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# Craving for the future: The brain as a nutritional prediction system

## **Short Title:**

The brain as a nutritional prediction system

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## **Abstract**

In the last decades, predictive coding has emerged as an important framework for understanding how the brain processes information. It states that the brain is constantly inferring and predicting sensory data from statistical regularities in its environment. While this framework has been largely applied to sensory processing and motor control, we argue here that it could also serve as framework for a better understanding of how animals regulate nutrient homeostasis. Mechanisms that underlie nutrient homeostasis are commonly described in terms of negative feedback control, which compares current states with a reference point, called setpoint, and counteracts any mismatches. Using concepts from control theory, we explain shortcomings of negative feedback as a purely reactive controller, and how feed-forward mechanisms could be incorporated into feedback control to improve the performance of the control system. We then provide numerous examples to show that many insects, as well as mammals, make use of feed-forward, anticipatory mechanisms that go beyond the prevailing view of homeostasis being achieved through reactive negative feedback. The emerging picture is that the brain incorporates predictive signals as well as negative feedback to regulate nutrient homeostasis.

## **Highlights**

- A powerful hypothesis in neuroscience posits that the brain is a predictive system
- Nutrient homeostasis is typically described in terms of negative feedback
- Control theory explains how feed-forward mechanisms can support feedback control
- Many insects, like mammals, employ feed-forward mechanisms for nutrient homeostasis

## **Introduction**

Nutrients have profound effects on the fitness of animals. Insects use a fascinating repertoire of behaviors to ensure nutrient homeostasis. Assassin bugs inject lethal saliva to liquefy their nutritious prey; ants organize in complex societies to acquire, distribute and even produce food; and female mosquitoes will undergo a dangerous maneuver to extract precious proteins from overwhelmingly powerful hosts.

While consuming sufficient nutrients is essential to survival, excessive intake of nutrients such as carbohydrates and protein can have severe negative consequences on life history traits [1–7]. Animals have therefore evolved sophisticated mechanisms to regulate the intake of specific nutrients [8–11]. These behavioral mechanisms are just one part of the complex interplay of processes that ensure relative constancy in the nutritional *milieu intérieur*, the processes conceptualized by Walter Cannon as homeostasis [12]. Despite Cannon's more comprehensive view on the regulatory mechanisms underlying homeostasis [13], the physiological and neuronal circuit mechanisms that regulate nutrient intake are nowadays often viewed as negative feedback processes: the regulatory system is thought to measure the deviation of levels of a nutrient from a hypothetical setpoint (the required amount of nutrients). Any deviation from this setpoint will trigger a compensatory response that alters intake of the nutrient in order to revert

to the setpoint value. This control system is an important part of the regulation of feeding behavior, and has been extremely successful in advancing our understanding of the mechanisms that implement homeostasis [14–16]. However, it fails to explain many important aspects of nutritional homeostasis. One of the major drawbacks of such reactive feedback systems is that the animal must experience the lack of a nutrient, and all its negative consequences, before the homeostatic response is triggered.

We would like to argue that, while intuitive and widely employed, this reactive system is only a part of the regulatory framework underlying nutritional homeostasis. From a control-theoretic view, it would be hugely advantageous for biological systems to predict future changes in internal nutrient levels and external nutrient availability. Such prediction allows for homeostatic responses to prevent deviations before the system incurs the costs of a nutritional shortfall. We will discuss anticipatory homeostasis from a control theory perspective, present examples for such anticipatory homeostatic responses in nutrient regulation, discuss circuit and molecular mechanisms underlying anticipatory responses in the context of reproduction, and present evidence for the wide use of such predictive homeostatic responses. It should become clear that predictive homeostasis is likely to be the norm and not the exception. As such, the implementation of predictive regulatory frameworks leads to an overarching understanding of biological regulation ranging from predictive sensory coding in the brain to predictive gene regulation at the cellular level.

