Degeneracy in hippocampal physiology and plasticity

Rahul Kumar Rathour and Rishikesh Narayanan*

Cellular Neurophysiology Laboratory, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India.

*** Corresponding Author**

Rishikesh Narayanan, Ph.D.
Molecular Biophysics Unit
Indian Institute of Science
Bangalore 560 012, India.

e-mail: rishi@iisc.ac.in
Phone: +91-80-22933372
Fax: +91-80-23600535

Abbreviated title: Degeneracy in the hippocampus

Keywords: hippocampus; degeneracy; learning; memory; encoding; homeostasis; plasticity; physiology; causality; reductionism; holism; structure-function relationships; variability; compensation; intrinsic excitability

ABSTRACT

Degeneracy, defined as the ability of structurally disparate elements to perform analogous function, has largely been assessed from the perspective of maintaining robustness of physiology or plasticity. How does the framework of degeneracy assimilate into an encoding system where the ability to change is an essential ingredient for storing new incoming information? Could degeneracy maintain the balance between the apparently contradictory goals of the need to change for encoding and the need to resist change towards maintaining homeostasis? In this review, we explore these fundamental questions with the mammalian hippocampus as an example encoding system. We systematically catalog lines of evidence, spanning multiple scales of analysis, that demonstrate the expression of degeneracy in hippocampal physiology and plasticity. We assess the potential of degeneracy as a framework to achieve the conjoint goals of encoding and homeostasis without cross-interferences. We postulate that biological complexity, involving interactions among the numerous parameters spanning different scales of analysis, could establish disparate routes towards accomplishing these conjoint goals. These disparate routes then provide several degrees of freedom to the encoding-homeostasis system in accomplishing its tasks in an input- and state-dependent manner. Finally, the expression of degeneracy spanning multiple scales offers an ideal reconciliation to several outstanding controversies, through the recognition that the seemingly contradictory disparate observations are merely alternate routes that the system might recruit towards accomplishment of its goals. Against the backdrop of the ubiquitous prevalence of degeneracy and its strong links to evolution, it is perhaps apt to add a corollary to Theodosius Dobzhansky's famous quote and state "nothing in physiology makes sense except in the light of degeneracy".

Highlights

- Degeneracy is the ability of structurally distinct elements to yield similar function
- We postulate a critical role for degeneracy in the emergence of stable encoding systems
- We catalog lines of evidence for the expression of degeneracy in the hippocampus
- We suggest avenues for research to explore degeneracy in stable encoding systems
- Dobzhansky wrote: “nothing in biology makes sense except in the light of evolution”
- A corollary: “nothing in physiology makes sense except in the light of degeneracy”

TABLE OF CONTENTS

1. Introduction **5**

2. Degeneracy: Foundations from the perspective of an encoding system **8**

2.1. Degeneracy vs. compensation *10*
2.2. Dissociation between different forms of homeostasis *15*
2.3. Baseline vs. plasticity profile homeostasis *17*
2.4. Encoding and homeostasis within the degeneracy framework *20*
2.5. Curse-of-dimensionality or evolutionary robustness *22*
2.6. Error correction mechanisms *24*

3. Degeneracy at multiple scales in the hippocampus **27**

3.1. Degeneracy in the properties of channels and receptors *29*
3.2. Degeneracy in neuronal physiological properties *32*
3.3. Degeneracy in calcium regulation and in the induction of synaptic plasticity *38*
3.4. Degeneracy in signaling cascades that regulate synaptic plasticity *42*
3.5. Degeneracy in the expression of synaptic plasticity *44*
3.6. Degeneracy in the induction and expression of non-synaptic plasticity *46*
3.7. Degeneracy in metaplasticity and in maintaining stability of learning *51*
3.8. Degeneracy in the generation and regulation of local field potentials *54*
3.9. Degeneracy in neural coding *56*
3.10. Degeneracy in learning and memory *60*

4. The causality conundrum **63**

4.1. Inevitable flaws in an experimental plan to establish causality that leaps across multiple scales .. *63*
4.2. Degeneracy: The way forward *67*

5. Conclusions **70**

ACKNOWLEDGMENTS **72**

REFERENCES **73**

1. Introduction

The pervasive question on the relationship between structure and function spans every aspect of life, science and philosophy: from building architectures to the mind-body problem, from connectomics to genomics to proteomics, from subatomic structures to cosmic bodies and from biomechanics to climate science. Even within a limited perspective spanning only neuroscience, the question has been posed at every scale of brain organization spanning the genetic to behavioral ends of the spectrum. Efforts to address this question have resulted in extensive studies that have yielded insights about the critical roles of protein structure and localization, synaptic ultrastructure, dendritic morphology, microcircuit organization and large-scale synaptic connectivity in several neural and behavioral functions.

