NEUROSCIENCE

REVIEW

M. E. Hasselmo et al. / Neuroscience 456 (2021) 143–158

The Unexplored Territory of Neural Models: Potential Guides for Exploring the Function of Metabotropic Neuromodulation

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Abstract—The space of possible neural models is enormous and under-explored. Single cell computational neuroscience models account for a range of dynamical properties of membrane potential, but typically do not address network function. In contrast, most models focused on network function address the dimensions of excitatory weight matrices and firing thresholds without addressing the complexities of metabotropic receptor effects on intrinsic properties. There are many under-explored dimensions of neural parameter space, and the field needs a framework for representing what has been explored and what has not. Possible frameworks include maps of parameter spaces, or efforts to categorize the fundamental elements and molecules of neural circuit function. Here we review dimensions that are under-explored in network models that include the metabotropic modulation of synaptic plasticity and presynaptic inhibition, spike frequency adaptation due to calcium-dependent potassium currents, and afterdepolarization due to calcium-sensitive non-specific cation currents and hyperpolarization activated cation currents. Neuroscience research should more effectively explore possible functional models incorporating under-explored dimensions of neural function.

This article is part of a Special Issue entitled: Metabotropic Regulation of Synaptic Plasticity.

Key words: computational neuroscience, biophysical simulations, acetylcholine, dopamine, presynaptic inhibition, neuromodulation.

INTRODUCTION

The space of possible neural models is enormous and insufficiently explored. Existing neural models have primarily clustered around familiar modeling frameworks. This review will address the focus of existing models and attempt to point out unexplored realms that need more exploration. In particular, the focus on rapid neurotransmission needs to be supplemented by exploration of the functional role of slower metabotropic receptor effects.

Many neurally inspired models focus on the rapid feedforward transmission of information through the nervous system. For example, a broad range of current research focuses on feedforward models of visual categorization that model the process of visual images rapidly activating a set of neural processing units in multiple subsequent layers (Rumelhart et al., 1986; McClelland and Rumelhart, 1988; He et al., 2015; LeCun et al., 2015; Simonyan and Zisserman, 2015; Krizhevsky et al., 2017). The use of multiple layers results in these being referred to as ‘‘deep neural networks” or ‘‘deep learning.” These models are essentially modeling the ionotropic excitatory effects of glutamate at synapses within the nervous system, such as the excitatory transmission from retina to thalamus, from thalamus to primary visual cortex, and from primary visual cortex to extrastriate visual areas mediating progressively more complex visual processing (Yamins and DiCarlo, 2016). Other artificial neural network models incorporate extensive recurrent connections to model network dynamics, but still focus on rapid excitatory synaptic transmission at afferent synapses or intrinsic synapses (Sussillo and Abbott, 2009; Sussillo et al., 2015). In the mammalian cortical systems, the rapid transmission of information is largely mediated by glutamatergic synaptic transmission involving the synaptic release of glutamate that causes rapid opening of ion channels in glutamatergic AMPA and NMDA receptors (Cotman and Monaghan, 1986; Sherman, 2016). The dynamics of excitatory activation are regulated by fast GABAergic synaptic transmission mediated by ionotropic $GABA_A$ receptors (Rabow et al., 1995) and the deep learning and recurrent neural network

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https://doi.org/10.1016/j.neuroscience.2020.03.048
0306-4522/

models address the effects of rapid excitatory and inhibitory synaptic transmission and demonstrate strong capacities for behaviors such as visual categorization. However, these models neglect the slower dynamics of metabotropic receptors. This impairs the ability of deep learning and recurrent models to implement internal regulatory mechanisms for network behavioral functions, including internal regulation of transitions between encoding and retrieval and off-line consolidation (Hasselmo, 2006), internal regulation of directed and sustained attention (Hasselmo and McGaughy, 2004), and the contextual gating of higher order cognitive representations (Hasselmo and Stern, 2018).

In contrast to these models focused on fast dynamics, many of the physiological properties of individual neurons undergo regulation by a range of different neuromodulatory neurochemicals that activate metabotropic receptors. These receptors respond to neurochemicals by activating intracellular second messenger pathways that require energy-consuming enzymatic activation, hence the term metabotropic. Metabotropic receptors modulate a range of neural functions that are important to behavior (Hasselmo, 1995, 2006). Some of the dimensions of physiological neural function that are regulated by metabotropic mechanisms are summarized in Fig. 1. Deep learning and recurrent neural network models address dimensions of neural functions such as synaptic plasticity and depolarization. However, those models do not explore a number of dimensions of function shown in the figure, including spiking adaptation, persistent spiking, presynaptic inhibition, rebound spiking, nonlinear dendritic interactions, inhibitory gating and modulation of synaptic plasticity. Metabotropic receptors influence all of these dimensions of function as described briefly here and at greater length in the section on dimensions of metabotropic effects below.

Neurochemicals can influence the intrinsic properties described above and in Fig. 1 via a range of metabotropic receptors including metabotropic glutamate receptors (mGluRs) (Walker et al., 2017),

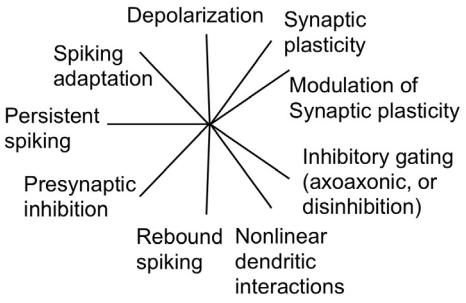


Fig. 1. A sketch of the many dimensions of neural function that are modulated by metabotropic receptors. Many of these dimensions have not been extensively explored in models of neural circuits. The underexplored dimensions include many different intrinsic physiological parameters. Underexplored dimensions include metabotropic modulation of intrinsic dynamics such as spike frequency adaptation, persistent spiking and rebound spiking. Underexplored dimensions of the modulation of synaptic interactions include presynaptic inhibition, disinhibitory circuits or effects such as axoaxonic inhibition. Underexplored dimensions also include the complex nonlinear interactions of voltage-dependent conductances in the dendritic tree.

metabotropic GABA receptors (e.g. $GABA_B$ receptors) (Ault and Nadler, 1982), muscarinic acetylcholine receptors (Hasselmo, 2006), most of the serotonin receptor subtypes (Matias et al., 2017; Lottem et al., 2018) and all receptors to dopamine (Durstewitz and Seamans, 2002) and norepinephrine (Usher et al., 1999). As reviewed more extensively in later sections of this article, these metabotropic receptors can influence neuronal properties including long-term synaptic plasticity (Burgard and Sarvey, 1990; Hasselmo and Barkai, 1995; Patil et al., 1998; Fernandez de Sevilla et al., 2008), short-term presynaptic inhibition of synaptic transmission (Ault and Nadler, 1982; Hasselmo and Bower, 1992; Hasselmo and Schnell, 1994; Fernandez de Sevilla et al., 2002; Fernandez de Sevilla and Buno, 2003) and intrinsic properties of membrane potential regulated by voltage and calcium-dependent conductances such as spiking adaptation, persistent spiking and rebound spiking (Madison and Nicoll, 1986; Barkai and Hasselmo, 1994; Heys et al., 2010). A broad body of research has addressed the functional role of these modulatory receptors (Hasselmo, 1995, 2006), but the space of possible functional models has not been fully explored. This paper will describe some under-explored dimensions of the space of possible functional neural models.

