Neuromodulation of Circuits with Variable Parameters: Single Neurons and Small Circuits Reveal Principles of State-Dependent and Robust Neuromodulation

Eve Marder, Timothy O'Leary, and Sonal Shruti

Volen Center and Biology Department, Brandeis University, Waltham, Massachusetts 02454; email: marder@brandeis.edu, toleary@brandeis.edu, sshruti@brandeis.edu

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stomatogastric nervous system, central pattern generators, neuropeptides, biogenic amines, intrinsic excitability, synaptic strength

Abstract

Neuromodulation underlies many behavioral states and has been extensively studied in small circuits. This has allowed the systematic exploration of how neuromodulatory substances and the neurons that release them can influence circuit function. The physiological state of a network and its level of activity can have profound effects on how the modulators act, a phenomenon known as state dependence. We provide insights from experiments and computational work that show how state dependence can arise and the consequences it can have for cellular and circuit function. These observations pose a general unsolved question that is relevant to all nervous systems: How is robust modulation achieved in spite of animal-to-animal variability and degenerate, nonlinear mechanisms for the production of neuronal and network activity?

Contents

INTRODUCTION

All nervous systems, large and small, are modulated by numerous amines, neuropeptides, gases, and other molecules (Bargmann 2012, Brezina 2010, Harris-Warrick & Johnson 2010, Levitan 1988, Marder 2012, Stein 2009, Taghert & Nitabach 2012). At the extreme, alterations in modulatory tone are likely to underlie changes in arousal, mood, and other global states of brain networks that dramatically influence an animal's behavior (Alekseyenko et al. 2010, 2013; Beverly et al. 2011; Lee & Dan 2012; Liu et al. 2012). Neuromodulators also have more focused actions that may influence the properties of single neurons, synapses, or local circuits (Marder 2012). Despite the ubiquitous nature of neuromodulatory control systems and their clear relevance for understanding circuit dynamics and behavior (Bargmann 2012, Blitz & Nusbaum 2011, Brezina 2010, Nusbaum & Blitz 2012, Taghert & Nitabach 2012), several fundamental questions relevant to neuromodulation remain mysterious. In this review, we draw on a large literature on the effects of neuromodulators on well-characterized small circuits found in invertebrates to illustrate and elucidate some of the fundamental puzzles and conundrums posed by neuromodulation. Although these issues are easily illustrated in small nervous systems, the general principles we articulate are as relevant to neuromodulation in the human brain as they are in *Caenorhabditis elegans*, crustaceans, or mollusks. We regret that space limitations preclude our doing justice to most of the elegant work on neuromodulation in small invertebrate circuits.

We first discuss numerous issues relevant to the modulation of single neurons, which almost certainly are general features of all nervous systems. We then discuss some computational and experimental studies of modulation of small circuit dynamics. Although we illustrate principles using known small circuits, admittedly with their specific idiosyncrasies, the reader who steps back will see general principles that rise above the system specifics. For example, the challenges in understanding the action of a peptide in the crustacean nervous system frame many of the issues relevant to understanding how modulatory substances such as dopamine influence behavior in mammals. Finally, we pose a significant challenge for future studies: to understand how neuromodulation can be tuned in concert with other circuit properties so that individuals can respond reliably and appropriately to neuromodulatory inputs.

MODULATION OF SINGLE NEURONS AND SYNAPSES

Modulators exert their action by altering the strength of synapses and the conductances and other properties of intrinsic membrane channels (Harris-Warrick & Marder 1991). Therefore the distribution and expression level of different ion channels and receptors are pivotal in determining a cell or network response to a neuromodulator (Marder 2012, Marder & Thirumalai 2002).

Neuromodulation of Single Neurons with Similar Behavior Can Depend Critically on Underlying Parameters

A large number of computational studies have demonstrated that similar neuronal properties can result from vastly different sets of membrane conductances (Goldman et al. 2001; Golowasch et al. 2002; Sobie 2009; Taylor et al. 2006, 2009), and a growing number of experimental studies have shown that identified neurons can have widely varying conductance densities of ionic currents and synaptic strengths (Goaillard et al. 2009; Ransdell et al. 2013; Rinberg et al. 2012; Roffman et al. 2012; Schulz et al. 2006, 2007; Swensen & Bean 2005; Tobin et al. 2009). **Figure 1*a*** shows an example of model neurons with substantially different sets of conductance densities but with very similar membrane potential waveforms. **Figure 1*b*** shows data from an experimental study in which voltage-clamp measurements of conductance densities were made from isolated Purkinje neurons with very similar waveforms. Again, it can be seen that very similar membrane potential trajectories can arise from quite different sets of conductances.

These data raise three related questions. First, can neurons with variable underlying conductances give robust or reliable responses to modulation (Goldman et al. 2001, Szücs & Selverston 2006)? Second, can neurons with similar sets of conductances nonetheless respond differently

