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Trends in Neurosciences

Review

Network motifs in cellular neurophysiology

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Concepts from network science and graph theory, including the framework of network motifs, have been frequently applied in studying neuronal networks and other biological complex systems. Network-based approaches can also be used to study the functions of individual neurons, where cellular elements such as ion channels and membrane voltage are conceptualized as nodes within a network, and their interactions are denoted by edges. Network motifs in this context provide functional building blocks that help to illuminate the principles of cellular neurophysiology. In this review we build a case that network motifs operating within neurons provide tools for defining the functional architecture of single-neuron physiology and neuronal adaptations. We highlight the presence of such computational motifs in the cellular mechanisms underlying action potential generation, neuronal oscillations, dendritic integration, and neuronal plasticity. Future work applying the network motifs perspective may help to decipher the functional complexities of neurons and their adaptation during health and disease.

Highlights

The functional building blocks of single neurons can be conceptualized as network motifs that span the molecular and cellular scales of neuronal physiology.

Single-neuron functions and neuronal plasticity emerge from interactions across several network motifs that span different neuronal compartments.

Network motifs in cellular neurophysiology display various forms of degeneracy: disparate molecular components can yield the same network motif, representing component degeneracy; similar neural function can be achieved by network motifs with the same architecture but variable edge strengths, representing edge degeneracy; and the same neuronal function can be achieved through different network motifs, representing motif degeneracy.

The functional modularity of network motifs allows targeted manipulation of specific motifs towards achieving physiological goals or devising cures for pathology.

Network motifs are functional building blocks of complex biological systems

Complex biological systems are composed of many components that interact with each other to yield precise physiological outcomes [1–6]. A well-established and productive route to quantitatively analyze such **complex systems** (see Glossary) is to describe the system as a network (or, mathematically, a graph) of components, referred to as 'nodes', whose interactions are defined by 'edges' (Figure 1). Complex systems are often represented by complex networks, defined as networks that are neither deterministically ordered (simple networks) nor completely random (random graphs) [3,4,6–9]. Instead, complex networks manifest small patterns of specific interactions, called **network motifs**, that occur at frequencies higher than those in randomized networks [6,8]. In the context of information-processing systems, the fundamental utility of the network motifs formulation is that individual network motifs perform specific information-processing functions, thus acting as functional building blocks or computational primitives of complex biological networks [5,6,8,10–13]. Functions in complex systems emerge through dynamic interactions among several types of well-defined network motifs (Figure 1), each characterized by signature function and dynamics, together yielding a function-based modular representation of complex networks [1,4–8,10–14].

The network motifs perspective can be especially useful because biological systems typically manifest **degeneracy**, whereby precise functional outcomes are achieved by recruiting disparate components [2,15–18]. In these scenarios, viewing complex systems as a collective of functionally specified building blocks offers important advantages over considering them as a conglomeration of individual components that may or may not be involved in achieving a function. Within David Marr's three levels of how a system could be understood [19] – computational theory, representation/algorithm, and hardware implementation – the network motif-based approach embodies evaluation of biological questions from the perspective of the computational problem that the system is solving rather than of the hardware that is involved in implementing this computational problem.

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Formalisms involving network motifs as building block patterns have provided deep insights into complex biological systems across different **scales of analysis**. A domain in which network motifs have perhaps been most widely applied concerns the transcription regulatory networks that control gene expression. This perspective yielded, for instance, crucial insights into the convergent evolution of network motifs as fundamental building blocks across species [5,6,8,10,20]. The presence of networks motifs has also been illustrated in molecular signaling associated with metabolic pathways and neural plasticity, where each motif is associated with signature functional characteristics [13,20–23]. For instance, the presence of a negative feedback loop motif is functionally associated with stability and noise suppression [13,21,24,25], whereas its expression coupled with a positive feedback motif results in oscillations [10,12,13,26]. With reference to networks of neurons, there are network motifs that are not merely limited to the widely prevalent feedforward and feedback inhibition motifs, but also extend to other motifs that sustain characteristic functions [11,27–34]. The utility of the network motifs formalism extends to analyzing brain-wide interactions [28,35–40], evaluating ecological networks [5,6,8,41–43], assessing influence in social networks [5,10,44], determining the stability and **robustness** of financial networks [45,46], and deducing the reliability of electrical transmission networks [47].

Several functionally well-defined network motifs (Figure 1) have been found to be common across scales. For instance, the negative feedback loop motif is widely prevalent in gene regulatory and signaling networks [21,24,25,48], manifests as feedback inhibition in the context of networks of neurons [27,31,34], and as cross-species interactions in predator–prey networks [5,8,41,43]. Among the contributions of the network motifs perspective is the observation that motif structure and its functional specifications are common despite fundamental differences in what constitutes the nodes and how the interactions are defined by the edges. As elucidated by the aforementioned examples, this tool allows analysis of the stability, robustness, and resilience of complex systems through dynamical interactions across identified functional modules [1,4–8,10–13], which is particularly useful in understanding and targeting pathological conditions. Specifically, understanding the precise set of functional motifs that have been impaired can provide deeper insights into the forms of compensation that might occur during pathological conditions or that might be necessary for reversing them [14].

Despite such widespread recognition of the utility of the network motifs perspective across scales, the potential of the network motifs perspective for better understanding the complexities of single-neuron function and neuronal plasticity has not been fully harnessed. Specifically, there are single-neuron studies that assess dendritic structure and function [49,50], neural plasticity [21–23,51], noise suppression [52], and **neuronal oscillations** [53–57] from the network motifs perspective. However, unlike other scales of analysis illustrated above, an integrative conceptualization of single-neuron function and adaptation using the network motifs perspective has been largely lacking. In this review, we systematically build a case for the ubiquitous presence of the several common network motifs in neuronal physiology and plasticity. We focus on network motifs that seamlessly span both cellular and molecular scales towards mediating complex single-neuron functions and implementing different forms of plasticity that achieve stable adaptation in neural systems. Through focused examples, we illustrate the utility of this framework for deciphering the complexities of single-neuron function and adaptation therein.

Network motifs implement single-neuron functions

Network motifs are ubiquitous in cellular neurophysiology (Figure 1 and Table 1), where nodes span different scales of biological organization and edges interconnect molecular components and cellular variables (Figure 2A). The cross-scale nature of motifs in cellular neurophysiology constitutes a crucial distinction between them and the typically within-scale motifs assessed in

Glossary

Complex system: a system formed by many interacting elements that give rise to collective behavior.
Continual learning: the ability of a system to learn many tasks sequentially, without forgetting knowledge obtained from the preceding tasks, especially in scenarios where the data for the old tasks are not available while learning new tasks.
Degeneracy: the ability of disparate combinations of components to yield similar functional outcomes.
Homeostasis: a self-regulating process by which biological systems can maintain a relatively stable equilibrium between interdependent elements while adjusting to changing environmental conditions.
Intrinsic burst: a brief sequence of high-frequency action potentials elicited through interactions among components that are intrinsic to a neuron.
Intrinsic resonance: the ability of neurons or their compartments to respond maximally to a periodic stimulus at a specific frequency (resonance frequency) through interactions among components that are intrinsic to a neuron.
Metaplasticity: a change in the physiological or biochemical state of neurons that alters their ability to generate specific patterns of neuronal plasticity.
Network motifs: small patterns of interactions among the components of a complex network system that occur at significantly higher numbers than in a randomized network. Network motifs are the functional building blocks of complex systems.
Neuronal oscillations: rhythmic or repetitive patterns of neuronal activity. Oscillations that cross action-potential threshold (e.g., regular spiking/bursting) are supra-threshold oscillations. Oscillations below action-potential threshold are sub-threshold oscillations. Subthreshold oscillations with action potentials in a subset of oscillatory cycles are mixed-mode oscillations. Intrinsic oscillations emerge through interactions among components that are intrinsic to a neuron, whereas network oscillations require synaptic interactions across neurons for emergence.
Pleiotropy: the ability of the same biological component to be involved in

