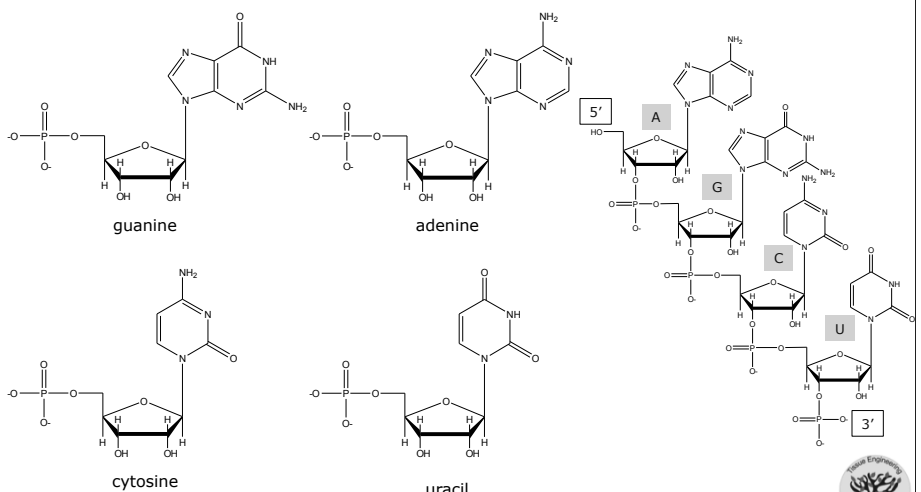
Deoxyribonucleic Acid

- DNA is transcipted into RNA, ribonucleic acid
  - This process allows DNA to remain within the nucleus of the cell and produce RNA which then diffuses from the nucleus through the nuclear pores
- RNA Nucleotides
  - RNA is identical to DNA, except
    - RNA has a ribose backbone, rather than the DNA deoxyribose backbone
    - RNA substitutes uracil for thymine
  - RNA nucleotides are activated by adding 2 phosphate radicals, forming a triphosphate



Transcription

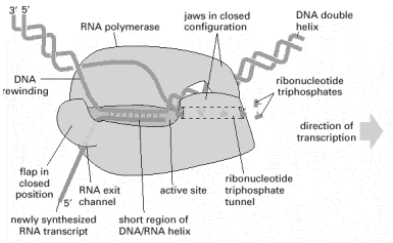
Ribonucleic Acid



Transcription

Ribonucleic Acid

- RNA polymerase recognizes a specific DNA sequence, upstream of the gene, known as the promoter
- RNA polymerase binds the DNA promoter
- Polymerase binds initiates DNA unwinding for approximately 20 bases
  - DNA strands temporarily separate and one of the strands is then used as a template for RNA synthesis while the other remains inactive
- Polymerase moves down the DNA strand
  - Unwinding continues
  - Polymerase adds RNA nucleotides to the end of the newly forming RNA chain
    - First, H bonding the DNA base and the complementary RNA base
    - Second, polymerase breaks 2 of the high energy phosphate bonds on a RNA nucleotide, utilizing the released energy to cause a covalent linkage of the remaining phosphate with the ribose on the end of the growing RNA chain



Alberts et al.,
Molecular Biology of the Cell

Transcription

Ribonucleic Acid

- At the end of the gene, polymerase recognizes a chain-terminating sequence, causing polymerase to break free from the DNA
  - Polymerase can then be reused
- The high affinity of the two DNA chains for one another causes the reforming of the DNA helix, releasing the newly synthesized RNA
- The RNA sequence is complementary to the encoding DNA

Encoding DNA	ACGCTAGTGACTAATCGGTCACCTTAG
Resulting RNA	UGCGAUCACUGAUUAGCCAGUGGAAUC

Transcription

Ribonucleic Acid

- Messenger RNA
  - Carries the genetic information encoding proteins from the nucleus to the cytoplasm
  - Long, single RNA strands that are suspended in the cytoplasm
  - Several hundred to several thousand nucleotides long
  - Contain codons that are exactly complimentary to DNA
    - Codons are nucleotide triplets that encode for a specific amino acid
    - Most amino acids are encoded by more than one codon
    - One codon represents a starting point for protein synthesis
    - Three codons represent a stopping point for protein synthesis