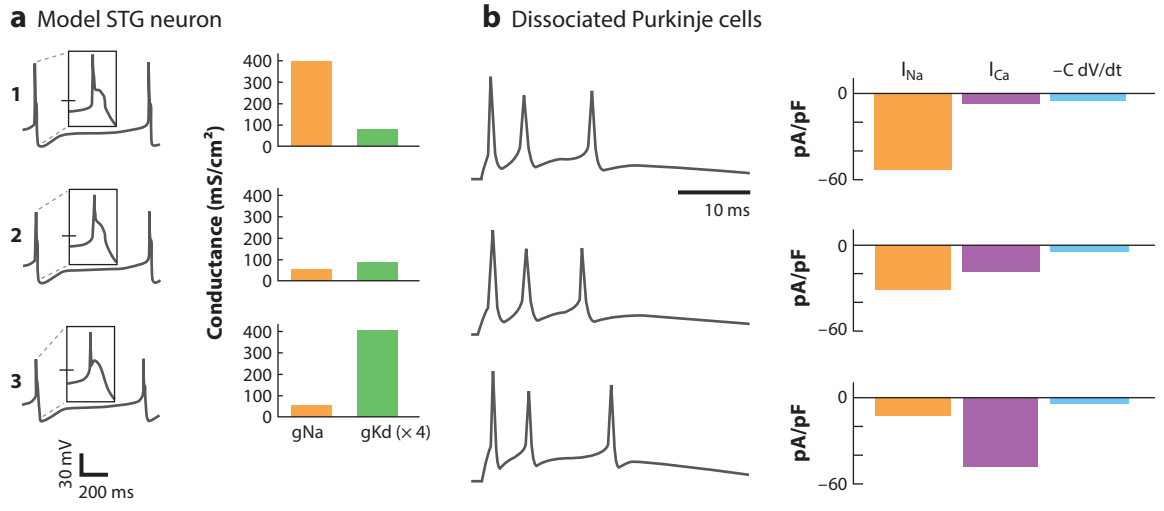


Figure 1

Neurons produce stereotyped physiological behavior with variable underlying membrane conductances. (*a*) Example membrane potential traces from three different single-spike bursting model neurons, adapted from **Figure 2** in Golowasch et al. (2002). Values of two of the six conductance densities in each model are shown to the right of each trace. The time base of each inset is 50 ms; the horizontal tick in the insets corresponds to −30 mV. (*b*) Current-clamp recordings of three dissociated Purkinje neurons showing similar burst-firing behavior, adapted from Swensen & Bean (2005), figure 2A. The voltage-dependent contributions of fast sodium (I_{Na}), calcium (I_{Ca}) and net ionic membrane currents (−C dv/dt) measured in each of the neurons are shown to the right. Abbreviation: STG, stomatogastric ganglion.

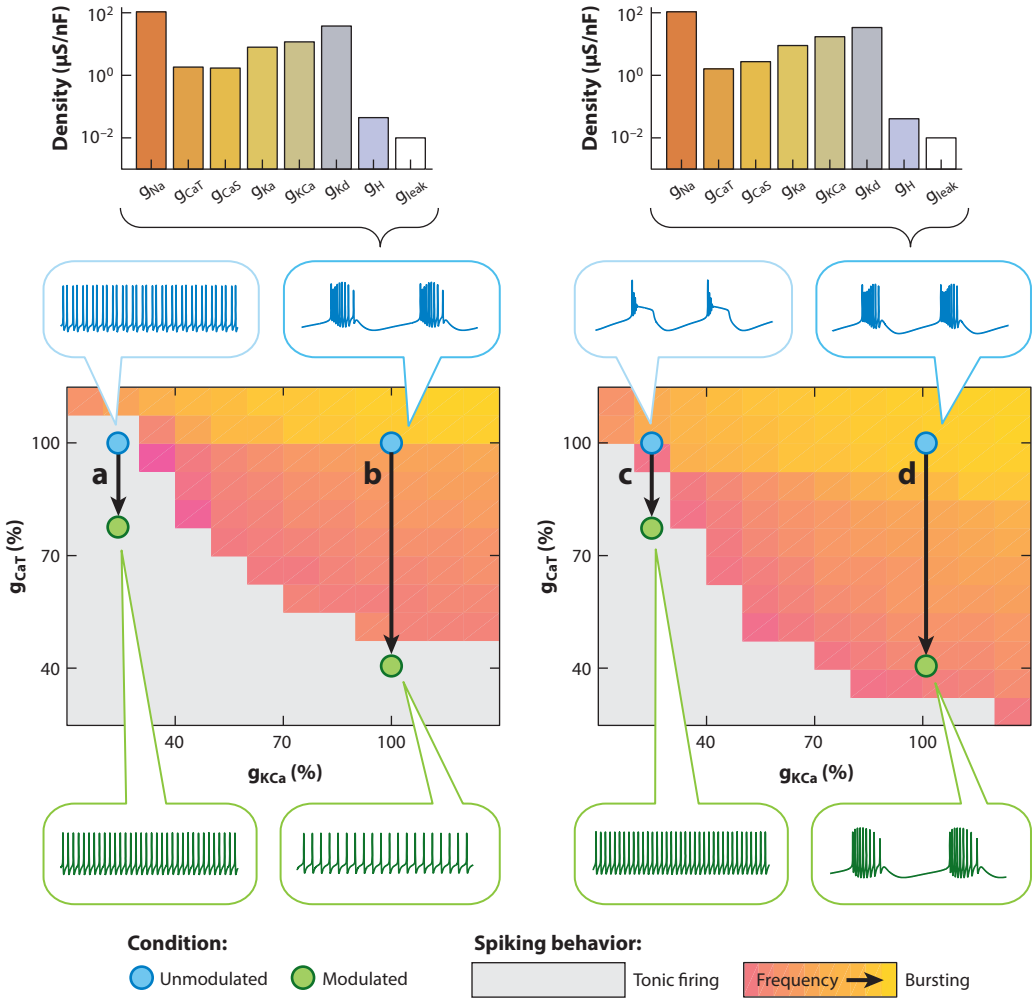


Figure 2

Consequences of precise neuromodulation in populations of neurons with variable underlying conductances. Parameter maps showing conductance densities and corresponding behavior of a population of conductance-based model neurons. The middle heat maps show the regions of conductance values that produce two distinct types of membrane potential behavior, tonic spiking (*gray regions*) and burst firing (*colored regions*, *shaded according to burst frequency*), as a function of two of the seven voltage-dependent conductances in the model (g_{CaT}, a transient calcium conductance, and g_{KCa}, a calcium-dependent potassium conductance). The left and right plots show the same regions of conductance space for models in which the remaining five conductances have different underlying values. The membrane potential behavior of four base-case neurons is shown (*a–d*, *top insets*). The underlying conductances for cases *b* and *d*, which have similar membrane potential activity, are displayed at the top of the figure. Modulation causing a 20% (cases *a* and *c*) and 60% (cases *b* and *d*) change in g_{CaT} is indicated by the vertical arrows and results in the membrane potential behavior in the bottom insets. The time base for each trace is 200 ms.

to modulation or perturbation (Goldman et al. 2001)? And third, should we expect qualitatively different responses to neuromodulation or perturbation from neurons of the same cell type?

