Cell PRESS

An information hypothesis for the evolution of homeostasis

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A prevailing view among physiologists is that homeostasis evolves to protect organisms from damaging variation in physiological factors. Here, we propose that homeostasis also evolves to minimize noise in physiological channels. Fluctuations in physiological factors constitute inescapable noise that corrupts the transfer of information through physiological systems. We apply information theory to homeostasis to develop two related ideas. First, homeostatic regulation creates quiet physiological backgrounds for the transmission of all kinds of physiological information. Second, the performance of any homeostatic system influences information processing in other homeostatic systems. This dependence implies that multiple homeostatic systems, embedded within individual organisms, should show strongly nonadditive effects.

Information theory illuminates homeostasis

The concept of homeostasis originated over 140 years ago [1–3] and is now a core framework in physiology [4–7] [Porter, R., ed. (2012) *The Merck Manual Online*, http://www.merckmanuals.com/professional/index.html], having both important modern extensions [8–11] and crucial implications for understanding organismal ecology and evolution [8]. The consequences of poor homeostasis can be dire: when key physiological factors fall outside narrow ranges, organisms can show catastrophic breakdown in important systems, leading to severely impaired performance. Indeed, over the past 100 years, these consequences have come to define both the proximate and ultimate reasons for why organisms are homeostatic: to avoid damage, and thereby loss of fitness, when physiological factors reach extreme levels.

We believe, however, that this conception of homeostasis-as-safety-net is incomplete, and we propose that homeostasis also evolves to minimize noise in physiological channels [12]. This focus on noise emerges from hybridizing older ideas about the mechanisms of homeostasis with concepts from information theory [13]. The idea has the status of an 'untested hypothesis', meaning that few data are available for evaluating it, even though its internal structure is logically consistent and appealing. After presenting the hypothesis, we suggest several kinds of tests.

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Keywords: communication; emergent properties; entropy; homeostasis; information theory; Metazoa; noise; physiology; private channels; regulation; signal processing.

0169-5347/$ – see front matter

 http://dx.doi.org/10.1016/j.tree.2012.10.021

A brief history of homeostasis

Homeostasis depends on control systems [14], which attempt to regulate physiological factors within some bounds. Control systems use negative feedback [15,16] (Figure 1a), in which sensors compare the level of a factor against some (possibly variable) set point and produce a signal proportional to the deviation. This signal prompts cells, tissues, or organs to do physiological work to counteract the deviation; the system tries to minimize the error between the measured level of the factor and its set point. The mechanisms underlying such systems are diverse [9].

Although this view of homeostasis has deep roots [3], its modern incarnation traces to the work of Claude Bernard [1,2,17] during the late 1800s. Bernard's insight was that the internal space of each animal (le milieu intérieur) was separate and distinct from its external environment, and was well regulated. His most famous dictum describes the significance of le milieu intérieur: 'The stability of the internal environment is the condition for a free and independent life' [17]. It is well known now that stability *per se*, in le milieu intérieur, may be neither strictly possible nor even desirable in many circumstances [9], and that stability in some factors may be obtained by variability in others [10]. Nevertheless, the idea of stability underlies all conceptions of homeostasis and its variants.

Many later physiologists contributed to the idea of homeostasis [2,3], but the most important was Walter Cannon [4,7], whose seminal works appeared during the late 1920s and early 1930s. Cannon coined the term 'homeostasis', and he integrated different types into a coherent framework. Among other factors, Cannon focused on five (pH, temperature, plasma osmolality, glucose, and calcium) that are critical to the normal functioning of most organisms [4]. There are obviously other factors under homeostatic control, but Cannon's insight is no less true today: those five factors are controlled within narrow bounds and lead to significant dysfunction when those bounds are crossed (Box 1). Their importance follows from their universal biochemical effects. Temperature and pH have unavoidable effects on the structure and function of enzymes and functional RNAs; temperature and plasma osmolality have fundamental effects on the integrity and function of membranes; glucose is a key currency for moving and storing energy; and calcium plays leading roles in muscle physiology and multiple signaling pathways. Even when particular lineages evolve unusual physiology with respect to one or more of the factors, their physiology will still be at risk from fluctuations of those factors.

