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SYMPOSIUM

Feedback Control as a Framework for Understanding Tradeoffs in Biology

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Synopsis Control theory arose from a need to control synthetic systems. From regulating steam engines to tuning radios to devices capable of autonomous movement, it provided a formal mathematical basis for understanding the role of feedback in the stability (or change) of dynamical systems. It provides a framework for understanding any system with regulation via feedback, including biological ones such as regulatory gene networks, cellular metabolic systems, sensorimotor dynamics of moving animals, and even ecological or evolutionary dynamics of organisms and populations. Here, we focus on four case studies of the sensorimotor dynamics of animals, each of which involves the application of principles from control theory to probe stability and feedback in an organism's response to perturbations. We use examples from aquatic (two behaviors performed by electric fish), terrestrial (following of walls by cockroaches), and aerial environments (flight control by moths) to highlight how one can use control theory to understand the way feedback mechanisms interact with the physical dynamics of animals to determine their stability and response to sensory inputs and perturbations. Each case study is cast as a control problem with sensory input, neural processing, and motor dynamics, the output of which feeds back to the sensory inputs. Collectively, the interaction of these systems in a closed loop determines the behavior of the entire system.

Introduction

The idea that organisms can be understood as a hierarchy of organizational levels—from molecules to behavior—seems intuitive. Indeed, a dominant paradigm in biological science involves a reductionist approach in which a phenomenon at a particular level of organization is described as a consequence of the mechanisms at a lower level. For example, the mechanisms underlying behavior might be described in terms of the activity of a set of neurons, or the behavior of a single neuron might be understood in terms of its the properties of its membrane.

However, each level of organization exhibits emergent properties that are not readily resolved into components (Anderson 1972), suggesting the need for an integrative approach. The case for taking an integrative view is strengthened by considering a fundamental organizational feature inherent to biological systems: feedback regulation. Living systems ubiquitously exploit regulatory mechanisms for maintaining, controlling, and adjusting parameters across all scales, from single molecules to populations of organisms, from microseconds to years. These regulatory networks can form functional connections within and across multiple levels (Egiazaryan and Sudakov 2007). This feedback often radically alters the dynamic character of the subsystems that comprise a closed-loop system, rendering unstable systems stable, fragile systems robust, or slow systems fast. Consequently, the properties of individual components (e.g., biomolecules, cells, and organs), the communication channels that link them (e.g., chemical, electrical, and mechanical), and the signals carried by those channels (e.g., phosphorylation, action potentials, and forces), can only be understood in terms of the performance of the complete feedback control system. Understanding the role of individual components in the context of a complete feedback system is the purview of control systems theory (Astrom and Murray 2008). Control theory provides a suite of tools and language for describing biological feedback control systems (Roth et al. 2014).

An organism comprises a complex patchwork of feedback control systems that cut across traditional levels of biological organization. Thus, understanding biological systems requires an understanding of what feedback can (and cannot) do. Feedback can be used to dramatically enhance robustness and performance of a system. However, its benefits are not endless: there are inherent, often inescapable, tradeoffs in feedback systems, and control theory provides precise quantitative language to address such tradeoffs (Freudenberg and Looze 1985; Middleton 1991; Looze et al. 2010).

Perhaps nowhere are feedback control tradeoffs—such as the intricate balance between stability and change—more immediately relevant than in the controlled movement of animals. Although measures of performance, such as speed and efficiency, are essential to some behaviors, some measure of stability almost invariably plays a role, as the fastest animal would have poor locomotor performance if the smallest irregularity in the surrounding environment was sufficient to cause it to crash, fall, break, or fail (Dickinson et al. 2000). Yet, animals do not seem to adopt the most stable, conservative designs—e.g., aggressively regulating the rate of convergence and bringing the animal to rest as quickly as possible may be inefficient from a different perspective (Ankarali et al. 2014).

There is no single definition of ''stability'' or ''change'' that is ideally suited for all biological systems. In neuromechanical terms, however, ''change'' can be defined in terms of the responsiveness or maneuverability of the motor system (Sefati et al. 2013) to a sensory stimulus—i.e., the ''bandwidth'' of the system. ''Stability'' on the other hand, refers most generally to the ability of a system to reject external perturbations, but can also refer to the ''persistance'' of a system (Byl and Tedrake 2009; Ankarali et al. 2014).

After providing a short historical perspective on feedback control and biology, we review a diversity of sensorimotor feedback control systems. The methods reviewed in this article are remarkably conserved, despite categorical differences in species (vertebrates and invertebrates) and locomotor modalities (terrestrial, aquatic, and aerial). Indeed, one of the sensorimotor behaviors, a social behavior termed the jamming avoidance response (JAR) in the weakly electric fish, requires no movement, but yet enjoys the same basic modeling tools and approaches as used for sensorimotor feedback systems based on movement.

A brief history of feedback control and living systems

In the latter part of the 18th century, James Watt and Matthew Boulton invented an ingenious device that provided feedback control for the steam engine. In this device, modeled after similar mechanisms used in windmills and millstones (Hills 1996), the passage of steam was controlled by a governor (Fig. 1) in which the rotational velocity of the engine's output was ''sensed'' by two masses suspended from an articulating lever system. As the rotation rate of the engine increased, the centripetal acceleration raised the masses closing the throttle to the engine. Thus, the output of the engine was sensed by a physical mechanism that influenced the input of steam into the engine. The governor is an elegant physical instantiation of a closed-loop feedback system: the spin-rate of the mass depends on, and controls, the flow of steam through the system.

That concept of a governor—a closed-loop feedback system—has its tendrils in evolution and ecology. Indeed, the idea that feedback plays a central role in evolution owes its origins to Alfred (Darwin and Wallace 1858):

> The action of this principle is exactly like that of the centrifugal governor of the steam engine, which checks and corrects any irregularities almost before they become evident; and in like manner no unbalanced deficiency in the animal kingdom can ever reach any conspicuous magnitude, because it would make itself felt at the very first step, by rendering existence difficult and extinction almost sure soon to follow.