Figure 2 explores these issues using a computational model with seven voltage- and time-dependent conductances as well as a leak conductance. The behavior of the models as a function of their low-threshold Ca^{2+} conductance (g_{CaT}) and Ca^{2+}-activated K^+ conductance (g_{Kca}) is

shown as regions of the parameter space that produce bursting or tonic firing. Note that these regions are similar in form but are not identical because of the differences in other conductances in the two models. The membrane-potential waveforms of two models (points *b* and *d*) are quite similar, and the conductance densities, although not identical, are also relatively similar. But, at much lower values of g_{KCa}, the neuron at point *a* fires doublets of spikes, whereas the neuron at the same location in the other map (point *c*) fires short bursts of action potentials with long plateaus.

Several important points relevant to state-dependent neuromodulation can be seen in **Figure 2**. A large change in one conductance (in this case g_{CaT}) can produce relatively little change in behavior (the neuron shown in point *d* maintains its bursting behavior despite a large modulatory change in conductance). The same change in conductance in the neuron shown at point *b* produces a qualitative change in activity: It brings the neuron across the boundaries between tonic firing and bursting behavior (Goldman et al. 2001). Even a small neuromodulatory change acting on the neurons at points *a* and *c* will produce qualitative changes in behavior. Nonetheless, at different starting values of g_{KCa}, much larger changes in g_{CaT} have little or no obvious effect on the neuron's firing properties. In summary, the effect of a modulatory substance that alters one or more of the voltage-dependent conductances of a neuron depends not only on how strong its action is on its target conductance, but also on the values of all the other conductances in the neuron (**Figure 2**).

This example illustrates complications that are inherent even when a single membrane conductance is modulated. It is important to remember that the same neuromodulator can act on numerous voltage-dependent currents in the same neuron and that this can be mediated by one or more receptors (Boyle et al. 1984, Braha et al. 1993, Harris-Warrick et al. 1995, Kiehn & Harris-Warrick 1992, Spitzer et al. 2008, Thompson & Calabrese 1992, Tobin & Calabrese 2005).

Degenerate Neuromodulatory Actions Can Hide Differences in Underlying Mechanisms

Neurons and circuits routinely respond to many neuromodulatory substances, some of which may elicit responses that closely resemble each other (Marder & Bucher 2007, Marder & Eisen 1984, Swensen & Marder 2000). One example is shown in the response of the isolated anterior burster (AB) neuron from the lobster stomatogastric ganglion. This neuron responds to the application of cholinergic agonists, amines, and many neuropeptides with robust bursts of attenuated action potentials riding on top of a large depolarizing slow wave (Ayali & Harris-Warrick 1999, Flamm & Harris-Warrick 1986, Harris-Warrick & Flamm 1987, Hooper & Marder 1987, Marder & Eisen 1984). **Figure 3*a*** shows an example of AB neurons that were silent prior to the application of dopamine, serotonin, or octopamine. In each case, the amines elicited strong bursting. Nonetheless, the underlying mechanisms of the bursts evoked by dopamine and serotonin differ significantly. The dopamine-elicited bursts depend strongly on underlying Ca^{2+} currents, and the slow wave persists in the presence of TTX and in reduced Na^+ saline (**Figure 3*b***) (Harris-Warrick & Flamm 1987). In contrast, TTX entirely suppresses the serotonin- and octopamine-elicited bursts, but these persist in low Ca^{2+} concentrations (**Figure 3*b***). These data are consistent with the different neuromodulators activating bursts that initially look the same but, by acting on different currents, result in bursts with different underlying mechanisms (Epstein & Marder 1990, Harris-Warrick & Flamm 1987).

Activity Can Alter the Effects of Neuromodulators

The R15 neuron of *Aplysia* fires in bursts that are strongly modulated by serotonin and ELH (egg-laying hormone) (Adams & Benson 1985) via mechanisms that depend on intracellular $[Ca^{2+}]$

