New insights from small rhythmic circuits

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Perspective

New insights from small rhythmic circuits

Eve Marder, Sonal Kedia and Ekaterina O. Morozova

Abstract

Small rhythmic circuits, such as those found in invertebrates, have provided fundamental insights into how circuit dynamics depend on individual neuronal and synaptic properties. Degenerate circuits are those with different network parameters and similar behavior. New work on degenerate circuits and their modulation illustrates some of the rules that help maintain stable and robust circuit function despite environmental perturbations. Advances in neuropeptide isolation and identification provide enhanced understanding of the neuromodulation of circuits for behavior. The advent of molecular studies of mRNA expression provides new insight into animal-to-animal variability and the homeostatic regulation of excitability in neurons and networks.

Addresses

Volen Center and Biology Department, Brandeis University, Waltham, MA 02454, USA

Corresponding author: Morozova, Ekaterina O. (morozova.e.o@gmail.com)

(Kedia S.)

(Morozova E.O.)

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Introduction

Many early researchers who wished to understand how circuit dynamics arise from the properties of neurons and their synaptic connections turned to small rhythmic circuits found in invertebrates [1], and this continues today [2**]. While these circuits were initially called 'simple' it became apparent that despite having small numbers of neurons, nothing about them was simple. Indeed, many fundamental principles, now clearly relevant to larger circuits, came first from small, invertebrate circuits. The explosion of new technologies tantalizes us with the hope that the secrets of how larger brain circuits work will reveal themselves. We highlight new insights that are still coming from small circuits of well-identified neurons. Today, as in the past, it is the ability to unambiguously identify neurons, and then establish their connectivity, that is crucial for understanding how a circuit works. A recognizable and well-defined output pattern can be key for interpreting the results of circuit perturbation, so much of what we discuss comes from rhythmically active central pattern generating circuits, with their easily measurable functional outputs.

Space limitations force us to make difficult choices about papers and topics. Notably, we have not treated the large topics of developmental reconfigurations [3*], the use of small circuits in the design of robotic controllers, or much valuable work from *Drosophila* [4**], *C. elegans* and other preparations.

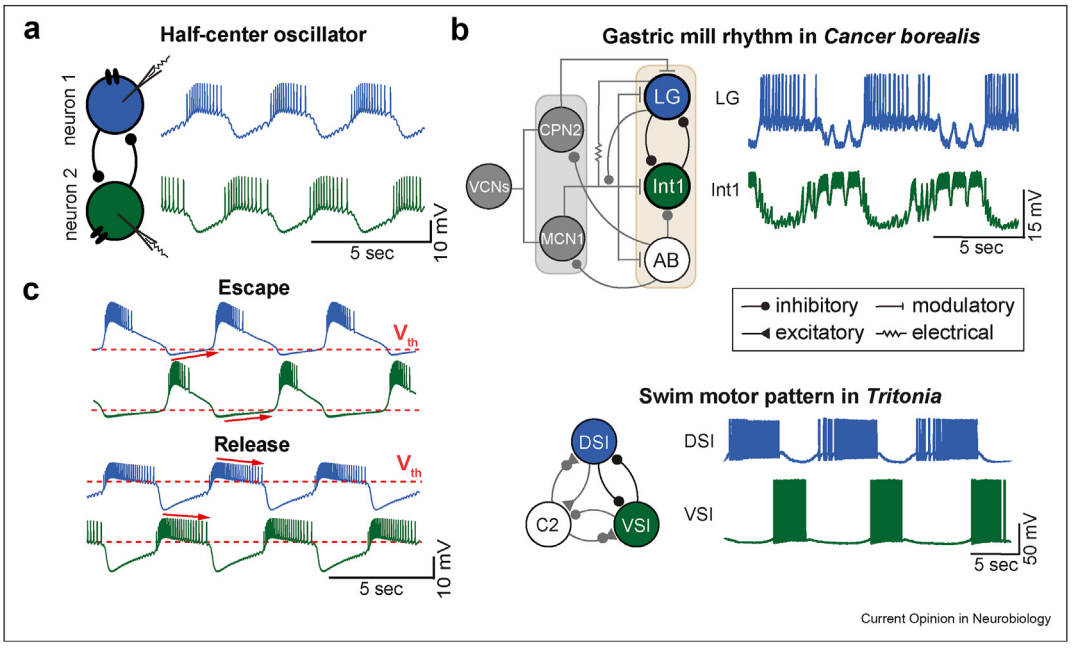
Reciprocal inhibition and half-center oscillators

Reciprocal inhibition was one of the earliest circuit elements recognized, both for its role in contrast enhancement in the *Limulus* retina [5] and for controlling alternating patterns of activity in movement [6]. Here, we focus on work on reciprocal inhibition in rhythmically active invertebrate circuits (Figure 1) although there is an important literature in the spinal cord of developing and adult vertebrates [7,8].

Reciprocal inhibition is at the core of left-right alternation in many motor systems such as *Clione* [9], *Dendronotus*, and *Tritonia* [10–12] swim circuits and the leech heartbeat system [13–19]. In some systems, the two neurons that participate are copies of the same neuron and can be loosely thought of as 'identical' although no two biological neurons are ever truly identical (Figure 1a). In other instances, more complex circuits have embedded motifs of reciprocal inhibition between neurons of different cell types, and these neurons may make and receive different sets of synaptic inputs (Figure 1b).

Early theoretical work [20] defined two distinct mechanisms that can account for the activity transitions between the two reciprocally inhibitory neurons in a half-center oscillator. In the escape mode the off-on transition depends on the inhibited cell depolarizing past its synaptic threshold (Figure 1c). In the 'release' mode the on/off transition depends on the active neuron falling below its synaptic threshold

Figure 1



Network based reciprocal inhibition. a) Schematic of a half-center network consisting of two neurons connected by reciprocally inhibitory synapses. Traces in blue and green demonstrate the alternating bursting pattern of activity generated by such networks. **b)** Half-center oscillators are the building blocks of many CPGs. Top: a simplified circuit diagram of the gastric circuit of *Cancer borealis* with a half-center oscillator between LG and Int1 neurons forming its core. Intracellular recordings from LG and Int1 showing an alternating bursting pattern of activity. Figure is modified from [106]. Bottom: a circuit diagram of the *Tritonia* swim CPG, consisting of three types of interneurons: cerebral cell (C2), dorsal swim interneuron (DSI) and ventral swim interneuron (VSI) connected with reciprocal inhibitory and excitatory connections. To the right of the diagram are the intracellular recordings from DSI and VSI showing an alternating bursting pattern of activity. Figure modified from [12]. **c)** Example traces from half-center oscillators built with dynamic-clamp operating with either escape (top) or release (bottom) mechanism based on differences in the synaptic threshold (V_{th}) Figure modified from [23*].

