Collected Conceptual Frameworks 1st edition

Joel Michael, PhD, Professor Emeritus, Rush Medical College, Chicago, jmichael40@gmail.com

This document contains conceptual frameworks for five physiology core concepts that have been constructed and validated as of April 2021. In addition, there is a proposed sixth core concept that has been "unpacked," but for which no conceptual framework has yet been completed.

Description of Conceptual Frameworks

A conceptual framework is a hierarchically organized statement of the ideas that make up a core concept that has gone through the development process summarized below. It is intended to explicitly and systematically describe the component ideas that make up the core concept. We have referred to the process of building a conceptual framework as "unpacking" the core concept.

Development of a Conceptual Framework for a Physiology Core Concept

The process used to develop these conceptual frameworks is fully described in *Advances in Physiology Education* (respective publications listed below with each conceptual framework) and "Core Concepts of Physiology: A New Paradigm for Teaching Physiology[1]." To develop these conceptual frameworks, the researchers gathered feedback from physiology faculty through surveys and discussions at conference poster sessions, presentations and workshops. This feedback led to the refinement of the frameworks through multiple revisions and ensured three types of validity.

- **Content validity:** Frameworks are accurate and appropriate.
- **Face validity:** The language of each conceptual framework was clear and unambiguous.
- **Construct validity:** The content is important and relevant for undergraduate physiology.

A summary of the conceptual framework development process is provided below.

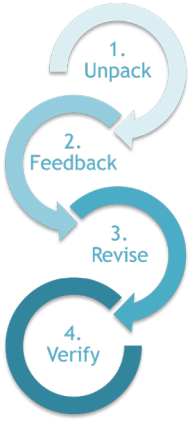
Description of Conceptual Framework Development Process

1. Two or more authors "unpack" a core concept into sub-ideas through several iterations and reaching consensus on a draft framework.

2. The consensus draft framework was shared with physiology faculty for feedback via workshops and surveys.

3. The draft framework was revised in response to the feedback collected from 35 to 50 physiology faculty.

4. The revised conceptual framework was shared once again with physiology faculty, who verified the importance of each item in framework via faculty surveys.



Validated conceptual frameworks are not available for every core concept. For example, the core concept of structure ↔ function has been "unpacked" and a conceptual framework proposed but **not** validated.

[1]Michael, J. Cliff, W., McFarland, J., Modell, H. and Wright, A. (2017). ©2017 American Physiological Society. Springer-Verlag NY. DOI: 10.1007/978-1-4939-6909-8
http://www.springer.com/us/book/9781493969074

Structure ↔ Function was "unpacked" and published by Joel Michael in 2021. See the list below in this document.

Other core concepts of physiology await unpacking and conceptual framework development by physiology educators and researchers. An individual or group of educators/researchers might unpack a core concept:

- to include missing items from existing unpacked core concepts or conceptual frameworks,
- to help students with a core concept for which there is not an existing conceptual framework, and
- to share with the physiology community as a starting point for further work.

We encourage others to develop, share and use these tools.

Use of Conceptual Frameworks

A conceptual framework is a tool for both teachers and students of physiology to facilitate student mastery of the discipline.

Conceptual frameworks are **not** descriptions of the science that underlies each of the core concepts. They are also **not** attempts to define what factual knowledge students should learn in their physiology course.

Viewed as instruments for teaching and learning, instructors can use, edit and modify these conceptual frameworks for use in their own courses.

Please send any comments about these conceptual frameworks to Joel Michael, PhD, at jmichael40@gmail.com.

FLOW DOWN GRADIENTS CONCEPTUAL FRAMEWORK

Michael J, McFarland J (2011). The core principles ("big ideas") of physiology: results of faculty surveys. *Adv Physiol Educ* 35: 336-341. doi.org/10.1152/advan.00004.2011 (reformatted using consistent numbering scheme)

> **Flow down gradients:** The transport of "stuff" (ions, molecules, blood and air) is a central process at all levels of organization in the organism, and this transport is described by a simple model. Ions crossing a cell membrane, blood flowing in blood vessels, air flowing in airways and chyme moving down the gastrointestinal tract are all processes that result from the interaction of an energy gradient and the resistance to flow that is present.