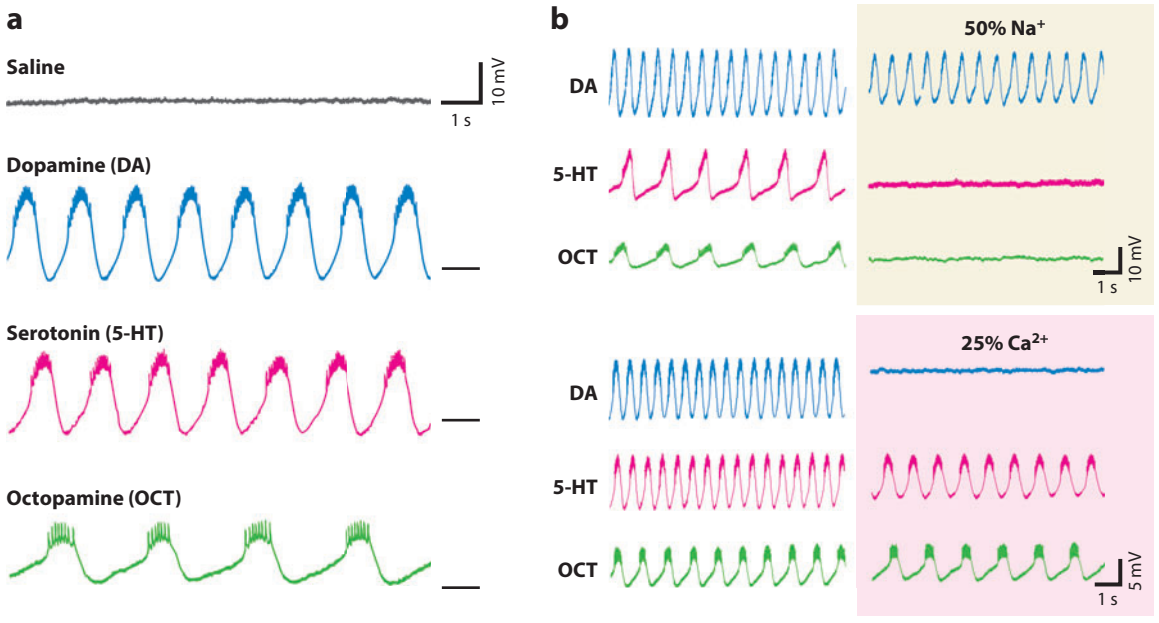


Figure 3

Convergence of distinct modulatory mechanisms on single-neuron behavior. (*a*) Neuromodulator-dependent induction of rhythmic bursting a pharmacologically isolated anterior burster (AB) cell in the stomatogastric ganglion in *Panulirus interruptus*. Shown are a saline (control) recording of a silent AB cell and bursting induced by bath application dopamine (100 μM), serotonin (10 μM), and octopamine (100 μM). Horizontal lines indicate the resting potential of the control recording. Figure adapted from Harris-Warrick & Flamm (1987, figure 1). (*b*) Manipulating extracellular cation concentration reveals distinct mechanisms of modulator-induced bursting. (*Top*) Left traces show recordings from the same isolated neuron in dopamine (100 μM), serotonin (10 μM), and octopamine (100 μM). The neuron was silent in the absence of a neuromodulator (not shown). Right traces show the same neuron in each modulatory condition, 5–7 min after Na^+ concentration was reduced to 50% by equimolar replacement with Tris. (*Bottom*) A separate experiment on a different isolated AB cell showing responses to dopamine (100 μM), serotonin (10 μM), and octopamine (100 μM) in control saline (*left traces*) and with Ca^{2+} replaced with equimolar Mg^{2+} (*right traces*). Figures adapted from Harris-Warrick & Flamm (1987, figures 4, 6).

and cAMP (cyclic adenosine monophosphate) (Kramer & Levitan 1990). Consequently, and as illustrated in one study (Kramer & Levitan 1990), changes in neuronal activity that influence intracellular [Ca^{2+}] also influence the modulation of R15 by serotonin and ELH. The general principle of this study is that the effects of any modulator that acts via second-messenger signal transduction pathways will be altered by any other synaptically or intrinsically driven processes that alter the states of those second-messenger systems (Yu et al. 2004). Because most neuromodulators act via second-messenger systems, researchers expect that modulator action will be constantly influenced by the ongoing activity patterns of the target neuron or muscle, which also modify the intracellular second-messenger pathways of the neuron, in a sense producing cross talk between modulator actions (Antonov et al. 2010, Braha et al. 1993, Yu et al. 2004). As a result, the same modulator may produce disparate responses in the same neuronal target (Spitzer et al. 2008).

When neuromodulators converge onto the same intracellular second-messenger pathways or onto the same membrane current, they may interact in interesting and nonlinear fashions (Brezina 2010). For example, in crustaceans, many peptide neuromodulators bind to different classes of receptors but eventually activate the same membrane current, I_{MI} (Golowasch & Marder 1992,

Swensen & Marder 2000). In this case, the effects of the modulators can saturate and occlude each other. In other cases, low concentrations of one modulator may enhance the actions of another because of the amplification steps engaged in signal transduction pathways.

MODULATION OF CIRCUITS

We know that modulators alter circuit function. In principle, this alteration could occur if a neuromodulator influenced only one or a few members of the circuit and if neurons which themselves are direct targets for modulation influenced the activity of other circuit neurons. Alternatively, a modulator may act on many, or most, of the neurons of a circuit in a more widespread fashion. Relatively few biological systems have been examined extensively enough to assess this uncertainty, but in the stomatogastric ganglion some modulators clearly act on many circuit neurons while others have more restricted cellular targets (Swensen & Marder 2001).

Modulation of Circuit Dynamics Can Be State Dependent

There are numerous examples in the literature of neuromodulatory actions that depend on the physiological state and initial level of activity in a network (Nadim et al. 2008, Nusbaum & Marder 1989, Weimann et al. 1997, Williams et al. 2013) and, presumably, on the circuit mechanisms that are responsible for those differences in activity. For example, the neuropeptide proctolin strongly increases the frequency of the pyloric rhythm of the crustacean stomatogastric ganglion (STG) when the initial frequency is low, but it has little or no effect on frequency when the starting frequency is high (Hooper & Marder 1987, Nusbaum & Marder 1989). In contrast, the inhibitory allatostatin peptides elicit little effect on robust pyloric rhythms but show much more dramatic effects when the starting frequency is lower (Skiebe & Schneider 1994, Szabo et al. 2011).

A recent modeling study at the circuit level (Gutierrez et al. 2013) makes many of the same points that we have made previously at the single-neuron level. This study examines the behavior of a five-neuron network (**Figure 4*a***), loosely inspired by the connectivity of the crab STG, and examines the circuit mechanisms that control the relative coordination of fast and slow oscillators connected through a hub neuron via electrical synapses (**Figure 4*a***) (Gutierrez et al. 2013). In the model circuit, the f1 and f2 neurons are fast oscillators and reciprocally inhibit each other. The s1 and s2 neurons are slow oscillators and also reciprocally inhibit each other. The f2 and s2 neurons are electrically coupled to a hub neuron (hn), which is also inhibited by the f1 and s1 neurons (**Figure 4*a***). This network can show many different behaviors, depending on the strengths of the electrical and chemical synapses in the network (**Figure 4*b***). Four of these behaviors are shown in **Figure 4*b***. In case 1, the f1, f2, hn, and s2 neurons are firing at the same frequency, whereas s1 is not following but instead firing every other cycle. In case 2, all five neurons are firing at the same frequency. In case 3, f1 is alone firing rapidly, but the other 4 neurons are firing slowly. In case 4, f1 and f2 are firing rapidly, but hn is firing with s1 and s2 in a slow rhythm.

The parameterscape (**Figure 4*c***) is a visualization tool that displays the relative behaviors possible for this five cell circuit as the strength of the electrical synapse (g_{el}) and chemical synapse from f1 and s1 to the hn (g_{synA}) is varied. The locations in parameter space of the four examples in **Figure 4*b*** are labeled as points in the parameterscape, and the distinct frequency relationships can be read off. This visualization demonstrates clearly how different forms of network coordination emerge as a function of changes in parameters.