THE UNDER-EXPLORED SPACE OF NEURAL MODELS

The scientific exploration of new domains of knowledge can benefit from a clear characterization of what is known and what is not known. For example, the collection of knowledge in Europe about the (Eurocentric) geography of the earth progressed via the creation of maps that plotted degrees of latitude and longitude, clearly showing the current maps of known territory, and leaving blank the range of locations on the sphere of the earth that had not been mapped by European explorers (see Fig. 2). Similarly, the understanding of chemistry benefited from the development of the periodic table of the elements that could quantify the known elements and predict the potential properties of unknown elements (Mendeleev, 1869).

Neuroscience has made tremendous advances in understanding molecular ionotropic and metabotropic receptor subtypes and their potential physiological mechanisms. In addition, there have been several waves of exploration of the potential functional capabilities of ever larger networks of interacting neurons. However, there are many regions and dimensions of the functional space of models that have been under-explored. The space is multidimensional and difficult to plot in a simple graph, but Figs. 3 and 4 provide an effort to demonstrate the breadth of unexplored model space in neuroscience.

Fig. 3 plots the number of intrinsic conductances incorporated into individual neurons in computational neuroscience or connectionist models versus the number of layers or regions in the individual models. The intrinsic parameters plotted on the *y*-axis in Fig. 3

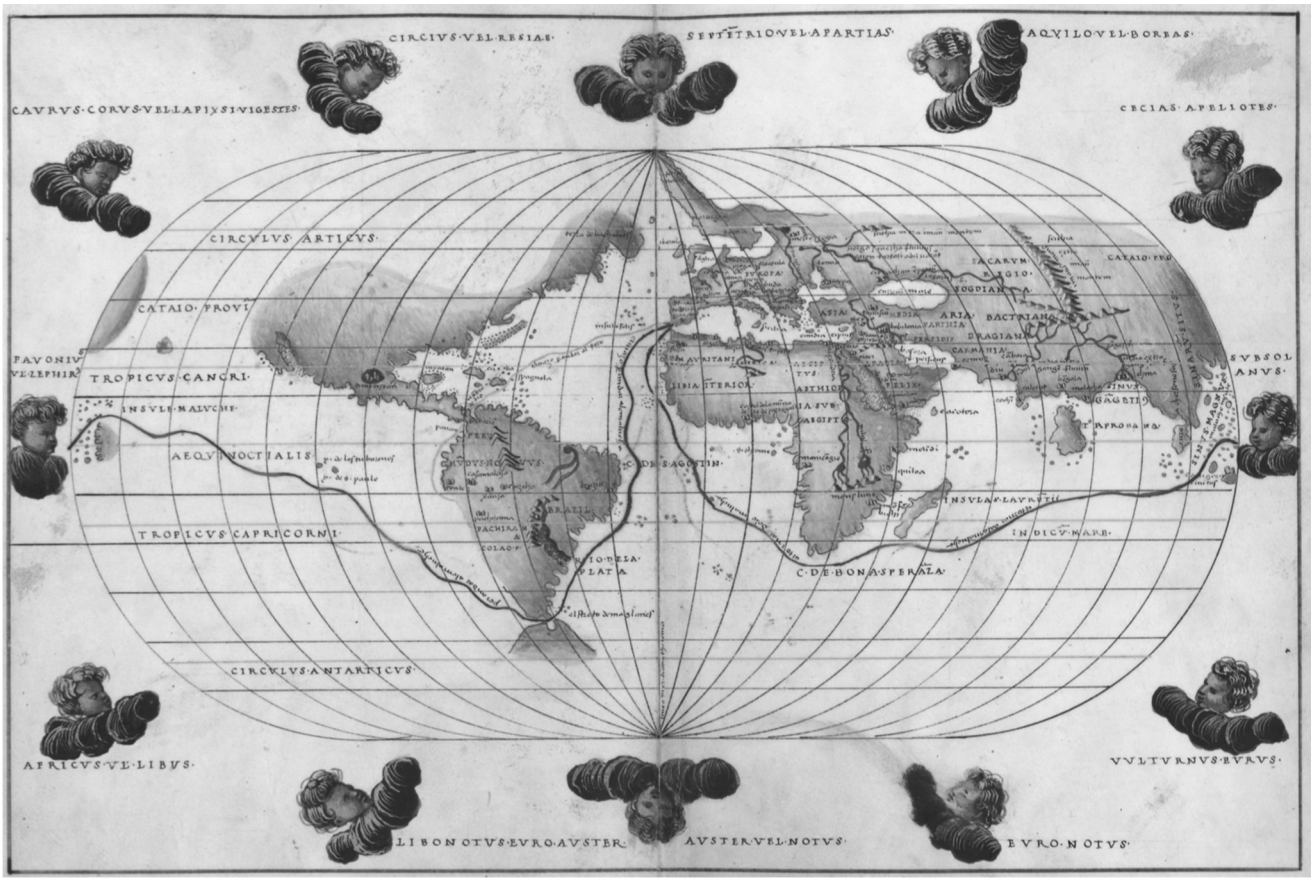


Fig. 2. Example of mapping of explored and unexplored territory. This map was created as part of an atlas by the cartographer Battista Agnese from Genoa (U.S. Library of Congress, online catalog 1071805) to show the known territory of the world and the approximate trajectory of Magellan's circumnavigation of the globe. The map shows how the lines of latitude and longitude provided a unifying framework for plotting the territory previously explored by European explorers, and explicitly delineated the regions of the globe unexplored by Europeans (such as the western coast of North America and the South Pacific). A framework of unexplored space could be useful for guiding exploration of new parameter space by computational neuroscience models.

include intrinsic conductances due to voltage-dependent and calcium-dependent intrinsic conductances as well as ionotropic and metabotropic receptors. As can be seen in the plot, due to the constraints of simulation complexity, most models of intrinsic conductances focus on the function of neurons in a single region with a relatively small number of synaptic connections. The figure provides the citations for a sampling of computational neuroscience models that spread out vertically along the *y*-axis with varying numbers of intrinsic parameters per neuron but very few layers or regions (open circles in figure). In contrast, recent research on artificial neural network models have incorporated ever larger numbers of regions or layers (e.g. deep neural networks) while incorporating only very simplified intrinsic neuronal properties, as can be seen by the models spread horizontally along the *x* axis. These deep neural networks primarily use highly simplified representations of connections with single values representing the instantaneous strength of the effects of excitatory ionotropic glutamatergic synapses or inhibitory $GABA_A$ receptors. In these deep neural network models, individual units have simple rectified linear input output functions (ReLU) which represent the spiking threshold and define firing rate increases with depolarization. These models spread out along the *x* axis with varying number of layers, but a fixed small number of intrinsic parameters. This plot focuses on illustrating the broad unexplored space that could involve multi-region models using biophysically detailed models of intrinsic conductances. The lack of metabotropic receptors in artificial neural networks models may reflect a lack of communication between fields.