F1 Flow is the movement of "stuff" from one point in a system to another point in the system.

F1.1 Molecules and ions in solution move from one point to somewhere else.

F1.2 Fluids (blood and chyme) and gases (air) move from one point to another.

F1.3 Heat moves from one point to another.

F2 Flow occurs because of the existence of an energy gradient between two points in the system.

F2.1 Differences in concentration (concentration gradients) cause molecules and ions in solution to move towards a region of lower concentration.

F2.2 Differences in electrical potential (potential gradients) cause ions in solution to move.

F2.3 Differences in pressure (pressure gradients) between two points in a system causes substances to move toward a region of lower pressure.

F2.4 Differences in temperature (temperature gradients) between two points cause heat to flow.

F3 The magnitude of the flow is a direct function of the magnitude of the energy gradient that is present; the larger the gradient the greater the flow.

F4 More than one gradient may determine the magnitude and the direction of the flow.

F4.1 Osmotic (concentration gradient) and hydrostatic pressures together determine flow across capillary walls.

F4.2 Concentration gradients and electrical gradients determine ion flow through channels in cell membranes of neurons and muscle cells.

F5 There is resistance or opposition to flow in all systems.

F5.1 Resistance and flow are reciprocally related; the greater the resistance, the smaller the flow.

F5.2 Resistance is determined by the physical properties of a system.

F5.3 Some resistances are variable and can be actively controlled.

F5.3.1 Ion channels in the membrane can open and close (increasing resistance).

F5.3.2 Arterioles and bronchioles can constrict and dilate.

F5.3.3 Piloerection can increase the resistance to heat flow in many mammals.

HOMEOSTASIS CONCEPTUAL FRAMEWORK

McFarland, J, Wenderoth, MP, Michael, J, Cliff, W, Wright, A, Modell, H (2016). A conceptual framework for homeostasis: development and validation. *Adv Physiol Educ* 40: 213-222. doi.org/10.1152/advan.00103.2015 (reformatted using consistent numbering scheme)

Homeostasis: The internal environment of the organism is actively maintained constant by the function of cells, tissues, and organs organized into negative feedback systems. The role of negative feedback in regulating the functions of the body is a particularly powerful core concept in that it describes so much of organ system physiology.

H1 The organism maintains a stable internal environment in the face of fluctuating external environment.

H1.1 The organism's internal environment differs from its external environment.

H1.2 As the external environment changes, homeostatic processes maintain a more or less stable internal environment.

H1.3 If homeostatic variables change too much cells cannot function normally and may die.

H1.4 A limited number of variables (i.e., regulated variables) of the internal environment are maintained stable via homeostatic processes in order to sustain cell function.

H1.5 Some variables remain within a normal range over time but are not homeostatically regulated variables (e.g., blood hematocrit, testosterone).

H1.6 Depending on the particular system, the regulated variable may be kept within a very narrow range or within a much wider range.

H1.7 Homeostatic (i.e., regulatory) mechanisms operate all the time to determine the value of the regulated variable.

H1.8 Homeostatic mechanisms depend on resources in the external environment, which may limit the ability of the negative feedback to restore a variable to its normal range.

H2 Any change to a regulated variable (a perturbation) that results in an error signal will result in a physiological response to restore the regulated variable toward to its normal range.

H2.1 The regulated variable is held stable by a negative feedback system.

H2.2 Not all negative feedback systems are homeostatic.

H2.3 The process of responding to a perturbation requires an action by a sensor, a control center and an effector (the components of a negative feedback system).

H2.4 The sensor, control center, and effectors may be physically far from or near to each other in the body, and can even exist in the same cell.