Transcription

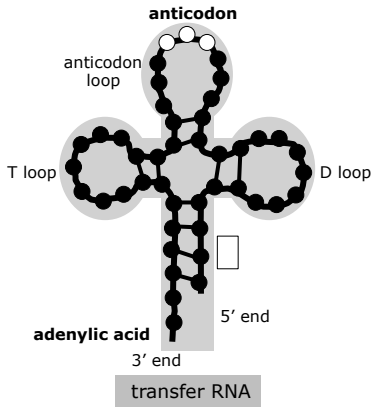
Ribonucleic Acid

Amino Acid	RNA Codon					
Alanine	GCU	GCC	GCA	GCG		
Arginine	CGU	CGC	CGA	CGG	AGA	AGG
Asparagine	AAU	AAC				
Aspartic Acid	GAU	GAC				
Cysteine	UGU	UGC				
Glutamic Acid	GAA	GAG				
Glutamine	CAA	CAG				
Glycine	GGU	GGC	GGA	GGG		
Histidine	CAU	CAC				
Isoleucine	AUU	AUC	AUA			
Leucine	CUU	CUC	CUA	CUG	UUA	UUG
Lysine	AAA	AAG				
Methionine	AUG					
Phenylalanine	UUU	UUC				
Proline	CCU	CCC	CCA	CCG		
Serine	UCU	UCC	UCA	UCG	AGC	AGU
Threonine	ACU	ACC	ACA	ACG		
Tryptophan	UGG					
Tyrosine	UAU	UAC				
Valine	GUU	GUC	GUA	GUG		
Start codon	AUG					
Stop codon	UAA	UAG	UGA			

Transcription

Ribonucleic Acid: Transfer RNA

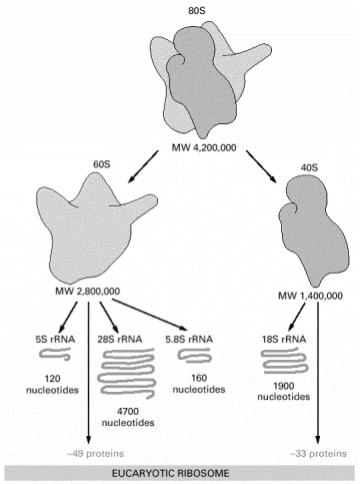
- Transports activated amino acids to the ribosomes to be used in protein assembly
- Small, approximately 80 nucleotides long
- Each type of transfer RNA combines specifically with 1 of the 20 amino acids that are to be incorporated into proteins
- In ribosomes, each specific transfer RNA recognizes a specific messenger RNA codon, and therefore delivers the appropriate amino acid to the appropriate place in the newly forming amino acid chain, or protein
- Structure: Cloverleaf
  - Andenylic acid is located at the 3' (-OH) end and is the location of amino acid binding
  - Anticodon is located at the opposite end
  - Anticodon ensures mRNA codon specificity



Transcription

Ribonucleic Acid: Ribosomal RNA

- Forms ribosomes with ~75 proteins
- Constitutes ~60% of the ribosome
- Structure on which protein are synthesized
- Always functions with the other forms of RNA
  - mRNA encodes the codon
  - tRNA delivers the amino acid
- Ribosomes
  - Composed of 2 units: small subunit and large submit
    - Small subunit: 1 RNA molecule and ~33 proteins
    - Large subunit: 3 RNA molecules and ~49 proteins
  - mRNA and tRNA first bind the small subunit during protein synthesis
  - Large subunit provides enzymes for peptide bonding

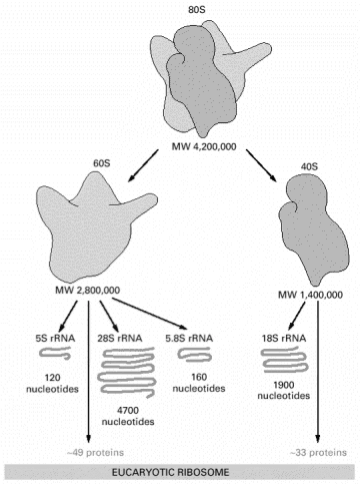


Alberts et al.
Molecular Biology of the Cell

Transcription

Ribosomal Formation

- Ribosomal RNA is encoded by DNA found on five chromosomal pairs
- Each chromosome contains many duplicates of the genes due to the large amount of ribosomal RNA required
- Ribosomal RNA collects in the nucleolus
  - Nucleolus size is roughly related to the amount of protein being synthesized by the host cell
  - Ribosomal proteins also bind ribosomal RNA in the nucleolus
  - These complexes are then released out of the nucleolus and nucleus
  - In the cytoplasm, ribosomes are further processed into the mature, functional form

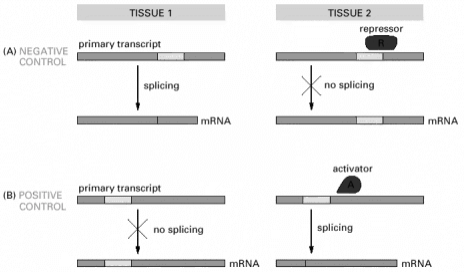


Alberts et al.
Molecular Biology of the Cell

Transcription

Post-Transcription Modification

- After the RNA is released into the nucleoplasm, it still must be further processed before leaving the nucleus
- Processing allows for the removal of unwanted sequences of RNA nucleotides
  - Sequences occur throughout the strand
  - Sequences account for almost 90% of the RNA
- RNA splicing proteins cut the RNA, remove unwanted sequences, and reconstitute the RNA strand
- This strand is known as messenger RNA, or mRNA