The exploration of parameter space is partly a product of the limitations on computing time that restricts the complexity of neurons that can be incorporated in a large scale model with large numbers of neurons and a large number of synaptic parameters for connections between those neurons. For large scale simulations with complex intrinsic properties, simulating a single second of neural time can take hours. Fig. 4 depicts examples of individual computational models in terms of the number of parameters of intrinsic conductances (reflecting the complexity of individual neurons) versus the number of synaptic parameters (reflecting the number of neurons and the connectivity between neurons). Here the models trend downward from left to

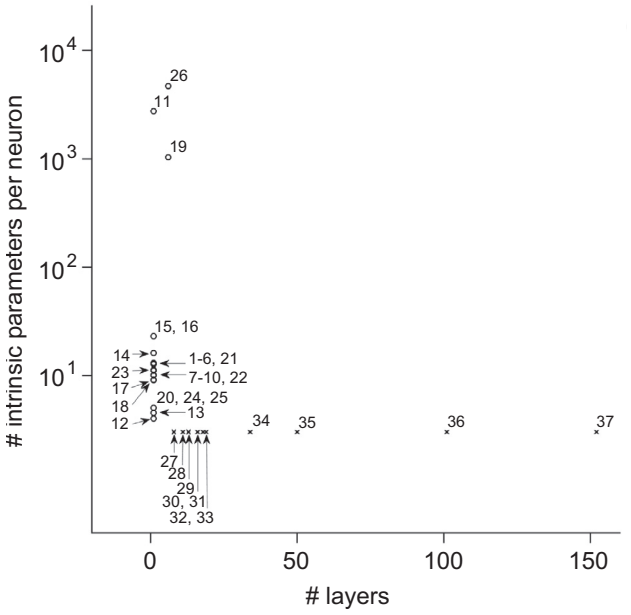


Fig. 3. Diagram of the space of neural models showing number of layers or regions in the model on the *x* axis, with number of intrinsic parameters per modelled neuron on the *y*-axis. This diagram was designed to highlight the strong difference in exploration by different types of neural models. Computational neuroscience models (open circles) cluster vertically along the *y*-axis, as they contain large numbers of parameters for representing the dynamics of membrane conductances, including those modulated by metabotropic receptors, but they usually focus on a single regions or functional layer. In contrast, artificial neural network models (labelled with *x*) cluster horizontally along the *x*-axis as they contain ever-increasing numbers of processing layers as models become more sophisticated, but almost uniformly represent neuron intrinsic properties with a simple rectified linear input–output function, which at most has parameters of threshold, slope and bias. Note that some citations refer to review of multiple models. The citations in the figure are numbered as follows: 1–10 (Destexhe et al., 1994b), 11 (Poirazi et al., 2003), 12 (Izhikevich, 2003), 13 (Hasselmo et al., 1995), 14–17 (Destexhe et al., 1996), 18, 19 (Traub et al., 2005), 20 (Potjans and Diesmann, 2014), 21 (Nadim et al., 1998), 22 (Lytton et al., 1997), 23 (Hill et al., 2003), 24 (Bartos et al., 2002), 25 (Wang and Buzsaki, 1996), 26 (Markram et al., 2015), 27 (Krizhevsky et al., 2017), 28–32 (Simonyan and Zisserman, 2015), 33–37 (He et al., 2015).

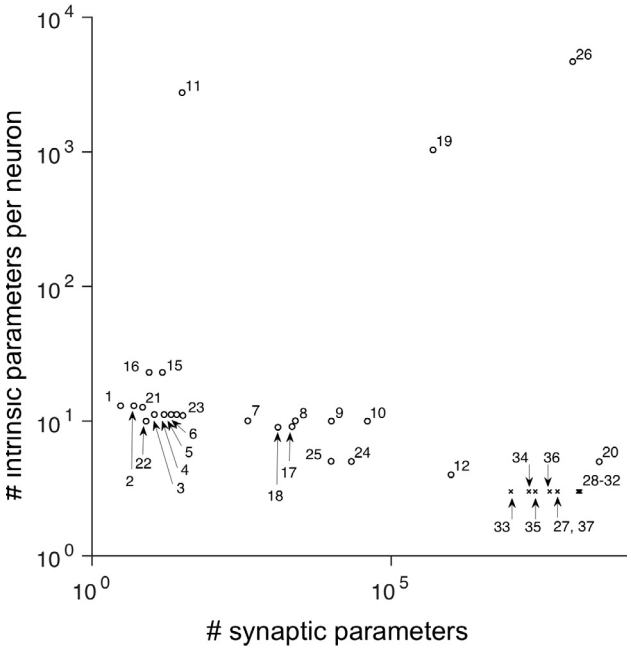


Fig. 4. Number of total intrinsic parameters versus number of synaptic parameters. This diagram shows the same models plotted for number of intrinsic parameters per neuron versus total number of synaptic parameters in the simulation (which scales with number of neurons and connections between neurons). Computational neuroscience models are marked with open circles and artificial neural network models with x. Here the distribution covers the space of possible models somewhat more extensively. However, the difficulty of combining large numbers of intrinsic conductances with large populations of neurons is highlighted by the sparsity of models in the upper right.

right along the *x* axis, as models with more synaptic connections have fewer intrinsic parameters per neuron. A few models have succeeded in exploring the space in the upper right with large numbers of neurons and extensive intrinsic conductances. However, the space can still only be sparsely explored relative to the number of functionally relevant dimensions due to computational and analytical limitations.

The plots in Figs. 3 and 4 were not intended to include all neural models, but compares a subset of recent artificial neural network deep learning models with models classified as "Realistic Networks" on the ModelDB database (senselab.med.yale.edu). For the intrinsic parameters, conductance parameters and shape parameters were counted once for each compartment of the neuron model, but environmental parameters such as temperature and ion reversal potentials were counted once for the whole model.

Together, Figs. 3 and 4 highlight the dichotomy between models that focus on multiple feedforward layers of processing versus the computational function of metabotropic receptors. This dichotomy partly arises from the focus of artificial neural network deep learning models on fast sensory processing of sensory stimuli (such as visual images) or on recurrent neural networks using fast synapses to generate network dynamics. These models contrast with computational neuroscience models that address the complex dynamics of neural circuits that include the broadly distributed influence of neuromodulatory agents activating metabotropic receptors. Fig. 5 schematizes the broad range of temporal and spatial scales of the effects of neuromodulators and hormones that activate metabotropic receptors. The difficulty of simulating biophysically detailed models makes it particularly difficult to simulate metabotropic receptor effects with their slower time courses. Metabotropic receptor effects require long duration simulations to model the transitions between different functional phases. These modulators strongly regulate the physiological effects that provide a range of possible functional dimensions shown in Fig. 1 that could be incorporated into models. In the future, research should converge on an accurate model of brain function that exists somewhere in this multi-dimensional space, but we do not yet know what are the most functionally relevant dimensions, and how to simplify the representation of this space in a manner

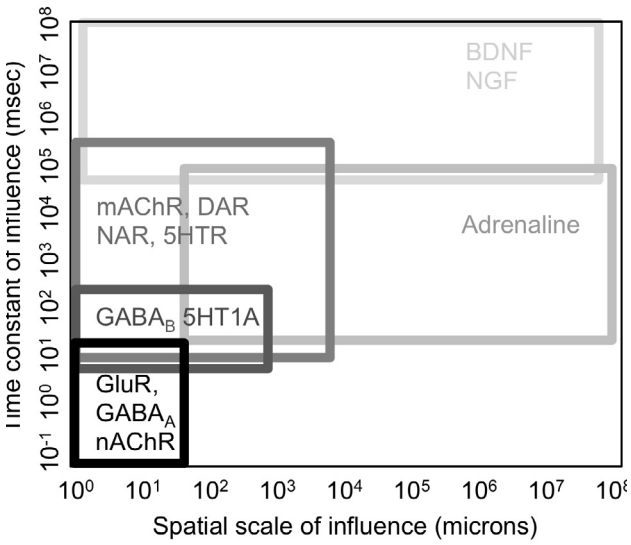


Fig. 5. Time constant and spatial distribution of neuromodulator effects compared to neurotransmitter effects. The lower left corner shows the fast time course and narrow spatial range of ionotropic receptors such as glutamate (GluR), GABAA and nicotinic acetylcholine (nAChR) receptors. The rest of the diagram shows the approximate time course (*y*-axis) and spatial scale (*x*-axis) of the effects of metabotropic receptors for some common neuromodulators and hormones. mAChR = muscarinic acetylcholine receptor, DAR = dopamine receptors, NAR = norepinephrine receptors, 5HTR = serotonin receptors. Hormones BDNF = brain derived neurotrophic receptor. NGF = nerve growth factor. The focus on fast conductances in most artificial neural network models partly arises from the very broad scope of potential time courses and spatial distributions for neuromodulatory effects at metabotropic receptors.

that allows effective knowledge of what we know and prediction of what we need to explore further.