The question on the relationship between structure and function has spawned wide-ranging debates, with disparate approaches towards potential answers. At one extreme is the suggestion that structure defines function (Buzsaki, 2006):

> "The safest way to start speculating about the functions of a structure is to inspect its anatomical organization carefully. The dictum "structure defines function" never fails, although the architecture in itself is hardly ever sufficient to provide all the necessary clues."

Within this framework, the following is considered as a route for understanding neural systems and behavior (Buzsaki, 2006):

> "First, we need to know the basic "design" of its circuitry at both microscopic and macroscopic levels. Second, we must decipher the rules governing interactions among neurons and neuronal systems that give rise to overt and covert behaviors."

The other extreme is the assertion that "form follows function", elucidated by Bert Sakmann (Sakmann, 2017), quoting Louis Sullivan:

> "Whether it be the sweeping eagle in his flight, or the open apple-blossom, the toiling work-horse, the blithe swan, the branching oak, the winding stream at its base, the drifting clouds, over all the coursing sun, form ever follows function, and this is the law. Where function does not change, form does not change".

Within this framework, the approach to understanding neural structure function relations was elucidated as (Sakmann, 2017):

> "The approach we took, in order to discover structure-function relations that help to unravel simple design principles of cortical networks was, to first determine functions and then reconstruct the underlying morphology assuming that "form follows function", a dictum of Louis Sullivan and also a Bauhaus design principle."

A third approach embarks on addressing the structure-function question by recognizing the existence of ubiquitous variability and combinatorial complexity in biological systems. This was elucidated in a landmark review by Edelman and Gally, who presented an approach to structure-function relationship by defining degeneracy (Edelman and Gally, 2001):

> "Degeneracy is the ability of elements that are structurally different to perform the same function or yield the same output. Unlike redundancy, which occurs when the same function is performed by identical elements, degeneracy, which involves structurally different elements, may yield the same or different functions depending on the context in which it is expressed. It is a prominent property of gene networks, neural networks, and evolution itself. Indeed, there is mounting evidence that degeneracy is a ubiquitous property of biological systems at all levels of organization."

They approach degeneracy and the structure-function question from an evolutionary perspective, noting (Edelman and Gally, 2001):

> "Here, we point out that degeneracy is a ubiquitous biological property and argue that it is a feature of complexity at genetic, cellular, system, and population levels. Furthermore, it is both necessary for, and an inevitable outcome of, natural selection."

From this perspective, the supposition that a one-to-one relationship between structure and function exists is eliminated, thereby yielding more structural routes to achieving the same function. This perspective posits that biological complexity should be viewed from the

62 evolutionarily advantageous perspective of providing functional robustness through degeneracy.
63 Further, the degeneracy framework provides the system with higher degrees of freedom to recruit
64 a state-dependent solution from a large repertoire of routes that are available to achieve the same
65 function.

66 The advantages of biological variability (Foster *et al.*, 1993; Gjorgjieva *et al.*, 2016;
67 Goldman *et al.*, 2001; Katz, 2016; Marder, 2011; Marder and Goaillard, 2006; Marder *et al.*,
68 2015; Marder and Taylor, 2011; O'Leary and Marder, 2014; Prinz *et al.*, 2004; Taylor *et al.*,
69 2009), degeneracy (Drion *et al.*, 2015; Edelman and Gally, 2001; Leonardo, 2005; O'Leary *et al.*,
70 2013; Whitacre and Bender, 2010; Whitacre, 2010) and complexity (Carlson and Doyle, 2002;
71 Edelman and Gally, 2001; Stelling *et al.*, 2004; Tononi *et al.*, 1996, 1999; Weng *et al.*, 1999;
72 Whitacre, 2010), especially in terms of their roles in achieving robust function, have been widely
73 studied and recognized in several biological process, including those in simple nervous systems.
74 However, this recognition has been very limited in the mammalian neuroscience literature, where
75 the focus is predominantly on explicitly assigning (or implicitly assuming) unique causal
76 mechanistic relationships between constituent components and emergent functions. Here, we
77 focus on the mammalian hippocampus, a brain region that has been implicated in spatial
78 cognition, learning and memory, and review several lines of evidence that point to the existence
79 of degeneracy in hippocampal physiology and plasticity. We argue that the elucidation of
80 degeneracy spanning multiple scales could result in resolution of several existing controversies
81 in the field, and provide an ideal setup to design experiments to understand neuronal systems,
82 their adaptability and their responses to pathological insults.