State dependence of modulation is easily seen using the arrows in **Figure 4*c***. Modulator A increases the strength of g_{synA}. At some starting values of parameters, even a small change in g_{synA} can bring the network across boundaries of qualitative network behavior. For example, if

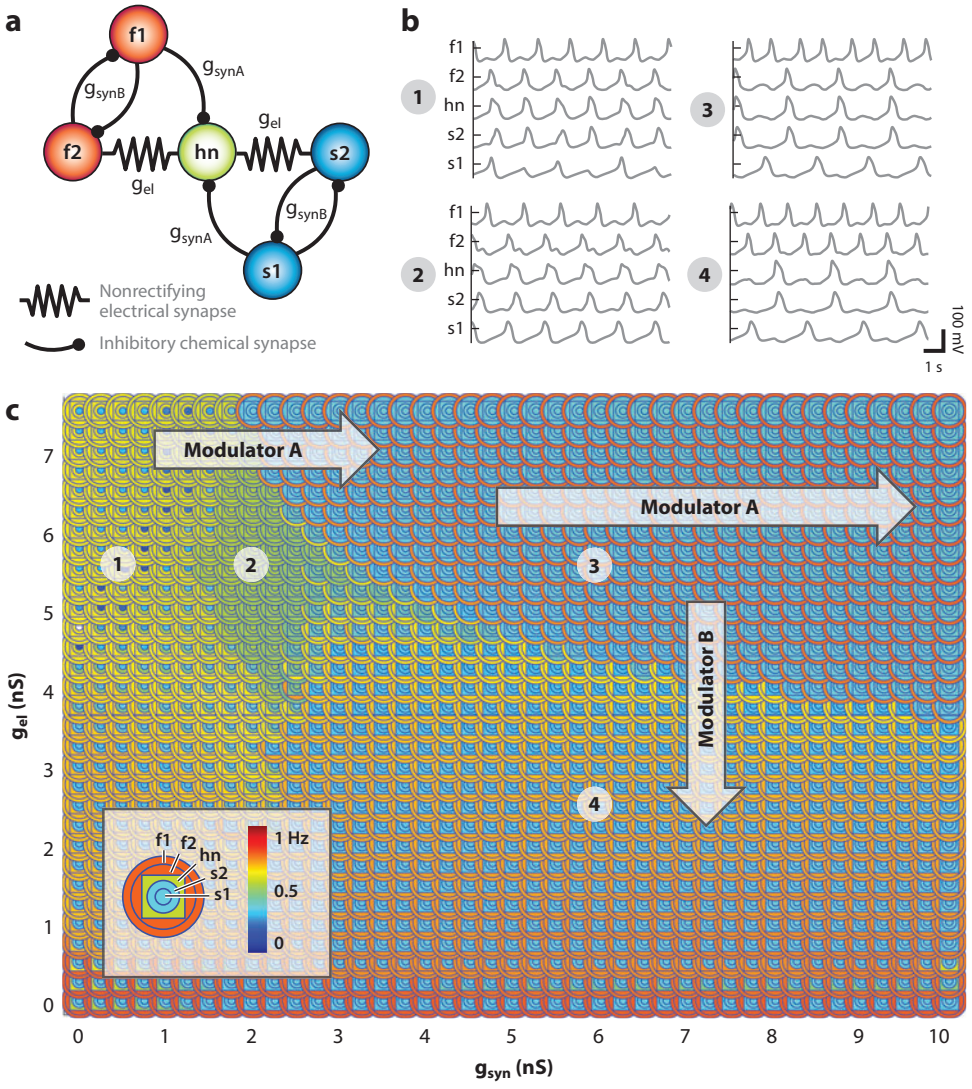


Figure 4

A simple conductance-based model rhythm-generating network captures general principles of neuromodulation in small circuits. (*a*) Model circuit diagram from Gutierrez et al. (2013). Each neuron is a conductance-based oscillating Morris–Lecar model neuron. Synaptic connections are graded, inhibitory chemical synapses (*black blobs*, g_{syna}, g_{synb}) or nonrectifying electrical synapses (resistor symbols, g_{el}). The intrinsic properties of the neurons are tuned to produce two identical fast-bursting cells (f1, f2), two slow cells (s1, s2), and an intermediate-frequency hub neuron (hn); see reference for full simulation details. (*b*) Example circuit activity for different combinations of synaptic parameters g_{syna} and g_{el} as indicated in the parameter map (panel *c*). (*c*) Parameter map, or parameterscape, encoding circuit output as a function of two of the synaptic conductance strengths, g_{syna} and g_{el}. Each symbol in the parameterscape shows the bursting frequency of the five neurons in the circuit in a color-coded ring, as shown in the legend. The hub neuron is represented as a concentric square. Arrows indicate putative modulatory changes in circuit parameters.

we start in region 1, in which all neurons but s1 are active together and s1 is left behind at a much lower frequency, a relatively modest increase in g_{synA} brings the network into an entirely different coordination mode in which all neurons but f1 are slow. But, a much larger change in g_{synA} elicited by modulator A does not alter the network coordination (starting in region 3). In contrast, a relatively small change in g_{el} elicited by modulator B crosses the boundaries between areas of different network coordination (**Figure 4*c***).

This kind of state dependence of modulator action on network coordination can be seen in biological systems. **Figure 5*a*** shows the connectivity for the ~27 neurons of the STG of the crab, *Cancer borealis*. Two distinct rhythms coexist in the STG: the pyloric rhythm and the slower gastric rhythm. Some cells in the STG are capable of participating in both rhythms. When the neuropeptide CCAP was applied to two different preparations (with different starting levels of activity), the IC neuron fired in time with either the fast pyloric rhythm (preparation 1) or the gastric mill rhythm (preparation 2) (Weimann et al. 1997).

