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RESEARCH ARTICLE

Biological Theories in the Domain of Physiology: Stability and Transformation as Two Governing Principles

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Physiology has produced a rich theoretical foundation that applies to all known life forms, from microbes, to plants and animals, including humans. Compared with evolutionary theories, physiological theories have received much less attention and critical analysis from biologists and philosophers. Physiology includes many theories that are "local," applying to particular sub-disciplines or organ systems. An overarching theory of physiology is homeostasis, first offered by Claude Bernard, and ultimately named and illustrated by Walter Cannon. Homeostasis conveys that life relies on a "stability of the internal milieu" to persist in face of an incompatible external environment. Various authors have offered clarifications, amendments, and outright replacement concepts for homeostasis. These alternatives have been motivated in part by the constrained notion that homeostasis does not admit changes that are readily observable in responses to normal environmental challenges and diseases or stresses. A less constrained view of homeostasis accommodates those concerns. Physiology includes processes that control transformative changes that homeostasis was never intended to address. These are generally reproductive, growth, and developmental transformations, and associated specializations such as migrations and metamorphoses. Evolution has generated a wide variety of such transformations, all of which must be implemented by physiological mechanisms. Some, such as metamorphosis, are non-ambiguous examples that are not accounted for by homeostasis alone. A new theoretical framework, named kinorhesis here, is proposed to encompass those transformations and the non-homeostatic processes that control them. The theoretical foundations of physiology deserve greater attention not only in the professions, but also in biology education. There is an imbalance created by teaching the relevance of physical sciences to biology without emphasizing the primacy of biological theories, including theories in evolution and physiology, which are not based in physics or chemistry and could not be deduced from any amount of physical-science knowledge.

Keywords

homeostasis • evolution • reproduction • natural selection • metabolism • phenotype • determinism • vitalism

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1. Context

Darwin's theories of natural selection and sexual selection are the most recognizable theories in biology (Darwin 1859, 1874). In philosophy books and journals, evolution is far and away the predominant biological topic (Godfrey-Smith 2014; Kampourakis 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. Also like evolution, these empirical products of physiology exist within an abstract framework of explanatory and predictive theories. This paper is intended to offer some new views on physiological theory, and to invite professional philosophers to explore the theories of physiology more fully.

Axiom: "To be alive is to be in possession of a physiology." This statement has two implications that undergird this paper. First, living beings are different from non-living matter because of physiology and the consequences of physiological principles. And secondly, physiology is what provides evidence that an organism is alive or dead, and whether it is autonomous or dependent. Building an understanding of the theoretical framework of physiology is an ongoing project of biology and philosophy.

Theodosius Dobzhansky titled his 1964 lecture with the statement that "nothing makes sense in biology except in the light of evolution" (Dobzhansky 1964, 449). This distilled a scientific consensus that evolutionary theory provided an essential basis for understanding and explaining biology. Evolutionary theory provides a way of understanding the changes to heritable traits in populations, communities, and species through time. However, the theories of evolution do not address the other central problem of biology: how are individual and collective organisms alive? It is the remit of physiology to study and explain how organisms maintain stable functions during their individual lifetimes, and how they grow, develop, reproduce, and consequently perpetuate their kind and their hereditary material. So, in the manner of Dobzhansky, we can say that *nothing is alive except by the rules and processes of physiology*. Microbes, plants, and animals are not merely bags of chemicals arranged in interesting ways. They are the necessary products of the origin of physiology at the junction between prebiotic evolution and biological evolution.

The perspectives here align ontologically with views from process philosophy (Nicholson and Dupré 2018; Seibt 2023), while acknowledging that substantialism has had a dominant position in biology. The contrasting notions of whether a given reality is specified by processes that are in flux, or rather substances that have fixed properties, have ancient roots, with Heraclitus (6th century BCE) advocating for processes in flux, and the likes of Democritus (4th century BCE) championing substances, including immutable atoms. We are generally taught to think of biological entities as being built of "things" (cells, molecules, atoms). But an alternative view is that a given biological reality can be the consequence of the processes that specify it on a continuing basis, while the substances flow transiently through this process and on into other processes. It is outside the intentions of this paper to review process philosophy in the context of biology, and interested readers are referred to the references above, and references found in them. A short quote will put the perspective in context: "Once we transition from an ontology of substances to an ontology of processes, it is no longer incoherent or mysterious to assert that the properties of the parts are partially determined by the properties of the whole – a claim, by the way, that biologists (especially physiologists and embryologists) have been making for centuries on the basis of their empirical investigations" (Dupré and Nicholson 2018, 27). The processes of physiology operate from subcellular to community levels, and impose functional consequences on the evolution of relationships among the constituent elements of complex living beings.