At about the same time that Darwin and Wallace were forging the principles of evolution, the concept of the governor in feedback control extended deeply into dynamical systems theory with James Maxwell's early contribution ''On Governors'' (1867) in which he laid out the mathematical formulation for the equations of motion of a governor and a speed-dependent term throttling down the rate of spin. The major contribution of this work was his generalization to a broad class of closed-loop feedback

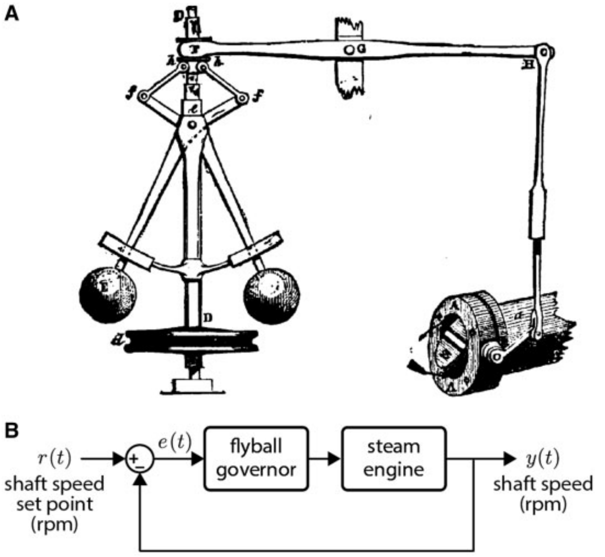

Fig. 1 (**A**) Schematic of the Watt–Boulton centrifugal "flyable" governor (copyright expired; see http://copyright.cornell.edu/resources/publicdomain.cfm) and (**B**) a simplified feedback diagram.

systems, with the novel idea that the input and output of such systems are inextricably linked (as they are in living systems). Maxwell is, in many ways, one of the founding contributors to the theory of control systems.

Following Maxwell, the theory of systems and controls takes on a rich history with a focus on quantifying the stability and performance of dynamical systems with the seminal contributions of Aleksandr Lyapunov, Harry Nyquist, and Hendrik Bode (among many others) in the late 19th and early 20th centuries. These and subsequent historic contributions of control theory to engineering domains—from tuning radios to aircraft controllers, and much more—are summarized in a short history of the field by Bennett (1996).

The ideas of Wallace and Maxwell can be traced to living systems in a host of contributions. For example, at the time of Maxwell, the French physiologist Claude Bernard developed the idea (later termed "homeostasis") and suggested that physiological systems maintain a constant internal environment ("la milieu interieur") via physiological feedback. Interestingly, glucose control and its consequences to diabetes was a key example of feedback developed by Bernard. Indeed, this concept of feedback and control is a hallmark of the sort of biological systems we study and teach.

In the latter part of the 19th century and early 20th century, the contributions of dynamical-systems theory to living systems began to form with an initial focus on neural systems and cybernetics. The Russian physiologist Pyotr Anokhin for example, developed the idea of "back afferentiation" (feedback) in the neural control of sensorimotor systems and reflexes [for a review, see Egiazaryan and Sudakov (2007)]. Anokhin's "functional systems theory" has all the hallmarks of dynamical-systems and control theory we use in cybernetics and in systems biology today.

While Anokhin was delving into neural systems, reflexes, and control, Norbert Wiener, a pioneer in mathematics and engineering, had begun to focus much of his attention on the control laws associated with animals and machines, essentially founding the domain of cybernetics (Wiener 1948). Along with the contributions of Ludwig von Bertalanffy (1968), whose mathematical models of the growth of animals are still used today, the fields of cybernetics and von Bertalanffy's "general systems theory" gave rise to the burgeoning fields of systems neuroscience, systems biology, and robotics. Indeed, the sort of integrative biology we outline in this article is in every sense "systems biology" without the restriction of attention solely to genetic and molecular scales, but with all the requisite mathematical underpinnings that began with Watt and Maxwell.

Four systems that walk the proverbial tightrope

We turn our focus to the dynamics and control of motor behavior in animal systems (neuromechanics) to illustrate basic conceptual issues surrounding the application of control theory that address the apparent dichotomy between stability and change. Specifically, we provide four examples of control-theoretic analyses of neuromechanical systems. For each example, we describe the most important features of the control system at hand, point out any task-relevant tradeoffs, and discuss how the organism walks the proverbial tightrope.

A second, but equally important, goal is to review the application of control-theoretic analyses in interpreting the roles of constituent components of a biological feedback control system. The specific physical details of individual components of the system are most meaningfully described in the context of the intact control circuit. With this goal in mind, we review rapid thigmotaxis (i.e., "wall-following") by cockroaches, tracking of refuges by weakly electric fish, the abdominal reflex in hawk moths, and the JAR, again in weakly electric fish.

Thigmotaxis (wall-following) in cockroaches

Central to understanding how animals manage stability and change is evaluating performance in challenging contexts (Dickinson et al. 2000). Crucially, this involves creating significant deviations from steady-state behavior. Moreover, it encourages us to consider organisms and behaviors that have evolved in environments in which the pressures, and potential tradeoffs, between stability and change may be finely balanced. Locomotion is particularly challenging when it is difficult to move (surfaces can be irregular and deformable) (Daley and Biewener 2006; Sponberg and Full 2008; Li et al. 2009, 2013), the surrounding fluid can be turbulent and cluttered, or difficult to sense (some highly visual animals navigate in very low light (Warrant and Dacke 2011), and others behave in complex auditory (Stamper et al. 2008) or olfactory landscapes. Behaving in such environments can be advantageous for avoiding competition and predation, and enabling intraspecific interactions.

Despite significant neural resources dedicated to vision, many species of cockroach navigate cluttered environments in low intensities of light (Bell et al. 2007). Rapid locomotion through rough, cluttered, or deformable terrain can render vision unreliable, particularly given its longer latencies compared with other senses (Franklin and Wolpert 2011). Sensor latency can pose fundamental limits on neural control, and delays are an inevitable part of processing information in biological wetware (Cowan et al. 2006; Sponberg and Full 2008; Elzinga et al. 2012; Ristroph et al. 2013; Fuller et al. 2014). One strategy that cockroaches use is to probe their environment using their antennae as tactile sensors, mechanically detecting and following vertical surfaces (or ‘‘walls’’) during rapid running (Fig. 2A) (Camhi and Johnson 1999; Cowan et al. 2006; Lee et al. 2008). Thousands of mechanoreceptive hairs lining the cockroach's antennae are activated on contact and bending (Schafer and Sanchez 1973; Schaller 1978; Camhi and Johnson 1999; Cowan et al. 2006). The mechanics of the antenna itself passively maintains the orientation of the antenna in a ‘‘J’’ shape against the wall (Fig. 2A) (Mongeau et al. 2013). The cockroach runs while maintaining close proximity to the wall and tracks turns and irregularities in the surface. This behavior enables remarkably high-bandwidth maneuvers, necessary for maintaining the high-speed performance associated with escape and navigation; cockroaches reportedly respond to corrugations in a wall with up to 25 turns per second (Camhi and Johnson 1999). Blinding the animals does not significantly impair performance and they do not require contact from their body or legs to follow walls (Camhi and Johnson 1999).

