Contents

1 Animals and Environments

Introduction

- What is physiology?
  - Form and function of organisms; the study of how organisms work.
- Central questions of physiology: mechanism and origin.
  - Mechanism:
    - Refers to the components of living organisms and understanding how components interact to enable the organism to function.
  - Origin:
    - Asks why a mechanism exists, or what is the mechanistic adaptive significance of the mechanism.
  - Mechanism and adaptive significance are distinct concepts; knowing about one doesn't necessarily mean you know anything about the other.
- Krogh's principle:

  > "For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied."

  - This idea is central to disciplines that rely on the *comparative method*.
  - Other key concepts:
    - There is unity in diversity; many organisms are very much alike at the most fundamental levels.
    - The differences are subject to particular niches and often highly specialized that allow for biologist to study more complex systems.
    - The similarities allow us overcome technical limitations via animals that are easier to study.
- Physiology subdisciplines:
  - Mechanistic: emphasizes the mechanisms by which organisms perform their life functions.
  - Evolutionary: emphasizes evolutionary origins and the adaptive significance of traits.
  - Comparative: emphasizes the way in which diverse phylogenetic groups resemble and differ from each other.
  - Environmental: emphasizes the ways in which physiology and ecology interact.

- Integrative: emphasizes the importance of all levels of organization, from genes to proteins and tissues to organs in order to better understand whole physiological systems.

Homeostasis

- Important ideas to remember:
  - Organisms are structurally dynamic; form stays relatively static while individual cells recycle frequently.
  - Most cells are exposed to the internal environment, not external.
  - Internal cells may vary or kept constant with the environment.
- Temperature regulation:
  - **Conformity**: organism's internal temperature correlates with external temperature in a particular range of temperatures.
  - **Regulation**: internal environment is held mostly constant using celluar mechanisms.
- **Homeostasis**: the coordinated physiological processes that maintain a relatively constant state in the organism.
  - Positive feedback: less common in homeostasis due difficulty in regulation; leads to runaway effect easily.
  - Negative feedback: more common in homeostasis due to self correcting nature.
  - **Effector**: executes the change in action that produces an effect, e.g. signals to increase temperature.
  - **Sensor**: sense changes in environment and sends information to the effector.

Physiology and Time

- Timeframes of physiological change:
  - **Acute**: short-term, reversible, and quick to adapt to changes in environment. Usually minutes to hours.
  - **Chronic**: long-term after prolonged exposure to new environments. Changes are usually reversible, but often slower.
    - Chronic can be termed acclimation, or phenotypic plasticity/flexibility.
    - Repetitive acute responses usually lead to chronic responses.

  - **Evolutionary**: changes due to alteration in gene frequencies in populations exposed to new environments.

- Acclimation is not the same as adaption.
  - *Adaption* is an evolutionary trait present at high frequency in a population due to survival/reproductive advantages.
  - Not all traits are adaptations.
  - The amount of natural variation in a trait must be considered across populations, species etc.

2 Molecules and Cells in Animal Physiology

Cell Membrane Review

- Major cell memberane structures:
  - **Glycoproteins**: carbohydrate chain attached to a protein.
  - **Glycolipids**: similar to glycoproteins, but attached to lipid molecules of CO_2 as the pyruvate molecules are processed..
  - *Glycocalyx*: combination of glycoproteins and glycolipids on the surface of cell.
  - **Integral proteins**: embedded in phospholipid bilayer.
  - **Peripheral proteins**: associated with one side of the bilayer.
- **Unsaturated phospholipid**: whey hydrocarbon tails contain double bonds (less hydrogen).
  - Increase membrane fluidity due to extra space created.
- The fluidity of the cell membrane allows proteins to from complexes and dynamically change shape.

Enzyme Fundamentals

- **Enzymes**: a protein catalyst that plays two primary roles: accelerating and regulating chemical reactions.
- *Substrates*: the initial reactants of the reaction that an enzyme catalyzes.
- **Enzyme-substrate-complex (E-S)**: a combination of enzyme (E) with a molecule of substrate (S) that starts a reaction.
  - Usually stabalized by non-covalent bonds.
  - The substrate is converted to a product by first becomeing an *enzyme-product complex (E-P)*, then dissociates to yield free product and free enzyme.
  - $E + S \rightleftharpoons \text{E-S} \rightleftharpoons \text{E-P} \rightleftharpoons E + P$
- **Saturation kinetics**:
  - **V$_{max}$**: the maximum velocity of a reaction and is determined by:
    - The number of active enzyme molecules of CO_2 as the pyruvate molecules are processed. present relative to substrate.
    - The catalytic effectiveness of each enzyme molecule.
    - These properties usually undergo heavy selection pressure.

- *Saturated*: all enzymes are occupied by a substrate molecule nearly all the time and now unable to increase reaction velocity.
- **Hyperbolic**: asymptotically approaches V_{max}
  - Tends to happen when enzymes have just one substrate binding site.
  - Or when substrate sites behave independently
- **Sigmodal**: approaches V_{max} with a sigmodal trajectory.
  - When multiple sites influence each other.
- **Turnover number (k_{cat})**: the total effectiveness, expressed as the number of substrate molecules coverted to product per second by each enzyme molecule when saturated.
  - Depends partly on the *activation energy* of the enzyme-catalyzed reaction.
  - **Activation energy**: the energy required for the substrate to enter the *transition state*.
  - **Transition state**: the intermediate chemical state between substrate and product.
  - Enzymes lower the activation energy required to enter transition state.