83 The rest of the review is organized into four sections. In the first of these sections, we
84 explore the foundations of degeneracy, especially from a perspective of an encoding system such

as the hippocampus, and outline distinctions between different forms of homeostasis and their interactions with encoding-induced adaptations. In the second section, we build an argument that theoretical and experimental literature, spanning multiple scales of analysis, presents abundant support for the prevalence of degeneracy in almost all aspects of hippocampal physiology and plasticity. The third section explores the important question on the feasibility of establishing one-to-one structure-function relationships in systems that exhibit degeneracy through complexity. The final section concludes the review by briefly summarizing the arguments and postulates presented here on degeneracy in encoding within the degeneracy framework.

2. Degeneracy: Foundations from the perspective of an encoding system

Akin to the much broader span of physics from the subatomic to the cosmic scales, and very similar to studies on other biological systems, neural systems are studied at multiple scales of analysis (Fig. 1A). Although understanding neural systems *within* each of these scales of analysis is critical and has its own right for existence, a predominant proportion of neuro-scientific research is expended on *cross-scale emergence* of function through *interactions* among constituent components. One set of studies focus on the emergence of functions in a specified scale of analysis as a consequence of interactions among components in the immediately lower scale of analysis. An elegant example to such analysis is on the emergence of neuronal action potentials (a cellular scale function) as a consequence of interactions (Hodgkin and Huxley, 1952) between sodium and delayed rectifier potassium channels (molecular scale components). Another set of studies focus on the relationships between function at a specified scale of analysis and components that are integral to a scale that is several levels apart. With specific reference to the hippocampus, assessing the molecular- or cellular-scale components (*e.g.*, receptors,

synapses) that are *causally* responsible for learning and memory (a behavioral scale function that is several scales apart from the molecular/cellular scales) forms an ideal example for studies that belong in this category (Bliss and Collingridge, 1993; Kandel *et al.*, 2014; Martin *et al.*, 2000; Mayford *et al.*, 2012; Neves *et al.*, 2008a).

Healthy and invigorating debates related to the philosophical and the scientific basis of such analyses, with themes ranging from broad discussions on reductionism *vs*. holism (Bennett and Hacker, 2003; Bickle, 2015; Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017; Panzeri *et al.*, 2017) to more focused debates on the specific cellular components that are involved in specific aspects of coding and behavior (Bliss and Collingridge, 1993; Gallistel, 2017; Kandel *et al.*, 2014; Kim and Linden, 2007; Martin *et al.*, 2000; Mayford *et al.*, 2012; Mozzachiodi and Byrne, 2010; Neves *et al.*, 2008a; Otchy *et al.*, 2015; Titley *et al.*, 2017; Zhang and Linden, 2003), have contributed to our emerging understanding of neural systems and their links to behavior. Several studies have covered the breadth and depth of these debates (Bargmann and Marder, 2013; Bennett and Hacker, 2003; Bickle, 2015; Jazayeri and Afraz, 2017; Jonas and Kording, 2017; Kandel *et al.*, 2014; Katz, 2016; Kim and Linden, 2007; Krakauer *et al.*, 2017; Lazebnik, 2002; Marder, 1998, 2011, 2012; Marder *et al.*, 2014; Marder and Thirumalai, 2002; Mayford *et al.*, 2012; Panzeri *et al.*, 2017; Tytell *et al.*, 2011), and will not be the focus of this review.