other complex biological networks [5,6,8,10,11,20,21,29,35–37]. Action potential generation constitutes an elegant example that illustrates the concept of simple network motifs and the intricate interactions among different cross-scale motifs (Figure 2B). These motifs implement a well-defined cellular-scale physiological outcome through interactions between different molecular components through clearly identifiable network motifs. A fast positive feedback loop involving voltage-gated sodium channels rapidly amplifies membrane voltage to yield the rising phase of an action potential. The same voltage variable forms a delayed negative feedback loop with voltage-gated potassium channels to suppress voltage [58–60]. An activation-coupled inactivation process in voltage-gated sodium channels [61] mediates an autoregulatory motif that shuts down the positive feedback loop. The delayed negative feedback loop and the autoregulatory suppression of the positive feedback loop mediate the falling phase of the action potential [58–60]. Together, there are intricate functional interactions between three distinct network motifs, two of which span different scales, that generate the action potential (Figure 2B).

Within this framework, voltage-gated ion channels implement positive or negative feedback loop motifs depending on whether they amplify or suppress voltage upon depolarization. In realizing different complex cellular-scale functions, it is crucial to account for the timescales of the loops. For instance, the generation of **intrinsic bursts** [62,63] or spike-frequency adaptation [64,65] requires interactions between slower positive and negative feedback motifs (Figure 2C) with faster spike-generating loop motifs (Figure 2B). Such interactions between different network motifs, each involving cellular variables (membrane voltage, calcium) and molecular components (ion channels, cytosolic buffers, membrane pumps), yield intricate cellular functions such as intrinsic bursting, spike-frequency adaptation, and graded persistent activity [66] (Figure 2C,D).

In addition to network motifs involved in action potential firing properties, there are crucial network motifs that regulate the subthreshold physiology of neurons. For instance, a slow negative feedback loop at the subthreshold level implements a diversity of neuronal functions including suppression of neuronal excitability, voltage sag, and **intrinsic resonance** through suppression of low-frequency components and class II/III neuronal excitability [52,54,56,57,67–70]. The slow kinetics of the negative feedback is central to each of these functions, without which targeted suppression of low-frequency inputs would be infeasible. Any motif that implements such a slow negative feedback loop, in conjunction with the passive properties of the neuron which provide suppression of higher frequencies, yields intrinsic resonance where neurons respond maximally to an intermediate frequency value (Figure 2E).

Importantly, such a negative feedback loop can be implemented through voltage-dependent activation of an outward current (K_v7) or voltage-dependent deactivation of an inward current (HCN). Thus, the sign of the feedback loop motif is not merely dependent on the sign of the current through the channel but is also governed by the coupling of channel activation to voltage. These observations show that the clarity of the implemented function is attained by viewing the network motif in its entirety, comprising the interacting nodes and the connecting edges.

Slow negative feedback loops yield subthreshold neuronal oscillations when they interact with a fast positive feedback loop (Figure 2F) or with noise [6,53–56]. Mixed-mode oscillations, involving subthreshold oscillations and spikes, can be achieved by interaction of the slower positive/negative feedback motifs (Figure 2F) with faster spike-generating positive/negative feedback motifs (Figure 2B). These observations (Figure 2A–F) also emphasize that the mapping between ion-channels and network motifs is not one-to-one, and there are scenarios where several ion-channels participate in each motif or a given motif is implemented by one of several ion channels.

multiple functional processes. Degeneracy refers to many-to-one mapping between components and the function implemented, whereas pleiotropy defines one-to-many mapping in the same context. Together, degeneracy and pleiotropy complete many-to-many mapping between components and functional outcomes in complex systems.

Robustness: a property of systems which ensures that the function of a system is maintained despite the presence of external and internal perturbations.

Scales of analysis: scales refer to range of values encompassing smallest and largest magnitudes of a measured item within the scope of the study. Temporal scales in biology can range from less than a millisecond (e.g., action potential) to days and beyond (e.g., behavioral ecology). Spatial scales within biology range from nanometers (e.g., molecular dynamics) to kilometers and beyond (e.g., the biosphere). We use this phrase to distinguish the size/spatial scales that span the molecular–cellular–network–behavioral levels of biological organization.