▷ **Enzyme-substrate affinity**: The proclivity of the enzyme to form a complex with the substrate when they meet.

- Likely complex formation results in high-affinity.
- Unlikely complex formation results in low-affinity.
- Affinity affects the shape of the reaction velocity.
  - Higher affinity produces a steeper velocity, and a lower affinity produces a more linear result.
  - Enzyme concentration is not changed.
- **Half-saturation constant, K_m**: the substrate concentration required to attain one-half maximum reaction velocity.
  - K_m and enzyme-substrate affinity are inversely related.
  - i.e. low-affinity enzyme has a greater K_m.

▷ **Molecular Flexibility**:

- **Conformation**: the three-dimensional shape of a protein.
  - Stabalized mostly by weak, noncovalent bonds—hydrogen, van der Waals, hydrophobic, electrostatic, etc.

    - Weak interactions allow for easy yet stable conformational changes.
  - Enzyme molecules composed of two, three or our proteins are called *dimeric*, *trimeric*, or *tetrameric* respectively.
- Enzymes catalyze reversible reactions in both directions.
  - This is because they accelrate the approach towards equilibrium (principles of mass action).
- **Ligand**: any molecule that selectively binds by noncovalent bonds to structurally and complementary sites on a specific protein.
- **Cooperativity**: the interactions between multiple binding sites that may facilitate or inhibit the binding of other sites.
  - Can either positive or negative; facilitating or inhibiting binding on the same molecule.
  - *Homotropic cooperativity*: facilitation or inhibition of the same ligand.
  - *Heterotropic cooperativity*: influences on the binding of other ligands.
  - Interactions occur at a distance, resulting in delayed, or rippling responses.
  - **Allosteric modulation**: the modulation of the catalytic properties.
    - **Allosteric sites**: nonsubstrate-binding regulatory sites for nonsubstrate ligands that modulate the catalytic properties.
    - *Allosteric modulators*: the nonsubstrate ligands.
    - Allosteric **activation**:increases and **inhibition**:impairs affinity, thus the catalytic activity.
- **Isozymes**: enzymes that catalyze the same chemical reaction but differ in amino acid sequence.
- **Interspecific enzyme homologs**: different molecular forms of an enzyme coded by homologous gen loci in different species.
  - Isozymes and interspecific enzyme homologs often differ in their catalytic and regulatory properties.
  - Functional differences often prove to be adaptive in different environments.

3 Genomics

Genomics

- **Genomics**: study of the genomes—the full set of genetic material—of organisms.
- Metods of genomics:
  - Computational biology and bioinformatics use various computational methods to process large amount of genomic data.
  - **High-throughput**: methods of analyzing large data with out much human attention and mostly computation.
  - **Annotation**: laborious direct human interpretation.
- The overarching goals of genomics is to elucidate the evolution and the current functioning of genes and genomes.
- **Gene families**: genes that share distinctive DNA base sequences and *tend* to code for functionally similar proteins.
- **Postgenomic era**: the study of species after genome is sequenced.

Transcriptomics

- **Transcriptomics**: the study of which genes are transcribed to make mRNA and the rates at which they are transcribed.
  - aka transcription profiling.
  - Implies the study of great numbers of mRNAs.
- **Transcriptome**: a species full set set of mRNA molecules. It represents the full complement of genes being transcribed at any given time.
  - Time is emphasized; it's a snapshot transcription activity during the observed period.
  - Very useful in comparative methods.
- Methods of transcriptomics:
  - **DNA microarrays**: aka gene chips; a high throughput method tht allows simultaneous analysis of large number of mRNAs.
  - **mRNA sequencing**: aka RNA-Seq; similar to microarrays, but can identify both known and novel transcripts.
    - More sensitive than microarrays.
    - Readily applicable across wide range of species.

- **Gene manipulation**: studies that permit the direct assessment of gene function by directly altering its expression.
  - **Gene deletion**: aka gene knockout; breaking or disurbing function of an animal's gene to interfere with proteins, creating deficient or inferior phenotypic traits.
    - **Forced overexpression**: inverse of gene deletion; experimentally increasing synthesis of the mRNA.
    - **Compensation**: phenotypic alterations of that tend to make up for the manipulation done by forced expression or gene deletion.
  - **RNA interference (RNAi)**: allows specific mRNA targets to be silenced in animals with *normal* genomes.
    - **Normal genomes**: wild type that is not artificially manipulated.
    - RNAi is reversible.
  - **CRISPR/Cas**: used to edit nuclear DNA in eukaryotic cells.
    - Can be used to insert sequences that then can be transcribed and tranlasted, providing insights on protein function.

Proteomics

- **Proteomics**: the study of proteins being synthesized by cells and tissues.
  - Implies simultaneous study of large numbers of proteins.
  - Predicting proteins from gene transcription is still very difficult; transcription, translation, and post-translational processing are all regulated dynamically and independently.
- **Two-dimensional gel electrophoresis**: the primary proteomics method that separates complex mixtures of samples using two different protein properties.
  - Separated by isoelectric points and then molecular weights.

