INVITED PAPER

What Is Stress? A Systems Perspective

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Synopsis The term "stress" is used to describe important phenomena at multiple levels of biological organization, but finding a general and rigorous definition of the concept has proven challenging. Current models in the behavioral literature emphasize the cognitive aspects of stress, which is said to occur when threats to the organism are perceived as uncontrollable and/or unpredictable. Here we adopt the perspective of systems biology and take a step toward a general definition of stress by unpacking the concept in light of control theory. Our goal is to clarify the concept so as to facilitate integrative research and formal analysis. We argue that stress occurs when a biological control system detects a failure to control a fitness-critical variable, which may be either internal or external to the organism. Biological control systems typically include both feedback (reactive, compensatory) and feedforward (predictive, anticipatory) components; their interplay accounts for the complex phenomenology of stress in living organisms. The simple and abstract definition we propose applies to animals, plants, and single cells, highlighting connections across levels of organization. In the final section of the paper we explore some extensions of our approach and suggest directions for future research. Specifically, we discuss the classic concepts of conditioning and hormesis and review relevant work on cellular stress responses; show how control theory suggests the existence of fundamental trade-offs in the design of stress responses; and point to potential insights into the effects of novel environmental conditions, including those resulting from anthropogenic change.

The challenge of defining stress

My chapter defines the concept of stress. I am not certain whether one who undertakes this task either has an enormous ego, is immeasurably stupid, or is totally mad. (Levine 1985)

Ever since Selye (1950) introduced the term in biology, the task of defining stress has been fraught with difficulties and ambiguities (Le Moal 2007; Romero et al. 2009; Koolhaas et al. 2011). Selye used the word "stress" to denote the specific physiological response that organisms mount to nonspecific demands, including both negative challenges (e.g., starvation, infection) and positive challenges (e.g., foraging or mating opportunities; Selye 1976). The initial definition has been narrowed in later research, first with the notion that stressors are actual or perceived threats to the homeostasis of the organism, and then with the emphasis—particularly strong in the behavioral literature—that stress is specifically triggered by perceptions of unpredictability and/or uncontrollability (Levine and Ursin 1991; McEwen and Wingfield 2003; Ursin and Eriksen 2004; Romero et al. 2009; Ursin and Eriksen 2010; Koolhaas et al. 2011). These ideas are rooted in concepts from control theory, such as feedback and feedforward regulation (Bechhoefer 2005; Albertos and Mareels 2010; Åström and Murray 2012; Frank 2018a). However, the connections between biological models of stress and the formal theory of control systems are seldom discussed explicitly, and their implications have not been explored in any detail. Moreover, the increasing emphasis of behavioral models on the cognitive aspects of prediction and coping (Ursin and Eriksen 2010; Koolhaas et al.

2011) makes them ill-suited to describe stress in organisms that lack a nervous system (e.g., plants; Hirt 2009), or even at the level of individual cells (Kültz 2005). When researchers in animal, plant, and cellular physiology describe responses to threats and challenges as stress, they may be referring to entirely different phenomena—or, alternatively, the convergent vocabulary may reflect the existence of a shared conceptual core. An integrated perspective on stress has been hindered by the fact that stress is typically studied at a single biological scale, and the interaction with other scales is rarely investigated (Romero et al. 2015).

In this paper we adopt the perspective of systems biology (Kitano 2002), and take a step toward a general definition of stress by unpacking the concept in light of control theory. Specifically, we argue that *stress occurs when a biological control system detects a failure to control a fitness-critical variable*, which may be either internal or external to the organism. As we detail below, detection does not imply a cognitive appraisal but merely a measured discrepancy between the target state of the variable and its actual state. To qualify as control failures, discrepancies must be large and/or persistent, reflecting the system's inability to anticipate or rapidly address the challenge (what counts as "large" and "persistent" necessarily depends on the particular variable and its relation to fitness). Biological control systems typically include both feedback (reactive, compensatory) and feedforward (predictive, anticipatory) components; their interplay accounts for the complex phenomenology of stress in living organisms.

Our goal is not to advance a new theory of stress or propose an alternative to existing models, but to clarify the concept so as to facilitate integrative research and—ultimately—formal analysis. The definition of stress we propose is meant to be as simple and abstract as possible; it does not depend on the cognitive, physiological, and molecular mechanisms that mediate or respond to challenges in any particular case. For instance, feedforward anticipatory responses do not require a nervous system and can be implemented by relatively simple biochemical pathways (Zhang et al. 2009). Thus, our definition is consistent with current models of stress in the behavioral literature (reviewed in the next section); these models will be the main focus of this paper, since our expertise lies mainly in vertebrate systems. However, the same definition applies equally well to cellular stress responses, highlighting connections across levels of biological organization and facilitating integration between different disciplinary traditions. We believe that explicitly redefining stress in

the language of control theory will promote conceptual clarity in a field marred by redundant and often ambiguous terminology. Even more importantly, this approach suggests several interesting implications and novel directions for research, as we discuss in the final section of the paper.

Current models of stress in the behavioral literature

In this preliminary section we briefly survey current conceptions of stress in the behavioral literature, describing their main concepts, and highlight some recurring themes. We begin with the *allostasis model* proposed by McEwen and Wingfield (2003), which has profoundly influenced subsequent theorizing in this area. This model focuses on the physiological adjustments required to maintain stability through change, or *allostasis* (Sterling and Eyer 1988). Allostatic responses adaptively shift the set point of homeostatic systems to match anticipated changes in the environment or in the organism's state (including transitions between life history stages). For example, the homeostatic set points of metabolism and body temperature shift between day and night, and even more dramatically during hibernation. When a prey spots a predator nearby, the autonomic system increases the set point of heart rate in anticipation of flight, even before actual escape behavior is initiated. In the model, stress is defined as a threatening event that elicits a physiological and/or behavioral allostatic response in addition to those imposed by the normal life cycle. Allostatic responses tend to have immediate benefits and long-term costs. Rising levels of physiological mediators such as glucocorticoids increase energy availability to deal with present challenges, but deplete the individual's reserves and may result in tissue damage, particularly if exposure to stress is severe and/or chronic. The cumulative effect of allostasis is called *allostatic load*. When environmental conditions require more work to be done to maintain physiological stability, allostatic load increases and can lead to two types of overload. If the energy necessary to maintain homeostasis exceeds the energy available to an organism, an "emergency life history stage" will be initiated. If energetic demands are not exceeded and allostatic responses are sustained for too long, metabolic imbalances and pathological damage can result.