### **Reaction and prediction**

Groundbreaking work over the last few decades has shed light on numerous mechanisms underlying nutrient homeostasis [14–18]. In general, these mechanisms implement *reactive* homeostasis in the form of negative feedback control, using deviation of a nutritional variable from a hypothetical setpoint value to trigger counter-regulatory responses (Figure 1a). Control theory is an interdisciplinary branch of engineering and mathematics that studies the mathematical formalization of controlling dynamical systems to achieve a desired or optimal behavior [19]. Mathematically, achieving this goal requires stability, controllability and observability of states. One of the key concepts of control theory is *feedback*, which closes the causal link by feeding back outputs of the control process as inputs into the process. Advantages of feedback control are stability and robustness, because it ensures stable convergence towards a given setpoint against unexpected perturbations. Furthermore, it can be easily implemented, as it does not require prior knowledge about the control system or how changes in output will affect the variable of interest.

However, feedback control has significant limitations. First, it is reactive, and as such, can only respond to perturbations that have already occurred, even if these are detrimental to the controlled system. Thus, in the context of nutrition, the animal must experience a lack of nutrients, which can be detrimental to physiological systems, before mounting a regulatory response. Second, its responses are critically sensitive to the gain used for regulation [19]. While a high gain leads to fast responses by the controller, it also renders the controller highly susceptible to sensory noise. Third, the time it takes for the controller to affect a response in the

controlled variable provides an additional delay that could exacerbate the error [20]. For example, appropriate food may not be immediately available, and foraging in a time of need uses up precious time and resources. Taken together, there is a speed-accuracy tradeoff in how rapidly a feedback controller can compensate for errors in the controlled variable. In order to overcome these limitations of pure feedback control, control systems are often complemented by feed-forward mechanisms that are able to model and predict future states of the controlled variable [13].

The temporal dynamics of external and internal environments, although complex and irregular, are deterministic and predictable. As such, a controller that can adapt through learning or evolution to recognize such correlative patterns, and use predictive sensory cues to drive regulation in anticipation of future perturbations, would have significant advantages compared to a purely reactive controller. In particular, using signals that are strongly correlated with time-delayed perturbations of the controlled variable would further increase fitness in the face of environmental and sensory uncertainty. Predictive signals could be integrated at different levels of the control system, for example by directly modulating the setpoint to which negative feedback operates, or by providing an additional input to the feedback controller (Figure 1b) [13]. Another possibility is the use of so-called internal models of future states, i.e., *forward models*, which have largely been discussed in the context of motor control [21]. Indeed, evidence for internal models and predictive control has recently been found in prey pursuit of dragonflies [22]. Such a feed-forward mechanism does not operate in isolation, but is integrated into a feedback control system by summation of predictive feed-forward and error-based feedback terms (Figure 1c). Given these advantages, we could expect that such feed-forward signals would be integrated with feedback mechanisms to achieve nutrient homeostasis across species.

### **Food for the next generation**

Animals' nutritional needs are not constant across their lifespan, but change across different timescales depending on changes in physiology. Many of these changes in needs are predictable, and therefore animals can use physiological signals to predict changes in nutritional needs and mount an anticipatory behavioral response (feeding). For example, production of eggs requires a significant investment of nutrients only during periods of reproductive activity. If an animal were to use a purely reactive homeostatic system, production of eggs would lead to a reduction in nutritional reserves, which would trigger a compensatory behavioral response. A pure feedback system would require that the animal experiences a nutritional deficit in order to mount a behavioral response. However, since egg production is tightly coupled to nutrient availability in many insect species [23–25], this system would be sub-optimal because it would lead to periodic reductions in the rate of egg production as nutrient stores are reduced (Figure 2a). Rather, since reproduction is triggered by specific physiological signals, females could use these signals to alter nutrient intake in anticipation of their needs, and thus maintain sufficient nutrient levels to support a high rate of egg production (Figure 2b).