FRAMEWORK OF CELLULAR MODELS

The success of theoretical frameworks in other fields of science arises from the capacity to find unifying principles without itemizing every feature of the physical system. For example, in Physics, the ideal gas law described interacting properties of pressure, volume and temperature without quantifying the position and velocity of every molecule of gas in a volume. Similarly, the periodic table of elements described systematic principles of the mass and properties of chemical interaction of different elements before there was scientific understanding of underlying factors such as electron orbitals and the number of electrons and protons in an atomic nucleus. Only later were these properties linked to number of electrons and electron orbits, and even later were unified with an elegant mathematical framework of the Schrödinger equation. So far, much of theoretical neuroscience at the network level has focused on the unproven assumption that firing rate provides an accurate summary of neural activity. However, this firing rate code does not account for phenomena such as the fact that spiking phase contains information about behavioral variables such as position (O'Keefe and Recce, 1993; Skaggs et al., 1996). There must be more to a neural code than vectors of firing rate.

Neuroscience suffers from a shortage of unifying principles. This can be observed just by the heterogeneity of undergraduate teaching. A physics program can teach undergraduates for four years with theories that are almost unanimously accepted by all physics faculty. Similarly, there is a mass of knowledge in chemistry and electrical engineering that requires years to impart to students. In contrast, undergraduate courses in neuroscience contain a vast quantity of disparate information based on experimental data, but once computational neuroscience teaching moves beyond the generally accepted principles at the cellular level, it reaches the realm of many competing unproven hypotheses about network function.

Most of the accepted principles of neural function pertain to the function of individual neurons. Central theories of neuroscience that are almost unanimously accepted include the use of cable theory for describing passive membrane potential dynamics (Rall, 1959, 1989), the role of voltage-sensitive sodium and potassium currents in action potential generation (Hodgkin and Huxley, 1952), and the use of the Hodgkin-Huxley formalism for describing other voltage-sensitive intrinsic conductances such as A current or M current (Brown and Adams, 1980; Yamada et al., 1989). Other widely accepted theories include the mechanisms of synaptic transmission at the neuromuscular junction and central glutamatergic synapses (Eccles, 1982), and the mechanisms of receptor kinetics (Destexhe et al., 1994a). These theories are vitally important, but mostly apply at the cellular and molecular level.

As noted above, the Hodgkin-Huxley formalism provided an initial unifying quantitative theory for replicating the properties of a broad range of membrane conductances (Hodgkin and Huxley, 1952). This theory uses first order differential equations to describe voltage-sensitive channels in terms of the voltage-dependence of the steady state and the time constant of activation variables m and inactivation variable h for the voltage-sensitive sodium conductance. Similarly, for other, slower voltage-dependent conductances such as the A current, the M current, and the H current, the voltage-dependence of the steady state and time constant of activation can be experimentally derived and simulated using the Hodgkin Huxley formalism (Brown and Adams, 1980; Rush and Rinzel, 1995).

There has been much less focus on potential unifying principles that account for the substantial redundancies in the physiological effects of membrane conductances on the physiological properties of neurons. For example, the phenomenon of spike frequency accommodation can be simulated by interactions of a range of different conductances including the M current and the calcium-dependent potassium current (IAHP) (Yamada et al., 1989; Traub et al., 1991; Barkai and Hasselmo, 1994). The focus on physiological phenomena rather than just conductance parameters is important, because the interaction of multiple membrane conductances does not always depend on the interaction of the mean value of

conductances, but instead depends on specific combinations of conductances (Prinz et al., 2003). These parameters are degenerate, such that many combinations of parameters can result in the same physiological phenomena. Another important factor that influences the use of network models is the difficulty of reproducing models due to the tremendous complexity of these models. Reproducibility of methods and results could be achieved by following guidelines (Gutzen et al., 2018) providing sufficient details about the procedures and model parameters and performing quantitative validation of the models using standardized statistical test metrics.

A potential mathematical unification of physiological properties was developed by Izhikevich to combine together long-term influences on cellular membrane potential including both voltage-dependent and calcium-dependent conductances (Izhikevich, 2003, 2004). This provides one of the potentially best mathematical tools for addressing the common principles of physiological function that can arise from a diversity of membrane conductances, including many that involve metabotropic receptors. In particular, the Izhikevich model describes a broad range of neuronal function using four parameters (Izhikevich, 2003, 2004). Thus, this could allow mapping of cellular physiological properties to a four-dimensional space. Adding synaptic connectivity parameters would expand this space, but could still provide a multi-dimensional map of unexplored model space to guide future exploration. Most experimentally described neurons will fall within specific ranges of this model space (a lower dimensional manifold), but it is highly likely that only a tiny percentage of this experimentally-relevant range of model space has been explored. Random exploration of the space may not be productive. The exploration should be guided by implementation of specific desired functional properties by neural circuits of different scales.

Simpler neural network models have been developed that generate spiking activity without the full complexity of the Hodgkin-Huxley representation of conductances (Amit and Brunel, 1997; Compte et al., 2000; Sommer and Wennekers, 2001; Maass et al., 2002). These models provide a framework for analyzing fundamental properties of the functional dynamics of spiking networks. Many of these spiking models use linear or exponential integrate and fire neurons that generate spikes, but the neurons in these network do not contain extensive slow conductance dynamics (Compte et al., 2000; Rasmussen and Eliasmith, 2014; Ocker and Doiron, 2019). These models focus on the dynamics of network spiking due to interactions with fast synaptic connectivity, without addressing the function of slower conductances under the regulation of metabotropic receptors.

The molecular pathways for the influence of metabotropic receptors have been described in a range of studies focused on the coupling of metabotropic receptors with G-proteins (Andrade et al., 1986). These G-proteins mediate activation of second messenger pathways that include the activation of the enzyme phospholipase C to convert phosphatidylinositol 4,5-bisphosphate into diacyl glycerol and inositol triphosphate (Pian et al., 2007), or that cause activation or inactivation of the enzyme adenylate cyclase which synthesizes cyclicAMP from adenosine triphosphate (Nicoll, 1988). Some models have addressed the kinetics of these pathways (Nair et al., 2014, 2016). However, there is a shortage of experimental data on the kinetics of second-messenger pathways activated by metabotropic receptors, hampering the capacity to directly map individual metabotropic influences to specific time courses of effect on membrane potential. This lack of knowledge about the kinetics of second messenger pathways is a major difficulty for linking metabotropic receptors to the time constants of their functional role in neural circuits. However, the principles of homeostatic self-regulation of cellular properties suggest that neurons might genetically code a particular physiological phenotype and tune the interaction of internal conductances to maintain a stable physiological phenotype (Marder and Prinz, 2002; Turrigiano, 2007, 2011).

DIMENSIONS OF METABOTROPIC RECEPTOR EFFECTS

The plots in Figs. 3 and 4 provide a general idea of the scope of unexplored space for neural models. The actual space of possible neural models is high dimensional and difficult to illustrate in a single figure, but a rough sketch is provided in Fig. 1. Here we will review just a few dimensions of metabotropic function that have received attention at the single cell level, but could be explored more thoroughly in terms of network function.