The concept of allostasis has been revised and extended in what is perhaps the most comprehensive model of stress to date, the *reactive scope model* (Romero et al. 2009). This model is less focused on energetic expenditures, applies to a greater range

of contexts (including those in which energy is not the limiting factor), and allows for more explicit predictions about individual differences in stress susceptibility. Mediators of the stress response (e.g., glucocorticoids, heart rate, behavioral responses such as aggression and locomotion) have a normal range termed the reactive scope, which encompasses anticipatory changes that follow circadian and seasonal fluctuations (*predictive homeostasis*), as well as temporary increases following unpredictable threats (*reactive homeostasis*). If levels of mediators (e.g., hormone concentrations) exceed the normal reactive scope too often or for too long they begin to induce pathological damage (*homeostatic overload*); if they fall too low they become insufficient to maintain homeostasis (*homeostatic failure*). Both outcomes should lead to diminished fitness. Genetic and developmental factors as well as prior experiences may narrow or expand the reactive scope, leading to individual differences in stress susceptibility. The development of individual differences is also the focus of the *adaptive calibration model* advanced by Del Giudice et al. (2011) and Ellis and Del Giudice (2014). This model combines the concept of allostasis with the insight that repeated, chronic stress carries important information about life history-relevant features of the environment (e.g., danger, unpredictability, availability of resources). As the organism develops, the stress response system integrates this information and contributes to the regulation of key life history trade-offs, with broad-ranging effects on maturation, behavior, and physiology—including physiological reactivity to future stressors.

Whereas the allostasis and reactive scope models tend to focus mainly on physiological processes, the *cognitive activation theory of stress* (CATS; Ursin and Eriksen 2004, 2010) takes an explicitly cognitive perspective on stress. The model defines stress as a general alarm response that occurs when there is a discrepancy between expectancy and reality. Expectancies correspond to the homeostatic set values of motivational systems and can be violated by threats to the organism, homeostatic imbalances, novelties, and so on. The alarm response triggered by discrepancies involves non-specific physiological arousal and persists until the discrepancy is resolved. The CATS quantifies expectancies by their strength, by the perceived probability of the expected event, and by the event's positive or negative affective connotation (valence). Building on these notions, the model attempts to formalize intuitive concepts such as anxiety, helplessness, and hopelessness based on the perceived probability and valence of future

events, coupled with learned expectations about the relationships between coping responses and outcomes.

As is apparent from this brief overview, a common thread of many current models of stress is that they do not exclusively focus on reactive or compensatory responses (those deployed after the challenge has occurred), but place considerable emphasis on the importance of anticipatory responses. The latter have been described by different authors as "allostasis," "predictive homeostasis," or "adaptive homeostasis" (with somewhat different implications; see Romero et al. 2009; Davies 2016). In a recent effort to clarify the concept of stress, Koolhaas et al. (2011) argued that stressors should be clearly distinguished from everyday challenges, and narrowly defined as fitness-threatening situations that involve significant unpredictability and/or uncontrollability. Unpredictable events can be identified by the lack of anticipatory responses, whereas uncontrollable events are marked by absent or delayed physiological recovery. In this perspective, the most stressful events for an animal are those in which previously predictable/controllable situations suddenly deteriorate, causing a rapid failure of both anticipatory and reactive processes. This framework synthesizes many key aspects of the existing approaches, including the allostasis model, reactive scope model, and CATS. It also inherits a markedly cognitive conception of stress: adopting the CATS formulation, the authors frame prediction as expectancies about probable outcomes, and note that the occurrence of stress is crucially influenced by the animal's perception, internal representations, and memory of previous experiences. As noted above, defining stress in cognitive terms permits a sophisticated analysis of behavioral and physiological responses to challenges (for details see Koolhaas et al. 2011), but further separates the study of stress in animals from that of analogous phenomena that occur at the cellular level or in organisms without a nervous system. In the next section we show how, by explicitly considering the control-theoretic underpinnings of current models of stress, one can formulate their main insights in a more general way that does not rely on cognitive assumptions (while also accounting for the role of cognitive processes when they are relevant).

Stress in a systems perspective

To survive and reproduce, organisms need to constantly control the state of myriad dynamic processes at multiple levels of organization, from single cells

and their components (e.g., cellular respiration) to multicellular individuals (e.g., temperature control, circulation) to interactions between organisms (e.g., predator avoidance, competition for social rank). From this vantage point, organisms can be viewed as intricate collections of nested control systems. In the simplest cases, biological control systems maintain homeostasis by keeping a well-defined physiological variable (e.g., temperature, blood pressure, glucose concentration) within an optimal range around a set point. In more general terms, biological control can be framed as the pursuit of fitness-relevant goals which may depend on the state of complex variables such as social rank or offspring health and survival. Such variables are often partly or fully external to the organism (as illustrated by offspring survival); the effective regulation of both "internal" and "external" variables may require the organism to interact with its environment and sometimes modify it (e.g., searching for food, protecting offspring, choosing a location with appropriate temperature). Regardless of their nature and complexity, all control systems ultimately rely on two basic strategies, that is, feedback and feedforward control. The properties and limitations of these two types of regulation have been worked out in control theory, which is one of the main contributors to systems biology (see Kitano 2002; Bechhoefer 2005; Albertos and Mareels 2010; Åström and Murray 2012; Khammash 2016; Frank 2018a). In what follows, we review some basic concepts of control theory (see also the Glossary at the end of the paper) before applying them to the problem of defining and understanding stress.

