Neuromodulation in Small Networks

Alex H. Williams[1,2], Albert W. Hamood[2] and Eve Marder[2]
[1]University of California, San Diego, La Jolla, CA, USA
[2]Brandeis University, Waltham, MA, USA

Definition

Neuromodulators are signaling molecules that induce long-lasting or network-wide changes in electrical activity, canonically through metabotropic G-coupled protein receptors. In contrast to classical neurotransmission, which directly opens ion channels, neuromodulators can act either synaptically or extra-synaptically (e.g., hormonal pathways) to modify neuronal activity. Because neuromodulators can simultaneously target many neurons, our understanding of their function on networks has progressed furthest in small systems with known connectivity. In particular, much research has been conducted within invertebrate central pattern generator (CPG) networks. These networks exhibit spontaneous electrical discharges that drive rhythmic muscle contractions to produce simple behaviors such as chewing, breathing, and locomotion.

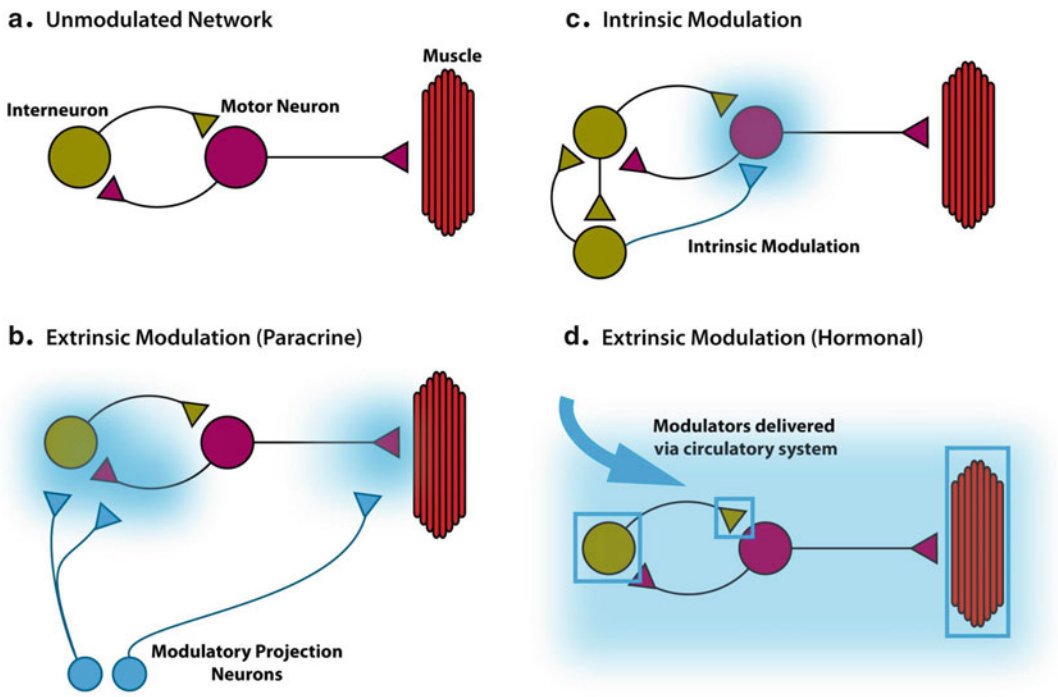
Detailed Description

Neuromodulation, while often receiving less attention than direct synaptic communication between neurons, is a vital and ubiquitous feature of neuronal networks of all sizes. Modulation may be achieved by traditional small-molecule neurotransmitters, such as dopamine (DA) or GABA, or by small peptides and may act locally within a small network or globally across the entire nervous system. The diversity of function achieved by neuromodulation is a critical feature of neural systems that must be considered by computational neuroscientists as they strive to build accurate models of brain function.

Modulation can be distinguished from synaptic transmission by its limited spatial and temporal specificity. In the mammalian brain, modulatory substances such as dopamine, norepinephrine, histamine, serotonin (5-HT), and acetylcholine are broadly released by projections capable of producing lasting effects through much of the central nervous system (CNS) simultaneously. In smaller networks modulators can serve a similar function; they may be released locally to affect a small group of cells in a central pattern generator or may be released in a paracrine fashion or as circulating hormones, influencing computation at many foci.

Work done with invertebrate systems, especially those of central pattern-generating networks, has shown that modulatory substances can affect neural computation at essentially every level of function (Fig. 1), adding richness and flexibility to circuitry that is not readily apparent from even the most accurate map of synaptic connectivity. Modulation may act directly on membrane conductances in the soma or spike generating regions of neurons, driving oscillations or affecting changes in gain (Marder 2012). After action potentials are generated, neuromodulation can shape features of spike propagation in axons (Ballo et al. 2012). When these signals reach their targets, neuromodulation may again be present to modify information transmission both at synapses between neurons (Zhao et al. 2011; Marder 2012; Nusbaum and Blitz 2012) and at the final nervous system output to muscles (Brezina et al. 1996, 2000, 2003).

Furthermore, the application of a single modulator can affect multiple targets within a neuromuscular system. For example, the application of the neuropeptide myosuppressin elicits two dramatic effects on cardiac output in lobsters: a decrease in heart rate and an increase in cardiac muscle contraction force (Fig. 2a). The first effect appears to result from changes in the intrinsic dynamics of the cardiac CPG, which slows the rhythmic activity of motor neurons (Fig. 2b). The second effect stems from an increase in muscle sensitivity to neural input, perhaps by modulating the neuromuscular junction (Fig. 2c).