In *Drosophila melanogaster* [26,27], as in many insect species [28–33], virgin females produce

eggs at a low rate, and mating leads to a drastic increase in egg production. This increase in egg production is driven largely by male seminal fluid proteins (SFPs), which are transferred to the female during copulation [26]; in *D. melanogaster*, the major stimulator of egg production is Sex Peptide [34,35]. This high rate of egg production requires an investment of specific nutritional resources: dietary protein/amino acids are necessary for egg production [3,36], while increasing dietary sodium correlates with increasing egg production rates [10]. In order to ensure the intake of these nutrients, flies increase their intake of yeast [11,37,38] /amino acids [39] and sodium [10] after mating.

These nutrient-specific appetites are not driven by a deficit induced by the use of nutrients for egg production, since genetic manipulations that prevent egg production leave these appetites intact [10,37]. Rather, the same signal that induces egg production, Sex Peptide, acts as a predictive signal that induces appetites for the nutrients required for egg production. At the circuit level this feed-forward regulation is implemented by Sex Peptide silencing the activity of a small group of neurons in the reproductive tract, and consequently their postsynaptic partners, which send the signal to the brain [40–43]. As a result, this silencing induces appetites for both yeast and salt, as well as stimulating egg laying (Figure 3). This anticipatory regulation means that the female does not have to experience a drop in egg production capacity in order to initiate the necessary nutritional responses (Figure 2b). It also ensures that virgin females do not suffer the costly consequences of excessive protein intake, maximizing their lifespan and thus their opportunity to find a mate. Importantly, mated females still show nutrient-controlled feedback regulation of appetite, since amino acid deprivation increases yeast appetite [11,37]. This highlights the integration of feedback and feed-forward systems to ensure homeostasis.

Another, more extreme version of this anticipatory regulation of feeding behavior by reproduction is seen in ixodid ticks [44]. Females of these species feed on around 200-300 times their initial body weight in host blood, the vast majority of this engorgement happening only after mating has occurred. In these species, vitellogenesis and egg maturation occur only after the engorgement phase, indicating that blood feeding is not driven by a nutritional deficit induced by egg production. Rather, the effect of mating on blood feeding is driven by a pair of SFPs, voraxin alpha and beta. This coupling with mating state is important because females mate when attached to the host, and a fully engorged virgin female would be unable to reattach to the host, and thus mate, if it lost attachment.

### **Prediction beyond reproduction**

Anticipatory regulation of feeding behavior is widespread beyond reproduction. Circadian variation in feeding behavior may reflect anticipation of nutritional demands across the day [45]. In mice, for example, activity of vasopressin neurons in the SCN drives drinking before the sleep period in anticipation of water loss during sleep [46]. As well as predicting internal nutritional needs, animals, including bees, can use circadian cues to anticipate external nutrient availability at specific locations [47]. Animals can also anticipate seasonal variations in nutrient availability or requirements. Female *Culex pipiens* undergo a switch from blood feeding to sugar gluttony in anticipation of diapause, when protein requirements for egg production are reduced and sugars

are required to survive, and this switch drastically increases survival [48,49]. Likewise, larvae of *Sarcophaga crassipalpis* accumulate large reserves of lipid and protein in anticipation of nutritional needs during diapause [50]. What is more, the nervous system anticipates not only future changes in physiological requirements, but also the future effects of consumption on physiology: in vertebrates the activity of neurons controlling hunger, thirst and diuresis is modulated by sensory cues in anticipation of the physiological consequences of eating and drinking [51–56]. Whether such rapid modulation of hunger and thirst neurons also occurs in invertebrates, however, is unknown. Such modulation could occur at the level of recently-described neurons in the *Drosophila* brain that regulate thirst, feeding and protein appetite [57–61]. Indeed, pre-activation of the latter two neurons has been shown to drive persistent appetite even after their activation is terminated [60,61], much like AgRP-expressing neurons in the mammalian arcuate nucleus [62], suggesting they may fulfil a similar functional role. An indication that sensory input can directly alter central processes in insects could be deduced from the well-documented direct effect of chemosensory input on aging and physiology [63–66]. Such direct reprogramming of the physiology of the animal by taste and odors is likely to be an anticipatory adaptation to the imminently following food ingestion.