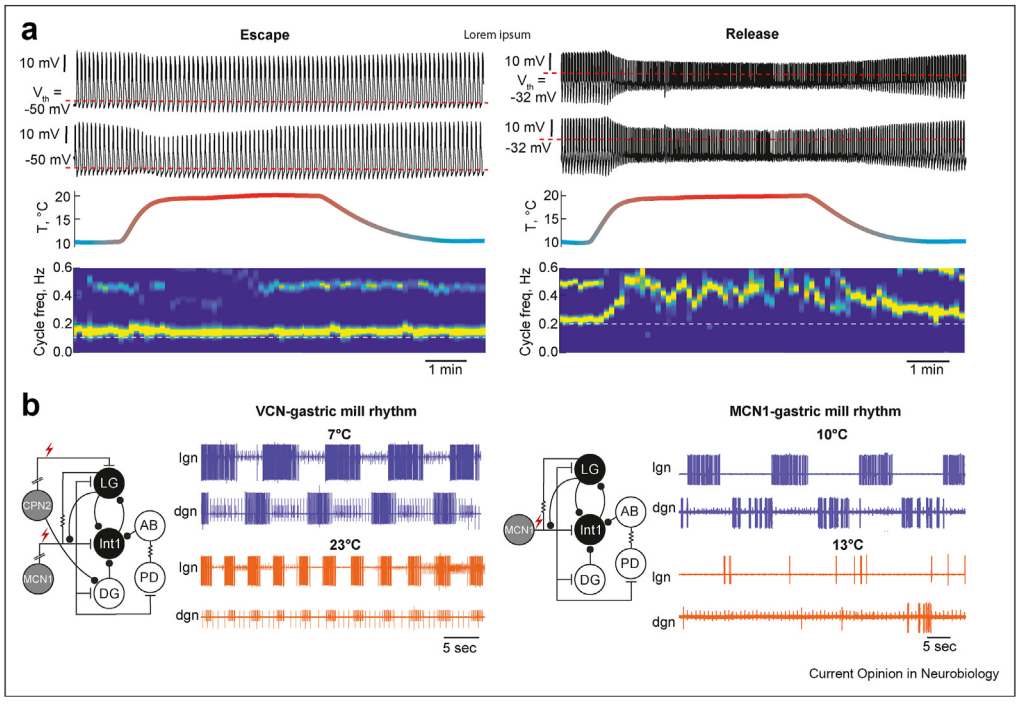
(Figure 1c). While these two modes can be rigorously distinguished in theoretical work, often transitions show mixed modes of activity [21].

A recent theoretical study is among the first to address the dynamics that can occur in half-center oscillators composed of neurons with different intrinsic properties [22**]. In this study the authors generated a series of model networks with a variety of conductances, characterized their stability, and attempted to find correlation motifs associated with that stability. For example, altering I_A and I_{Cas} in opposite directions results in similar effects on circuit stability, and decreasing I_H produces losses of rhythmicity. Understanding the relationship between half-center parameters and circuit stability to perturbation is the subject of another recent paper on half-center oscillators [23*]. In this work, the authors used the dynamic clamp to construct half-center oscillators from biological neurons, as has been done previously [24–26] but examined extensively the differential responses of half-centers in release and escape modes to perturbations [23*].

Figure 2 illustrates that the mechanism of oscillation strongly influences the response of the network to perturbation, in this case temperature. Figure 2a compares the responses of dynamic-clamp constructed half-centers in escape and release modes to a 10 °C increase in temperature [23*]. In the left panel, the raw physiological traces show that the temperature change only modestly altered the activity of the circuit in the escape mode, as is seen by the almost invariant cycle frequency illustrated in the spectrogram at the bottom. In contrast, in the right panel, when the circuit is in the release mode, the temperature increased the frequency of the half-center and made its activity more irregular, seen in the spectrogram.

Figure 2b contrasts the effects of temperature on two forms of the gastric mill rhythm of the stomatogastric ganglion (STG) [27*,28]. These two forms of the rhythm share the strong reciprocal inhibition between LG and Int1 (see connectivity diagrams) but are activated by stimulation of different descending modulatory neurons. While these two modes of activation are degenerate in the sense that they both activate rhythms characterized by alternation between the DG and LG neurons (Figure 2), they are differentially robust to temperature changes (Figure 2b). At control temperatures they show similar properties (Figure 2b), but the

Figure 2



Temperature robustness of small rhythmic circuits. a) Response of reciprocally inhibitory circuits with escape and release mechanisms and temperature-independent synaptic and H currents to an increase in temperature. Top panels show membrane potential oscillations of two neurons forming half-center oscillators in escape (left) and release (right) during a temperature step. Middle panel shows the saline temperature. Bottom panels show the spectrograms of the first neuron's voltage traces in both right and left panels. Bright yellow band corresponds to the cycle frequency of oscillations. Modified from [23*]. **b)** Differential sensitivity of gastric mill rhythms generated by stimulation of disparate modulatory pathways to an increase in temperature. Left panel: A simplified circuit diagram of VCN-gastric mill rhythm and corresponding extracellular recordings of the lateral gastric nerve (lgn) and the dorsal gastric nerve (dgn) showing robust firing of LG and DG neurons during gastric mill rhythm evoked by stimulation at 7 °C and 23 °C. From [27*]. Right panel: A simplified circuit diagram of MCN1-gastric mill rhythm and corresponding extracellular recordings of lgn and dgn showing firing of LG and DG neurons during gastric mill rhythm evoked by stimulation at 10 °C and sporadic firing of these neurons at 13 °C. From [28]. Circuit symbols defined as in Figure 1.

MCN1 activated rhythm is less robust, and 'crashes' at lower temperatures. There are a number of potential explanations for this: 1) different descending pathways activate circuits operating by different mechanisms [23*] and 2) the strength of the modulatory drive evoked in one pattern of stimulation is significantly higher than the other [29], as we know that activation of a modulatory current can restore oscillatory activity to a release half-center circuit that has lost activity at high temperatures [23*]. Moreover, we know that some neuropeptides can increase the temperature range of stable pyloric rhythm activity [30,31**] and gastric mill activity [32].

Recent work in the leech heartbeat system has focused on the roles of I_H and the Na^+/K^+ pump on the range of stable alternating half-center patterns of activity [19**]. This work combines computational and experimental data to argue that comodulation of multiple processes is more effective at extending functional operating ranges than modulation of a single current or process.

Additional effects of environmental influences on neurons and circuit mechanisms

The previous section focused on the effects of temperature on half-center driven circuit mechanisms. There is a growing literature on other aspects of the effects of temperature and other environmental influences on small circuits. A recent study documents unexpected blue-light responses of neurons in the crab STG that may allow the animal to be sensitive both to its depth and the time of year [33**]. Stein and Harzsch [34**] provide an excellent review of changes in ocean environments and the effects of these changed environments on the appreciable contribution of marine crustaceans to the earth's biomass. Most notable are the well-known effects of increased sea water temperature and decreased mean ocean pH [34**], with concomitant changes in dissolved O_2 levels. In most cases, the effects of oxygen, temperature, and pH on isolated crustacean circuits have been studied in isolation [35–37], while in the wild, these

effects are linked, as pH and oxygen levels vary as a function of ocean temperature [38**]. The obligatory metabolic trade-offs of the biological compensations that occur as animals live close to their temperature limits [38**] highlight the importance of understanding the compensatory mechanisms that neurons and circuits employ to cope with multiple stressors, and the interactions among those multiple stressors. For example, a recent study on the pyloric pacemaker neurons [39*] showed that loss of bursting activity follows different dynamical mechanisms in response to extremes of temperature and pH.

Faria et al. [38**] argue that animals die at extremes of temperature when their metabolic demands become too extreme. The effects of temperature extremes on neuronal and circuit robustness are revealed with *in vitro* experiments in dissected preparations and continuously exchanged saline [27*,30,37,40,41*]. When the effects of temperature were studied on the pyloric rhythm of crabs, the isolated *in vitro* and the *in vivo* rhythms were almost indistinguishable over the temperatures most commonly encountered in the wild, but at higher temperatures, the *in vivo* and *in vitro*-recorded rhythms diverged [42]. A recent study, DeMaegd and Stein [41*] studied the effects of temperature on axonal conduction velocity in three identified motor neurons from the crab, *C. borealis* and showed that temperature has a modest effect on propagation and spike timing in different axons.

