BIOLOGICAL THEORIES IN THE DOMAIN OF PHYSIOLOGY

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Abstract

Physiology has produced a rich theoretical foundation that is now understood to apply to all known life forms from microbes to plants and animals, including humans. Physiological theories are equal in scope to evolutionary theories, but they have received much less attention and critical analysis from biologists and philosophers. Four Theories (Principles) are identified here. These are Homeostasis, Positive Feedback, Growth and Development, and Reproduction. These are undergirded by the universal biological property of Metabolism.

Physiology provides the basis for identifying organisms as functionally integrated agents. Evolution and physiology are the primary theoretical domains of biology. The former explains the origins of species and the latter explains the operations of individuals. Physiological individuals (organisms) often, but not always, coincide with evolutionary units of selection (evolutionary individuals), viruses being an obvious exception.

The theoretical and practical relationships between physiology and evolution have not been sufficiently explored. Visible or otherwise directly observable features (anatomical traits, behaviors, etc.) are generally considered to be the organism's phenotype. Those phenotypic properties are directly consequent to physiological processes and principles, which are not *per se* encoded in the genome (homeostasis, positive feedback, etc.). Neither biologists nor philosophers have sufficiently considered how physiology translates and mediates the connection between genotype and phenotype.

Focusing on the centrality and unique ideas of physiology provides ways to navigate between superstitious life force notions and simplistic physicalism that presumes, but fails, to explain the nature of biological entities. The theoretical foundations of physiology deserve greater attention in basic biology education. There is an imbalance created by teaching the relevance of physical sciences to biology without acknowledging the primacy of biological theories, such as homeostasis and natural selection, which are not based in physics or chemistry and could not be deduced from any amount of physical science knowledge.

A. Context

Biology is not generally thought of as a theoretical discipline in the way of physics and chemistry. Darwin's theories of natural selection and sexual selection are the most recognizable theories in biology. In books and journals regarding the philosophy of biology evolution is far and away the predominate topic (Godfrey-Smith, P. 2014; Kampourakis, K. 2013). Philosophy has paid much less attention to physiology as a home of biological theories. Like evolution, physiology is rich with facts, findings, and practical implications. But also like evolution, these empirical products of physiology exist within an abstract framework of explanatory and predictive theories. This paper is, in part, an invitation to professional philosophers who can explore the theories of physiology more fully.

The great geneticist Theodosius Dobzhansky wrote in 1964 that *"nothing makes sense in biology except in the light of evolution"* (Dobzhansky, T. 1964). Today we add that: *"nothing is biologically alive except by the rules of physiology"*. Microbes, plants and animals are not merely bags of chemicals arranged in interesting ways, regardless of what our science teachers may have told us. These organisms are the necessary products of the emergence of physiology at the junction between prebiotic and biological evolution.

Ernest Rutherford colorfully proclaimed, "All science is either physics or stamp collecting". It is true that biological research and teaching is by-and-large empirical rather than theoretical, but this is true in all of science including day-to-day physics. Even the fabulous Hubble and Webb space telescopes are instruments for collecting empirical physics, after which theorizing may follow. While Darwin sailed around the world gathering and describing specimens, he was "stamp collecting" in Rutherford's words. But when he created mental abstractions to explain the differences he observed, he was doing theoretical science.

For this essay I would prefer to use the word "theory" in a sense that is more formal and encompassing than it sometimes has been used in biology and medicine. Some things that are called theories in biology are empirical generalizations, but not formal theories. Two prominent examples are germ theory and the theory of independent gene assortment. Each of these is a useful generalization, but both have many exceptions and there are no *a priori* reasons to accept their universality. It is easy to see how life can operate without adherence to these generalizations. The theories we are concerned with here are essential. In their absence life would seem to be impossible. To steer clear of the vernacular meanings of theory within biology, we can use the term "governing principles" (or simply Principles). The governing principles discussed here are specific to biology. That is, they do not apply to non-biological materials or systems, and, most importantly, they could not be deduced or derived from any amount of knowledge about physics or chemistry.

This essay will focus on physiology as an abstract and theoretical discipline. A small number of physiology principles encompass the discipline and make predictions that are consciously and unconsciously used to guide research and affirm the plausibility of findings and conclusions. The work that a practicing physiologist does is almost always reductive, empirical, and directed at a particularly interesting question or a practical concern. But physiology, like evolution, derives its power not from individual discoveries and examples, but rather from its encompassing theories.