Metabolomics

- **Metabolomics**: study of organic compounds in the cells and tissues other than macromolecules coded by the genome.
    - **Metabolites**: compounds currently being processed by metabolism and the majority of metabolomics focus of study.
        - e.g. sugars, amino acids, and fatty acids.
- **Nuclear magnetic resonance (NMR)**: primary method of metabolomics that is capable of detecting and quantifying a large variety of compounds through identification of unique signatures in the NMR spectrum.

4 Physiological Development

Epigenetics

- **Epigenetics**: modifications in gene expression with no change in DNA sequence that are transmitted when genes replicate.
- **Marked**: aka tagged; when DNA is modified in way to alter expression.

Mechanisms of Epigenetic Marking

- **DNA methylation**: addition of methyl groups to cytosine residues in DNA.
  - Generally represses of silences the gene.
  - **DNA methyltransferase 1 (DNMT1)**: an enzyme acts to perpetuate the pattern of methylation in daughter cells.
  - **Methylome**: the set of all methylated sites.
- **Histone modification**: modified histones that that can make DNA more or less accessbile for transcription.
  - Can be modified by methylation, acetylation, phosphorylation, or other covalent bonding of chemical groups at specific sites.
  - Also has mechanisms for perpetuation, e.g. small RNA molecules play a role.

- **Epigenome**: the global summary of marks or a set of epigenetic marks in a cell.

Epigenetic Inheritance

- **Mitotic inheritance**: aka somatic; perpetuation of marks during the process of cell division by mitosis within an individual.
- **Meiotic inheritance**: aka transgenerational; perpetuation of marks during meiosis that results in passing of marks to offspring.

- Research is continuing to provide strong evidence that epigenetics can radically alter physiology.
- Epigenetic marking may also play large roles in lifelong effects due early-life and prenatal environments.

5 Transport of Solutes and Water

Passive Transport

- **Equilibrium**: the state at which a of minimum capacity to do work under locally prevailing conditions.
  - A change toward equilibrium is always in the direction of decreasing work potential.

Concentration gradients

- General definition: the difference in concentration between two solutions or regions.
- More accurately: $\frac{C_1 - C_2}{X}$ where X is the distance separating (boundary layer) the regions of concentration of solute particles, making it a colligative property.
- **Fick diffusion equation**: $J = D\frac{C_1 - C_2}{X}$
  - J is the net number of solute molecules passing into the low-concentration region from the high-concentration of solute particles, making it a colligative property.
  - **Diffusion coefficient (D)**: proportionality factor determined by the permeability of the membrane or epithelium as well as the temperature.
- Each solute diffuses according to its own concentration of solute particles.
- **Simple diffusion**: aka diffusion; moves solute from an area of high solute concentration to an area of low solution concentration.
  - Does not use energy as it can only move material in the direction of the concentration gradient and towards equilibrium.

Electrical gradients

- **Electrical gradient**: difference in charge across a membrane.
- Many solutes bear electrical charge that affects the diffusion of such solutes.
- **Bulk solution**: solution not in contact with with a membrane.
  - Has a net charge of zero, this regions do not differe in charge.
  - Lack of net charge does not affect diffusion in the bulk solution, though does affect diffusion across the cell membranes of epithelia.
  - *Bulk flow*: physical kinetic movement of fluid, typically due to pressure.
- **Electrochemical gradient**: gradient consisting of the chemical gradient (concentration gradient) and the electrical gradient.

Biological Aspects of Diffusion

- **Ion channels**: integral membrane protein that permits the passive transport of inorganic ions by diffusion through the membrane.
  - Some can be selective for certain ions, such as Na^+, Cl^-, and K^+
  - Even the least selective discriminate between anions and cations
  - **Gated channels**: ion channels that can open and close due to the proteins allowing for conformational changes.
    - **Voltage-gated**: responds to voltage change.
    - **Stretch-gated**: aka tension gated: responds to physical tensions.
    - **Phosphorylation-gated**: responds due to changes in protein phosphorylation.
    - **Ligan-gated**: responds due to extracelluar signaling.
- **Permeability**: the ease at which the solute can move through the membrane by diffusion.
  - Changed by use and quantity of ion channels
- **Faciliated diffusion**: the process of spontaneous passive transport of molecules of ions across a biological membrane via transmembrane integral proteins.
  - Always occurs in the direction of electrochemical equilibrium.
  - Solutes are transported faster than they are in simple diffusion.
  - Solutes must bind reversibly with biding sites on transporter proteins.
  - Temperature dependence is substantially different due to presence of an activated binding event.

Active Transport

- **Active Transport**: the movement of molecules across a cell membrane that is against the concentration gradient.
- **Primary active transport**: uses protein pumps that normally use ATP.
  - Often transports metal ions such as Na^+, K^+, Mg^{2+}, and Ca^{2+}
  - Most enzymes used are transmembrane ATPases, such as the sodium-potassium pump, which moves three Na^+ ions out of the cell for every two K^+ moved into the cell.
- **Secondary active transport**: uses potential energy derived through movement of ions (using transporter proteins and ATP) across the electrochemical gradient.