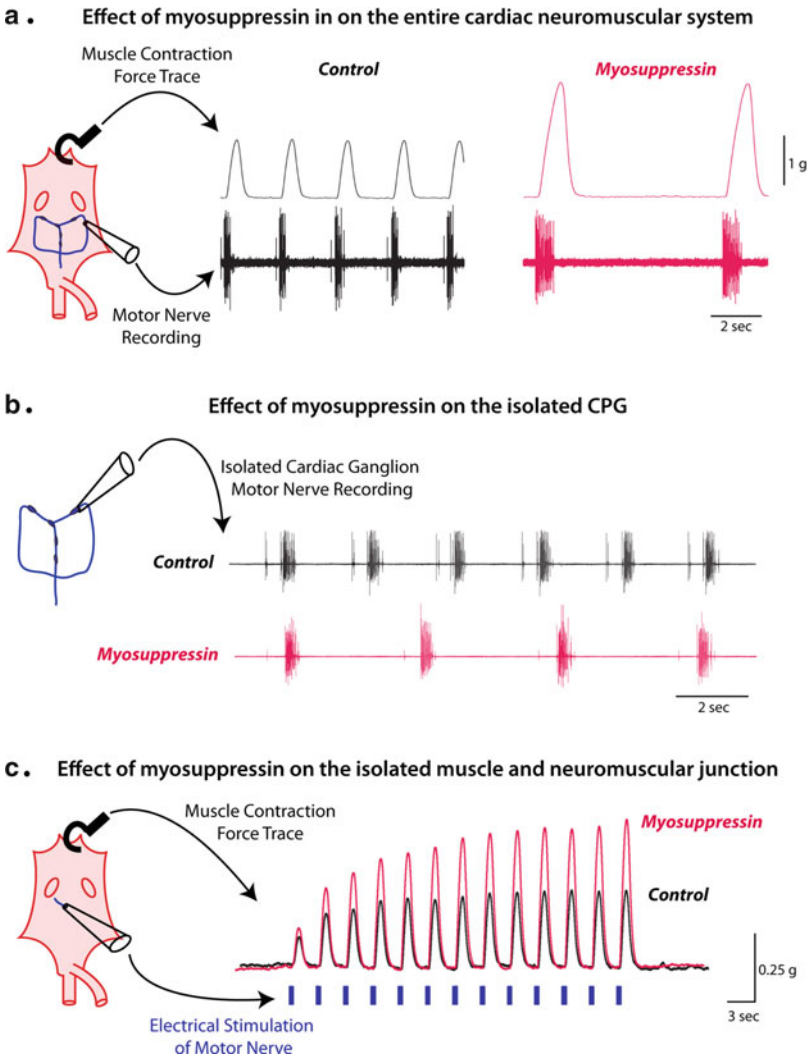
Neuromodulation in Small Networks, Fig. 1 Neuromodulators can be delivered by multiple mechanisms and can target multiple components of a network. (**a**) A schematic diagram of a simple motor network without any modulatory influences. (**b**) A network that is subject to modulation by projection neurons that are extrinsic to the motor network (at *bottom*, in cyan). (**c**) A network that is subject to modulation from internal sources (cyan *synapse*). (**d**) A network that is affected by hormonally delivered neuromodulators. The entire system is bathed in low levels of modulator (cyan *background*), and individual components of the network that express receptors are specifically targeted (shown schematically as cyan *boxes*)

The diversity of modulatory targets, modulatory substances, and sites of modulatory action in the nervous system is striking and perhaps even staggering; evolution has evidently found heavily modulated neuronal environments advantageous, without regard for how difficult it might be to understand such networks as an observer. The task for the computational neuroscientist is to first understand the power of neuromodulation to affect networks at all levels and to consider that even at the level of relatively simple, small networks, modulation grants a much wider range of function, and significantly more computational power than can be otherwise achieved. This entry summarizes what is currently known about neuromodulation in the context of small invertebrate pattern-generating networks, with a focus on results which are relevant to the computational neuroscientist, especially those that involve explicit in silico investigation.

Neuromodulators Affect Neural Systems at the Network Level

Neuromodulation May Be Required for Network Output

While neuromodulation is classically thought to provide functional tuning to the output of preconfigured neuronal networks, in some cases, modulation is required for small pattern-generating networks to produce any functional output at all. This requirement may arise from either intrinsic modulation, in which the modulatory sources are located within the network itself, or from extrinsic modulation, in which



Neuromodulation in Small Networks, Fig. 2 Crustacean myosuppressin (a peptide hormone) modulates the cardiac system at multiple sites (All data are reproduced, with permission, from Stevens et al. (2009)). (**a**) The effect of myosuppressin in semi-intact heart preparations, in which motor neuron activity and muscle output are simultaneously recorded. Myosuppressin elicits a decrease in heart rate and an increase in cardiac muscle contraction force. (**b**) The effect of myosuppressin on the isolated cardiac ganglion, which contains the cardiac CPG. Myosuppressin elicits a decrease in motor neuron burst frequency, which appears to be responsible for the decrease in heart rate in panel *A*. (**c**) The effect of myosuppressin on a stimulated cardiac muscle preparation. Myosuppressin increases contraction force to the same electrical stimulation, which appears to be responsible for the increase in muscle contraction amplitude in panel *A*

modulatory signals originate from distal regions of the animal and may be released either locally or hormonally (Fig. 1).

Extrinsic Modulatory Requirement

In the stomatogastric ganglion (STG) of crustaceans, neuromodulatory inputs from anterior sources, such as the paired commissural ganglia (CoG), are required for the production of two rhythmic motor patterns which operate at different frequencies: the pyloric and gastric mill rhythms (Marder and Bucher 2007). When these inputs are severed or pharmacologically blocked, either the network falls completely silent or the

frequency of these rhythms decreases substantially. One important target of this modulation is an excitatory inward current present in many stomatogastric neurons known as I_{MI} (Swensen and Marder 2000, 2001). The activation of this current is necessary to induce spontaneous bursting in pacemaker cells, which drive the rest of the CPG network. This is a classic example of network reliance on extrinsic modulation.

Intrinsic Modulatory Requirement

In the *Tritonia* swim network, the dorsal swim interneurons (DSI) are part of the canonical CPG and participate in rhythm generation through direct ionotropic neurotransmission; however, they also signal through metabotropic receptors to modulate the strength of a synapse in the circuit between two other neurons known as VSI and VFN. Swimming behavior in this animal is an episodic response to sensory inputs, which involves a switch from a non-bursting to a transient bursting mode. A computational study that searched the space of parameters in a network constrained by the topology of the *Tritonia* swim CPG found that it is difficult to construct a network with static parameters capable of matching this *in vivo* behavior; most bursting models either were oscillatory indefinitely or produced intrinsic bursting without a sensory trigger (Calin-Jageman et al. 2007). Because both the bursting and non-bursting modes of this network are relatively stable, the intrinsic modulation is required to alter network parameters during canonical output, thus allowing the CPG to perform its function.

Neuromodulators Can Fine-Tune Network Output

In addition to providing a drive that may be essential for network function, modulatory substances often tune features of output more subtly. These tuning functions, especially when conferred by a diverse range of modulatory substances, grant substantial flexibility to networks that is often important for behavior, allowing output features to be adjusted without changing the canonical pattern. Two experimental systems have provided detailed examples of these modulatory tuning controls, but these are representative of what is seen in all nervous systems.

Crustaceans. In the STG of crabs and lobsters, a wide variety of modulatory substances are capable of influencing properties of the pyloric rhythm while maintaining its triphasic output pattern (Marder and Bucher 2007). A detailed investigation of modulation of the various cells of the pyloric CPG found that while many different modulators converge on the same inward current (I_{MI}) in different neurons, the subset of circuit neurons upon which each substance acts is different (Swensen and Marder 2000). Thus, each modulator is capable of influencing the network in a slightly different manner, producing distinct outputs that vary in features such as spikes per burst of motor neurons and phase relationships (Marder 2012). The ability of targeted modulation to evoke different versions of the pyloric rhythm was experimentally verified in a dynamic clamp study, in which the modulatory input current was computationally simulated in a neuron called PY while a modulator that does not affect this current was bath-applied to the STG. This manipulation was able to mimic the network effects of a different modulator which biologically turns on the equivalent current in PY (Swensen and Marder 2001).