The word "*Physiology*" is from the Latin term for Natural Philosophy, Physiologia (Greek, Phusiologia). In the 17th century the discipline of physiology developed through the work of prominent physicians describing the functions of the human body. Despite the large predominance of human focused investigation, the governing principles and rules of physiology apply to plants, animals and microbes from mycoplasma and rotifers to redwoods and blue whales, as well as to humans. The history of the Nobel Prize in Physiology or Medicine is instructive. Once Nobel's will was read in 1896, implementing his wishes fell to the Karolinska Institute. The only faculty member who had worked directly with Alfred Nobel, Jöns Johansson, led the process for the Physiology or Medicine prize and "after some deliberations and compromises, 'the domain of physiology or medicine' was understood to encompass the theoretical as well as the practical medical sciences" (Ringertz N 1998), Nobel awards have been given for studies of bacteria, bees, corn plants, birds, and mammals, including humans.

B. Thesis

This is my central thesis: Physiology is a *theoretical and abstract* discipline and its Principles govern the functions of all known life. By "abstract", we mean that physiological knowledge "exists in thought or as an idea, but not having a physical or concrete existence" and is "not based on a particular instance" (Oxford English Dictionary). Philosophers may wonder about this emphasis since they consciously work with abstractions as a matter of course. However, biologists tend to resist the notion of abstraction and its associations with religious or superstitious thinking. Physiological abstractions include not only the overarching theories, but also the approaches to everyday discoveries and generalizations. These everyday discoveries are expressed in the form of "models" or "mechanisms", which are metaphorical and visual representations of actions occurring at molecular, cellular and organismal levels. Professional philosophers have delved deeply into the nature of and relationships between abstract and concrete realities. For our purposes concrete denotes that which is made of or made from physical matter. A bullet and its trajectory are both concrete. But a diagram or equation explaining how forces and frictions act on the bullet is an abstraction.

Not all biological disciplines are abstract and theoretical in the same way as physiology. For instance, zoology and its subsidiary "-ologies" such as mammalogy, ichthyology, entomology, or anatomy and embryology are examples of disciplines that are about "things" rather than ideas and theories. The objects in these disciplines can be studied and described empirically, without abstraction. Reflect on physiology's companion discipline, anatomy. One can, and normally does, study anatomy by using non-living material. Corpses, frozen tissues, organs fixed in formalin, and microbial bodies attached to electron microscopy grids are the common objects of study for anatomy. But these are clearly dead. And they are dead because they are no longer in possession of their physiology. They still have the same ions, atoms, sugars, DNA, and all sorts of complex molecules. But these are no longer governed by the physiology of the individual. It would be nonsensical to design a physiology experiment based on a dead organism even though we might have to kill the (non-human) subjects of an experiment in the process of studying their physiology. When one studies anatomy and ascribes function to a body part or relationships between structures in preserved specimens, they must call upon principles (theories) from physiology and/or evolution.

Physiology provides generalized explanations for how living biological entities operate. It does this by identifying relationships and interactions among biological parts (molecules, cells, tissues, organs, *etc.*) that operate together to make an individual. These processes have evolved to provide stability, continuity, and perpetuation of organisms. Physiological processes operate through chemical and physical entities, and evolved though unguided processes of natural selection. However, physiological processes are typically described metaphorically using teleological (*i.e.*, purpose-oriented) language (Lennox, J.G., Kampourakis K. 2013) such as "mechanism", and highly simplified and stylized visual abstractions similar to engineering diagrams. Use of these types of language tools has sometimes been dealt with harshly. For example a recent paper by Ratti and Germain (2022) insisted that physiology should eliminate the use of the word "function" because of its potential and actual teleological meanings. While careless or intentionally misleading language can be a legitimate problem, this particular contest would seem more sincere if the authors had simultaneously taken on chemistry for using "function" and "functional groups" to describe the workings of parts of molecules.

A typical exposition of a physiological process would be a description of how insulin participates in regulating the storage of glucose (Figure 1). One would read the diagram as showing that glucose is absorbed from the gut and goes to the pancreas where it causes the secretion of insulin, which goes to the liver and muscle causing glucose storage in the form of glycogen. It doesn't take much thought to realize that this reading is massively simplified, ignoring myriad cells, water molecules, proteins, electrons, neutrons, quarks, and all manner of things that are truly part of the scheme, but better ignored in service of communicating effectively. Abstraction, whether through language, illustration, or mathematics, is an essential part of learning, understanding, and communicating.

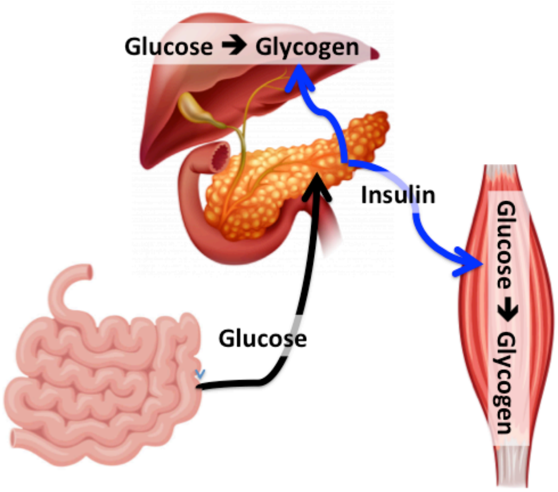

Figure 1. A diagram illustrating the mechanism by which insulin regulates glucose storage in the muscle and liver. The four anatomical elements are the intestines, pancreas, skeletal muscle and liver. The arrows are intended to illustrate aspects of the system that are dynamic (changing through time) and specific (events happen in particular organs). The figure is explained further in the text.