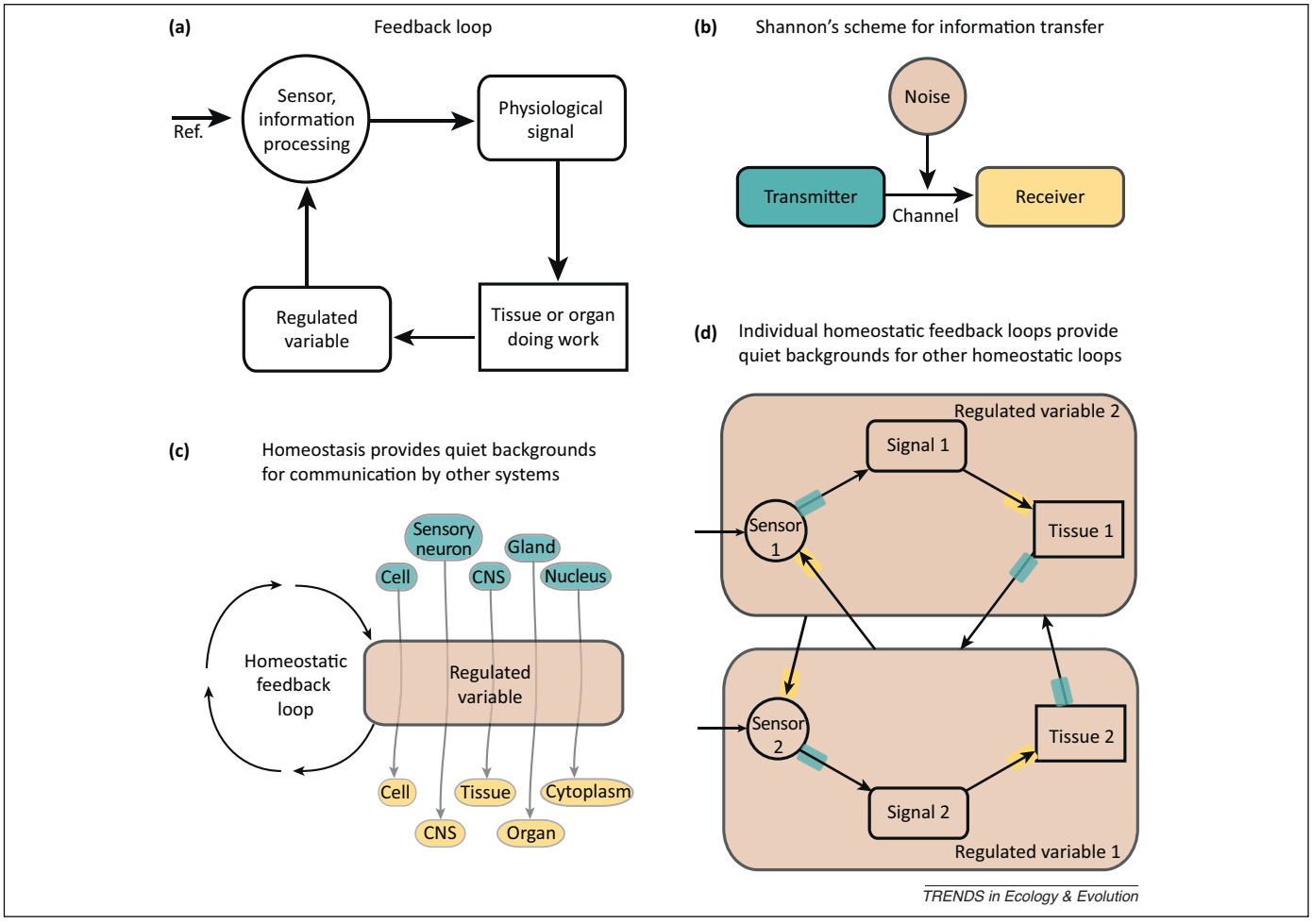

Figure 1. Homeostasis and information transfer. **(a)** Schematic of a typical negative feedback loop underlying physiological homeostasis. Physiological sensors monitor the level of some factor, and compare it to a reference signal or set point (labeled 'Ref.'). Those sensors then produce signals (nerve impulses, endocrine molecules, cell surface proteins, etc.) whose levels are inversely proportional to the deviation from the reference, and which direct other physiological entities (i.e., cells, tissues, or organs) to do work that counteracts the deviation. **(b)** Shannon's scheme for information transfer. Transmitters encode and send out signals along a channel; those signals are received and decoded at the other end. Noise can corrupt the signal, either in transit or during the transmitting or receiving steps. This schematic is simplified from the one that Shannon showed, which described the process as having separate devices for the source and transmitter of information and, similarly, separate devices for the receiver and the destination. For our purposes, that distinction is less relevant. **(c)** The variables regulated by homeostasis provide quiet physiological backgrounds for the transmission of any kind of information within organisms. **(d)** The parts of a feedback cycle are coupled communication systems. In the first system, the sensor (indicated by blue squares) communicates, via some kind of physiological signal, with the tissues or organs doing physiological work (yellow squares). In the second system, the working component communicates (blue squares) with the sensor via the regulated variable (yellow squares). Homeostasis of one variable creates a quiet background for the communication that occurs within other homeostatic feedback loops; that is, multiple homeostatic systems likely are self-reinforcing. Abbreviation: CNS, central nervous system.

Here, we reopen what has been considered a settled question: what processes drive the evolution of homeostatic systems? The importance of homeostasis is obvious when it fails spectacularly: animals with severe disturbance of one or more of the five factors can exhibit convulsions, severe respiratory distress, tetany, coma, death, and so on (Box 1). The mistake has been to assign those symptoms as the main reason for the evolution of homeostasis. We suggest that these symptoms may, in some contexts, bear only tangentially on its evolution; they are clearly important when they