Degenerate mechanisms in small circuits

There is a growing literature that suggests that circuits can have degenerate solutions, that is similar looking behavior with different underlying parameters across individuals [12,43,44,45,46,47**,48,49,50**,51*]. While it is often assumed that genetically identical animals produce similar behavior, this turns out not to be invariably the case. There are numerous studies in worms, flies, fish, and mice, that indicate that genetically identical animals show behavioral diversity similar to that shown in wild-caught animals [52*,53,54,55**, 56]. Moreover, repeated performance of the same task is often associated with variable activity in the network generating this task [57**]. New work in *Aplysia* suggests a plausible set of synaptic mechanisms that can account for some of this variability [57**].

Although degenerate mechanisms exist and can produce similar motor patterns, because of the differences in their underlying parameters, these solutions are differentially sensitive to extreme perturbations such as those described in the previous section [31**,58,59*]. An example of this is seen in a recent study in *Aplysia* that illustrates that some changes in task switching can only occur from one of the possible, seemingly degenerate network states [51*]. Moreover, evolutionary studies illustrate that similar motor patterns can result from different connectivity patterns and that seemingly similar looking connectivity can result in differences in behavior [60].

Neurons that switch among networks

Neurons can switch their participation between networks [48,51*,61,62,63,64,65,66], in some cases as a function of modulation of synaptic strength [48,61]. New studies [67**,68*] address the regulation of intrinsic properties in switching [67**,68*].

Fahoum and Blitz [67**] studied the effects of modulatory neuron activation on switching of neurons between the fast pyloric and slower gastric mill rhythms of the STG of the crab (Figure 3a). Specifically, the LPG neuron switches its participation from exclusively the pyloric rhythm, to being part of the gastric mill rhythm as modulatory inputs are activated. Nonetheless, hyperpolarization of other gastric mill neurons does not prevent this switching, arguing that it does not depend on specific synaptic inputs from other neurons [67**].

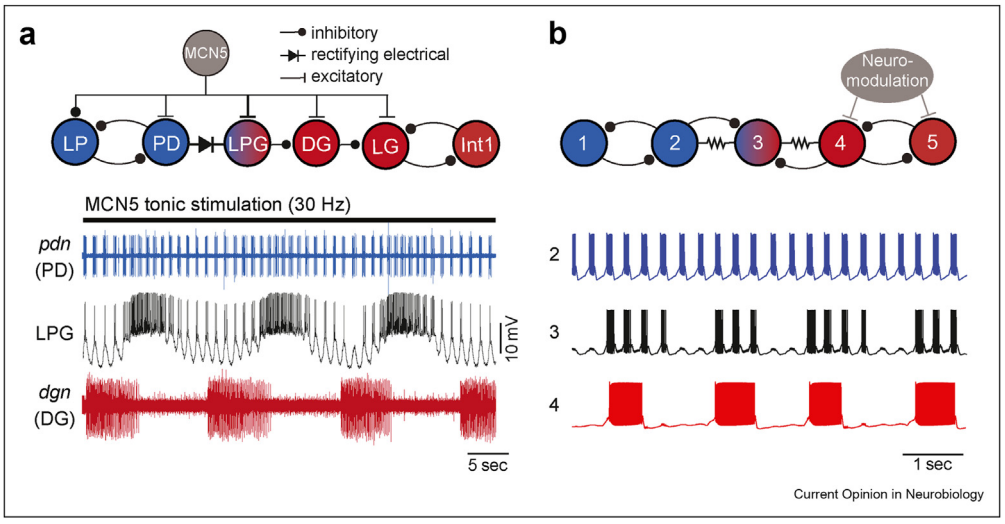
Drion et al. [68*] is a computational study (Figure 3b) that builds on earlier work [48], and illustrates that the properties of half-center oscillators are strongly influenced by the presence of a slow negative conductance. Moreover, a five-cell circuit with the same architecture as Gutierrez et al. [48] shows increased stability and switching between fast and slow behaviors that depend on the presence of the slow negative conductance gated by modeling neuromodulatory inputs [68*].

Neuropeptide and amine modulation of small circuits

All circuits are subject to neuromodulation. Studies on small circuits have revealed extraordinary richness in modulatory systems and showed that most modulatory neurons release several cotransmitters, including neuropeptides and small molecules [69,70] (Figure 4). One of the challenges in understanding the organization of neuromodulatory systems is to quantitatively characterize the varieties of motor patterns evoked under different modulatory conditions. A new paper [71**] uses unsupervised dimensionality reduction methods to characterize the dynamics of ordered, disordered and modulated STG rhythms (Figure 4b).

While comodulation is likely the rule rather than the exception in the regulation of many networks, comodulation systems are often difficult to study rigorously. A new study [72**] quantitatively compares the actions of several peptide neuromodulators on synaptic strength and intrinsic excitability. By looking at single and dual applications of two peptides (CCAP and proctolin) on the same target neurons, the authors establish that the actions of the cotransmitters appear to add linearly on

Figure 3



Modulation of intrinsic properties enables switching between networks. a) A simplified circuit diagram of fast (pyloric) and slow (gastric) networks with a lateral posterior gastric (LPG) neuron in the middle that switches between the networks based on the neuromodulatory conditions. Top trace: extracellular pyloric dilator nerve (pdn) recording PD neurons spikes marking the pyloric rhythm; middle trace: an example intracellular trace of the LPG neuron showing dual pyloric and gastric mill-timed bursting during the stimulation of the projection modulatory commissural neuron 5 (MCN5); bottom trace: extracellular dgn recording with dorsal gastric (DG) neuron spikes marking the gastric rhythm. Figure modified from [67**]. **b)** A simplified network inspired by the crustacean pyloric and gastric networks represented by two half-center oscillator circuits generating fast and slow rhythms coupled with a hub neuron, following precedent of [48]. Circuit neurons include a slow negative conductance and are weakly connected. Voltage traces of model neurons 2 (fast or pyloric), 3 (hub) and 4 (slow or gastric), from top to bottom (courtesy of Guillaume Drion).

the synaptic strengths, but not so when looking at a voltage-dependent intrinsic current [72**].

Many modulators act on voltage-dependent currents, or themselves have voltage-dependent actions. Consequently, modulators may display a number of state-dependent actions [73*], including an interaction between the frequency of the action of the target network and the modulator action (Figure 4c). Figure 4d shows that the effects of a modulator can depend critically on the mechanisms underlying circuit function.