Another well-studied crustacean motor circuit is the cardiac ganglion, which controls the frequency and strength of heart contractions. Neuromodulators are delivered to this system hormonally through the hemolymph or directly through extrinsic nerve fibers from the central nervous system. These modulators fine-tune both heart rate and cardiac muscle contraction force to meet behavioral demands (Fig. 2; Cooke 2002), for example, by eliciting an increase in heart rate when lobsters run on an underwater treadmill (Guirguis and Wilkens 1995).

Mollusks. Well-studied modulated small networks also exist in mollusks, such as the snail Lymnaea and the sea slug *Aplysia*. An extensively studied CPG controls feeding behavior in *Aplysia* by operating a sequence of muscle contractions important for both ingestive and egestive feeding behavior (Cropper et al. 2004).

A diverse set of neuropeptides have been characterized which shape a number of features of this network, including activation of fictive feeding patterns in quiescent preparations (Sweedler et al. 2002) and inhibition of motor neuron spiking (Furukawa et al. 2001). Neuropeptides also inhibit muscle contraction in the periphery at both the esophagus and stomach (Fujisawa et al. 1999; Furukawa et al. 2001).

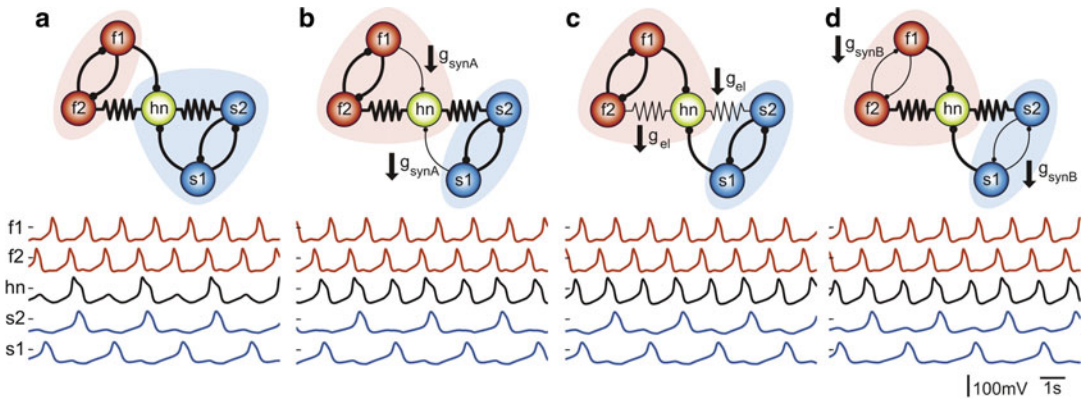
This modulation can also alter the specific details of the neuromuscular transform at these output synapses. The neuromuscular junction of the Aplysia accessory radula closer (ARC) muscle is modulated by an extensive array of modulatory neuropeptides released from interneurons and sensory neurons, which provide the ability to tune various features of this function. These substances act presynaptically to regulate the release of ACh onto muscles to initiate contraction and also act through G protein-coupled receptors to alter many features of muscle contraction such as latency, amplitude, and relaxation rate (Brezina 2010). This scenario gives the animal extensive control despite the paucity of direct innervation; only two motor neurons innervate the ARC muscle. A semi-realistic model containing interactions between neurons, modulators, and musculature at the periphery argues that modulation improves performance and appears to be required for the range of spiking behaviors, both regular and irregular, apparent in the biology (Brezina et al. 2005). This work again emphasizes the important function of modulation to give networks the ability to more flexibly control output than is possible with fixed network parameters.

Neuromodulators Can Switch Network Modes and Circuitry Through Multiple Mechanisms

Neuromodulation is also able to switch small neural networks between multiple modes, allowing for a much greater flexibility and diversity of responses than is obvious only from considering the connectome, or connectivity, of the system.

In *C. elegans*, the entire wiring diagram of the nervous system is known from electron micrograph reconstructions; a description of the connections among the 302 neurons was published decades ago (White et al. 1986). Yet it remains difficult to reliably identify important features of network function, due to the presence of extensive neuromodulation. More than 200 neuropeptide genes have been identified, the protein products of which actively reconfigure circuitry in response to sensory stimuli and environmental factors (Bargmann 2012). This modulation affects circuitry in a variety of ways. In one example, octanol avoidance in well-fed animals is mediated by a nociceptive sensory neuron called ASH. Following starvation, octanol avoidance behavior becomes distributed among three nociceptive neurons (Chao et al. 2004). The well-fed state can be mimicked by exogenous application of modulatory substances such as serotonin, dopamine, octopamine (OA), and some neuropeptides (Horvitz et al. 1982). In addition to influencing which neurons participate in particular behaviors, the same neuron may play a role in strikingly different behaviors depending on modulatory tone. The aforementioned ASH neuron, for example, is also capable of driving social aggregation behavior, but does so only when the activity of a modulatory neuropeptide, npr-1, is low (Bargmann 2012). Thus, the well-known wiring diagram in this species serves more as a starting point for analysis of functional circuitry than an end, as which connections are active and important at any given time depends extensively on neuromodulation.

In the mollusk *Aplysia*, the feeding CPG network also features modulation that switches the modes of network output. Here, the same underlying circuitry supports both ingestive and egestive feeding behavior, and the expression of either depends heavily on neuromodulation. Neuropeptides have been implicated in biasing network output for either ingestion or egestion (Jing and Weiss 2001; Kupfermann and Weiss 2001; Morgan et al. 2002), and even thought to play a more direct role in network switching (Vilim et al. 2010). Vilim et al. (2010) showed that two structurally related peptides have distinct actions on neurons in the network, yet can work together



Neuromodulation in Small Networks, Fig. 3 Computational model of switching network behaviors with neuromodulation. (**a**) The "baseline" model network, consisting of five oscillating cells. The hub neuron (hn, in *green*) oscillates at the frequency of the slowly oscillating half center (s1 and s2, in *blue*), twice as slow as the quickly oscillating half center (f1 and f2, in *red*). (**b–d**) Three example circuit manipulations, which may be induced via neuromodulatory mechanisms, which switch the behavior of the hub neuron to oscillating at the frequency of the fast half center (Figure reproduced from Gutierrez et al. (2013))

to cause a switch between these two network modes and to depress contractions in feeding muscles.

The idea that neuromodulation can switch small rhythmic networks between operational modes was investigated in a recent modeling study using a reduced model system motivated by the linked oscillators present in the STG. Gutierrez et al. (2013) created a simplified network of model neurons in which two oscillatory pairs of neurons, one with a fast period and one with a slow period, were coupled through a "hub" neuron, which was capable of oscillating in time with either pair (Fig. 3a). The authors found that there were many potential targets within the network at which modulation influenced the behavior of the hub neuron. Significantly, the three entirely different circuit mechanisms could switch the hub neuron from oscillating with the fast pair to oscillating with the slow pair (Fig. 3b–d). Altering network parameters is a key feature of neuromodulation, as is a diversity of targets within neural systems, and thus this work implies that neuromodulation is likely to be a key player in networks that feature the coupling of multiple oscillatory units.