In several insect species, regulation of nutrient intake is thought to be mediated to a large extent by modulation of behavioral responses to specific chemosensory stimuli [67–69]. Indeed, deprivation from specific nutrients has been shown to modify the responsiveness of specific chemosensory receptor neurons in both flies [70] and locusts [67,71], suggesting an elegant neuronal implementation of negative feedback control. Whether predictive mechanisms generally act through modulation of chemosensory responses is unclear. In the case of salt intake, its stimulation by mating is due at least in part to a modulation of salt taste responsiveness [10]. To understand predictive homeostasis, it will be important to identify at which circuit nodes the response to food is modulated by predictive signals.

### **Prediction beyond nutrition**

Anticipation of physiological states is not limited to the regulation of nutrition. In the vertebrate cardiovascular system, feed-forward signals drive changes that provide blood supply in proportion to muscular output, even in the absence of afferent feedback; and anticipatory mechanisms adjust the properties of negative feedback control depending on circadian signals and behavioral state [72]. In fact, predictive homeostasis is not exclusive to the nervous system, or even to multicellular organisms: many microbes optimize their physiology to future conditions using “adaptive prediction”. For example, since transitions from one part of an animal host to another involve predictable changes in external conditions (eg. pH, mineral abundance), gut microbes can use current conditions to predict future conditions, and alter gene expression in such a way as to optimize future fitness [73]. Microbes also show circadian variation in gene expression that anticipates nutritional needs [74]. Thus, predictive homeostasis is widespread throughout biological control systems, providing an essential complement to feedback control that increases fitness by preventing deviations from optimal conditions *before they occur*.

## **Conclusion**

The central idea of the brain as a predictive system dates back to Helmholtz [75], who postulated that the brain constantly generates sensory data to match incoming stimuli with internal models of the environment and our bodies. While it has been shown that the brain can infer the statistical structure of the external environment [76–78] and predict sensory consequences from chosen motor actions [79,80], we have outlined here how animals also predict their internal nutritional states, and use these predictions to guide feeding decisions. The emerging picture is that insects and mammals employ feed-forward, anticipatory mechanisms that go beyond the current view of homeostasis being achieved through reactive negative feedback. A mechanistic understanding of how the brain controls nutrition must therefore take into account feed-forward regulation. Interestingly, feed-forward regulation is an integral part of some neuroscience models of human decision-making that are based on homeostatic frameworks [81–83]. Therefore understanding the biological implementation of predictive homeostasis might also provide insights into cognition across phyla.

A deeper understanding of how predictive systems aid homeostasis requires answering some key questions: How are these predictive mechanisms implemented at a cellular and molecular level? How are anticipatory signals integrated into neural circuits that implement negative feedback control of feeding? And, more speculatively, how are these anticipatory signals integrated into control systems on evolutionary timescales [84]? Ultimately, elucidating feed-forward mechanisms guiding homeostasis will require quantitative analysis and description of behavior, circuit dynamics and organismal physiology, using insights from theoretical frameworks, such as optimal control [85] and active inference [83,86]. These questions will provide plentiful fruit for future understanding of how Bernard's *milieu interior* is maintained by the harmonious interactions of myriad parts.

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## Figure legends

### Figure 1: Examples of control-theoretic models for achieving nutrient regulation.

- A) In negative feedback control, the control system measures the *controlled variable* and subtracts (hence negative) it from a *setpoint*. Any deviation from the setpoint (or *feedback error*) leads to a *control output* that regulates the *behavior* of the system to revert the controlled variable to the setpoint value. In most systems, controlled variables do not respond instantaneously to a change in output but with a certain delay due to the *response dynamics* of the system.
- B) Predictive stimuli which correlate with future changes in the controlled variable could be used to change the setpoint, the feedback error, or the controller in order to improve the performance of negative feedback control by reducing (ideally avoiding) the occurrence of an error signal.
- C) A *forward model* allows for predicting future states of the controlled variable based on predictive stimuli. Importantly, such a feed-forward mechanism does not work on its own, but the controller combines predictive feed-forward and error-based feedback terms by summation.

