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Rediscovering Bernard and Cannon: Restoring the Broader Vision of Homeostasis Eclipsed by the Cyberneticists

William Bechtel[1], Leonardo Bich[2]

[1]Department of Philosophy, University of California, San Diego, CA, USA, wbechtel@ucsd.edu
[2]Department of Philosophy, IAS-Research Centre for Life, Mind and Society, University of the Basque Country (UPV/EHU), Donostia-San Sebastian, Spain, leonardo.bich@ehu.eus

Abstract

Since Cannon, inspired by Bernard's discussion of the conditions required for free and independent life, introduced the term *homeostasis*, many have embraced it as the main theoretical principle guiding physiology and medicine. Nonetheless, critics have argued that *homeostasis* is too limiting and have advanced a variety of alternative concepts such as *heterostasis*, *rheostasis*, and *allostasis*. We argue that the critics target a much narrower understanding of homeostasis put forward by the cyberneticists and that Bernard and Cannon embraced a far broader understanding that can accommodate the alternatives advanced by the critics and provide an integrated theoretical framework for physiology.

Keywords: homeostasis; negative feedback; setpoint; control; organism

1. Introduction

One hundred years after Cannon introduced homeostasis as a basic principle in physiology, it continues to be extensively invoked as "the central organizing principle upon which the discipline of physiology is built, the very concept we need to return to in order to integrate function from molecule to the intact organism" (Billman, 2020, 2).[1] The popular textbook characterization of homeostasis, however, stems not from Cannon but from the cyberneticists.[2] On this view, organisms employ negative feedback control mechanisms to maintain critical physiological variables at constant values. Like the familiar thermostat, these mechanisms are characterized by setpoints that specify the value to be maintained. A host of physiological theorists have criticized this conception of homeostasis as too narrow to provide an adequate account of the control processes employed by organisms to maintain themselves and have advanced new concepts to supplement or supplant *homeostasis* (Hagen, 2021). In doing so, the critics have accepted the cyberneticist's account of homeostasis as negative feedback to a setpoint, which eclipsed the much broader vision embodied in the foundational work of Bernard and Cannon. Bernard and Cannon focused primarily on the organism in which homeostatic mechanisms are operative and on how organisms maintain conditions in which they could carry out the activities through which they maintain themselves.

Our goals are to re-introduce the framing on physiological regulation developed by Bernard and Cannon and to show that it can be extended to embrace the regulatory phenomena advanced by

[1] Billman's paper is widely cited across diverse specializations of physiology—according to Google Scholar, 352 times as of September 24, 2024. And, of course, the concept has been invoked by many who do not cite Billman's paper. Homeostasis has figured in attempts to restructure the physiological curriculum (Michael et al., 2017). In their textbook, Widmaier, Raff, and Strang (2016) claim that physiology as a discipline is centered on coordinated homeostatic control mechanisms. Recently, philosophers focused on evolution have addressed whether evolvability is a central organizing concept in evolutionary biology (Hansen et al., 2023). Villegas et al. (2023), for example, have focused on its role in different investigatory activities in evolutionary biology. Although we cannot develop a similar analysis here of the roles played by homeostasis, its widespread invocation in physiology suggests that such an analysis would be informative.

[2] See Modell et al. (2015) or Widmaier, Raff, and Strang (2016) for examples of the impact of the cybernetic view on education in physiology.

the critics of homeostasis. The point of extending rather than supplanting the original conception of homeostasis is that, appropriately broadened, homeostasis provides an integrative perspective on the processes through which organisms regulate themselves so as to perform the activities required to remain alive. We begin in section 2 by discussing how the cyberneticists restricted homeostasis to negative feedback involving setpoints. The restricted conception has proven useful: it has stimulated biologists to investigate negative feedback processes and, in some cases, attribute setpoints. Critics, however, have argued that this restricted conception does not exhaust the means by which organisms regulate their activities to maintain themselves. In section 3 we examine three of these criticisms and introduce several of the alternative concepts these theorists have advanced. In section 4 we turn to Bernard and discuss the context in which he advanced an account in which the maintenance of what he termed the internal environment enabled birds and mammals to live free and independent lives. Then in section 5 we turn to Cannon, describing how he built upon Bernard's framework in coining the term *homeostasis* and the types of processes he presented as subserving homeostasis. Finally, in section 6 we show how the proposed alternatives to homeostasis discussed in section 3 can be situated and integrated within the broader conception of the maintenance of the internal environment introduced by Bernard and the account of homeostasis developed by Cannon.

2. Homeostasis as Control by Negative Feedback: The Legacy of the Cyberneticists

Negative feedback control involves a control mechanism detecting when the output of a process departs from a target or setpoint and initiating action on the process to bring its output back to the target. It was not invented by the cyberneticists; rather they popularized, formalized and made central to their framework a mode of control that has been realized repeatedly by designers of artifacts (Mindell, 2002). The first known application was in the 2nd century BCE by Ktesibios in Alexandria. In his design of a water clock, he used negative feedback to maintain a constant flow of water into the receptacle in which time was registered by the height of the water. To keep the flow constant, he employed a float that was connected to a valve that opened when the float dropped below the target level and closed when it reached it. The same idea was implemented in other technologies, such as thermostats (Mayr, 1970). An especially prominent and consequential implementation was in the centrifugal governor Watt invented to control steam engines. It registered increases and decreases in speed using a pair of flyweights attached to a spinning spindle that would spread apart as the spindle turned more rapidly or come together when it slowed down. Watt linked this apparatus to the valve regulating steam flow so that it opened when the balls move closer together and closed when they moved apart, thereby maintaining a constant speed. Watt's governor inspired Maxwell (1868) to develop a mathematical analysis of the operation of governors. Employing this formal analysis, designers made extensive use of negative feedback in new technologies in the early 20th century such as missiles that corrected their trajectory to hit their target even if the target took evasive action.

Inspired by the fact that technologies that employed negative feedback to regulate their actions to pursue a goal state or setpoint (the target value to be maintained), Rosenbleuth, Weiner, and Bigelow invoked negative feedback to account for purposeful behavior. Their contention was that only systems employing negative feedback had their own, intrinsic, purpose: "All purposeful behavior may be considered to require negative feedback" (Rosenblueth, Wiener, and Bigelow, 1943, 20). They conclude by proposing that negative feedback provides a basis for understanding teleology in a manner that does not invoke undefined final causes: "Teleological thus becomes synonymous with behavior controlled by negative feed-back and gains therefore in precision by a sufficiently restricted connotation" (p. 24).[3] Building on this idea, beginning in 1946 Wiener organized a series of Macy Conferences that advanced negative feedback (characterized as circular causation) as a central explanatory concept for explaining biological, behavioral, and social phenomena (Pias and Von Foerster, 2016). Soon after Wiener (1948) introduced the term *cybernetics*, derived from the Greek term for a person steering a ship towards a target location.

One of the attractive features of control through negative feedback was that it lends itself to mathematical analysis. The target value for a variable is characterized as the setpoint and the actual value is compared to it. The resulting difference is then employed to determine the response. Hammel (1965) advanced what he termed *the law of the controlling system*:

$R - R_o = \alpha_R (T_h - T_{set})$

[3] Jonas (1953) criticized this approach to teleology because it ignores the larger system in which a feedback mechanism operates and which is the source of goals: in the case of biological mechanisms this is the organism (see also Bich, 2024b).

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where R is the regulated metabolic level, R_o is the basal metabolic level, $R - R_o$ is the thermoregulatory response, T_h is the measured value and T_{set} is the temperature setpoint. To see how this effects control, one needs to complete the causal loop by recognizing that T_h is itself partially determined by $R - R_o$, as shown in Figure 1.