An illustration of the abstract and theoretical nature of physiology is the idea of "homeostasis" (Billman 2020), which has no independent concrete existence. It is a theoretical statement about how biological entities maintain their autonomous lives. But even though it is abstract, the idea of homeostasis is as near and natural to physiologists as the air they breathe.

Understanding the primacy of physiological principles brings one to the realization that the functions described abstractly by physiology are the real entities of biology. The ions, atoms, and molecules of a biological entity have physical substance. However, these are transient entities that are merely employees of the physiological processes. These many processes that are governed by physiology's Principles are the persistent means of life's existence.

C. Governing Principles of Physiology

To argue that physiology is an abstract and theoretical discipline it is essential that one be able to state physiological Principles with enough precision that they are both heuristically and epistemically valuable, and subject to criticism and argument. It would be formally correct to refer to these Principles as Theories. However the word theory is freighted with all sorts of ambiguities that make it difficult to use here. The following are my candidates for Principles that are foundational to physiology:

HOMEOSTASIS. Life is only possible because organisms maintain internal states within optimal and survivable limits. The Homeostasis Principle encompasses a seemingly limitless variety of short to intermediate term processes that maintain internal conditions within acceptable tolerances. Claude Bernard, in the 1870s, was the first to articulate an explicit theory that stabilizing regulatory processes are central to life. In his "Lectures on the Phenomena Common to Plants and Animals" Bernard stated, *"a free and independent existence is possible only because of the stability of the internal milieu"* (Bernard, C. 1974, translation, Hoff and others). This is still today my favorite articulation of homeostasis, even though the principle wouldn't be named until late in the 1920s by Walter Cannon (Cannon, W.B. 1939). Homeostatic regulation relies primarily on negative feedback as a first line in the organism's defense against external or internal changes that could push it beyond sustainable limits. A corollary law within the homeostasis principle is the universal presence of membrane boundaries that provide physical and functional separations of interior and exterior compartments. Homeostatic processes are how organisms avoid becoming too hot or too cold, too salty or too dilute, and regulate all sorts of other variables.

POSITIVE FEEDBACK. Dynamic events at cellular and organismal levels must be able to occur while the rest of the organism stays within the relatively constant boundaries of homeostasis. Organisms amplify small initial changes into much larger outcomes by employing Positive Feedback. Blood clotting and childbirth are two familiar human examples of processes that require positive feedbacks. Movement of microorganisms upward along a nutrient concentration gradient uses positive feedback. Electrochemical excitation of cells employs a positive feedback system that was mathematically described by A. L. Hodgkin and A. F. Huxley (1952), and muscle contraction relies on calcium-dependent calcium release (*i.e.,* positive feedback). In contrast to the stabilizing role of negative feedbacks, positive feedbacks destabilize the system to drive discreet processes. An imaginary organism with homeostasis but without positive feedback systems would be neither dead nor alive, perpetually in a state of ultimate ennui.

GROWTH AND DEVELOPMENT. The physiological Principle of Growth and Development asserts that the living histories of organisms are tightly regulated along predictable trajectories. C. H. Waddington called this *homeorhesis*, which he defined as a "regulated flow or trajectory", in contrast to the regulated "state" implication of homeostasis (Waddington 1957). These regulated life histories are governed by feed-forward mechanisms. Many of the feed-forward mechanisms operate by links between gene expression and developmental outcomes, some of which are encoded by "homeotic genes" (Gehring and Hiromi 1986). The life cycle of a given organism is the consequence of an organized and regulated flow of events that build upon one another by these feed-forward relationships. The regulation along a predictable growth and developmental pathway occurs through time within a context of continuously current or updated homeostasis.

REPRODUCTION. Whether long-lived or short-lived, all organisms are subject to eventual death, which is overcome by reproduction or self-replication. The Principle of Reproduction asserts that organisms not only replace themselves by reproduction, but also must be capable of producing an excess of offspring. Reproduction introduces variability from one generation to the next through this reproduction. Variability comes from primary mutations of the genetic codes and from recombination of genetic information between individuals and populations. By virtue of variability from generation to generation populations create ranges of physiological potentials that can respond to changing circumstances by evolution.

Each of these governing principles encompasses many predictions about how organisms behave and react to internal and environmental conditions. They also tell us what to expect from reductive experiments.