Following walls (hereafter ‘‘wall-following’’) by cockroaches provides an excellent example of a smooth-pursuit or tracking task (Cowan et al. 2006; Lee et al. 2008). An external reference signal, in this case the wall's position, is detected by a sensor—the antenna—and the animal's brain and body cooperate to regulate the distance from the wall (Fig. 2). A simple ethological description of wall-following is that the animal ‘‘tries’’ to maintain a certain distance from a surface. This qualitative description of the behavior is unfulfilling because it is neither mechanistic—how the animal ‘‘tries’’ is not well understood—nor predictive—we cannot predict how the animal will recover from perturbations or when its performance will degrade. A classic approach in neuroethology would be to identify neurons potentially involved in the behavior and determine what their responses are to a variety of mechanical disturbances. However, the challenge is that many models may explain observed patterns of encoding but the relevant mechanisms may be difficult to identify without rejectable hypotheses derived from quantification of the animal's dynamics. For example, a mechanoreceptive neuron may appear to respond to deflections of the antenna, but its time constants may be too long (or too short) to play a role in the wall-following behavior. Control-theoretic approaches to understanding the dynamics of both the neural processing and the body's movement enable testable predictions that inform behavioral, neurophysiological, and biomechanical experiments.

The control-theoretic approach characterizes wall-following as a feedback-regulated behavior (Fig. 2B). Using biomechanical models for the dynamics of the body—either stride-averaged (Cowan et al. 2006) or continuous (Lee et al. 2008)—we can implement different hypothesized models for how the nervous system processes the error signal (i.e., the mechanical bending of the antenna) and compare the resulting dynamics of the whole feedback system to kinematics of cockroaches following turns in walls. This has led to the discovery that the animal must encode more than just the position of the wall. The simplest control model that matches behavior requires the position and rate of approach of the wall (i.e., the lateral velocity of the wall relative to the cockroach) (Cowan et al. 2006). Such a proportional-and-derivative (PD) controller is ubiquitous in controlled engineering systems. However, while the latency of the initial turn is low, the turning response persists for much longer than the stimulus (Lee et al., 2008). The dynamics of the system filters the sensory input in time. Electrophysiology of the antennal nerve revealed that the population of mechanoreceptors in the antennal nerve could encode both position and

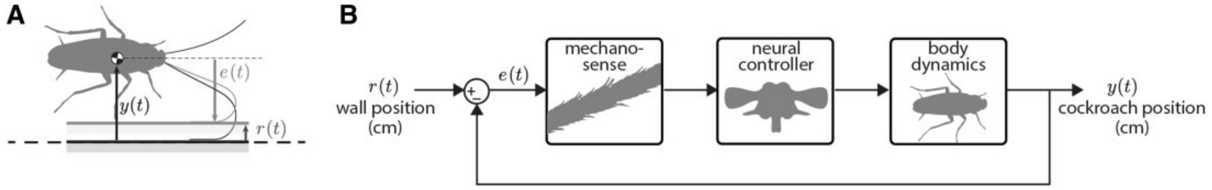

Fig. 2 (**A**) Schematic depicting a cockroach following a wall and (**B**) a simplified block-diagram representation of wall-following behavior in cockroaches. The reference signal is the position of the wall in some global reference, $r(t)$. The difference between the wall and the cockroach's position, $y(t)$, is the error signal, $e(t)$. The error is encoded in antennal mechanoreceptors and transformed by the nervous system, ultimately causing changes in motor commands that act through the animal's body dynamics to alter its own position, thereby regulating this feedback error to a desired reference point.

velocity and that the neural response even at this first stage of processing is already temporally matched to the turning response rather than to the stimulus (Lee et al. 2008). In other words, the mechanosensory processing seems to be tuned to the demands imposed on the control system by the mechanics and the delay in neural processing. A hallmark of a high-performance control system is the ability to achieve large responses over a wide range of frequencies in response to stimuli (change) without skirting too close to the instabilities that can result from high-gain, large-latency feedback (stability).

Multisensory tracking of a moving refuge in weakly electric fish

The glass knifefish, *Eigenmannia virescens*, is like an ‘‘aquatic hummingbird'': it hovers in place with extraordinary precision, making rapid and nuanced adjustments to its position in response to moving stimuli (Rose and Canfield 1993a, 1993b; Cowan and Fortune 2007; Roth et al. 2011); see Fig. 3A. Here, we investigate the integration of locomotor biomechanics (Sefati et al. 2013) (Fig. 3B), multisensory integration (Stamper et al. 2012b), and adaptive control (Roth et al. 2011) that enable this animal to balance stability and change (Fig. 3).

As a model organism, weakly electric knifefish are most widely studied for their namesake, an active electrosensory system. An electric organ (EO) in the tail emits a weak electric field. Electroreceptors distributed over the surface of the body (most densely about the head) detect objects in the near field as small disturbances in transdermal potential. Using this electrosense in conjunction with vision, fish perform a wide variety of localization and tracking behaviors. As in the analyses presented for the wall-following behavior in cockroaches, we again demonstrate how a control-theoretic approach can be used to quantify and model behavior. For the fish, we further extend the modeling tool to quantitatively probe the categorical shifts in behavior and the interplay between visual and electrosensory modalities (Fig. 3C).