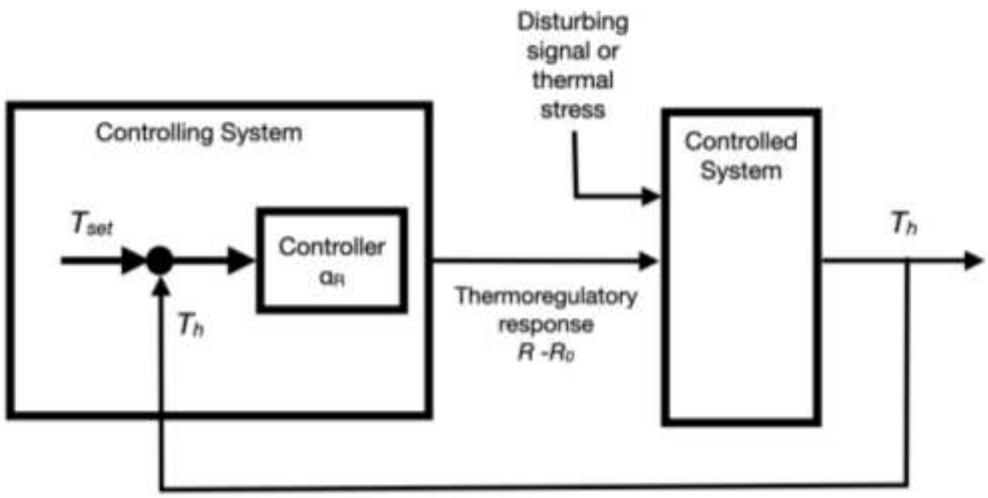

Figure 1. Negative feedback control of the regulated variable T_h (core body temperature) based on its difference from the target value or setpoint T_{set}.

The cyberneticist's characterization of negative feedback control was widely embraced by physiologists seeking to understand the self-regulatory processes in living organisms. Hammel himself applied it to the regulation of core body temperature. He treated the preoptic area (POA) of the hypothalamus as operating much like a thermostat. Neurons in this region register when the temperature in the brain differs from the setpoint and send outputs to effectors such as brown adipose tissue (initiating thermogenesis and shivering) and the rostral raphe pallidus (initiating vasoconstriction in the skin).

This framing of negative feedback control as operating to maintain setpoints was applied to characterize the control of a wide range of physiological systems (for examples, see Ramsay and Woods, 2014) and many physiologists simply equated homeostasis with control via negative feedback. This is evident in two prominent characterizations of homeostasis for students from the latter part of the 20th century:

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Cannon's word, homeostasis embraces the fixed, or constant, internal environment, but then goes on to suggest dynamic, self-regulating processes that serve to maintain that constancy or to return the internal environment to normal should it get out of whack. This is the concept now referred to as negative feedback, that is, if there is a deviation in one direction, there is a reaction in the opposite direction (Langley, 1965, 9).

The term homeostasis is used by physiologists to mean maintenance of static, or constant, conditions in the internal environment. . . . Essentially all . . . control mechanisms of the body . . . operate by the process of negative feedback (Guyton, 1982, 3).

Although, as we discuss in the next section, there is now debate about the utility of characterizing homeostasis in terms of setpoints, such references are still extremely common. For example Davis and Müller (2015) assert "homeostatic systems require a set point that precisely defines the output of the system." Nijhout, Best, and Reed (2019) maintain "Homeostatic set points are absolute values, not relative. . . . The set points reside in the hypothalamus." Recent proposals articulating central concepts of physiology for pedagogical purposes make setpoints a defining feature of homeostasis (Modell et al., 2015; Beckett et al., 2023). In a prominent text meant for students, Libretti and Puckett (2023) assert "Homeostasis would not be possible without setpoints, feedback, and regulation."

3. Challenges to Homeostasis as Limited to Negative Feedback to a Setpoint

The cyberneticist's construal of homeostasis as negative feedback both inspired research into negative feedback processes that kept variables near setpoints and criticisms that such processes do not exhaust the means organisms employ to maintain themselves. The critics typically do not deny that there are cases in which negative feedback maintains setpoints but have advanced a number of additional concepts, intended either to supplement or replace homeostasis understood in those terms. In this section, we briefly discuss three of these criticisms delineating the insufficiency of homeostasis and introduce the various concepts that these critics have

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advanced[4]. Each of the criticisms addresses the notion of setpoint, the idea that organisms maintain variables at specific values by negative feedback.

The first group of critics argue that setpoints need not be fixed. This line of argument was pioneered by Selye (1973), who argued that as a result of stress, organisms often reset setpoints to cope with the stressor. He advanced the term *heterostasis* (heteros = other; stasis = fixity) to describe a process that "resets the thermostat" to maintain a higher state of defense by artificial exogenous intervention (p. 443). He contended that this was not in conflict with homeostasis, which he took to assume a fixed setpoint: homeostasis represented a short-term response to occurrent stressors whereas heterostasis involved longer-term adjustments involving changing the setpoint.

Hammel (1990) presented such adjustments to setpoints as a feedforward process that complemented feedback regulation and offered examples in which animals adjust their target core body temperature when they detect altered conditions in their environment. Hammel did not introduce a new term, but incorporated feedforward processes within his conception of homeostasis. Mrosovsky (1990), however, argued that the phenomenon is sufficiently widespread and important to merit a new name, *rheostasis*: "A change in the defended level of the internal environment is an elaboration, not a contradiction, of homeostasis. It is sufficiently common, however, and it has enough ramifications to merit its own name, rheostasis" (p. 13). In invoking the term Mrosovsky explicitly alludes to rheostats designed by engineers: "a rheostat precisely and vividly exemplifies a device whose setting may easily be adjusted." Mrosovsky offers fever as an example of rheostasis: when challenged by a pathogen, birds and mammals increase (in some cases decrease) the temperature setpoint they maintain—for example, humans shiver and add bedding to maintain a higher setpoint. Raising the temperature setpoint is interpreted as creating a less hospitable environment for pathogens.

The examples so far involve organisms changing the setpoint for negative feedback processes in response to perceived conditions. A second group of critics focus on how organisms can

[4] For a detailed analysis of these criticisms focused on work on the regulation of body temperature, see Bechtel and Bich (2024).

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anticipate conditions that have not yet arisen and adjust the setpoint for negative feedback accordingly. Most animals anticipate daily changes in their environment on the basis of endogenously generated circadian rhythms—oscillations whose period approximates the daily cycle of light and dark on our planet. Circadian research in the 20th century documented that most physiological variables vary over the course of 24 hours. Accordingly, in a volume dedicated to Cannon on the occasion of the 50th anniversary of his development of the concept of homeostasis, circadian biologist Moore-Ede (1986) noted a prima facie conflict between circadian rhythmicity and homeostatic responses that serve to keep conditions constant: “At first glance the demonstration of endogenously generated rhythms in physiological variables which can persist independent of fluctuations in environmental conditions would seem to be antithetical to the very idea of homeostasis”(p.737). Moore-Ede, however, argued for reconciling the two by differentiating two varieties of homeostasis: “reactive homeostasis—corrective actions in response to a change which has already occurred”—and “predictive homeostasis—corrective responses initiated in anticipation of a predictably timed challenge”(p.738). Moore-Ede argued for the importance of predictive homeostasis by noting that many physiological responses, for example, those requiring the synthesis of specific proteins, require considerable time so that, if the organism is to respond successfully to environment changes, it must prepare its response before changes are experienced.

While Moore-Ede retained the term *homeostasis* in his concept of *predictive homeostasis*, Mrosovsky (1990) incorporated it under his alternative concept of rheostasis, introducing a distinction between reactive and programmed rheostasis. He illustrated programmed rheostasis with the phenomenon of mammalian hibernation.[5] In his earlier research, Mrosovsky (1971) had demonstrated that even during hibernation animals regulate their internal temperature, just at a lowered setpoint. He quotes Heller, Colliver, and Beard’s (1977, 58): “Clearly, then, hibernation is a state in which the mammalian regulator of Tb [core body temperature] is reset to a lower level, and it is not a state during which the thermoregulatory system is inactivated”. Moreover,

[5] Bernard and Hammel both discussed hibernation but treated it as a failure of the animal’s ability to maintain its internal environment. For Bernard, a hibernating mammal is like a seed, allowing its temperature and other variables to be set by the environment.