- **Antiporter**: one substrate is transported across the membrane while the other is contransported in the opposite direction.
- **Symporter**: two substrates are transported in the same direction across the membrane.
- Na^+, K^+, or H^+ ions are usually the ones moving down the gradient and used to transport the desired ion up the relative gradient.

Diversity and Modulation of Channels and Transporters

- **Multiple molecular forms**: many forms of a channel and transporter proteins are common.
  - Different species have evolved differnet molecular forms, which can modulate function and efficiency.
  - Allows for opportunities for adaptation.
- **Modulation by gene expression**: common channels and transporters can be modulated throughout a lifetime via gene expression responses to environmental circumstances.
- **Noncovalent and covalent modulation**: both ligand (often noncovalent) binding and phosphorylation (covalent) allow for rapid regulation of channels and transporters.
- **Insertion-and-retrieval modulation**: the location of proteins in the membrane allow for another way of regulating activity.
  - Some proteins are held in reserve, and inserted into the membrane when necessary.
  - Inverse is also true, some proteins can be retrieved from the membrane in order to modulate usage.
  - Often only takes minutes for modulation to occur.

Colligative Properties of Aqueous Solutions

- **Colligative properties**: the properties of solutions that depend on the ratio between solute particles and solevent molecules.
  - Not dependent on the nature of the chemical species present.
  - Effects include: relative lowering of vapour pressure, elevation of boiling point, depression of freezing point, and *osmotic pressure*.
- **Vapour pressure**: the pressure of the vapour which is in equilibrium with that liquid.

  - Vapour pressure of a solvent is lowered when a non-volatile solute is dissolved in it to form a solution.
- **Boiling and freezing points**: additions of solute help stabilize the solvent in the liquid phase, lowering chemical potential, and thus a lower tendency to move to gas phase or solid.
  - **Freezing point depression**: lowering of freezing point of a solvent with the addition of a solute that is insoluble in the solid solvent.
  - **Boiling point elevation**: increased by the by the addition of a non-volatile solute.
  - Both are proportional to the lowering of vapour pressure in a dilute solution.

Osmosis

- **Osmosis**: the spontaneous net movement of solvent molecules through a selectively permeable membrane into a region of higher solute concentration.
  - Can be made to do work.
  - The primary means by which water is transported into and out of cells.
  - **Turgor**: the force and which the cell pushes the plasma membrane against the cell wall.
  - Turgor is largely mantained by osmosis across the cell membrane between the interior and its relatively hypotonic environment.
- **Osmotic pressure**: the external pressure required to be applied so that there is no net movement of a solvent across the membrane.
  - The semipermeable membrane allows the passage of solvent molecules but not the solute particles.
  - Also defined as the measure of tendency of a solution to take in pure solvent by osmosis. "Water wants to go where solutes are"
  - **Osmotic gradient**: the difference in pressure between the solution and the pure liquid solvent when the two are in equilibrium across a semipermeable membrane.
    - Formula: $K\frac{\Pi_1 - \Pi_2}{X}$
    - i.e., the rate at which water crosses the membrane by osmosis.
    - Similar to the Fick equation for concentration gradient, except $\Pi_{1\&2}$ are the osmotic pressures of the solutions on each side of the membrane, and K is the osmotic permeability of the membrane + temperature.

  - Proportional to the concentration of solute particles, making it a colligative property.
  - **Isosmotic**: when two solutions have the same osmotic pressure.
  - When solution $A < B$ in terms of osmotic pressure then:
    - A is **hyposmotic** to B — A has less solutes than B
    - B is **hyperosmotic** to A — B has more solutes than A.
    - The direction of net water movement by osmosis is from hyposmotic solution into the hyperosmotic one, i.e., $A \rightarrow B$
- ▷ Water is still capable of diffusing directly thorugh lipid membranes.
- ▷ **Aquaporins**: water-channel proteins that greatly increase water transport.
  - Water transport through aquaporins is strictly passive.
- ▷ Nonpermeating solutes often create persistent osmotic-gradient componenets across semipermable membranes.
  - Plays a important role in blood, as blood pressure forces water out, but proteins create persistent tendency to take up water; termed colloid osmotic pressure of the blood.
- ▷ Passive solute transport and osmosis interact.
  - **Solvent drag**: when solute moves with water crossing the membrane.
  - Tends to alter electrochemical gradients which plays a continuous role in rates of passive transport of both water and solutes.
- ▷ Active solute transport provides a mean to control passive water transport.
  - Water transport is strictly passive, though control of solutes indirectly allows for metabolic water transport.

Osmoregulation

Excerpt from Chapter 27: Water and Salt in Physiology ↦

- ▷ **Osmoregulation**: the active regulation of the osmotic pressure of an organism's body fluids.
  - Detected by osmoreceptors, primarily found in the hypothalamus.
  - Acts to maintain homeostasis of the water content and electrolyte concentration.
- ▷ **Osmoconformers**: match their body osmolarity to their environment actively or passively.
  - Most marine invertebrates are osmoconformers.