Weakly electric knifefish hunt nocturnally, their specialized electrosensory system allowing them to navigate their environment and localize small prey items in low light (MacIver et al. 2001). During the day, they hide from predators, finding refuge among the roots of trees or other natural shelter. In the laboratory, these fish exhibit a similar refuge-seeking behavior, hiding in short lengths of pipe, filter fixtures, or any other refuge provided for them. More impressively, fish smoothly and robustly track their refuge as it is moved (Fig. 3A). How do sensorimotor control strategies differ across this repertoire, in response to different categories of exogenous motion, and how do visual and electrosensory cues contribute to these behaviors?

Knifefish are agile. An undulating ribbon-fin runs along the underside of the body, enabling knifefish to rapidly alternate between forward and backward swimming without changing body orientation. In experiments, this remarkable ability is often leveraged to constrain the behavior to a line of motion, reducing the spatial dimension of the task to a single degree of freedom. Fish were first observed swimming side-to-side in response to laterally moving plates and rods, termed the ‘‘following'' response (Heiligenberg 1973b; Matsubara and Heiligenberg 1978; Bastian 1987a, 1987b) and later experiments explored similar behavior in response to refuges that were moving longitudinally (fore–aft) (Rose and Canfield 1991, 1993a; Cowan and Fortune 2007; Roth et al. 2011; Stamper et al. 2012b). In the case of longitudinal tracking of refuges, the fish maintains a ‘‘goal'' position within the refuge, perceiving the error between its position and that of the refuge and swimming forward or backward, thereby minimizing this positional error (Fig. 3A and C).

Linear control-theoretic tools were used to characterize the (frequency-dependent) relationship between

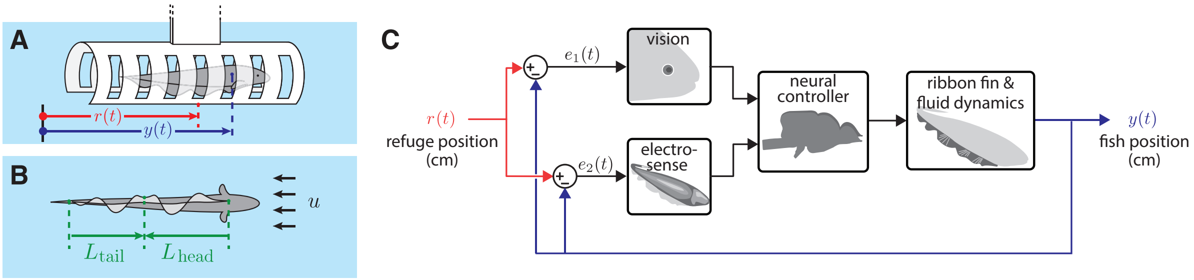

Fig. 3 (**A**) The knifefish (*Eigenmannia virescens*) in a moving shuttle. Positions are measured from a fixed reference frame to tracking points on the refuge and on the animal's body. (**B**) A schematic depicting the counter-propagating wave kinematics of the knifefish's ribbon fin. As ambient flow velocity, *u*, increases, fish recruit a larger portion of the fin for L_{head}, the wave component responsible for forward thrust. (**C**) A block diagram depicting the knifefish's reference-tracking behavior. The moving shuttle provides the reference signal, *r*(*t*), with the output, *y*(*t*) being the position of the swimming fish. Parallel visual and electrosensory modalities measure the relative position of the shuttle [the sensory slip, *e*(*t*)]. The neural controller (CNS) weights and filters signals from the sensory blocks and outputs commensurate with motor commands. Subsequently, these motor commands generate movement as dictated by the biomechanics of the fish body and the interaction of the body and ambient fluid.

sensing and swimming in this smooth-pursuit behavior (Cowan and Fortune 2007). Interestingly, however, subsequent investigations revealed important deviations from the linear model proposed (Cowan and Fortune 2007). When comparing the responses to complex motion (in this case, sums of sinusoidal trajectories across a broad band of frequencies) and pure sinusoidal stimuli, fish exhibited performance suggesting qualitatively different underlying models (Roth et al. 2011). This failure of the so-called superposition property of linear systems, revealed an interesting nonlinearity: fish tune their control policy to improve behavior with respect to the spectral content of the stimulus. Although this adaptive tuning improves the response to a limited class of stimuli (and these may well be of greater ethological relevance), performance suffers in response to signals that contain a broader range of frequencies.

Another tradeoff is manifest as a nonlinearity in the context of active sensing. When visual cues are limited in the environment (e.g., under low illumination or in murky waters), fish rely predominantly on electrosensation. Under such circumstances, a conflict arises between the goal of the task of tracking—to remain stationary within the tube—and the needs of the electrosensory system—which requires active movements to prevent adapting to a constant sensory stimulus. In low light, the animal performs a rapid back-and-forth shimmy superimposed on the tracking response. These volitional motions are not correlated with the refuge's motion and can be discriminated from the tracking response by their frequency. While these active oscillations are significant, tracking performance with respect to the motion of the stimulus remains nearly constant (Stamper et al. 2012b). It is posited that these oscillations serve to enhance electrosensory acuity and permit a high level of performance in the absence of salient visual stimuli. Fish employ a strategy in which tracking error and expended energy are compromised for improved sensing and tracking of the stimulus.

While we present the tracking behavior as a model system for the study of smooth pursuit and sensory integration, the locomotor strategy also illustrates a behavioral tradeoff. Knifefish routinely partition the ribbon-fin into two counter-propagating waves (Sefati et al. 2010; Ruiz-Torres et al. 2013), recruiting the frontal portion of the fin to generate forward thrust (a wave traveling from head-to-tail) with the rear section (tail-to-head wave) generating an opposing force. In stationary hovering, these opposing forces cancel each other. These waves meet at the "nodal point" (Fig. 3B); simulations on a biomimetic robot reveal that the net fore-aft thrust is linearly dependent on this kinematic parameter (Curet et al. 2011; Sefati et al. 2013). Moreover, when compared with simpler strategies (e.g., recruiting the whole fin and modulating the speed of a single traveling wave), the use of counter-propagating waves significantly improves the fore–aft maneuverability (by decreasing the effort expended in control) and concurrently enhances the passive stability (stabilization without active feedback control) by providing a damping-like force to reject perturbations, thus simplifying the neural control.