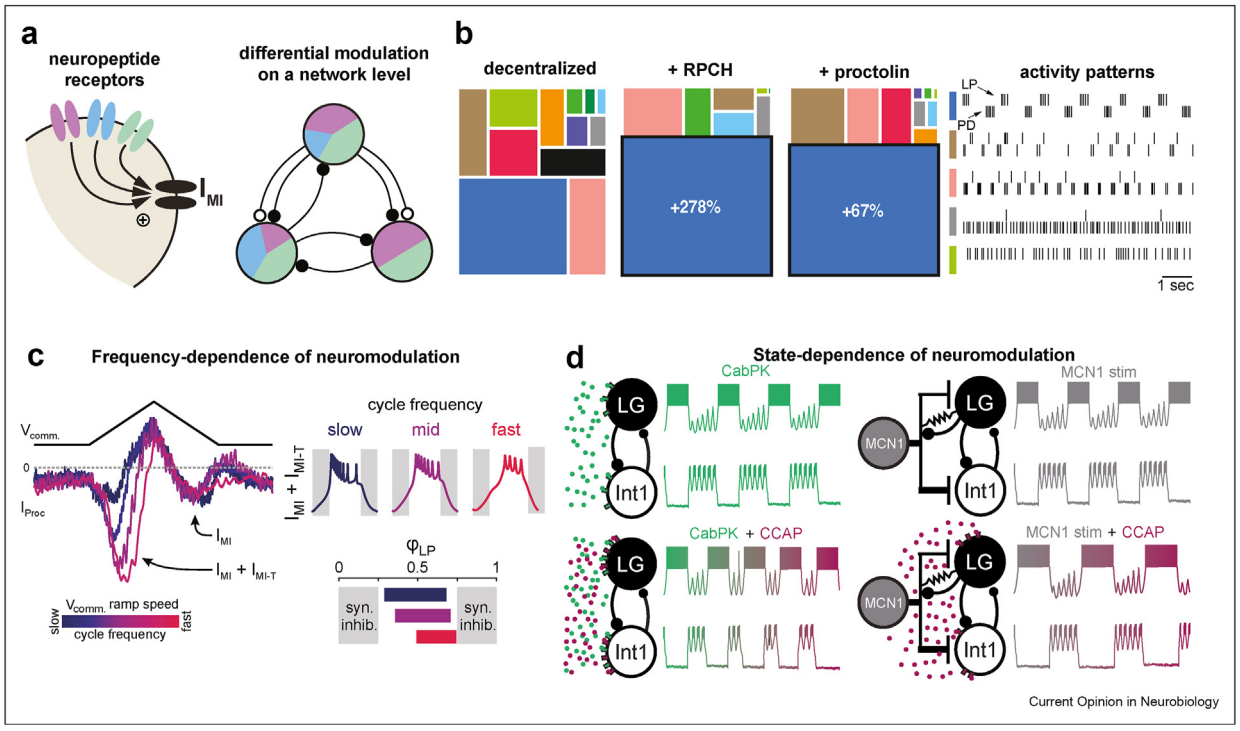
The effects of modulators on the strength of gap junctions are often overlooked, but gap junction regulation is crucial in the retina and in many body organs [74]. The crustacean cardiac ganglion produces synchronous activity that is necessary for a robust heartbeat. The cardiac ganglion is modulated by many amines and peptides [75], two of which are serotonin and dopamine [76*]. While both serotonin and dopamine are generally excitatory, serotonin can desynchronize bursts but dopamine promotes stable bursting, associated with strengthening of the gap junction coupling [76*].

There are hundreds of crustacean neuropeptides [77**, 78*,79,80**,81**], consisting of approximately 20 neuropeptide families, with multiple isoforms in most of these families. Many of these neuropeptides are biologically active. This richness raises several fascinating questions:

a) Are the same isoforms released from all presynaptic release sites?
b) How many different isoforms are found in a given presynaptic neuron?
c) Do different isoforms show differential stability towards degradation and therefore different time courses of action?
d) How different are the dose-response curves of different isoforms of the same peptide?

New advances in Mass Spectroscopic Imaging (MSI) [77**] should bring us closer to resolving the first two of these issues. In MSI, a laser beam is used to generate mass spectrometry profiles at specific tissue localizations, and then these spectra can be analyzed to determine accurately which peptides are where in a tissue [77**,80**]. There are many mass spectrometry methods under development, some of which can be combined with traditional microscopy. However, the resolution and 3D reconstructions for peptides are still not as good as can be done with quality confocal techniques with antibodies [77**]. While the high-quality visualizations in 3D now available with conventional immunocytochemistry provide excellent anatomical localizations, peptide antibodies are

Figure 4



Neuropeptidergic modulation of small circuit activity. a) Left: Different neuropeptides acting through different receptors have convergent action on the same inward voltage-dependent current (I_{MI}) in crustacean STGs. Right: Divergent neuromodulatory actions at the cellular and network level occur due to differential expression of peptide receptors across neurons in a network. **b)** Left: Probability distributions of states corresponding to different firing patterns in pyloric networks in decentralized condition (with modulatory projections blocked) and with bath application of modulators RPCH or proctolin. Right: Example spike trains of LP and PD neurons corresponding to several distinct circuit activity states shown in the treemaps. Figure modified from [71**]. The numbers in the blue boxes refer to the changes in probabilities of the regular triphasic state with the addition of neuromodulators. **c)** Peptide-activated currents are dependent on oscillation frequency. Left: Proctolin-activated currents for different slopes of voltage ramps. Magnitude of a transient component of proctolin-activated current (I_{MI-T}) depends on the slope of the ramp. Right: Voltage waveforms and activity phases of a model LP neuron at different burst frequencies. Frequency-dependence of I_{MI-T} shifts the burst phases in a model of LP neuron. Figure modified from [73*]. **d)** Schematic representations of gastric circuits with different configurations but similar outputs responding differently to neuromodulation. CabPK peptide application (top left, green traces) and MCN1 stimulation (top right, gray traces) generate different gastric circuit configurations with similar rhythms, represented by schematic activity patterns of LG and Int1. Application of a peptide hormone (purple) increases the cycle frequency of CabPK rhythm by reducing interburst interval (bottom left), but decreases the MCN1-rhythm frequency by prolonging the burst duration (bottom right). Figure modified from [59*]. Circuit symbols defined as in Figure 1.

unlikely to adequately distinguish among all isoforms. Thus, the hope for the future is that MSI localization of peptides in anatomical samples will reach the precision of the best light microscopy except in specific cases [82].

Even when multiple isoforms of a peptide family interact with the same receptor, it is likely that they do so with different affinities [83*] and may show differential stability in physiological hemolymph [84–86]. There are no systematic studies that directly compare large numbers of peptide family members for stability in hemolymph and their dose-dependent actions. Recent studies call attention to the importance of post-translational modifications in the physiological function of peptides [87*]. In the STG of the lobster, *Homarus americanus*, specific antibodies demonstrate that non-amidated and amidated forms of the C-allatostatin peptides are found in different anatomical locations. In the cardiac ganglion of the same species, it was shown that these different forms differ in their physiological actions [82,83*].

Many neuropeptides are released both hormonally and from descending modulatory neurons. Hemolymph modulator composition is altered by feeding and differs between fed and unfed crabs [80**,88*]. Fed crabs showed modified STG motor patterns [89*]. While this is not surprising, there are relatively few instances in which the connections between circulating hormones elicited by feeding and specific changes in circuit configurations are established [89*].

In the feeding system of *Aplysia*, ingestion and egestion are antagonistic behaviors, and fascinating new work argues that persistent effects of cAMP are important for maintaining a persistent network state [90**,91], as the animal switches between these two behaviors. An intriguing study in the *Aplysia* feeding system suggests a new mechanism for driving a rhythmic behavior that results from organelle-derived intracellular calcium oscillations [92**].

Homeostasis regulation and ion channel correlations

In long-lived animals, be they crabs or humans, the lifetime of proteins is much shorter than the animal's lifetime. Consequently, the proteins in long-lived neurons must be continuously replaced while the animal maintains its characteristic function. The first computational models and experiments relevant to this problem date back to the 1990s [93,94]. Since then, the work on homeostatic regulation of synaptic strength and intrinsic excitability has become a major research interest in both small and large circuits [95,96**,97,98,99*,100,101,102**]. Despite the large amount of attention paid to these issues by workers who use rodent preparations, interesting and fundamental work is still being done by workers on small circuits [102**,103**].

There are strong correlations in mRNA expression of ion channel genes in single identified crustacean neurons [102**]. In a fascinating set of experiments, Santin and Schulz [103**] studied the correlated expression of ion channel genes in single PD neurons from the crab STG. They found that silencing the neurons and removing their synaptic and modulatory inputs produced a loss of some of the characteristic correlations in ion channel expression in these neurons but that these correlations were maintained when the neurons were voltage-clamped to their control voltage waveforms. These results extend and confirm earlier studies [104,105], suggesting that the specific patterns of correlated channel expression arise in an ongoing manner from continuous interactions between activity and programs of gene expression.

Conclusions

Small circuits with identified neurons continue to provide significant advantages for understanding how circuit dynamics arise from the properties of individual neurons. Insights from computation, molecular analyses, and biochemistry are supplementing insights from electrophysiology and behavior. Using these systems, one can hope to achieve the time-honored goals of integrating information from intracellular signaling to circuit function to behavior.

