



ELSEVIER



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

Samuel J Walker^a, Dennis Goldschmidt^a and Carlos Ribeiro

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.

Address

Behavior and Metabolism Laboratory, Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon 1400-038, Portugal

Corresponding author: Ribeiro, Carlos (Carlos.Ribeiro@neuro.fchampalimaud.org)

^aThese authors contributed equally to this study.

Current Opinion in Insect Science 2017, **23**:96–103

This review comes from a themed issue on **Molecular physiology**

Edited by **Carlos Ribeiro** and **Matthew Piper**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 4th August 2017

<http://dx.doi.org/10.1016/j.cois.2017.07.013>

2214-5745/© 2017 Published by Elsevier Inc.

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 [8,9,10^{**},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

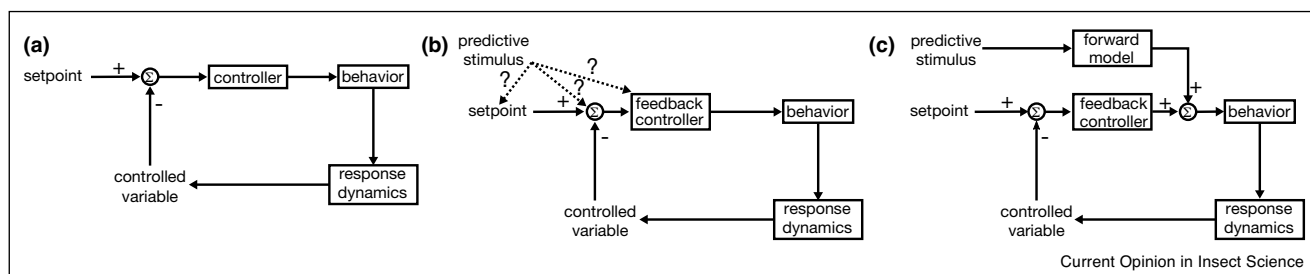
Groundbreaking work over the last few decades has shed light on numerous mechanisms underlying nutrient homeostasis [14–18]. In general, these mechanisms implement *reactive* homeostasis in the form of negative feedback control, using deviation of a nutritional variable from a hypothetical setpoint value 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 toward 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, that is, *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 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 1b,c). 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

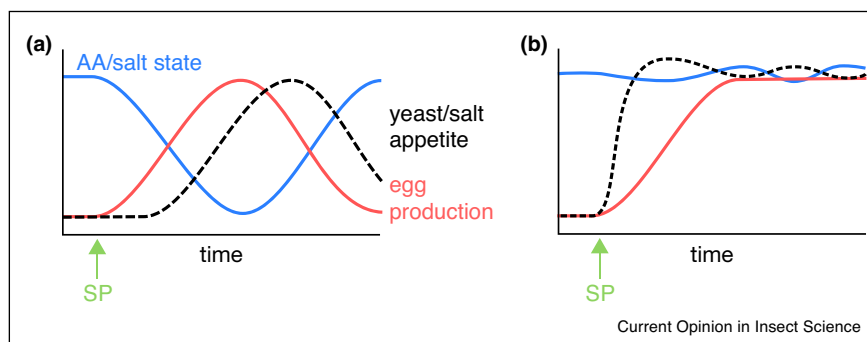
Animals' nutritional needs are not constant across their lifespan, but change across different timescales depending on changes in physiology. Many of these changes in needs are predictable, and therefore animals can use physiological signals to predict changes in nutritional needs and mount an anticipatory 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 [3,36,37,38**], 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*,39,40]/amino acids [41] and sodium [10**] after mating.