Feedback and feedforward control

In feedback or closed-loop control, the current set point or goal (*reference input*) is compared with the actual state of the system (i.e., the system's *output*) to obtain an error signal. For example, a thermostat may detect a discrepancy between the room temperature (output) and the temperature set point. The error signal is used to generate an action, so as to bring the state of the system closer to the reference input (e.g., the thermostat may activate a heater). However, other causal factors (*disturbances*) may be acting on the system at the same time; for example, someone may open a window, letting cold air into the room. The joint effect of control actions and disturbances determines the system's output, which is then measured and compared with the reference, closing the control loop (Fig. 1A). The weight assigned to the feedback channel (*feedback gain*) determines the effect of error signals on the

controller's behavior, so that a higher-gain controller responds to a the same amount of discrepancy with a larger corrective action. In total, feedback controllers track the system's output in real time, progressively narrowing the gap between the goal and the state of the world through moment-to-moment self-correction. As a rule, the system's output is not directly available for comparison but has to be estimated or measured indirectly, for example through cascades of chemical reactions or sensory organs. Measurement processes—broadly defined to include sensory processes and the associated neural computations—inevitably introduce some stochastic error (or *noise*) in the loop, and engender a fundamental trade-off between the controller's tracking speed and its ability to reject unwanted noise. If the output is measured with higher temporal resolution—thus increasing the ability to track rapid changes in the state of the system—more irrelevant noise will enter the feedback channel and be amplified, causing undesired fluctuations in the response. Conversely, effective filtering of unwanted noise reduces the tracking speed of the control system (Bechhoefer 2005; Albertos and Mareels 2010). A powerful way to employ feedback controllers is to nest multiple feedback loops within one another, yielding a *feedback cascade*. In this type of hierarchical arrangement, the inner control loop regulates a lower-order variable (i.e., pursues a lower-order goal) and thus simplifies the control problem faced by the controller in the outer loop. For example, regulation of blood pressure (the higher-order variable) depends on nested feedback loops that control lower-order variables such as heart rate, stroke volume, and vasoconstriction (Sterling and Eyer 1988).

The main strength of feedback control lies in its flexibility, that is, the ability to respond to unknown or unanticipated disturbances. More generally, feedback control has an intrinsically self-correcting nature; for this reason, it does not require an accurate preexisting model of the system in order to function properly. However, feedback systems are also highly sensitive to noise and rely on accurate measurement of the output. Another crucial limitation of feedback control is that it depends on the ability to track real-time changes in the system. Slow chemical reactions, neural computation, physical inertia in the system—these and other factors introduce delays and response lags in the feedback loop, with the result that the performance of feedback control deteriorates. Beyond a certain threshold, delays in the feedback loop may destabilize the system and lead to erratic, uncontrolled behavior (Bechhoefer 2005; Albertos and Mareels 2010; Frank 2018a).
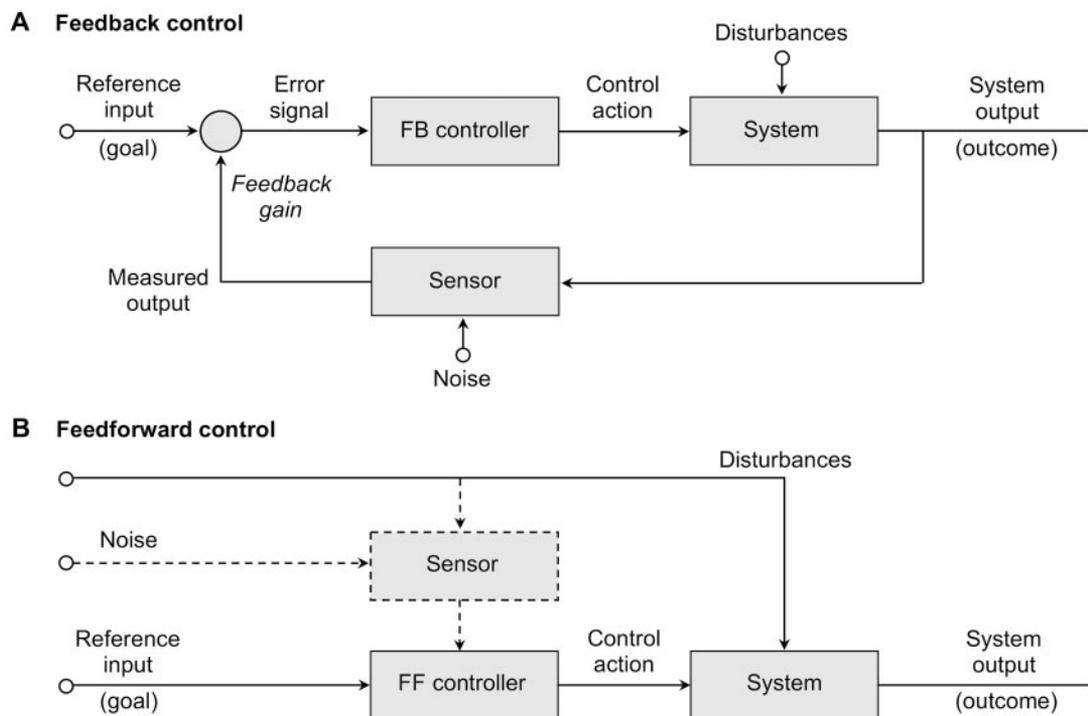
Fig. 1 Schematic representation of (**A**) a feedback or closed-loop control system and (**B**) a feedforward or open-loop control system. Feedforward controllers may employ information about past and present disturbances (dashed box and arrows) to predict future states of the system and determine the appropriate control actions. FB, feedback; FF, feedforward.

While feedback controllers can flexibly respond to disturbances and changes in the system after they have occurred, they are intrinsically unable to anticipate them. When disturbances can be anticipated (or ignored altogether), feedforward or open-loop control becomes an effective option, allowing for improved robustness and the reduction or elimination of response delay. The term "open-loop" highlights the fact that the system output is not used to determine control actions (i.e., there is no feedback channel closing the loop between input and output). The simplest forms of open-loop control make no attempt to predict the future state of the system, and produce fixed actions that follow an inflexible course once initiated. Such "ballistic" responses are often optimal in the context of rapid defensive mechanisms, such as protective reflexes (e.g., blinking, pain-induced limb retraction) or the initial phase of the cellular response to heat shock (Shudo et al. 2003; Albertos and Mareels 2010). In more complex feedforward controllers, the reference input is combined with an implicit or explicit model of the system to generate a control action (or sequence of actions) based on the predicted behavior of the system over time; if the model is correct and there are no major unforeseen disturbances, such an anticipatory response will yield the desired output without further correction. Feedforward processes may integrate information about current disturbances (obtained from sensors) as well as past states of the system (stored in some form of memory); to generate control actions, a controller may compute predictive estimates of future states of the system (Fig. 1B). In sum, feedforward regulation ranges from simple reflexes to complex cognitive simulations of future events that integrate preexisting knowledge about the likelihood of potential outcomes, the influence of contextual variables, and so on. For simplicity, in this paper we treat "prediction" and "anticipation" as synonyms, regardless of whether a control system actually computes estimates of future states. The advantages of feedforward controllers over their feedback counterparts include reduced sensitivity to noise (robustness), greater dynamic stability, and the fact that they do not require accurate, real-time measurement of the system's output. At the same time, sophisticated feedforward regulation requires an accurate internal model of the system and enough information about its current state so that future disturbances can be successfully anticipated. Most crucially, feedforward controllers are unable to respond to unanticipated events that occur while the current action is unfolding.