Membrane potential. There is still a tendency to describe metabotropic receptors in terms of synaptic transmission rather than neuromodulation, resulting in simplistic descriptions of modulatory metabotropic receptor effects as ‘‘excitatory” or ‘‘inhibitory.” This description is an oversimplification, but in some cases modulatory activation of metabotropic receptors does cause direct changes in membrane potential. For example, activation of the metabotropic receptor $GABA_B$ or the serotonin receptor $5HT_{1A}$ generates a G-protein mediated process that directly opens potassium channels (Andrade et al., 1986), causing a relatively rapid hyperpolarization with an onset time constant of about 10 msec and a decay time constant of 100 ms. Activation of muscarinic receptors causes a transient activation of potassium channels causing hyperpolarization (Gulledge and Kawaguchi, 2007; Gulledge et al., 2007; Desikan et al., 2018) followed by a slower closing of potassium channels that causes a long, slow depolarization of membrane potential over 20–30 s (Cole and Nicoll, 1984; Barkai and Hasselmo, 1994). These effects have been incorporated in some network models (Barkai et al., 1994; Hasselmo and Wyble, 1997), but phenomena such as the biphasic influence of muscarinic receptors on membrane potential have not been modeled.

Spike frequency adaptation. In addition to direct effects on membrane potential, metabotropic receptors also indirectly influence the frequency of ionotropic spiking activity. For example, a majority of cortical neurons referred to as ‘‘regular spiking neurons” show a

reduction of spike frequency during sustained depolarization, called spike frequency adaptation (McCormick et al., 1985). This is due to calcium influx through calcium-dependent receptors causing activation of calcium-dependent potassium currents (IAHP). This specifically prevents the neurons from firing in a regular manner, but instead results in a predominant ("regular") pattern in which there is a decrease in firing rate (adaptation). Several metabotropic receptors reduce the AHP current, resulting in more sustained spiking response to depolarization (Madison and Nicoll, 1984). These receptors include muscarinic acetylcholine receptors, beta-adrenergic receptors and serotonin $5HT_2$ receptors (Madison and Nicoll, 1986; Madison et al., 1987; Barkai and Hasselmo, 1994). The suppression of adaptation has been shown to enhance encoding in functional models (Barkai et al., 1994; Hasselmo and Wyble, 1997), but again has not been incorporated into most network models.

Modulation of synaptic plasticity. Synaptic plasticity appears to depend on the ionotropic NMDA receptor, but the mechanisms of synaptic modification are complex. Metabotropic receptors have been shown extensively to modulate synaptic plasticity in a range of systems (Hasselmo, 1995). For example, activation of muscarinic receptors has been shown to enhance long-term potentiation in cortical structures including the hippocampus (Burgard and Sarvey, 1990; Fernandez de Sevilla et al., 2008), the piriform cortex (Hasselmo and Barkai, 1995), and primary visual cortex (Brocher et al., 1992). Similarly, norepinephrine enhances long-term potentiation in the hippocampus (Hopkins and Johnston, 1988), and dopamine enhances long-term potentiation in the basal ganglia (Wickens, 2009). More recently, studies have focused on modulation of spike-timing dependent plasticity (STDP), which includes effects of modulators on the synaptic change induced by specific timing of pre- and post-synaptic spikes (Pawlak et al., 2010; Sugisaki et al., 2011). These effects could influence the mechanisms for synaptic plasticity on a behavioral time scale as well (Bittner et al., 2015, 2017). Simulations of the metabotropic modulation of synaptic plasticity demonstrate how modulation by neurochemicals such as acetylcholine can enhance encoding of novel stimuli (Hasselmo et al., 1995; Hasselmo and Wyble, 1997; Hasselmo, 2006). Simulations have also addressed the interaction of nonlinear dendritic dynamics with synaptic plasticity (Saudargiene et al., 2005; Ebner et al., 2019).

Presynaptic inhibition. Another under-explored dimension of metabotropic receptors concerns the presynaptic inhibition of synaptic transmission, in which a neuromodulator influences the release of neurotransmitters. This can include autoreceptor effects, in which release of a transmitter reduces further release of the same transmitter. For example, activation of presynaptic metabotropic glutamate receptors can strongly regulate glutamate release (Koerner and Cotman, 1981; Hasselmo and Bower, 1991). This can also involve a modulator influencing the release of other neurotransmitters. For example, when acetylcholine activates presynaptic muscarinic M4 receptors (Dasari and Gulledge, 2011), this strongly reduces glutamate release and the size of synaptic potentials at glutamatergic synapses in the hippocampus (Yamamoto and Kawai, 1967; Valentino and Dingledine, 1981; Hasselmo and Schnell, 1994; Fernandez de Sevilla et al., 2002; Fernandez de Sevilla and Buno, 2003; Hasselmo, 2006), piriform cortex (Hasselmo and Bower, 1992), and neocortical structures including somatosensory cortex (Gil et al., 1997) and auditory cortex (Hsieh et al., 2000). Other presynaptic modulators of synaptic transmission include GABA, which can regulate the release of glutamate via activation of presynaptic $GABA_B$ receptors (Ault and Nadler, 1982; Isaacson et al., 1993; Tang and Hasselmo, 1994; Molyneaux and Hasselmo, 2002). Dopamine has been shown to alter the strength of NMDA conductances in cortical neurons (Cepeda et al., 1992; Seamans et al., 2001). Another phenomenon involves presynaptic inhibition of GABA release based on depolarization of the postsynaptic target neuron, which causes presynaptic inhibition via cannabinoids acting as retrograde messengers (Wilson and Nicoll, 2001). Presynaptic inhibition has been shown to enhance encoding by preventing interference from retrieval of prior associations in models of cortical circuits (Hasselmo and Wyble, 1997; Hasselmo, 2006), but has not been addressed in most network models.

Afterdepolarization and persistent spiking. Many experimental studies on modulation focus on spiking activity directly induced by depolarizing current injection. However, neuromodulators can cause neurons to maintain their spiking after the end of a depolarizing current injection by activating an afterdepolarization caused by cation currents activated by calcium influx during spiking. For example, cholinergic activation of muscarinic receptors can cause persistent spiking in neurons of the entorhinal cortex (Klink and Alonso, 1997; Egorov et al., 2002; Reboreda et al., 2007; Yoshida et al., 2013), the prefrontal cortex (Haj-Dahmane and Andrade, 1999), the cingulate cortex (Zhang and Seguela, 2010), and the hippocampus (Jochems and Yoshida, 2013; Knauer et al., 2013). The persistent spiking requires a balance of calcium dependent afterdepolarization currents and calcium-dependent afterhyperpolarization currents (Fransén et al., 2006). These phenomena of afterdepolarization and persistent spiking have been shown to have potentially important network effects for working memory for novel information (Fransén et al., 2002; Hasselmo and Stern, 2006).

Rebound spiking. Many neurons show the capacity to generate rebound spikes after a sustained period of hyperpolarization. This can be mediated by the hyperpolarization activated cation current (H current), which reacts to membrane potential hyperpolarization by allowing depolarizing current through the membrane (Chen et al., 2001). The H current is mediated by the HCN channel, which stands for Hyperpolarization-activated Cyclic-Nucleotide gated channels. This channel was specifically named for the gating by the second messenger cyclicAMP (Santoro et al., 1998, 2000; Wainger et al., 2001), and has been shown to be suppressed by second messenger pathways and by metabotropic recep-

tor effects such as muscarinic acetylcholine receptors (Heys et al., 2010; Heys and Hasselmo, 2012). This rebound spiking could have important functional effects in regulating the phase of neural firing (Rotstein et al., 2005; Ferrante et al., 2016; Shay et al., 2016).