Declaration of interest

None.

Acknowledgements

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** of outstanding interest

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This is an outstanding, comprehensive and recent review of many of the same topics treated here. The reader is referred to this review for additional insight and background to many of the issues raised.

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This paper describes a beautiful example of limits of genetic determinism through the effects of environmental factors on circuit wiring. The authors studied synapse numbers and synaptic partners in isogenic flies raised at two different temperatures. They found that temperature has a profound effect on the numbers of synaptic connections in photoreceptor neurons. These wiring differences give rise to robust behaviors in these flies at their rearing temperature demonstrating that circuits can develop in a manner that is adapted to the environment, even when starting with identical genetic blueprints.

4. ** Ravbar P, Zhang N, Simpson JH: **Behavioral evidence for nested central pattern generator control of *Drosophila* grooming**. *Elife* 2021, **10**:e71508.
The authors use behavioral experiments in *Drosophila* to look at the relationships between multiple movements that are part of behavioral sequences in grooming. This study also looks at the effects of temperature on these actions and shows that "nested" CPGS (those called in sequence in a behavior) are influenced to the same degree by temperature.

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19. ** Ellingson PJ, Barnett WH, Kueh D, Vargas A, Calabrese RL, Cymbalyuk GS: **Comodulation of h- and Na^+/K^+ pump currents expands the range of functional bursting in a central pattern generator by navigating between dysfunctional regimes**. *J Neurosci* 2021, **41**:6468–6483.
Neuromodulators influence CPG activity by changing several ionic conductances simultaneously. For example, the modulator myomodulin changes both I_H and electrogenic Na^+/K^+ pump currents in the leech heart interneuron half-center oscillator (HCO) despite which the HCO remains stable in its presence. The authors modeled the effect of maintaining a negative correlation between I_H and the electrogenic Na^+/K^+ pump, mimicking the effects of myomodulin on the network, and found that the model neurons maintain half-center activity when the two currents change together. The paper highlights the potential value of the multimodal action of neuromodulators.

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22. ** Onasch S, Gjorgjieva J: **Circuit stability to perturbations reveals hidden variability in the balance of intrinsic and synaptic conductances**. *J Neurosci* 2020, **40**:3186–3202.
This theoretical study explored the stability of a large family of half-center oscillator circuits composed of non-identical conductance-based model neurons. The authors changed intrinsic conductances either singly or in combination. They classified the ways in which network outputs varied upon changing conductances singly. The occurrence of particular emergent 'stability states' was found to correlate with modifications of specific conductances across families of degenerate starting states. They also characterized the cumulative impact of changing conductances with high or low correlations.

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In this work the authors use the dynamic clamp to construct half-center oscillators from two Gastric Mill (GM) neurons of the crab, *Cancer borealis*, that are otherwise uncoupled. The dynamic clamp is used to add a modeled I_H and modeled synapses, thus allowing the authors to alter those parameters in the half-center at will. They then directly compared the stability of half-centers in the release and escape modes, as a function of sensitivity to parameters, and to changes in temperature. These experiments highlight the fact that a circuit's dynamical mechanism can significantly alter the way it responds to perturbation.

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Single oscillatory circuits from poikilotherms are known to maintain a robust functional output over a wide range of temperatures despite being composed of differentially temperature sensitive components. An additional challenge is for multiple temperature-robust oscillators to maintain functional synchrony. The authors demonstrate remarkable conservation of coupling between two oscillatory circuits in the *C. borealis* STG over a range of temperatures. Their findings hint at mechanisms that operate at an additional level of coordination to maintain temperature-invariant integer coupling in this system.

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29. Städele C, Stein W: **Neuromodulation enables temperature robustness and coupling between fast and slow oscillator circuits**. *Front Cell Neurosci* 2022, **16**, 849160.

30. Haddad SA, Marder E: **Circuit robustness to temperature perturbation is altered by neuromodulators**. *Neuron* 2018, **100**:609–623.

31. ** Alonso LM, Marder E: **Temperature compensation in a small rhythmic circuit**. *Elife* 2020, **9**, e55470.
Temperature affects the conductances and kinetics of all membrane currents, but does so in a manner that depends on the details of the protein's structure. Consequently, each membrane conductance depends differently on temperature, and this raises the question of how neuronal circuits can operate over a range of temperatures. In this paper the authors used genetic algorithms to find pyloric rhythms that were robust over a range of temperatures, and show that these neurons can produce smooth transitions between current mechanisms that facilitate their expression of this robustness.

32. DeMaegd ML, Stein W: **Neuropeptide modulation increases dendritic electrical spread to restore neuronal activity disrupted by temperature**. *J Neurosci* 2021, **41**:7607–7622.

33. ** Kedia S, Marder E: **Blue light responses in *Cancer borealis* stomatogastric ganglion neurons**. *Curr Biol* 2022, **32**:1439–1445 e1433.
The authors describe the unusual and direct sensory response of a CPG to light. Specific wavelengths of light are capable of changing pyloric network activity in the *C. borealis* STG by changing the excitability of the pacemaker neurons. The circuit exhibits a stable increase in burst frequency and firing in light that is not driven by opsins but more likely by a second messenger pathway linked to an ionic conductance.

34. ** Stein W, Harzsch S: **The Neurobiology of Ocean Change - insights from decapod crustaceans**. *Zoology (Jena)* 2021, **144**, 125887.
This is an excellent review of the impact of climate change on the neural systems of marine life. The authors collate data tracking changes in multiple ocean water parameters such as temperature, salinity, pH and dissolved oxygen and consider their effects on marine crustaceans, a group with enormous ecological and economic impact. They present the effects of changing each of these parameters independently on nervous system output and organismal development and discuss the importance of studying the collective impact of multifaceted environmental changes.

35. Haley JA, Hampton D, Marder E: **Two central pattern generators from the crab, *Cancer borealis*, respond robustly and differentially to extreme extracellular pH**. *Elife* 2018, **7**:e4187.

36. Clemens S, Massabuau JC, Meyrand P, Simmers J: **A modulatory role for oxygen in shaping rhythmic motor output patterns of neuronal networks**. *Respir Physiol* 2001, **128**:299–315.

37. Tang LS, Goeritz ML, Caplan JS, Taylor AL, Fisek M, Marder E: **Precise temperature compensation of phase in a rhythmic motor pattern**. *PLoS Biol* 2010, **8**, e1000469.

38. ** Faria SC, Bianchini A, Lauer MM, Zimbardi A, Tapella F, Romero MC, McNamara JC: **Living on the edge: physiological and kinetic trade-offs shape thermal tolerance in intertidal crabs from tropical to sub-Antarctic South America**. *Front Physiol* 2020, **11**:312.
The thermal tolerance of a species has contributions from phylogeny and its environment. Temperatures close to an animal's thermal limits impact available oxygen and lactate buildup. The authors studied aerobic and anaerobic metabolic processes and enzyme kinetics at the limits of thermal tolerance of 12 different intertidal crab species collected from temperature zones ranging from tropical to sub-Antarctic. They found that tropical and sub-tropical crabs respond differently to acute temperature stress compared with sub-Antarctic,

although oxygen consumption and lactate buildup increased with temperature in all species.

39. * Ratliff J, Franci A, Marder E, O'Leary T: **Neuronal oscillator robustness to multiple global perturbations**. *Biophys J* 2021, **120**:1454–1468.
A fascinating question is whether robustness to one perturbation implies either a greater robustness to other perturbations, or a trade-off between resilience to different perturbations. Here the authors study the effects of pH and temperature on the pacemaker neurons of the stomatogastric ganglion and find that the pacemaker 'crashes' by different paths in response to extremes of temperature and pH.

40. Tang LS, Taylor AL, Rinberg A, Marder E: **Robustness of a rhythmic circuit to short- and long-term temperature changes**. *J Neurosci* 2012, **32**:10075–10085.