Alberts et al., Molecular Biology of the Cell

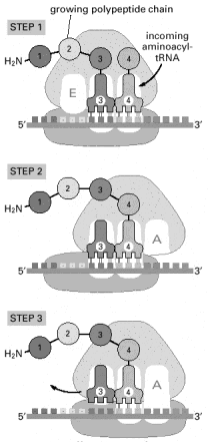
- *Intron:* The portion of the DNA sequence which, upon transcription, is removed by splicing; this DNA does not encode the target gene
- *Exon:* The portion of the DNA sequence which, upon transcription, is retained after splicing; this DNA does encode the target gene

Translation

Translation is the process of protein synthesis from mRNA

- Messenger RNA travels through the ribosome, starting at a start codon
- The ribosome reads the mRNA, collects the appropriate tRNA for the particular codon, adds the amino acid from the tRNA to the growing amino acid chain, and then releases the tRNA
- When a stop codon is realized, the end of a protein molecule is signaled and the protein is released into the cytoplasm
- Note that there is no specificity for a ribosome for a protein – any ribosome can produce any protein, given the appropriate mRNA
- A few proteins are synthesized directly into the ER – while amino acid assembly is occurring – this pulls ribosomes to the surface of the ER, forming the granular ER

- Polyribosomes
  - Many ribosomes can translate a mRNA molecule at the same time
  - Thus, clusters of 3 to 10 ribosomes – polyribosomes – can be observed on a single mRNA molecule



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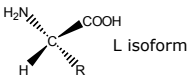
Molecular Biology of the Cell

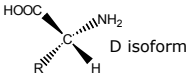
Proteins

Protein Structure

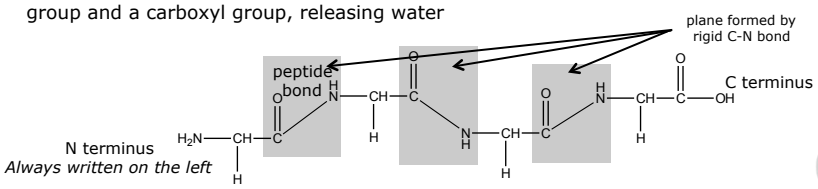
- Proteins are polymeric amino acids, where the amino acid sequence determines the protein function
- An amino acid is formed from
  - A central alpha-carbon, with one lone hydrogen
  - An amino (NH_2) group
  - A carboxyl (COOH) group
  - An R side chain group – determines the type of amino acid
- The central carbon atom is asymmetric, allowing the formation of L and D isomers
  - Proteins consist exclusively of L-amino acids
- At physiological pH (7.4) both the amino group and carboxyl group are ionized (amino group is NH_3^+ / carboxyl group is COO^-)
- Proteins are formed from a condensation reaction between an amino group and a carboxyl group, releasing water