Griesemer (2013) analyzed the concept of formalization as a means of categorizing biological sciences. He argued that disciplines could be placed along a continuum from "exact" disciplines that are formalized, to disciplines that are formalizable in principle but as yet inexact, to those that are "inexact" and by their nature not formalizable. Formalization, in Griesemer's account, is often by way of mathematization, but also via graphical models and articulation of unambiguous principles. The forms of exact sciences are analyzable independent of their empirical subjects. It is in Griesemer's sense of an exact science that I would want to use the word "theory". However, a caution is that the term theory in biology has often been applied to empirical generalizations that are not formal. 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 and does operate without adherence to these generalizations. Along with the term theory in the formal sense, I will use the term "governing principle" to refer to theories that we suppose to be fundamental.

The theories (governing principles) discussed here are specific to biology. The evolutionary theories of natural selection and sexual selection are specific to biology. When physicists, cosmologists, and chemists talk about evolution in the physical universe (I am excluding imaginary scenarios like L. Smolin's hypothetical competition among "multiverses") their objects (matter, energy, and elements) may evolve in the generic sense of changing over time, but they are not living, competing, reproducing, and dying, so theories of biological evolution do not apply. Like evolution, physiological theories also are specific to biology. That is, they do not apply to non-biological materials or systems, and, most importantly, like evolutionary theories, they could not be deduced or derived from any amount of knowledge about physics or chemistry.

The word *physiology* derives from the Latin term for Natural Philosophy, physiologia (Greek, phusiologia), which from ancient times encompassed all scientific and proto-scientific efforts to understand physical and biological nature. In the 17th century, the discipline we now recognize as physiology developed through the work of prominent physicians studying 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 1998). Nobel awards have been given for physiological studies of bacteria, bees, corn plants, birds, and mammals, including humans.

2. Thesis

My central thesis is that physiology is a *theoretical and abstract* discipline and its governing principles apply to 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). Physiological abstractions include not only the overarching theories, but also 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, it suffices to accept that 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. Being concerned with how things work, not merely describing what things do and what they are made of, is what distinguishes physiology.

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 we recognize that 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. When one studies anatomy and ascribes a function to a body part or to relationships between structures in preserved specimens, they must call upon theories from physiology and 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 have evolved though unguided processes of natural selection. However, physiological processes are typically described metaphorically using language that is often teleological (i.e., purpose-oriented; Lennox and Kampourakis 2013), along with 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, it is doubtful that physiologists will abandon the word "function" before chemists stop 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 illustrating 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. It ignores both the many actions of each component that are not directly relevant to this mechanism, and the myriad cells, water molecules, proteins, electrons, neutrons, quarks, and all manner of things that are relevant, but better ignored in service of understanding and communicating.

3. Theories in Physiology

There are a number of local theories throughout the disciplines of physiology that are routinely used in experiments, medical practice, and teaching about how the systems operate. Some of these, such as the "gas laws" and hydrodynamic flow theories, are imports from the associated physical sciences. Theories explaining neuronal bioelectric transmission are hybrid physical and biological theories. Others, such as the "second messenger" theory of receptor signal transduction are useful empirical generalizations. Another set of widely used empirical generalizations

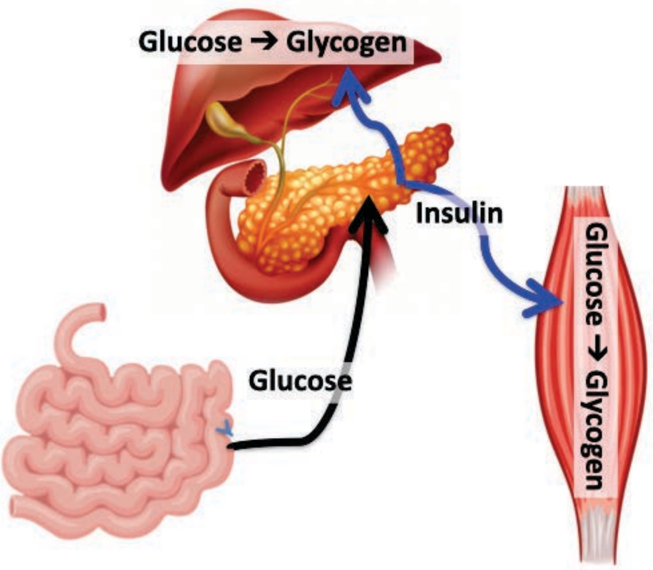

Figure 1: A diagram illustrating the mechanism by which insulin regulates glucose storage in the muscle and liver. The four anatomical elements are the intestines, pancreas, skeletal muscle and liver. The arrows are intended to illustrate aspects of the system that change through time and are specific to particular organs.

treated as "theories" are various "scaling rules" relating variables like body mass, longevity, and metabolic rate. For instance, metabolic rate, and consequently drug metabolism, generally is proportional to body mass raised to the ¾ power (or maybe ⅔). These local physiology abstractions are all interesting and important, and often challenging for first year medical students accustomed to memorizing body parts and metabolic reactions. But these sorts of local theories are not our focus here.