Degenerate Modulation of Circuits

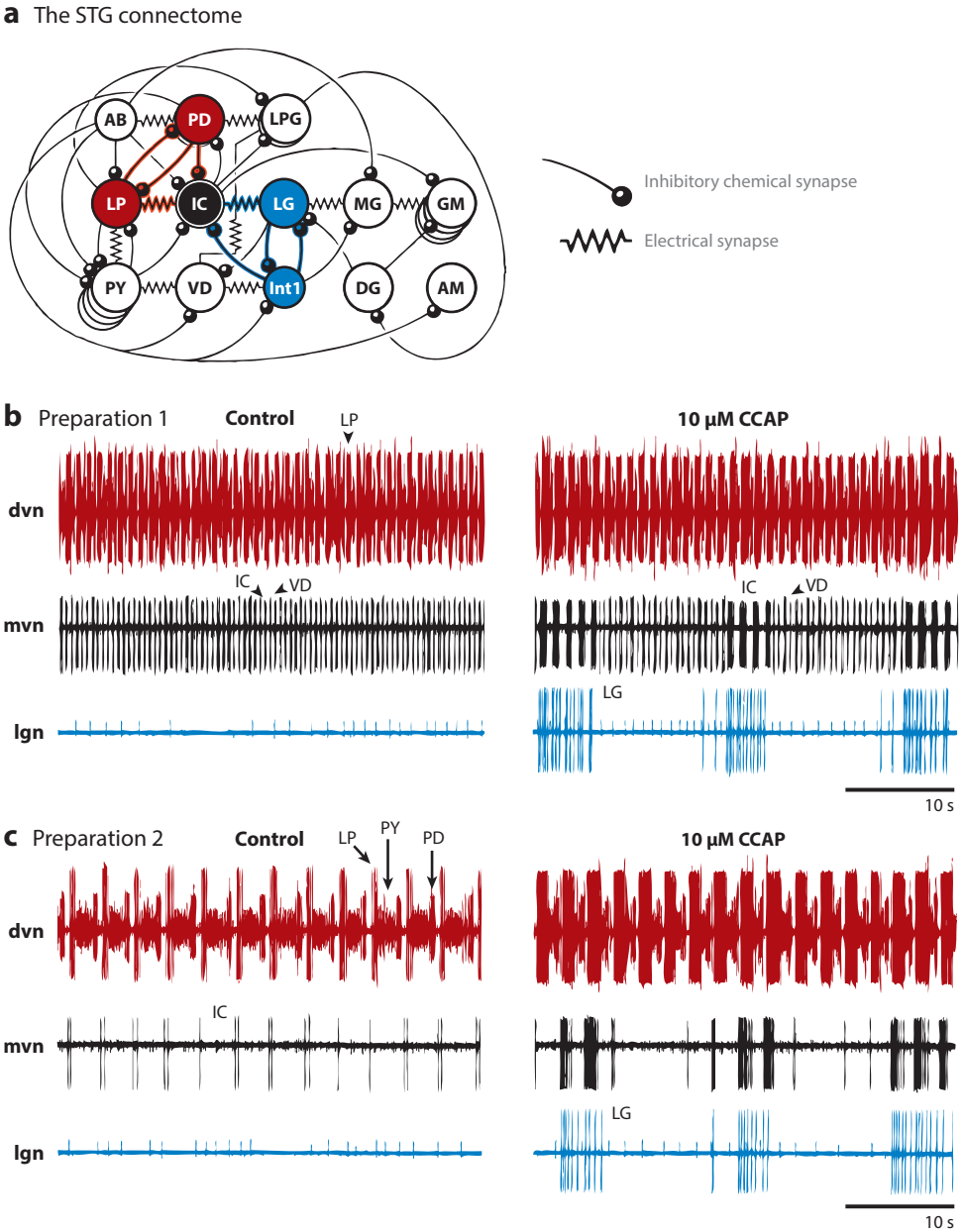
Modulators can act in numerous ways on neuronal circuits to produce changes in circuit dynamics that resemble each other but arise from quite different circuit mechanisms (Beverly et al. 2011, Gutierrez et al. 2013, Kintos et al. 2008, Nadim et al. 2008, Rodriguez et al. 2013, Saideman et al. 2007a). For example, in *C. elegans*, robust thermosensory behaviors depend on different circuit configurations at different temperatures, and neuromodulation plays a crucial role in setting the temperature range of these circuits and thus their behavior (Beverly et al. 2011). Similarly, octanol avoidance can be generated by different sets of sensory neurons (Chao et al. 2004) depending on modulatory status (Harris et al. 2010, Mills et al. 2012, Wragg et al. 2007), which in turn depends on whether the animal is starved or fed.

In the stomatogastric nervous system, very similar gastric mill rhythms are elicited by two different manipulations: activation of the specific modulatory projection neuron MCN1, or bath application of the neuropeptide CabPK (**Figure 6**). The network mechanisms engaged by these two treatments are shown schematically. In the MCN1 activated rhythm, DG (the dorsal gastric cell) is not necessarily activated, and the AB inhibition of Int1 is not required (**Figure 6*a***). In contrast, CabPK application activates DG, and the AB inhibition of Int1 is necessary for this rhythm (**Figure 6*b***) (Kintos et al. 2008; Rodriguez et al. 2013; Saideman et al. 2006, 2007a,b). Although the previous work shows that similar gastric rhythms can be generated by different circuit mechanisms, different forms of the gastric rhythm can also be activated by stimulation of various sensory inputs, and several of these employ the same core circuitry (White & Nusbaum 2011).

Behavioral Selection by Neuromodulation

Understanding how animals use internal state and sensory inputs to produce one behavior or another or different forms of related behaviors is a fundamental problem in neuroscience (Briggman & Kristan 2008, Flavell et al. 2013, Kristan 2008, Palmer & Kristan 2011, Taghert & Nitabach 2012). In many instances, behavior choice depends on changes in internal states that are produced by activating specific sets of neuromodulatory inputs (Friesen & Kristan 2007; Jing et al. 2007, 2008; Wagenaar et al. 2010; Wu et al. 2010). The previous history of activation of some network elements can produce what has been termed latent modulation, a change in the way the network responds to a subsequent stimulus (Dacks & Weiss 2013), as shown in the *Aplysia* feeding network. Buccal motor outputs can be either ingestive or egestive (Jing & Weiss 2001),

depending on which sets of higher-level interneurons are activated (Morgan et al. 2000, 2002); however, prestimulation of the input CBI-2 can enhance both subsequently evoked ingestive and egestive behaviors, although these behaviors are mutually exclusive (Dacks & Weiss 2013). This observation is similar to that seen in *C. elegans*, where a G protein–coupled receptor, npr-1, can affect two behaviors elicited by the same sensory neuron (Bargmann 2012) and neuropeptides can alter the responses of olfactory neurons (Chalasani et al. 2010).