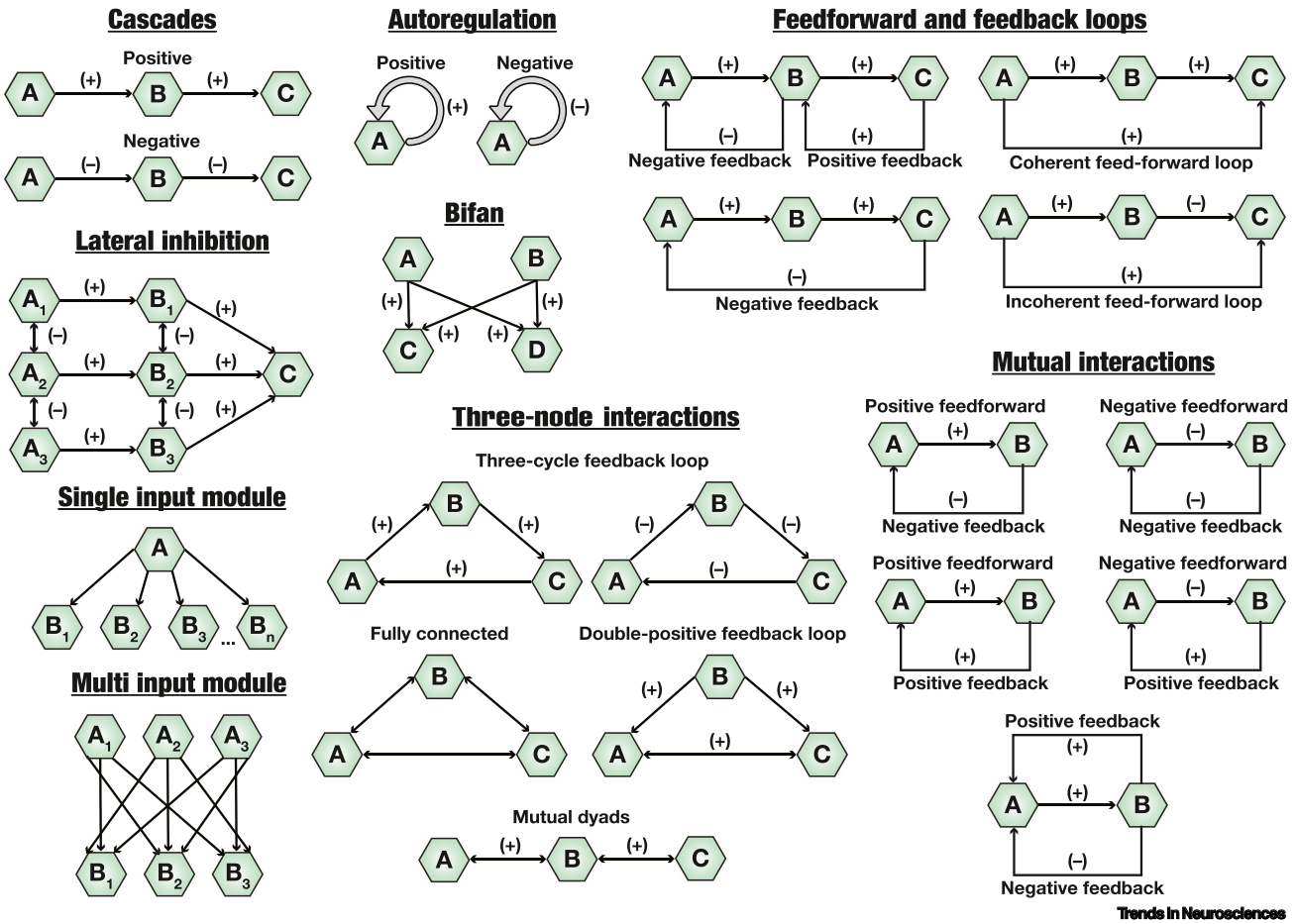

Figure 1. Examples of network motifs. The hexagons represent nodes. The lines connecting them represent edges, and the arrows represent the directed nature of the network motifs from the source node to the target node. A positive sign above the edges represents either (i) the activation of the target node by the source node, if the target node represents a molecular component, or (ii) an increase in the variable represented by the target node by the source node, if the target node represents a cellular variable. A negative sign represents either inhibition of a molecular target node or reduction in the target cellular variable by the source node. A cascade represents a sequence of feedforward activation or inhibition of multiple nodes that does not result in redirection of edges back from any of the target nodes to any of the prior source nodes. Lateral inhibition represents multiple cascades organized into multiple layers where the components within a layer manifest mutual inhibition. Single- or multi-input modules are two layers of nodes that show unidirectional connectivity with single or multiple origin nodes, respectively. Autoregulation represents a network motif where the activation of a component results in either enhanced (positive) or reduced (negative) activation of the same component. A bifan represents two source nodes, each regulating two target nodes. Feedforward and feedback loops: a loop represents a sequence of activation or inhibition of multiple nodes that involves redirection of edges feeding back from at least one of the target nodes to at least one of the prior source nodes. Coherence (with reference to coherent vs incoherent loops) in feedback loops involving more than two edges represents the consistency of the positive sign on the edges along the loop that connect the different nodes. Of the several motifs involving three-node interactions, some motifs represent loops whereas a mutual dyad represents reciprocal connectivity between the three nodes of the triad. Mutual interactions between two-node motifs can involve positive and/or negative feedback loops.

The set of network motifs expressed in a particular neuron are neuron-specific, and the properties and expression strengths of individual molecules define the edge strengths. For instance, weak or strong voltage-dependency of individual ion channels defines the strength of the edge between voltage to specific molecular nodes and the channel density and kinetics define the strength of the edge between the molecular node back to the voltage node [15,17,69,71]. In addition, most biological processes are stochastic, and there is considerable neuron-to-neuron heterogeneity in edge strengths even within neurons of the same subtype. Overlooking either heterogeneity or stochasticity could result in oversimplified interpretations of network motifs and their interactions [15,17,54,71–76].

Table 1. Functional roles of key network motifs in cellular neurophysiology and neural plasticity

Network motif	Components involved	Neurophysiological or neural plasticity outcomes
Negative autoregulation	Fast sodium channels	Inactivation of voltage-gated fast sodium channels during an action potential (e.g., Figure 2B)
Positive autoregulation	Leak channels and various voltage-gated ion channels	Propagation of synaptic voltage from dendrites to the soma (e.g., Figure 3)
	Fast sodium channels	Action potential propagation from the axon initial segment to the axon terminal (e.g., Figure 3)
	Dendritic sodium channels	Backpropagation of action potentials from the soma to a dendrite (e.g., Figure 3)
Negative feedback	KDR channels	Repolarization phase of the action potential (e.g., Figure 2B)
		Afterhyperpolarization (e.g., Figure 2C)
	Voltage-gated calcium and calcium-gated potassium channels	Spike-frequency adaptation (e.g., Figure 2C)
		Intrinsic bursting (e.g., Figure 2C)
	HCN/K_v7 channels	Resonance (e.g., Figure 2E)
		Voltage sag
		Post-inhibitory rebound, rebound spiking, and rebound bursting
	Calcium-dependent enzymes and their substrates, other signaling cascades	Homeostatic plasticity, activity-dependent enhancement of intrinsic excitability (Figure 4)
Positive feedback	Fast sodium channels	Depolarization phase of the action potential (e.g., Figure 2B)
	NMDA receptor, NaP and LVA calcium channels	Plateau potentials (e.g., Figure 2C)
	Voltage-gated calcium channels and dendritic sodium channels	Depolarizing after-potential (DAP) (e.g., Figure 2C)
	Calcium-dependent enzymes and their substrates, other signaling cascades	Hebbian synaptic plasticity, activity-dependent enhancement of intrinsic excitability (Figure 4)
Coupled negative and positive feedback	HCN/K_v7 and NaP	Intrinsic peri-threshold membrane potential oscillations (e.g., Figure 2F) Mixed-mode oscillations
	T-type calcium channels	Voltage and calcium oscillations (e.g., Figure 5C)
	Calcium-dependent enzymes and their substrates, other signaling cascades	Error-correcting mechanism combining learning and homeostasis (e.g., Figure 4, Figure 5D)
Cascade or positive feedforward or simple regulation	Diffusion and other active network motifs including ion channels and calcium-handling mechanisms	Cross-compartmental propagation of voltage and calcium across somata, axons, and dendrites (Figure 3)
Recurrent loops	Voltage-gated calcium channels and calcium-dependent depolarizing currents	Graded persistent activity (e.g., Figure 2D)
Bifan	Calcium- and voltage-sensitive channels	Graded persistent activity, bursting, and spike-frequency adaptation (e.g., Figure 2C,D)
Mutual dyad	Branch points in neuronal morphology	Signal propagation across neuronal compartments
Biased input-segregated output	Voltage-gated channels and cable properties	Input processing in neurons with active dendritic structures: segregation, selective amplification, and location-dependent filtering (Figure 3)
Multi-input module	Voltage- and calcium-dependent channels	Bursting, spike-frequency adaptation (e.g., Figure 2C)
	Calcium-dependent enzymes and their substrates, other signaling cascades	Concomitant calcium-dependent neural plasticity in several components (e.g., Figure 2B,C)
Dimensionality expansion/single-input module	Calcium-dependent enzymes and their substrates, other signaling cascades	Concomitant calcium-dependent neural plasticity in several components (e.g., Figure 4C,D)
	Voltage- or calcium-dependent channels	Several intercoupled network loops dependent on a single variable (e.g., Figure 2B,F, Figure 3, and Figure 5C,D)

Spatial interactions among network motifs in cellular neurophysiology

The physiology and structure of a neuron go well beyond its cell body. A typical neuron is a spatially extensive structure that includes dendrites, dendritic spines, an axonal initial segment,