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he describes how, during hibernation, mammals adjust their setpoint further to periodically warm themselves, which enables them to eliminate end products of metabolism such as urea.

In recognition that organisms can change their setpoints in anticipation of changing environmental conditions, Sterling and Eyer (1988) introduced the concept of *allostasis* as a replacement for *homeostasis*. For Sterling (2004, 18), the capacity to anticipate situations and alter setpoints ("using prior information to predict demand and then adjusting all parameters to meet it") distinguishes allostasis from homeostasis. Schulkin and Sterling (2019) include circadian rhythms as an example of an evolutionarily acquired ability to anticipate change but also appeal to activities organisms learn to perform in anticipation of future conditions.

The first two challenges to homeostasis conceived as negative feedback to a setpoint focus on how setpoints are changeable either in response to changing conditions or in anticipation of such changes. The third group of critics challenges the very appeal to setpoints. In engineered systems, there is often a physical component that embodies the setpoint. Typically, it is a component, as in a thermostat, that can be acted on and thus reset. In invoking the language of setpoint in biology, researchers have often assumed that there is likewise a component in the organism that can be set and, in response to anticipatory processes such as circadian rhythms, reset. The failure to find a component that functions as a setpoint would be expected to function leads some to reject the notion. Romanovsky (2018), for example, argued that the POA, which Hammel considered to be the likely locus of the body temperature setpoint, doesn't function as a comparator of current temperature with a setpoint. He contends that the notion of setpoint is best set aside. In making his case, he invokes The Commission for Thermal Physiology of the International Union of Physiological Sciences' (2001) entry on set-point, which includes a note that the use of the term "has evoked much confusion, as it has been used for different phenomena." One of three notions it distinguishes entails "a central reference signal (which obviously does not exist explicitly in the thermoregulatory system)."

While Romanovsky proposes dropping appeals to setpoints in physiology, others propose understanding them metaphorically. Ramsay and Woods (2014) assert "In physiology, the term set point is used metaphorically to indicate that a regulatory system operates as if there was an engineering type of set point or reference signal, that is, a set point is a hypothetical construct that is inferred by assessing whether an animal defends a given value of one or another variable using behavioral and/or physiological responses" (230). Critics like Romanovsky, however, reject even the metaphorical use of setpoint, in large part because it suggests that there is just one process regulating each physiological variable. Often research has revealed numerous regulatory processes that all have effects on a given variable. Reflecting this, Romanovsky (2004, 2007), whose focus is on the regulation of core body temperature, recommends replacing setpoint with *balance point*. The prime benefit, he contends, is that it "redirects the scientific search from looking for the location of the set point (or building a new model of it) to studying the multiple feedback, feedforward, and open-loop components that contribute to thermal balance in the thermoregulatory system operating as a federation of independent thermoeffector loops"(2007, 43).[6]

In advancing their argument for replacing homeostasis with allostasis, Sterling and Eyer (1988) emphasized that not only are individual variables affected by multiple control mechanisms but also that these mechanisms affect other variables that the organism needs to control. For example, as behavioral activity increases blood pressure, many other processes in the organism are changed, including increase in metabolism and energy production, suppression of immune responses, etc. Accordingly, Sterling and Eyer (1988, 636) contend: "to maintain stability an organism must *vary* all the parameters of its internal milieu and match them appropriately to environmental demands. We refer to this principle as allostasis, meaning 'stability through change'."

As we have shown, critics of what they take to be the limited perspective provided by homeostasis, understood as involving negative feedback to a setpoint, have advanced a variety of alternative concepts to supplement or replace it.[7] At present, researchers employ a plethora of

[6] Similarly, the literature on the control of body weight also challenges the existence of setpoints and the use of this notion, replacing it with that of *settling point* (Müller, Bosy-Westphal, and Heymsfield, 2010).

[7] In parallel to physiology, a similar criticism has been advanced in developmental biology by Waddington (1968). In order to account for the specificity of developmental regulation, which stabilizes processes (epigenetic trajectories) rather than variables, he introduced the alternative notion of *homeoresis.* In line with the critics of the

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notions, and there has been little effort to relate them or integrate them into an inclusive, coherent framework. This, though, was what Bernard and Cannon sought to provide. Accordingly, some theorists, such as Carpenter (2004), have argued that Cannon's notion of homeostasis should be maintained as a unifying perspective. He makes his case by arguing that Cannon's focus was on control and showing that control processes are far more inclusive than negative feedback to a setpoint. In addition to direct and parametric feedback, he argues they include feedback based on an efference copy, hierarchical combinations of these, and occasional random internal perturbations. While Carpenter usefully gathers multiple control processes under the common label *homeostasis*, he does not articulate what integrates them, and how they relate to the theoretical notion of homeostasis. To establish the basis for integration, we return to Bernard and Cannon and show how they developed their understanding by focusing on conditions organisms need to maintain to perform their diverse activities.

4. Bernard's focus on Conditions Required for "Free and Independent Life"

Cannon (1929, 400) traces his conception of homeostasis to a passage in Bernard's last publication, which Cannon translates as "It is the fixity of the 'milieu interieur' which is the condition of free and independent life" (Bernard, 1878, 113).[8] Cannon immediately goes on to cite a subsequent passage from Bernard that is less often noted: "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment" (121). We will return to the second passage below, but begin with the first sentence Cannon quotes, a sentence widely quoted in presenting Bernard as providing the inspiration for the concept of homeostasis. The term Bernard used, "fixité", is most often translated as constancy, giving rise to the view that, like the cyberneticists, Bernard envisaged the mechanisms of organisms as working to maintain specific values of physiological variables. However, Bernard himself follows up the sentence Cannon quoted with the statement "the mechanism that makes it possible is that which assures the maintenance within the internal environment of *all the conditions necessary for the life of the elements*" (emphasis added). This

cybernetic view of homeostasis, he argued against feedback as the only stabilization mechanism, proposing to consider also absorbing buffering as the means by which a biological system compensates for perturbations.

[8] Unless otherwise noted, the translations from Bernard are due to Langley (1973).

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points to a much less restrictive view that looks to the goal of these mechanisms. Bernard's emphasis is on maintaining conditions sufficient for a "free and independent life" for an organism.

The reference to "free and independent life" points to a further feature of Bernard's discussion that is often neglected. Bernard makes the statement in the context of distinguishing three forms of life, which he labels *latent* (as manifest in seeds), *oscillating*, and *constant or free*. Bernard labeled the second *oscillating* since in it physiological variables oscillate[9] under the influence of the environment: "The beings whose vital manifestations can vary within wide limits under the Influence of cosmic conditions are beings with life that is oscillating or dependent on the external environment" (103). These organisms include all plants, invertebrates, and coldblooded vertebrates. Only birds and animals exhibit "free and independent life," in which "life . . . unrolls along a constant course, apparently indifferent to the variations in the cosmic environment, or to the changes in the material conditions that surround the animal" (112). Further, the milieu interieur whose regulation makes this possible does not consist of all organs within the organism, but specifically "the lymph or plasma, the liquid portion of the blood which in the higher animals perfuses the tissues and constitutes the ensemble of all the interstitial fluids, is an expression of all the local nutritions, and is the source and confluence of all the elementary exchanges" (112-113).

Although Bernard characterizes free and independent life as "indifferent to the variations in the cosmic environment," the processes maintaining the internal environment require attending to the external environment and countering external processes that disrupt the conditions to be maintained. By doing so the animal can carry on its activities independently of it. Thus, Bernard says "far from being indifferent to the external world, the higher animal is on the contrary in a close and wise relation with it, so that its equilibrium results from a continuous and delicate compensation established as if by the most sensitive of balances" (113). In his detailed examination of Bernard's research practices, Holmes (1986) suggests that by emphasizing how blood provided a form of independence from the external world and focusing his inquiries on the

[9] A better term might be reactive. There is no indication that, in deploying the term *oscillating*, Bernard envisioned endogenously generated rhythms.