Stabilizing pitch via visuomotor abdominal reflex in hawk moths

Here, we examine the problem of active pitch control of pitch by the hawk moth, *Manduca sexta*, as a platform to explore the relationship between open-loop experiments and closed-loop stability and

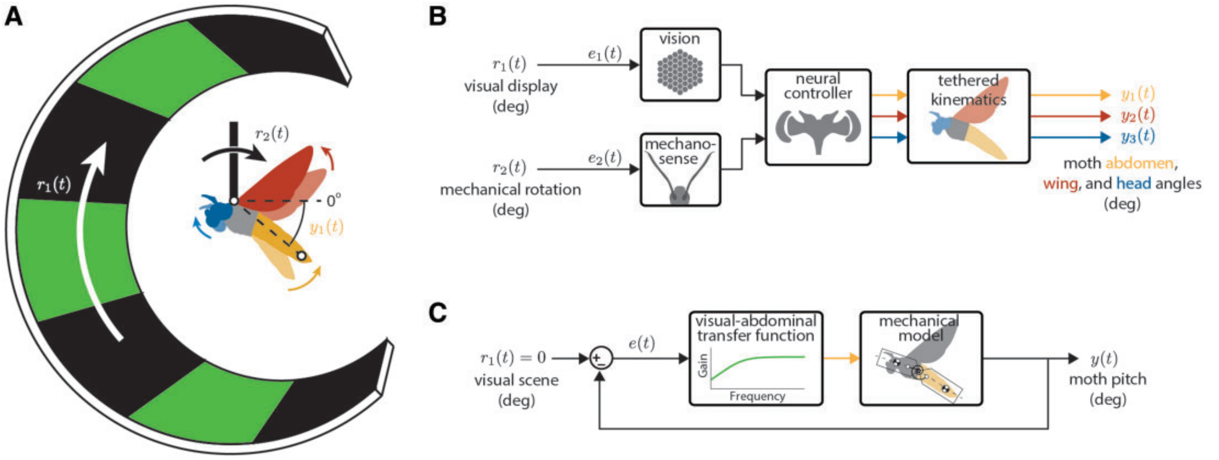

Fig. 4 (**A**) Experimental setup for measuring responses to visual perturbations of pitch in *M. sexta*. The moth is attached to a rigid tether and placed in a cylindrical LED arena. During bouts of flight the moth is presented with either an isolated visual stimulus, $r_1(t)$, by rotating a green and black striped pattern on the visual display, an isolated mechanical stimulus, $r_2(t)$ by physically rotating the moth and the arena, or a coupled visual and mechanical rotation. The moth responds to the rotations by moving its abdomen [yellow, $y_1(t)$], wings [red, $y_2(t)$] and head [blue, $y_3(t)$]. (**B**) Block diagram of the different sensory and motor systems known to be engaged during open-loop tethered flight. Error signals, $e_i(t)$, represent perceived visual (eyes) and mechanical (antennae) sensory information relative to environmental reference signals, $r_i(t)$. Sensory systems independently encode the modality-specific signals and are then fused and processed by the nervous system. Neural commands are relayed to different motor systems to achieve new kinematic states. (**C**) Block diagram combining open-loop experimental data (visual-abdominal transfer function) and dynamics models (mechanical model) to estimate the behavior of the closed-loop system (Dyhr et al. 2013).

maneuverability. The inherent instability of flapping flight requires active, feedback-based strategies for control (Wu and Sun 2012; Liang and Sun 2013). This has led to the evolution of numerous sensory specializations, most notably in the form of visual and mechanical senses (Pringle 1948; O'Carroll et al. 1996; Sane et al. 2007; Taylor and Krapp 2007), that collectively inform the animal about its state in the environment. This information, in turn, is used to coordinate motor systems to direct movement (Fig. 4).

The bulk of research on flight control has focused on how the wings are used to generate and modulate aerodynamic forces. Much less attention has been paid to the role of deformations of the body—or "airframe"— for flight control. The hawk moth displays strong abdominal movements in response to open-loop visual rotations during tethered flight. Control theory can provide key insights about the importance, and possible advantages, of such movements for controlling flight.

Numerous experimental preparations have been developed for investigating sensory and motor responses that involve restraining or confining animals to access physiological signals and to allow for better experimental control of the sensory inputs available to the animal. For hawk moths, these include an arena for tethered, virtual flight for performing behavioral experiments (Fig. 4A) to immobilized and dissected preparations for electrophysiological recordings (Hinterwirth and Daniel 2010; Theobald et al. 2010). However, these types of manipulations dramatically change the dynamic context of the animal. The difficulty then is linking physiological signals and behavioral responses from restrained preparations to free-flight movements, such that causal links can be made between changes in sensing, movement, and flight path.

It is here that the analytic techniques of control theory provide unique affordances for understanding how animals control flight. Control theory provides a framework for interpreting data from restrained experimental preparations in the context of the free-flight dynamics via mathematically explicit dynamical models derived from the basic physics and mechanics of flight. In turn, these studies provide predictions about movements that can be compared with natural flight behaviors.

Hawk moths are accomplished fliers and spend much of their time during flight hovering in front of flowers while feeding. Hovering flight is an equilibrium mode of flght that makes the modeling particularly tractable for control-theoretic analyses. Dyhr et al. (2013) took advantage of these simplified dynamics to test the utility of abdominal responses for stabilization of pitch. Previous studies had suggested that abdominal movements were of minor importance for the control of flight (Hedrick and Daniel 2006; Cheng et al. 2011), but without a control-theoretic analysis of free flight, it is difficult to exclude a crucial role for the deformation of the airframe (redistribution of mass).

Free flight is a closed-loop behavior such that the animal's movements influence subsequent stimuli. Restraining an animal so that open-loop responses—in which animal's movements no longer influence the sensory input—can be measured and often generate stronger responses and more data, simplifying the quantification of the sensorimotor transform. However, these data can only be interpreted in their closed-loop context (Roth et al. 2014). Dyhr et al. (2013) combined behavioral experiments, in the form of open-loop responses during tethered flight, with a model of the flight dynamics of hovering to generate a control-theoretic model of closed-loop visual-abdominal control (Fig. 4). Using this model, they were able to show that visually evoked abdominal movements were sufficient for stabilization of pitch during hovering flight, independent of any modulation or redirection of the wing forces.