OPEN QUESTION: DOES NEUROMODULATION POSE A SPECIAL PROBLEM FOR HOMEOSTATIC REGULATION OF EXCITABILITY AND SYNAPTIC STRENGTH?

A large and growing body of both computational and experimental work argues that the number and distribution of ion channels and receptors expressed by neurons are regulated so that neurons maintain an activity level appropriate to their network function (Baines et al. 2001; Davis 2006; LeMasson et al. 1993; Liu et al. 1998; O'Leary et al. 2010, 2013; O'Leary & Wyllie 2011; Pratt & Aizenman 2007; Pratt et al. 2003; Turrigiano 2008, 2011). This raises a potential problem: Can neuronal excitability or network parameters be tuned so that multiple different neuromodulatory substances, which can be thought of as a variety of different perturbations, alter network performance in the desired direction? Possible answers to this question are illustrated in **Figure 7**, which shows a cartoon of how circuit output depends on two network parameters such as synaptic or intrinsic conductances.

The hypothetical circuit produces two distinct, behaviorally important motor patterns: a motor pattern associated with a basal unmodulated state, A, and a distinct "modulated" state, B. In keeping with experimental observations, the circuit parameters across a population of individuals show variability (Goaillard et al. 2009), and the parameters in each case have been tuned by some activity-dependent process to maintain the unmodulated circuit in the basal state. But what is needed to ensure that a modulator with specific cellular actions will produce a reliable change in behavior across individuals? The problem is posed in **Figure 7*a***. Here, the same modulatory action fails to produce similar responses to all the individuals with similar starting behavior. Note that in some cases the modulator brings the network across its state boundaries, but in other cases it fails to do so.

This problem may be solved in two distinct ways. One possibility is shown in **Figure 7*b***. In this case, the modulatory effect is not specifically tuned in each individual (arrows are all identical), but the circuit parameters are restricted to portions of the parameter space that will allow the modulator to produce its appropriate action. This case requires the regulatory mechanism to somehow sense how far each circuit is from the transition and tune the circuit parameters such that the modulator reliably pushes the circuit through a transition. Alternatively, both the circuit parameters and the modulator effect could be coordinately tuned (**Figure 7*c***). This possibility would predict differences in how individual circuit parameters respond to a modulator because the length and direction of the arrows need to differ. Such a model is consistent with the variable effects observed in modulator-induced membrane currents across different individual preparations (Goaillard et al. 2009). However, we do not know how the cellular mechanisms in the circuit sense

Figure 5

Identical neuromodulatory manipulations in the same circuit can produce distinct physiological changes in different animals. (*a*) The connectivity diagram, or connectome, of the stomatogastric ganglion (STG) in *Cancer borealis*. On the left are the neurons that routinely participate in the faster pyloric rhythm, and on the right are neurons that routinely participate in the slower gastric mill rhythm. The five neurons shown in color are in the configuration modeled in **Figure 4**, with the inferior cardiac (IC) neuron in the hn position. (*b*) Extracellular recordings of the dorsal ventricular nerve (dvn, *red*), the median ventricular nerve (mvn, *black*), and the lateral gastric nerve (lgn, *blue*). Cells in panel *a* are colored according to their respective output nerve; bursts of action potentials from each of the cells are indicated. Bath application (10 μM) of the endogenous neuropeptide CCAP (Stangier et al. 1987) induces a version of the slow gastric rhythm evident in the bursts of action potentials in the lgn and a modulating envelope of activity in the mvn (*right*). Adapted from Weimann et al. (1997, figure 2). (*c*) Similar to panel *b* but in a different preparation. A distinct version of the gastric rhythm is induced by CCAP application under identical recording conditions.