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interaction of tissues with the internal environment, Bernard sometimes backgrounded how the internal environment was affected and responded to the external environment.

Bernard's (1878) discussion of fixité of the milieu interieur is the culmination of his two-decades long engagement with the question of how the internal environment figures in living organisms. By contextualizing Bernard's often cited comments on the importance of maintaining the constancy of the internal environment within that history of inquiry, we can better understand his perspective. Beginning in 1854, Bernard presented annual lectures at the Collège de France, where he was expected to provide a broad conceptual framing of experimental medicine. The year before, another physiologist, Robin, advanced a distinction between the solid parts of the body that carry out actions and the fluids of the body that maintain them. In that context, Robin characterized the fluids as providing an interior environment:

> these fluids comprise the conditions of action, playing with respect to the solids the role which the external environment plays with respect to the entire organism. Finally, they establish the liaison between the interior and the exterior, between the general environment and the organized being. If the general environment disappears or is altered, the agent ceases to act; if the humours (this 'milieu' de l'intérieur) are altered, then all activity ceases in the solids, just as if they had . . . been destroyed" (Robin, 1853).

Bernard adopted this perspective in his first lecture in *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme* (Bernard, 1859). He contrasts the physicist's or chemist's focus on external conditions with that of the physiologist, for whom internal conditions "have to take priority in all physiological experiments." Tissues, he goes on to assert, "are, in reality, removed from direct external influences and protected by a true internal environment (milieu interieur) mostly constituted by fluids circulating in the body" (8). Tissues are not part of the internal environment but are protected by it. The fluids of the body act as a dynamic buffer against environmental perturbations. In his third lecture he turned specifically to blood, treating it as both the repository of the activities of the solid tissues and the source of their nutrients. He also focused on critical properties of blood, such as temperature. Traditionally body heat was thought to be produced by the blood. Based on detailed temperature measurements, Bernard concluded that heat was not generated in the blood but in the various tissues; the blood served to equalize the temperature through the body. Beyond that, he focused on how the blood served to protect tissues from large variation in temperature and sketched a mechanism by which a stable temperature might be maintained:

> It can be said that, in higher animals, tissues do not really feel the effects of temperature of the environment because they are steeped in another environment, a liquid internal environment which is the blood wherein the organs live like the embryo in the fluids which surround him . . . the animal carries in itself an environment which has its own temperature, 38 to 40°C. Therefore, it is here that one should look for the mechanism whereby an animal can maintain a constant temperature in spite of such large variations of the external temperature (51-52).

After obtaining evidence that arterial blood is sometimes warmer and sometimes colder than venous blood, he proposed that "the constancy of temperature results from a sort of equilibrium between acquisitions [from tissues] and the losses [to the tissues]. This equilibrium between production and loss is regulated by the nervous system" (p. 150; translation by Holmes). The idea seems to be that when one part of the body produces heat and so warms the blood adjacent to it, other tissues will cool it down.

Holmes relates how Bernard began to articulate a far more dynamical conception of the blood—that it has "a tendency to be corrupted and vitiated" by the solid parts of the organism it serves and so must undergo "incessant renovation and purification" (Bernard, 1867, 67; translation by Holmes). He went on to characterize this as resulting from "an essential equilibration between all of the chemical transformations which are carried out in the intraorganic milieu and the variable vital activity of the diverse secretory and excretatory systems" (88). Bernard began to characterize the equilibratory processes as enabling organisms to resist the environment. The sources of heat within the animal "enable it to react against the ambient environment, and to resist it."

Later on, Bernard introduced his conception of three forms of life that became the focus of his most developed thoughts about the internal environment with which we started (Bernard, 1878). He focused on several features of the blood that higher animals must maintain: water, heat, oxygen, and [energy] reserves. When he discusses water, he refers to "relative constancy" and emphasizes such things as thirst serving to replenish water when it is low. Moreover, he invokes

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a multiplicity of mechanisms ("secretion, exhalation, ingestion, and circulation which transport the ingested and absorbed fluid") as maintaining water in "effectively fixed proportions." When he turns to temperature, Bernard also identifies an "ensemble of mechanisms" and refers to temperature as "closely fixed." In the case of oxygen, he refers to keeping the quantity "more or less constant." What is clear is that Bernard did not envision absolute constancy, but only conditions within the range in which the tissues could function without impairment, and that he saw such maintenance as the product of a complex dynamic of processes. Moreover, while he only envisioned "constant or free" life for birds and mammals, he recognized the same needs in other organisms. Because they could not maintain these conditions within the required range, the conditions in which their tissues had to act varied with changes in the external environment. Accordingly, their ability to perform the activities of life varied along with the external environment.

Bernard's understanding of how birds and mammals are able to maintain a free and independent life is much more nuanced than has been generally recognized. Although he employed the notion of fixité or constancy, maintaining constancy in the internal environment was not itself the objective; rather, his primary focus was on these animals maintaining conditions suitable to perform the activities of life. In particular, he saw this ability as being served by the activities involved in maintaining the fluids that constitute the internal environment in conditions appropriate for the functioning of the organism. In developing the notion of the constancy of the internal environment, Bernard's ultimate focus was on how organisms maintain themselves in viable states.

5. Cannon's Broad Understanding of *Homeostasis*

Cannon's focus was likewise on the organism. His early research examined how animals respond to stressful challenges by mobilizing resources—for example, promoting glucose production by the liver to provide energy needed for muscle movements. This research revealed the role of adrenaline in initiating responses and led to his investigation of the role of emotions such as anger and rage in triggering such responses. Out of this he developed his characterization of fight or flight as the alternative responses to threats (Cannon, 1915). In this early work Cannon was

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already focused on physiological responses that maintained the organism, but it was in his work on endocrine regulation that he began to focus on the maintenance of a “steady state.” Yet, as he made clear in Cannon (1925), his focus was less on the steady state itself than on the physiological activities that maintained it and the usefulness of the concept for guiding research:

> The existence of steady states in the body and some agencies maintaining them have, of course, long been recognized. On this occasion I am laying emphasis upon these states because of an interest in some tentative general considerations with regard to physiological factors regulating them, and in the possible bearing of these considerations on problems of internal secretion. As they may have value in suggesting lines of research and bases for critical judgment, they may be worthy of attention (31).

Cannon articulates his “tentative general considerations” in a set of six principles. Some of this suggest that he limited his focus to simple mechanical procedures such as negative feedback to maintain them. For example, in the first principle he introduces agencies that act to keep a “balance”: “in an open system, such as our bodies represent, complex and subject to numberless disturbances, the very existence of a poised or steady state is in itself evidence that agencies are at hand keeping the balance, or ready to act in such a way as to keep the balance. . . .” and in the second he appeals to “an automatic arrangement whereby any tendency towards change is effectively met by increased action of the factor or factors which resist the change. . . .” In his fifth principle, though, he notes that, with disturbance, many agencies operated “at the same time or successively.”

After listing the propositions, he adds an important note qualifying the notion of a steady state:

> In the foregoing statements the expression "ready to act" has been used as an alternative to "acting" because in certain instances there is evidence that the situation is not kept balanced by direct and immediate opposition of active agencies, but is allowed to move to and fro within limits or within critical points, possibly under control of simple physico-chemical adjustments, and only when these limits are passed are the more complex and indirect physiological agencies (i.e., those involving reactions peculiar to the organization of living beings) brought into play (33).

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Cannon's idea of ongoing variation within a range will be illustrated below. What is important is that the responses that he will characterize under the term *homeostasis* involve agencies that are elicited only with larger-scale variations that threaten the viability of the organism.