H3 Homeostatic processes require a sensor inside the body ("what can't be measured can't be regulated").

H3.1 Sensors detect the regulated variable and respond by transducing that stimulus into a different signal.

H3.2 Sensors respond within a limited range of stimulus values.

H3.3 Sensors generate an output whose value is proportional to the magnitude of the input to the sensor (i.e., the stimulus).

H3.4 Sensors are constantly active (not just active when the regulated variable is not at the set point value or outside of a 'normal' range).

H3.5 An organ system may employ a variety of types of sensors (e.g., chemoreceptors, baroreceptors, mechanoreceptors, etc.) to regulate variables associated with that organ system

H4 Homeostatic processes require a control center (which includes an integrator).

H4.1 The control center is part of the endocrine and/or the nervous system.

H4.2 The integrator receives a signal from the sensor.

H4.3. The integrator is a component of the control center.

H4.4 Physiological systems have a normal range for a regulated variable (a so-called set point).

H4.5 The integrator continuously determines the difference between the signal from the sensors the set point (i.e., the normal range of the regulated variable).

H4.6 The value of the difference (between the signal from the sensor and the set point) is used by the control center to calculate a change in the signals going to the effectors (i.e., targets).

H4.7 It is possible in some circumstances and in some systems for the set point to change.

H5 Homeostatic processes require "effectors" or target organs or tissues.

H5.1 Physiological targets or effectors are cells, tissues, or organs (unlike "effector molecules" in biochemistry).

H5.2 The action of the effectors or targets is the physiological response that results in physical or chemical changes in the internal environment.

H5.3 The response of the effectors determines the value of the regulated variable.

H5.4 The response of the effectors can result in changes in non-regulated variables that in turn alter the regulated variable.

CELL-CELL COMMUNICATIONS CONCEPTUAL FRAMEWORK

Michael, J, Martinkova, P, McFarland, J, Wright, A, Cliff, W, Modell, H, Wenderoth, MP (2017). Validating a conceptual framework for the core concept of "cell-cell communication." *Adv Physiol Educ* 41: 260-265. doi.org/10.1152/advan.00100.2016

Cell-cell communications: The function of the organism requires that cells pass information to one another to coordinate their activities. These processes include endocrine and neural signaling.

CC1 A cell synthesizes and releases a chemical messenger.

CC1.1 A cell synthesizes a messenger molecule.

CC1.2 Messenger molecules can be proteins (or peptides), steroids or amines.

CC1.3 The rate of release of a messenger from a cell is determined by the "sum" of the stimuli for release and the stimuli that inhibit release.

CC1.4 Chemical messengers are present at very low concentrations in the blood compared to other biologically active molecules such as ions and nutrients.

CC1.5 The greater the net stimulus for release the higher the rate of release of the messenger.

CC1.6 Cells release messengers by exocytosis or diffusion across the cell membrane.

CC1.7 Cells that release messengers can be anywhere in the body.

CC2 Transport of messenger molecules is determined by the chemical nature of the messenger.

CC2.1 The solubility of the molecule determines how it is transported to its target cells.

CC2.1.1 Protein/peptide and amine messengers are generally water soluble and are transported in solution.

CC2.1.2 Steroid messengers are lipid soluble and are transported bound to protein carrier molecules in the blood.

CC2.1.3 Some amine messengers are transported bound to transport proteins and others are carried in solution.

CC2.2 The extracellular fluid concentration of a messenger molecule depends on the balance between production/release and elimination of the messenger.

CC2.3 Only the messenger in solution and free to diffuse is biologically active.

CC3 The messenger must bind to a receptor protein in or on its target cell to produce a response.

CC3.1 Each messenger molecule can only bind to a specific receptor molecule.

CC3.2 A cell can only respond to a messenger for which it has receptors.

CC3.3 The solubility of the messenger determines the location of its receptor protein in/on the target cell.

CC3.3.1 Water soluble messengers have receptors that on the target cell membrane.