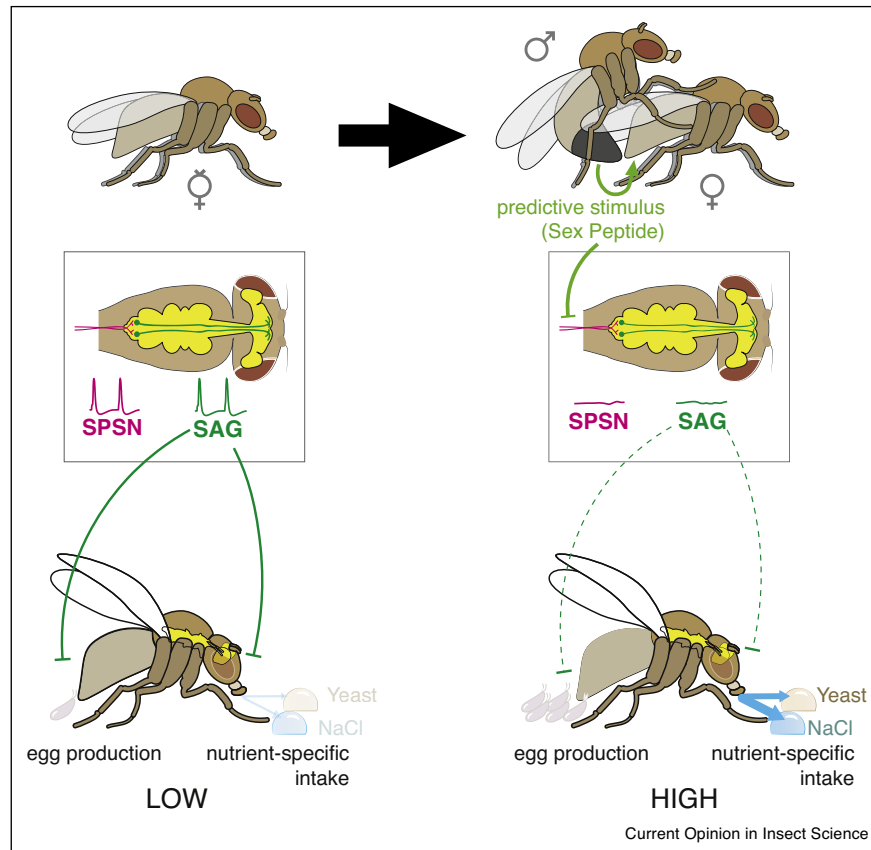
These nutrient-specific appetites are not driven by a deficit induced by the use of nutrients for egg production, since genetic manipulations that prevent egg production leave these appetites intact [10**,39]. Rather, the same signal that induces egg production, Sex Peptide, acts as a predictive signal 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 [10**,39,42–45]. 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

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.

intake, maximizing their lifespan and thus their opportunity to find a mate. Importantly, mated females still show nutrient-controlled feedback regulation of appetite, since deprivation from yeast increases yeast appetite [11^{*},39]. This appetite is induced by the lack of any essential amino acid, and can be suppressed by specific commensal bacteria, though surprisingly these microbes do not appear to provide the fly directly with the missing amino acids [38^{**}]. The combination of these feeding regulatory systems 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 [46]. 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 [47]. In mice, for example, activity of vasopressin neurons in the SCN drives drinking before the sleep period in anticipation of water loss during sleep [48^{*}]. As well as predicting internal nutritional needs, animals, including bees, can use circadian cues to anticipate external nutrient availability at specific locations [49]. 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 [50,51]. Likewise, larvae of *Sarcophaga crassipalpis* accumulate large reserves of lipid and protein in anticipation of nutritional needs during diapause [52]. 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 [53^{••},54^{••},55^{••},56–58]. 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 [59–62,63[•]]. Indeed, pre-activation of the latter two neurons has been shown to drive persistent appetite even after their activation is terminated [62,63[•]], much like AgRP-expressing neurons in the mammalian arcuate nucleus [64], suggesting they may fulfill 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 [65[•],66–68]. 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 [14,69–71]. Indeed, deprivation from specific nutrients has been shown to modify the responsiveness of specific chemosensory receptor neurons in both flies [72] and locusts [69,73], 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 [74]. 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 (e.g. 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 [75]. Microbes also show circadian variation in gene expression that anticipates nutritional needs [76]. 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 [77], 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 [78–80] and predict sensory consequences from chosen motor actions [81[•],82[•]], 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 [83–85]. 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 [86]? 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 [87] and active inference [85,88]. These questions will provide plentiful fruit for future understanding of how Bernard’s *milieu interior* is maintained by the harmonious interactions of myriad parts.

Conflict of interest

None declared.