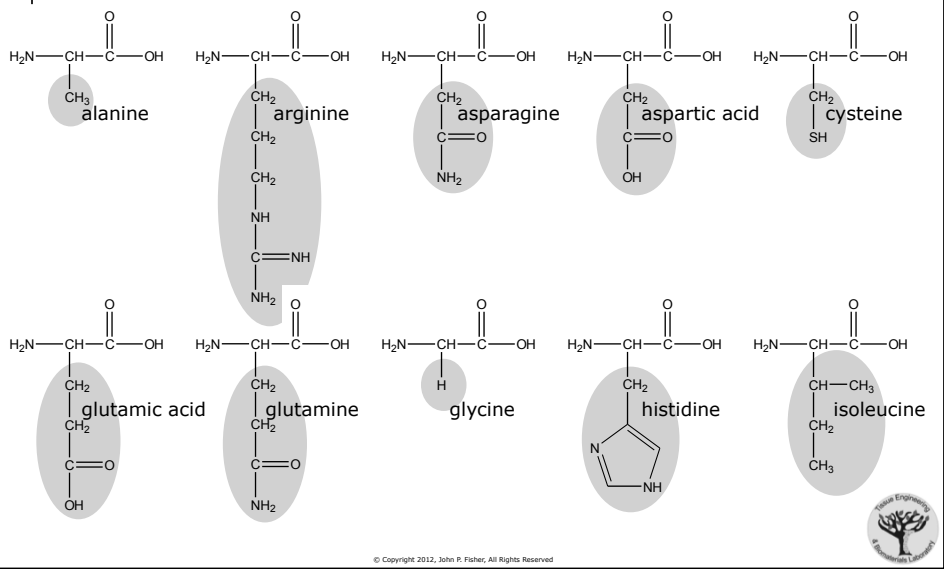
L isoform



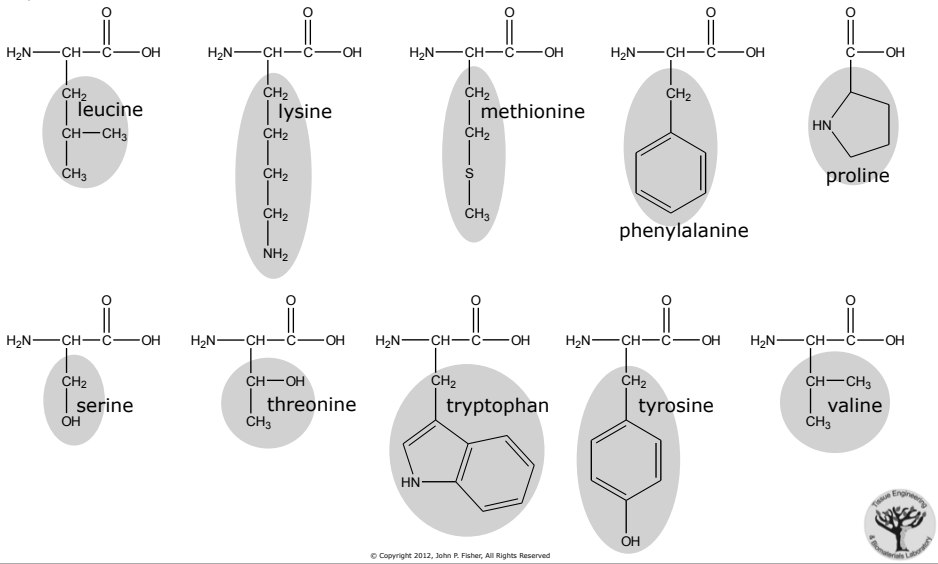
D isoform



Amino Acids



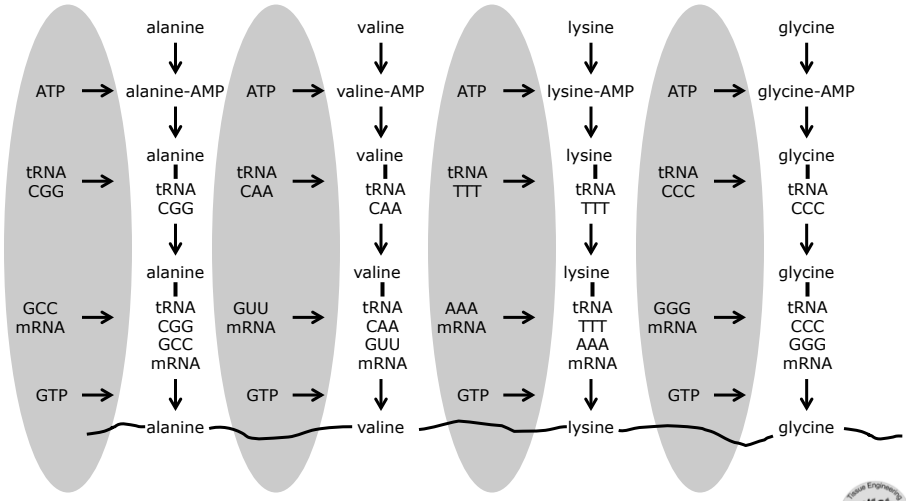
Amino Acids



Amino Acids

AMINO ACID	3L Abbreviation	1L Abbreviation	Side Chain Property
Alanine	ALA	A	nonpolar
Arginine	ARG	R	basic
Asparagine	ASN	N	uncharged
Aspartic Acid	ASD	D	acidic
Cysteine	CYS	C	nonpolar
Glutamic Acid	GLU	E	acidic
Glutamine	GLN	Q	uncharged
Glycine	GLY	G	nonpolar
Histidine	HIS	H	basic
Isoleucine	ILE	I	nonpolar
Leucine	LEU	L	nonpolar
Lysine	LYS	K	basic
Methionine	MET	M	nonpolar
Phenylalanine	PHE	F	nonpolar
Proline	PRO	P	nonpolar
Serine	SER	S	uncharged
Threonine	THR	T	uncharged
Tryptophan	TRP	W	nonpolar
Tyrosine	TYR	Y	uncharged
Valine	VAL	V	nonpolar

Protein Synthesis



Four high energy bonds are required to synthesize a single peptide bond

Control of Genetic Functions

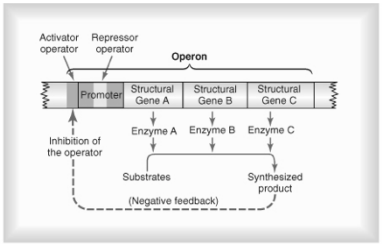
Regulation

- As each cell's phenotype is in large part described by its protein expression, and all cells within a single organism are genetically equivalent, there needs to be a strict regulation of protein expression
- Genetic regulation
  - The degree of gene activation is controlled
- Enzymatic regulation
  - The activity of formed enzymes (proteins) is controlled