Although this work demonstrated the importance of deformation of the airframe for flight control, other actuator systems are clearly involved. The wings are certainly the most important structures for controlling flight, but head movements have an established role in modulating both visual and mechanosensory information (Hinterwirth and Daniel 2010; Dyhr et al. 2013). Understanding how movements of the wings, body, and head are coordinated is a promising future direction for research. Future work in this area will require integrating realistic aerodynamic models with the dynamics of rigid bodies to understand how multi-input control is achieved. This problem is also exciting from the standpoint of multisensory integration, as hawk moths use multiple sensory modalities (e.g., visual and antennal mechanosensory) (Sane et al. 2007; Hinterwirth and Daniel 2010) for flight control. Furthermore, investigations into the coordinating, multiple motor pathways may highlight the importance of proprioceptive feedback mechanisms for flight control, an area that has been relatively unexplored. The tractability of *M. sexta* as an experimental organism both for behavioral and for physiological studies, coupled with the relatively simple dynamics of hovering flight, make it a promising model organism for understanding the sensorimotor processes underlying locomotor control.

Jamming avoidance in weakly electric fish

As the previous examples show, control theory is a useful tool for understanding sensorimotor systems, especially during behaviors that are robust and repeatable. However, escape responses represent a behavioral category in which the animal actively tries to avoid a particular sensory condition. From a control-systems perspective, the behavior is transient; it "escapes" to the nearest stable equilibrium. The response is not amenable to perturbation analyses that we have used so far, and modeling such a response requires a different approach, such as experimentally "closing" the loop. Here, we re-examine weakly electric fish in the context of just such an unstable sensorimotor escape behavior.

In addition to sensing the environment for behaviors such as tracking, described above, the electric organ's discharge (EOD) is used for social communication. In wave-type fish, each individual produces a continuous, pseudo-sinusoidal EOD whose frequency and amplitude can remain remarkably constant for many hours, and even days (Bullock et al. 1972). However, if two nearby fish have frequencies F_1 and F_2, their electric fields interact to produce a "beat" at the difference-frequency $|dF| = |F_1 - F_2|$. When the two frequencies are within a few Hertz of each other, the emergent low-frequency beat detrimentally interferes with electroreception, thereby "jamming" the ability of the fish to detect obstacles and prey (Heiligenberg 1973a; Bastian 1987a). Some species of these fish, particularly those that form social groups (Stamper et al. 2010), can rapidly change their frequencies to avoid such interference. This behavior is termed the JAR.

The neural computation that underlies the JAR in the glass knifefish, *E. virescens*, has been elucidated via a half-century of research (Heiligenberg 1991; Fortune 2006). The JAR can be predicted on the basis of a single parameter, the dF which can be used to predict the structure of electrosensory beats. Using parallel receptor systems, the fish encodes modulations of amplitude and of the relative phase of zero crossings in the beats to drive a motor response that serves to increase the magnitude of the dF.

This is not the whole story, however. Each individual tends to return to its own internal EOD set point of frequency in the absence of a low $|dF|$. The set point can drift over long periods of time, but over the timescales of the JAR (seconds to minutes) the EOD's set point remains constant. This return to baseline likely serves to maintain the EOD within the range of frequencies that match the tuning properties

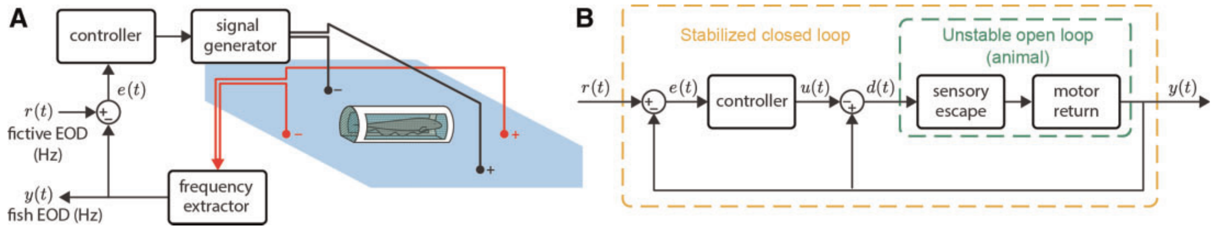

Fig. 5 (**A**) Experimental setup to identify the JAR in *E. virescens*. The fish is placed in a tube in the experimental tank, and recording electrodes (red) aligned with the body axis are used to measure the EOD. The EOD is amplified and its frequency is extracted. This frequency is fed to the controller, which generates the appropriate input frequency based on a control law. A signal generator outputs a sinusoid at the input frequency, which is then played into the tank through the stimulus electrodes (black), through a stimulus isolation unit (SIU). (**B**) Block diagram representation of the same experimental paradigm. The reference, $r(t)$, output, $y(t)$, input, $u(t)$, and *dF*, $d(t)$, are all frequency signals relative to the baseline frequency of the fish. We seek to identify the unstable open loop (green dashed box) using the stabilized closed loop (orange dashed box). The *dF* computation is modeled to have a lumped delay. The delayed difference initiates the sensory escape, which competes with the motor return to produce the output EOD frequency.

of each individual's own electrosensory receptors. For example, if a fish were producing a 400 Hz EOD, its receptors would be most responsive to EOD frequencies within a range of ∼300–500 Hz (Scheich et al. 1973).

How do individuals balance the need for maintaining electrosensory stability while still being able to rapidly change the frequency of the EOD during the JAR? To address this question, Madhav et al. (2013) modeled the JAR in terms of a low-order feedback control system that includes both the return to baseline (stability) and the stimulus-driven escape (change). Parsing this feedback control diagram (Fig. 5) requires understanding that the JAR operates on frequencies of signals. Specifically, the system computes the instantaneous difference between an exogenous input (conspecific frequency) and the autogenous output (self frequency) as shown in Fig. 5. This difference is dynamically processed by the CNS which in turn modulates the output, creating a closed feedback loop.