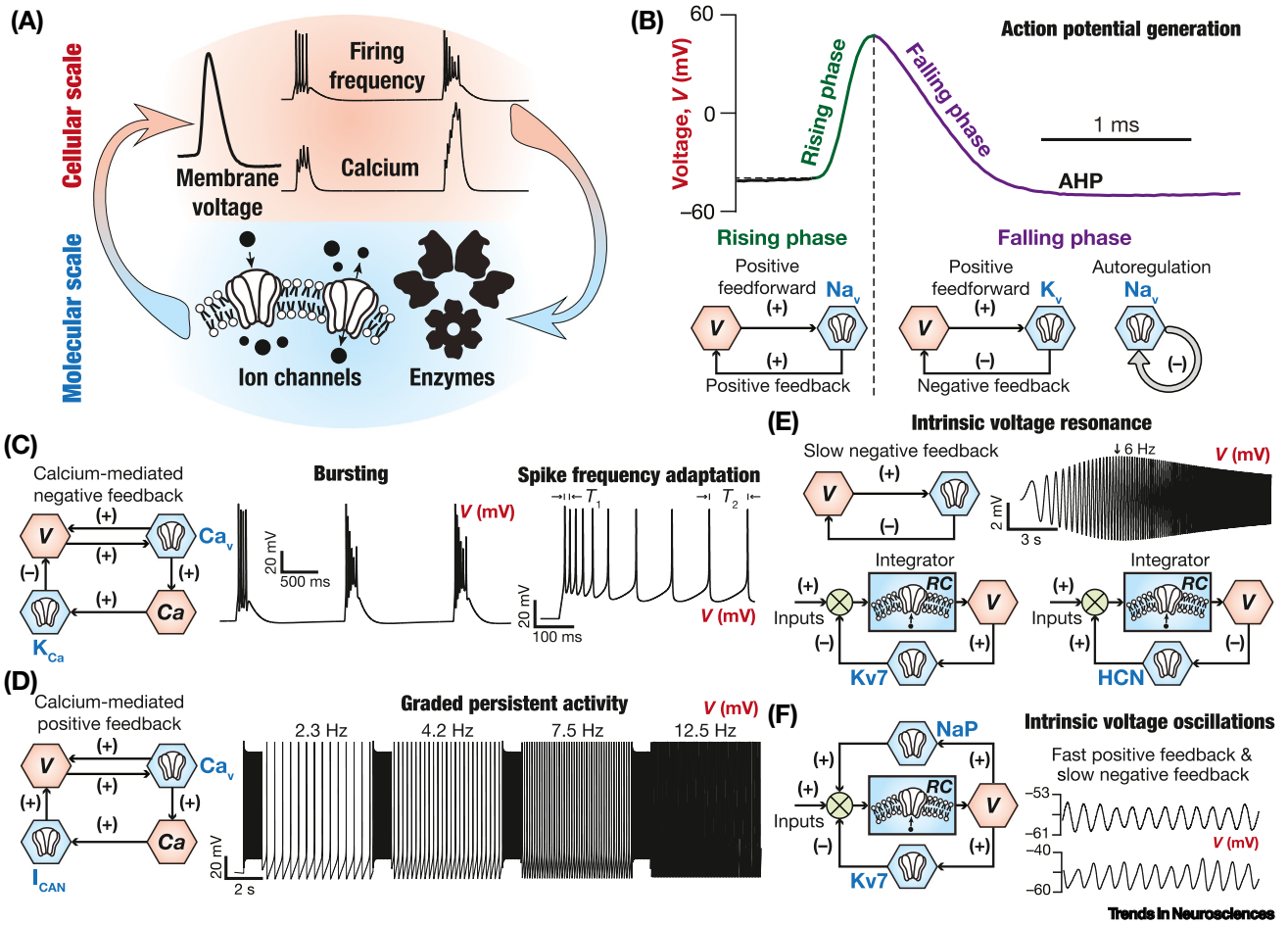

Figure 2. Network motifs in cellular neurophysiology. (A) Network motifs in cellular neurophysiology involve cross-interactions among cellular properties and molecular components. (B) Action potentials result from interactions between several network motifs: (i) a positive feedback loop mediated by voltage-gated sodium (Na_v) influx, yielding the rising phase; (ii) a delayed negative feedback loop mediated by voltage-gated potassium (K_v) efflux, contributing to the falling phase; and (iii) an autoregulatory mechanism in sodium channels, where inactivation is dependent on activation, that contributes to the falling phase. A single cellular-scale node (voltage) connects to several molecular-scale nodes (ion channels), which make positive or negative feedback edges onto the voltage node. (C) Bursting and spike-frequency adaptation emerge due to interactions between the spike-generating network motifs (panel B) with a slower calcium-mediated negative feedback loop. Voltage-gated calcium channels (Ca_v) and calcium-activated potassium channels (K_{Ca}) yield a four-node negative feedback loop. (D) A four-node calcium-mediated positive feedback loop mediates graded persistent activity in entorhinal cortical neurons, along with spike-generating network motifs. I_{CAN}: nonspecific calcium-sensitive cationic current. In (C) and (D) the impact of calcium of Ca_v through calcium-dependent inactivation is not shown. (E) Resonance in neurons stems from slow negative feedback loops (that suppress low-frequency, but not high-frequency, inputs) which are mediated by ion channels that are activated by depolarization and yield hyperpolarization upon activation (e.g., K_v7), or by channels that are deactivated by depolarization and yield depolarization upon activation (e.g., HCN). (F) Intrinsic voltage oscillations require resonance and a fast positive feedback loop to amplify damped oscillations. Traces shown are for a 3 s period [54]. Abbreviations: AHP, afterhyperpolarization; *RC,* resistor–capacitor circuit.

the axonal arbor, and boutons. Because molecular components are expressed across all compartments, such a spatial organization translates to bidirectional cascade motifs (Figure 1) that interconnect several network motifs that define each compartment (Figure 3). Each neuronal compartment is endowed with different sets of network motifs (Figure 3), including positive and negative feedback loops involving cellular and molecular components (Figures 2 and 3). The edges that connect these different compartment nodes are defined by neuronal morphology, the passive and active properties of the connecting nodes, and the diffusion characteristics of the different molecular components. The strength of the edge between a dendritic spine node and the parent dendritic node is constricted by the diffusion barrier imposed by the geometry