The Property of Metabolism within living entities needs to be included in addition to these four physiological Principles. All activities of living organisms depend on nutrient acquisition and substrate utilization, and are actualized by energy transfer, molecular biosynthesis, and excretion of waste end products. Living organisms share many basic metabolic pathways and these shared reactions speak to the unity of all life. Universal metabolic pathways exist alongside highly specific variations that evolved to meet particular needs and exploit specific environments. The organism is a flow-through system within which nutrients are moved about, chemically changed, stored, bonded, degraded, and eventually excreted. All this happens via exquisitely regulated and interconnected reactions. Through these processes the inevitable increase of overall entropy is channeled into work while macromolecular structures are built, repaired, and demolished as needs be.

D. Materialism, Atomism, and Reductionism

Looking at physiology as abstract and theoretical runs up against the habit of thinking and speaking in concrete material terms. Biology students are taught to think in terms of materialism to a degree that cells and brains can seem merely to be very special bags of chemicals. Materialism, which is approximately synonymous with "physicalism", emphasizes the primacy of matter, *i.e.,* physical "stuff" (Stoljar 2022).

Materialism/physicalism has been a powerful and productive antidote to earlier ways of thinking that emphasized non-material entities such as animal and plant spirits, souls, Platonic archetypes, and similar substances that are inherently not subject to observation and experiments. Philosophical dualisms that separated the mind from the body, the physical from the spiritual, or the body from the soul have been discredited primarily because they are not testable in a scientific sense. They are also poor guides for discovering things that are of practical use. Theories and abstractions are, like souls and spirits, non-material entities. But they differ in that theories are themselves testable, and they are guides for formulating predictions that are testable by observation and experiment. Just as importantly, they provide frames of reference for productive work that will yield practical benefits.

“Nothing exists except atoms and empty space; everything else is opinion”, (Democritus *circa* 400 BCE). No one gets very far into a basic course in the sciences without being regaled with the insights of the materialist philosophers of Ancient Greece, represented most often by Democritus (*c*. 460-370 BCE). Democritus and other philosophers of the Age articulated the notion that the world we perceive is made up of innumerable fundamental entities they termed "atoms". Atoms move about in the void of space according to the rules associated with each of their types. The colliding and combining of these restless atoms are the causes of the properties of macroscopic objects, and of the changes we observe in the world. The atomist theory remained largely unchallenged until the end of the 19th century. Lucretius (*De Rerum Natura*), in the first century BCE elaborated on the atomist theory and made materialism relevant to biology by articulating an early version of biological evolution.

No one doubts the brilliance and incisiveness of Democritus and other ancient philosopher-scientists. In an age dominated by superstition and supernaturalism their revelations about the nature of the world around them were remarkable and inspiring. But biology today is well past a time when the choice must be between atomism and superstition.

One of the more charming and ridiculous illustrations of how much we cling to atomist/materialist formulations is from the 2015 Disney animated movie "Inside Out". The main character, Riley, is upset by circumstances in her young life and her emotions cause chaos to her memories. Memories are portrayed as colored spheres (atoms?). Riley's emotions get out of control and jumble her memory spheres up terribly. But don't worry, after much commotion Riley is put whole and happy. Needless to say we don't completely know what memories are, but we can be confident that they are more process than particle, so we won't be seeing tiny memory spheres in the brain.

The fact that Riley's memory spheres look remarkably like Democritus' atoms is neither surprising nor coincidental. Our minds evolved to be well equipped to deal with discreet objects that might be useful or threatening. Dealing with abstract processes that consist of many different things happening at once, such as evocation of a memory, is much more difficult. To overcome this difficulty we construct mental perceptions into concrete objects. Objects such as rivers and human beings, on down to atoms and their particles, are static simplifications that gloss over the complicated dynamic processes that actually create and maintain those objects. It took about 2500 years for physicists to find out that atoms consist of smaller and less material things (like electrons), so the atomist theory was fundamentally incorrect. But biology still operates with a heavy dose of Democritus-style materialism.

Reductionism is sometimes conflated with materialism and has gotten something of a bad rap among many physiologists. But nothing in this essay should be taken as a criticism of reductionism *per se*. Here I use the term reductionism to refer to either research or teaching methods that explain a particular function of a complex system by identifying how components of that system are relevant to the function. The notion of reductionism was reframed interestingly and profitably into concepts of "decomposition and localization" by Bechtel and Richardson (2010). My research group's experiences are typical of how these approaches are used. When we wanted to understand how the hormone prolactin stimulates milk synthesis we engaged in a 20 years-long effort of reductionist experiments (or decomposition and localization). We studied the pituitary gland that secretes prolactin, the mammary gland cells that make milk, the mammary cell proteins that bind the hormone, the enzyme that gets activated, and the transcription factors and DNA sequences that cause the milk genes to be turned on (Horseman and Gregerson 2014). We took our question from the level of the whole animal to a level where the biology we were interested in met up with chemistry that we were not particularly interested in. Our question fell within the Principle of Growth and Development. The story illustrates an important strength and a limitation of reductionism, which is that in every step along the way we were ignoring everything about each component except that which was relevant to our question. The approach is fantastically successful for comprehending a particular function. But it is completely incapable of apprehending the full complexities of any moderately complicated system.