CC3.3.2 Lipid soluble messenger have receptors that are inside the target cell, usually in the nucleus but in some cases in the cytoplasm as well.

CC3.4 The number of receptors for a particular messenger can be relatively small or relatively large, and is variable.

CC3.5 There can be more than one type of receptor for the same messenger on different target cells.

CC3.6 Thus the same messenger can produce different responses in the same type of target cells wherever they may be in the body.

CC3.7 Cells have a large variety of different receptors, thus enabling them to respond to a large number of different messengers.

CC4 Binding of the messenger molecule to its receptor gives rise to signal transduction.

CC4.1 A single messenger molecule bound to its receptor can activate or alter many more molecules in the target cell; this is called amplification.

CC4.1.1 Because target cell response is a multi-step process, and amplification occurs at each step, a single molecule can activate or alter many more molecules; the more steps in the intracellular signaling process the greater the amplification can be.

CC4.1.2 Given that messenger molecules are scarce, if the signal is not amplified it will have little physiological effect.

CC4.1.3 Because the target cell response is a multi-step process there are many points at which different inputs (other messengers) can modify the outcome/response. This is referred to as integration.

CC4.2 Because the target cell response is a multi-step process, a particular messenger molecule can have more than one effect in a target cell.

CC4.3 There are two basic mechanisms for transduction, both of which result in amplification.

CC4.3.1 Binding of a messenger molecule to its receptor can activate a cascade of intracellular second messengers which result in altered enzyme activity.

CC4.3.2 Binding of a messenger molecule to its receptor can alter the processes of translation and transcription in the cell nucleus, thus altering the concentration of a specific enzyme in the cell.

CC4.3.3 The speed of the response of the two systems is different.

CC4.3.3.1 The speed of response in a second- messenger system is fast since second messenger molecules are already present in the cell.

CC4.3.3.2 The speed of response in transcription and translation systems is slower because new molecules have to be synthesized.

CC4.3.4 Persistence of the response to messenger molecules also differ.

CC4.3.4.1 In second-messenger systems, the half-life of the molecules that get activated is short, and the responses can be terminated quickly.

CC4.3.4.2 In translation/transcription-based systems, the half-life of the molecules (proteins) produced is longer, so, the responses persist longer.

CC5 Binding of the messenger molecule to its receptor alters cell function.

CC5.1 The response of the target cell is a function of the target cell and not the messenger molecule. That is to say, the response to a given messenger is determined by the physiology of the target cell.

CC5.2 Alteration of target cell function is always the result of altering enzyme activity, whether caused by second-messenger alteration of enzyme activity or by changes in translation/transcription, causing the appearance of more enzyme molecules.

CC6 Termination of a messenger signal is accomplished in several ways.

CC6.1 The messenger signal goes away because the messenger molecule is no longer released or it is broken down.

CC6.2 The messenger molecule is removed from the receptor.

CC6.3 The receptor+messenger complex is internalized and ceases to generate a signal.

CC7 Some cells can communicate with neighboring cells electrically; they are electrically coupled.

CC7.1 Electrically coupled cells have gap junctions that span their two membranes.

CC7.2 Current can flow from one cell, when electrically excited, to neighboring cells.

CC7.3 These currents then electrically excite the second cell.

CELL MEMBRANE CONCEPTUAL FRAMEWORK

Michael J, Modell H. (2019). A conceptual framework for the core concept of "cell membrane." *Adv Physiol Educ* 43: 373–377; doi:10.1152/advan.00051.2019

Cell membrane: Plasma membranes are complex structures that determine what substances enter or leave the cell. They are essential for cell signaling, transport, and other processes. Every cell has a membrane separating the constituents of the cell from the extracellular compartment. The properties of membranes are thus an important determinant of the functions of the cell.

CM1 The cell membrane is a lipoprotein bilayer.