Control of Genetic Functions

Genetic Regulation

- An operon is a sequence of genes located one after another on the same chromosomal DNA that controls enzyme formation
  - The constitutive genes are called structural genes
  - The expression of the operon is controlled by an upstream promoter
    - A repressor operator in the promoter can be bound by a regulatory protein, controlling RNA polymerase binding to the promoter
  - Operon expression is also controlled by a further upstream activator operator
    - When bound by an activator protein, operon expression is promoted

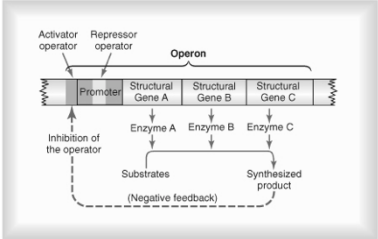


Guyton & Hall. Textbook of Medical Physiology, 11th Edition

Control of Genetic Functions

Genetic Regulation

- Negative feedback control
  - Expression of the structural genes can catalyze substrates to form products that, in turn, regulate operon expression
    - Substrate can be a repressor protein that binds the promoter and prevents expression
    - Substrate can interfere with activator operator's promotion of operon expression
    - Down regulation of substrate expression, due to lack of enzymer expression, can in promote operon expression



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Control of Genetic Functions

Genetic Regulation

- Other methods of genetic regulation include
  - Regulatory genes
  - Many operons under same regulatory proteins, regulons
  - Intermediate operon positioning
  - RNA regulation
  - Protein regulation
  - Histone regulation

Control of Genetic Functions

Enzymatic Regulation

- Some cell activities are controlled by intracellular inhibitors or activators that act directly on specific intracellular enzymes
- Enzyme inhibition
  - Synthesis of inhibitors that block enzyme function, typically at the beginning of the signaling cascade
- Enzyme activation
  - Normally inactive enzymes are activated to induce some signaling cascade
    - Lack of ATP induces cAMP levels that promote glucose utilization, and thus the replenishing of ATP levels
    - Purine / pyrimidine balance
      - Purine synthesis inhibits purine synthesis and promotes pyrimidine synthesis
      - Pyrimidine synthesis inhibits pyrimidine synthesis and promotes purine synthesis

Genetic Control of Cell Reproduction

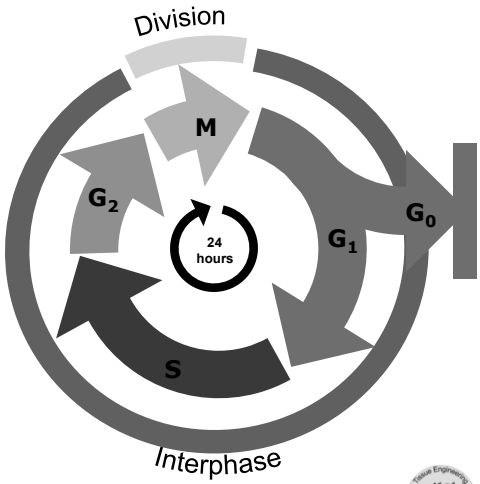
The control of cell and tissue growth is a fundamental application of genetic control

- Cell division is a regulated mechanism, known as mitosis
- Under no inhibition, the life cycle of an eucaryotic cell can be as little as 10 to 30 hours
- Cell division takes approximately 30 min, so most of the cell lifespan is spent outside mitosis in a phase termed interphase
- The lifespan of a cell can be as little as 10 hours and as long as the lifetime of the organism

Genetic Control of Cell Reproduction

Cell Division

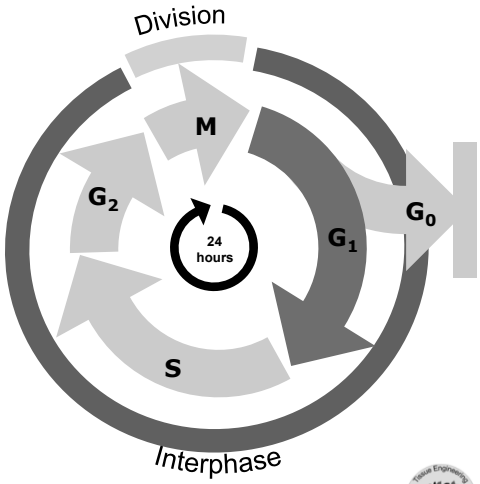
- Occurs in an orderly manner, following a series of logical steps
- G_1: Gap Phase
- G_0: Gap Phase
- S: DNA Synthesis Phase
- G_2: Gap Phase
- M: Mitosis Phase