E. Vitalistic and Deterministic Anti-Physiology

Living subjects are obviously different from non-living objects. Reconciling this difference has been a challenge that has led down two main paths, both badly flawed. One path has been built on the notion that there are non-physical "life forces" that provide the impetus to convert non-living material into life (souls, spirits, *élan vitale*). The second path, termed "determinism" holds that life is merely a particular example of the way that physics operates (Hossenfelder 2022; Hoefer 2023). This physical determinism holds sway over modern biology in many ways.

The vitalist notion is that material stuff that would otherwise not be alive is motivated by some non-material life force so as to perform the goal-directed functions that sustain and reproduce life. On one hand positing an invisible "force" seems a lot like physics, where four invisible forces (electromagnetic, weak nuclear, strong nuclear, and gravity) are said to control the behavior of matter. But vocabulary is the only similarity between physical forces and vital forces. Physical forces are theories to explain specific measurable behaviors of matter. Gravity explains the attraction between masses, electromagnetism explains magnetism and electric charges, the weak force explains radioactive decay, and the strong force explains nuclear structure. Each force has particular properties that connect it with the behaviors it explains. Vital forces, souls, and spirits have no similar explanatory power. They have no particular properties that connect the "force" to properties of life. It is this lack of specificity that causes these vital force ideas to be untestable and therefore outside the domain of science.

Determinism claims that all biological events are traceable to prior causes, which has a common sense appeal (Harris 2012; Sapolsky 2023). More explicitly, the determinist would say that if one were to know initial conditions (of the entire universe), the laws of physics, and all the forces acting on an object, one could calculate the conditions of that object at any subsequent or previous point in time (Hossenfelder 2022; Hoefer 2023). The obvious appeal of this idea is that it provides a context for making predictions on grounds that seem scientific. It is also undeniable that there are many instances in our experience where we can observe causes and their effects. But it is equally undeniable that the relationships between causes and events are normally either ambiguous or intractably complex. Despite its common sense appeal, as an actual scientific proposition determinism is as problematic as is vitalism.

Statements made in support of determinism in any really interesting biological cases are always accompanied by excuses. "If we could know all the prior events..."; "It's so complex that you'll just have to believe me..."; "Even though you think it's random it's really not ...", *etc*. Taking a position that the universe in general, and living things in particular, operate deterministically in ways that are unknowable is purely a statement of faith. It is no more scientific than claiming that an unknowably complex being (God) determines the outcome of everything; Spinoza (1677, reprinted 2020) and others have made this philosophical claim. It is very hard to understand why physicists are eager to push biologists to believe in physical determinism. Modern physics admits a fundamental role of indeterminism in quantum mechanics. And even though quantum physics operates at extremely small scales, quantum computing and quantum energy transfer during photosynthesis (Romero et al. 2014) have demonstrated that the indeterminate quantum universe is very much relevant to our macroscopic world.

Determinism has yet another problem. A positive assertion can never be proven scientifically, *per se*. Science can exclude possible answers by experiments and observations that disprove a hypothesis or theory. But the best that a positive assertion can do is to gain the status of "best remaining explanation" after other explanations have been disproven. Determinism is certainly the mother of all positive assertions in which even moderately complex events have incalculable numbers of alternative explanations! Determinism is legitimately a philosophical point of view. For those who believe in the doctrine of predestination it is a religious point of view. But asserting that complex events can be explained scientifically by a simplistic physical determinism ought not be considered scientific. In evolution and physiology probabilities and statistical contingency are necessary to deal with extreme complexity, uncertainty, and inherent variability.

Vitalism and physical determinism are both attempts to explain biology from outside of biology, *i.e.,* from religion or physics. Darwin showed that explaining the evolution of life is possible but it requires principles that are inherently biological (Natural Selection, *etc.*). Physiology provides for explaining the operation of life but this also requires principles that are not to be found within physics or elsewhere other than in biology (Homeostasis, *etc.*).

E. Physiological Principles and the Organism

Axiom: "To be alive is to be in possession of a physiology." I want to draw attention to two aspects to this statement. First, living beings are different from non-living matter because of physiology. And second, physiology is what distinguishes a living organism from a corpse.