Cannon first used the term "homeostasis" the following year in a short paper in a Jubilee volume for Richet. He begins that paper quoting from Richet (1900): "The living being is stable. It must be so in order not to be destroyed, dissolved, or disintegrated by the colossal forces, often adverse, which surround it. . . . In a sense it is stable because it is modifiable—the slight instability is the necessary condition for the true stability of the organism (246)." Richet's intention is not totally clear, but it seems that "the true stability of the organism" is not a state of no change, but one in which whatever variation there is does not threaten to destroy, dissolve, or disintegrate the organism. The "true stability" is what enables the organism to carry out the activities that, in turn, maintain it.

As Keller (2008) discusses, at the time Cannon was developing his ideas, principles of thermodynamics, developed by physicists in the 19^{th} century, were influencing both chemistry and biology. In this context, terms such as "constancy," "fixity," "equilibrium," "stability" and "steady state" were widely invoked, but they were also used in diverse ways. A central principle, expressed in the second law of thermodynamics, is that closed systems progress to a steady state of highest entropy (disorder). Biologists recognized that these high entropy states were not the steady states found in organisms. Already at the time, Hill (1931) characterized "the steady state" in membranes and tissues as "very far from equilibrium." He described the role of "delicate governors and . . . a continual expenditure of energy" in maintaining these states. In those same years, von Bertalanffy introduced a theory of the steady state in thermodynamically open systems to be applied to living systems (von Bertalanffy, 1952). As Keller discusses in the second part of her paper (Keller, 2009), later in the 20^{th} century, theorists such as Prigogine and Stengers (1984) would develop accounts of how order could emerge in conditions far from equilibrium. Although these ideas were not yet fully fleshed out when Cannon was developing his concept of homeostasis, he recognized that organisms were not closed systems, but ones open to their environment, and that the means by which organisms maintained themselves were, accordingly, more complex than those generating equilibrium in closed systems. Such

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considerations led him to coin a new term, *homeostasis*: “The steady states of the fluid matrix of the body are commonly preserved by physiological reactions, i.e., by more complicated processes than are involved in simple physico-chemical equilibria. Special designations, therefore, are appropriate:--‘homeostasis’ to designate stability of the organism; ‘homeostatic conditions,’ to indicate details of the stability; and ‘homeostatic reactions,’ to signify means for maintaining stability” (Cannon, 1926, 91). He then restates the six propositions from his previous paper, this time using the terms “homeostatic conditions,” “homeostatic agents,” and “homeostatic state.”

Cannon characterized his new concept in greater detail in a 1929 paper in *Physiological Reviews* entitled “Organization for Physiological Homeostasis.” He begins by identifying predecessors in addition to Richet who identified “self-regulatory arrangements” in physiology, beginning with Pflüger’s (1877, 76) statement: “The cause of every need of a living being is also the cause of the satisfaction of the need.”[10] He next quotes Frédéricq (1885, xxxv) as emphasizing the agential dimension of regulatory mechanisms in living organisms: “The living being is an agency of such sort that each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance. The higher in the scale of living beings, the more numerous, the more perfect and the more complicated do these regulatory agencies become. They tend to free the organism completely from the unfavorable influences and changes occurring in the environment.” He then quotes the passages from Richet and Bernard noted above.[11]

After this framing, Cannon provides what he terms a definition of homeostasis:

> The highly developed living being is an open system having many relations to its surroundings—in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs and bony levers. Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced.

[10] Pflüger explicates what he has in mind in terms of conditions the organism requires to carry out its activities: “I designate every altered condition of the living organism, which has to be transformed into a different condition in the interest and welfare of the individual or its kind, as cause of need.”

[11] In introducing Bernard’s notion of the fluids of the body, Cannon makes the interesting comment: “This fluid matrix is made and controlled by the organism itself.”

> Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant. The term "equilibrium" might be used to designate these constant conditions. That term, however, has come to have exact meaning as applied to relatively simple physico-chemical states in closed systems where known forces are balanced. . . . The coordinated physiological reactions which maintain most of the steady states in the body are so complex, and are so peculiar to the living organism, that it has been suggested (Cannon, 1926) that a specific designation for these states be employed—homeostasis (1929, p. 400).

He goes on to explain that he employed "homeo" as an abbreviation for *homoio*, the Greek word for similar, not "homo" to make explicit that what was maintained was not the same state but only a similar one that "admits some variation." While he uses the word *stasis* in the term, he constantly refers to *conditions*. From this discussion, it seems clear that in introducing *homeostasis* he was not limiting it to negative feedback maintaining a setpoint.

Like Bernard, Cannon focused on the fluids of the body, explicating homeostasis in terms of how organisms maintain the fluid matrix that supports their activities. In his account, Cannon expands modestly on the four conditions on which Bernard had focused ("water, heat, oxygen, and [energy] reserves"), distinguishing *material supplies* such as glucose, water, calcium, etc. and what he calls *environmental factors*, such as temperature, osmotic pressure, etc.

In discussing each, Cannon characterized a target range, not a specific value, and focuses on the risks when values fall too far outside the range. Thus, for temperature, he asserts: "The normal daily variations of body temperature in man range between 36.3℃ and 37.3℃; though it may fall to 24℃ and not be fatal, that level is much lower than is compatible with activity; and if the temperature persists at 42-43℃, it is dangerous because of the coagulation of certain proteins in nerve cells."

Cannon details a multitude of procedures, which he refers to as "agencies," that organisms invoke when one of these variables fall outside the target range to restore the disturbed variable "back towards the mean position." With respect to supplies, he describes two classes of

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agencies—storage by inundation (the flooding of areolar connective tissue both under the skin and around muscle) and storage by segregation (in which material is bound into other structures for storage). He illustrates the process in the case of regulating blood glucose with his only figure (Figure 2). The normal range, which he labels *common variation*, is between 70 and 130 milligrams per deciliter. When glucose concentration reaches 130 mg/dl, some of the glucose inundates areolar tissue, from which it can flow back into the blood when glucose concentrations in the blood drop. It is also segregated in the liver and muscles by being converted to glycogen. When it drops below 70 mg/dl, more glucose is typically released from segregation by reactions that convert glycogen to glucose. These, for Cannon, represent normal processes, not extreme responses. Only if glucose concentration drops much further (e.g., to 45 mg/dl) are there serious symptoms; Cannon thus refers to the range from 45 to 70 mg/dl as the "margin of safety." At the other end of the range, only when glucose exceeds 180 mg/dl does it overflow into the kidney, resulting in glycemia.

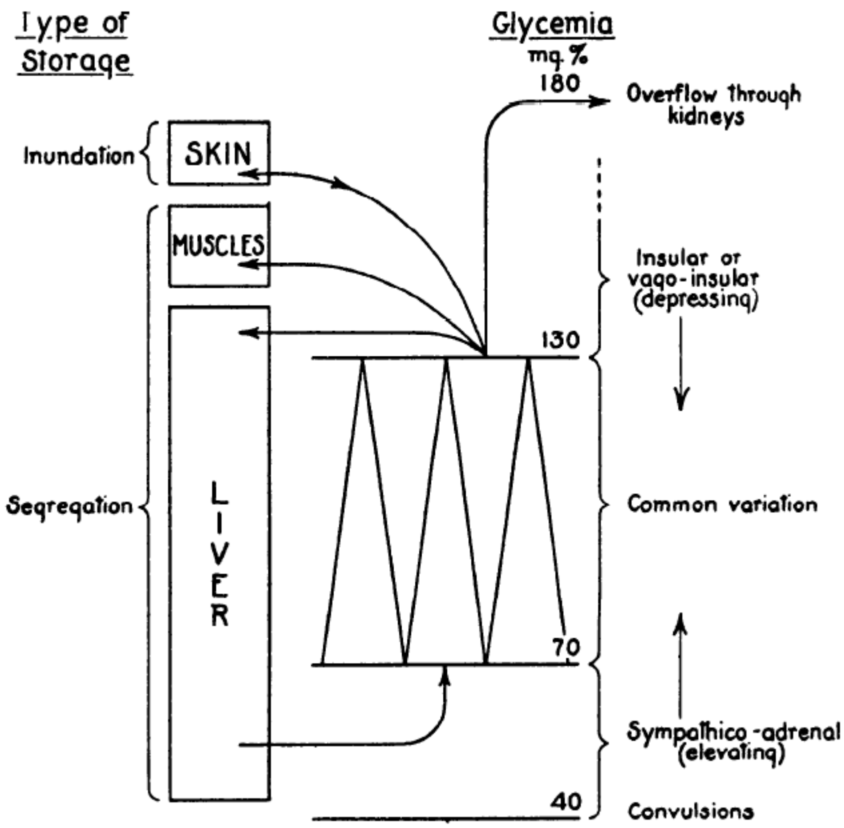

Figure 2. The one figure Cannon used to illustrate homeostasis. Common variation in blood glucose is shown in the middle with various processes that act to keep it in the range indicated. From Cannon (1929).