Individual models have incorporated these individual effects, focusing on questions about the function of individual modulators or conductances. However, few models have combined the metabotropic modulation of these physiological effects in a cohesive theoretical framework that accounts for the functional role of multiple interacting conductances and their regulation by multiple metabotropic pathways.

NETWORK LEVEL THEORY AND DIMENSIONS OF METABOTROPIC RECEPTOR EFFECTS

There are a few theories at the network level that have been influential. Here we will review the potential role of metabotropic receptors in some existing network level theories, and the need for further research.

The Hebb rule. The Hebb rule addresses the important network memory function that arises from synaptic modification that depends upon the conjunction of presynaptic and postsynaptic activity (Hebb, 1949). The Hebbian property of synaptic modification has been supported by a number of experimental studies in the hippocampal formation including extracellular recording (McNaughton et al., 1978; Levy and Steward, 1979), and intracellular recording (Gustafsson and Wigstrom, 1986; Wigstrom et al., 1986; Gustafsson et al., 1987; Gustafsson and Wigstrom, 1988). This basic principle was extended to address the detailed timing of presynaptic and postsynaptic spikes in specific cases (Levy and Steward, 1983; Markram et al., 1997; Bi and Poo, 1998). As noted above, metabotropic receptors have been shown to modulate the mechanisms of synaptic plasticity, including the regulation of Hebbian modification by direct influences on NMDA receptors or indirect effects on the molecular pathways mediating synaptic plasticity. The Hebb rule has been used in a wide range of network models, but most models do not focus on the modulation of Hebbian modification, which could provide a method for regulating the network dynamics for encoding, retrieval or consolidation (Hasselmo, 1999, 2006).

Associative memory function. The basic principle of the Hebb rule or spike timing dependent plasticity have been explored in a wide range of network functional contexts. Within the domain of memory research, the important role of Hebbian modification has been proposed in associative memory function in the hippocampus (Marr, 1971; McNaughton and Morris, 1987), as supported by behavioral data from blockade of NMDA receptors (Morris et al., 1986). In these associative memory models, a vector represents the neural activity of a population of neurons, and the effective retrieval of a previously stored memory is commonly measured by the dot product (inner product) of the retrieved vector with the previously encoded vector (Anderson, 1972; Kohonen, 1972; Hopfield, 1982, 1984; Kohonen, 1984; Hasselmo et al., 1992). These models do not yet address how these memory vectors can represent the full scope of encoded experience, which includes representation of agents and objects and their behavioral trajectories within an environment (Hasselmo, 2009; Hasselmo et al., 2010). In addition, as described next, models of associative memory do not usually address the modulatory mechanisms for the shift in functional dynamics between encoding and retrieval for associative memory.

Associative encoding versus retrieval. An important aspect of associative memory function concerns the difference in dynamics during encoding versus retrieval (Hasselmo et al., 1995; Hasselmo, 2006). Most associative memory models have specific dynamics during encoding, in which the external input is clamped on the network to set the pattern to be encoded, and modifiable recurrent synapses undergo Hebbian modification without altering the postsynaptic pattern of activity (Anderson, 1972; Kohonen, 1972, 1984; Hopfield, 1982, 1984). In contrast, during retrieval in these models, the external input provides an initial cue, but modifiable recurrent synapses dominate the network retrieval dynamics without undergoing modification, Physiological mechanisms for this transition between encoding and retrieval dynamics could involve activation of metabotropic receptors (Hasselmo, 2006). Specifically, cholinergic activation of muscarinic receptors can simultaneously enhance synaptic modification (Hasselmo and Barkai, 1995; Fernandez de Sevilla et al., 2008), while also causing presynaptic inhibition of glutamate release (Hasselmo and Schnell, 1994; Hasselmo et al., 1995; Fernandez de Sevilla et al., 2002; Hasselmo, 2006). Modeling shows that this presynaptic inhibition prevents previously modified synapses from interfering with the new pattern of input being encoded (Hasselmo and Schnell, 1994; Hasselmo et al., 1995; Hasselmo and Wyble, 1997; Hasselmo, 2006).

Attractor dynamics. Another common network mechanism that receives extensive attention in the field concerns attractor dynamics (Hopfield, 1982, 1984; Amit, 1988). The usual mechanism for attractor dynamics concerns the use of excitatory recurrent connections to drive neural activity into a previously encoded pattern. This essentially concerns the dynamics of retrieval, which as noted above needs to be separated from the dynamics of encoding for associative memory function (Hasselmo et al., 1995; Hasselmo and Wyble, 1997). Attractor dynamics have been proposed in many models of the maintenance of sustained activity for working memory function (Compte et al., 2000). Stable mechanisms of attractor dynamics could also apply to the bistable dynamics of single neuron persistent spiking mediated by the interaction of metabotropic receptor effects on afterdepolarization (via the CAN current) and afterhyperpolarization (via the AHP current) (Fransén et al., 2006). Some biophysical models show how detailed modulation of synaptic transmission and intrinsic currents by metabotropic receptors could regulate attractor dynamics for working memory function in behavioral tasks with a delay period (Durstewitz et al., 2000b; Fransén et al., 2002), but most network models do not incorporate this modulation of attractor dynamics.

Regulation of attention. Modulatory systems that regulate norepinephrine and acetylcholine have been shown to play a role in sustained attention and selective attention (Hasselmo and McGaughy, 2004), as demonstrated by enhancement of attention by drugs such as amphetamines and caffeine. This modulation of attention depends upon metabotropic receptor effects and has been incorporated in some neural circuit models of attention effects (Hasselmo et al., 1997; Patil and Hasselmo, 1999; Pauli and O'Reilly, 2008). Most classical neural network models do not have internal mechanisms for self-regulation of attention (LeCun et al., 2015; Krizhevsky et al., 2017), but attention has started to be incorporated in some recent network models (Vaswani et al., 2017).

Self-organization of feature detectors. The Hebb rule has also been used extensively in models of the self-organization of feature detectors in the primary visual cortex (Miller et al., 1989). In contrast to associative memory function, self-organization can occur if the modifiable synapses are the predominant influence on postsynaptic activity (Hasselmo, 1995). The role of Hebbian modification dependent on NMDA receptors has been supported by changes in network feature detector properties after blockade of NMDA receptors (Sato and Stryker, 2008). The influence of modulators such as acetylcholine and norepinephrine has also been shown in experimental studies of the self-organization of feature detectors (Bear and Singer, 1986). However, most neural network models develop feature detectors by using gradient descent based on error correction at individual synapses (Rumelhart et al., 1986; McClelland and Rumelhart, 1988; He et al., 2015; LeCun et al., 2015; Simonyan and Zisserman, 2015; Krizhevsky et al., 2017), rather than using metabotropic modulation of unsupervised self-organization, though recent models incorporate more biophysical mechanisms for credit assignment (Richards and Lillicrap, 2019).

Reinforcement learning. The concept of learning guided by reward has a long history in the field of psychology. A large body of mathematical research focused on properties of classical and operant conditioning. As a brief overview, the Rescorla-Wagner learning rule accounted for a range of experimental phenomena in the learning literature (Rescorla and Wagner, 1972). This can be seen as a precursor to the development of the temporal difference learning rule (Sutton, 1988), in which the value of actions can be propagated back through a sequence of states and actions. This framework resulted in the theory that the activity of dopaminergic neurons could reflect the temporal difference error in the temporal difference learning rule (Schultz et al., 1997). Reinforcement learning models of the behavioral function of dopamine commonly use the relatively abstract formalism of reinforcement learning (Schultz et al., 1997; Daw et al., 2005) rather than the detailed biophysics of metabotropic modulation of intrinsic conductances, but some approaches integrate more detailed neural dynamics of dopamine (Hazy et al., 2010).