An armadillo and a stone are easy to tell apart despite their similar outward appearances. All physical and chemical principles apply to both the stone and the armadillo. But physiological principles apply to the armadillo but not the stone. Although being dead is not like being a stone we sometimes say that something is "stone dead". A living armadillo is different from a dead armadillo and a stone in the same way; the living armadillo has a physiology, which neither the stone nor the dead animal has. Being dead is not the absence of an anatomy, it is the absence of a physiology. In fact seeing details of anatomy depends on causing death so as to immobilize structures and preserve a moment in time and space. Dead is also not the absence of physics. Atoms and subatomic particles move in accordance with physical laws and if one were small enough to watch them it would be impossible to know whether their habitat was a dead armadillo or a live one, or at some miniscule level a stone. The anatomies and material substances of the organism and its corpse may be indistinguishable. But the living organism has an autonomous physiology and the dead one's physiology has expired. It is, in fact, the autonomous physiology of the individual that defines it as a living thing.

Aspiring to the most precise language and logic possible, various philosophers have attempted to define and delineate what it is to be a Biological Individual (review, Wilson and Barker 2024). Out of the many arguments put forward, the most concise and compelling is the idea that biological individuals can be distinguished on the basis of whether they are physiological entities (Physiological Individuals) or evolutionary entities (Evolutionary Individuals), or both. (Figure 2). Quoting from Thomas Pradeu (2016) the category of Biological Individuals includes two different subcategories:

"1. The subcategory of an *evolutionary individual*: a selective unit, that is, an entity that should be considered as *one unit* from the point of view of natural selection;

2. The subcategory of a *physiological individual*: a physiological unit, that is, a functionally integrated and cohesive metabolic whole, made of interdependent and interconnected parts."

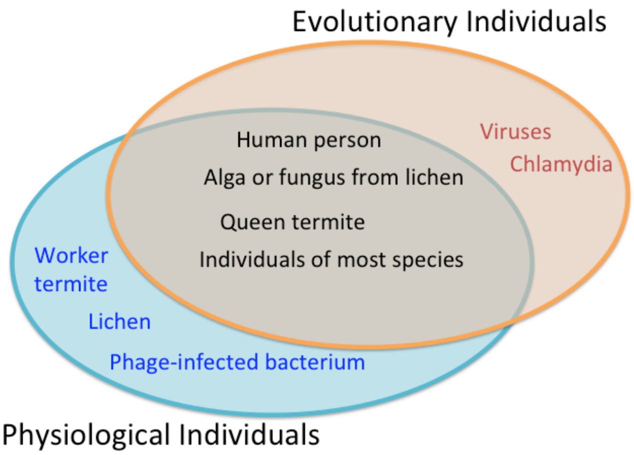

Figure 2. A diagram illustrating the relationships between sets of biological individuals, as defined by Pradeau (2016). Evolutionary individuals (rust-colored oval) are defined as units of selection in the course of evolution, and share a genome with others of their species. Physiological individuals (blue-colored oval) are defined as functionally autonomous biological units that take in nutrients, metabolize them, and maintain their autonomy through homeostasis. Individuals of most biological species are simultaneously evolutionary and physiological units. Familiar exceptions are extreme symbionts such as lichen in which the physiology of two types of genetically distinct individuals (fungus and alga in this case) are coupled into a composite autonomous unit, and extreme parasites such as viruses which have no autonomous physiological activity outside of their host.

The most common usage of the word "organism" coincides with the physiological individual according to Pradeu's definitions. Often, but not always, the physiological and evolutionary individual coincides in a particular organism. There are, however, many instances where physiological and evolutionary individuals are not synonymous. Viruses, colonial species such as ants and termites, and composites such as lichen and corals are examples in which the boundaries of the physiological and evolutionary individual do not coincide (Figure 2).

Physiological autonomy of organisms can be asserted on the basis of boundary membranes and differences between internal and external environments. But these assertions feel insufficient because they lack specificity and explicitness and, frankly, they lack liveliness. It is much more satisfying to illustrate autonomy through specific physiological processes. For example, metabolism sustains an organism's existence regardless of what the mixture of nutrients is in its environment (within limits). The individual is recognizably perpetuated even if the nutrient environment changes, which illustrates its physiological autonomy. A very powerful illustration of physiological autonomy is the nature of the Circadian Biological Clock.

Circadian clocks are systems of linked feedback partners that cycle with a period of approximately a solar day (*circa,* about + *dies,* day). Circadian biological clocks evolved from different genetic substrates at least 4 times (in bacteria, fungi, plants, animals) (Dunlap JC 1999; Saini, et al. 2019). Despite their separate origins and genetic components, all these clocks share some common properties. For our purposes the most informative common feature of circadian clocks is the persistence of their cycles in the absence of external cues. As shown in Figure 3 the circadian cycle persists at a period that is approximately, but never exactly, equal to a 24-hour day (Bunning 1967). This persistent cycle time is called the "free-running period" and can be either longer or shorter than 24h. The free-running period is strongly heritable and species-specific. Under typical environmental conditions the circadian clock is reset by a small amount each day to keep it synchronized. A free-running circadian clock could not exist in the absence of autonomous physiological control.