Acknowledgements

We thank members of the Behavior and Metabolism laboratory for helpful discussions, as well as Gil Costa for illustrations. This work was supported by the Human Frontier Science Program Project Grant RGP0022/2012 and the BIAL Foundation grant 283/14 to CR. SJW was supported by Marie Curie FP7 Programme FLiACT (ITN) grant to CR. DG is a member of the Champalimaud International Neuroscience Doctoral Programme and is supported by the FCT fellowship PD/BD/114273/2016. Work at Champalimaud Research is generously supported by the Champalimaud Foundation.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Grandison RC, Piper MDW, Partridge L: **Amino-acid imbalance explains extension of lifespan by dietary restriction in *Drosophila***. *Nature* 2009, **462**:1061-1064.
 2. Lee KP, Simpson SJ, Clissold FJ, Brooks R, Ballard JWO, Taylor PW, Soran N, Raubenheimer D: **Lifespan and reproduction in *Drosophila*: new insights from nutritional geometry**. *Proc Natl Acad Sci U S A* 2008, **105**:2498-2503.
 3. Piper MDW, Blanc E, Leitão-Gonçalves R, Yang M, He X, Linford NJ, Hoddinott MP, Hopfen C, Soultoukis GA, Niemeyer C *et al.*: **A holidic medium for *Drosophila melanogaster***. *Nat Methods* 2013 <http://dx.doi.org/10.1038/nmeth.2731>.
 4. Solon-Biet SM, McMahon AC, Ballard JWO, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG *et al.*: **The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice**. *Cell Metab* 2014, **19**:418-430.
 5. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng C-W, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J *et al.*: **Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population**. *Cell Metab* 2014, **19**:407-417.
 6. Le Gall M, Behmer ST: **Effects of protein and carbohydrate on an insect herbivore: the vista from a fitness landscape**. *Integr Comp Biol* 2014, **54**:942-954.
 7. Clark RM, Zera AJ, Behmer ST: **Nutritional physiology of life-history trade-offs: how food protein-carbohydrate content influences life-history traits in the wing-polymorphic cricket *Gryllus firmus***. *J Exp Biol* 2015, **218**:298-308.
 8. Berthoud H-R, Seeley RJ: *Neural and Metabolic Control of Macronutrient Intake*. CRC Press; 1999.
 9. Mayntz D, Raubenheimer D, Salomon M, Toft S, Simpson SJ: **Nutrient-specific foraging in invertebrate predators**. *Science* 2005, **307**:111-113.
 10. Walker SJ, Corrales-Carvajal VM, Ribeiro C: **Postmating circuitry •• modulates salt taste processing to increase reproductive output in *Drosophila***. *Curr Biol* 2015, **25**:2621-2630.
- This study demonstrates that female fruit flies increase their salt and yeast intake after mating leading to augmented egg production. Surprisingly, this nutrient-specific regulation is independent of egg production rate, but requires instead signaling of a Sex Peptide Receptor circuitry. These findings provide the neuronal circuit implementation of a feed-forward, anticipatory mechanism for nutrient homeostasis in *Drosophila*.
11. Corrales-Carvajal VM, Faisal AA, Ribeiro C: **Internal states drive • nutrient homeostasis by modulating exploration-exploitation trade-off**. *eLife* 2016, **5**:e19920.
- On the basis of the quantitative analysis of image-based tracking, the authors find that internal states given by mating and amino acid deprivation modulate several observable parameters related to nutrient-specific exploitation and exploration in *Drosophila melanogaster*.
12. Cannon WB: *The Wisdom of the Body*. WW Norton & Co; 1932.
 13. Carpenter RHS: **Homeostasis: a plea for a unified approach**. •• *Adv Physiol Educ* 2004, **28**:180-187.