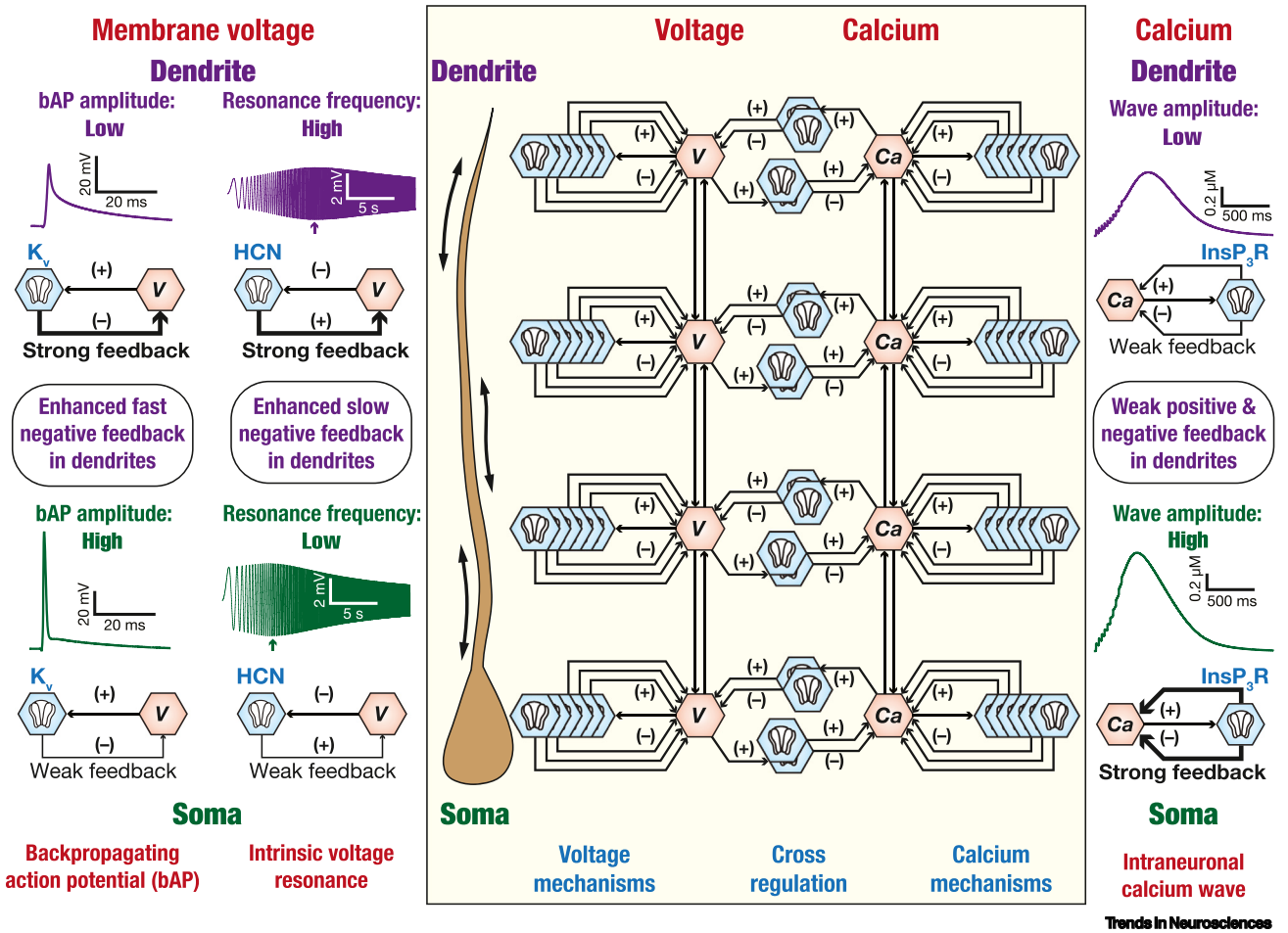

Figure 3. Spatial interactions among network motifs in cellular neurophysiology. Network motifs in cellular neurophysiology are spatially spread across the neuron and could show location-dependent manifestation. The shaded box shows structural connectivity spanning different sets of motifs (and/or disparate edge strengths of same motifs) that constitute each neuronal compartment along the somatodendritic axis. Each neuronal compartment is depicted by a voltage and a calcium node at the cellular scale, accompanied by several active voltage-regulating and calcium-regulating molecular mechanisms. Bidirectional flows of voltage and calcium are depicted as edges between the compartment-specific voltage and calcium nodes. The left column shows the impact of differential spatial distributions of two different network motifs on voltage responses. (i) K_v channels that mediate a fast negative feedback loop are at higher density in dendrites. The consequently strong negative feedback in the dendrites results in a smaller backpropagating action potential (bAP) in dendrites, yielding a somatodendritic gradient in bAP amplitude. (ii) HCN channels mediate a slow negative feedback loop and are at higher densities in dendrites. The consequent strong negative feedback motif in dendrites yields a higher resonance frequency in dendrites than in the soma. The right column shows the impact of the differential distribution of calcium-regulating mechanisms [including inositol trisphosphate receptors ($InsP_3Rs$) whose somatic density is higher] on calcium wave amplitude along the somatodendritic axis. $InsP_3Rs$ have a bell-shaped dependence on calcium concentration, thus mediating a conjunctive calcium-dependent negative and positive feedback motif. The strong versus weak feedback loops at the soma versus the dendrite translate to higher calcium wave amplitude at the soma.

of the structures. A branch point can act as a mutual dyad motif (Figure 1). Thus, the specific set of network motifs that define the structural aspects of a single neuron is governed by the detailed morphometry of individual neurons [49]. Importantly, each compartment of this structure is not defined by repeating set of identical motifs coupled with precise edge interactions, but manifest pronounced heterogeneities in the set of nodes and edges that define each compartment. Different neuronal compartments are known to express disparate sets of ion channels, based on the specific functional roles that they play. For instance, the axonal initial segment expresses different ion channels at varied densities and kinetics [77–79], implying that different sets of network motifs with varied edge strengths identify this compartment and facilitate its function as a spike-initiating compartment.

Active dendrites endowed with different active components such as voltage- or calcium-gated ion channels have been extensively studied for heterogeneities in ion-channel expression and kinetics [80–82]. Heterogeneities in network motifs that define each dendritic compartment have been demonstrated to endow neurons with exquisite functional capabilities. The transient potassium channel, which mediates a fast negative feedback loop with voltage, is expressed at a higher density in distal dendrites, thereby yielding stronger negative feedback in distal dendrites (Figure 3). The differential strength of the fast negative feedback loop translates to a somatodendritic gradient in the backpropagating action potentials (Figure 3), a functional characteristic that plays crucial roles in neural plasticity, among others [83–85]. HCN channels that mediate a slow negative feedback loop with voltage express at higher density in dendrites, thereby yielding stronger negative feedback in dendrites. Functionally, this results in greater suppression of dendritic voltages and higher resonance frequency in dendrites compared to the soma (Figure 3), and these together contribute to differential processing of inputs at different dendritic locations [67,68,70]. Specific expression profiles of fast and slow negative feedback motifs across different dendritic compartments mediate segregation [86,87] and location-dependent filtering [68,70,88], resulting in a biased input-segregated output motif with reference to neuronal outputs. With reference to calcium, differential expression of calcium channels on the endoplasmic reticular membrane along the somatodendritic axis and morphological differences translate to gradients in calcium wave amplitude [89,90] (Figure 3). Thus, gradients in physiological measurements within a single neuron are mediated by cross-compartmental heterogeneities in network motifs and edge strengths.

A single neuron is thus an intricate and complex network constructed from several heterogeneous compartments, each endowed with disparate network motifs that drive cellular function. It is therefore not surprising that a single neuron is endowed with complex functional capabilities that can be modeled as a network [50,91,92]. The array of network motifs and the specific set of interactions among them depend on the specific neuronal subtype. Even within individual neuronal subtypes, there is widespread neuron-to-neuron heterogeneity in motifs, their structural and molecular composition, and interactions among them [15,17,54,71,93–96].

Network motifs in neuronal plasticity

Network motifs in cellular neurophysiology are not limited to the manifestation of the characteristic functional properties of individual neurons but are prevalent across all aspects of neuronal plasticity (Table 1). The fundamental requirements for individual neurons to change arise from the need to accomplish adaptation (learning) targets and to maintain **homeostatic** balance. In addition, there are perturbations (e.g., stochastic, pathological) to neuronal function which could trigger plasticity in cellular variables (Figure 4A). Irrespective of what defines such a need, cellular plasticity is implemented by recruiting specific network motifs [21,22], including calcium-dependent activation of signaling cascades that impose changes to specific components (channels, receptors) that induce cellular plasticity (Figure 4A). Thus, network motifs observed in neuronal plasticity are also cross-scale motifs (Figure 4A) that involve a broader set of molecular components than those mediating physiological characteristics.