Variability and Robustness of Neuromodulatory Signaling

An essential requirement of neuronal systems is to produce robust behaviors despite the intrinsic variability and randomness of biological systems (Marder and Goaillard 2006). Many network parameters vary over severalfold ranges: the maximal conductances of ionic currents, the strength of chemical synapses, and the strength of modulator-invoked currents (Marder and Taylor 2011; Roffman et al. 2012). This variability is not entirely random: it may result from homeostatic regulation mechanisms that tune intrinsic conductances and synaptic strengths such that functional output is maintained despite stochastic channel turnover and environmental perturbation (O'Leary and Wyllie 2011; Williams et al. 2013b). The inherent variability in the underlying structure of CPGs poses a problem for robust modulation, because altering network properties will yield variable effects depending on the initial parameters of the circuit (Grashow et al. 2009).

Most commonly, the effects of neuromodulators are qualitatively robust but quantitatively variable; neuromodulators generally affect measures of network activity in the

same direction, but the magnitude of these effects is variable. In many cases the variability in a neuromodulatory effect is correlated with visible characteristics of baseline network activity. For example, in rhythmically bursting leech heart interneurons, the application of myomodulin usually increases burst frequency and intra-burst spike frequency; the magnitude of this change ranges from 0% to 50% across preparations and is correlated with the baseline frequency and intra-burst spike frequency of the rhythm (Tobin and Calabrese 2005). In another example from the crustacean STG, a number of neuromodulators produce consistent increases in the cycle frequency of the pyloric CPG upon their application, but these effects are only significant when the initial frequency of the pyloric rhythm is low (Nagy and Dickinson 1983; Nusbaum and Marder 1989; Skiebe and Schneider 1994; Fu et al. 2007; Ma et al. 2009). These results have an intuitive explanation: the excitatory effects of a modulator can saturate when the system is already excited to begin with (similarly, the firing rate of a spiking neuron will saturate at some frequency due to the absolute refractory period). Additionally, the saturating nature of these modulators is sensible from a design perspective, because they can function to stabilize network output within physiologically useful bounds (Marder 2012).

A number of other experiments have reported more perplexing results, in which modulators do produce qualitatively distinct effects on network activity across preparations. Wiwatpanit et al. (2012) reported that the application of the neuromodulatory peptide C-type allatostatin (C-AST) to the heart of the lobster *Homarus americanus* produced a continuum of effects on the peak contraction force of the cardiac muscle. In some preparations, C-AST produced a significant decrease in peak force, in others it produced increases in peak force, in still others it showed biphasic responses in which peak contraction force first decreased, and then steadily increased over time; and sometimes no effect was observed at all (Wiwatpanit et al. 2012). A recent study showed that these qualitatively opposing results arise not only from variability in the effects of AST-C but from the nonlinear neuromuscular interface and variability in baseline CPG activity (Williams et al. 2013a).

Similar inconsistencies were observed in the STG of the spiny lobster *Panulirus interruptus*. Here, bath application of 5-HT produced a substantial increase, decrease, or no change at all in the cycle frequency of the pyloric rhythm, variability which was linked to the expression levels of different 5-HT receptors (Spitzer et al. 2008). These results are less intuitive from a design perspective, which provides an opportunity for theoretical work to bring clarity to these issues.

Interactions Between Neuromodulators

Due to experimental constraints, it is common for researchers to characterize neuromodulators one at a time, under controlled conditions. This does not, however, capture the complexity of biological systems, in which many different modulators are simultaneously present. The surprisingly large number of neuropeptide modulators has given rise to the field of neuropeptidomics, which seeks to characterize all bioactive peptides for a given species. Using mass spectrometry and transcriptome mining techniques, 31 families of crustacean neuropeptides have been identified, some of which contain over two dozen isoforms within a single species (Christie et al. 2010). Genetic techniques have identified large numbers of neuropeptides in *C. elegans* (Husson et al. 2007; Li and Kim 2008) and *D. melanogaster* (Clynen et al. 2010). Additionally, modulatory neurons can co-release several modulators or transmitters onto one or more neural targets (Nusbaum et al. 2001). How can we extrapolate results from carefully controlled, *in vitro* experiments on neuromodulation to understand the messier organization of real biological systems?

Modulators Act Through Convergent and Divergent Chemical Signaling Pathways

Understanding the interactions of multiple signaling molecules is a difficult but frequently studied problem within the field of systems biology

(Boonen et al. 2009). Within this conceptual framework, neuromodulators, including neurotransmitters, hormones, and growth factors, form complex signaling networks that both diverge and converge (Fig. 4). A signaling pathway is said to branch or diverge when an upstream element acts on multiple downstream targets, such as a modulator that binds to two different receptors. Different pathways are said to converge when two or more upstream elements act on the same downstream target, for example, two different modulators that activate the same signal transduction pathway. In general, upstream elements can either activate or repress downstream targets. Given the complexity of such signaling networks (Fig. 4a), and the nonlinearities inherent in biochemical processes and electrical signaling in neurons, it is unsurprising that the effects of multiple neuromodulators on network activity are not simply additive (Mesce 2002).