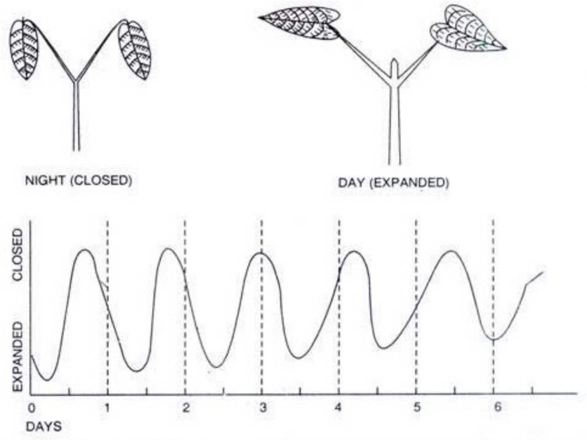

Figure 3. A diagram illustrating the free-running circadian cycle of leaf movements in the common bean plant. At the top are drawings showing how the leaves droop at night (closed position) and become erect for the day (open position). The graph shows a tracing of a leaf movement over several days in constant darkness conditions. Each dashed vertical line defines a 24 hour interval. Note that in the absence of daily light cues the leaf movements drift later and later relative to the 24 hour days (free-run), illustrating the autonomy of this physiological process. From Bunning, E, 1967, The Physiological Clock.

The circadian clock example is particularly useful because physiological autonomy is logically self-evident from the existence of intrinsic clocks with cycle periods that are similar, but not identical, to the solar day.

F. Summing Up and Looking Forward

Theory and abstraction are ever present but often are unacknowledged in biology. The obvious exception to this is in the subject of evolution where Darwin's theories of natural and sexual selection are as present and immediate as Einstein's theories of general and special relativity are in physics. Evolution leans heavily on theory because, at least in part, its subject matter is often not directly accessible. Evolution can use theory and abstraction to interpret and interpolate incomplete data in fossil and genetic records. Evolutionary theories also provide discipline in the way that Dobzhansky spoke of (D0bzhansky 1964). They are required to make sense of the history and current diversity of biology. While evolution and physiology concern themselves with very different biological time scales (generations on the one hand, and individuals on the other), there is an important and largely unexplored relationship in the genotype-to-phenotype problem (Figure 4). Physiology is the sum of the processes by which the genotype is translated into visible and otherwise evident phenotypic traits.

I have made a case that physiology is the home of a second set of essential biological theories. The theories (Principles) identified here include Homeostasis, Positive Feedback, Growth and Development, and Reproduction. These are undergirded by the biological Property of Metabolism. Physiological principles need to be consistently applied just like those in evolution or in physics. There are consequences to doing science without reference to a strong framework of principles. The preponderance of biological research is paid for under the broad umbrella of biomedicine where "impact", rather than durability, often motivates the research process from inception to publication and publicity. In this environment the kind of discipline that theory brings to other disciplines like physics is sometimes hard to find.

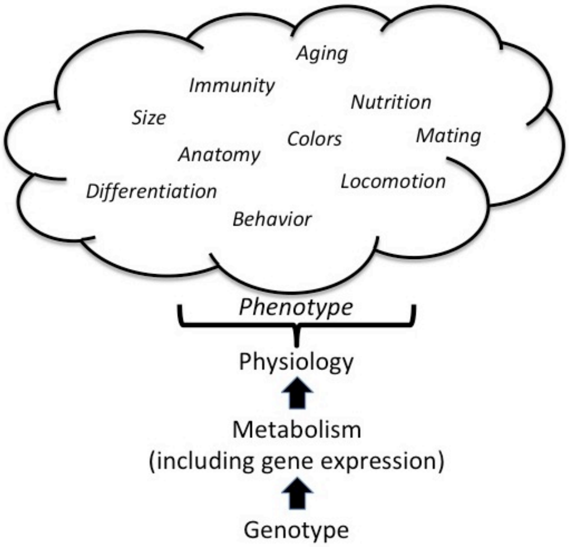

Figure 4. Genotype, the object of natural selection, is translated into phenotype, the subject of natural selection (cloud), through metabolism and physiology.