Example biophysical models. All of these network principles have proven highly useful and productive in generating new models and new experiments for testing those models. Thus, they have served an important purpose. However, none of these frameworks account for the broad categories of widespread conductances modulated by metabotropic receptors as described above. On the positive side, many network models have been constructed to replicate the dynamical properties of neural circuits (Traub et al., 1989, 1992, 2005; Rotstein et al., 2005; Markram et al., 2015; Bezaire et al., 2016). In addition, there are some examples of network models that have focused on individual modulatory agents and individual functions and effectively included subsets of these modulatory effects on synaptic transmission and intrinsic conductances (Traub et al., 1992). These biophysical models have been used to address the circuit mechanisms for network oscillatory dynamics (Traub et al., 1989, 1992, 2005; Rotstein et al., 2005; Markram et al., 2015; Bezaire et al., 2016), including the regulation of both theta and gamma frequency oscillations by metabotropic receptors for acetylcholine (Traub et al., 1992; Whittington et al., 2001) and metabotropic glutamate receptors (Whittington et al., 1995). These network oscillatory dynamics could be regulated by modulatory input from the medial septum to the hippocampus and entorhinal cortex (Dannenberg et al., 2015, 2017; Robinson et al., 2016). Simulations show that functional dynamics for encoding and retrieval can occur on different phases of theta rhythm oscillations (Hasselmo et al., 2002) which can depend on regulation of spiking and synaptic plasticity by changes of inhibition at different phases of theta (Cutsuridis and Hasselmo, 2012; Saudargiene et al., 2015).

In another set of biophysical models, the dopaminergic modulation of attractor dynamics was explored in detailed models of the prefrontal cortex (Durstewitz et al., 2000b,a; Durstewitz and Seamans, 2002). These models have addressed the potential functional role of dopaminergic modulation of synaptic receptors such as NMDA receptors. They have also incorporated dopaminergic modulation of other intrinsic conductances that influence membrane potential. Similarly, there have been models of the cholinergic modulation of intrinsic persistent spiking and its potential role in regulating working memory function in delayed match to sample tasks (Fransén et al., 2002, 2006). There have also been models of cholinergic modulation of associative memory function, with a focus on how cholinergic enhancement of spiking to afferent input and cholinergic presynaptic inhibition of modifiable recurrent synapses could enhance encoding relative to retrieval or consolidation dynamics (Barkai et al., 1994; Hasselmo et al., 1995; Hasselmo, 2006). Often, these network level models have adopted mechanisms from more artificial neural network models and implemented them using more biophysically detailed simulations. There have not been many examples where simulations of metabotropic receptor effects on intrinsic conductances have been used to endow networks with novel functions, though the effect of drugs on behavior suggest an important functional role of these metabotropic receptor effects. As an example of the essential role of modulators in cognition, at high doses, the muscarinic receptor antagonist scopolamine causes

a major impairment of cognitive function and puts subjects into a state of delirium (Safer and Allen, 1971).

POSSIBLE THEORETICAL FRAMEWORKS FOR PLOTTING THE EXPLORED AND UNEXPLORED SPACE OF MODELS

How can we start a map of the explored and unexplored space of network models? Unfortunately, in contrast to the simple two-dimensional surface of the earth, the multidimensional nature of this space makes a simple framework for mapping unclear. A few possible frameworks are briefly reviewed here.

Multi-dimensional parameter space. One way of seeing the unexplored space is to generate plots of the parameter space as suggested in Figs. 1, 3 and 4, where intrinsic parameters are plotted relative to each other or relative to parameters such as number of neurons and number of layers or regions. These provide a broad message about the lack of exploration of intrinsic parameters in multi-layer/multi-region functional models. More detailed models could explore the functional dynamics obtained from different combinations of parameters. This has been done in some explorations of parameter space (Prinz et al., 2003). However, because each parameter has the potential to add a dimension for exploration, this is an enormous space. In the study by Prinz et al. (2003), variation of 8 maximal conductance values in a lobster stomatogastric ganglion model produced a database of 1.7 million models, which took over a month of simulation on a high-performance computing cluster. Processing speed has increased since then, but characterizing a parameter space by random or grid spaced sweeps is computationally demanding. Exhaustive automated exploration may not be fruitful unless we have a clear theoretical framework for evaluation of the different points in the model space.

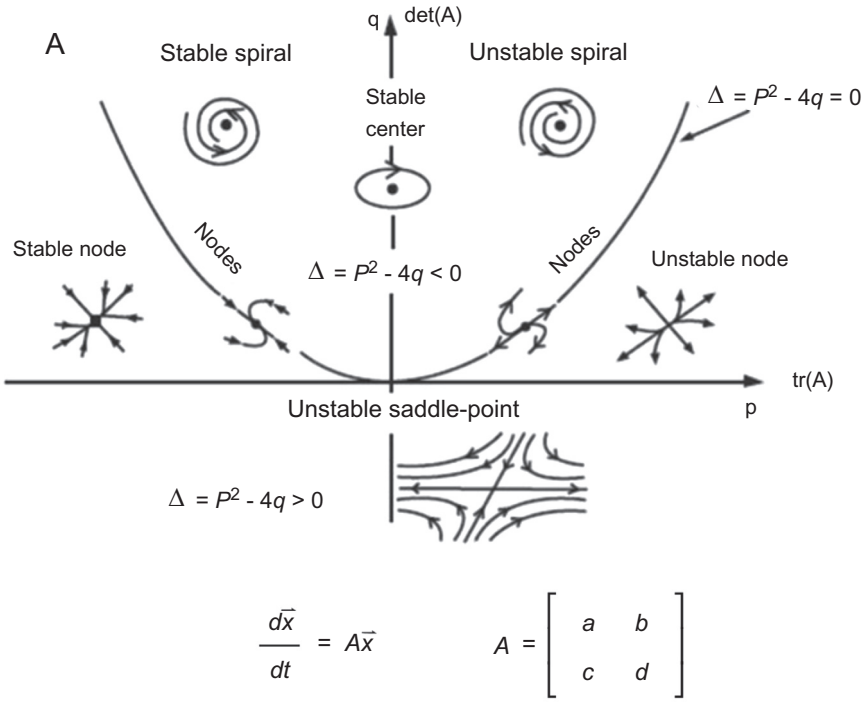
Many efforts have been made to optimize parameters to fit specific sets of data based on matching to physiological data (Markram et al., 2015; Gorur-Shandilya et al., 2018). However, experimental data does not yet provide detailed parameters for all the intrinsic conductances and all the different effects of metabotropic receptors on these conductances in the broad variety of cell types in neural circuits. In addition, experimental recordings reveal variability between individual cells or different animals, and modeling shows that obtaining parameter ranges or obtaining an average value is insufficient to replicate physiological properties (Golowasch et al., 2002). Modeling also demonstrates the degeneracy of parameter space (Prinz et al., 2004; Stelling et al., 2004; Marder et al., 2014; Alonso and Marder, 2019; Rathour and Narayanan, 2019), such that many different combinations of parameters can replicate the same physiological phenomena. This suggests that neural systems may be structured to generate physiological properties rather than fixed parameter ranges. These redundancies could contribute to the robustness that neural systems can show in response to changes in environment such as changes in temperature (Marder et al., 2015). Research may be better guided by matching the physiological properties of neurons rather than attempting to replicate the full parameter space of a neuron.