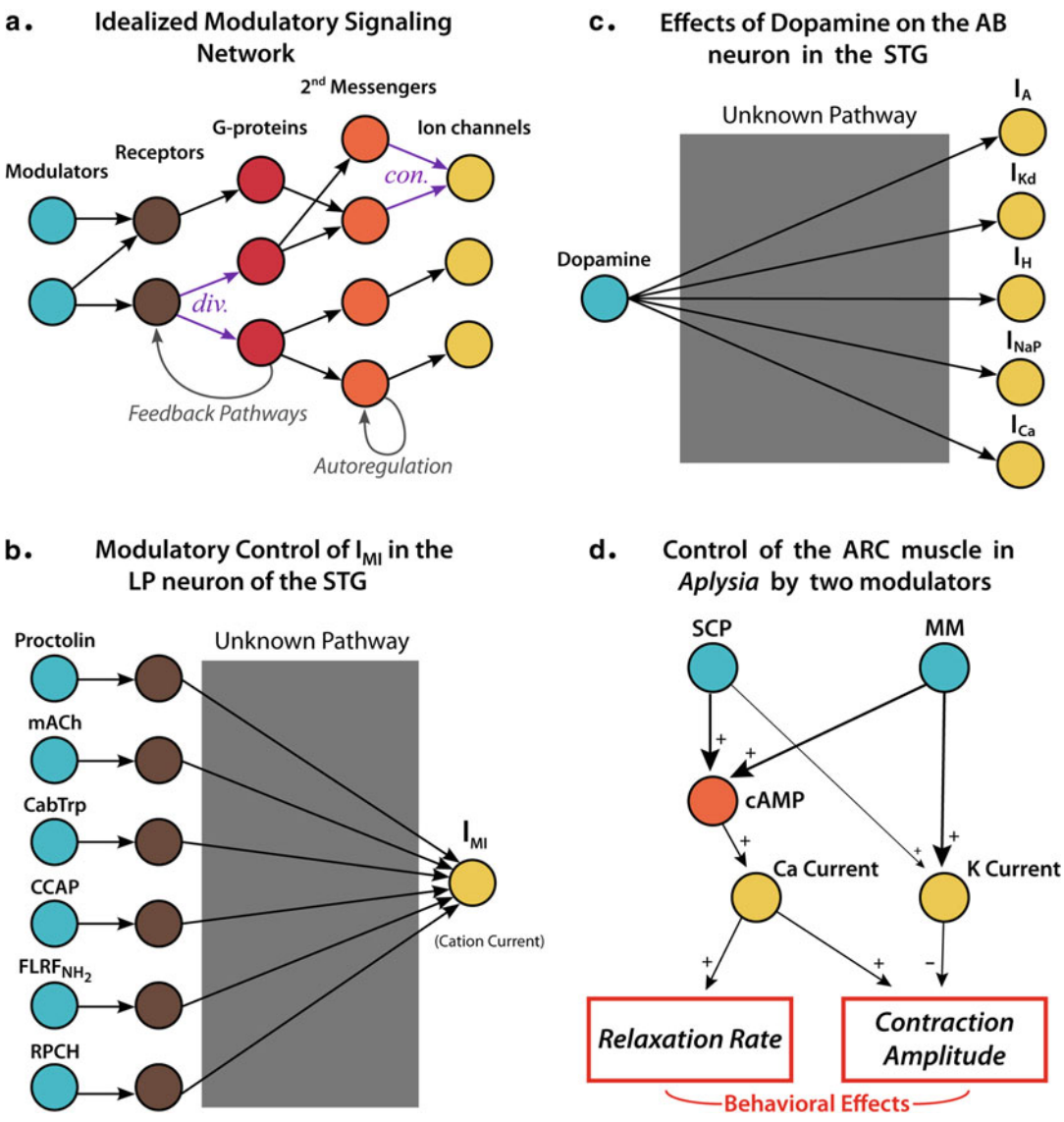
Neuromodulatory signaling pathways have been shown to converge on common targets in many vertebrate and invertebrate systems (Kaczmarek and Levitan 1987). In the crustacean STG, at least six different modulators activate the same voltage-dependent current (see Fig. 4b; Swensen and Marder 2001). Thus, when two of these modulators are applied in high concentrations to isolated cells, they can occlude each other's effects. There are two points that may be drawn from these observations. First, the simultaneous application of several modulators can produce saturating effects due to convergence; it is possible, therefore, that convergence is a mechanism that safeguards the network from overmodulation (Marder 2012). Second, neuromodulatory signaling pathways exhibit degeneracy, defined as the ability for distinct elements to elicit the same functional output (Tononi et al. 1999). Degeneracy within a system is thought to contribute to its robustness, for example, by providing the ability to withstand partial deletions, and its evolvability, by allowing changes to be functionally incorporated (Whitacre 2010).

Individual modulators can also simultaneously tune multiple network parameters through divergent signaling pathways. For example, dopamine activates five different currents in the anterior burster neuron of the crustacean STG (Fig. 4c; Harris-Warrick et al. 1998; Harris-Warrick and Johnson 2010). Divergence may be advantageous in two respects. First, divergent structure increases the computational complexity and capabilities of the signaling network. Effectively, this structure stores information about how the neuronal circuit should be tuned in response to changing levels of a neuromodulator (Brezina and Weiss 1997; Brezina 2010). Divergence may also provide the network with a stability mechanism by scaling parameters with opposing effects. For example, dopaminergic modulation of the STG has been shown to activate both inward and outward currents across different cells in the circuit. Harris-Warrick and Johnson (2010) have suggested that this balance may allow dopamine to alter the bursting activity of STG neurons without depolarizing or hyperpolarizing the cells too much, which could either cause them to firing tonically or fall silent (Harris-Warrick 2010).

Nonlinear Interactions Between Modulators

In theory, the structure of neuromodulatory signaling pathways can accommodate many complex and nonlinear interactions between modulators (Brezina and Weiss 1997; Alon 2006). However, relatively few studies have directly examined combinatorial interactions between different neuromodulators. Preliminary results, however, suggest that interactions between modulators can produce complex and behaviorally relevant effects:

- In the pre-Bötzinger complex of mice, the pharmacological blockade of the excitatory modulator substance-P produces little to no response, as long as two other excitatory modulators, serotonin and noradrenaline, are present. However, during the chronic blockade of serotonergic and noradrenergic receptors, the acute blockade of substance-P produces significant decreases in respiration frequency (Doi and Ramirez 2010).
- In the cardiac sac of the spiny lobster *Panulirus interruptus*, the application of the



Neuromodulation in Small Networks, Fig. 4 Modulatory signaling pathways contain convergent and divergent structure. (**a**) A schematic diagram showing two hypothetical modulators that exert physiological changes through G protein-coupled receptors. These biochemical pathways contain divergent (example labeled "div." in *purple*) and convergent (example labeled "con.") pathways. In principle, it is possible for modulatory pathways to include feedback and autoregulatory connections (in *gray*), but these possibilities are poorly understood within the current literature. (**b**) An example of convergence in crustacean STG: six different modulators converge to activate the same voltage-dependent current in the lateral pyloric (LP) neuron (see Swensen and Marder 2000). (**c**) An example of divergence in the crustacean STG: the application of one modulator (dopamine) alters the activity of five different ionic currents (see Harris-Warrick et al. 1998). (**d**) The signaling pathways of two neuropeptides that affect the contraction dynamics of the ARC muscle in Aplysia contain convergent and divergent connections (see Brezina et al. 1996)

neuropeptide proctolin alone does not induce rhythmic bursting. However, the application of red pigment-concentrating hormone (RPCH) appears to potentiate the effects of proctolin, allowing it to elicit a strong motor pattern. This can occur even when RPCH is

applied at low, subthreshold levels (Dickinson et al. 1997).