CM1.1 The bilayer consists of two layers of phospholipid molecules, each with a polar head (hydrophilic) and two non-polar (hydrophobic) tails.

CM1.2 The cell membrane includes a number of different types of molecules, including proteins (the fluid mosaic model).

CM1.2.1 Some proteins are embedded in and span the membrane.

CM1.2.2 Some proteins are attached to either the interior or exterior of the membrane

CM2 The cell membrane participates in a variety of mechanisms that maintain the integrity of cells and make possible the specialized function of any cell.

CM2.1 The cell membrane creates a closed space that contains the biochemical "machinery" needed for the cell to live and reproduce.

CM2.2 The cell membrane helps to determine solute concentrations inside the cell to preserve the viability of the cell and the continuation of its specialized functions.

CM2.2.1 Lipid soluble molecules (O_2, CO_2, urea) can passively diffuse across the membrane through the lipid portion of the membrane.

CM2.2.2 Water and water-soluble substances (ions, most organic molecules) can only cross the membrane via mechanisms that involve membrane proteins.

CM2.2.2.1 Water and some ions traverse the membrane by passive diffusion down an energy (osmotic or electrochemical) gradient through fluid filled channels (membrane spanning proteins).

CM2.2.2.2 Some substances (e.g., ions, glucose, amino acids) traverse the membrane passively down a gradient via carrier molecules (proteins) in the membrane.

CM2.2.2.3 Some substances traverse the membrane against a concentration gradient using ATPase powered pumps (primary active transport).

CM2.2.2.4 Some substances traverse the membrane against a concentration gradient using membrane transporters that move one species across the membrane against a concentration gradient and one species along a concentration gradient generally created by an ATPase located on at a different location on the cell membrane (secondary active transport).

CM2.2.2.5 The membrane also participates in the processes of endocytosis and exocytosis, energy-requiring processes that move things across the membrane in vesicles.

CM2.2.2.6 Some cell membranes have connections to adjacent cells (gap junctions) that allow movement of substances from one cell to another along an electrochemical gradient.

CM2.3 The cell membrane participates in cell-to-cell communication.

CM2.3.1 Some cell membranes contain voltage-gated ion channels (proteins).

CM2.3.2 Some cell membranes contain ligand-gated ion channels (proteins). When ligands are bound to the receptor site, the ion channel opens or closes.

CM2.3.3 Some cell membranes contain receptors (proteins) that, when bound to a ligand, activates a second messenger system within the cell.

CM2.3.4 Some cell membranes contain enzymes (e.g., acetylcholinesterase) that remove a ligand from the cell receptor site.

CM2.4 Some cell membranes help maintain the integrity of tissues (e.g., epithelium) by forming junctions between cells.

CM2.4.1 Tight junctions form between certain cells (e.g., epithelial cells) near the apical side of the cell.

CM2.4.1.1 Tight junctions limit the passage of various substances (molecules, ions, water) through the space between cells.

CM2.4.1.2 They block the movement of membrane components within the fluid mosaic from the apical to the basolateral side of the cell.

CM2.4.2 Adherens junctions and desmosomes provide strong mechanical attachments between adjacent cells.

CM2.5 The membranes of some cells (e.g., lymphocytes) contain proteins that serve as cell recognition proteins and participate in the organism's immune system.

MASS BALANCE CONCEPTUAL FRAMEWORK

Michael J, Modell H. (2021). Validating the core concept of "mass balance." *Adv Physiol Educ.* 45: 276-280. doi:10.1152/advan.00235.2020

Mass balance: The contents of a system, or compartment in a system, is determined by the inputs to and the outputs from that system or compartment. This is a simple general model that applies to all physical systems.

MB1 A compartment is a definable (describable) space in the body and has a measurable volume.

MB2 Compartments contain matter (mass) of different kinds (gas, liquid, solutes, solids).

MB3 Compartments have measurable inputs and outputs of matter.