Genetic Control of Cell Reproduction

G_1: Gap Phase

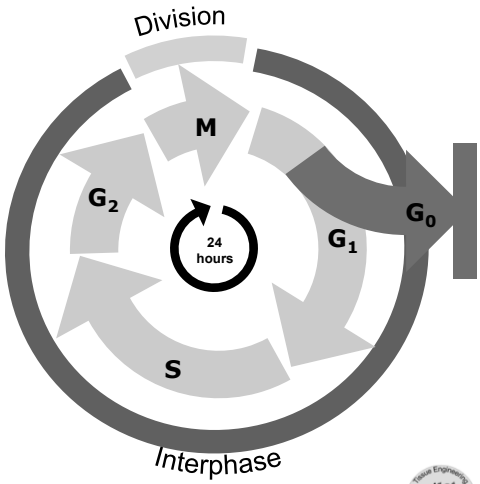
- Gap between the completion of mitosis and the beginning of DNA synthesis
- Provides time for cytoplasmic cell growth
- Cell monitors its environment and its own size
- Then takes a decisive step that commits it to DNA replication and cell division
- The greatest variation in time for completion of the cell cycle between cell types occurs in the G_1 phase



Genetic Control of Cell Reproduction

G_0: Gap Phase

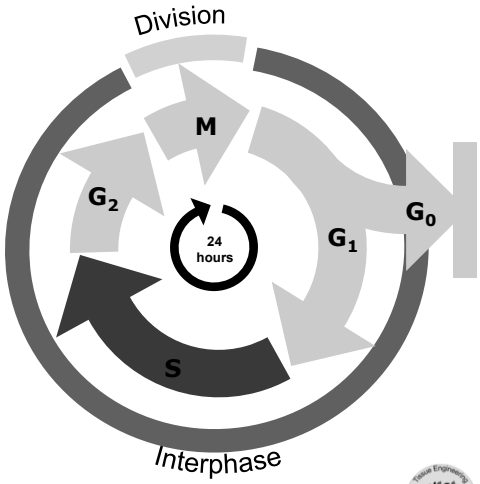
- Pause in cell cycle
- Cells can remain in G_0 for days, weeks, or years
- Most mammalian cells are reluctant to proliferate indefinitely
  - Approximately 50 division limit
- Cells which have reached their limit of divisions enter into G_0 and are never released
- Populations have defined endings, but individuals do not
  - Protect against mutations
  - Protect against unconstrained growth (cancer)



Genetic Control of Cell Reproduction

S: DNA Synthesis Phase

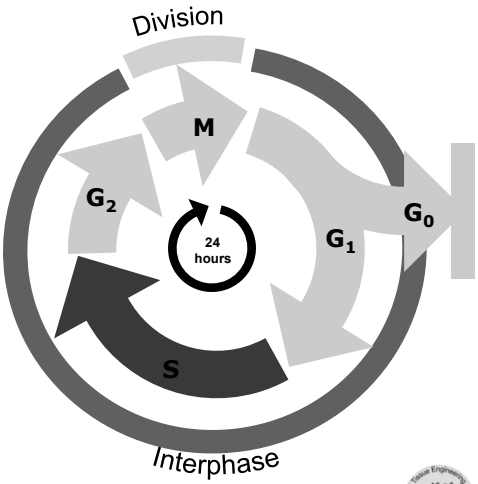
- Replication of the nuclear DNA
- About 30% of cells in culture will be in S phase at any given time
- Since DNA doubles in S phase, it can be assayed to identify the state of an individual cell



Genetic Control of Cell Reproduction

S: DNA Synthesis Phase

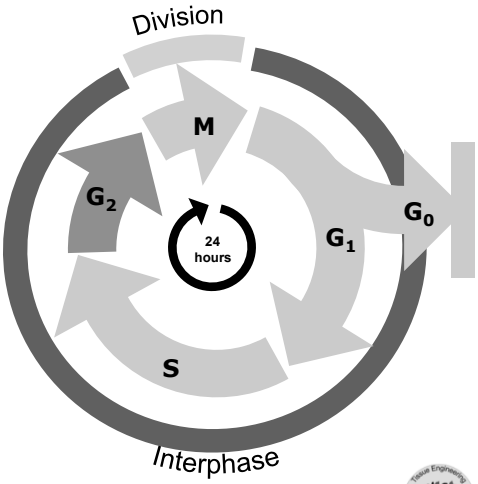
- Replication of the nuclear DNA
  - Both DNA strands are replicated, and replication occurs from end to end
  - DNA polymerase attaches to and moves along the strand while DNA ligase bonds successive nucleotides to one another
  - Each new formed strand H-bonds to its template, forming two new helixes
  - Newly formed helixes are cut and then respliced so that they may be separated
- Proofreading
  - DNA polymerase and ligase splice in new sequences where genetic mutations have arisen



Genetic Control of Cell Reproduction

G_2: Gap Phase

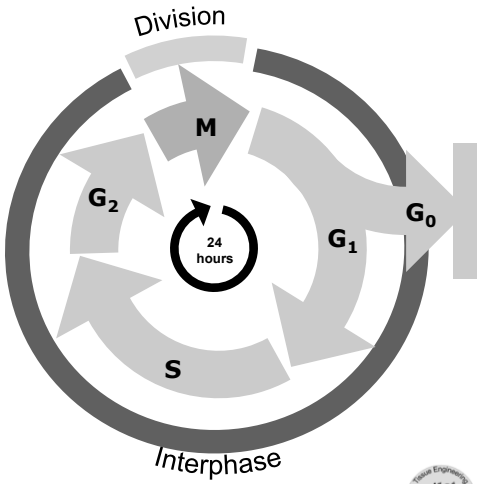
- Gap between the completion of DNA synthesis and the beginning of cell division
- Provides time for cytoplasmic cell growth
- Allows time for the cell to ensure that DNA replication is complete
- Ceases with chromosome condensation