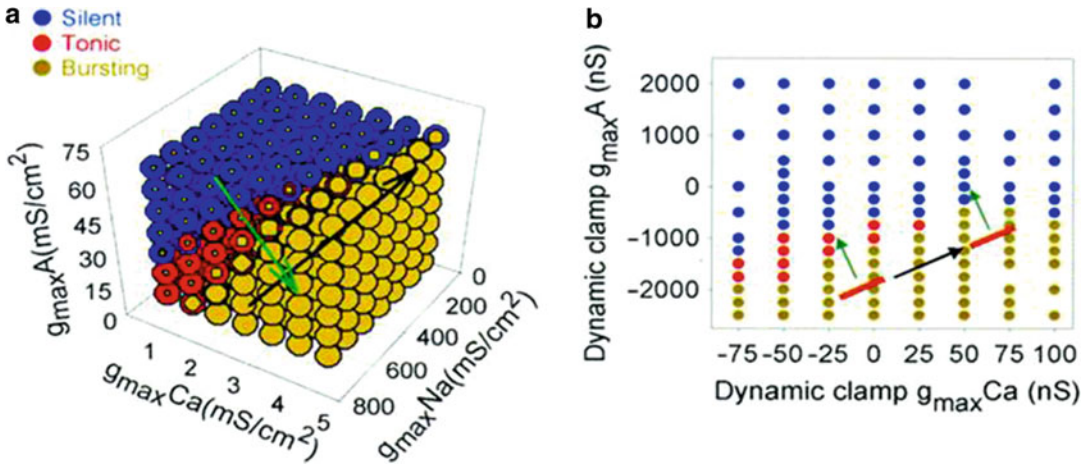
- In the medicinal leech (*Hirudo medicinalis*), fictive swimming motor patterns can be induced by the application of either serotonin or octopamine, and this effect is lost when the modulator is washed out of the preparation. However, the reverse effect is observed when both modulators are simultaneously applied. During the initial application of both modulators, little to no fictive swimming patterns is produced, but upon washout of the modulators, strong rhythmic pattern is observed (Mesce et al. 2001).
- In the moth *Manduca sexta*, heart rate is controlled by a variety of neuromodulators including the excitatory modulators octopamine and type-2 cardioacceleratory peptides (CA_2). The application of octopamine at subthreshold levels substantially potentiates the heart's response to CA_2, but the subthreshold application of CA_2 does not significantly affect the heart's response to octopamine (Prier et al. 1994).
- A study of neuromuscular transmission in the yellow crab *Eriphia spinifrons* and the crayfish *Procambarus clarkia* showed that the application of octopamine consistently lessened the excitatory effects of 5-HT, even though octopamine alone produced variable effects across preparations, either increasing or decreasing transmission (Djokaj et al. 2001).

What mechanisms can explain these interactions between modulators? It is possible that different modulatory pathways interact directly through excitatory and repressive connections between their signaling cascades, similar to other chemical signaling networks that have been extensively investigated in *E. coli* (Alon 2006). While this possibility is of outstanding interest, it has not been seriously tested to date, because neuromodulatory signaling pathways in small invertebrate networks are not well-characterized.

Even without direct chemical interactions, the complexities inherent within neuron membrane dynamics admit the possibility of nonlinear interactions between modulators. Goldman et al. (2001) examined this second possibility in a conductance-based model neuron and in biological STG neurons. By simulating the activity of the model neuron across many different maximal conductance combinations, they constructed a map of neural activity across a conductance space (Fig. 5a). A similar (but more restricted) map was experimentally determined by varying maximal conductance parameters of injected dynamic clamp currents (Fig. 5b). Within both of these maps, each point represents a different set of maximal conductances, the activity pattern of the neuron at that point is represented by its color, and the effects of a modulator can be visualized as a vector that moves the model from one point to another. This serves as a simple, but useful, approximation of biological modulation as modulators can have many other effects in addition to changing the maximal conductance of an intrinsic current. In Fig. 5, the black arrows show the effects of a modulator that largely preserves neural activity, in what Goldman et al. (2001) refer to as an insensitive direction of modulation. In contrast, the modulatory shift denoted by the green arrow qualitatively changes the behavior of the model cell, considered a sensitive direction of modulation. In Fig. 5b, note that the black modulator can shape the effect of the green modulator in a nonlinear fashion: the green modulator produces tonic spiking behavior when applied alone, but produces bursting behavior when co-applied with the black modulator. This result stems from the fact that the boundaries between qualitatively different activity patterns in conductance space are curved (i.e., nonlinear).

How Many Modulators Are Needed to Control Network Output?

Modulators can alter the activity of individual neurons and connected networks, but to what degree can they precisely control this output? Within the parameter space of a circuit, the effects of a single neuromodulator can be visualized as pushing the network along a one-dimensional path. In Fig. 5, we approximated these paths as vectors, but these paths would be more realistically captured as nonlinear curves



Neuromodulation in Small Networks, Fig. 5 Neuromodulators can tune network parameters in sensitive (*green arrows*) and insensitive (*black arrows*) directions through global parameter space (Data is reproduced, with permission, from Goldman et al. (2001)). (**a**) A global activity map of a single-compartment model neuron when the maximal conductances of three voltage-dependent currents are independently varied. Each dot illustrates the activity pattern of the neuron in that region of parameter space. (**b**) A similar activity map for a biological neuron when the strength of two dynamic clamp currents is altered

(see Brezina and Weiss 1997). Additionally, these curves would have finite length since the effects of a modulator saturate at high concentrations. This one-dimensional case can be easily generalized. The coordinated actions of two neuromodulators can move the system along a finite, two-dimensional surface in parameter space. This is analogous to two linearly independent vectors that define a 2D plane; when the two modulators are combined at different concentrations, the network is moved in a unique direction within a 2D region of space. In general, a system with N distinct modulators can independently control the parameters of the network within a finite N-dimensional region (Brezina and Weiss 1997). Equivalently stated, a neuromodulatory system requires at least N distinct modulators to independently control N different network parameters. However, modulators may hold less combinatorial power in practice, as they may be co-released under naturalistic conditions (Nusbaum et al. 2001).

One notable experimental study on the accessory radula closer (ARC) muscle of Aplysia supported this basic theoretical framework; the authors demonstrated that two features of muscle output, the amplitude and relaxation rate of muscle contractions, could be independently controlled by changing the relative concentrations of two neuropeptide signals (Brezina et al. 1996). Because small neuronal networks tend to be influenced by many different neuromodulators, it is possible that modulatory systems are designed to have broad control over network parameters (Brezina 2010). However, the extent of neuromodulatory control over circuit parameters remains an open experimental question in many systems.

Implications for Modeling

The extensive study of neuromodulation in small, pattern-generating invertebrate networks has led directly to modeling work described here and must also serve to inform modelers as they grapple with future issues, particularly in light of recent focus on obtaining the synaptic wiring diagram from more complex systems. While there is a wealth of invaluable information present in the connectome, when similar "wiring diagrams" of neuromodulation have been attempted, the results can be at least as complex, even in small systems (Brezina 2010).

The extensive convergence and divergence of modulator actions, the huge number of modulatory substances, and the wide variety of cellular and network properties which are thereby affected amount to a staggering amount of complexity and flexibility which allows even very small networks to perform a variety of highly tuned and behaviorally relevant functions. Further, these actions and substances still elude complete description, as even in very well-studied systems, entire new families of modulatory neuropeptides are still being discovered.