Within the purview of degeneracy, the emergence of specific combinations of higher-scale functions (within the limits of biological variability) could be achieved (Fig. 1B) through interactions among disparate parametric combinations in a lower scale (Edelman and Gally, 2001; Foster *et al.*, 1993; Gjorgjieva *et al.*, 2016; Goldman *et al.*, 2001; Marder, 2011; Marder and Goaillard, 2006; Marder *et al.*, 2015; Marder and Taylor, 2011; O'Leary and Marder, 2014; Prinz *et al.*, 2004; Rathour and Narayanan, 2012a, 2014; Srikanth and Narayanan, 2015; Stelling

132 *et al.*, 2004; Taylor *et al.*, 2009). A straightforward corollary to this is that robust homeostasis in
133 the maintenance of specific combinations of higher-scale functions in the face of perturbations
134 there would be achieved through very different routes involving disparate parametric
135 combinations in a lower scale (Fig. 1C). For instance, a change in neuronal firing rate at the
136 cellular scale owing to external perturbations involving pathological insults or behavioral
137 experience could be compensated for by different sets of changes to synaptic or intrinsic
138 parameters (at the molecular scale) to achieve activity homeostasis (Gjorgjieva *et al.*, 2016;
139 Hengen *et al.*, 2016; Nelson and Turrigiano, 2008; Turrigiano, 2011; Turrigiano, 1999, 2008;
140 Turrigiano and Nelson, 2004). Thus, under the degeneracy framework, different uncorrelated
141 clusters in the lower-scale parametric space could result in similar, if not identical, functional
142 outcomes in the higher-scale measurement space, thereby suggesting a many-to-one relationship
143 between the lower-scale parameters and higher-scale measurements (Edelman and Gally, 2001;
144 Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017). Prominent lines of experimental evidence in
145 support of degeneracy in neural systems have come from demonstrations of remarkable animal-
146 to-animal variability in constituent components in providing analogous functional outcomes,
147 and/or from results on many-to-many mappings between neural activity and behavior (Marder,
148 2011; Marder and Goaillard, 2006; Marder and Taylor, 2011; O'Leary and Marder, 2014; Schulz
149 *et al.*, 2006; Schulz *et al.*, 2007; Vogelstein *et al.*, 2014).
150

151 **2.1. Degeneracy *vs.* compensation**

152 A common misconception relating to degeneracy is that systems exhibiting degeneracy should
153 compensate for the removal of a specific lower-scale component by recruiting other structural
154 components there to yield the same higher-scale function. A corollary to this misconception is

155 that an inability to compensate for the removal of a component is interpreted as evidence for the
156 absence of degeneracy. For instance, consider an experiment where the "usefulness" of a specific
157 gene is being tested by assessing deficits in a specific behavior after knockout of the gene under
158 consideration. If the knockout resulted in the behavioral deficit, degeneracy is determined to be
159 absent and the gene considered essential. On the other hand, for the case where there was no
160 behavioral deficit, the gene is either considered non-essential or the result is interpreted as the
161 expression of degeneracy where other components have compensated for the knockout.

162 There have been several warnings against such oversimplified interpretations, especially
163 considering that biological systems are dynamic adaptive systems and not static (Edelman and
164 Gally, 2001; Grashow *et al.*, 2010; Marder, 2011; Marder and Goaillard, 2006; Marder and
165 Taylor, 2011; O'Leary *et al.*, 2014; Taylor *et al.*, 2009; Wagner, 2005). Specifically, although the
166 biological system adapts to the "unplanned" absence of the single gene (Edelman and Gally,
167 2001), it is not always essential that the adaptations result in compensation of one specific
168 behavioral readout (of the several possible readouts (Jazayeri and Afraz, 2017; Krakauer *et al.*,
169 2017)). Any compensation has been argued as a statistical result of the tradeoffs that are inherent
170 to this complex, adaptive and nonlinear system that manifests degeneracy that is *emergent* across
171 multiple scales of organization (Edelman and Gally, 2001; O'Leary *et al.*, 2014). It has also been
172 postulated that the compensatory process, and not the deletion, could have resulted in a specific
173 deficit (O'Leary *et al.*, 2014), especially because of the remarkable dissociation between different
174 forms of homeostasis (see Sec. 2.2).

175 Further, especially given the ubiquitous variability across animals in terms of constituent
176 components that elicit analogous behavior, it is clear that the impact of deletion of one specific
177 component would be differential. This implies that the simplistic generalizability on the presence

178 or absence of degeneracy based on a single parameter and a single measurement is untenable in
179 complex adaptive systems. Additionally, with reference to the specific example of gene deletion,
180 it is also important to distinguish between the acute impact of a lack of a protein that is tied to the
181 gene and the developmental knockout (and associated compensatory mechanisms) of the
182 specified gene (Edelman and Gally, 2001; Grashow *et al.*, 2010; Marder, 2011; Marder and
183 Goaillard, 2006; Marder and Taylor, 2011; O'Leary *et al.*, 2014; Taylor *et al.*, 2009).