The challenge in identifying the dynamics of the JAR was two-fold. First, the tendency of the output to diverge from the input renders the system locally unstable. Effective techniques for identifying a system's dynamics rely on analyzing persistent responses to perturbations; however, in this case, these perturbations destabilize the system, making it impossible to apply such techniques. This challenge was overcome by stabilizing the behavior, using an experimentally closed loop (Fig. 5). This stable closed-loop system was systematically perturbed and the responses were used to identify a linear model, which describes the unstable open-loop behavior in the local neighborhood of the baseline frequency of the fish. Second, predictions of responses in real-world scenarios requires understanding the global nonlinear nature of the behavior. A different category of closed-loop experiments was used to identify a characteristic "escape curve", which serves as the nonlinear signature for the JAR for each individual. Identifying this curve for each individual allows us to populate all the parameters of the global model.

In the global model, the computational algorithm of the JAR was expressed as a competition between the stable motor dynamics (return to baseline) and the need to adapt to changing social settings (sensory escape). Comparatively simple behavioral experiments can now be used to fit parameters of this model, which can, in turn, predict responses to naturalistic or novel artificial stimuli. For example, this model captures the asymmetry between rises and falls in EOD frequency, for which a neural correlate was described previously (Metzner 1993). This model could also be used to predict social interactions between two individuals without considering the details of each individual's behavioral characteristics. This model also forms a basis for future work investigating complex social interactions of three or more individuals, in which higher-order electrosensory envelopes can drive behavior (Stamper et al. 2012a).

Discussion

We have seen from the above examples that control-theory and system-identification tools give us a quantitative framework in which to interpret comparative organismal studies of locomotion. In wall-following behavior in cockroaches, we tested hypotheses about neural encoding derived from the sufficiency of simple control laws and mechanical models. In the examples of swimming fish and flying moths, we understood the contributions of multiple sensory signals and multiple actuators (a.k.a. multiple-input, multiple-output, or MIMO) to the production of movement. Along the way we discovered new principles about how animals are dynamically tuned to their environment. This perspective allows us to relate the results of closed- and open-loop experiments and test hypotheses about stability and maneuverability. With the JAR, we saw how control theory applies to behaviors that move not in physical space, but in the realm of the EOD frequencies that these animals use for infraspecific signaling and communication. These questions of stability, change, sensing, and movement are fundamental to the emerging field of systems neuromechanics. We can use the language of control theory to translate between open- and closed-loop experimental preparations (Roth et al.2014), allowing us to relate the functional mechanisms of individual components to the integrated performance of the intact, behaving animal, just as the early pioneers, such as Bernard, Anokhin, and Wiener, envisioned.

Closing the loop from biology to control theory

Just as control theory affords rich insight into the role of stability and change in living systems, there is a feedback loop that couples research on living systems back to the tools we need from control theory. It is crucial to realize that while control-theoretic tools can enable biologists to tackle challenging problems of great significance (biomedical, evolutionary, and environmental) the same can be said of the impact of biology on the development of tools in engineering and control theory. We recall that in fields such as physics and fluid dynamics, the need for models and mathematical formalisms continues to spur the development of powerful computational and analytic methods.

As biological phenomena are much more complex—chemically, physically, and organizationally—than inorganic phenomena, a cause-and-effect understanding of such complex systems will inevitably foster innovative analytic, computational, and technological advances. Some key examples emerging today include the need for new analytic methods for estimating the dynamics of freely behaving animals (Revzen and Guckenheimer 2012) and new engineering approaches to synthetic biology (Kang et al. 2013).

Integrating empirical and physics-based models

The nervous system processes the sensory information for closed-loop control of task-level locomotion, such as tracking behavior (Rose and Canfield, 1993b; Cowan and Fortune 2007). In control-systems terminology, the mechanical "plant" defines the way motor signals are transformed into forces and movements, and so discovering the neural controller (Ekeberg 1993; Frye and Dickinson 2001; Nishikawa et al. 2007; Roth et al. 2011; Miller et al. 2012) of a biological system greatly benefits from a task-specific mechanical model of the underlying locomotor dynamics (Cowan and Fortune 2007; Cowan et al. 2006; Sefati et al. 2013). Low-dimensional, task-specific models for the locomotor mechanics enable the application of control-systems analysis to understand the neural mechanisms for sensorimotor processing (Blickhan and Full 1993; Holmes et al. 2006; Cowan et al. 2006; Hedrick and Robinson 2010; Tytell et al. 2011; Ding et al. 2013). These simple descriptive mechanical models, sometimes termed "templates" (Full and Koditschek 1999; Holmes et al. 2006), are essential for understanding stability and control in biological systems (Blickhan and Full, 1993; Schmitt and Holmes, 2000; Sefati et al., 2013).

More elaborate models, sometimes termed "anchors" (Full and Koditschek 1999; Holmes et al. 2006) can facilitate the exploration of more detailed questions about closed-loop control. Multidisciplinary approaches integrate computational models and experiments with biomimetic robots to study the locomotor mechanics in more detail and with higher accuracy (Miller et al. 2012). With advances in computing, high-fidelity simulations have categorically improved our understanding of various locomotor strategies in different species (Mittal 2004; Wang et al. 2004; Luo et al. 2008; Shirgaonkar et al. 2008; Tytell et al. 2010). On the other hand, biomimetic robots enable us to experimentally validate the mechanical models (Wang et al. 2004; Lauder et al. 2007; Sefati et al. 2012, 2013), and to explore the effect of parameters beyond their biological ranges, providing insight as to where the biological performance lies within reach of the wider range of possible mechanical solutions (Curet et al. 2011; Sefati et al. 2013).

Neurophysiology

How can the insights concerning the role of feedback in the maintenance of stability and the control of change at the organismal level be used to decode neurophysiological mechanisms used in the brains of animals? First we need to determine what we want to learn from, and about, the nervous system. In terms of whole-animal control, the nervous system is simply one part of the closed-loop system. In this context, understanding the inputs and outputs of the nervous system under behaviorally relevant conditions might be sufficient. The nervous system can remain a black box that is used to better understand the behavior at the organismal level in its native closed-loop state. Alternatively, we may use insights from behavior as a tool for understanding the properties of the nervous system as a functional unit. Indeed, studying the nervous system within a closed-loop behavioral task is perhaps the best route for understanding the functional structure and organization of the nervous system. In this case, behavior is used to understand the sets of computations within the black box.