MB4 The amount of matter in the compartment is determined by the initial amount in the compartment, the rate at which matter enters the compartment, and the rate at which matter leaves the compartment (or is destroyed in the compartment).

MB4.1 If input equals output, the system is in the steady state, and the amount of matter in the compartment is constant.

MB4.2 If input is greater than output, the amount of matter in the compartment will increase.

MB4.3 If input is less than output, the amount of matter in the compartment will decrease.

Applications of mass balance

MB-A1 The mass of **liquid** entering or leaving a compartment in a period of time refers to the flow rate of the liquid, regardless of solute content.

MB-A2 The mass of **gas** in the gas phase entering or leaving a compartment in a period of time is the total flow rate of gas times the fraction of the total that is the gas in question (e.g., flow of air times the fraction of oxygen in air).

MB-A3 **Solute** in a liquid medium (e.g., plasma) may be dissolved (e.g., O_2, CO_2, free hormone, ions, glucose) or bound to a carrier (e.g., oxygen bound to hemoglobin, steroid hormone bound to a protein carrier).

MB-A3.1 In some cases, the solute may be carried in multiple forms (e.g., carbon dioxide gas and carbon dioxide in the form of bicarbonate).

MB-A3.2 Solutes are carried in the medium by bulk flow.

MB-A3.3 The quantity of mass entering or leaving a compartment in liquid/medium over a period of time is calculated by multiplying the concentration of the mass (mass/volume) in the medium by the liquid flow rate (volume/time).

MB-A4 The rate of change of mass in **solid** form (e.g., bone) is determined by the rate of formation of the solid and rate of degradation of the solid.

STRUCTURE ↔ FUNCTION: A PROPOSED CONCEPTUAL FRAMEWORK

This is **NOT A VALIDATED CONCEPTUAL FRAMEWORK**, rather it is an example of how an individual can usefully "unpack" a core concept.

Michael J (2021). What do we mean when we talk about "structure/function" relationships? *Adv Physiol Educ* 45: 880-885. doi:10.1152/advan.00108.2021

> **Structure ↔ function:** The functions of molecules, cells, tissues, or organs are determined by their form (structure). Structure and function (from the molecular level to the organ system level) are intrinsically related to each other."

SF1 Every physical object is made up of some number of component parts arranged in a particular 3-D **structure**. The objects of interest in physiology span all levels of organization from molecules and ions to organ systems.

SF2 Biological objects interact with one another in a variety of ways that give rise to the **functions** carried out by a biological organism (respiration, energy production, internal transport, reproduction, etc.).

SF3 Biological **structures** constrain the features of the **functions** that they generate (at every level of organization).

SF3.1 The arrangement of elements making up a tissue or organ (its **structure**) determines it **function**. Examples include:

SF3.1.1 Conduction of cardiac excitation.

SF3.1.2 The flow of blood through the heart and the heart valves.

SF3.1.3 Excitation-contraction coupling in skeletal muscle.

SF3.2 The physical dimensions (surface area, thickness - **structure**) are determinants of the flux of substances across a transport barrier (**function**). Examples include:

SF3.2.1 The alveolar-pulmonary capillary interface.

SF3.2.2 Capillary beds in all organs.

SF3.2.3 The intestinal mucosa (villi and microvilli) determines absorption of nutrients.

SF3.3 The 3-D **structure** of proteins determine their **function**. Examples include:

SF3.3.1 The 3-D **structure** of channels and transporters determines their specificity, permeability and their **function** as

gates.

SF3.3.2 The 3-D **structure** of enzymes determines their activity (**function**).

SF3.3.3 Binding of H^+, O_2, and CO_2 to Hb alters its **structure** and thus its binding capacity for H^+, O_2, and CO_2 (**function**).

SF4 Changes in **function** can give rise to changes in the **structures** that generate them. Examples include:

SF4.1 Exercise changes fiber types in skeletal muscle.

SF4.2 Effects of exercise and gravity on bone density.

SF4.3 Effects of exercise on the heart.