The complementary strengths of feedback and feedforward control can be combined by integrating

the two strategies within a single control system. For example, predictive estimates generated by a feedforward controller can be used to compensate for the delays introduced by feedback loops and reduce the effects of sensor noise. Conversely, the errors caused by an imperfect predictive model of the system can be corrected and smoothed out by introducing reactive feedback loops (Bechhoefer 2005). Unsurprisingly, most biological regulatory systems include both anticipatory and reactive components (Barrett and Simmons 2015). This is true across organismal systems and even at the cellular level: for example, the biochemical pathways that mediate responses to oxidative damage not only include nested feedback loops that respond to the concentration of the damaging molecules and their metabolites, but also feedforward processes that sense early cues of danger and proactively activate other components of the system (Zhang et al. 2009, 2010; more on this below). In allostasis and predictive homeostasis, a feedforward controller anticipates the future state of the system (e.g., changes in physical activity, food scarcity) and responds by adaptively adjusting the reference input of a homeostatic feedback controller, which in turn regulates the output variable (e.g., blood pressure, metabolic rate). The brain itself can be conceptualized as a complex controller that integrates feedback and feedforward processes (Franklin and Wolpert 2011). Taking this idea one step further, proponents of *active inference* models argue that all of cognition and behavior can be explained as the result of predictive computations; in this perspective, what feedback pathways do is carry information about prediction errors (Friston 2010; Pezzulo et al. 2015). Crucially, predictive computations do not necessitate a complex nervous system. Even relatively simple biochemical networks can compute mathematical functions (from addition/subtraction and multiplication/division to roots and polynomials; Buisman et al. 2009), implement switches and oscillators (Miller et al. 2005; Novák and Tyson 2008), and even perform associative learning (McGregor et al. 2012).

Stress as control failure

The concepts reviewed above suggest a simple but general definition of stress as control failure. Specifically, stress occurs when a biological control system detects a failure to control a fitness-critical variable. By fitness-critical we mean a variable with the potential to significantly impact the survival and/or reproductive success of the organism (Koolhaas et al. 2011); depending on context, this may extend

to related organisms (inclusive fitness; see West and Gardner 2013). The term "fitness-critical" underscores the idea that not all aspects of the world with some relevance to fitness are automatically sources of stress. Some variables have a disproportionate impact on survival and reproduction; organisms are selected to rapidly detect deviations from the desired state of those variables and to forcefully respond to control failures. Note that mild and/or short-lived deviations from the system's goal or regulatory range are expected in any realistic control system, and do not automatically qualify as failures. However, large and/or persistent discrepancies indicate that the organism is unable to achieve control over key aspects of its internal functioning and/or external environment—in other words, that the organism's fitness is threatened.

The state of the controlled variable is usually known only indirectly through processes of measurement and estimation (which in the most complex cases may include sensory and cognitive components, with multiple layers of inference). Incorrect estimates of the state of the system can lead the controller to detect large, persistent discrepancies when they are not present. An animal may mistake a shadow for a dangerous predator; defective baroreceptors may incorrectly sense a threatening drop in blood pressure; and so on. In all these cases, stress and stress responses occur in absence of an actual threat to fitness. Conversely, discrepancies that go undetected by the control system (e.g., failing to spot an approaching predator) do not engender stress even if they may result in damage to the organism and substantial fitness costs.

By this definition, an event or challenge becomes a stressor if it results in a failure to control a fitness-critical variable (as detected by the control system); this captures the key features of threat and uncontrollability emphasized by current models (Koolhaas et al. 2011). As we detail below, unpredictability refers to a particular kind of control failure in which anticipatory (feedforward) responses are lacking or inadequate. A single control failure represents an instance of acute stress; repeated failures over time indicate the existence of difficult or even intractable problems in the organism and/or its environment (and may be described as a type of chronic stress). Fitness-critical variables can be internal or external to the organism: to a mother with dependent offspring, a predator threatening the offspring can be a tremendous stressor, and failures to control offspring health and survival can be expected to be extremely stressful. While the classic concept of homeostasis suggests an emphasis on internal variables

(e.g., glucose concentration, blood pressure, oxidative damage), our definition underscores that biological control and its failures apply to multiple fitness-relevant domains, which may extend well beyond the borders of the individual organism. Depending on the nature of the control system under consideration, one may identify various categories of stress—social, energetic, cardiovascular, immune, oxidative, and so on. In this paper, we are not concerned with specific stressors and the relevant responses, but only with the general concept of stress and its invariant features across systems, organisms, and levels of analysis.

In line with the current literature, stress as a condition is distinguished from both the event that induces it (stressor) and the response enacted to resolve it (stress response). Especially when dealing with internal states, it is important to draw a clear distinction between the physiological variables that the organism is attempting to control and those that mediate the response. As an illustration drawing from vertebrate physiology, consider the case of energetic stress induced by starvation (the stressor). The fitness-critical variable that the organism is failing to control is blood glucose concentration (or, more abstractly, energy availability); the response of the organism may include a temporary elevation of glucocorticoids and other hormones, which stimulate glucose release and—if successful—eventually restore energetic homeostasis. While glucocorticoid secretion may be upregulated by changing the feedback set point of the hypothalamic–pituitary–adrenal (HPA) axis, the focal variable that defines the presence or absence of stress is the concentration of glucose, and not that of glucocorticoids (though the latter may be used as indicators to *infer* a state of stress). The larger system that includes both glucose and glucocorticoid regulation can be described as a feedback cascade, with glucose regulation as the outer loop (higher-order goal) and glucocorticoid regulation as the inner loop (lower-order goal). This is a crucial point that may generate confusion if not properly understood; in particular, it should be noted some models of stress (notably the reactive scope model; Romero et al. 2009) focus on the homeostatic regulation of mediators rather than that of fitness-critical variables *per se*. In contrast, the definition we propose focuses on the regulation of fitness-critical variables (e.g., blood glucose or energy availability); the regulation of specific mediators (e.g., glucocorticoids) is treated as a subproblem in the generation of appropriate responses. Of course, the nature of biological adaptation is such that, in many cases, fitness-critical variables are hierarchically nested within one another (e.g., achieving the potential for successful reproduction requires sufficient energy reserves; building up energy reserves requires sufficient day-to-day energy availability; and so on). This is not a problem for our definition, as long as the proper level(s) of analysis and the nature of the stressor(s) are correctly identified in any given case.