184 In addition to these strong arguments against a one-to-one link between compensation
185 and degeneracy, it is also important to consider the specifics of the expectations on the specific
186 function that degeneracy is defined for and what functional deficit is to be compensated. Let's
187 consider the example of the emergence of membrane potential resonance in neurons as an
188 example to illustrate this argument (Fig. 2). The emergence of resonance requires the expression
189 of a resonating conductance, and the biophysical constraints on what makes a resonating
190 conductance are well established (Cole, 1968; Das *et al.*, 2017; Hodgkin and Huxley, 1952;
191 Hutcheon and Yarom, 2000; Mauro, 1961; Mauro *et al.*, 1970; Narayanan and Johnston, 2008).
192 Hippocampal pyramidal neurons express several resonating conductances: the hyperpolarization-
193 activated cyclic nucleotide-gated (HCN) nonspecific cation channels, the *M*-type potassium
194 (KM) channels and the *T*-type calcium (CaT) channels, of which HCN and CaT channels exhibit
195 overlapping voltage dependencies (Das *et al.*, 2017; Hu *et al.*, 2009; Hu *et al.*, 2002; Narayanan
196 and Johnston, 2007, 2008; Pike *et al.*, 2000; Rathour and Narayanan, 2012a).

197 Let's first consider an example where the function on which degeneracy is assessed is
198 qualitatively defined as the *expression* of membrane potential resonance (Fig. 2A). Whereas a
199 passive neuron does not express resonance, the presence of the HCN and/or the CaT channels
200 would result in the expression of resonance. This implies degeneracy in the function, where

201 similar functionality (in this case, the expression of resonance) is through disparate components
202 (channel combinations). In this scenario, depending on the variable expression profiles of HCN,
203 CaT and other modulating channels, removal of only one of them could still result in the
204 expression of resonance in specific neurons (Das *et al.*, 2017; Rathour *et al.*, 2016; Rathour and
205 Narayanan, 2012a, 2014). However, removal of both HCN and CaT channels would result in a
206 deficit in the assessed function, where resonance ceases to express. In this scenario, the
207 requirement or usefulness of HCN or CaT channels to the expression of resonance is easily
208 discernable by acute blockade experiments, although it would be difficult to predict (a) synergy
209 between different channels that are expressed towards the emergence of resonance with such
210 one-channel-at-a-time pharmacological blockade experiments; and (b) possible compensatory
211 mechanisms involving changes in kinetics or voltage-dependence properties of other channels,
212 say KM channels, in a double knockout scenario (Marder, 2011; Marder and Goaillard, 2006;
213 O'Leary *et al.*, 2014; Rathour and Narayanan, 2012a, 2014; Taylor *et al.*, 2009).

214 In most encoding or homeostatic scenarios involving changes in constituent components,
215 however, the functional outcome that is expected is a more quantitative readout of, say, firing
216 rate or calcium concentration altered or returned to *specific values*. Therefore, a widely
217 employed alternate interpretation (Foster *et al.*, 1993; Goldman *et al.*, 2001; Marder, 2011;
218 Marder and Goaillard, 2006; Marder *et al.*, 2015; Marder and Taylor, 2011; Prinz *et al.*, 2004;
219 Rathour and Narayanan, 2012a, 2014; Srikanth and Narayanan, 2015; Taylor *et al.*, 2009) is
220 where degeneracy is assessed as the ability of different structural components to elicit
221 *quantitatively* similar functional measurements. With reference to our chosen example, this
222 would translate to assessing degeneracy as the ability to achieve a *specific range of values* of
223 resonance frequency with disparate combinations of parameters (Fig. 2B). If achieving a specific

