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ROBUST CIRCUIT RHYTHMS IN SMALL CIRCUITS ARISE FROM VARIABLE CIRCUIT COMPONENTS AND MECHANISMS

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Abstract

Small central pattern generating circuits found in invertebrates have significant advantages for the study of the circuit mechanisms that generate brain rhythms. Experimental and computational studies of small oscillatory circuits reveal that similar rhythms can arise from disparate mechanisms. Animal-to-animal variation in the properties of single neurons and synapses may underly robust circuit performance, and can be revealed by perturbations. Neuromodulation can produce altered circuit performance but also ensure reliable circuit function.

Introduction

The central pattern generating circuits found in invertebrates have been the source of numerous fundamental insights into the generation of rhythmic motor patterns, brain oscillations [1, 2, 3, 4] and some of the synaptic mechanisms that control oscillator precision [5]. Computational and experimental studies have demonstrated that some individual neurons can generate bursts of action potentials that can drive circuit oscillations (Fig. 1). In other cases, circuit oscillations arise as a consequence of synaptic connections among neurons that are themselves not bursting neurons [6, 7, 8] (Fig. 1).

A wealth of data has shown that neuromodulators and modulatory neurons can reconfigure oscillatory networks, changing their frequency, phase relationships, and the functional interactions among neurons [9*, 10, 11*, 12, 13*]. Notably, neurons can switch among different rhythms, and the same neuron can be part of oscillatory circuits with very different cycle periods [14, 15, 16, 17, 18].

A more recent body of work on small rhythmic circuits has shown that circuit parameters, such as ion channel densities or synaptic strengths, can be widely variable across animals in the population yet still produce rhythmic motor patterns that are normal, or “good enough” [19, 20, 21, 22*, 23**, 24, 25**, 26*]. In this review, we focus on recent work that

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illuminates the issues raised by variability in system components for robust rhythm generation.

Variability in System Components Across Animals

Many small central pattern generating circuits have been studied for more than 40 years. This means that data have been collected from the same identified neurons and synapses over extended periods of time, without the confounds that arise when experimentalists are sampling neurons from a large population of unidentified or poorly identified neurons. Consequently, it is not an accident that work on identified neurons has generated much of what we know about animal-to-animal variability of neuronal structure, conductance densities, and synapse strengths.

Anatomical variation

Characteristic anatomical branching and projection patterns have been classically used in identifying neurons in insect and other invertebrate preparations. That said, at a finer scale of analysis, intracellular dye-fills of identified neurons in invertebrates show clear evidence of animal-to-animal variations in soma positions and branching patterns [27, 28, 29]. For example, a recent study of the Anterior Gastric Receptor (AGR) neuron in the crab stomatogastric ganglion (STG) shows large variations in the number of branches that AGR makes in the STG neuropil [28].

Most identified neurons in the lobster STG are found in the same number in every preparation. For example, all STGs have 2 Pyloric Dilator (PD) and 1 Lateral Pyloric (LP) neurons. However, in the lobster, *Homarus americanus*, the number of Pyloric (PY) neurons varies from 3–7 across animals [30**], providing the opportunity to ask what the consequences of this variability is for the motor output of the system. In a fascinating study, Daur et al. [30**] show that the difference in the number of motor neurons innervating a target muscle was compensated by changes in the short-term plasticity of their synapses, thus maintaining constant function.

Variation in intrinsic and synaptic conductance-densities and gene expression

A growing number of studies have now measured densities of voltage-dependence currents, mRNAs for channels, and the strengths of synaptic connections in identified neurons across adult animals [19, 20, 21, 22*, 23**, 24, 25**, 31, 32, 33*, 34*, 35**, 36]. These studies demonstrate the relevance of theoretical and computational studies that show that similar single neuron and circuit performance can arise from widely disparate values of membrane and synaptic conductances [8, 26*, 31, 36, 37, 38, 39*, 40, 41, 42*].