occur, but organisms in those situations may be fatally compromised already. Instead, we develop the argument that homeostasis acts to minimize the effects of physiological noise on information transfer, which is integral to day-to-day functions and therefore may affect fitness to a greater extent. This shift in perspective is equivalent to focusing away from the capacity of homeostatic systems to do physiological work and, instead, towards the components of homeostatic systems devoted to processing and interpreting information [18,19].

Information theory and biology

Information theory was crystallized by Claude Shannon [13], whose work during the late 1940s was driven by problems in engineering. As communications hardware became more complex, engineers needed better frameworks for analyzing flows of information. Shannon's most important concept is outlined in the first figure in his 1948 paper (redrawn here in Figure 1b): information is encoded and sent over a channel by a transmitter, is corrupted by noise, and then is received and decoded at the end of the channel. Shannon's core insights are summarized in Box 2. Although several authors have expressed misgivings about, or even hostility to, applying information theory to biological problems [20–22], information theory has nevertheless been useful in many fields. It was championed early by Quastler

Box 1. Homeostasis of key physiological factors

Cannon identified five key factors that were regulated by physiological systems: pH, temperature, osmolality, glucose, and calcium. In most homeothermic vertebrates, the levels of these factors are regulated within narrow bounds. Because the five factors are central to human health, the medical literature on them is enormous. Using information from The Merck Manual Online [Porter, R., ed. (2012) *The Merck Manual Online*, http://www.merckmanuals.com/professional/index.html], we compiled the current state of knowledge on the normal range of each factor in adult humans, and the consequences of going out of these bounds (Table I). The normal ranges refer to values for most healthy adults. Symptoms become progressively more severe the further outside the normal range the factors go. Two other relevant considerations are spatial variation within a body and characteristic timescale of the disturbance. For example, pH in working muscles may fall locally far below the normal pH range in the blood without undue local damage; longer and more systematic disturbances are more dangerous.