Genetic Control of Cell Reproduction

M: Mitosis Phase

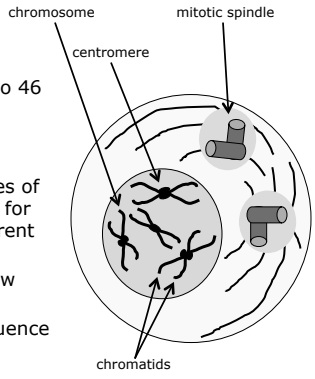
- Two parts of the M Phase
  - Mitosis, or nuclear division
    - Prophase
    - Prometaphase
    - Metaphase
    - Anaphase
    - Telophase
  - Cytokinesis, or cell fission



Genetic Control of Cell Reproduction

Prophase

- Initiation is not a sharply defined event
- DNA condenses into chromosomes
  - Humans have $6x10^9$ nucleotide pairs organized into 46 chromosomes, 2 of which are sex chromosomes
  - The 46 chromosome molecules vary in size from $50x10^6$ to $250x10^6$ nucleotide pairs
  - Humans, and all diploid organisms, have two copies of each chromosome (maternal and paternal) except for the sex chromosomes, thus humans have 24 different chromosomes (22 x 2 + 2 = 46)
- Each chromosome is duplicated in the S phase, and now consists of two chromatids
- Two sister chromatids are held together by a DNA sequence known as a centromere
- Mitotic spindle forms
  - Composed of microtubules and proteins
  - Formation occurs outside nucleus, between separating centrosomes (microtubule organizing location)

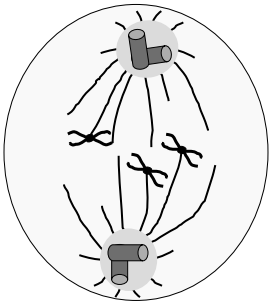


prophase

Genetic Control of Cell Reproduction

Prometaphase

- Initiation is a sharply defined event: nuclear membrane disruption
  - Membranes remnants form nuclear envelope vesicles
- Microtubules enter the nuclear region
- Kinetochore microtubules attach to the centromere on individual chromosomes
- Polar microtubules align between the spindle poles
- Astral microtubules are outside the spindle poles

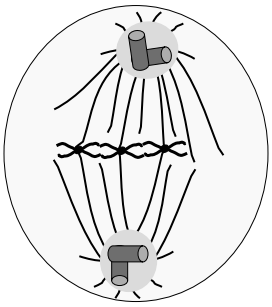


prometaphase

Genetic Control of Cell Reproduction

Metaphase

- Initiation is not a sharply defined event
- Kinetochore microtubules align the chromosomes in one plane halfway between the spindle poles
- Each chromosome is held in tension at the metaphase plate by paired kinetochores and their associated microtubules, which are attached to opposite poles of the spindle

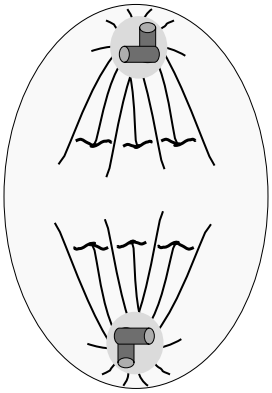


metaphase

Genetic Control of Cell Reproduction

Anaphase

- Initiation is a sharply defined event: separation of the chromosome complex into two chromatids
- Each chromatid moves toward it spindle pole (1μm / min)
- During the first portion of anaphase (anaphase A), kinetochore molecules shorten as chromatids approach spindle poles
- During the second portion of anaphase (anaphase B), polar microtubules lengthen to move the poles apart
- Anaphase lasts only a few minutes



anaphase

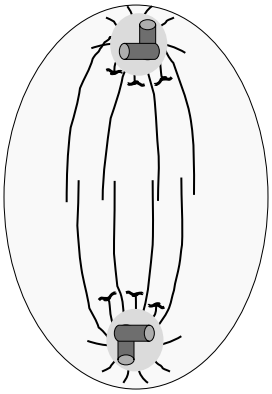
Genetic Control of Cell Reproduction

Telophase

- Initiation is a sharply defined event: separated chromosomes arrive at the spindle poles
- Polar microtubules continue to elongate
- Nuclear envelope begins to reform around each daughter chromosome