Experimental data from the STG showed intriguing sets of correlations in conductance expression [19, 20, 21, 32, 35**]. In contrast, in the leech heartbeat system, specific sets of correlations between measurements of network parameters and circuit performance were not seen [36]. A number of modeling studies have explored the relationships between conductance correlations and a variety of physiological functions [38, 39*, 43]. Recent studies with the dynamic clamp explored the consequences of correlated changes in conductance values for stable neuronal [35**] or network function [44]. Specifically, Zhou

et al [35**] showed that phase invariance of one identified STG could be explained by linear correlations in just three-voltage-gated currents.

Recent modeling studies demonstrate that correlations in conductances can arise from simple homeostatic tuning rules [45**, 46**]. New experimental work argues that neurons and networks may be protected against over-modulation by combinations of low and high affinity receptors that regulate conductance densities [47*] and maintain conductance ratios [48*].

Variability in Circuit Structure Revealed by Perturbations

If, as now seems to be the case, each crab or leech or snail, has found through development and experience, a set of membrane and synaptic conductances that are sufficient for behavior, the question then becomes how consistently can animals with these potentially quite disparate solutions to circuit performance respond appropriately to the neuromodulation and environmental perturbations that they will routinely experience? This is a telling question, as it is certainly the case that there must be perturbations that will distinguish individual animals with different sets of circuit parameters.

Figure 2 illustrates this essential conundrum: how reliable can a population of animals be, if they have substantially distinct circuit structures? Figure 1 shows four versions of a network with different sets of circuit parameters. Modest perturbations, presumably those representing the kinds of stimuli that the animals are expected to experience, result in reliable changes in circuit output. More extreme perturbations produce entirely distinct circuit outcomes, as their underlying structures are unlikely to allow all of them to produce a stereotyped response [34*].

The above interpretation would predict that extreme perturbations might produce distinct responses from a seemingly identical set of animals. An example of this is seen in a recent study [49**] in *Tritonia* in which animals with normal circuit outputs under control conditions were differentially affected by lesioning a specific pathway. Temperature is a global perturbation that influences every biological process to a greater or lesser degree [50*]. The effects of acute temperature changes were studied on the pyloric rhythm of the crab, *Cancer borealis* [51*, 52*, 53, 54**]. Over a permissive range of temperatures (those the animals routinely see), all preparations showed a characteristic temperature-dependent change in pyloric rhythm frequency, and maintained the phase relationships of the motor pattern. More extreme temperature ranges showed partial or complete disruptions of the oscillatory pacemaker [51*] and the entire circuit [54**], with each preparation “crashing” in a different way, as suggested by Figure 2.

Neuromodulation Can Reveal Variability or Diminish its Impact

Neuromodulators can alter the output of oscillatory circuits and motor patterns in numerous ways [11*]. Most members of a population of networks with different underlying structure can respond reliably to modulators, although individuals may respond differently from the mean [7]. There are many examples of state-dependent neuromodulation that depend on history [55] or initial conditions [56, 57]. There are also examples of neuromodulators that

produce what appear to be paradoxical and opposing effects when applied to preparations that at first glance appear similar. For example, serotonin applications to lobster STGs can produce widely disparate actions, although all preparations appear similar prior to serotonin application [58]. This occurs because of variable contributions of signal transduction actions triggered by different receptor types [58]. In this case, the underlying differences in receptor and signal transduction pathways were invisible until the serotonin challenge. The neuropeptide allatostatin can either increase or decrease contraction amplitude in the heart of the lobster, *Homarus americanus* [59*]. This is explained by non-linearities in the neuromuscular transform of the heart [60*].

In a set of intriguing studies, the Baro lab [47*, 48*, 61, 62] has studied the effects of high and low concentrations of dopamine, mediated by different receptors and signal transduction pathways on channel expression and motor pattern generation in the STG. These studies highlight the importance of distinguishing between the modulatory tone that can arise from steady but low concentrations of a neuromodulator and the changes that can occur with short-term activation by higher concentrations [47*, 48*, 61, 62]. The potential importance of modulatory tone in maintaining stability is also demonstrated by studies showing that serotonin [63] and dopamine [64*] can compensate for temperature-dependent decreases in muscle contraction.