- This article explains a variety of models from control theory in the context of homeostatic control systems, emphasizing how physiological control goes far beyond negative feedback alone. It also highlights the need for a unified approach to homeostasis as a goal of physiological systems.
14. Dethier V: *The Hungry Fly: A Physiological Study of the Behavior Associated with Feeding*. Harvard University Press; 1976.
 15. Pool A-H, Scott K: **Feeding regulation in *Drosophila***. *Curr Opin Neurobiol* 2014, **29**:57-63.
 16. Sternson SM: **Hypothalamic survival circuits: blueprints for purposive behaviors**. *Neuron* 2013, **77**:810-824.
 17. Simpson SJ, Raubenheimer D: *The Nature of Nutrition: A Unifying Framework from Animal Adaptation to Human Obesity*. Princeton University Press; 2012.
 18. Itskov PM, Ribeiro C: **The dilemmas of the gourmet fly: the molecular and neuronal mechanism of feeding and nutrient decision making in *Drosophila***. *Front Decis Neurosci* 2013, **7**:12.
 19. Sontag ED: *Mathematical Control Theory: Deterministic Finite Dimensional Systems*. edn 2. Springer-Verlag New York Inc.; 1998.
 20. Richard J-P: **Time-delay systems: an overview of some recent advances and open problems**. *Automatica* 2003, **39**:1667-1694.
 21. Wolpert DM, Ghahramani Z, Jordan MI: **An internal model for sensorimotor integration**. *Science* 1995, **269**:1880-1882.
 22. Mischiati M, Lin H-T, Herold P, Imler E, Olberg R, Leonardo A: • **Internal models direct dragonfly interception steering**. *Nature* 2015, **517**:333-338.
- By quantifying body and head position and orientation, the authors present the first conclusive evidence for predictive internal models in an insect. Dragonflies use both forward and inverse models of their own body dynamics, as well as an internal model of prey trajectory, in combination with feedback from the visual system to guide predictive head rotations and interception steering.
23. Wigglesworth VB: **Nutrition and reproduction in insects**. *Proc Nutr Soc* 1960, **19**:18-23.
 24. Friend WG, Choy CT, Cartwright E: **The effect of nutrient intake on the development and the egg production of *Rhodnius prolixus* Stål (Hemiptera: Reduviidae)**. *Can J Zool* 1965, **43**:891-904.
 25. Boggs CL, Gilbert LE: **Male contribution to egg production in butterflies: evidence for transfer of nutrients at mating**. *Science* 1979, **206**:83-84.
 26. Gillott C: **Male accessory gland secretions: modulators of female reproductive physiology and behavior**. *Annu Rev Entomol* 2003, **48**:163-184.
 27. Avila FW, Sirot LK, LaFlamme BA, Rubinstein CD, Wolfner MF: **Insect seminal fluid proteins: identification and function**. *Annu Rev Entomol* 2011, **56**:21-40.
 28. Kocher SD, Tarpay DR, Grozinger CM: **The effects of mating and instrumental insemination on queen honey bee flight behaviour and gene expression**. *Insect Mol Biol* 2010, **19**:153-162.
 29. Tanaka ED, Hartfelder K: **The initial stages of oogenesis and their relation to differential fertility in the honey bee (*Apis mellifera*) castes**. *Arthropod Struct Dev* 2004, **33**:431-442.
 30. Sirot LK, Poulson RL, McKenna MC, Girnary H, Wolfner MF, Harrington LC: **Identity and transfer of male reproductive gland proteins of the dengue vector mosquito, *Aedes aegypti*: potential tools for control of female feeding and reproduction**. *Insect Biochem Mol Biol* 2008, **38**:176-189.
 31. Jin ZY, Gong H: **Male accessory gland derived factors can stimulate oogenesis and enhance oviposition in *Helicoverpa armigera* (Lepidoptera: Noctuidae)**. *Arch Insect Biochem Physiol* 2001, **46**:175-185.
 32. Reinhardt K, Naylor RA, Siva-Jothy MT: **Ejaculate components delay reproductive senescence while elevating female reproductive rate in an insect**. *Proc Natl Acad Sci U S A* 2009, **106**:21743-21747.