Table I. Typical bounds for common physiological factors, and consequences of crossing them

Factor	Normal range	Symptoms when below normal range	Symptoms when above normal range
Serum pH	7.35–7.45	Hyperventilation, hypometabolism and inhibition of anaerobic glycolysis, poor cell volume regulation, changes in ionic balances, insulin resistance, disrupted heart function, and decreased systemic blood pressure	Hypoventilation, tetany, seizures, lethargy, delirium, stupor, changes in ionic balances, stimulation of anaerobic glycolysis, changes in heart function and patterns of blood flow
Core temperature	35–38 °C	Progress from shivering and lethargy to confusion, irritability, hallucinations, slow breathing and heart beat, coma, and death	Cramps, edema, nausea, delirium, seizures, fainting, heat exhaustion, and heatstroke
Plasma osmolality	275–290 mOsm kg^{-1}	Headache, confusion, stupor, altered personality, lethargy, seizures, and coma	Thirst, confusion, neuromuscular excitability, overactive reflexes, cerebrovascular damage, seizures, and coma
Fasting plasma glucose	3.3–5.6 mmol l^{-1}	Sweating, nausea, warmth, anxiety, tremulousness, palpitations, and possibly hunger and paresthesias. Insufficient glucose in brain causes headache, blurred or double vision, confusion, difficulty speaking, seizures, and coma	Onset of diabetes mellitus, osmotic diuresis caused by section of glucose into the urine, leading to high frequency of urination, polyuria, and excessive thirst and dehydration. Severe dehydration can lead to weakness, fatigue, and changes in mental status
Serum calcium	2.2–2.6 mmol l^{-1}	Paresthesias, tetany, seizures, encephalopathy, heart failure, muscle cramps, and dry or scaly skin	Polyuria, constipation, muscle weakness, anorexia, vomiting, abdominal pain, confusion, delirium, coma, and heart arrhythmia

[23] and has played significant roles subsequently in neurobiology [24–26], evolutionary theory [27,28], developmental and molecular biology [29–31], plant and animal communication [32–35], and ecology [36–41]. Oddly, since early work by Wiener [14], physiologists have had little interest in information theory, with some notable exceptions [42].

In physiology, the utility of information theory stems from its ability to analyze noise in communication systems (Figure 1c). Similar to engineered systems, evolved physiological systems perform worse when subjected to more noise. Note that, although Shannon's schematic (Figure 1b) indicates that noise enters while the message is in transit, he clearly meant ([13], p. 19) that noise also could enter at either terminus. In a physiological context, this distinction is equivalent, for example, to (i) a nontarget tissue altering circulating levels of some hormone versus (ii) modified blood pH altering receptor sensitivity in a target tissue; both effects constitute noise. In Shannon's terms, noise disrupts physiological signals by adding uncertainty (entropy) to messages: in noisy environments, physiological entities have less certainty about what other effectors (i.e., other cells, tissues, or organs) direct them to do (see [24] and Box 2). At a functional level, more noise also decreases the rate of information transfer across the channel.

A core problem for organisms is how to assure, despite noise, that physiological parts communicate clearly and rapidly with one another. There are four possible solutions. The first is to send redundant signals; for example, trains of action potentials or many copies of a chemical signal. However, redundancy requires higher expenditures of materials and energy and forces lower rates of information transfer [13]. The second is to minimize the proximity, in space or time, between transmitter and receiver. Signals traveling over smaller distances, or moving through the body more rapidly, may be less susceptible to noise. Such an effect may drive the evolution of signaling systems both into more local, proximate versions (i.e., cell to cell), whenever more global control is unnecessary; and into rapid nervous signaling whenever the metabolic resources are available.

The third is to use channels that are less prone to noise or to filter out noise using physical or neural mechanisms. For example, the physical and neural properties of hearing organs often discard frequencies containing mostly noise, allowing the organism to use frequencies containing more useful information [43]. In electronics, analogous devices are called band-pass filters, notch filters, or high- or low-pass filters. In physiological systems, an example of a band-pass filter (which discards high and low frequencies) would be a molecular receptor whose characteristic time constant for responding is matched to the frequency in which the most informative variation occurs (e.g., odorant receptors in insects [35]). A related idea is to use private channels, in which information is sent via channels subject to less noise because they are used by few or no other systems (unusual molecules or dedicated nervous pathways). For example, some hormone systems have

Box 2. Information theory

Shannon describes the term H, which he calls entropy (also called uncertainty) (Equation [I]):

$$H(x) = -\sum_{i=1}^{n} p_i(\log_2 p_i) \quad [I]$$

where p_1 through p_n is the set of probabilities of finding x in states 1 through n (Equation [I] will be familiar to ecologists and evolutionary biologists as Shannon's diversity index). As an example, consider an N-sided die [29]. Without additional knowledge of the relative probabilities of each side occurring, we assume that they are equally likely ($p_i = 1/N$), in which case $H(x) = \log_2 N$; this is the maximum entropy of the system. We then examine the system and discover that its sides occur with unequal probabilities. Now knowing the probability of each state, we calculate the new entropy of the system. This new entropy is smaller than the maximum entropy, and the difference between the new and maximum entropies is the information gained about the system.