We are concerned here with governing principles that can be applied broadly to physiology across the kingdoms of life, and which can draw many specific instances into a unified conceptual framework, encompassing multiple sub-disciplines and functions. These general governing theories should not only have broad explanatory power, but they should also articulate with one another in the context of whole organisms, which is not necessary for local theories.

3.1. The Physiology of Stability: Homeostasis

The theory of homeostasis has been a bedrock of physiology for a century. Homeostasis has come to encompass 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 1885 [1974]). The principle wouldn't be named and expanded upon until late in the 1920s by Walter Cannon (Cannon 1929, 1939). Homeostasis manages two essential tasks. First, it maintains internal environments compatible with life in the face of external environments that are hostile, like our highly oxidizing atmosphere and surroundings that are too dry if you're a terrestrial being. Secondly, homeostatic processes resist large or rapid changes to the internal milieu.

Homeostasis, like other familiar overarching concepts, has been subjected to both reasonable debate and unreasonable caricature. An important example of unreasonable treatment is the idea that homeostasis implies anything like "constancy." This was neither stated nor implied by Bernard or Cannon, and hasn't been observed in any physiological data. Two types of variations should be expected in homeostasis, as in all of biology. First, there will be a greater or lesser degree of statistical randomness that is generated by the workings of a complex system. This randomness is an inherent property, not a "sampling error." And secondly, one will find heritable variability of the type described by Darwin and central to natural selection. In addition to these inherent variabilities, there are physiological variations associated with how organisms are contending with the environment, disease, and other challenges. These kinds of variation have generated discussion and controversies, and we will examine some of them below.

After considering the main controversies and alternative interpretations of homeostasis, I will contend that the theory of homeostasis is fundamental, broadly encompassing, and durable. This will involve referring to various publications that have offered alternative interpretations on the limits of the homeostasis theory. Those alternative views, in my estimation, fail to make a case for constraining homeostasis to a narrow meaning so as to open the door for other theories to explain special cases. If we admit the broadest possible interpretation of homeostasis we can stipulate that this broad view of homeostasis does what Bernard claimed; that is, it provides a necessary degree of stability for "a free and independent existence." With this broad view of homeostasis, it is then possible to ask whether there is an entire category of physiological processes and events that are not accounted for by homeostasis. I believe this is the case, and that transformative life history processes lie outside the domain of homeostasis, and can be unified under a different theoretical treatment.

Before examining critiques and alternative constructions for homeostasis, it is useful to look back at Cannon's original formulations (Cannon 1929). As Cannon endeavored to define homeostasis, one of his first statements was that "the internal conditions are held *fairly constant*" (emphasis added). This "fairly constant" criterion is consistent with his deliberate choice of the prefix "homeo" (similar) over "homo" (same), so that homeostasis was a neologism for "similarly standing." Cannon sets his expectations for homeostasis very clearly by cataloging the "relatively uniform" levels of various blood parameters based on the consequences of exceeding those limits. For example, blood glucose lower than 70 mg/dl results in hypoglycemia and above 180 results in glucose in the urine. Sodium rising from 0.3 to 0.6 percent causes cellular dehydration, calcium falling from 10 mg/dl to 5 mg/dl causes convulsions. And so on, through various other variables. By cataloging ranges of an extensive variety of blood variables Cannon established that the generalization of a "fairly constant" internal environment was compatible with wide limits of values to be considered within the homeostatic ranges.

Homeostasis finds its greatest practical impact within the practice of medicine where restoration of homeostasis and preventing disruptions to homeostasis are primary imperatives. The values of physiological variables that are considered clinically homeostatic are referred to as "normal values" or, more precisely, normal ranges. These clinical normal ranges have a loose but informative relationship to the cybernetic term "set-point," which physiologists use to designate an imaginary target value that the system will return to after having been disturbed.

The relationship between normal clinical values and homeostatic set-points is instructive. The normal values reflect not a set-point for a physiological variable, but rather a homeostatic range. When the values move outside the normal range, homeostasis has an increasingly difficult time and medical interventions may be needed to try to avoid decompensation (breakdown of homeostasis). These larger deviations from normal values are the same kinds of limits that Cannon (1929) recognized when he laid out numerous examples of the relative constancy of the internal milieu. So homeostatic levels, as illustrated by human values for which we have by far the most data, are a "normal range" that contains within it an imaginary but meaningful "set-point." This normal range is nested within a broader homeostatic range where the system can function to restore itself to "normal." Outside this broader range, the system is likely to fail. This view of homeostasis from the perspective of clinical usefulness maps very closely onto the homeostatic "reactive scope" model offered by Romero et al. (2009).