A thorough consideration of the full richness of modulation will serve computational neuroscience well: their intrinsic and extrinsic origins; their diverse site of action, at every level of neuronal computation; their ability to gate network output entirely or simply fine-tune it; their extensive overlapping convergence and divergence; and their complicated interactions and modulatory connectome. All of these important features of neuromodulation are present even in small networks and are critical to reaching a proper theoretical understanding of circuit function both at this level and at the level of the entire nervous system.

References

Alon U (2006) An introduction to systems biology: design principles of biological circuits. Chapman & Hall, London

Ballo AW, Nadim F, Bucher D (2012) Dopamine modulation of I_H improves temporal fidelity of spike propagation in an unmyelinated axon. J Neurosci 32:5106–5119

Bargmann CI (2012) Beyond the connectome: how neuromodulators shape neural circuits. Bioessays 34:458–465

Boonen K, Creemers JW, Schoofs L (2009) Bioactive peptides, networks and systems biology. Bioessays 31:300–314

Brezina V (2010) Beyond the wiring diagram: signalling through complex neuromodulator networks. Philos Trans R Soc Lond B Biol Sci 365:2363–2374

Brezina V, Weiss KR (1997) Analyzing the functional consequences of transmitter complexity. Trends Neurosci 20:538–543

Brezina V, Orekhova IV, Weiss KR (1996) Functional uncoupling of linked neurotransmitter effects by combinatorial convergence. Science 273:806–810

Brezina V, Orekhova IV, Weiss KR (2000) Optimization of rhythmic behaviors by modulation of the neuromuscular transform. J Neurophysiol 83:260–279

Brezina V, Orekhova IV, Weiss KR (2003) Neuromuscular modulation in *Aplysia*. II. Modulation of the neuromuscular transform in behavior. J Neurophysiol 90:2613–2628

Brezina V, Horn CC, Weiss KR (2005) Modeling neuromuscular modulation in *Aplysia*. III. interaction of central motor commands and peripheral modulatory state for optimal behavior. J Neurophysiol 93:1523–1556

Calin-Jageman RJ, Tunstall MJ, Mensh BD et al (2007) Parameter space analysis suggests multi-site plasticity contributes to motor pattern initiation in *Tritonia*. J Neurophysiol 98:2382–2398

Chao MY, Komatsu H, Fukuto HS et al (2004) Feeding status and serotonin rapidly and reversibly modulate a *Caenorhabditis elegans* chemosensory circuit. Proc Natl Acad Sci USA 101:15512–15517

Christie AE, Stemmler EA, Dickinson PS (2010) Crustacean neuropeptides. Cell Mol Life Sci 67:4135–4169

Clynen E, Reumer A, Baggerman G et al (2010) Neuropeptide biology in *Drosophila*. Adv Exp Med Biol 692:192–210

Cooke IM (2002) Reliable, responsive pacemaking and pattern generation with minimal cell numbers: the crustacean cardiac ganglion. Biol Bull 202:108–136

Cropper EC, Evans CG, Hurwitz I et al (2004) Feeding neural networks in the mollusk *Aplysia*. Neurosignals 13:70–86

Dickinson PS, Fairfield WP, Hetling JR, Hauptman J (1997) Neurotransmitter interactions in the stomatogastric system of the spiny lobster: one peptide alters the response of a central pattern generator to a second peptide. J Neurophysiol 77:599–610

Djokaj S, Cooper RL, Rathmayer W (2001) Presynaptic effects of octopamine, serotonin, and cocktails of the two modulators on neuromuscular transmission in crustaceans. J Comp Physiol A 187:145–154

Doi A, Ramirez J-M (2010) State-dependent interactions between excitatory neuromodulators in the neuronal control of breathing. J Neurosci 16:8251–8262

Fu Q, Tang LS, Marder EE, Li L (2007) Mass spectrometric characterization and physiological actions of VPNDWAHFRGSWamide, a novel B type allatostatin in the crab, *Cancer borealis*. J Neurochem 101:1099–1107

Fujisawa Y, Furukawa Y, Ohta S et al (1999) The Aplysia mytilus inhibitory peptide-related peptides: identification, cloning, processing, distribution, and action. J Neurosci 19:9618–9634

Furukawa Y, Nakamaru K, Wakayama H et al (2001) The enterins: a novel family of neuropeptides isolated from the enteric nervous system and CNS of *Aplysia*. J Neurosci 21:8247–8261

Goldman MS, Golowasch J, Marder E, Abbott LF (2001) Global structure, robustness, and modulation of neuronal models. J Neurosci 21:5229–5238

Grashow R, Brookings T, Marder E (2009) Reliable neuromodulation from circuits with variable underlying structure. Proc Natl Acad Sci USA 106:11742–11746

Guirguis MS, Wilkens JL (1995) The role of the cardioregulatory nerves in mediating heart rate responses to locomotion, reduced stroke volume, and neurohormones in *Homarus americanus*. Biol Bull 188:179–185

Gutierrez GJ, O'Leary T, Marder E (2013) Multiple mechanisms switch an electrically coupled, synaptically inhibited neuron between competing rhythmic oscillators. Neuron 77:845–858

Harris-Warrick RM, Johnson BR (2010) Checks and balances in neuromodulation. Front Behav Neurosci 4:47

Harris-Warrick RM, Johnson BR, Peck JH et al (1998) Distributed effects of dopamine modulation in the crustacean pyloric network. Ann N Y Acad Sci 860:155–167

Horvitz HR, Chalfie M, Trent C et al (1982) Serotonin and octopamine in the nematode *Caenorhabditis elegans*. Science 216:1012–1014

Husson SJ, Mertens I, Janssen T, Lindemans M (2007) Neuropeptidergic signaling in the nematode *Caenorhabditis elegans*. Prog Neurobiol 82:33–55

Jing J, Weiss KR (2001) Neural mechanisms of motor program switching in *Aplysia*. J Neurosci 21:7349–7362

Kaczmarek LK, Levitan IB (1987) Neuromodulation: the biochemical control of neuronal excitability. Oxford University Press, New York

Kupfermann I, Weiss KR (2001) Motor program selection in simple model systems. Curr Opin Neurobiol 11:673–677

Li C, Kim K (2008) Neuropeptides WormBook, ed. The C. elegans Research Community, WormBook, doi/10.1895/wormbook.1.142.1, http://www.wormbook.org

Ma M, Szabo TM, Jia C et al (2009) Mass spectrometric characterization and physiological actions of novel crustacean C-type allatostatins. Peptides 30:1660–1668

Marder E (2012) Neuromodulation of neuronal circuits: back to the future. Neuron 76:1–11

Marder E, Bucher D (2007) Understanding circuit dynamics using the stomatogastric nervous system of lobsters and crabs. Annu Rev Physiol 69:291–316