41. * DeMaegd ML, Stein W: **Temperature-robust activity patterns arise from coordinated axonal Sodium channel properties**. *PLoS Comput Biol* 2020, **16**, e1008057.
Robust functioning of neuronal output across a wide range of temperatures, despite multiple underlying Q_{10}s, has been well-described for the pyloric network of the *C. borealis* STG. The authors probe the effects of temperature on action potential propagation to test the temperature-robustness of spike timing. They found that temperature has a modest effect on propagation and spike timing in axons that have different physical parameters. From modeling studies they conclude that coordinated changes in sodium channel maximum conductances and activation gate time constants across different temperatures can achieve this result.

42. Soofi W, Goeritz ML, Kispersky TJ, Prinz AA, Marder E, Stein W: **Phase maintenance in a rhythmic motor pattern during temperature changes *in vivo***. *J Neurophysiol* 2014, **111**: 2603–2613.

43. Prinz AA: **Degeneracy rules!** *J Physiol* 2017, **595**:2409.

44. Prinz AA, Bucher D, Marder E: **Similar network activity from disparate circuit parameters**. *Nat Neurosci* 2004, **7**:1345–1352.

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

46. Marder E, Goaillard JM: **Variability, compensation and homeostasis in neuron and network function**. *Nat Rev Neurosci* 2006, **7**:563–574.

47. ** Alonso LM, Marder E: **Visualization of currents in neural models with similar behavior and different conductance densities**. *Elife* 2019, **8**, e42722.
This manuscript introduces a new visualization tool that shows the contribution of different ionic conductances to voltage waveforms. This visualization makes it easy to see how different values of conductances can nonetheless produce similar activity patterns. This work provides insight into why individual neurons or networks with similar behavior can respond very differently to perturbations

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

49. Rodriguez JC, Blitz DM, Nusbaum MP: **Convergent rhythm generation from divergent cellular mechanisms**. *J Neurosci* 2013, **33**:18047–18064.

50. ** Olivares E, Izquierdo EJ, Beer RD: **A neuromechanical model of multiple network rhythmic pattern generators for forward locomotion in *C. elegans***. *Front Comput Neurosci* 2021, **15**, 572339.
Pacemakers and stretch receptor feedback are mechanisms that are believed to underlie locomotion control in *C. elegans*. This computational study explores the possibility of multiple CPGs contributing to locomotion, as an alternative mechanism. They find effective solutions in which gap junctions play a crucial role.

51. * Wang Y, Weiss KR, Cropper EC: **Network degeneracy and the dynamics of task switching in the feeding circuit in *Aplysia***. *J Neurosci* 2019, **39**:8705–8716.
Egestive motor behavior in Aplysia can be elicited through two stimulation paradigms- repetition priming and positive biasing. The authors find that only one method invokes the involvement of an interneuron, B20, and this makes it more difficult to switch to other behaviors (ingestion). Thus, these degenerate circuits can have larger consequences on future behaviors such as task-switching.

52. * Smith MA, Honegger KS, Turner G, de Bivort B: **Idiosyncratic learning performance in flies**. *Biol Lett* 2022, **18**, 20210424.
This study characterizes individual learning differences amongst isogenic flies. Some flies were better learners than others in many iterations of classical Pavlovian conditioning paradigm, such as to different aversive modalities and different odor cues. Stochastic processes through development can hence lead to significant differences in learning capacities of isogenic individuals.

53. Werkhoven Z, Bravin A, Skutt-Kakaria K, Reimers P, Pallares LF, Ayroles J, de Bivort BL: **The structure of behavioral variation within a genotype**. *Elife* 2021, **10**:e64988.

54. Stern S, Kirst C, Bargmann CI: **Neuromodulatory control of long-term behavioral patterns and individuality across development**. *Cell* 2017, **171**:1649–1662 e1610.

55. ** Linneweber GA, Andriatsilavo M, Dutta SB, Bengochea M, Hellbruegge L, Liu G, Ejsmont RK, Straw AD, Wernet M, Hiesinger PR, *et al.*: **A neurodevelopmental origin of behavioral individuality in the *Drosophila* visual system**. *Science* 2020, **367**:1112–1119.
This paper tracks down the neural basis for differences in individual behaviors amongst isogenic flies. Individual flies vary in their abilities to orient towards a visual object. Stochastic differences in wiring in a visual system circuit, the dorsal cluster neurons, give rise to nonheritable variations in right/left wiring asymmetry among individuals. These wiring asymmetries are further responsible for improved orientation of individuals towards a visual object. Wiring stochasticity can therefore lead to pronounced differences in individual behaviors.

56. Sakai O: **Comparison of personality between juveniles and adults in clonal gecko species**. *J Ethol* 2018, **36**:221–228.

57. ** Zhang G, Yu K, Wang T, Chen TT, Yuan WD, Yang F, Le ZW, Guo SQ, Xue YY, Chen SA, *et al.*: **Synaptic mechanisms for motor variability in a feedforward network**. *Sci Adv* 2020, **6**: eaba4856.
Motor behaviors produced repeatedly vary each time they're performed. The authors address the neuronal underpinnings of variability in motor behavior production within an animal using an *Aplysia* feeding circuit. They compare two neurons that elicit feeding motor programs, one more variably than the other, and find that a weaker synaptic connection and high synaptic noise drive output variability highlighting circuit-level mechanisms that can underlie variable behaviors.

58. Lyttle DN, Gill JP, Shaw KM, Thomas PJ, Chiel HJ: **Robustness, flexibility, and sensitivity in a multifunctional motor control model**. *Biol Cybern* 2017, **111**:25–47.

59. * Powell DJ, Marder E, Nusbaum MP: **Perturbation-specific responses by two neural circuits generating similar activity patterns**. *Curr Biol* 2021, **31**:4831–4838 e4834.
Similar circuit activities can arise from very different mechanisms and different circuit configurations. This paper studies the gastric mill as an example of this phenomenon. Activating a sensory neuron that acts via different synapses in each circuit configuration has a surprisingly similar effect on the gastric mill output. A modulator that activates the same ionic current in the same neuron however produces different outputs in each configuration. There exists an interesting overlap and divergence of circuit response based on the underlying configuration/mechanism.

60. Gunaratne CA, Sakurai A, Katz PS: **Variations on a theme: species differences in synaptic connectivity do not predict central pattern generator activity**. *J Neurophysiol* 2017, **118**: 1123–1132.

61. Dickinson PS, Mecsas C, Marder E: **Neuropeptide fusion of two motor pattern generator circuits**. *Nature* 1990, **344**:155–158.

62. Hooper SL, Moulins M: **Switching of a neuron from one network to Another by sensory-induced changes in membrane-properties**. *Science* 1989, **244**:1587–1589.

63. Hooper SL, Moulins M: **Cellular and synaptic mechanisms responsible for a long-lasting restructuring of the lobster pyloric network**. *J Neurophysiol* 1990, **64**:1574–1589.

64. Hooper SL, Moulins M, Nonnotte L: **Sensory input induces long lasting changes in the output of the lobster pyloric network**. *J Neurophysiol* 1990, **64**:1555–1573.

65. Weimann JM, Marder E: **Switching neurons are integral members of multiple oscillatory networks**. *Curr Biol* 1994, **4**: 896–902.

66. Meyrand P, Simmers J, Moulins M: **Dynamic construction of a neural network from multiple pattern generators in the lobster stomatogastric nervous system**. *J Neurosci* 1994, **14**: 630–644.