Notwithstanding the validation of homeostasis that comes from medical practices, there have been many serious efforts to clarify what is meant by homeostasis and to offer alternative concepts. Fortunately, those efforts have been summarized and reviewed expertly in several major papers (Houk 1988; McEwen and Wingfield 2010; Ramsay and Woods 2014; Modell et al. 2015; Davies 2016; Billman 2020; Bechtel and Bich 2024). I do not intend to provide an analysis of these individual competing concepts, which readers can find in the cited references. I will focus on some commonalities, and highlight some particularly strong or unique concepts.

One common thread among papers that have defined and critiqued homeostasis, going back to Cannon, is that most have focussed exclusively on issues drawn from mammalian organ systems physiology. Early on, Hans Selye (1956) advocated using "heterostasis" when addressing mammalian physiological responses to stresses. The term "allostasis" was offered as an alternative to heterostasis in a paper that focused on human pathology (Sterling,1988); subsequent studies expanded this to "stress" responses in other mammals. Davies (2016) suggested the term "adaptive homeostasis" for adjustments to set points during responses to stressors, toxins, or exertion. Dale Bauman used the term "homeorhesis" (Bauman and Currie 1980) to categorize adjustments of nutrient flows for mammalian pregnancy and lactation, and implied that the concept could be applied to other circumstances. "Anticipatory homeostasis" or "predictive homeostasis" have been suggested as terminology for adjustments that accommodate predictable environmental changes such as daily (circadian) and seasonal cycles (McEwen and Wingfield 2010). Contrariwise, "reactive homeostasis" applies to responses to unpredictable perturbations. The term "rheostasis" was offered by Mrosovsky and bears similarities with allostasis in that each offers to address "stability through change" (Mrosovsky 1990). Rheostasis dealt more with normal changes in animal functions, and less with pathophysiology. Particular topics of interest for rheostasis have been circadian and annual rhythms (Mrosovsky 1990; Stevenson 2023).

As the various modifications or amendments to homeostasis have been offered, there has been steady resistance from those who have continued to believe that homeostasis is a large enough theory to deal with the concerns that have been raised (Bechtel and Bich 2024; Dallman 2003; Romero et al. 2009). Overall, these efforts to find alternative concepts have required confining and constricting homeostasis. One favorite tactic is to point out supposed flaws in the idea of "set-points" for homeostatic regulation. This usually has taken the form of asserting that a stable state that is different from "normal," such as a fever, is incompatible with the notion of a set-point. But every engineered device that I'm familiar with has a set-point that is adjustable, so there's nothing incompatible about the notion of adjustable set-points. While it is true that some have taken the engineering metaphors to extremes (Guyton 1991), asserting that rigid set-points are the *sine qua non* for homeostasis is a straw-man argument. Neither Bernard nor Cannon had any notions of set-points, but were able to articulate the principle of homeostasis with enduring clarity. The constraining of the idea of homeostasis not only runs counter to the broad conceptions of Bernard and Cannon, but also to the natural evolution of the homeostasis concept toward including more, rather than fewer physiological functions.

The abstract regulatory notions of cybernetics (Weiner 1961; Guyton 1991) have been a mixed blessing for the theory of homeostasis. Although many biologists have expressed the assumption that physiology simply adopted cybernetic ideas from engineering, the originator of cybernetics, Norbert Weiner, studied biology and understood physiological regulation. As a mathematician and philosopher, Weiner was able to model common features underlying regulatory communication in biological and non-biological systems (Weiner 1961). The cybernetic terms, which include not only set-points, but also "sensors," "amplifiers," "gain," "feedback," "error," etc., greatly facilitate communication about how biological regulation takes place (especially for teaching purposes). They also provide the kind of simplifying assumptions that are absolutely necessary to do any sort of mathematical or quasi-mathematical treatment of homeostatic regulation. The obvious limitation of cybernetic modeling in physiology is that biological systems are so much more complex than physical systems that fully modeling the details of physiological systems is normally not feasible. Physiological systems evolved by natural selection, and continue to evolve by fits and starts and endless re-jiggering of preexisting processes and mechanisms. The evolutionary history can often illuminate physiological regulation, but also can obscure relevant mechanisms behind species differences and adaptations.

The cybernetic-style language used to describe homeostatic responses has been remarkably successful in the only two ways that really matter. First, "negative feedback" is a heuristic statement that a homeostatic response should involve at least one mechanism in which the regulated variable is in a reflex loop with the means of its regulation. This general feature of homeostasis guides physiological research in ways that are sometimes very obvious and conscious, and other times not. Secondly, the directness of the cybernetic homeostasis language, as contrasted with the sophistication and occasional obfuscations of the alternatives, is essential for teaching physiology. I would never want to try to teach an undergraduate biology student or a first-year medical student physiology without language about set-points, sensors, and negative feedbacks.