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A proponent of cybernetics might view Cannon's figure as simply illustrating negative feedback—whenever glucose concentrations exceed the boundaries of the normal zone, agencies act to restore it. But it is notable that these agencies are not presented in terms of comparing measured values to setpoints to initiate responses. Rather, the organism is simply organized to perform these restorative actions when conditions merit. This is particularly clear in his discussion of inundation—when the quantity of a substance such as glucose increases too much, it flows into the areolar tissue, from which it flows back out when the quantity decreases. He presents segregation in much the same way. For example, the reaction between glucose and glycogen is responsive to the concentration of glucose—when it is low, glycogen is metabolized to glucose and when it is high, glucose is metabolized to glycogen.

Far from limiting homeostasis to negative feedback, Cannon presents a far more nuanced account of regulation. He adopted the name *homeostasis* to reflect that the conditions maintained may vary, often over a significant range, as in the case of blood glucose. The agencies he invokes to maintain physiological variables within the target range do not have to make comparisons to setpoints and initiate responses when the variable fails to match the setpoint. Nothing Cannon says rules out such processes, but his focus is broader. He identifies a wide variety of processes that act to maintain physiological variables within ranges in which the tissues of the organism can perform their activities.

6. Bernard's and Cannon's Framework Can Encompass the Alternatives to Homeostasis

Bernard's conception of organisms maintaining the fixité of the internal environment and Cannon's conception of homeostasis are far broader than the characterization in terms of negative feedback to a setpoint promoted by the cyberneticists. The critics of the negative feedback accounts of homeostasis highlight phenomena that neither Bernard nor Cannon considered. However, their perspective on organisms maintaining conditions inside themselves in which they could carry out the activities crucial to life can accommodate the phenomena for which many of the critics have proposed novel names for concepts intended to extend or supplant homeostasis. However, little effort has been made to put into perspective these competing yet often overlapping concepts, to analyze how they are related, and to assess how

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many phenomena of physiological regulation they cover. We contend that this piecemeal proliferation of alternative and competing concepts is neither needed nor helpful, unless reframed as trying to provide a more refined subcategorization within a wider integrated framework for physiological control. A more integrated conception would allow us to provide a more coherent picture and provide a common background for discussing and comparing the more specific proposals, as well as exploring how they can be deployed together in the service of a common goal, that of maintaining conditions in which an organism can perform its activities.

In this concluding section we return to the three arguments raised against the narrow negative-feedback account and discuss in turn how Bernard's and Cannon's understanding can be extended to incorporate the regulatory activities the critics have pointed to. The key is that for both Bernard and Cannon the focus was on how (at least higher) organisms regulate their internal conditions so that they can carry out the activities they need to perform to continue their existence. That is, the maintenance of conditions suitable for the continued activities of the organism, not the means for doing so, is the focus. As both Bernard and Cannon discussed, there are a variety of means for doing so and they welcomed the identification of yet other means. Moreover, they recognized that these can interact with each other in complex ways. Keeping that in mind can provide the integrated perspective which Carpenter (2004) contended the concept of *homeostasis* provides. He approached the issue by subsuming negative feedback to a setpoint and other modes of regulation under a general category of control. We have offered the complementary approach of focusing on the goal of control—maintaining the conditions in which organisms can perform their activities—as a framework capable of relating and integrating the different modes of control.

The first challenge maintained that setpoints that organisms maintain through their regulatory processes are not fixed. It is true the Bernard spoke of fixité and Cannon of steady state. As we have discussed, however, their actual discussions emphasize a dynamical perspective. Bernard used phrases such as "relative constancy." Cannon chose the term *homeostasis*, not *homostasis*, to emphasize that an organism maintains a similar state (one that "admits some variation"), not the same state. He talks about processes preventing "wide oscillations" of physiological variables. While is true is that neither of them addressed organisms maintaining different

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conditions at different times, that is not, as Selye, Hammel, and Mrosovsky readily acknowledge, in conflict what Bernard and Cannon proposed. As Selye notes, it involves taking a longer temporal perspective than the responses on which Bernard and Cannon focused. Moreover, Selye and the others do not allow just any change in the conditions being maintained—they countenance changes that serve to enable the organism, over the longer-term, to maintain conditions in which they can perform their activities. Raising the core body temperature an animal maintains 1-2° C. to combat an infection serves that end, whereas raising it 4-5° C. does not serve that end. Keeping the focus on maintaining conditions in which the organism, both in the short and longer term, can perform the activities needed to live provides a perspective for evaluating what adjustments in target values are in the interest of the organism.

The second challenge focused on the ability of animals not just to react to current challenges but to anticipate them and prepare responses in advance. Endogenous circadian oscillations provide organisms a means to anticipate conditions that change over the course of a day and to change their internal state accordingly. Although some familiarity with circadian oscillations dates back to the Greeks, Wunderlich (1868) was conducting his experiments recording body temperature multiple times each day and finding variations just as Bernard was developing his ideas. In noting the regular variability in physiological variables, Cannon refers to the daily variation in core body temperature Wunderlich identified: "The normal daily variations of body temperature in man range between 36.3°C. and 37.3"C" (1929, 402). He does not identify the source of the variation and does not present such variability as an adaptive response of the organism or view the agencies that maintain variables as operating differently at different times of day. Yet, as Moore-Ede (1986) emphasized, embracing circadian rhythmicity as one of the strategies through which organisms maintain themselves is not inconsistent with homeostasis. As more recent researchers have emphasized, adjusting activities of the organism at different times of days is actually a means to maintain homeostasis in its broader sense (Lamia, Storch, and Weitz, 2008). The key is the state the organism maintains at a time is one that is suitable for different tissues (or the immune system) to perform the activities needed for the survival of the organism. This is not just compatible with Bernard's and Cannon's framing, but reflects the same perspective on the organism as maintaining conditions for its components to perform their activities.

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Mrosovsky (1990) and Sterling and Eyer (1988) identify additional ways in which organisms anticipate conditions and adjust the values of physiological variables. They contend that these are sufficiently different from homeostasis to justify different terms. Given the emphasis both Bernard and Cannon put on the dynamic nature of physiological regulation, it is doubtful that either would have found such adjustments to be incompatible with their conceptual framing of maintaining appropriate conditions for the functioning of the organism. At the time they were working there were not tools to determine how organisms are able to anticipate the internal states that best enable their functioning. In the past 40 years huge progress has been made in determining how circadian rhythms are maintained both centrally and in individual tissues in the organism (Bechtel, 2024). Researchers are advancing accounts of how these regulate physiological processes, for example, how organisms adjust the core body temperature they maintain. Research is developing on how learning also results in anticipatory changes in regulatory functions in the organism. Were they working today, both Bernard and Cannon would likely have been eager consumers of such research and incorporated changing targets into their account of how organisms regulate their internal conditions.