The concept of stress as control failure is illustrated in Fig. 2. The figure depicts a schematic control system with both feedback and feedforward components. The controlled variable can be jointly affected by disturbances in the environment as well as the organism's own behavior and physiology (summarized as the "state of the organism" in the figure). Of course, controllers can only modify the state of the external environment through the organism's behavior, which is why there are no arrows pointing directly from the controllers to the environment. When the feedforward controller anticipates a disturbance, it can act directly by triggering a response against the disturbance (arrow pointing to the state of the organism) or indirectly by shifting the reference input of the feedback controller. In the latter case, the anticipatory response can be described as an instance of allostasis. In the case of energetic stress discussed above, the organism may be able to predict an impending period of scarcity (disturbance); for example, based on seasonal cues that winter is approaching or declining rates of energy intake over a certain time span. Anticipatory responses to prevent starvation may range from changes in foraging behavior (e.g., leaving the current foraging patch; increasing food intake to build up energy reserves) to allostatic changes that modify the set point of feedback-regulated systems, including the HPA axis.

For an example at the cellular level, consider the biochemical pathways that protect the cell from oxidative damage (Zhang et al. 2009, 2010). Oxidative damage is caused by reactive oxygen species and other reactive compounds (e.g., electrophiles), which can be produced as metabolites of foreign molecules (xenobiotics). The critical controlled variable in this case is the cell's redox environment; deviations from the set point are detected by sensor proteins and relayed to a gene regulatory network in the nucleus (the feedback controller), which in turn activates the expression of antioxidant and detoxifying enzymes (a compensatory response directed at restoring homeostasis). By our definition, a persistent failure to maintain the redox environment within acceptable limits would qualify as oxidative stress. The system is organized as a feedback cascade, with a main outer loop that controls the overall activity of the
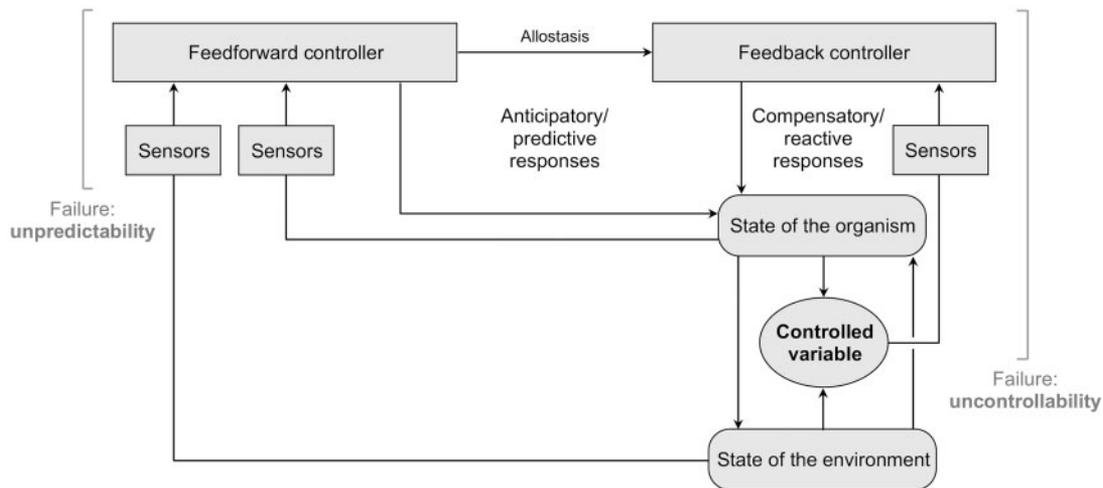
Fig. 2 An idealized biological control system with both feedback and feedforward components. For simplicity, the figure does not show reference inputs, disturbances, or sensor noise (see Fig. 1 for details). The controlled fitness-critical variable (in boldface) may be a joint function of the organism and environment. The feedback controller enacts compensatory/reactive responses to challenges that produce discrepancies between the goal (reference input) and the measured state of the variable. The feedforward controller enacts anticipatory/predictive responses to challenges; anticipatory responses that change the reference input of the feedback controller represent instances of allostasis. Note that the control system may involve complex cascades and nested control loops (not shown). Stress occurs when the control system detects a failure to keep the fitness-critical variable within the target range (uncontrollability). Unpredictability refers to failures of the feedforward component to anticipate a challenge and/or respond appropriately; such failures may or may not lead to stress, depending on whether they ultimately result in a failure to control the fitness-critical variable.

regulatory network and multiple inner loops that fine-tune the expression of specific enzymes. The feedforward component is provided by *xenosensors*, nuclear receptors that detect potentially dangerous xenobiotics *before* they are converted into reactive metabolites. Activated xenosensors trigger various anticipatory responses, both directly by inducing the expression of specific detoxifying enzymes and indirectly by upregulating the activity of the main feedback controller (an instance of allostasis; for details see Zhang et al. 2009, 2010).

Because biological control systems are complex and involve the interplay of multiple components (Fig. 2), control failures—and hence stress—can arise for a variety of distinct reasons. On the one hand, some environmental challenges may be intrinsically hard to predict and/or address, for example because of their intensity (e.g., wildfires, potent toxins), their stochastic nature (e.g., floods, rare predators), or their evolutionary novelty (e.g., invasive predators, novel pollutants). On the other hand, uncontrollability and unpredictability are always joint functions of the environment and the organism; challenges that are manageable for some individuals may exceed the regulatory capacity of others who lack resources, skills, and/or knowledge. As a result, previous stressors may either increase or decrease the organism's ability to effectively deal with subsequent challenges (see Romero et al. 2009; Taff and

Vitousek 2016). For example, prolonged exposure to stress may deplete an organism's resources, thus reducing its ability to cope with similar challenges in the future. Conversely, if dealing with a stressor provides useful information and improves the organism's predictive models, future events may become more predictable and controllable (more on this below). Dysfunctions within the organism may play the role of endogenous stressors (e.g., autoimmunity, circulatory diseases) or—more indirectly—negatively impact the control system's ability to respond to stress, resulting in delayed, insufficient, or inappropriate responses to challenges.