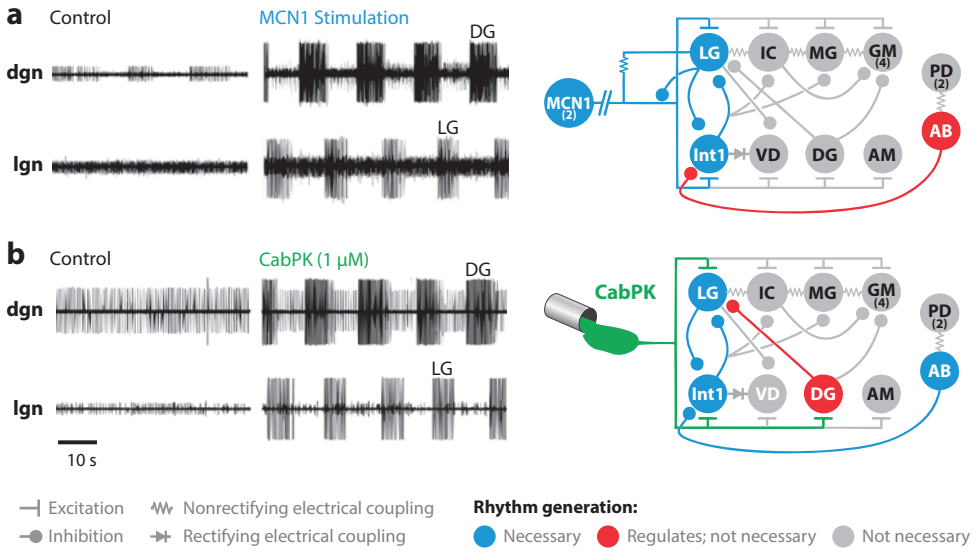


Figure 6

Distinct modulatory mechanisms can converge on the same transition in circuit behavior. (*a*) The gastric mill rhythm can be induced by stimulating the modulatory projection neuron MCN1, as seen in the slow rhythm induced in the extracellular recordings of the lateral and dorsal gastric nerves (lgn and dgn, respectively). (*Right*) A schematic of the gastric mill circuit configured by MCN1 stimulation. In this case, modulatory input by MCN1 excites LG and Int1, inducing bursting. Circuit symbols: excitation (*t-bars*); inhibition (*filled circles*); nonrectifying electrical coupling (*resistors*); rectifying electrical coupling (*diode*). Parallel lines crossing the MCN1 axon represent additional anatomical distance between the MCN1 soma and its axon terminals in the STG. Numbers in parentheses indicate the cell copy number per nervous system for each neuron type when there is more than one neuron. (*b*) Bath application of the neuropeptide CabPK (10 μM) elicits the same gastric mill motor pattern as does MCN1 stimulation but via a distinct circuit configuration (*right*) in a different preparation. In this case, CabPK excites LG, Int1, and DG, and AB activity is necessary for a gastric rhythm. Adapted from Saideman et al. (2007a) and Rodriguez et al. (2013).

deviations from desired modulator effects and which plasticity mechanisms or learning rules exist to shape the modulatory response itself.

A single desired output from a neuron or network can result from multiple sets of conductance parameters (Goldman et al. 2001, Golowasch et al. 2002, Prinz et al. 2004, Taylor et al. 2009), but not all these solutions will respond to a given neuromodulatory influence in the same way (Szücs & Selverston 2006). The space of reliable responses may still be large (**Figure 4**), and achieving reliable modulation may be mitigated by restricting the solutions that biological circuits tend to find during development (Grashow et al. 2009). Nonetheless, the requirement to respond appropriately to neuromodulation adds a constraint to the set of solutions that homeostatic tuning processes should find. Another possibility is that the neuromodulatory receptors and their downstream signaling pathways are themselves tuned to the particular cells and circuits in which they function. If the latter is true, we must then ask how this tuning signal is encoded and what mechanisms underlie the regulation of the modulator receptors and signaling components.

Some neuromodulatory influences, such as those that occur daily or every several hours during feeding or sleep/wake transitions (Lee & Dan 2012, van den Pol 2012), may produce changes in activity on timescales that are relatively rapid compared with slower homeostatic tuning processes. In this case, the changes in activity produced by modulation would contribute directly to the signals

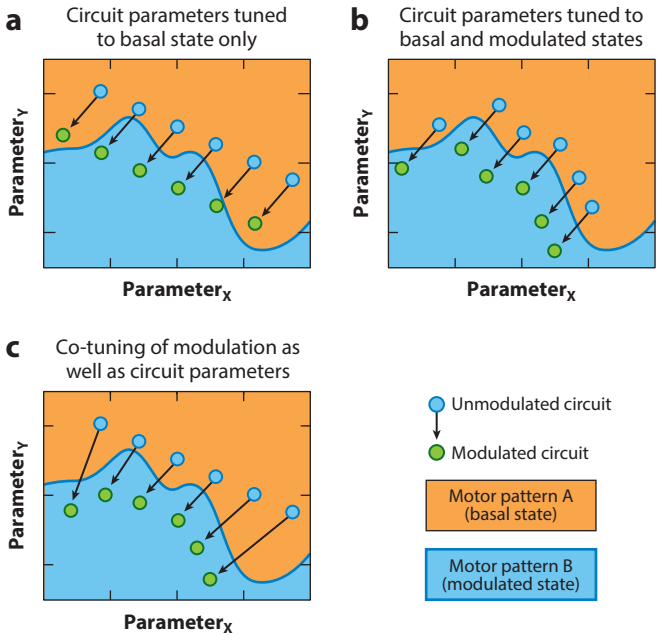


Figure 7

How are neuromodulator actions tuned to produce reliable behavioral switches in variable circuits whose components are homeostatically tuned? Shown are cartoons of parameter space for a motor circuit in which two behaviorally important activity patterns (A and B) can be produced by modulating two parameters, X and Y (e.g., synaptic or intrinsic conductances). Green points depict the unmodulated parameters, which have been homeostatically tuned to produce a basal output (pattern A). Arrows indicate a quantitative change in both parameters that is produced by a neuromodulator or group of modulators that are responsible for switching activity to motor pattern B. (*a*) A scenario in which unmodulated circuit parameters are tuned, but the magnitude and direction of the modulatory change are not. (*b*) An alternative scenario in which circuit parameters are tuned to give basal output, but in a way that guarantees reliable transition to the modulated state without tuning the effect of the modulator. (*c*) A final scenario in which parameters as well as the modulatory effects are tuned to reliably switch each instance of the network from pattern A to pattern B.

used by neurons as they regulate their conductance densities, and one can imagine that modulator receptors together with their downstream targets can be coregulated. The problem becomes much more challenging when a network must respond appropriately to a modulatory state that is rare or intermittent. In that case, one must suppose that evolutionary pressures constrain the set of solutions available to the homeostatic tuning processes to those that will allow the modulatory processes to move circuit performance in the desired direction. In the absence of such constraints, one imagines that brain disorders such as mental illness and seizures might be far more common than they are.

CONCLUDING REMARKS

We know that neuromodulators are responsible for producing the circuit configurations that evoke specific behaviors. But we are only starting to understand some of the mechanisms that control the neuromodulatory complement of individual neurons (Birren & Marder 2013, Dulcis et al. 2013) and how the release of modulatory substances is controlled (van den Pol 2012). These processes need to be well matched with the processes that control the properties of the target

circuits. A remaining challenge is to understand how this matching occurs and thus how networks can function reliably in response to their rich neuromodulatory control systems.

In the examples we have discussed, a common set of themes has emerged. First, modulators act by altering parameters of single neurons and synapses and, consequently, circuits. Second, synaptic and intrinsic membrane parameters themselves vary by organism. Third, how membrane currents and synapses interact means that modulation can exhibit state dependence and nonlinearities. These principles are likely common to all nervous systems, from small to large. A major set of challenges is to understand how nervous systems can operate in basal conditions and respond appropriately to many neuromodulatory perturbations in spite of having intrinsically variable components.

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Contents

Indexes

Errata

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