There are some negative feedbacks that are relatively simple, such as osmotic regulation of antidiuretic hormone secretion. These simple feedback loops are never brought up as examples when concerns are raised about homeostasis. The complicated ones, like mammalian thermoregulation, provide much ammunition for those concerns. Thermoregulation involves sensing core temperatures (visceral circulation, brain) and multiple subdivisions of "shell" temperature (skin, extremities), with multiple neural targets for afferent circuits. Then there is a panoply of effector parts and processes, including behaviors, vascular adaptations, metabolism, brown adipose, shivering, and osmotic adjustments. But the complexity is not cause for giving up on the language of homeostasis (Romanovsky 2007). Negative feedback, writ large, is still how mammals regulate body temperature, even though there are multiple specific feedbacks, each with its own operating range and temporal kinetics. After all is said and done there is, in fact, a normal value for core body temperature (about 36.5–37.5 C), whether we call it a set-point or not.

Having positioned myself in league with other animal physiologists who contend that a theory of homeostasis can be large enough to answer the concerns of those who have offered alternative names and ideas (Dallman 2003; Romero et al. 2009; Bechtel and Bich 2024), I want to briefly show the broad reach of the homeostasis theory across the kingdoms of biology.

Vascular plants, like animals, are eukaryotic macroorganisms that occupy diverse ecological niches globally. They maintain a stable internal milieu that circulates among the roots, stems, leaves, and flowers, which provides and distributes nutrients, removes wastes, and facilitates water and gas exchange (Taiz et al. 2022). Like animals, their physiology is regulated in part by a variety of hormones including auxins, gibberellins, ethylene, and various biogenic amines related to serotonin and epinephrine. Several aspects of homeostasis in plants are mediated by stomata, which are regulated pores that are primarily found in leaves. The opening and closing of stomata is affected by light, carbon dioxide, humidity, and internal signals such as the circadian cycle. Feedback regulation of transpiration to regulate water loss operates via turgor pressure in vacuoles of guard cells surrounding the stomata. The inevitable water loss via transpiration and evaporation from leaves requires that sodium and chloride are tightly controlled and excluded to prevent osmotic concentration of the sap and dehydration of cells. In salt-tolerant plants such as mangroves, salt homeostasis is aided by salt-secreting "glands" at the base of leaves. Distribution of sugars from leaves (where they are synthesized) to roots and fruits (where they are stored) requires that sap sugar levels are homeostatically regulated within a range where the cost of transport does not exceed the energy of the nutrients, and the viscosity of the sap does not interfere with flow.

Free-living bacteria homeostatically regulate a wide range of internal variables, from pH and ionic strength to macromolecular crowding and turgor, which determine cell shape (Wood 2001; Poolman 2023). An internal pH is regulated to establish a charge differential, so that the cytoplasm is negative relative to the surrounding fluid. This provides for a proton motive force that is used to energize ATP synthesis, and consequently a host of transport and biosynthetic processes. Cell turgor and volume are regulated in part by feedback control of the OpuA transporter in *Lactococcus*. The increased osmolality and ionic strength associated with volume depletion activates OpuA, which transports the osmolyte glycine-betaine, drawing in water to restore volume and switch OpuA transport off. Homeostatic regulation in bacteria has been explored in only a few example species, and given the astonishing diversity and environmental tolerances of bacteria, the opportunities for interesting and odd regulatory processes seems limitless.

We have examined the breadth of homeostasis from two perspectives. First, despite alternative names and concepts, the theory of homeostasis is flexible enough to do what Bernard imagined – to provide stable conditions for autonomous lives – and what Cannon documented – to control ranges of variations that are compatible with life. It is helpful to notice that names for all of the alternative concepts share one of the Greek roots with homeostasis (allo-*stasis*, *homeo*-rhesis, rheo-*stasis*, etc.), indicating that they all retain their focus on physiological stability. These concepts offer adjectival specifications to homeostasis, but do not supplant its broad theoretical reach. Second, homeostasis is a theory that informs how all living things, from microbes to advanced plants and animals, maintain sufficient stability for their independent lives. It is remarkable to reflect on the success of this theory, built on mammalian physiology and validated by human medicine, to inform the physiology of all living organisms.

Homeostasis performs the classic task of theory for physiology, in that it unites a wide scope of physiological knowledge and observations under a single conceptual framework. But homeostasis, even in its broadest construct, does not address how physiology propels organisms (or cells) to move from their current functional status into an authentically new life stage. Homeostasis, in Bernard's words, addresses a circumscribed "free and independent existence," but has nothing to say about the perpetuation of that existence by transformations that are core topics of physiology. The physiology of reproduction, growth, and development have always been absent from homeostasis, but present in physiology textbooks, societies, and publications. This is appropriate, because these processes require transformative changes that are outside the stabilizing regulatory processes for which homeostasis is responsible. A full accounting of physiology includes both homeostasis and transformative change, operating as integrated partners. Physiological processes that cause genuine transformations of functions, morphologies, behaviors, and metabolism require a complementary theory of physiology.