The balance between plasticity and stability is fundamental to all learning systems. A tilt towards the homeostatic side of the balance hampers adaptation goals, whereas a tilt in favor of plasticity could trigger pathological changes to neuronal physiology (Figure 4B). The plasticity–stability balance is maintained by structured and concomitant changes to several components that involve several cross-scale network motifs. Motifs implementing plasticity-stability balance also play crucial roles during development, neuromodulation, and pathological conditions [97–101]. Developmentally, cellular features such as the expression of specific ion channels and dendritic

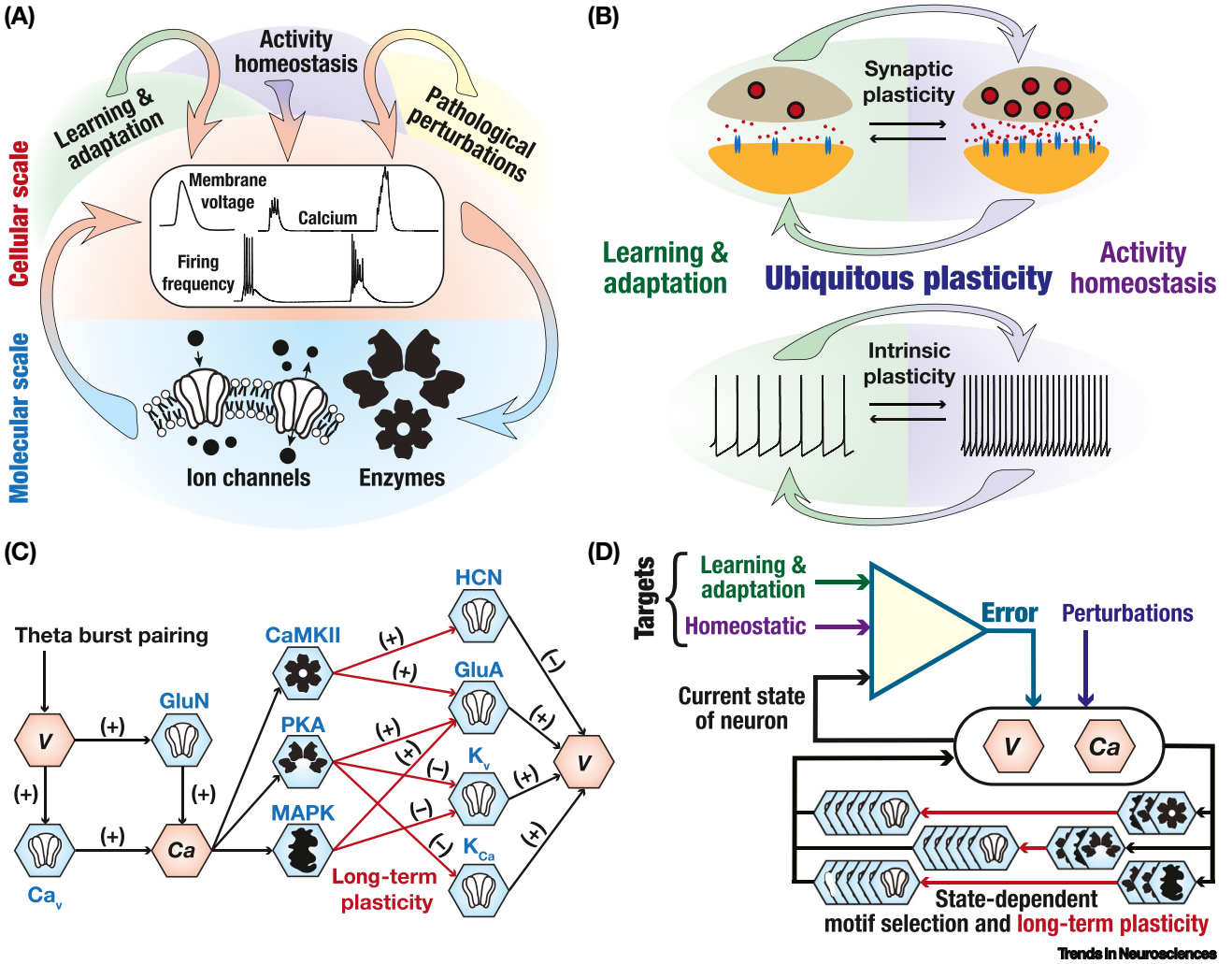

Figure 4. Network motifs in neural plasticity. (A) Factors and components governing network motifs that are involved in neural plasticity. Alterations to cellular-scale properties (membrane voltage, calcium concentration, and firing frequency) result in specific activation of certain molecular components (ion channels and enzymes) which regulate neurophysiological characteristics through short-term dynamics and long-term plasticity. Cellular-scale measurements and the molecular components recruited are governed by learning and adaptation goals, activity homeostasis, and pathological perturbations. (B) The plasticity–stability balance regulates network motifs in neural plasticity. The balance between homeostasis and plasticity that achieves learning and adaptation targets is crucial and dictates the choice of network motifs that implement different forms of plasticity. Plasticity is ubiquitous and could be in synaptic, intrinsic, or other components. Different forms of plasticity could play learning or homeostatic roles in a system- and context-dependent manner. (C) An example of the intricate interactions among a variety of network motifs involved in neural plasticity. Theta burst pairing alters somatodendritic voltage and calcium profiles, which in turn activate a variety of downstream signaling molecules. These signaling cascades induce long-term plasticity (red edges), and either up- or downregulate specific channels and receptors to yield long-term plasticity of voltage responses. The convergence of several network motifs in implementing neural plasticity is typical across different cell types subjected to disparate activity patterns. (D) Global cell-wide interactions among different network motifs (in neuronal plasticity) in meeting physiological targets and in responding to perturbations. Different contextual and cell-specific heterogeneities define motif selection in achieving targets and implementing robustness to perturbations.

arborization mature postnatally [98,99]. From the network motifs perspective, such a maturation process corresponds to changes in the set of motifs available in functionally defining a specific neuron. Epilepsy provides a case in point of pathological plasticity that can be conceptualized via network motifs. Specifically, in hippocampal neurons, epilepsy has been linked to the loss of fast and slow negative feedback loops owing to the loss of inactivating potassium [100] and HCN [101] channels, respectively (Figure 3).

Plasticity processes in neurons are widespread and involve adaptation of synaptic, morphological, and intrinsic properties (Figure 4B) [102–106]. Importantly, however, the prevalence of plasticity does not imply that plasticity occurs in arbitrary fashion. We argue that there are well-defined network motifs that impose clear constraints on the ensemble of components that undergo plasticity and the direction of change in each component. Neural plasticity associated with theta burst pairing (TBP) in hippocampal neurons [70,84,107–110] is an elegant example of the intricate constraints placed on components that change together. TBP increases calcium, which connects to several molecular nodes (enzymes) through edges, and these together induce long-term plasticity (up- or downregulation) of specific ion channels, which themselves mediate positive or negative feedback motifs with membrane voltage (Figure 4*C*). There is specific structure to the set of nodes and edges that are present, together yielding a well-defined and constricted plasticity space spanned by TBP activity (Figure 4*C*). Such intricate plasticity motifs that implement structured plasticity manifolds are associated with different plasticity paradigms across several neuronal subtypes [17,105,106,111–115].

Network motifs involved in implementing neuronal plasticity (e.g., Figure 4C) mediate adaptation, driven by internal and external state changes, in the set of network motifs (e.g., Figure 2) involved in cellular neurophysiology (Figure 4D). The complexity associated with network motifs involved in neuronal plasticity can be appreciated by noting that several such plasticity motifs (e.g., Figure 4C) are present across each cellular compartment (e.g., Figure 3). Cellular plasticity emerges as a conglomeration of spatial interactions across all network motifs governing physiology and plasticity, and spanning all compartments. In addition, the manifestation of **metaplasticity** [116] implies that these plasticity motifs are not fixed but continually change through plasticity in cellular and molecular components.

From a broader perspective, the conceptualization of neural plasticity through network motifs extends beyond implementation of cellular plasticity (Figure 4D). For instance, in the formation of engram cells that encode a specific context, a subset of these neurons (single/multi-input module motifs; Figure 1) undergo synaptic and intrinsic plasticity [112,113,117] to form a biased input segregator network motif. Homeostasis in neural systems is studied as a negative feedback network motif that alters specific molecular components towards homeostatic regulation through synaptic and/or intrinsic changes [15,71,75,102–104,118–122]. In **continual learning** systems [123], the broader feedback motif should convey errors in both stability and learning targets, where learning-related error signals recruit physiology and plasticity motifs that implement cellular outcomes in a state-dependent manner (Figure 4D). The components implementing these targets depend on several factors, including the current state of the neuron, the spatiotemporal characteristics of neuronal inputs, the stability and adaptation targets, and perturbations [18,71,97,106,118].