67. ** Fahoum SH, Blitz DM: **Neuronal switching between single- and dual-network activity via modulation of intrinsic membrane properties**. *J Neurosci* 2021, **41**:7848–7863.
Oscillatory neurons that drive rhythmic outputs need to function flexibly, including being able to switch their participation from one network to another. This study sheds light on the different mechanisms of network switching. The authors describe the neuromodulation-induced intrinsic changes in LPG neurons of the crab STG that drive network participation in the gastric mill rhythm as opposed to the synaptically driven participation in the pyloric rhythm.

68. * Drion G, Franci A, Sepulchre R: **Cellular switches orchestrate rhythmic circuits**. *Biol Cybern* 2019, **113**:71–82.
This paper is a nice overview of the influences of small network studies on the world of robotics and robust movement modeling. The authors suggest a model inspired by neuromodulatory mechanisms that allows for fast adaptation of circuits without changing synaptic strengths or connections. They extend their previous studies with single cells and half-center oscillators to show that a slow negative conductance allows for circuit tunability and robust control in modeled STG inspired circuits.

69. Nusbaum MP, Blitz DM, Marder E: **Functional consequences of neuropeptide and small-molecule co-transmission**. *Nat Rev Neurosci* 2017, **18**:389–403.

70. Marder E: **Neuromodulation of neuronal circuits: back to the future**. *Neuron* 2012, **76**:1–11.

71. ** Gorur-Shandilya S, Cronin EM, Schneider AC, Haddad SA, Rosenbaum P, Bucher D, Nadim F, Marder E: **Mapping circuit dynamics during function and dysfunction**. *Elife* 2022, **11**: e76579.
The ability to classify different network states is a valuable tool for studying network dysfunction. The authors use unsupervised learning techniques to parse a large repository of real-world data from the pyloric network in different conditions to construct maps of different functional regimes and study stereotypies in movements across these states under different conditions.

72. ** Li X, Bucher D, Nadim F: **Distinct co-modulation rules of synapses and voltage-gated currents coordinate interactions of multiple neuromodulators**. *J Neurosci* 2018, **38**:8549–8562.
Co-modulation is a well-known feature of neural systems. This is a beautiful study of the effects of comodulation on network output. The authors found that comodulation generated simple linear additive effects at the level of synapses but a neuromodulatory current responded in a sub-linear fashion, suggesting the involvement of two opposing intracellular target pathways. The study highlights the complex interactions of modulators that act simultaneously and the difficulties of extrapolating their cumulative effects based on individual analyses.

73. * Schneider AC, Fox D, Itani O, Golowasch J, Bucher D, Nadim F: **Frequency-dependent action of neuromodulation**. *eNeuro* 2021, **8**. ENEURO.0338-21.2021.
The effect of a neuromodulatory current on a neuron is dependent on the target neuron's activity. The authors studied this relationship in LP neurons of the *C. borealis* STG using proctolin to activate a modulatory current, I_{MI}. They found that I_{MI} amplitude and peak time are dependent on pyloric cycle frequency and used voltage ramps with different slopes to uncover two kinetically different currents activated by proctolin. I_{MI} is composed of an additional calcium-permeable fast inactivating current that is activated by positive ramps and is slope-dependent. They further modeled the differential effects of the two I_{MI} components on oscillatory activity. The study demonstrates an important feature of neuromodulator effects, namely their relationship to various features of network activity.

74. Neyton J, Trautmann A: **Acetylcholine modulation of the conductance of intercellular junctions between rat lacrimal cells**. *J Physiol* 1986, **377**:283–295.

75. Cruz-Bermudez ND, Marder E: **Multiple modulators act on the cardiac ganglion of the crab, *Cancer borealis***. *J Exp Biol* 2007, **210**:2873–2884.

76. * Lane BJ, Kick DR, Wilson DK, Nair SS, Schulz DJ: **Dopamine maintains network synchrony via direct modulation of gap junctions in the crustacean cardiac ganglion**. *Elife* 2018, **7**: e39368.
Neuromodulation is a means for networks to achieve flexibility. Underlying degeneracies in intrinsic conductances and circuit configurations can interact with neuromodulation to produce non-uniform effects. The authors examine the effects of two biogenic amines, serotonin and dopamine on the large cells of the *C. borealis* cardiac ganglion, which are known to have variable maximal conductance values even within an animal. Both modulators impact a K^+ conductance that is important for maintaining network synchrony, but dopamine has an excitatory effect while serotonin leads to a loss of synchrony. They found that dopamine increases gap junction coupling, potentially increasing synchrony. They demonstrate a novel way for neuromodulators to maintain synchronous output in the face of degeneracy.

77. ** Buchberger AR, DeLaney K, Johnson J, Li L: **Mass spectrometry imaging: A review of emerging advancements and future insights**. *Anal Chem* 2018, **90**:240–265.
This is an outstanding review of new methods in mass spectroscopy and peptide imaging.

78. * Buchberger AR, DeLaney K, Liu Y, Vu NQ, Helfenbein K, Li L: **Mass spectrometric profiling of neuropeptides in *Callinectes sapidus* during hypoxia stress**. *ACS Chem Neurosci* 2020, **11**: 3097–3106.
The authors utilize a marine invertebrate, *Callinectes sapidus*, known to experience and survive a wide range of hypoxia stress to study the impact of changing O_2 environments on neuropeptide families involved in stress responses. They use different mass spectrometry techniques to quantify neuropeptide content in different tissues with various severities of hypoxia and find that each tissue has unique expression profiles under different states of hypoxia.

79. DeLaney K, Buchberger AR, Atkinson L, Grunder S, Mousley A, Li L: **New techniques, applications and perspectives in neuropeptide research**. *J Exp Biol* 2018, **221**:jeb151167.

80. ** DeLaney K, Hu M, Hellenbrand T, Dickinson PS, Nusbaum MP, Li L: **Mass spectrometry quantification, localization, and discovery of feeding-related neuropeptides in *Cancer borealis***. *ACS Chem Neurosci* 2021, **12**:782–798.
This study compares the neuropeptides present in the nervous system of the crab, *Cancer borealis,* in fed and unfed animals. Remarkably, the number of peptides that change in response to feeding is quite large, illustrating that the neuropeptide composition and milieu is not accounted for by a change in only a few feeding related constituents.

81. ** Hu M, Helfenbein K, Buchberger AR, DeLaney K, Liu Y, Li L: **Exploring the sexual dimorphism of Crustacean neuropeptide expression using *Callinectes sapidus* as a model organism**. *J Proteome Res* 2021, **20**:2739–2750.
In this study, the authors document sex differences in neuropeptides in the crab, *C. sapidus* using mass spectrometry. Obviously, peptides known to play a role in reproduction differ, but also there were a number of sex differences in peptides of other classes.

82. Christie AE, Miller A, Fernandez R, Dickinson ES, Jordan A, Kohn J, Youn MC, Dickinson PS: **Non-amidated and amidated members of the C-type allatostatin (AST-C) family are differentially distributed in the stomatogastric nervous system of the American lobster, *Homarus americanus***. *Invertebr Neurosci* 2018, **18**:2.

83. * Dickinson PS, Armstrong MK, Dickinson ES, Fernandez R, Miller A, Pong S, Powers BW, Pupo-Wiss A, Stanhope ME, Walsh PJ, *et al.*: **Three members of a peptide family are differentially distributed and elicit differential state-dependent responses in a pattern generator-effector system**. *J Neurophysiol* 2018, **119**:1767–1781.
Neuropeptides come in many isoforms that may exert similar actions through a common receptor. This paper shows that contrary to this belief, members of a peptide family, C-type allatostatins produce different effects on neuronal activity in the cardiac neuromuscular system and are distributed differentially in the American lobster.

84. Nusbaum MP, Marder E: **A neuronal role for a crustacean red pigment concentrating hormone-like peptide: neuromodulation of the pyloric rhythm in the crab, *Cancer borealis***. *J Exp Biol* 1988, **135**:165–181.