33. Shahid M, Siddiqui A, Omkar, Mishra G: **Mating alters the rate of development of ovarioles in the ladybird, *Propylea dissecta* (Coleoptera: Coccinellidae).** *EJE* 2016, **113**:44-50.
34. Liu H, Kubli E: **Sex-peptide is the molecular basis of the sperm effect in *Drosophila melanogaster*.** *Proc Natl Acad Sci U S A* 2003, **100**:9929.
35. Chapman T, Bangham J, Vinti G, Seifried B, Lung O, Wolfner MF, Smith HK, Partridge L: **The sex peptide of *Drosophila melanogaster*: female post-mating responses analyzed by using RNA interference.** *Proc Natl Acad Sci U S A* 2003, **100**:9923.
36. Drummond-Barbosa D, Spradling AC: **Stem cells and their progeny respond to nutritional changes during *Drosophila* oogenesis.** *Dev Biol* 2001, **231**:265-278.
37. Piper MDW, Soultoukis GA, Blanc E, Mesaros A, Herbert SL, Juricic P, He X, Atanassov I, Salmonowicz H, Yang M *et al.*: **Matching dietary amino acid balance to the in silico-translated exome optimizes growth and reproduction without cost to lifespan.** *Cell Metab* 2017, **25**:610-621.
38. Leitão-Gonçalves R, Carvalho-Santos Z, Francisco AP, Fioreze GT, Anjos M, Baltazar C, Elias AP, Itskov PM, Piper MDW, Ribeiro C: **Commensal bacteria and essential amino acids control food choice behavior and reproduction.** *PLoS Biol* 2017, **15**:e2000862.
- This study demonstrates that in *Drosophila* essential amino acids and two gut bacteria species are key modulators of yeast appetite. Removing any one essential amino acid from the diet produces a strong and specific appetite for proteinaceous food. However, flies harboring the appropriate microbiome do not develop a yeast appetite. Surprisingly, the bacteria do not seem to suppress this specific appetite by providing amino acids. These findings provide the nutritional and microbial basis for understanding the feedback signals regulating protein homeostasis in *Drosophila*.
39. Ribeiro C, Dickson BJ: **Sex peptide receptor and neuronal TOR/S6K signaling modulate nutrient balancing in *Drosophila*.** *Curr Biol* 2010, **20**:1000-1005.
40. Vargas MA, Luo N, Yamaguchi A, Kapahi P: **A role for S6 kinase and serotonin in postmating dietary switch and balance of nutrients in *D. melanogaster*.** *Curr Biol* 2010, **20**:1006-1011.
41. Uchizono S, Tabuki Y, Kawaguchi N, Tanimura T, Itoh TQ: **Mated *Drosophila melanogaster* females consume more amino acids during the dark phase.** *PLOS ONE* 2017, **12**:e0172886.
42. Häsemeyer M, Yapici N, Heberlein U, Dickson BJ: **Sensory neurons in the *Drosophila* genital tract regulate female reproductive behavior.** *Neuron* 2009, **61**:511-518.
43. Yang C, Rumpf S, Xiang Y, Gordon MD, Song W, Jan LY, Jan Y-N: **Control of the postmating behavioral switch in *Drosophila* females by internal sensory neurons.** *Neuron* 2009, **61**:519-526.
44. Rezával C, Pavlou HJ, Dornan AJ, Chan Y-B, Kravitz EA, Goodwin SF: **Neural circuitry underlying *Drosophila* female postmating behavioral responses.** *Curr Biol* 2012, **22**:1155-1165.
45. Feng K, Palfreyman MT, Häsemeyer M, Talsma A, Dickson BJ: **Ascending SAG neurons control sexual receptivity of *Drosophila* females.** *Neuron* 2014, **83**:135-148.
46. Kaufman WR: **Gluttony and sex in female ixodid ticks: how do they compare to other blood-sucking arthropods?** *J Insect Physiol* 2007, **53**:264-273.
47. Xu K, Zheng X, Sehgal A: **Regulation of feeding and metabolism by neuronal and peripheral clocks in *Drosophila*.** *Cell Metab* 2008, **8**:289-300.
48. Gizowski C, Zaelzer C, Bourque CW: **Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep.** *Nature* 2016, **537**:685-688.
- The authors show that circadian output from the suprachiasmatic nucleus drives anticipatory thirst before sleep onset, via vasopressin-mediated excitation of OVL1 thirst neurons, which compensates for water loss during sleep.
49. Antle MC, Silver R: **Neural basis of timing and anticipatory behaviors.** *Eur J Neurosci* 2009, **30**:1643-1649.