- **Osmoregulators**: tightly regulate their body osmolarity through internal conditions.
  - More common in animals.
- **Volume conformity**: passive changes in body-fluid volume.
- **Volume regulation**: regulation of the total amount of water in a body fluid.
- There is also ionic regulation and conformity that are subject to ion-specific physiological controls.
- Influx of H_2O will tend to lower osmotic pressure, dilute ions, and increase volume.

7 Nutrition, Feeding, and Digestion

Fundamentals of Animal Energetics

- **Energy metabolism**: the sum of the processes by which animals acquire energy, channel energy into useful functions, and dissipate energy.
  - Catabolic processes: breaking down of organic molecules to release energy.
  - Anabolic processes: use of energy to construct molecules.
- **Second law of thermodynamics**: the total entropy of an isolated system can never decreases over time.
  - **Isolate systems**: part of the material universe that does not exchange matter or energy with its surroundings.
  - Energy can be thought of both the capacity to do work, of the capacity to increase order.
  - **Thermodynamic equilibrium**: the state of maximum entropy; the state isolated systems spontaneously evolve towards.
- Animals require energy from teh outside because energy is necessary to create and maintain their essential internal organization.

Forms of Energy

- **Chemical Energy**: energy liberated or required when atoms are rearranged into new configurations.
- **Electrical Energy**: energy that a system posseses by virtue of separation of electrical charges.
- **Mechanical Energy**: energy of organized motion in which many molecules move simultaneously in teh same direction.
- **Molecular kinetic energy (heat)**: energy of random atomic-molecular motion.

- **Physiological work**: any process carred out by an animal that increases order.
  - All forms of energy are capable of doing work, though not equally capable of doing physiological work.
  - Chemical energy can be used by animals, directly or indirectly, to do all forms of physiological work (totipotent).
  - Electrical and mechanical energy are both heavily used in animasl, though cannot be used for everything.
    - E.g., electrical energy used to set ions in motion and mechanical energy to pump blood, but neither can synthesis proteins.
  - Animals cannot use heat to do any form of physiological work.
- **High-grade energy**: energy that can do physiological work; chemical, electrical, and mechanical.
- **Low-grade energy**: heat, which cannot do physiological work.
- **Degrade**: when the use energy to perform a function and dowgrade it to form heat.
- Transformations of high-grade energy are always innefficient.
  - **Efficiency of energy transformation**: a ratio between output and input of high-grade energy.
    - Typically much less than a 1:1 ration.
    - ATP at most uses about 70% of the energy released from glucose into bonds of ATP.
    - Only a maximum of 25%-30% of energy is liberated and used for muscular motion.
- **Ingested chemical energy**: energy in the chemical bonds of food that animals use to do physiological work.
  - **Fecal chemical energy**: chemical-bond energy in compounds that are unable to be digested or absorbed.

- **Absorbed energy**: portions of chemical-bonds that are able to assimilated and used

Major Functions of Physiological Work

- **Biosynthesis**: the process that synthesizes body constituents, such as proteins and lipids, by the use of absorbed energy.
  - Some absorbed energy remains in chemical form since productsare often organic molecules themselves.
  - During growth, chemical energy accumulates in the form of biosynthesized products.
  - Also produces organic compounds that are exported from the body during ht animals life.
  - All steps are inefficient, thus Biosynthesis produces heat and products.
- **Maintenace**: all the processes that maintain the integrity of the animal's system.
  - e.g., circulation, respiration, nervous coordination, gut motility, and tissue repair.
  - Energy used for Maintenace is degraded entirely to heart within the body is majority of cases.
  - **Internal work**: mechanical work that takes place inside an animals's body.
    - Many forms of maintenace, such as blood circulation and gut motility, are types of internal work.
- **External work**: application of mechanical forces on objects outside of an animal's body.
  - Much of absorbed chemical energy is used to fuel external work.
  - Some energy leaves the body as mechanical energy transmitted to the environment.
  - Energy of external work is stored if it is converted into increased potential energy of position.

Metabolic Rate

- **Metabolic rate**: the rate at which an animal consumes energy.
  - Heat is always to dominant component of the metabolic rate.
  - Knowing average metabolic rates of animals allows for calculations of chemical energy usage.
- calorie (cal): the amount of heat need to raise the temperature of 1g of water by 1 °C.
  - kilocalorie (kcal): 1000 cal, often written as Calorie.
  - One calorie is equivalent to 4.186 J (joule).
  - Watts: joules/second.
  - Metabolic rates are often expressed as calories per unit of time or watts.

Principal Significance of Metabolic Rates

- The metabolic rate ie one of most important determinants of how much food it needs.
  - Adults food need depend almost entirely on metabolic rates.
- The total rate of heat production provides a quantitative measure of the total activity of all its physiological mechanisms.
  - Metabolic rate typically correlates with the intensity of living.
- Ecologically the metabolic rate measures the drain the animal places on the physiologically useful supplies of the ecosystem.