The notion of a setpoint was not part of either Bernard's account of maintaining the internal environment or Cannon's notion of homeostasis. Accordingly, it is not something their accounts need to abandon. As we have noted, one of the factors motivating those arguing for abandoning setpoints is that there are generally a host of different processes operative at once in the organism. As part of their argument for allostasis, Sterling and Eyer's contend that "to maintain stability an organism must *vary* all the parameters of its internal milieu and match them appropriately to environmental demands." This, however, would not have been news to either Bernard or Cannon. Bernard refers to an "ensemble of mechanisms" that work together to maintain a viable internal environment. The focus, again, is on the goals of regulation, not the specific means. Moreover, it was the fact that organisms coordinate multiple responses to maintain themselves that led Cannon to introduce the term *homeostasis*: "The coordinated physiological reactions which maintain most of the steady states in the body are so complex, and so peculiar to the living organism, that it has been suggested (Cannon, 1926) that a specific designation for these states be employed—homeostasis" (Cannon, 1929, 400). The example of regulating blood glucose from Cannon illustrates how different processes are involved in

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maintaining that variable. It is a small step (but of great importance) to add that an adjustment to address blood glucose will also affect other conditions the organism needs to maintain (e.g., core body temperature).

Rather than introducing new notions and accounts in response to the limitations perceived in the cyberneticists' equating homeostasis with negative feedback, we urge returning to Bernard and Cannon for the resources for understanding and integrating the diverse strategies, including negative feedback, through which organisms maintain themselves. What is common to Bernard and Cannon and important in theorizing about regulation within living organisms is the focus on the organism (Bechtel and Bich, 2024) and the need to maintain it in conditions in which its various activities can be carried out. On the one hand, equating homeostasis with negative feedback had the effect of limiting researchers' focus to distinct variables and identifying a setpoint for each. On the other hand, the piecemeal introduction of new *ad hoc* concepts to account for specific regulatory phenomena beyond simple negative feedback has the opposite effect of producing a proliferation of independent competing notions, with a consequent fragmentation and loss of clarity regarding how they are related, which to choose, and how to employ them. In contrast to these two strategies, Bernard and Cannon were focused on conditions in organisms that enabled them to perform the activities they need to perform to remain alive. Focusing on this physiological goal may provide a fruitful way to avoid these extremes and develop an integrated account of regulation.

In closing, we note one additional respect in which Bernard's and Cannon's framework may require extension. Bernard explicitly focused just on warm-blooded animals; as a physician, Cannon focused on humans. This may have been in part influenced by their focus on blood and other fluids of the body as providing the environment in which tissues operate. Bernard assumed that prokaryotes, plants, fungi, invertebrates, and cold-blooded vertebrates enjoyed no buffering from the environment and each of their physiological processes directly responded to external conditions. A broader, and now more standard, interpretation of internal environment is that it encompasses all the conditions within the organism in which its various mechanisms operate. There are a multitude of ways that organisms other than warm-blooded mammals maintain conditions within themselves. Even prokaryotes sense conditions within themselves and base actions, such as locomotion or forming biofilms or spores, in response to internal conditions. All organisms perform activities to maintain themselves in the face of challenges and in this sense, all of them are autonomous (Moreno and Mossio, 2015; Bich, 2024a)—they construct (Maturana and Varela, 1980) and repair (Rosen, 1991) themselves and procure the materials and energy they need to live. They may not employ all the means for maintaining their internal state that Bernard and Cannon identified. In many cases, however, those they do employ are shared with the “higher animals,” making it appropriate to investigate homeostasis in all living organisms and to treat homeostasis as a unifying theoretical framework for understanding the control of physiological processes in all organisms.

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References

Bechtel, William. (2024). "Hierarchy or Heterarchy of Mammalian Circadian Timekeepers?" *Journal of Biological Rhythms* 0:07487304241286573. doi:10.1177/07487304241286573

Bechtel, William, and Leonardo Bich. (2024). "Situating Homeostasis in Organisms: Maintaining Organization through Time." *The Journal of Physiology* 602:6003-6020. doi:10.1113/JP286883

Beckett, Elizabeth A. H., Voula Gaganis, Anthony J. Bakker, Michelle Towstoless, Alan Hayes, Deanne H. Hryciw, Louise Lexis, and Kathy Tangalakis. (2023). "Unpacking the Homeostasis Core Concept in Physiology: An Australian Perspective." *Advances in Physiology Education* 47:427-435. doi:10.1152/advan.00141.2022

Bernard, Claude. (1859). *Leçons Sur Les Propriétés Physiologiques Et Les Altérations Pathologiques Des Liquides De L'organisme*. 2 vols. Vol. 1, Paris: Baillière.

Bernard, Claude. (1867). *Rapport Sur Les ProgrèS Et La Marche De La Physiologie GéNéRale En France*, Paris: Imprimerie impériale.

Bernard, Claude. (1878). *Leçons Sur Les Phénomènes De La Vie Communs Aux Animaux Et Aux Végétaux*, Paris: Baillière.

Bich, Leonardo. (2024a). *Biological Organization*, Cambridge: Cambridge University Press.

Bich, Leonardo. (2024b). "Organisational Teleology 2.0: Grounding Biological Purposiveness in Regulatory Control." *Ratio* 37:327-340. doi:10.1111/rati.12405

Billman, George E. (2020). "Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology." *Frontiers in physiology* 11:200. doi:10.3389/fphys.2020.00200

Cannon, Walter Bradford. (1915). *Bodily Changes in Pain, Hunger, Fear, and Rage; an Account of Recent Researches into the Function of Emotional Excitement*, New York, London,: D. Appleton and Company.

Cannon, Walter Bradford. (1925). "Some General Features of Endocrine Influence on Metabolism." *The American Journal of the Medical Sciences* 170:1–9.

Cannon, Walter Bradford. (1926). "Physiological Regulation of Normal States: Some Tentative Postulates Concerning Biological Homeostatics," In A. Pettit, ed., *A Charles Richet: Ses Amis, Ses Collègues, Ses élèves*, 91-93. Paris: Les Éditions Médicales.

Cannon, Walter Bradford. (1929). "Organization for Physiological Homeostasis." *Physiological Reviews* 9:399-431.

Carpenter, Roger Hugh Stephen. (2004). "Homeostasis: A Plea for a Unified Approach." *Advances in Physiology Education* 28:180-187. doi:10.1152/advan.00012.2004

Commission for Thermal Physiology of the International Union of Physiological Sciences. (2001). "Glossary of Terms for Thermal Physiology (Third Edition)." *Japanese Journal of Physiology* 51:245-280.

Davis, Graeme W., and Martin Müller. (2015). "Homeostatic Control of Presynaptic Neurotransmitter Release." *Annual Review of Physiology* 77:251-270. doi:10.1146/annurev-physiol-021014-071740

Frédéricq, Léon. (1885). "Influence Du Milieu Ambiant Sur La Composition Du Sang Des Animaux Aquatique." *Archives de zoologie expérimentale et générale* 3:xxxiv-xxxviii.

Guyton, Arthur C. (1982). *Human Physiology and Mechanisms of Disease*. 3rd ed, Philadelphia: Saunders.

Hagen, Joel Bartholemew. (2021). *Life out of Balance: Homeostasis and Adaptation in a Darwinian World*, Tuscaloosa: The University of Alabama Press.

Hammel, Harold T. (1965). "Neurons and Temperature Regulation," In WS Yamamoto and JR Brobeck, eds., *Physiological Controls and Regulations*. Philadelphia: Saunders.

Hammel, Harold T. (1990). "Negative Plus Positive Feedback," In J. Bligh, K. Voigt, H. A. Braun, K. Brück and G. Heldmaier, eds., *Thermoreception and Temperature Regulation*, 174-182. Berlin: Springer.

Hansen, Thomas F., David Houle, Mihaela Pavličev, and Christophe Pélabon. (2023). *Evolvability: A Unifying Concept in Evolutionary Biology?* 1st ed, Cambridge, Massachusetts: The MIT Press.

Heller, H. Craig, Gary W. Colliver, and James Beard. (1977). "Thermoregulation during Entrance into Hibernation." *Pflügers Archiv* 369:55-59. doi:10.1007/BF00580810

Hill, Archibald Vivian. (1931). *Adventures in Biophysics*, Philadelphia: University of Pennsylvania Press.