To estimate how much information is transferred from transmitter to receiver, we need to consider entropies of more than one entity. In physiological systems, this is equivalent to asking how much information is transferred between one physiological entity and another (e.g., a gland and an organ). To calculate this quantity in discrete terms, consider two N-sided dice. The joint entropy $H(XY)$ describes the entropy of the entire system. The information that one die has about the other is (Equation [II]):

$$I(X:Y) = H(X) + H(Y) - H(XY) \quad [II]$$

If the dice were independent, the information that X had about Y would be zero. However, if the state of one die depended on the state of the other, then one could predict which side was up on one die by knowing which was up on the other. The amount of information X has about Y can also be described by Equation [III]:

$$I(X:Y) = H(X) - H(X|Y) \quad [III]$$

where $H(X|Y)$ is the conditional entropy. This term is the uncertainty about the state of X given the state of Y. With two independent dice, the information that X has about Y is zero, because the conditional entropy is the same as the entropy of X alone (knowing the state of Y does nothing to improve our chances of predicting X). Thus, information can be described as measuring the deviance of a system from independence. In physiological systems, information transferred can be estimated as the statistical dependence of one subsystem (e.g., rate of transport by an epithelium) on another (e.g., rate of hormone secreted by a gland).

little crosstalk with other hormone systems and thus constitute semi-private channels (nevertheless, important ligand–receptor systems are still subject to global noise from Cannon's factors, including temperature [44] and pH [45]). In sensory ecology, private channels (e.g., ultraviolet [46,47]) are exploited by conspecifics but are not perceived by other potentially interacting organisms, such as predators or prey species.

The fourth route for escaping noise is to minimize it actively. This solution is possible for animals communicating externally with other animals [34], by positioning themselves in their environments so that signal generation or reception are particularly effective, or by communicating at less noisy times of the day. However, because they often will have poor control over the physical properties of the external channel (a colorful male fish trying to attract a female in a stream with a complex light environment), or over other animals whose own signals corrupt those of some focal animal (a bird singing in a forest filled with other calling animals), animals communicating with others often will be unable to minimize noise. Physiological systems, by contrast, are embedded in le milieu intérieur, whose properties are potentially under much finer control. In addition, physiological signalers and receivers, as well as the channels through which they communicate, share a genetic interest in the propagation of their shared genes. For physiological systems, therefore, we predict that minimizing noise (i.e., maintaining homeostasis) will be a key means of maximizing information transfer through channels of some given capacity.

Merging information into homeostasis

In organisms, the most important sources of physiological noise are precisely the factors (Box 1) that have received the most attention from physiologists studying homeostasis. These factors are important because variation in their levels affects the functions of the most basic components (i.e., membranes, proteins, and RNAs) of all biological systems. That is, variation in those factors constitutes inescapable noise that affects all physiological systems, including the homeostatic systems themselves. Because the noise is global (it affects all other physiological components in other homeostatic systems), lineages cannot filter it away or evolve private channels that avoid it; instead, the options are to send redundant signals, to minimize spatial and temporal proximity between transmitter and receiver, or to minimize variation in the noise-inducing factors. Our claim is that the latter (minimizing noise) is a key factor driving the evolution of homeostasis.