Calorimetry

- **Direct calorimeter**: a device that measures the rate at which heat leaves the animals body.
  - Not all work energy is converted to heat; some energy coneverted to mechanical or potential energy can be measure inaccurately.
- **Inderect calorimetry**: measures of an animals metabolic rate by means other than quantifying heat and work.
  - Indirect methods are often cheaper and easier.
- **Respirometry**: metabolic rate measured indirectly measured through respiratory gas exchange with the environment.
  - Rate of oxygen consumption provides a convenient and readily measured estimate of metabolic rate.
    - $C_6H_{12}O_6 + 6\,02 \longrightarrow 6\,CO_2 + 6\,H_2O +\ 2820\,kJ/mol$

- Glucose + Oxygen $\rightarrow$ Carbon Dioxide + Water + Energy

- Oxidization of an unknown quantity of glucose, but with known measurements of O_2 used or CO_2 produced, then you can calculate exact heat produced.
- Different food sources require different amount of O_2 and produce different amounts of CO_2 during catabolism, which causes issues with identifying correct conversion factor
- **Respiratory quotient (RQ)**: the metabolic signature that reveals particular food sources being oxidized.
  - $\frac{\text{moles of } CO_2 \text{ produced per unit of time}}{\text{moles of } O_2 \text{ consumed per unit of time}}$
  - RQ $\approx$ 0.7 = lipids.
  - RQ $\approx$ 0.83 = proteins.
  - RQ $\approx$ 1 = carbohydrate.
- The most common approach used today is measuring rate of O_2 and accepting relatively small potential errors ($\pm$5%-8%).
  - External work does not have to be measured in most cases.
  - Excludes anaerobic metabolism of the gut microbiome.
  - Does not work well for measurement of metabolic rate during anerobically fueled exercise.

- **Material Balance**: the measurement of the chemical-energy content of organic materials entering and leaving the animal's body.
  - Assumes that any energy that an animal ingests as chemical energy, but does not void as chemical energy, must be consumed.
  - If animal is currently gaining or losing biomass, then calculations will be off.
  - Animals can lose chemical energy in other ways that food, feces, or urine.
  - Best suited for long term measurements of average metabolic rates.

Factors of Metabolic Rates

- Physical activity and temperature of the environment are often the most influential factors.
- Other factors include: ingestion of food, age, gender, time, body size, reproductive condition, hormonal states, psychological stress, and salinity of ambient water.
- **Specific dynamic action (SDA)**: the increase in the metabolic rate caused by ingestion of food.
  - Not the greatest factor, but almost always must be taken into account.
  - Under many circumstances, if an animal has not eaten for a while, then consumes food, then metabolic rates will rise despite all other factors kept constant.
  - The magnitude of SDA represents the total excess metabolic heat production induced by the meal.
    - Roughly proportional to the amount of food eaten.
    - Protein foods exhibit relatively much higher SDA than other macromolecules.
  - **Diet-induced thermogenesis (DIT)**: long-term increase in metabolic rate induced by persistent overeating.

Basal vs Standard Rates

- **Basal metabolic rate (BMR)**: a standardized measure of metabolic rate the applies to homeotherms.
  - **Thermoneutral zone**: the range of environmental temperatures which the basal metabolic rate is minimal.
  - **Fasting**: when SDA effects of meal have ended.
  - Represents an animal that is in the thermoneutral zone, fasting, and resting.
- **Standard metabolic rate (SMR)**: a standardized measure of metabolic rate that applies to poikilotherms (ectotherms).
  - Represents metabolic rate of an animal is at rest and fasting.
  - A single animal may have many SMRs due to conformity of body temperatures.
- **Routine metabolic rate**: refer to metabolic rates of animals exhibiting regular, typically minimal, movements or behaviors.

Metabolic Scaling

- **Metabolic scaling**: the relation between metabolic rate and body size.
  - Energy needs of the species are not proportional to their respective body sizes.
  - Increases as a whole, but less significantly.
- **Weight-specific metabolic rate**: metabolic rate calculated per unit of body weight.
  - Decreases as weight increases, though it's not indirectly proportional.
- **Kleiber's law**: $M = aW^b$ ($B = B_o M^{3/4}$)
  - M (B): whole-body metabolic rates, unit of power—watts typically.
  - W (M): body weight, unit of mass—kg typically.
  - a (B_o)) mass-independent-normalization constant, unit of power/unit of mass.
  - b ($^3/_4$): mean observed allometric scaling factor.
    - **Allometric equation**: when b is not equal to 1, meaning a lack of proportionality.
  - Weight specific: $M/W = aW^{b-1}$
  - Logarithmic: $\log M = \log a + b \log W$, useful for comparing a wide range of species in a linear represention.
- Resting heart rate varies in functionally similar way as weight-specific BMR.
  - Small species tend to have higher heart rate than large ones.
  - However, heart weight per unit of body weight shows little relation to body size.
- Physiologists are not in consensus for the explanation to why we see consistent observed allometric relations.
  - Runer's law is based on heat loss on animal, but it predicts a lower rate ($b = 2/3$) and does not account for poikilotherms.
  - Fractal geometry of scaled circulatory systems may give rise to more concrete answer.