85. Szabo TM, Chen R, Goeritz ML, Maloney RT, Tang LS, Li L, Marder E: **Distribution and physiological effects of B-type allatostatins (myoinhibitory peptides, MIPs) in the**

stomatogastric nervous system of the crab *Cancer borealis*. *J Comp Neurol* 2011, **519**:2658–2676.

86. Cruz-Bermudez ND, Fu Q, Kutz-Naber KK, Christie AE, Li L, Marder E: **Mass spectrometric characterization and physiological actions of GAHKNYLRFamide, a novel FMRFamide-like peptide from crabs of the genus *Cancer***. *J Neurochem* 2006, **97**:784–799.

87. * Oleisky ER, Stanhope ME, Hull JJ, Dickinson PS: **Isoforms of the neuropeptide myosuppressin differentially modulate the cardiac neuromuscular system of the American lobster, *Homarus americanus***. *J Neurophysiol* 2022, **127**:702–713.
Similar to their findings with C-type allotostatins, the authors found that different structures of a neuropeptide, myosuppressin, elicit different responses from the *H. americanus* cardiac ganglion, solidifying the structure-function relationship of neuropeptide isoforms and circuit effects.

88. * DeLaney K, Hu M, Wu W, Nusbaum MP, Li L: **Mass spectrometry profiling and quantitation of changes in circulating hormones secreted over time in *Cancer borealis* hemolymph due to feeding behavior**. *Anal Bioanal Chem* 2022, **414**:533–543.
Neuropeptide diversity and localization are likely to exert multiple effects of neuronal circuits. The authors studied the distributions of neuropeptides in fed/unfed *C. borealis* and found profound changes in expression levels and spatial distributions upon feeding. They sequenced 69 novel putative neuropeptides and characterized the direct circuit effects of one of them.

89. * Cook AP, Nusbaum MP: **Feeding state-dependent modulation of feeding-related motor patterns**. *J Neurophysiol* 2021, **126**:1903–1924.
Exogenous neuromodulator actions on neural circuits have been widely studied. The authors address the pressing question of how a neuromodulator milieu that has behavioral relevance, that is, due to feeding, affects circuit function. They used hemolymph extracted from unfed and fed animals at multiple time points after feeding and found that fed hemolymph from different time points has a large and varying effect on both STG circuit outputs.

90. ** Perkins MH, Weiss KR, Cropper EC: **Persistent effects of cyclic adenosine monophosphate are directly responsible for maintaining a neural network state**. *Sci Rep* 2019, **9**:9058.
The authors study the persistence of circuit changes elicited by neuromodulators through the activation of second messenger pathways with longer timescales. cAMP can maintain different behavioral states, usually by activating protein kinase A (PKA). An *Aplysia* ingestive circuit that is primed through repetitive modulator release, stays in a state of increased excitability for over 15 min after priming. In this case the persistent effect needs cAMP presence continually and is not driven by PKA.

91. Perkins MH, Cropper EC, Weiss KR: **Cellular effects of repetition priming in the Aplysia feeding network are suppressed during a task-switch but persist and facilitate a return to the primed state**. *J Neurosci* 2018, **38**:6475–6490.

92. ** Bedecarrats A, Puygrenier L, Castro O'Byrne J, Lade Q, Simmers J, Nargeot R: **Organelle calcium-derived voltage oscillations in pacemaker neurons drive the motor program for food-seeking behavior in *Aplysia***. *Elife* 2021, **10**:e68651.
Motivated behaviors such as feeding can be variable and depend on a combination of internal and external factors. The authors study the intrinsic neuronal transformation that accompanies this behavioral change in an *Aplysia* feeding CPG and find that the internal drive to generate rhythmicity can arise from intracellular calcium oscillations that produce pacemaker output.

93. LeMasson G, Marder E, Abbott LF: **Activity-dependent regulation of conductances in model neurons**. *Science* 1993, **259**:1915–1917.

94. Turrigiano G, Abbott LF, Marder E: **Activity-dependent changes in the intrinsic properties of cultured neurons**. *Science* 1994, **264**:974–977.

95. Turrigiano GG: **The dialectic of Hebb and homeostasis**. *Philos Trans R Soc Lond B Biol Sci* 2017, **372**:20160258.

96. ** Wu YK, Hengen KB, Turrigiano GG, Gjorgjieva J: **Homeostatic mechanisms regulate distinct aspects of cortical circuit dynamics**. *Proc Natl Acad Sci U S A* 2020, **117**:24514–24525.
It is accepted that homeostasis modulates synaptic strength, membrane excitability, and firing rates. How this plays out at the neural circuit and network level is unknown. The authors identify changes in higher-order network properties of freely behaving rodents during prolonged visual deprivation. Their data reveal that functional pairwise correlations and their structure are subject to homeostatic regulation.

97. Cannon J, Miller P: **Synaptic and intrinsic homeostasis cooperate to optimize single neuron response properties and tune integrator circuits**. *J Neurophysiol* 2016, **116**:2004–2022.

98. Cannon J, Miller P: **Stable control of firing rate mean and variance by dual homeostatic mechanisms**. *J Math Neurosci* 2017, **7**:1.

99. * Miller P, Cannon J: **Combined mechanisms of neural firing rate homeostasis**. *Biol Cybern* 2019, **113**:47–59.
In this paper the authors describe the advantages and disadvantages of having more than one control mechanism that responds to a neuron's firing rate, and suggest the conditions under which two mechanisms can coexist.

100. O'Leary T, Williams AH, Franci A, Marder E: **Cell types, network homeostasis, and pathological compensation from a biologically plausible ion channel expression model**. *Neuron* 2014, **82**:809–821.

101. Tyssowski KM, Letai KC, Rendall SD, Tan C, Nizhnik A, Kaeser PS, Gray JM: **Firing rate homeostasis can occur in the absence of neuronal activity-regulated transcription**. *J Neurosci* 2019, **39**:9885–9899.

102. ** Northcutt AJ, Schulz DJ: **Molecular mechanisms of homeostatic plasticity in central pattern generator networks**. *Dev Neurobiol* 2019, **80**:58–69.
This is an outstanding review article that summarizes a now considerable body of literature on the correlations in ion channel expression under control and altered states in single invertebrate central pattern generating neurons. The review provides an up-to-date heuristic discussion about the plausible activity and non-activity-dependent mechanisms that could control the homeostasis of intrinsic excitability.

103. ** Santin JM, Schulz DJ: **Membrane voltage is a direct feedback signal that influences correlated ion channel expression in neurons**. *Curr Biol* 2019, **29**:1683–1688 e1682.
Ion channel correlations are an important feature of functional neuronal systems and need to be maintained in changing environments and over time. The authors show that membrane voltage alone is a key factor that can maintain multiple channel conductances through experiments comparing control pyloric circuits with a group silenced with TTX and a third that is chemically silenced and then forced to follow a fictive 'control' rhythm via voltage clamp. The lions' share of correlations is maintained solely by forcing the neurons to follow normal membrane activity patterns, but a few are susceptible to non-biologically driven activity implying a role for neuromodulation, GPCRs and intracellular pathways.

104. Khorkova O, Golowasch J: **Neuromodulators, not activity, control coordinated expression of ionic currents**. *J Neurosci* 2007, **27**:8709–8718.

105. Temporal S, Desai M, Khorkova O, Varghese G, Dai A, Schulz DJ, Golowasch J: **Neuromodulation independently determines correlated channel expression and conductance levels in motor neurons of the stomatogastric ganglion**. *J Neurophysiol* 2012, **107**:718–727.

106. Daur N, Nadim F, Bucher D: **The complexity of small circuits: the stomatogastric nervous system**. *Curr Opin Neurobiol* 2016, **41**:1–7.