Holmes, Frederic L. (1986). "Claude Bernard, the "Milieu Intérieur", and Regulatory Physiology." *History and Philosophy of the Life Sciences* 8:3-25.

Jonas, Hans. (1953). "A Critique of Cybernetics." *Social Research* 20:172-192.

Keller, Evelyn Fox. (2008). "Organisms, Machines, and Thunderstorms: A History of Self-Organization, Part One." *Historical Studies in the Natural Sciences* 38:45-75. doi:10.1525/hsns.2008.38.1.45

Keller, Evelyn Fox. (2009). "Organisms, Machines, and Thunderstorms: A History of Self-Organization, Part Two. Complexity, Emergence, and Stable Attractors." *Historical Studies in the Natural Sciences* 39:1-31.

Lamia, Katja A., Kai-Florian Storch, and Charles J. Weitz. (2008). "Physiological Significance of a Peripheral Tissue Circadian Clock." *Proceedings of the National Academy of Sciences* 105:15172-15177. doi:10.1073/pnas.0806717105

Langley, Leroy Lester. (1965). *Homeostasis*, New York,: Reinhold.

Langley, Leroy Lester. (1973). *Homeostasis: Origins of the Concept*, Stroudsburg, Pa: Dowden, Hutchinson & Ross.

Libretti, Sabrina, and Yana Puckett. (2023). *Physiology, Homeostasis*: StatPearls Publishing, Treasure Island (FL).

Maturana, Humberto R., and Francisco J. Varela. (1980). "Autopoiesis: The Organization of the Living," In Humberto R. Maturana and Francisco J. Varela, eds., *Autopoiesis and Cognition: The Realization of the Living*, 73-138. Dordrecht: Reidel.

Maxwell, James Clerk. (1868). "On Governors." *Proceedings of the Royal Society of London* 16:270-283.

Mayr, Otto. (1970). *The Origins of Feedback Control*, Cambridge, MA: MIT Press.

Michael, Joel, William Cliff, Jenny McFarland, Harold Modell, and Ann Wright. (2017). "The “Unpacked” Core Concept of Homeostasis," In Joel Michael, William Cliff, Jenny McFarland, Harold Modell and Ann Wright, eds., *The Core Concepts of Physiology: A New Paradigm for Teaching Physiology*, 45-54. New York, NY: Springer New York. doi:10.1007/978-1-4939-6909-8_5

Mindell, David A. (2002). *Between Human and Machine: Feedback, Control, and Computing before Cybernetics*, Baltimore: The Johns Hopkins University Press.

Modell, Harold, William Cliff, Joel Michael, Jenny McFarland, Mary Pat Wenderoth, and Ann Wright. (2015). "A Physiologist's View of Homeostasis." *Advances in Physiology Education* 39:259-266. doi:10.1152/advan.00107.2015

Moore-Ede, Martin C. (1986). "Physiology of the Circadian Timing System: Predictive Versus Reactive Homeostasis." *American Journal of Physiology* 250:R737-752. doi:10.1152/ajpregu.1986.250.5.R737

Moreno, Alvaro, and Matteo Mossio. (2015). *Biological Autonomy: A Philosophical and Theoretical Inquiry*, Dordrecht: Springer.

Mrosovsky, Nicholas. (1971). *Hibernation and the Hypothalamus*, New York: Appleton-Century-Crofts.

Mrosovsky, Nicholas. (1990). *Rheostasis: The Physiology of Change*: Oxford University Press.

Müller, M. J., A. Bosy-Westphal, and S. B. Heymsfield. (2010). "Is There Evidence for a Set Point That Regulates Human Body Weight?" *F1000 Med Rep* 2:59. doi:10.3410/m2-59

Nijhout, H. Frederik, Janet A. Best, and Michael C. Reed. (2019). "Systems Biology of Robustness and Homeostatic Mechanisms." *WIREs Systems Biology and Medicine* 11:e1440. doi:10.1002/wsbm.1440

Pflüger, Eduard. (1877). "Die Teleologisehe Meehanik Der Lebendigen Natur." Pflüger's Archiv:57-103.

Pias, Claus, and Heinz Von Foerster. (2016). *Cybernetics: The Macy Conferences 1946-1953*, Zurich ; Berlin: Diaphanes.

Prigogine, Ilya, and Isabelle Stengers. (1984). *Order out of Chaos*, New York: Bantam Books.

Ramsay, Douglas S., and Stephen C. Woods. (2014). "Clarifying the Roles of Homeostasis and Allostasis in Physiological Regulation." *Psychological Review* 121:225-247. doi:10.1037/a0035942

Richet, Charles. (1900). *Dictionnaire De Physiologie*. Vol. IV, Paris: Bailli~re et Cic.

Robin, Charles Philippe. (1853). *Traité De Chimie Anatomique Et Physiologique Normale Et Pathologique, Ou, Des Principes ImméDiats Normaux Et Morbides*, Paris: J.-B. Baillière.

Romanovsky, Andrej A. (2004). "Do Fever and Anapyrexia Exist? Analysis of Set Point-Based Definitions." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 287:R992-R995. doi:10.1152/ajpregu.00068.2004

Romanovsky, Andrej A. (2007). "Thermoregulation: Some Concepts Have Changed. Functional Architecture of the Thermoregulatory System." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 292:R37-46. doi:10.1152/ajpregu.00668.2006

Romanovsky, Andrej A. (2018). "The Thermoregulation System and How It Works," In Andrej A. Romanovsky, ed., *Handbook of Clinical Neurology*, 3-43: Elsevier. doi:10.1016/B978-0-444-63912-7.00001-1

Rosen, Robert. (1991). *Life Itself: A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life*, New York: Columbia University Press.

Rosenblueth, Arturo, Norbert Wiener, and Julian Bigelow. (1943). "Behavior, Purpose, and Teleology." *Philosophy of Science* 10:18-24.

Schulkin, Jay, and Peter Sterling. (2019). "Allostasis: A Brain-Centered, Predictive Mode of Physiological Regulation." *Trends in Neurosciences* 42:740-752. doi:10.1016/j.tins.2019.07.010

Selye, Hans. (1973). "Homeostasis and Heterostasis." *Perspectives in Biology and Medicine* 16:441 - 445.

Sterling, Peter. (2004). "Principles of Allostasis: Optimal Design, Predictive Regulation, Pathophysiology, and Rational Therapeutics," In Jay Schulkin, ed., *Allostasis, Homeostasis, and the Costs of Physiological Adaptation*, 17-64. Cambridge: Cambridge University Press. doi:10.1017/CBO9781316257081.004

Sterling, Peter, and Joseph Eyer. (1988). "Allostasis: A New Paradigm to Explain Arousal Pathology." *Handbook of of Life Stress, Cognition and Health*.

Villegas, Cristina, Alan C. Love, Laura Nuño de la Rosa, Ingo Brigandt, and Günter P. Wagner (2023), "Conceptual Roles of Evolvability across Evolutionary Biology: Between Diversity and Unification", in, *Evolvability: A Unifying Concept in Evolutionary Biology?*: The MIT Press, 35-54.

von Bertalanffy, Ludwig. (1952). *Problems of Life: An Evaluation of Modern Biological Thought*.

Waddington, Conrad Hal. (1968). "The Basic Ideas of Biology," In Conrad Hal Waddington, ed., *Towards a Theoretical Biology: Prolegomena*, 1-41. Chicago: Aldine Publishing Company.

Widmaier, Eric P., Hershel Raff, and Kevin T. Strang. (2016). *Vander's Human Physiology : The Mechanisms of Body Function*. Fourteenth international edition ed, New York, NY: McGraw-Hill Education.

Wiener, Norbert. (1948). *Cybernetics: Or, Control and Communication in the Animal and the Machine*, New York: Wiley.

Wunderlich, Karl Reinhold August. (1868). *Das Verhalten Der Eigenwärme in Krankheiten*, Leipzig: Otto Wigard.

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