"Kinorhesis" is proposed here as a unifying concept for the physiology of transformative changes. The term kinorhesis is based on the Greek roots of *kino*-, meaning to propel, and *rheo*-, meaning flow or current. Basing the term on roots that have different meanings from homeo-and -stasis is intended to signify that kinorhesis is not a modified version of homeostasis but, rather, a complementary concept. It has been possible to study and teach physiology under a rubric that is organized as "homeostasis + many other things that are not homeostasis." However, it seems that those non-homeostatic parts of physiology may share some important features and processes that could be heuristically and educationally valuable to explore.

3.2. The Physiology of Transformative Change: Kinorhesis

Here I introduce the concept of "kinorhesis" on a foundation of two representations. First, demonstrating a few familiar physiological phenomena that conspicuously illustrate the idea of transformative change. And secondly, showing that there are different physiological control processes at work in kinorhesis as compared with homeostasis.

Metamorphic life histories are common among both invertebrate and vertebrate species, and the most familiar are insects that have worm-like larval stages and transform into a highly specialized adult such as a fly, moth, or butterfly; and amphibians that transform from tadpoles into frogs or toads. The consequence of metamorphosis is that the organism becomes capable of living in new environmental circumstances and with new homeostatic imperatives. Life histories that can exploit different environments and ecological niches at different times have frequently been favored by evolution. Before metamorphosis, the tadpole is adapted to swim in an aquatic environment, absorb oxygen from the water, and feed on algae, and after metamorphosis, the frog or toad hops and walks about on land, breathes air, and hunts insects and other terrestrial prey. Metamorphosis is driven by hormones, with thyroid hormones playing a major role (Laudet 2011). Although metamorphosis is clearly physiological, no one could reasonably argue that metamorphosis is a homeostatic process.

The physiology of migrations is linked to transformative changes in many cases. Migrations of salmon to breed in freshwater and eels to breed in seawater entail physiological changes to processes such as osmoregulation and nutrition, coupled with morphological and behavioral transformations (Currie and Evans 2020).

Another familiar kinorhetic process is childbirth, or more generally mammalian parturition. Clearly not homeostatic, parturition is a vectorial, stepwise process of transformation from life as a fetus, whose physiology is completely integrated with that of the mother, to life as a physiologically autonomous individual that is responsible for its own internal milieu. Successful parturition is driven by a well-known positive feedback whereby uterine contractions increase pressure on the cervix initiating a neural reflex that stimulates pituitary oxytocin secretion. Oxytocin causes stronger uterine contractions, reinforcing the positive feedback, and forcing expulsion of the fetus(es). The positive feedback cycle is ultimately interrupted by the birth, allowing oxytocin secretion to fade.

The different outcomes of homeostasis (stability) and kinorhesis (transformation) imply that different control processes are at work in each. As discussed above, the stabilizing processes of homeostasis can be described at several levels of detail. Cannon had access to only large-scale descriptions of stabilization, but was able to illustrate that storing nutrients in different forms or compartments or excreting excesses could stabilize their levels in the internal milieu. As experimental physiology progressed, the concepts of negative feedback reflexes, sensors, and set-points developed, as hormonal, neural and cell-to-cell communications were discovered and abstract descriptions of regulatory processes could be built based on known substrates. Homogeneous cultures of free-living bacteria have provided descriptions of homeostatic control at much finer levels of molecular and cellular detail than is possible in plants or animals (Wood 2001; Poolman 2023). All these processes have in common the tendency of homeostatic regulation to resist change or restore the system in question to a previous state of stability.

In contrast to stabilizing homeostatic mechanisms, kinorhetic transformations employ two types of destabilizing processes, positive feedback loops and sequential control. Like negative feedback, these control functions have direct physical analogues that are used widely in engineering applications.

As the name implies, a positive feedback loop has the opposite effect of negative feedback. A change in the regulated variable causes additional change in the same direction, reinforcing and amplifying the value of the variable. Positive, in this context, is not to be confused with "favorable," it is simply a description of the direction of response to the feedback.

Small initial changes are amplified into much larger outcomes by positive feedback. If unchecked, positive feedback will result in a catastrophic runaway, as in chemical and nuclear explosions, or in certain forms of hemorrhagic shock. Fortunately, in physiology, positive feedbacks are generally limited by the system reaching an end-state at which the cycle of feedback is broken. Childbirth is a well-understood human example of a process that employs positive feedback. The end state of increasing uterine contractions during childbirth is delivery of the fetus and placenta.

Positive feedbacks occur in biological contexts other than kinorhesis, such as membrane action potentials and muscle twitches. In the kinorhesis context, positive feedback destabilizes an otherwise homeostatic system and propels the system toward some transformative change, such as parturition. In vascular plants, positive feedback involving ethylene secretion accelerates the ripening of fruits (Lin et al. 2009).