Marder E, Goaillard J-M (2006) Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 7:563–574

Marder E, Taylor AL (2011) Multiple models to capture the variability in biological neurons and networks. Nat Neurosci 14:133–138

Mesce KA (2002) Metamodulation of the biogenic amines: second-order modulation by steroid hormones and amine cocktails. Brain Behav Evol 60:339–349

Mesce KA, Crisp KM, Gilchrist LS (2001) Mixtures of octopamine and serotonin have nonadditive effects on the CNS of the medicinal Leech. J Neurophysiol 85:2039–2046

Morgan PT, Jing J, Vilim FS, Weiss KR (2002) Interneuronal and peptidergic control of motor pattern switching in *Aplysia*. J Neurophysiol 87:49–61

Nagy F, Dickinson PS (1983) Control of a central pattern generator by an identified modulatory interneuron in crustacea. I. Modulation of the pyloric motor output. J Exp Biol 105:33–58

Nusbaum MP, Blitz DM (2012) Neuropeptide modulation of microcircuits. Curr Opin Neurobiol 22:592–601

Nusbaum MP, Marder E (1989) A modulatory proctolin-containing neuron (MPN). II. State-dependent modulation of rhythmic motor activity. J Neurosci 9:1600–1607

Nusbaum MP, Blitz DM, Swensen AM et al (2001) The roles of co-transmission in neural network modulation. Trends Neurosci 24:146–154

O'Leary T, Wyllie DJA (2011) Neuronal homeostasis: time for a change? J Physiol (Lond) 589:4811–4826

Prier KR, Beckman OH, Tublitz NJ (1994) Modulating a modulator: biogenic amines at subthreshold levels potentiate peptide-mediated cardioexcitation of the heart of the tobacco hawkmoth Manduca sexta. J Exp Biol 197:377–391

Roffman RC, Norris BJ, Calabrese RL (2012) Animal-to-animal variability of connection strength in the leech heartbeat central pattern generator. J Neurophysiol 107:1681–1693

Skiebe P, Schneider H (1994) Allatostatin peptides in the crab stomatogastric nervous system: inhibition of the pyloric motor pattern and distribution of allatostatin-like immunoreactivity. J Exp Biol 194:195–208

Spitzer N, Cymbalyuk G, Zhang H et al (2008) Serotonin transduction cascades mediate variable changes in pyloric network cycle frequency in response to the same modulatory challenge. J Neurophysiol 99:2844–2863

Stevens JS, Cashman CR, Smith CM, Beale KM, Towle DW, Christie AE, Dickinson PS (2009) The peptide hormone pQDLDHVFLRFamide (crustacean myosuppressin) modulates the Homarus americanus cardiac neuromuscular system at multiple sites. J Exp Biol 212:3961–3976

Sweedler JV, Li L, Rubakhin SS et al (2002) Identification and characterization of the feeding circuit-activating peptides, a novel neuropeptide family of aplysia. J Neurosci 22:7797–7808

Swensen AM, Marder EE (2000) Multiple peptides converge to activate the same voltage-dependent current in a central pattern-generating circuit. J Neurosci 20:6752–6759

Swensen AM, Marder EE (2001) Modulators with convergent cellular actions elicit distinct circuit outputs. J Neurosci 21:4050–4058

Tobin A-E, Calabrese RL (2005) Myomodulin increases I_H and inhibits the Na/K pump to modulate bursting in leech heart interneurons. J Neurophysiol 94:3938–3950

Tononi G, Sporns O, Edelman GM (1999) Measures of degeneracy and redundancy in biological networks. Proc Natl Acad Sci USA 96:3257–3262
Vilim FS, Sasaki K, Rybak J et al (2010) Distinct mechanisms produce functionally complementary actions of neuropeptides that are structurally related but derived from different precursors. J Neurosci 30:131–147
Whitacre JM (2010) Degeneracy: a link between evolvability, robustness and complexity in biological systems. Theor Biol Med Model 7:6
White JG, Southgate E, Thomson JN, Brenner S (1986) The structure of the nervous system of the nematode *Caenorhabditis elegans*. Philos Trans R Soc Lond B Biol Sci 314:1–340
Williams AH, Calkins A, O'Leary T, Symonds R, Marder E, Dickinson PS (2013a) The neuromuscular transform of the lobster cardiac system explains the opposing effects of a neuromodulator on muscle output. J Neurosci 33(42):16565–16575
Williams AH, O'Leary T, Marder E (2013b) Homeostatic regulation of neuronal excitability. Scholarpedia 8:1656
Wiwatpanit T, Powers B, Dickinson PS (2012) Inter-animal variability in the effects of C-type allatostatin on the cardiac neuromuscular system in the lobster *Homarus americanus*. J Exp Biol 215:2308–2318
Zhao S, Sheibanie AF, Oh M et al (2011) Peptide neuromodulation of synaptic dynamics in an oscillatory network. J Neurosci 31:13991–14004

Neuromorphic Cognition

Giacomo Indiveri and Rodney Douglas
Institute of Neuroinformatics, University of Zürich and ETH Zürich, Zürich, Switzerland

Synonyms

Neuromorphic cognitive systems; Neuromorphic electronic systems; Neuromorphic real-time behaving systems

Definition

The hallmark of cognitive behavior is the ability of an agent to select an economically advantageous action based on immediate external stimuli as well as on their longer-term context. Neuromorphic cognition refers to the cognitive abilities of systems or agents implemented in neuromorphic electronic VLSI technology whose processing architecture is similar to the distributed, asynchronous one of biological brains. Neuromorphic agents are typically real-time behaving systems composed of multiple asynchronous event-based VLSI chips that integrate networks of silicon neurons and dynamic synapses together and that are interfaced to event-based neuromorphic sensors and robotic actuators. In order to express cognitive performance, these agents require a hardware infrastructure that supports local learning and decision making, for distributed communication and for the elaboration of state-dependent processing. We describe examples of such mechanisms and present a method for efficiently implementing neuromorphic cognition in these agents.

Detailed Description

Digital computers provide prodigious computational power and memory for the simulation of models of cognition. Nevertheless humans and many animals including insects still outperform the most powerful computers in real-world cognitive tasks. This disparity between the effectiveness of biological nervous systems and computers is primarily attributable to differences in their elementary processing devices and to the kinds of computational primitives they implement (Indiveri and Horiuchi 2011; Mead 1990). Rather than using Boolean logic, precise digital representations, and clocked operations, the nervous systems perform robust and reliable computation using hybrid analog/digital unreliable components; they employ distributed, event-driven, collective, and massively parallel mechanisms, and they implement adaptation, self-organizing, and learning strategies, on multiple spatial and temporal scales. Understanding these principles, and how they can lead to behaviors that exhibit cognitive qualities, remains a major challenge for science.

The goal of *neuromorphic cognition* is to understand the neural mechanisms used by the