The nature of unpredictability

Figure 2 helps clarify the distinction between the two defining features of a stressor, uncontrollability and unpredictability (e.g., Koolhaas et al. 2011; see above). While uncontrollability broadly refers to the inability to keep the variable of interest within the target range (right side of the figure), unpredictability refers to a particular kind of failure—that is, a failure of the feedforward component to anticipate a challenging event and/or respond appropriately to cues that predict its onset (left side of the figure). Predictive failures can take many different forms, each with somewhat different implications: for example, the control system may correctly predict

that a challenge is going to happen but fail to predict *when* or *how* it is going to play out. In turn, uncertainty and errors may arise from a number of different sources—including incorrect models of the organism and/or environment, lack of information about the state of the system, or noise in the sensors that relay that information. When predictions are uncertain and involve a large margin of error, a feedforward controller may trigger nonspecific anticipatory responses that are likely to be useful in a broad range of conditions. Alternatively, the controller may make a precise but incorrect prediction and enact an inappropriate response. Both of these cases are distinct from complete predictive failures marked by the absence of anticipatory responses. The current literature on stress emphasizes the latter case, equating unpredictability with the lack of anticipatory responses (Koolhaas et al. 2011); the approach we propose suggests a more nuanced view of unpredictability. As discussed above, feedforward controllers are especially vulnerable to the damaging effects of erroneous or incomplete predictive models. While failing to predict the onset of a stressor (false negatives) leads to the absence of anticipatory responses, erroneously predicting that a stressor will occur (false positives) may trigger unnecessary responses, including allostatic adjustments. Such unnecessary responses may be strong enough to destabilize the whole system and induce a state of stress. Setting the optimal balance between false positives and false negatives is a complex problem that depends on the frequency of different challenges, the reliability of cues, and the fitness costs of responding or failing to respond. Under many conditions, selection may favor the evolution of mechanisms that accept a relatively large rate of false positives as a safety measure (see Nesse 2001, 2005; Johnson et al. 2013; Sheriff et al. 2018).

Note that, by our definition, unpredictability only leads to stress if it ultimately results in a failure to control the critical variable. When this happens, the compensatory stress responses elicited by uncontrollability may prompt revisions of the predictive model employed by the feedforward controller. This idea is consistent with active inference models, according to which the primary role of feedback pathways in the nervous system is to carry information about prediction errors, which can be used to update the brain's feedforward models (see Pezzulo et al. 2015). It also dovetails with the recent hypothesis that acute stress triggered by unpredictability functions as a "teaching signal" for the brain—by boosting memory for the stressful event, enhancing bottom-up information processing (i.e., increasing the weight of feedback

signals), and facilitating rapid learning through mechanisms such as dopamine release (Trapp et al. 2018). In organisms without a nervous system or even single cells, simple forms of revision can take place at the molecular level. In the oxidative stress example, a hypothetical revision mechanism could be as simple as the upregulated expression of xenosensors following a sustained failure to restore redox homeostasis (i.e., oxidative stress). As a result, future exposure to similar amounts of xenobiotics would trigger the expression of larger amounts of detoxifying enzymes. This general pattern has been empirically demonstrated in yeast cells exposed to oxidative stress, which respond to subsequent stressors with increased transcription rates (Guan et al. 2012).

It is noteworthy that, in the approach we have outlined, prediction is treated as an integral component of physiological and behavioral control; as such, it applies equally to long-term adjustments and rapid responses to immediate challenges. For example, agonistic encounters and other social stressors seem to prime inflammatory mechanisms even before any physical damage occurs (see Takahashi et al. 2018). This broad view of prediction must be distinguished from the concept of predictive homeostasis in the reactive scope model (Romero et al. 2009), which is explicitly restricted to highly predictable changes on a seasonal, circadian, or life history scale. In the same model, anticipatory responses in the context of acute challenges are regarded as instances of reactive homeostasis (Romero et al. 2009, 380). This terminological difference should be kept in mind to avoid confusion.

Extensions and future directions
Hormesis and conditioning

In a variety of domains, empirical findings indicate that prior exposure to low-intensity challenges can have protective effects against later, more severe stressors of the same kind (Fig. 3A). Such *conditioning* effects have been documented in relation to toxins, hypoxia, cardiovascular and thermal stress, and other types of challenges (Calabrese et al. 2007; Calabrese 2016). Conditioning is regarded by many as a special case of *hormesis*, a broad class of biphasic responses in which exposure to low versus high levels of a certain agent (e.g., a toxin) has opposite effects on physiological responses and/or outcomes (typically beneficial at low levels and harmful at high levels; Calabrese and Baldwin 2003; Costantini et al. 2010; Fig. 3B). While there is some debate about the generality and evolutionary implications of hormesis (Forbes 2000; Thayer et al. 2005; Mushak 2009,
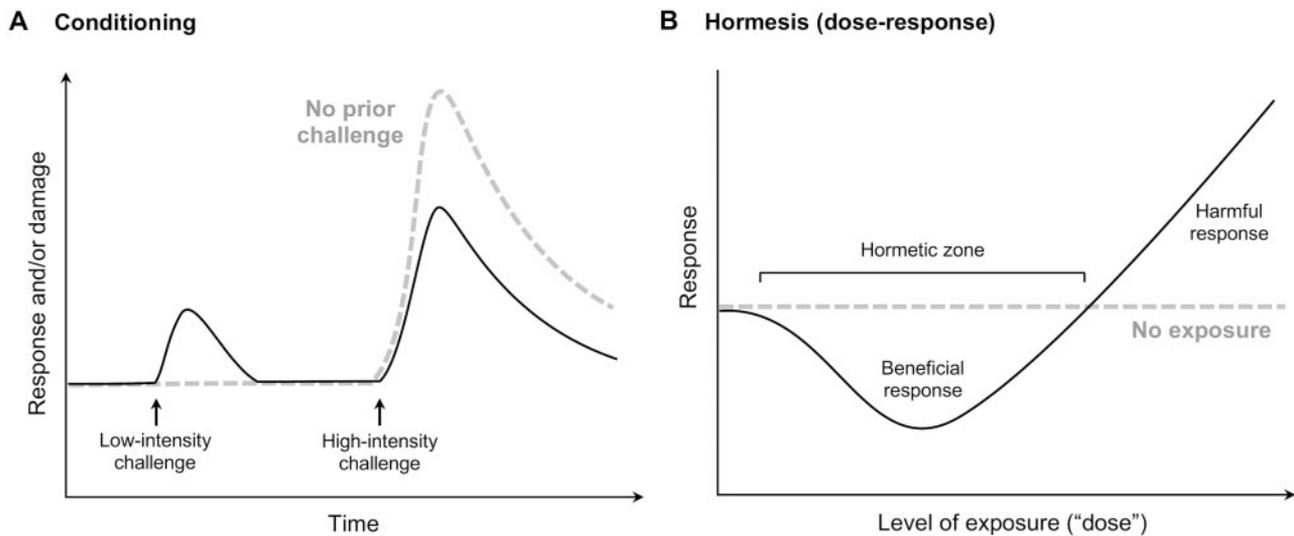
A Conditioning