Another class of processes that transformative change in otherwise homeostatic systems is sequential control. Sequential controls cause changes that are qualitative, not merely quantitative. The categorical changes caused by sequential controls govern the living histories of organisms, causing lives to play out in highly ordered and predictable patterns of growth and development. The life cycle of the fruit fly *Drosophila* is governed by sequential control as completion of each stage is a prerequisite for initiating the next stage (figure 2). The steroid hormone ecdysone is secreted at the end of each stage of development and activates expression of a stage-specific set of genes that determine the physiology and behavior of the fly at the next stage. The distinguishing features of sequential controls are that each phase culminates with signals to initiate the next phase, and the changes are qualitative, not merely quantitative.

Reproduction is transformational and undergirded by complex kinorhetic processes that readily illustrate positive feedback and sequential controls. Those kinorhetic processes are surrounded by homeostatically regulated chemical and physical variables (nutrients, ionic solutes, temperature, pressures, volumes, etc.). But the transformations that occur during reproduction cannot, *per se*, be characterized as homeostatic. The best-studied example is the human ovulatory sequence. As the egg cell develops, the cells surrounding the egg reach a level of estrogen secretion where feedback switches into a positive mode. This positive feedback causes explosive surges of gonadotropin that drive rapid changes to the ovary, which expels the egg (ovulation). Ovulation causes functional and morphological transformations of the ovarian follicle cells, which change their identity to the corpus luteum (yellow body) and switch to secreting large amounts of progesterone. Progesterone, in turn, controls the preparation of the uterus to accept the implantation of the embryo. This positive feedback and sequential control process is embedded in a much larger scheme that entails all of sexual development, mating, fertilization, and ultimately birth of the offspring. The whole set of transformational processes relies on linked kinorhetic control relationships.

To sum up the forgoing proposition, we envision that physiology requires two complementary governing principles. First, a comprehensive homeostasis theory that summarizes how or-

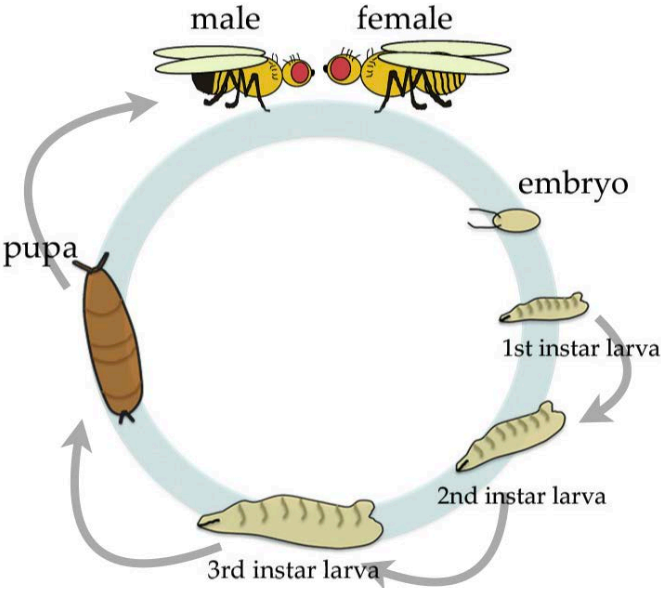

Figure 2: Drosophila life cycle depicting the major sequential control steps required to complete growth and metamorphosis. Arrows represent sequential control events driven by ecdysone surges toward the end of each instar and pupa stage. Revised from: Allocca M., S. Zola and P. Bellosta. 2018. "The Fruit Fly, *Drosophila melanogaster*: The Making of a Model (Part I)." *Drosophila melanogaster - Model for Recent Advances in Genetics and Therapeutics*. InTech. doi:10.5772/intechopen.72832.

ganisms maintain stability within the broad limits of autonomous survival (what Bernard called "a free and independent life"). And secondly, a theory that summarizes how physiology propels transformational changes during an organism's life history, which I propose naming "kinorhesis".

4. Physiological Principles and the Theory of the Organism

To reiterate: "to be alive is to be in possession of a physiology." The physiology about which we are concerned encompasses both the homeostatic processes that provide stability for living in the now, and the kinorhetic processes that propel transformative changes for growth, development, and reproduction so as to live and perpetuate into an uncertain future.

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 and not to the stone. The armadillo maintains a stable internal milieu and transforms through time from an embryo to an adult, and, ultimately, to a partner in reproduction. Although being dead is not the same as being a stone, a living armadillo is different from both a stone and a dead armadillo in the same way: the living armadillo has an autonomous 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. Death is also not the absence of physics, or of any particular kind of physics. Atoms and subatomic particles move in accordance with physical laws regardless of whether the armadillo is alive or dead, 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 minuscule level, a stone. The anatomies and material substances of the organism and its corpse may be indistinguishable. But the living organism is in possession of the processes of an autonomous physiology, and the dead one's physiology has expired. It is, in fact, the autonomous physiological processes of the individual that define it as a living thing.