8 Aerobic and Anaerobic Metabolism

Mechanisms of ATP Production

- **Burst exercise**: sudden intense exercise, generally leading to quick exhaustion.
- **Sustained exercise**: exercise that can be sustained at a steady rate for long periods of time.
- ATP is not transported form one cell to another.
  - Each cell must make it's own ATP.
  - ATP is not stored by cells to any substantial extent.
- The rate at which a cell can do muscular work depends on the rate the cell can produce ATP at the given moment.
  - ADP + P_i + energy from foodstuff molecules $\rightarrow$ ATP
  - ATP $\rightarrow$ ADP + P_i + usable energy by cell processes
  - P_i: inorganic phosphate ions, HPO_4^{2-}
  - Energy-demanding processes are dependent on the cellular mechanisms that drive this equation and can only happen as fast as such mechanisms.

Aerobic Catabolism

- **Aerobic catabolic pathways**: pathways that use O_2 to completely oxidize foodstuff molecules to CO_2 and H_2O in order to capture realeased energy into ATP bonds.
- Subdivided into four major reactions:
  - Glycolysis (in cytoplasm)
  - Krebs cycle (in mitochondrial matrix)
  - Electron transport chain (inner mitochondrial membrane)
  - Oxidative Phosphorylation (inner mitochondrial membrane)
- **Glycolysis**: the series of enzymatically catalyzed reactions in which glucose (or glycogen) is converted to pyruvic acid.
  - Occurs in the cytosol and is a oxygen-independent metabolic pathway.
  - Each molecule of glucose is converted into 2 pyruvate ($C_3H_3O_3^-$) molecules.

- **NAD**: small non-protein molecule that undergoes reversible oxidation and reduction; synthesized from niacin.
- 2 NADs are reduced into 2 $NADH_2$ per molecule of glucose catabolized.
- 2 ATPs are used and 4 are formed from each glucose processed, providing net yield of 2 APT per glucose.

◦ **Krebs (citric acid) cycle**: when pyruvic acid is oxidized in the mitochondria by cyclic series of enzymatic reactions.

- The 2 pyruvate molecules from glycolysis enter the mitochondria matrix by facilitated diffusion to start the cycle.
- Each pyruvate is oxidatively decarboxylated, forming CO_2 and a two-carbon acetyl group that is combned with coenzyme A to form acetyl coenzyme A (acetyl-CoA).
- Acetyl-CoA is the starting point for the citric acid cycle; can be obtained from oxidation of fatty acids too.
- Overall outcomes:
  - 6 carbons of each glucose molecule catabolized emerge in the form of 6 molecules of CO_2 as the pyruvate molecules are processed.
  - 8 molecules of $NADH_2$ and 2 molecules of $FADH_2$ are produced for each glucose molecule. (4/1 per pyruvate)
  - 2 molecules of ATP are produced for each glucose catabolized.
  - $C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O + 2820\,\mathrm{kJ/mol}$.

◦ O_2 is not a direct participant of glycolysis or the Krebs cycle, though it is essential.

- $NADH_2$ and $FADH_2$ are intermediate electron acceptors, but cannot serve as the final resting places for electrons due to limited quantity in cell.
- O_2 is required for the continuation of aerobic catabolism by acting as the final electron acceptor in the remaining steps, which generates the majority of ATP produced.

◦ **Electron Transport (respiratory) chain**: a series of complexes that transfer electrons via redox (reduction+oxidation) across a membrane that drives synthesis of ATP.

- The chain takes electrons from $NADH_2$ (complex I) and $FADH_2$ (complex II) and passes them through redox reactions by the use of accompanying H^+ ions, via ubiquinone/cytochrome ($b - c_1$ and c).

  - The electrons and are passed along to cytochrome oxidase, which reduces the O_2 to H_2O, acting as the final electron acceptor.
  - An adult human produces about 0.8 L of metabolic water per day in the process of voiding electrons from cells.
  - Pumps 10 H^+ for 1 oxygen (pair of electrons) reduced.
- **Oxidative phosphorylation**: the process of forming ATP from ADP vai the energy released in the transport of electrons through the electron-transport chain.
  - **Chemiosmotic hypothesis**: the indirect two-step process that pumps protons across the inner mitochondrial membrane, creating a electrochemical gradient far from equilibrium.
  - The proton motive energy (back-diffusion) is used by ATP-synthase to generate ATP from ADP.
  - **P/O ratio**: ratio between phosphate and oxygen; defined as the number of ATP formed per atom of oxygen reduced to water.
    - Current estimates in mammalian mitochondria: 1 ATP : 4.3 H^+.
    - Results in 2.3 ATP per oxygen, i.e., a P/O ratio of 2.3.
    - 2.3 represents the current maximum P/O ratio observed.
  - **Coupling**: the linkage of electron transport with oxidative phosphorylation.
    - Capable of being graded in its efficiency, ranging from 0 to 2.3.
    - Tightly coupled = P/O of 2.3
    - Uncoupled = P/O of 0.
  - **Uncoupling protein 1 (UCP1)**: can use back-diffusion protons to generate much greater degree of heat rather than ATP.
- **Net yield of ATP from aerobic catabolism**:
  - **Substrate level phosphorylation**: phosphorylations that occur in glycolysis and the Krebs cycle:
    - Altogether, 6 ATP molecule are formed.
  - Together, the electron transport chain and oxidative phosphorylation produce per molecular of glucose:
    - 2.3 ATP/$NADH_2$ and 1.4 ATP/$FADH_2$
    - With a max of 25 ATP.
  - 31 total genetrated, with 2 used at start of glycolysis.
  - Actual net yield: 29 ATP per glucose.