B Hormesis (dose-response)

Fig. 3 (**A**) Schematic representation of conditioning effects. Prior exposure to a low-intensity challenge (solid line) has a protective effect against a later, more severe challenge. Protective effects are indicated by less intense responses and/or reduced damage following the high-intensity challenge, compared with the condition in which the organism is not exposed to the low-intensity challenge (dashed line). (**B**) Schematic representation of hormesis in a classic dose–response framework. The shape of the dose–response curve is biphasic, with beneficial effects at low doses ("hormetic zone") and harmful effects beyond a critical threshold.

2013, 2016; Costantini et al. 2010), these effects are both theoretically and practically interesting. For example, conditioning is relevant to understanding the interacting effects of multiple challenges and stressors over time—a scenario that is likely common in natural populations (Romero et al. 2009). This is a major focus in the study of endocrine flexibility (Taff and Vitousek 2016), defined as reversible phenotypic plasticity of endocrine traits (e.g., glucocorticoid levels) in response to environmental stimuli. Multiple challenges over time can result in various possible patterns, both beneficial and detrimental to fitness; for example, exposure to stressors may not only impair future flexibility, but also enable a faster response to subsequent stressors (see Taff and Vitousek 2016). While conditioning effects likely contribute to determine the shape of such patterns, the literature on endocrine flexibility has remained largely disconnected from that on hormesis. Conversely, biomedical research on hormesis has often ignored the potential fitness costs of ostensibly beneficial conditioning effects (e.g., Costantini et al. 2014), which are of primary interest to evolutionary biologists who study plasticity.

From a mechanistic perspective, hormesis is easy to explain as a manifestation or byproduct of adaptive homeostatic control, consistent with the approach presented in this paper. Specifically, hormesis (including conditioning) may arise because low-intensity challenges induce compensatory feedback

responses that lead to "overcorrection" (Stebbing 1987); alternatively, low-intensity challenges may engage feedforward responses designed to anticipate future perturbations (Stebbing 2009). Recent work on cellular stress has started to put these ideas in quantitative form through detailed mathematical models of the biochemical networks that mediate responses to toxins, oxidative damage, and so on (Zhang and Andersen 2007; Zhang et al. 2009, 2010; Goulev et al. 2017). These models show that various specific mechanisms may produce hormetic effects, including delayed or nonlinear compensatory responses (Zhang and Andersen 2007; Zhang et al. 2009; Goulev et al. 2017) as well as high-gain anticipatory responses triggered by small perturbations (Zhang et al. 2009).

We suggest that insights gathered from models of cellular stress could be usefully applied to other biological systems, including animals with complex nervous systems. For example, fairly sophisticated mathematical models of the HPA axis in humans and rodents have been developed and refined (Stanojević et al. 2018). These models can be used to simulate the effect of challenges of variable intensity and that of repeated challenges over time, but—to our knowledge—have never been employed to explore the dynamics of conditioning. When feedforward control relies on cognitive processes, low-intensity challenges may contribute to calibrate or revise the predictive model by providing useful information about the environment and the organism,

in line with the idea that acute stressors function as "teaching signals" for the brain (Trapp et al. 2018). Interestingly, even single cells show forms of (noncognitive) memory for previous stress exposures (see Guan et al. 2012). This example highlights the commonalities that exist between vastly different levels of organization and the potential for cross-fertilization across disciplines.

Trade-offs in the design of stress responses

A systems perspective makes it possible to harness principles from control theory and apply them to long-standing questions about the evolved design of stress responses. One of these principles is the so-called *conservation of fragility* in feedback-regulated systems, an instance of the pervasive trade-offs between robustness and fragility that characterize both natural and artificial mechanisms (Csete and Doyle 2002; Kitano 2007; Khammash 2016; see also Bechhoefer 2005). The performance of a feedback controller can be modulated by changing its feedback gain (see Fig. 1A). Specifically, slow (low-frequency) disturbances can be eliminated more effectively by increasing gain; however, each increase in low-frequency stability (robustness) is inevitably compensated by an increase in high-frequency instability (fragility; Fig. 4). Above a critical frequency, disturbances are not reduced but amplified and may lead to catastrophic losses of control. A thermostat that is extremely effective at canceling out slow temperature changes (e.g., between night and day) may break into uncontrolled oscillations if exposed to high-frequency changes (e.g., if another heater in the room is turned on and off every few minutes). This phenomenon has been empirically documented in yeast cells: the biochemical pathways that respond to osmotic stress can be dysregulated by fast oscillatory inputs outside the ecological range, leading to uncontrolled hyperactivation of the system (Mitchell et al. 2015). From an alternative perspective, the trade-off between performance at low versus high frequencies can be framed as a trade-off between plasticity and homeostasis (Frank 2018b). Specifically, controllers with enhanced ability to reject short-term disturbances (homeostasis) will generally be less effective in adapting to slower, long-term changes in the environment (plasticity), and vice versa.