When scientists try to generalize without being disciplined by the application of theory there are practical consequences. Familiar examples of this are found in studies of human nutrition where proponents regularly ignore basic physiological principles while making claims about various nutrients, which end up being disproven or debunked. In order for a nutritional intervention to bring about a change in a normally functioning person it must operate under the constraints of both homeostasis and metabolism. If there is an actual disturbance in homeostasis, such as scurvy caused by vitamin C deficiency, then diet can have a profound effect by restoring homeostasis. Likewise, if there is an actual defect in metabolism, as in phenylketonuria, dietary intervention is effective (avoid phenylalanine). But if one is making profound nutritional claims in the context of intact metabolism and normal homeostasis they are not just making a claim about a nutrient, they are contradicting fundamental physiological principles. High fat or low fat diets eventually fail or become unsustainable because of metabolic adaptations and homeostatic control over appetites. Claims in evolution that are contradictory with natural selection do not go unchallenged. Claims that contradict physiological principles deserve the same level of scrutiny.

A different example that demonstrates the practical importance of physiology comes from our changing views of cancer. Classification of cancers has historically been almost entirely anatomical. They come from certain organs (pancreas, bowel, prostate, breast, etc.) and have certain microscopic anatomies (cell shapes, invasiveness, etc.). Now we know that cancers from different organs are often physiologically similar, regardless of anatomy. The consequence is new treatment approaches that specifically target physiological cancer types from completely different organs. Two examples of this are pembrolizumab (Keytruda) and olaparib (Lynparza).

In a less practical and more philosophical vein, physiology principles shift our focus from a preoccupation with tangible physical entities. Acknowledging these principles focuses our attention on critiquing and applying the aspects of our work that are abstract such as "feedback", and descriptions that are metaphorical such as "mechanisms" (Bechtel and Richardson, 2010; Machamer, *et al.* 2000). We use these abstractions constantly, but since they are largely taken for granted they are easily abused. I had a colleague tell me not long ago that he generally "retrofits his hypothesis", which I viewed as an absurd notion. If you start without a hypothesis, with a basis in theory, it is very easy to look through a collection of results and produce a diagram of a mechanism that seems plausible. The goal has become creating the metaphorical mechanism rather than using the metaphor to explain the physiology.

Humans have always believed and understood that there is something more to life than the tangible physical substance of it. The philosopher Henri Bergson is credited, and discredited, with authorship of the term *élan vital*, or vital principle, as an insensible force that animates living beings. His approach was different from other dualist philosophers and most religious thinkers because his vital principle unitarily encompassed all of life rather than associating with individual beings, as does a soul. He was ambitious in describing *élan vitale* as penetrating past, present, and future life. He was also modest in confessing that *élan vitale* therefore didn't explain very much (Bergson, H. 2018).

What we normally call the organism is, more explicitly, the autonomous physiological individual. Every experience with death of an individual (human or otherwise) teaches us that something intangible has departed while the physical substance has remained. We might call this spirit or soul if we lean on revelation. Or we can lean on exposition to understand that one intangible loss is the departure of one's individual physiology.

Physiology uses a set of universal principles (homeostasis, reproduction, etc.) that permit us to objectively and explicitly define what the individual autonomous organism is and is not. But that work is not done. How close does a symbiotic relationship have to be in order to be called a single individual? Surely the endosymbiosis of mitochondria and chloroplasts qualifies (Margulis 1992). But how about coral symbionts and nitrogen-fixing bacteria? Does a clone begin a new individual or extend an old? When does an individual life end? Does autonomy admit some, every, or no interventions at the end of life? When does an individual life begin? Is there a universal answer, or do we need different answers for different types of organisms? These are certainly not the only questions to be asked. They are merely invitations to do the asking.

Perhaps the most consequential aspect of elevating attention to theory in physiology, and in biology generally, should be on education. General biology courses and textbooks begin with one or more chapters on chemistry and physics. There are multiple reasons for this. One reason that is fully justified is that students may not have already taken chemistry and physics courses that provide some important background. Another less well-justified motivation seems to be a self-conscious effort to reinforce a materialist/physicalist perspective for students that may come to their course with religious or other non-materialist predispositions. The effort is to convey the idea that the foundations of biology are found exclusively in the "hard" physical sciences. This approach is missing any explanation that biology stands on principles that are completely outside of the physical sciences, and completely scientific. It is very possible that the exclusive reliance on validation from chemistry and physics paradoxically undermines the goal of reinforcing scientific thinking over superstition. Given that it is self-evident to students that living things are different from inanimate objects, leaning on physics and chemistry cannot, by itself, liberate them from unscientific assumptions and superstitions about living things.

Natural Selection and Homeostasis are ideal theories to introduce inherent Biological Principles into basic biology education. The former provides the basis for understanding the origins of species and the latter provides the basis for understanding the operations of individuals. Both of these are well-established principles that do not have their basis in physics and chemistry, and could not be derived from any amount of knowledge about physics and chemistry. In fact, both were articulated long before there was any knowledge about genes, DNA, biochemistry, or modern physics. Yet these are fully testable and completely natural Principles (Theories). Most of what the students will learn in General Biology will be understood best in light of the Theories of Natural Selection and of Homeostasis.

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