The central challenge in decoding neurophysiological mechanisms is that brains are typically composed of millions of independent neurons, each of which may have unique structure and function. Organism-relevant computations both for maintaining stability and for controlling change often are distributed over thousands to millions of neurons that act in parallel. Presently, we do not understand the nature of the coding systems that are used in single neurons, and it is unclear what sorts of dimensional reduction are possible across populations and networks of neurons. In other words, there appears to be no simple or obvious set of *a priori* constraints that control theory can contribute to decoding the neurophysiological activity of neurons in the brain. This problem is familiar to neuroscientists, as one of the long-standing challenges in the study of neural mechanisms is discovering strategies that effectively translate behavioral observations into feasible neurophysiological experiments.

This challenge stems in part from the fact that neurons are in the order of microns to tens of microns in diameter and use tiny electrical signals. As a result, the vast majority of neurophysiological experiments have relied on the placement of microelectrodes into anesthetized and/or immobilized animals or into neural tissues that have been removed from the animal. Obviously, the critical organism-level feedback systems that are essential for the control of behavior are disrupted in these sorts of experimental preparations. In other words, studies have been conducted in neural tissues in which the closed-loop control system has been opened by the elimination of feedback. This is important because it is almost certainly not possible to extrapolate the neural signals from data obtained in immobilized animals to make predictions about control in the intact behaving animal; a notable exception is electric fish, in which certain electrosensory behaviors remain intact in immobilized individuals (Fortune 2006). These studies in open-loop preparations cannot capture the dynamics of the closed-loop system, and further, are likely to be misleading (Szwed et al. 2003; Cowan and Fortune 2007; Roth et al. 2014).

Thankfully, improvements in neurophysiological techniques are now permitting the widespread recording of neurophysiological activity in the central nervous systems of awake, behaving animals (Nicolelis 2008) and with stunningly compact wireless and battery-less technologies coming to play a greater role (Thomas et al. 2012). Similarly, recently developed genetic and optogenetic manipulations (Boyden et al. 2005; Zhang et al. 2007) can be used in animals in which the behavioral control loop remains intact.

Characterizing and manipulating internal signals during movement

One of the strengths of control-theoretic approaches is that we can characterize the relationship between any two signals (e.g., neural, muscular, and mechanical) with the organism as a function of the underlying neuromechanical system. When we do gain physiological access we can use the same techniques to relate neural spiking to movement and sensory feedback to the activation of muscles. Although the examples in this article emphasized monitoring motor output while manipulating a single sensory reference, these signals do not need to be in the form of an external input leading to a kinematic output. Direct alteration of feedback, either through dynamic manipulation of sensory feedback or by applying perturbations directly to the constituent neural and mechanical systems during closed-loop or open-loop behavior, is the hallmark of the control-systems approach, but is among the least explored experimental approaches at present (Roth et al. 2014). The ability both to inject noise and to alter neural processing during behavior affords separation of the contributions of sensors, controllers, and body dynamics to behavior.

One example in which this approach has been used is the identification of the role of individual muscles in the control of movement during posture control, running, flight, and propulsion (Sponberg et al. 2011c; Sponberg and Daniel 2012; Ding et al. 2013). During restrained or free behaviors, these experiments precisely altered or "rewrote" the activation patterns of individual muscles and identified their role in shaping motor output. In systems in which the time constant of the dynamic response to perturbed motor commands is faster than the inherent sensory feedback that transmits delays, this also enables the characterization of open-loop plant dynamics during free behavior (Sponberg et al. 2011b). Alternatively, one can use an open-loop characterization of the mechanics portion of the system's dynamics. By replicating the same patterns of input to the muscle but in an isolated open-loop preparation we can measure the muscle's output of work (a ''workloop'') (Sponberg et al. 2011a). Other approaches are beginning to couple environmental forces to *in vitro* muscle function via artificially closing a feedback loop between a robotic model and a physiological preparation (Richards 2011; Richards and Clemente 2012). From a control-theoretic perspective the classic *in vitro* experimental approaches of neuroscience, muscle physiology, and biomechanics are simply ways to characterize subsystems of the animal (its neurons, muscles, and internal environment, respectively) and each result can be synthesized, in explicitly quantitative and mechanistic way, back into an understanding of the dynamics of behavior.

Feedback control in biological systems

Several of the articles in this issue highlight the role of feedback-regulation in the apparent dichotomy between stability and change across levels of biological organization, from molecular to ecological. For example, Grünbaum and Padilla (this issue) show how ecological demands can trigger phenotypic changes with complex temporal dynamics. Variations in the trophic environment triggers a switch between two phenotypes of radula (''teeth''), ultimately creating a history-dependent pipeline of radulae. From the perspective of control theory, these temporal dynamics may create a temporal filter—much like a ''moving average''—allowing the animal to be sensitive to newly available resources (i.e., facilitating change) while maintaining a memory of recently available resources (stability).

At the cellular level, feedback-regulation of ATP/ADP is thought to maintain energy homeostasis, but these homeostatic metabolic systems may also regulate the development of the respiratory structures and metabolic pathways that supply oxygen and carbon substrates for energy metabolism. Greenlee et al. (this issue) discussed how the development of larval insects' tracheal and metabolic systems appear to sustain both metabolic performance and plasticity in the dynamic developmental environment. Such regulation must not, of course, imperil the longer-term developmental outcomes of organisms (Hale, this issue): if developmental processes are too responsive to the environment, they could potentially have deleterious effects on adults' structure and performance.

One way to resolve this compromise between stable outcomes and responsiveness to changing resources may be to incorporate a combination of feedback and feedforward control. Indeed, this may help mitigate the tradeoff between preprogrammed developmental cascades—which may be able to produce consistent outcomes, but are unresponsive to environmental demands—and tight feedback regulation—which, while responsive to the environment, may introduce long-term inefficiencies. While tolerance of fault is a hallmark of feedback control, even complex feedback control systems are sensitive to certain categories of failure (Csete and Doyle 2002); such failures in regulatory networks manifest themselves as disease (Nijhout and Reed, this issue). In this way, understanding the mechanisms for feedback-regulation in the context of control theory may be a critical step in the treatment of certain diseases. This approach will require the development of new quantitative tools, such as network inference of gene regulatory processes (Ciaccio et al. this issue). When such feedback systems are analyzed using control theory, it may enable us to formalize our understanding of the processes that allow biological systems to walk the tightrope between stability and change.

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