Various philosophers have attempted to define and delineate what it is to be a biological individual, and the problem is more nettlesome than it might seem (for a review, see Wilson and Barker 2024). Out of the many arguments put forward, the most concise and compelling is the idea that biological individuals can be described on the basis of whether they are physiological entities (physiological individuals) or evolutionary entities (evolutionary individuals), or both. Quoting from Thomas Pradeu, 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. (Pradeu 2016, 807)

The most common usage of the word "organism" coincides with the physiological individual according to Pradeu's definitions. Our common experience is with organisms that are simultaneously physiological and evolutionary individuals vested in the same entity. 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 where the relationships between the physiological and evolutionary individual are unconventional or open to questions.

The physiological individual has generally been portrayed as the homeostatic individual at a particular moment in its life history. A fuller view that consciously considers the complete homeostatic/kinorhetic individual through all of its physiological states and transformations may provide new insights into the nature and evolution of biological individuals.

5. Summing Up and Looking Forward

It is fair to ask why, a hundred years after Cannon, should we need to reexamine homeostasis and consider a separate principle in physiology? But as the ongoing discussions and controversies over the scope of homeostasis illustrates, the situation isn't really settled, nor should it be. The controversies over concepts like allostasis continue to contribute to the unsettled question of whether "stresses" that are less than sufficient to cause homeostatic decompensation might cause long-term consequences. Physiology does not suffer from too much discussion about theory, or too many controversies about its theoretical framework. If anything, the demands of producing original research papers and chasing after funding have artificially limited how physiologists (and biologists more generally) find time and motivation to consider the contexts of our work. Also, topics in biology (especially those beyond evolution) deserve more attention from professional philosophers.

As a bedrock governing principle of physiology, homeostasis has certainly proven its value. In the practices of human and animal medicine, the maintenance and restoration of homeostasis are the most common motivations for interventions. Both Bernard and Cannon conceived that homeostasis was a feature of warm-blooded, "higher" animals. But, like many good ideas, homeostasis was bigger that its originators realized. And modern experimental biology has shown that not only "higher animals," but also "lower" animals, plants, and microbes of all sorts regulate their internal environments homeostatically.

When we examine homeostasis in its broadest reasonable conception, we see that it does not address physiological control processes that drive transformative changes during an organism's life cycle. Reproductive and developmental physiology have generally been absent from discourse about homeostasis, and for good reason. Certainly there are pathological situations in reproduction and development when homeostasis is challenged, but homeostasis does not drive the processes of reproduction, development, and other transformative changes. Physiological processes transform all or part of the organism from one "similarly standing" state to a new one; e.g., what had been an estrogen-secreting ovarian follicle is transformed into a progesterone-secreting corpus luteum.

Evolution requires that homeostasis and physiological control of transformations (called kinorhesis here) articulate in ways that are "fit" in the evolutionary sense. And there is not a single answer for what amounts to fitness. Mammals generally produce a few offspring and maintain their homeostasis through several cycles of reproductive transformations. In contrast, a salmon gives up on homeostasis at some point and migrates into a hostile environment where he or she will die after mating. And many butterflies and moths lack mouthparts and do not feed after emergence. These are not accidental disruptions to homeostasis; they are better viewed as evolutionarily selected kinorhetic adaptations.

Perhaps the most consequential aspect of elevating attention to theory in physiology should be on education. General biology and physiology textbooks tend to begin with one or more chapters on chemistry and physics. There are multiple reasons for this. One reason is that students may not have already taken chemistry and physics courses that provide some important background. A less justified motivation is to reinforce a materialist/physicalist perspective for students. Biological beings must, and do, obey the laws and theories of physics and chemistry. But physiology stands on scientific theories that are completely outside the physical sciences; natural selection and homeostasis being the obvious examples.

Homeostasis and kinorhesis are scientific theories to introduce physiological processes into basic biology education alongside evolutionary theories. Evolution provides the basis for understanding the history of species and the origins of characteristics (traits). Physiology provides the basis for understanding the operations of individuals, including their autonomous functions, reactions to their environments, and their transformations as they move through the stages of life. Both evolution and physiology are well-established theoretical disciplines that are fully compatible with the physical sciences, but their governing principles could never have been deduced from any amount of knowledge about physics or chemistry.

Physiological principles point to the idea that the functions that are described abstractly by physiology are the real defining entities of organisms. Even DNA, with its semiconservative replication mechanisms, is continuously repaired, renewed, remodeled, and reconfigured for changing expressions. The ions, atoms, and molecules of a biological entity are transient employees of the physiological processes. These many processes are implementations of governing physiological principles of stability (homeostasis) and transformation (kinorhesis).

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