- **Energetic efficiency**: assuming tight coupling, is estimated to be ≈60%-70%.
  - I.e., 60%-70% of chemical energy released by oxidizing glucose to CO_2 and H_2O is captured into chemical-bond energy of ATP.

Anaerobic Catabolism

- **Redox balance**: the inability of the electron transport chain to regenerate NAD and FAD from $NADH_2$ and $FADH_2$ in the absence of O_2.
  - Describes the cell's ability to remove electrons from a given compound as fast as electrons are added to it.
  - With out a balance, the cell will not be able to generate any ATP due to substrate level phosphorylation breakdown.
- Some tissues can produced ATP at a substantial rate without O_2, however, the mammalian brain lacks such ability.
- **Anaerobic glycolysis**: the sequence of reactions that converts glucose to lactic acid.
  - **Lactate dehydrogenase (LDH)**: the enzyme that catalyzes the reduction of pyruvic acid and produces lactic acid.
    - The rate limiter of anaerobic glycolysis.
  - Lactic acid is used as the final electron acceptor.
  - Only about 7% of free energy is released by the conversion of glucose to lactic acid; yielding vastly lower amounts of ATP compared to aerobic catabolism.
  - A cell must synthesizes significant amounts of LDH for the intracelluar process that must prevail during O_2 deprivation.
- Anaerobic glycolysis is not the only mechanism of anaerobic catabolism.
- When vertebrates use anaerobic glycolysis they must deal with the lactic acid once O_2 becomes available.
  - **Gluconeogenesis**: the conversion of lactic or pyruvic acid to glucose or glycogen; represents one path of lactic acid metabolisis.
  - The second path is for the carbon chains to be fully oxidized by the way of Krebs cycle and electron-transport chain, which makes 27 (requires already functioning electron transport chain).
- Often tissues that generate lactic acid export it to tissues that are better supplied with O_2.
- **Phosphagens**: Compounds that serve as temporary stores of high-energy phosphate bonds.

- Occurs in skeletal muscles of vertebrates and muscles of many invertebrates.
- Creatine phosphate if the phosphagen of vertebrate muscle, and some invertebrates.
- Arginine phosphate is most common for invertebrates.
- Synthesized by use of ATP to store energy, allowing for donate bonds back to ADP later.

Comparative Properties of the Mechanisms of ATP Production

▷ Four main mechanisms: aerobic catabolism by use of external O_2, anaerobic glycolysis, anaerobic ATP production by phosphagens, and aerobic catabolism by use of internal O_2.

- Each have their advantages and disadvantages in various circumstances, allowing for comparative analysis.

Mode of Operation

- **Steady state**: a state at which a reaction can go on indefinitely, free of intrinsic limitations. In terms of ATP production:
  - Can produce ATP as fast as it is used.
  - Uses raw materials (foodstuff molecules) no faster than they are replenished.
  - Chemical by-products (not ATP) are voided or destroyed as fast as they are made.
  - Does not cause other changes in cell function that progress to the point of disruption.
  - Nonsteady-state mechanisms violate one or more of the above, resulting in short lived processes.
    - Anaerobic glycolysis, phosphagen use, and aerobic catabolism using prexisting O_2 are examples of nonsteady-state mechanisms.
  - Aerobic catabolism using O_2 from environment is a steady state mechanism, but it does use nonsteady-state mechanisms as intermediate parts of the reaction.

ATP Yield, Accelration, Rate, and Flexiblity

- Since aerobic catabolism is a steady state mechansism, then the total yield only depends on access to O_2—though yield per use is still much higher than the others.
  - External anaerobic glycolysis has moderate (1.5 per use).
  - Phosphagens (0.4) and internal aerobic catabolism (0.2) has much less per use.
- External aerobic catabolism takes minutes to accelrate to rate of ATP production when needs are increased due to need to transport O_2—making it relatively slow compared to the others.
  - The other three mechanisms can accelrate very rapidly due to being self-contained in the cells.
- External aerobic catabolism has the lowest peak rate of ATP production, form 20–$30\ \mu\mathrm{mol}{\cdot}\mathrm{ATP}/\mathrm{g}{\cdot}\ \mathrm{min}$ depending on fuel source.
  - Anaerobic has generally high rate of 60.
  - Phosphagens have a very high rate, ranging from 96–360, though again it can't make a lot.
  - Interanal aerobic catabolism is also high, but not defined in the textbook.
- Anaerobic glycolysis generates lactic acid, which must be metabolized, leading to the lowest flexibility and longest recovery time of the mechanisms.
  - External aerobic catabolism is steady state, so as long as it as it's peak rate and continues to receive O_2, then it has no recovery time.
  - Both phosphagen and internal catabolism need new stores of O_2 and phosphagens (10s-30s), but theses are easier to restore in the cells comapred to the mobilization of lactic acid.
  - Lactic acid in humans can take 15-20 min for half dissipation, while up to 1-2 hours for full dissipation.
    - Frogs, fish, lizards and other poikilotherms often require much more.

9 Thermal Biology

Temperature and Heat

▷

Poikilothermy (Ectothermy)

▷

Homeothermy and Endothermy

▷