Because of robustness–fragility trade-offs, the evolution of stress responses is constrained in ways that may be not immediately intuitive. In particular, the conservation of fragility suggests that organisms may not respond to challenges and stressors as rapidly
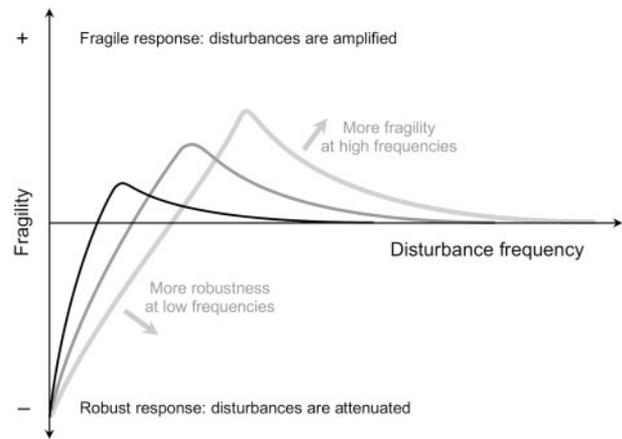

Fig. 4 Illustration of the conservation of fragility in feedback-regulated systems. Fragility is a function of the absolute effect of a disturbance on the system's output (see Fig. 1A). Positive fragility means that disturbances are amplified, potentially leading to uncontrolled oscillations. Negative fragility (robustness) means that disturbances are attenuated. Perfect control is obtained when disturbances are fully rejected (i.e., they have no effect on the output). By increasing the feedback gain, the system can be made more robust at low frequencies (slow disturbances); however, each increase in low-frequency robustness is matched by a corresponding increase in fragility at high frequencies (fast disturbances).

and intensely as they possibly could. By compromising performance and allowing for a certain "sloppiness" in the expression of physiological responses, they may reduce the risk of catastrophic failures when encountering challenges outside the optimal range. For example, animals are often limited in their ability to undergo rapid hormonal shifts in response to unpredictable events in the environment ("rapid endocrine flexibility"). A possible explanation is that the time lag between the event and the required phenotypic change would be too long for the response to be useful (Taff and Vitousek 2016). The conservation of fragility may contribute to explain why the expression of endocrine-mediated phenotypes has not evolved to be faster and more vigorous (e.g., as a means to prevent catastrophic failures, or to favor long-term plasticity over short-term homeostasis). Of course, the limitations of pure feedback control can be partially overcome by adding feedforward components to the system (Csete and Doyle 2002); however, this entails new points of fragility (e.g., sensitivity to prediction errors), as well as the additional costs of building and maintaining a more complex system. Interestingly, mathematical treatments of the HPA axis have dealt extensively with issues of dynamic stability (Savić 2008; Stanojević et al. 2018), but have not explicitly considered the role of robustness–fragility trade-offs in the design of the system.

Novel environments and evolutionary mismatches

Finally, a systems perspective may offer valuable insights into the stresses imposed by novel environments or stimuli, including those resulting from anthropogenic global change. Anthropogenic change can shift environmental parameters outside the range organisms have previously experienced (altered temperatures, carbon dioxide levels, etc.) or give rise to conditions that focal organisms have never encountered, such as the presence of invasive species (Sih et al. 2011). These novel conditions often function as stressors and may reduce fitness, by playing the role of ecological and evolutionary "traps" or engendering other evolutionary mismatches (see Schlaepfer et al. 2002; Somero 2012; Cofnas 2016). For example, climate change interferes with the timing of the activity-hibernation cycle of Arctic ground squirrels, which is regulated by a combination of feedforward mechanisms that anticipate the coming of spring (in both sexes) and feedback mechanisms that respond to temperature (in females; see Buck and Barnes 1999a, 1999b). With climate change, the short reproductive windows of male and female squirrels can become desynchronized, leading to intraspecific sex-dependent mismatch in reproductive timing—a likely source of stress for this species (Richter et al. 2017; Williams et al. 2017).

The outcomes of scenarios involving novel environmental conditions are intrinsically difficult to predict (Sih 2013). The approach we have presented in this paper may provide leverage by pointing to specific vulnerabilities of the various components of biological control systems (Fig. 2). Feedback components are more likely to be compromised when novel conditions exceed the range they have evolved to handle (uncontrollability), resulting in stress responses that are too weak to effectively compensate disturbances. Conditions that fall outside the evolved range may also drive a feedback controller into a zone of fragility, increasing the risk of catastrophic failure (see above; Mitchell et al. 2015). In most cases, however, the feedforward components of regulatory systems should be disproportionately affected by novel conditions, given their reliance on prediction and their dependence on accurate models of the environment (whether implicit or explicit). Predictive failures may occur for many different reasons. For instance, sensors may not recognize impending threats that fall outside their design limits, thus failing to activate anticipatory responses; indeed, it has been suggested that many failures to conduct appropriate behavioral responses to novel conditions stem from limited or imperfect information (Sih 2013). Even if sensors detect the novel threats, the controller may rely on an outdated model of the environment or utilize inappropriate decision-making rules (Schlaepfer et al. 2010). As a result, the control system may initiate maladaptive responses that fail to resolve the state of stress or even exacerbate it, with escalating costs and the possibility of sustained damage. While learning can potentially attenuate the impact of novel conditions on predictive mechanisms, learning processes are themselves constrained by past evolutionary history, and may fail to perform adaptively if conditions are sufficiently novel.

Conclusion

Unpacking the concept of stress in light of control theory reveals deep commonalities across levels of biological organization, and suggests a simple but general definition that is potentially amenable to formal analysis. The definition we have proposed is not meant as a replacement for existing models; rather, it is an opportunity for theoretical clarification and a stimulus to explore novel ideas and research directions. From our perspective, stress is a basic feature of all biological systems—and a truly unifying concept that will continue to inform research for decades to come.

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Glossary of control theory terms

Controller: a mechanism whose function is to match the value of a target variable to that of a reference input. The value of the controlled variable is the output of a system; the controller acts on the system to modify its output so as to keep the controlled variable close to the reference input.

Disturbance: an event (not produced by the controller) that changes the state of the system.

Error signal: the discrepancy between the measured system output and the reference input at a given time.

Feedback (closed-loop) control: a mode of control in which the system output is compared with the reference input, and the resulting error signal is used by the controller to determine the control action. Feedback control is reactive and can only correct the effects of disturbances after they have occurred.

Feedback gain: the weight assigned to the error signal in determining the response of the controller. A controller with higher feedback gain will respond more strongly to the same deviation from the reference input.

Feedforward (open-loop) control: a mode of control in which a model of the system is used to determine control actions, without feedback from the system output. Feedforward control can be used to anticipate future disturbances before they occur (to the extent that they can be successfully predicted).

Reference input: the desired value of the controlled variable. The reference input can be static (set point) or dynamic, and can be viewed as the "goal" of the controller.

Robustness/fragility: robustness is the ability of a system to maintain performance in the face of perturbations (broadly defined to include noise and uncertainty). Fragility is lack of robustness, or a system's sensitivity to perturbations. The robustness of a controller is a measure of its ability to reject disturbances and/or withstand the performance-degrading effects of noise (e.g., sensor noise) and uncertainty.

Sensors: mechanisms that measure the system output (and/or current disturbances) and relay that information to the controller. Sensors may introduce noise and delays in the control loop.

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