As noted above, the Izhikevich model (Izhikevich, 2003, 2004) provides a smaller, four dimensional parameter space that focuses on replicating physiological properties and can be explored for the combination of parameters that produce a range of qualitative phenomena such as adaptation, bursting, delayed spiking, rebound spiking and resonance. This could be useful, but requires a framework for mapping the simplified model back to the Hodgkin-Huxley space of individual conductances, and also requires some functional network framework for evaluating combinations of neurons. The functional mapping to network dynamics will require some framework for understanding what are the crucial features of network function to be tested with different parameters.

Mapping of dynamical systems. Another approach to exploring the space of neural models could be applying mathematical techniques from dynamical systems. Fig. 6A shows a framework that describes the functional properties of two-dimensional dynamical systems based on coupled differential equations. This framework shows how the dynamics of a two-dimensional system can be linked to the determinant and the trace of the dynamical system matrix A, allowing division of the system space into stable nodes, stable spirals, stable centers, unstable spirals, unstable nodes and unstable saddle points. This could be expanded to higher dimensional dynamical systems. Alternately, these component dynamical systems could be combined as elements in a larger scale network that incorporates individual elements of dynamical systems as described in the next section.

Unifying principles of network function based on network dynamics might exist. Modeling of invertebrate systems such as the stomatogastric ganglion demonstrate that highly similar dynamics of a network activity can be obtained in networks that vary widely in both intrinsic cellular parameters as well as network synaptic connectivity (Prinz et al., 2004). This suggests the validity of using similar nework dynamics as the elemental building block of network models.

Mapping of functional elements. Related to the dynamical systems approach, another approach could be an effort to define specific elements of function, in analogy with the definition of elements in chemistry. Obviously, the scale of neural circuits is far above that of individual atoms. However, the analogy could work if we consider that the properties of elements can be defined by the orbitals described by the Schrödinger equation. The Schrödinger equation starts with basic mathematical principles and derives the properties of individual atomic orbitals. When individual atomic orbitals are filled based on the number of electrons in different atomic elements, this results in the chemical properties of the different atomic elements. The discovery of periodic properties of chemical elements relative to atomic weight was described by Mendeleev and others (Mendeleev, 1869). This provided a framework for predicting the chemical properties and atomic weights



B

			Ti = 50	Zr = 90	? = 180
			V = 51	Nb = 94	Ta = 182
			Cr = 52	Mo = 96	W = 186
			Mn = 55	Rh = 104,4	Pt = 197,4
			Fe = 56	Ru = 104,4	Ir = 198
			Ni = Co = 59	Pd = 106,6	Os = 199
H = 1			Cu = 63,4	Ag = 108	Hg = 200
	Be = 9,4	Mg = 24	Zn = 65,2	Cd = 112	
	B = 11	Al = 27,4	? = 68	Ur = 116	Au = 197?
	C = 12	Si = 28	? = 70	Sn = 118	
	N = 14	P = 31	As = 75	Sb = 122	Bi = 210?
	O = 16	S = 32	Se = 79,4	Te = 128?	
	F = 19	Cl = 35,5	Br = 80	J = 127	
Li = 7	Na = 23	K = 39	Rb = 85,4	Cs = 133	Tl = 204
		Ca = 40	Sr = 87,6	Ba = 137	Pb = 207
		? = 45	Ce = 92		
		?Er = 56	La = 94		
		?Yt = 60	Di = 95		
		?In = 75,6	Th = 118?		

Fig. 6. Examples from other fields of potentially useful frameworks that could be utilized for mapping what is the explored space and what is the unexplored space of neural models. **(A)** The mathematical diagram shows the effective mapping of functional properties of linear coupled differential equations with constant coefficients described by the matrix A (Hirsch and Smale, 1974; Jira, 2015). As shown here, the parameters of the determinant of the matrix A (Det) and the trace of the matrix A (Tr) lay out all the types of functional dynamics, ranging from top left to top right as stable nodes, stable spirals, centers, unstable spirals, and unstable nodes. The curved line shows where the discriminant (Tr)ˆ2 – 4*Det = 0. On the bottom of the plot are saddle points (Hirsch and Smale, 1974). **(B)** This text from a German abstract of Mendeleev's work shows his initial sketch of the periodic table of the elements that systematized the properties of known elements. The empty points in table effectively predicted the range of atomic weights and chemical properties of undiscovered elements such as Gallium (Mendeleev, 1869).

of previously undiscovered elements (Fig. 6B), and ultimately led to the description of chemical properties in terms of the structure of atoms.

By analogy, the dynamical properties of local neural circuits could result in particular properties of interaction with other neural circuits. The basic principles of differential equations can be used to define different dynamical properties of the system and describe the borders of these elemental properties in parameter space. A similar approach could be used to describe the interaction of elementary dynamical systems describing local neural circuits. The properties of local circuit elements could combine into larger functional properties of interacting neural circuits that could be conceived as molecules of neural function. For example, dynamics of local circuits could mediate representations of properties of the world such as trajectories, borders, surfaces and combinations of properties. Of course, this raises the further question of how to combine the elements into molecular structures. In chemistry, these interactions involve changes in the energy state of the network. If the elements of neural circuit function are not assumed to be locked to specific neurons, but instead could spread between different circuits based on shared properties of neural circuitry, this could allow different dynamical elements to shift between different neural circuits to allow their interaction in a manner similar to chemical elements. This is a very speculative concept that needs to be explicitly simulated in biophysical simulations of neural circuits.

This article has attempted to describe the scope of unexplored territory in neural modeling. Unfortunately, we do not yet have a simple and generally accepted unifying framework for mapping out what is explored and unexplored in the space of neural models. Simple plots on dimensions such as number of intrinsic parameters versus number of synaptic parameters or number of layers show that current efforts have explored some dimensions in depth, without exploring the full space of

brain function. For example, computational neuroscience models have explored detailed models of single neurons without usually addressing the interacting function of large number of neurons or regions. In contrast, deep neural networks have explored the use of large number of layers and neurons while using highly simplistic intrinsic parameters of rectified linear unit (ReLU) input–output functions. The human brain simultaneously contains large numbers of neurons and regions as well as highly complex dynamics mediated by intrinsic conductances. A successful biophysical model that addresses aspects of human behavior will lie somewhere in the unexplored space involving both large numbers of neurons and regions and large numbers of intrinsic parameters.

The solution to this problem is not just to blindly explore the space of parameters. That would be unlikely to give insights even if it were possible. What is needed is more complex frameworks for building a structure of network theory that moves beyond feedforward or recurrent networks with simple intrinsic properties and complex intrinsic properties in small circuit simulations. We need more unifying structures of network models that address complex dynamics. This could involve more sophisticated focus on the categories of physiological responses of neurons, as shown in models that demonstrate shared properties with wide ranges of Hodgkin-Huxley conductances (Prinz et al., 2003, 2004), or in models that simplify the interaction of large numbers of conductances (Izhikevich, 2003, 2004). In addition, we need a framework for describing the elemental properties of different network subcomponents that could interact on multiple temporal and spatial scales, perhaps in analogy with the interaction of atoms to form molecules and larger scale chemical compounds.

ACKNOWLEDGEMENTS

This work supported by the National Institutes of Health, grant numbers R01 MH060013, R01 MH120073 and MH052090 and by the Office of Naval Research MURI N00014-16-1-2832, Office of Naval Research DURIP N00014-17-1-2304 and Office of Naval Research MURI N00014-19-1-2571. The authors have no conflicts of interest.

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(Received 10 December 2019, Accepted 31 March 2020)
(Available online 8 April 2020)