### Figure 2: Advantages of using additional feed-forward mechanisms over purely reactive feedback control to maximize nutrient availability for egg production upon mating.

- A) In a purely reactive controller based on negative feedback, nutrient-specific intake is controlled by the deviations of the internal nutrient levels from a given setpoint. For example, upon mating Sex Peptide stimulates female egg production, which requires proteins and sodium, and therefore would lead to a reduction in internal amino acid (AA)/sodium levels. The behavioral changes induced by this deviation from the setpoint would lead to an increase in yeast/salt appetite only after a delay. As a result, the fly would experience a reduction in internal AA/sodium levels, and consequently a reduction in egg production. AA/sodium levels only recover once feeding is initiated and nutrients are absorbed. While the relationship between egg production, yeast/salt intake and internal AA/sodium levels depends on the exact dynamics of the system, these periodic reductions in the egg production rate would significantly decrease the fitness of the animal.
- B) In a homeostatic system incorporating feed-forward regulation, Sex Peptide (SP) serves as a predictive signal for a subsequent increase in egg production, and thus an increase in AA/sodium turnover. Therefore, it is employed to induce an anticipatory increase in yeast/salt feeding. This anticipatory response supports the increased needs for subsequent egg production. Consequently, no significant deviations of the AA/sodium levels occur, which supports a constant high egg production rate.

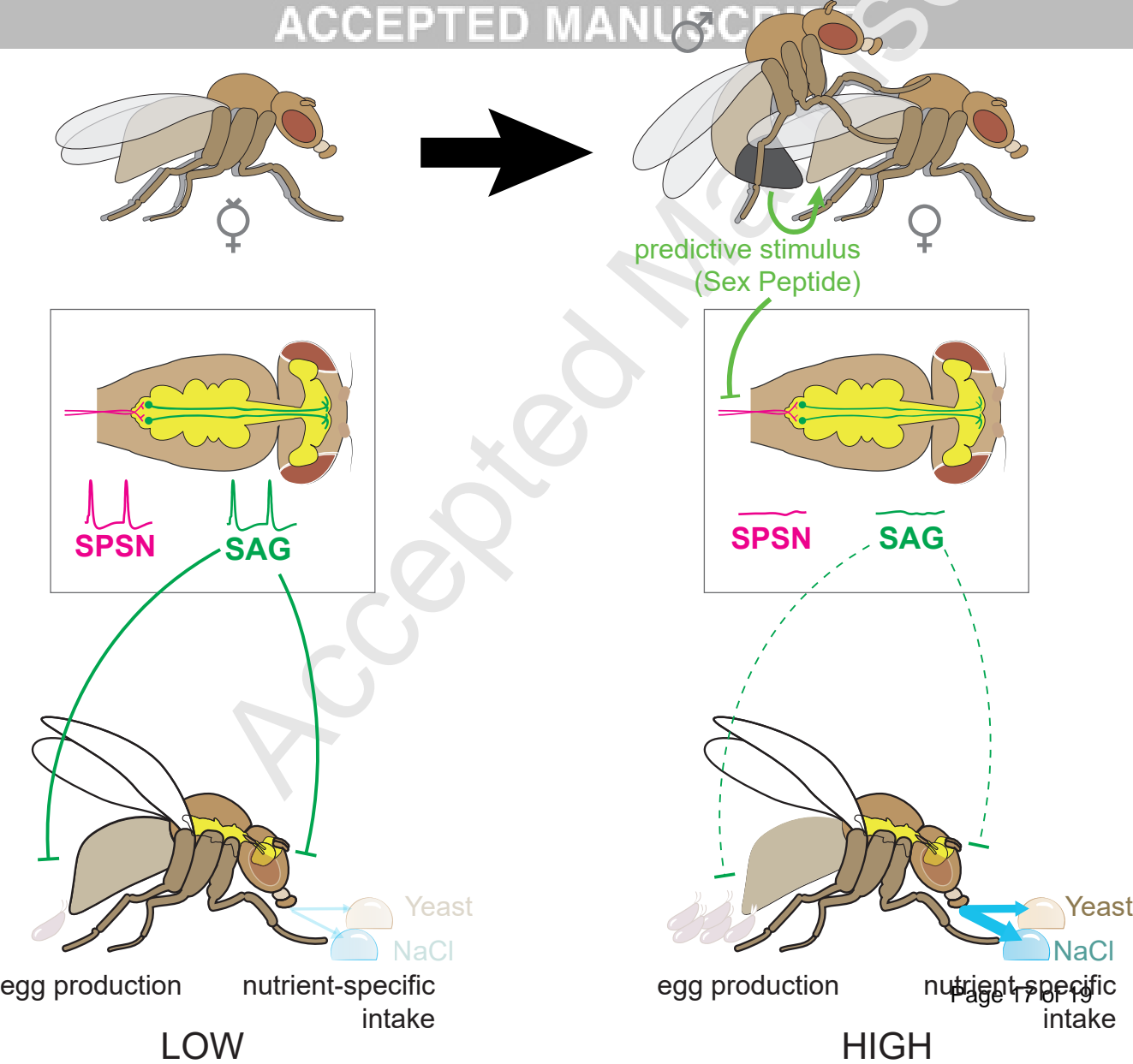
### Figure 3: Sex Peptide stimulates both egg production and anticipatory appetites necessary to support reproduction through a common SPSN-SAG neuronal circuit.