range of resonance frequency was the functional goal, and not the qualitative expression of resonance, then the possibilities are numerous. A resonating conductance is indeed required for the expression of resonance (Fig. 2B), but the goal is not to understand the expression of resonance, but to maintain resonance frequency at a specific value. In the presence of a resonating conductance, this goal could be achieved through very different structural routes either by altering other channel conductances or by altering properties of the resonating conductance itself. This implies the expression of degeneracy, where disparate parametric combinations could yield *quantitatively* similar resonance frequencies (Rathour and Narayanan, 2012a, 2014) across different models (Fig. 2C). Importantly, the order of degeneracy is rather large with the several active and passive properties, with the conductances, the voltage-dependence and kinetic properties of each of the several channels included. This also provides several routes to the emergence of compensation, where different channels and different parameters could differentially contribute to the emergence of similar functional measurements (Fig. 2C). We argue that this *quantitative* scenario with a large order of degeneracy is closer to the requirements of a system (at any given scale of organization) from the perspective of equilibrium and sustenance. The relevance of the qualitative scenario is rather limited to experiments that probe the expression of a specific phenomenon, which are "unplanned" from the evolutionary perspective there (Edelman and Gally, 2001).

Together, the question on the link between degeneracy and compensation should not be treated with simplistic ideas of linear interactions across components in a non-adapting system. The analyses should account for the specific definition of the function under consideration and the question on how degeneracy is defined. In addition, the nonlinear and synergistic interactions between different components that result in the specific function and animal-to-animal variability

247 in expression profiles of constituent components should be assessed as part of such analyses.
248 Finally, the possibility that "stochastic" compensatory process could be homeostatic or
249 pathological and importantly on whether the challenge that is being posed to the system by the
250 experiment is "planned" from the perspective of evolutionary convergence should also be
251 considered (Edelman and Gally, 2001; Grashow *et al.*, 2010; Marder, 2011; Marder and Taylor,
252 2011; O'Leary *et al.*, 2014; Taylor *et al.*, 2009).
253

254 **2.2. Dissociation between different forms of homeostasis**

255 It is clear from the examples presented above that the specific functional readout for which
256 robustness or homeostasis ought to be maintained is a very critical question within the
257 framework of degeneracy. Although degeneracy can be defined or observed with reference to
258 any function at any scale of organization, the answer to the question on what specific functional
259 homeostasis is absolutely essential from an evolutionary/neuroethological perspective isn't clear.
260 Even with reference to individual neurons, the literature has defined several forms of
261 homeostasis (Gjorgjieva *et al.*, 2016; Nelson and Turrigiano, 2008; Turrigiano, 2011; Turrigiano,
262 2008; Turrigiano and Nelson, 2004), with popular measures involving neuronal firing rate
263 (Hengen *et al.*, 2016), cytosolic calcium (Honnuraiah and Narayanan, 2013; O'Leary *et al.*, 2014;
264 Siegel *et al.*, 1994; Srikanth and Narayanan, 2015) or excitation-inhibition balance (Yizhar *et al.*,
265 2011). In addition, despite perpetual changes in afferent activity under *in vivo* conditions
266 (Buzsaki, 2002, 2006, 2015; Srikanth and Narayanan, 2015; Tononi and Cirelli, 2006), specific
267 neuronal subtypes maintain distinct functional signatures, say in terms of their excitability or
268 oscillatory or frequency selectivity measurements, that are different from other neuronal
269 subtypes even in the same brain region (Hoffman *et al.*, 1997; Migliore and Shepherd, 2002,

270 2005; Narayanan and Johnston, 2007, 2008; Pike *et al.*, 2000; Spruston, 2008; Zemankovics *et*
271 *al.*, 2010). Further, synaptic properties such as strength and release probabilities are also very
272 discernable across different synaptic subtypes (say excitatory *vs*. inhibitory) even on the same
273 postsynaptic neuron (Andrasfalvy and Magee, 2001; Andrasfalvy and Mody, 2006; Dittman *et*
274 *al.*, 2000; Koester and Johnston, 2005; Magee and Cook, 2000; Smith *et al.*, 2003). This
275 suggests the existence of some form of homeostasis that maintains these intrinsic and synaptic
276 measurements, including or apart from firing rate or calcium homeostasis or excitatory-inhibitory
277 balance, despite behaviorally driven encoding changes or perpetual activity switches that are
278 common in the hippocampus and other regions of the brain. Does maintenance of one of them
279 translate to maintenance of all of them? If not, which of these different forms of homeostasis are
280 absolutely essential for the animal from the evolutionary/neuroethological perspective?