50. Mitchell CJ, Briegel H: **Inability of diapausing *Culex pipiens* (Diptera: Culicidae) to use blood for producing lipid reserves for overwinter survival.** *J Med Entomol* 1989, **26**:318-326.
51. Robich RM, Denlinger DL: **Diapause in the mosquito *Culex pipiens* evokes a metabolic switch from blood feeding to sugar gluttony.** *Proc Natl Acad Sci U S A* 2005, **102**:15912-15917.
52. Adedokun TA, Denlinger DL: **Metabolic reserves associated with pupal diapause in the flesh fly, *Sarcophaga crassipalpis*.** *J Insect Physiol* 1985, **31**:229-233.
53. Chen Y, Lin Y-C, Kuo T-W, Knight ZA: **Sensory detection of food rapidly modulates arcuate feeding circuits.** *Cell* 2015, **160**:829-841.
- See annotation to Ref. [55**].
54. Betley JN, Xu S, Cao ZFH, Gong R, Magnus CJ, Yu Y, Sternson SM: **Neurons for hunger and thirst transmit a negative-valence teaching signal.** *Nature* 2015, **521**:180-185.
- See annotation to Ref. [55**].
55. Mandelblat-Cerf Y, Ramesh RN, Burgess CR, Patella P, Yang Z, Lowell BB, Andermann ML: **Arcuate hypothalamic AgRP and putative POMC neurons show opposite changes in spiking across multiple timescales.** *eLife* 2015, **4**:e07122.
- This study along with Refs. [53**,54**] shows that in the mammalian hypothalamic arcuate nucleus, the majority of AgRP-expressing 'hunger' neurons are rapidly inhibited, and POMC-expressing 'satiety' neurons excited, by sensory detection of food or food-predicting cues.
56. Garfield AS, Shah BP, Burgess CR, Li MM, Li C, Steger JS, Madara JC, Campbell JN, Kroeger D, Scammell TE *et al.*: **Dynamic GABAergic afferent modulation of AgRP neurons.** *Nat Neurosci* 2016, **19**:1628-1635.
57. Zimmerman CA, Lin Y-C, Leib DE, Guo L, Huey EL, Daly GE, Chen Y, Knight ZA: **Thirst neurons anticipate the homeostatic consequences of eating and drinking.** *Nature* 2016, **537**:680-684.
58. Mandelblat-Cerf Y, Kim A, Burgess CR, Subramanian S, Tannous BA, Lowell BB, Andermann ML: **Bidirectional anticipation of future osmotic challenges by vasopressin neurons.** *Neuron* 2017, **93**:57-65.
59. Jourjine N, Mullaney BC, Mann K, Scott K: **Coupled Sensing of hunger and thirst signals balances sugar and water consumption.** *Cell* 2016, **166**:855-866.
60. Albin SD, Kaun KR, Knapp J-M, Chung P, Heberlein U, Simpson JH: **A subset of serotonergic neurons evokes hunger in adult *Drosophila*.** *Curr Biol* 2015, **25**:2435-2440.
61. Park J-Y, Dus M, Kim S, Abu F, Kanai MI, Rudy B, Suh GSB: ***Drosophila* SLC5A11 mediates hunger by regulating K⁺ channel activity.** *Curr Biol* 2016, **26**:1965-1974.
62. Zhan YP, Liu L, Zhu Y: **Taotie neurons regulate appetite in *Drosophila*.** *Nat Commun* 2016, **7**.
63. Liu Q, Tabuchi M, Liu S, Kodama L, Horiuchi W, Daniels J, Chiu L, Baldoni D, Wu MN: **Branch-specific plasticity of a bifunctional dopamine circuit encodes protein hunger.** *Science* 2017, **356**:534-539.
- This study shows that a subset of dopaminergic neurons in the *D. melanogaster* brain is excited upon deprivation from dietary protein, and this activity increases feeding on yeast while suppressing feeding on sucrose, through two distinct output pathways.
64. Chen Y, Lin Y-C, Zimmerman CA, Essner RA, Knight ZA: **Hunger neurons drive feeding through a sustained, positive reinforcement signal.** *eLife* 2016, **5**:e18640.
65. Libert S, Zwiener J, Chu X, VanVoorhies W, Roman G, Pletcher SD: **Regulation of *Drosophila* life span by olfaction and food-derived odors.** *Science* 2007, **315**:1133-1137.
- This study demonstrates that exposure to food odors can modulate lifespan in *Drosophila*. When flies are kept on nutrient-poor diets, food odors reduce lifespan in a way that partially recapitulates the effect of increased nutrient intake, likely due to the predicted nutrient availability that usually accompanies food odors.
66. Waterson MJ, Chung BY, Harvanek ZM, Ostojic I, Alcedo J, Pletcher SD: **Water sensor ppk28 modulates *Drosophila* lifespan and physiology through AKH signaling.** *Proc Natl Acad Sci U S A* 2014 <http://dx.doi.org/10.1073/pnas.1315461111>.