In virgin females (left), Sex Peptide Sensory Neurons (SPSNs) are tonically active, and excite postsynaptic ascending neurons (SAGs) that suppress egg laying and salt/yeast appetites.

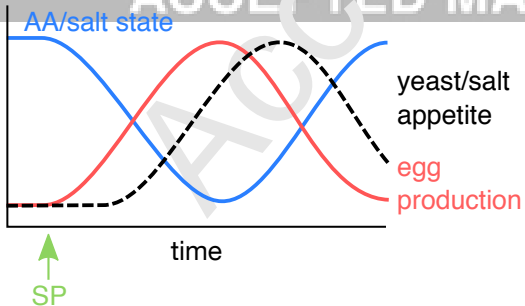


Following mating (right), Sex Peptide binding to its receptor in SPSNs silences their activity, releasing this inhibition of egg laying and concomitantly driving the anticipatory appetites for salt and yeast that support a constant high rate of egg production.

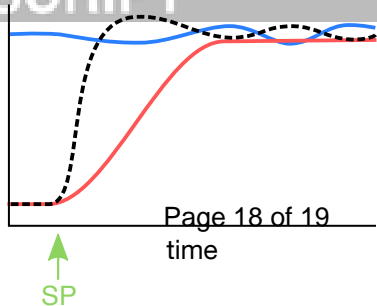
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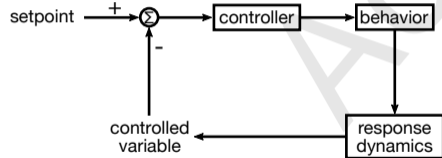
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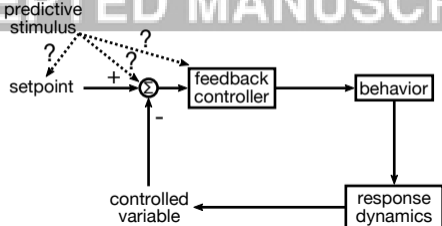
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