Degeneracy in Oscillator Interactions and Circuit Performance

Although most invertebrate central pattern generating circuits consist of small numbers of neurons, this does not mean that repeated actions that appear indistinguishable necessarily employ an invariant set of neurons. Indeed, in a recent study on the *Tritonia* escape swim system, optical methods showed that, while many of the neurons in the circuit show stereotyped activity from cycle-to-cycle, others are active in a much more intermittent and variable fashion [65*]. This is reminiscent of older studies on the variable participation of many neurons in the *Aplysia* gill withdrawal circuit [66, 67].

Even within a small circuit, neurons can switch in and out of different oscillatory subnetworks [14, 15, 16, 18], or can participate in two rhythms at the same time [17]. Nonetheless, the circuit mechanisms accounting for these switches have been difficult to unravel. A recent computational study uses a 5-neuron network that was loosely motivated by the connectivity in the crab STG, to ask what combinations of synaptic strengths create different network configurations [68*]. *Figure 3* shows an important take-home lesson from this study: there are three entirely different circuit mechanisms that can account for the same change in circuit behavior. This degeneracy in circuit function arises from the parallel pathways in this network that exist because of the electrical synapses. Because electrical synapses are ubiquitous features of many brain networks, it is likely that all large networks have parallel pathways and show this kind of degeneracy. Having multiple mechanisms that can give the same circuit transitions obviously increases the robustness of a network. Interestingly, the sensitivity to the strength of the chemical synapses in this network is strongly influenced by whether or not the electrical synapses are rectifying [69*].

A similar take-home message comes from a recent electrophysiological study on the gastric mill motor patterns of the STG [70*], in which different modulatory mechanisms elicit very similar motor patterns.

Changes in motor patterns that are recorded *in vitro* are not necessarily reflected in changes in movement and behavior, as there can be all kinds of filters at the level of muscle function and biomechanics. Therefore, recent studies showing parallelism between motor patterns and motor performance argue that many of the neural mechanisms studied *in vitro* are representative of *in vivo*, intact behavior [52*, 71*, 72*].

Chains of Coupled Oscillators to Produce Movement

In many animals, rhythmic movements depend on coordinated action of muscle groups in many body segments. Classical work on leech swimming [73], leech heartbeat [74], and lamprey swimming [75] was critical in posing questions of how appropriate movement could be generated by coupling of many segmental oscillators. New work seeks to understand peristaltic wave propagation in crawling *Drosophila* larvae [76*], *C. elegans* [77] and in the crayfish swimmeret system [78*, 79*], and further addresses the impact of parameter variability on segmental coordination [39*].

Conclusions

Brain rhythms and oscillations can have many functions in addition to generating rhythmic movements. Nonetheless, the study of small circuits that generate rhythmic movements has revealed principles of circuit organization and function that generalize to the organization of large circuits and the mechanisms by which they combine into functional units. In particular, it is clear that circuit function can be surprisingly robust to variations in many parameters. This is fortunate, as it keeps us from being hostage to the need for a perfect brain!

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HIGHLIGHTS

Analysis of small oscillatory circuits reveals variability in system parameters

Circuits with different parameter sets can be robust to moderate perturbations

Circuits with different parameter sets can be distinguished by extreme perturbations

Correlations in conductance expression can arise from homeostatic tuning rules

Degenerate circuit mechanisms can produce similar switches in circuit behavior

Figure 1.

Circuit oscillations can arise either from a bursting pacemaker neuron (left) or from circuit interactions (right). In each panel the neurons are first shown independently, then coupled by inhibitory synaptic interactions, as shown.

Figure 2.

Responses of circuits with variable parameters can be reliable to modest perturbations but reveal their underlying structure in response to an extreme perturbation. Ion channels are shown in red and blue and vary in number in the different circuit configurations. Synaptic strength is shown by the size of the symbols. Electrical coupling is shown with resistor symbols and the remaining synapses are inhibitory. The bottom neuron class in each circuit varies in number, as in Daur et al. [30**].

Figure 3.

Degenerate mechanisms for controlling the transition of the hn neuron from firing with the slow set of neurons to firing with the fast set of neurons. Note that each of three different changes in circuit parameters can produce virtually identical circuit outcomes. Taken from Gutierrez et al. [68**].