Noise reduction plays two main roles in how organisms function. First, it creates quiet backgrounds for intra-organismal communication of any kind (Figure 1c). In quiet backgrounds, physiological entities can encode information using more complex and nuanced codes, can send information more rapidly, and can be more certain about the states of other physiological entities. In addition, there is an important second role for noise reduction that hinges on identifying homeostatic systems as coupled pairs of transmitters and receivers (Figure 1d). In particular, because many of the factors that underlie noise are themselves subject to homeostatic regulation, the performance of any one homeostatic system will influence the performance of others. For example, even though different mechanisms control pH and temperature in homeothermic vertebrates, variable pH is a source of noise for temperature homeostasis and (conversely) variable temperature is source of noise for pH homeostasis. This reciprocal dependence implies that multiple homeostatic systems should show strongly nonadditive or emergent effects [8,48], and potentially nonintuitive pleiotropic effects on other physiological systems [49]. Likewise, conditions or mutations affecting one system will have cascading effects on others and may lead to dysfunction or breakdown across multiple systems simultaneously; in this context, death can be thought of as runaway noise, an emergent set of self-reinforcing dysregulations in multiple homeostatic systems simultaneously.

How does this new view differ from the traditional view of homeostasis? Both views focus on regulation and stability,

Box 3. Standard and new views of homeostasis

In the standard view of homeostasis, and also in the one advocated here, homeostatic feedback loops are thought to function as physiological controllers. The views differ in their interpretation of why physiological variables are controlled. Standard homeostasis recognizes that variables are controlled within some bounds, with the implications that variation within the confines of those bounds may be unimportant and that exceeding those bounds causes physiological dysfunction or damage, from minor to severe depending on the magnitude of the deviation. What emerges from this view is a three-part focus on: (i) the rapidly increasing dysfunction that occurs as the (poorly) regulated variable crosses one of its bounds; (ii) the capacity of the homeostatic system to counteract (or fail to counteract) the deviation, where capacity refers to, for example, the maximum rate at which kidneys can secrete urine, or the maximum rate that pH of the blood can be modified; and (iii) a single-system view, in which dysregulation of one variable is weakly connected to variation in other variables.

The information hypothesis for homeostasis suggests different foci: (i) the more modest effects, on suborganismal function and fitness, of patterns of variation in regulated variables even within their traditionally defined homeostatic bounds (a focus away from boundaries *per se*); (ii) the information processing components of homeostatic systems, rather than on the capacities of cells, tissues, or organs to do physiological work (see [18,19]); examples of these information components include the chemistry and concentrations of signals and receptors, and the structures and processes that integrate incoming signals to generate outgoing signals; and (iii) a multisystem view (see also [8]), in which dysregulation of one variable is strongly coupled, by the global noise it creates, to multiple other homeostatic systems.

The two views of homeostasis coexist on a continuum and, in some circumstances, may describe the same phenomenon. For example, the phenotypes listed in Table I in Box 1 may represent a form of generalized failure in information systems (information systems fail, leading to catastrophe). Conversely, the deviation of a physiological variable across some particular bound may be catastrophic precisely because that excursion introduces overwhelming noise into some other homeostatic system, The two views, however, still provide strongly divergent contexts in which to develop theory, apply empirical tests, and trace ecological and evolutionary consequences.

but they provide different explanations for why physiological factors are controlled (Box 3). In brief, the new view emphasizes dysfunctions arising from disturbance to communication networks at all levels of suborganismal organization, and it encompasses both (i) intra-organismal communication between cells and organs and signal transmission from external sensors to the central nervous system (Figure 1c); and (ii) effects of noise in particular factors on other homeostatic systems. The new view alters the conditions under which we expect to observe selection on homeostasis. In the standard view, selection occurs rarely, only when physiological factors reach extreme levels; and when selection does occur, it is largely on the capacity of the system to counteract the deviation, rather than on aspects of information transfer. In the new view, by contrast, the noise from poor homeostasis plays ongoing roles in how well organisms perform from moment to moment in their environments. Even without spectacular homoeostatic failures, organisms contending with large amounts of physiological noise likely would forage, fight, or pursue mates less well.