Complexity, degeneracy, and network motifs in cellular neurophysiology

Complex systems have been characterized as systems that manifest an interplay between functional specialization in individual subsystems and functional integration among these subsystems that yield specific system-wide outcomes [2]. For instance, a neuron involves several functionally specialized subsystems, such as ion channels, enzymes, ionic pumps, and cytosolic buffers, each of which has specific functions associated with it. Interactions among these functionally specialized subsystems yield functional integration [2] towards achieving specific cellular-scale outcomes such as action potential firing, resonance, and plasticity [15,17]. From the complex systems perspective, network motifs offer tools to quantify the functional interactions among several functionally specialized subsystems towards achieving specific emergent functions.

A key feature of complex systems is the manifestation of degeneracy – the ability of disparate combinations of subsystems to yield similar functional outcomes [2]. The network motifs perspective unveils the manifestation of a cascade of different forms of degeneracy associated with the physiology and plasticity of single neurons. Specifically, a given network motif could be implemented by different sets of molecular nodes, referred here as component degeneracy (Figure 5A). A compartmentalized cellular function can be implemented by same sets of network

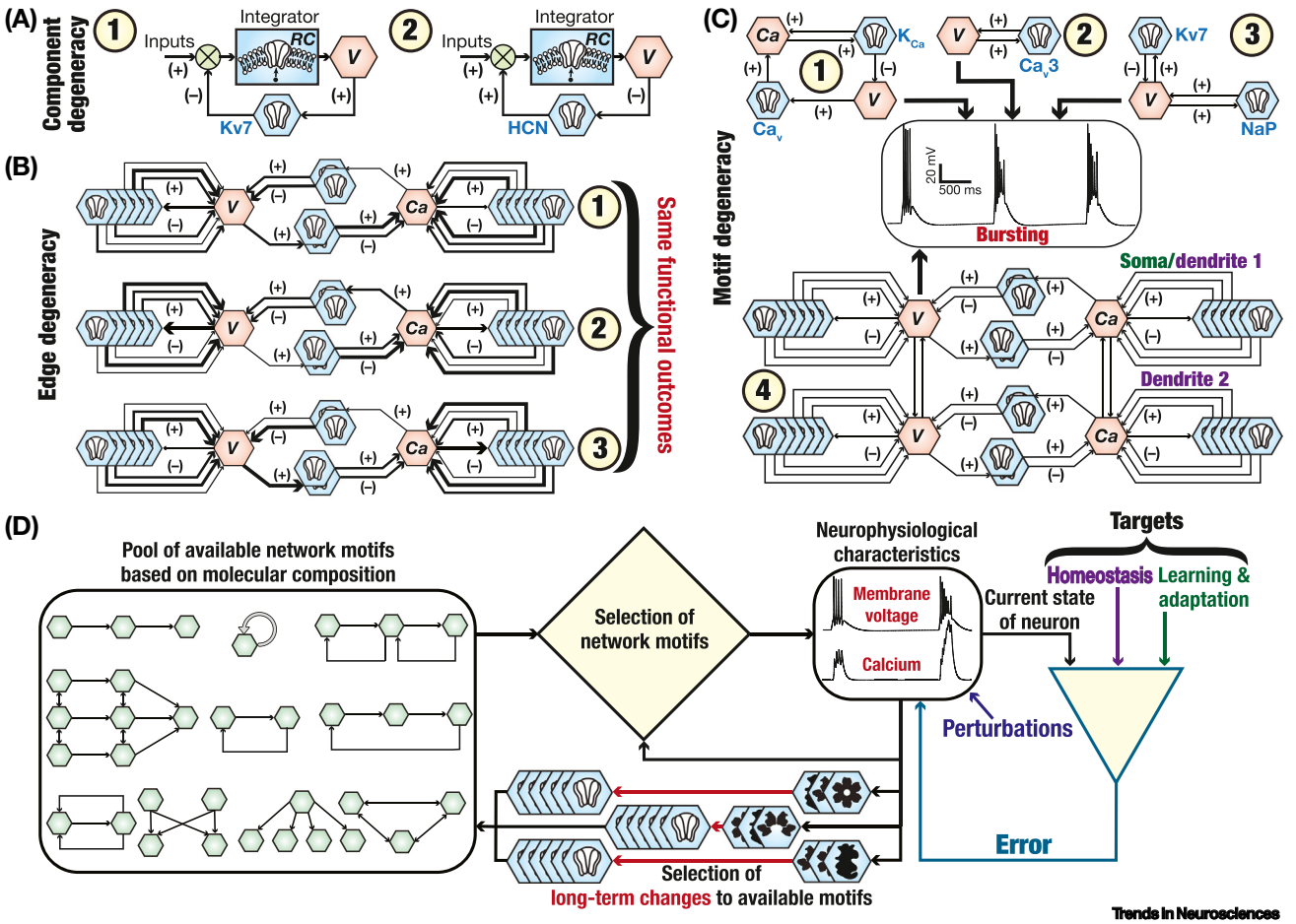

Figure 5. Degeneracy and network motifs in cellular neurophysiology. (A) Component degeneracy is observed when disparate molecular/cellular components implement the same network motif. An illustrative example is a slow negative feedback loop motif which can be implemented either by a slow depolarization-activated outward current (①: K_v7) or by a slow hyperpolarization-activated inward current (②: HCN). (B) Edge degeneracy defines a scenario where the components in different neurons are the same but the strengths of the edges are distinct across different neurons manifesting the same functions. The edge strength refers to the level of expression of ion channels and other molecular components. Thus, edge degeneracy refers to achieving characteristic functional outcomes despite cell-to-cell variability in expression profiles. The schematics depict three (①, ②, ③) illustrative examples, where disparate combinations of edge strengths yield similar functional outcomes. The term 'ion-channel degeneracy' has been used to describe phenomena such as those depicted in (B). However, edge degeneracy is broader because it is not limited to ion channels as components and may involve several other molecular components such as calcium-binding proteins. (C) Motif degeneracy refers to the ability of disparate network motifs to implement the same function. The schematic illustrates the example of disparate network motifs that achieve bursting in neurons through interactions of spike-generating network motifs (Figure 2B) with ① a calcium-driven slow negative feedback loop; ② T-type calcium channels; ③ persistent sodium (NaP) channels and a slow negative feedback loop (K_v7); ④ disparate sets of network motifs expressed in soma versus dendrites and spatial interactions across compartments. (D) Schematic synthesis of how network motifs involved in neuronal physiology and plasticity might interact with each other in settings that recruit distinct forms of degeneracy (panels A–C). There are specific learning and homeostatic targets that neurons must achieve in a manner defined by the present behavioral and network context. Algorithmically, an error signal computed from the current state of the neuron and its relation to these targets alters the physiological characteristics of the neuron. These changes, in turn, select specific signaling pathways towards inducing long-term plasticity (red arrows) in fixed combinations of ion channels and receptors (e.g., Figure 4C). The selection of ensembles of network motifs for inducing plasticity and for executing neurophysiological characteristics is driven by the current state of the neuron, the present behavioral and network context, and robustness to perturbations. Abbreviation: *RC,* resistor–capacitor circuit.

motifs with disparate edge strengths, referred to as edge degeneracy (Figure 5B), or by disparate combinations of different network motifs, defined as motif degeneracy (Figure 5C). Finally, overall neuronal physiology and plasticity emerge through disparate combinations of different network motifs, each implemented by disparate sets of components (Figure 5D). Degeneracy in the manifestation of characteristic physiological properties, in physiological properties across the dendritic arbor, in the emergence of plasticity profiles, and in encoding characteristics are well-established across several cell types [15–18,54,74,96,114,124].