67. Waterson MJ, Chan TP, Pletcher SD: **Adaptive physiological response to perceived scarcity as a mechanism of sensory modulation of life span.** *J Gerontol A Biol Sci Med Sci* 2015 <http://dx.doi.org/10.1093/gerona/glv039>.
68. Lushchak OV, Carlsson MA, Nässel DR: **Food odors trigger an endocrine response that affects food ingestion and metabolism.** *Cell Mol Life Sci* 2015, **72**:3143-3155.
69. Chapman RF: **Chemosensory regulation of feeding.** In *Regulatory Mechanisms in Insect Feeding*. Edited by Chapman RF, de Boer G. Springer US; 1995:101-136.
70. Simpson SJ, Raubenheimer D: **Feeding behaviour, sensory physiology and nutrient feedback: a unifying model.** *Entomol Exp Appl* 1996, **80**:55-64.
71. Wright GA: **To feed or not to feed: circuits involved in the control of feeding in insects.** *Curr Opin Neurobiol* 2016, **41**:87-91.
72. Inagaki HK, Ben-Tabou de-Leon S, Wong AM, Jagadish S, Ishimoto H, Barnea G, Kitamoto T, Axel R, Anderson DJ: **Visualizing neuromodulation in vivo: TANGO-mapping of dopamine signaling reveals appetite control of sugar sensing.** *Cell* 2012, **148**:583-595.
73. Simpson SJ, Simpson CL: **Mechanisms controlling modulation by haemolymph amino acids of gustatory responsiveness in the locust.** *J Exp Biol* 1992, **168**:269-287.
74. Dampney RAL: **Central neural control of the cardiovascular system: current perspectives.** *Adv Physiol Educ* 2016, **40**:283-296.
75. Brunke S, Hube B: **Adaptive prediction as a strategy in microbial infections.** *PLOS Pathog* 2014, **10**:e1004356.
76. Freddolino PL, Tavaoie S: **Beyond homeostasis: a predictive-dynamic framework for understanding cellular behavior.** *Annu Rev Cell Dev Biol* 2012, **28**:363-384.
77. von Helmholtz H: *Handbuch der physiologischen Optik.* Leipzig: Leopold Voss; 1867.
78. Srinivasan MV, Laughlin SB, Dubs A: **Predictive coding: a fresh view of inhibition in the retina.** *Proc R Soc Lond B Biol Sci* 1982, **216**:427-459.
79. Dyakova O, Lee Y-J, Longden KD, Kiselev VG, Nordström K: **A higher order visual neuron tuned to the spatial amplitude spectra of natural scenes.** *Nat Commun* 2015, **6**:8522.
80. Warrant EJ: **Sensory matched filters.** *Curr Biol* 2016, **26**:R976-R980.
81. Fujiwara T, Cruz TL, Bohoslav JP, Chiappe ME: **A faithful internal representation of walking movements in the Drosophila visual system.** *Nat Neurosci* 2017, **20**:72-81.
See annotation to Ref. [82*].
82. Kim AJ, Fenk LM, Lyu C, Maimon G: **Quantitative predictions orchestrate visual signaling in Drosophila.** *Cell* 2017, **168** 280–294.e12.
This study along with Ref. [81*] demonstrates that the activity of neurons in the visual processing pathway is modulated by flies' self-movement, in a way that is predictive of the expected visual consequences of movement.
83. Damasio AR: **The somatic marker hypothesis and the possible functions of the prefrontal cortex [and discussion].** *Philos Trans R Soc Lond B* 1996, **351**:1413-1420.
84. Paulus MP: **Decision-making dysfunctions in psychiatry — altered homeostatic processing?** *Science* 2007, **318**:602-606.
85. Pezzulo G, Rigoli F, Friston K: **Active inference, homeostatic regulation and adaptive behavioural control.** *Prog Neurobiol* 2015, **134**:17-35.
86. Robinson GE, Barron AB: **Epigenetics and the evolution of instincts.** *Science* 2017, **356**:26-27.
87. Giordano N, Mairet F, Gouzé J-L, Geiselmann J, de Jong H: **Dynamical allocation of cellular resources as an optimal control problem: novel insights into microbial growth strategies.** *PLOS Comput Biol* 2016, **12**:e1004802.
88. Seth AK, Friston KJ: **Active interoceptive inference and the emotional brain.** *Philos Trans R Soc B* 2016, **371**:20160007.