Testing the information hypothesis

Tests of the information hypothesis should be multipronged and should use a broad range of modern concepts and tools. First, control systems in organisms should be experimentally altered using genetic or pharmacological tools, with perturbations of components that process information (sensors, integrators, or receptors) and components that provide the capacity to do physiological work (transporting epithelia, organs, or tissues) [18,19]. Perhaps *in vitro* processes can be developed that contain the bare bones of homeostatic mechanisms [50]. When such manipulations can be done in living organisms, the effects on fitness should be assessed under natural conditions, without looking just for dire effects in the lab. Finding that even modest modification of homeostatic systems (e.g., changes in set points) leads to subtle depression of fitness would support our information hypothesis over the more established focus on physiological failure. Second, mathematical models and computer simulations, based on realistic biological details, should be used to establish stronger conceptual bases for what is likely, or possible [12,50–52]. As they have been in other fields, models will be most useful when they are coupled to experimental work [50].

Third, comparative analyses of signal structure (redundancy or statistical properties) should be done on homologous physiological systems in clades whose lineages have evolved different homeostatic abilities with respect to some physiological variable. These might be found in groups containing lineages that have invaded more variable and less variable environments. The general prediction is that, in noisy systems (those in which one or more of Cannon's factors are not tightly controlled), signal redundancy will be greater and rates of information transfer slower. In practical terms, comparing lineages quantitatively can be done several ways. For example, enzymes and receptors are often subject to allosteric control by multiple distinct compounds. Those compounds can be thought of as letters, and the combinations bound to a molecule as different words having distinct physiological effects. Shannon's work provides clear ways to calculate redundancy of this chemical language. In noisy systems, we expect the evolution of more redundancy, meaning fewer allosteric control sites or an increase in frequency of just a few of the modifying compounds. Additionally, in noisier physiological spaces, selection may favor systems in which molecules controlling threshold-activated systems are maintained at levels further away from the activation concentration; a kind of redundancy that prevents noise from accidentally altering some important cascade.

In the tests proposed above, the measured outputs span multiple levels of organization. This raises the important question of how to connect lower-level variation to variation in fitness. This problem has an appealing but practically difficult solution proposed by Arnold [53]: link up lower levels to performance using experimental manipulations of various kinds, often in the lab, but measure the relation of performance to fitness, when possible, in the wild. Understanding noise in homeostasis will involve similar level-spanning approaches.

Concluding remarks: links to ecology and evolution

The information hypothesis above is primarily physiological, but it has strong links to ecology and evolution. Information transfer among con- and heterospecifics influences where organisms go and what they do [54], and is a central

theme in sensory ecology [55]. Our view is that communication within and among cells [56] and organs is conceptually similar to communication among individuals in ecosystems. Moreover, the same homeostatic mechanisms that support intra-organismal communication also provide quiet backgrounds through which information from external sensors can flow. In this sense, homeostatic systems represent core devices for abstracting environmental information into useable forms, and they strongly influence what organisms pick out from the flood of environmental information washing over them [57]. It is possible too that homeostasis interacts with behavior in interesting ways: organisms may position themselves where their homeostatic systems can best provide quiet backgrounds [34,54], for example, the behavioral thermoregulation exhibited by many ectotherms.

Evolutionary biologists also grapple with core problems of homeostasis. First, homeostasis informs ideas about the origin of life, and may even have evolved before the first replicators [50,58]. Second, noise reduction plays key roles in development, which can be viewed as unfolding structure directed by information. For embryos, environmental variation is a double-edged sword: it can be an additional source of information used by embryos to modify their structures in adaptive ways (adaptive developmental plasticity [59]) and it can constitute disruptive noise. Homeostasis establishes quiet physiological backgrounds through which developmental information is transmitted clearly and environmental information abstracted appropriately. Finally, homeostatic mechanisms evolved to cope with short-term noise may have longer-term evolutionary implications [8,12], by allowing the accumulation of significant genetic variation for the capacities of organs and physiological systems while preventing the accumulation of genetic variation in components devoted to sensing, information processing, and control [18]. If so, the result should be hidden variation for capacity that first accumulates and is then exposed to selection suddenly during rare, unusual events [60,61].

Acknowledgments

We thank Tom Brekke, Ray Callaway, Thomas Förster, Erick Greene, Marty Martin, Tom Martin, John McCutcheon, Kristen Potter, John Terblanche, and two anonymous reviewers for discussion of, or comments on, the manuscript. This work was supported by The National Science Foundation (IOS 0844916) to H.A.W. and the University of Montana.

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