In this cascade of degeneracy, functionally specialized components integrate to yield specific network motifs; functionally specialized motifs then integrate to yield signature cellular-scale outcomes. Thus, network motifs form a functional intermediary between the molecular-scale components and cellular-scale outcomes. Whereas completely random combinations of components would not yield motifs with specific functions, there are several combinations of components that can achieve specific network motifs or functional outcomes (Figure 5A–C). Therefore, a fundamental question in complex systems manifesting degeneracy concerns how targeted selection of a specific ensemble of components is achieved (Figure 5D). The selection of specific components that implement cellular functions is governed by the current set of available motifs, the state of the neuron, the learning and homeostatic targets, and perturbations that the neurons encounter (Figure 5D). The set of available motifs is dynamic owing to plasticity in the expression profiles or properties of the different components. A measure of biological complexity could be achieved by a combination of the following [76,125,126]: the functional targets that are required to be achieved by the neuron, the disparate network motifs that need to interact together towards achieving these targets, the multiplicity of routes to achieve each network motif, and the possible disparate combinations of motifs that could achieve the functional targets.

Concluding remarks and future perspectives

The utility of network motifs in deciphering complex systems is well established [5,6,8,10,11,20,21,29,35–37]. We have discussed the application of network motifs in conceptualizing single neuron function, and highlighted the ubiquitous presence of network motifs across neurophysiology and neural plasticity (Table 1). The complexity of network motifs in cellular neurophysiology encompasses multiple timescales associated with the different motifs, spanning sub-millisecond periods (e.g., action potentials) to days and beyond (plasticity). This combinatorial complexity is accentuated by the intricate interactions among motifs across neuronal compartments at different timescales, the ability of network motifs to stably adapt to a changing environment, and the cascade of degeneracy that defines the components of and interactions among motifs (Figures 2–5). The network motifs perspective of neurophysiology and plasticity provides a detailed functional viewpoint that neither oversimplifies complex neural function (as a perceptron or an integrate-and-fire unit) nor delves into the properties of individual molecules. The network motifs perspective refines single-neuron functions by identifying [127] that: (i) a cellular event comprises distributed activity of network motifs that span the spatial extent of the entire cell (Figures 2 and 3); (ii) cellular events emerge as a complex ensemble, spanning the spatial extent of the cell, of several nonlinearly interacting motifs and spatially localized inputs; (iii) a cellular plasticity event comprises distributed plasticity of several specific components that change together, driven by network motifs that span the spatial extent of the entire cell (Figure 4); and (iv) cellular events are governed by a cascade of degeneracy involving multiple components and motifs (Figure 5).

The network motifs perspective can inform several future lines of research on neuronal physiology, plasticity–stability balance, and continual learning (see Outstanding questions). For instance, although degeneracy in neuronal physiology and plasticity is well-established, questions remain concerning how degeneracy is achieved in various scenarios and how individual neurons select

Outstanding questions

How do heterogeneity and stochasticity at the nodes and edges of different network motifs affect their individual functions and their contributions to cellular neurophysiology?

Is there a hierarchy of importance among the different network motifs that contribute to cellular neurophysiology? Does the development of individual network motifs depend on the existence of other motifs?

How do network motifs involved in neuronal plasticity relate to plasticity manifolds? What factors contribute to the structured nature of concomitant plasticity in different components?

How do neurons select specific nodes and motifs towards the emergence of specific neurophysiological outcomes? In the context of the manifestation of a cascade of degeneracy, how is one solution picked over the others?

How do the disparate sets of network motifs (in neurophysiology and neural plasticity) and changes to them contribute to the robustness of neuronal properties and their resilience to perturbations?

Perturbations could result in the loss of specific nodes or network motifs. Under what conditions and how can such loss be replaced by another set of nodes or motifs, resulting in compensation? Under what conditions is such compensation not possible, resulting in pathological scenarios?

Are any specific pathological conditions associated with loss of distinct network motifs? Could interventions that mitigate the pathology be implemented by identifying the loss of specific motifs?

Negative feedback motifs are ubiquitous in complex biological systems where they implement stabilization and error correction. How do negative feedback loops at different scales of organization (molecules, circuits, systems) and different timescales interact towards maintaining continual adaptation and stability in organisms?

Is there representational drift in the set of motifs that implement a fixed function? Given widespread degeneracy in neural

specific solutions from a pool of several possibilities. Considering these questions through the lens of Marr's levels of organization [19], the network motifs perspective views neural function and plasticity as a computational problem solved by the neuron, where each network motif performs specific computations. In this perspective, solutions to cell-wide computational problems are achieved by interactions among different network motifs that offer several **pleiotropic** and degenerate solutions, instead of focusing on the specific hardware that implements this computation. Finally, an algorithmic level can be conceptualized as the one that selects a solution, – which achieves specific adaptation targets and maintains robustness to perturbations – from a degenerate pool of possibilities [128] (Figure 5D). Thus, within Marr's framework, the question on degeneracy about how specific sets of heterogeneous elements combine to elicit the same function could be addressed if the set of network motifs mediated by these elements are elucidated.

function, could the same precise function in the same neuron be implemented by disparate motifs or components over time?

From a pathology standpoint, questions could be posed about the precise roles of aberrant motifs in mediating the cellular signatures of neurological disorders. If modular motifs are identified, it would be possible to rescue aberrant motifs through one of the several degenerate routes that yield such motifs. The identification of network motifs as building blocks for cellular neurophysiology and plasticity provides a structured foundation for understanding how neural plasticity and plasticity manifolds evolve during learning and pathology. Such a perspective involving aberrant motifs, instead of aberrant molecular components, would shift the focus to building or rescuing network motifs towards resetting pathological activity or plasticity [14,30,124,129].

Finally, from a modeling and machine learning perspective, network motifs in neurophysiology and plasticity could guide the construction of better neuronal models that effectively implement biological principles and efficiency. Computationally, single-neuron models that account for characteristic morphology, molecular properties, and signaling dynamics are exorbitantly complex. In addition, continuous updation of intrinsic, synaptic, and structural properties due to continual adaptation dramatically increases the computational cost. The computational cost of model implementation can be drastically reduced, without affecting physiological or plasticity outcomes, by substituting molecular and cellular components of neurons by the network motifs that they implement [49–52,54,130,131]. These functionally precise neuronal models built with network motifs could then be used to perform large-scale physiological analyses, probing diversity in motif expression across different neuronal subtypes. Networks of such diverse neurons, each of which could manifest cellular-scale degeneracy, could then be employed towards building artificial learning systems that mimic the ubiquitous biological plasticity that mediates stable continual learning. In implementing such multiscale synthesis, it is essential to recognize that no biological scale operates in isolation [11,58,60,106,132]. Molecular signaling motifs regulate cellular physiology and plasticity by changing molecular components and the set of available motifs (Figures 4 and 5). Similarly, interactions through chemical and electrical synapses across neurons strongly regulate cellular physiology and plasticity. In turn, cellular functions affect biochemical signaling networks and alter other neurons through synaptic interactions. Thus, it is essential that multiscale interactions are accounted for in evaluating complex biological systems, especially to ensure that network motifs at any identified biological scale are not assumed to be functioning in isolation.

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Author contributions

D.M. and R.N. conceptualized, illustrated, and wrote this review.

Declaration of interests

The authors declare no competing interests.

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