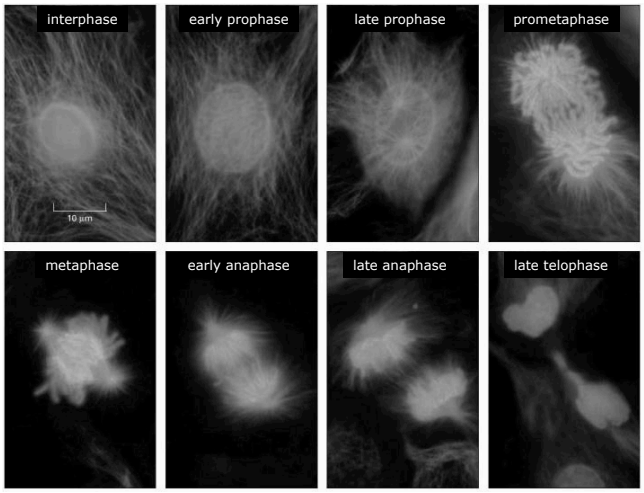
Cytokinesis

- Plasma membrane constriction
- Cleavage furrow formation
- Plasma membrane breakage
- Formation of two individual cells



telophase

Genetic Control of Cell Reproduction

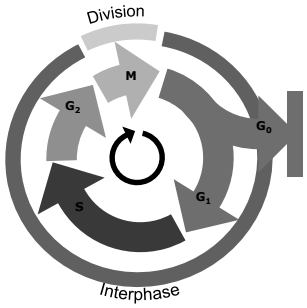


Alberts et al. Molecular Biology of the Cell

Genetic Control of Cell Reproduction

Duration

- The duration of the cell cycle can vary greatly
  - Fly embryos: 8 min
  - Mammalian embryos: 12 hr
  - Typical mammalian cell: 24 hr
  - Mammalian liver cell: 1 yr
- Embryonic cell division can occur so rapidly because the resting phases that typically allow for cytoplasmic cell growth are minimized, since division occurs without cell growth (hypertrophy)



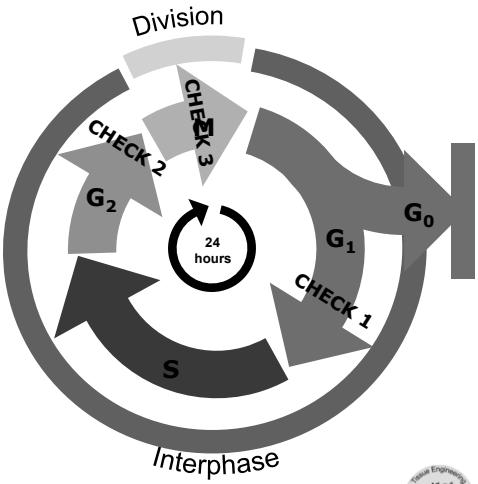
typical cell cycle

embryonic cell cycle

Genetic Control of Cell Reproduction

Control of the Cell Cycle

- The cell cycle is not a series of consecutive events that progress due to a set timeline
- The cell cycle is a series of consecutive events that assay cell status and then allow progression
- Check 1
  - Cell big enough?
  - Environment okay?
- Check 2
  - DNA replicated?
- Check 3
  - Chromosomes aligned?

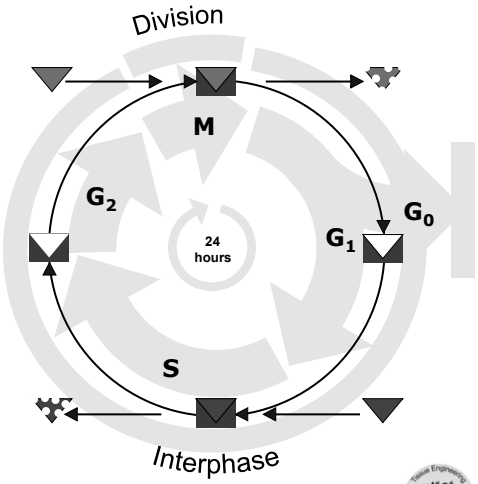


The Cell Cycle

Control of the Cell Cycle

- The cell cycle is controlled, in large part, by kinase proteins

- Cyclin dependent protein kinases (Cdk) induce downstream processes by phosphorylating selected proteins on serines and threonines
- Cyclins bind Cdk and control their ability to phosphorylate
  - Cyclins name refers to their ability to undergo a cycle of synthesis and degradation in each cell cycle
  - Mitotic cyclins bind Cdk during G2 and regulate entry into M phase
  - G1 cyclins bind Cdk during G1 and regulate entry into S phase



Genetic Control of Cell Reproduction

Cell Death

- Apoptosis
  - Programmed cell death
  - Synthesis and release of proteolytic enzymes that induce cell condensation, cytoskeletal disassembly, and cell surface changes that allow macrophage phagocytosis
  - Initiated by caspases
- Neucrosis
  - Cell death due to injury
  - Cells swell and burst, spilling their contents into the environment and thus causing local inflammation and injury