281 There are several lines of clear evidence that there are remarkable dissociations between
282 different forms of homeostasis (Srikanth and Narayanan, 2015). First, cellular- or network-scale
283 functions could robustly emerge with disparate combinations of molecular- or cellular-scale
284 parameters (Foster *et al.*, 1993; Marder, 2011; Marder and Goaillard, 2006; Prinz *et al.*, 2004;
285 Rathour and Narayanan, 2014; Taylor *et al.*, 2009). These observations suggest that precise
286 homeostatic balance at a lower scale (*e.g.*, ion channels expressed to exact conductance values)
287 is not essential for maintaining functional homeostasis at a higher scale. Second, even in the
288 same set of neurons/networks/animals, different measurements have different dependencies on
289 underlying parameters, and these dependencies could be variable. For instance, in the same
290 neuron, resonance frequency could have a larger dependence on one channel subtype with input
291 resistance being critically regulated by another channel, with the specifics of these dependencies
292 variable across different neurons of the same subtype (Fig. 3A). Studies have shown that
293 different channels could have differential and variable impact on disparate measurements from
294 the same neuron, even in a location dependent manner (Grashow *et al.*, 2010; O'Leary *et al.*,

295 2014; Rathour and Narayanan, 2014; Taylor *et al.*, 2009). Additionally, acute blockade of one
296 specific channel results in weakly correlated changes in different measurements in the same
297 neuron (Rathour *et al.*, 2016). This implies that changing individual constitutive components to
298 maintain robust homeostasis in one of the measurements does not necessarily translate to robust
299 homeostasis in all the other measurements.

300 Third, for maintenance of calcium homeostasis across neurons in a network or in neurons
301 that are subjected to perpetual switches in afferent activity, it is not essential that functional
302 homeostasis across different intrinsic or synaptic measurements is maintained. Specifically,
303 owing to inherent variability in different constitutive components, the channel conductance
304 values or neuronal intrinsic properties or synaptic strengths could be very different across
305 different neurons despite maintenance of precise calcium homeostasis in neurons or their
306 network (Gjorgjieva *et al.*, 2016; O'Leary *et al.*, 2014; Srikanth and Narayanan, 2015). Finally,
307 calcium and firing rate homeostasis have been shown to be dissociated whereby tremendous
308 variability in channel conductance values, firing rate and pattern of firing have been observed
309 despite efficacious maintenance of calcium homeostasis (O'Leary *et al.*, 2013; O'Leary *et al.*,
310 2014; Srikanth and Narayanan, 2015). Together, these studies establish that none of the
311 individual forms of homeostasis (in calcium concentration or in channel densities channel or in
312 intrinsic functional characteristics including neuronal firing-rate) necessarily translate to or
313 follow from any other among them (O'Leary *et al.*, 2013; O'Leary *et al.*, 2014; Rathour and
314 Narayanan, 2012a, 2014; Srikanth and Narayanan, 2015), implying clear dissociations between
315 different forms of homeostasis.

316 **2.3. Baseline *vs.* plasticity profile homeostasis**

317 An important and necessary cynosure in the physiology of encoding systems is their ability to
318 change in a manner that promotes adaptability to the environment. In other words, the ability to
319 undergo plasticity is an important requirement for it to encode or learn newly available

320 information from the environment. Such plasticity has been shown to be ubiquitous, spanning
321 cellular and network structures across almost all regions, and could be triggered by development
322 (Desai *et al.*, 2002; Desai *et al.*, 1999; Luo and Flanagan, 2007; Schreiner and Winer, 2007;
323 Turrigiano and Nelson, 2004; White and Fitzpatrick, 2007), by learning processes (Kandel, 2001;
324 Kandel *et al.*, 2014; Kim and Linden, 2007; Lamprecht and LeDoux, 2004; Narayanan and
325 Johnston, 2012; Titley *et al.*, 2017; Zhang and Linden, 2003) or by pathological insults (Beck
326 and Yaari, 2008; Bernard *et al.*, 2007; Brager and Johnston, 2014; Grant, 2012; Johnston *et al.*,
327 2016; Kullmann, 2002; Lee and Jan, 2012; Lehmann-Horn and Jurkat-Rott, 1999; Lerche *et al.*,
328 2013; Poolos and Johnston, 2012). A traditional method to study such plasticity mechanisms is to
329 subject neuronal or synaptic structures to specific activity patterns towards understanding the
330 rules for plasticity in specific components. Assessed through such protocols, distinct synapses
331 show signature profiles of plasticity in terms of the strength and direction of synaptic plasticity
332 elicited by specific activity patterns. Additionally, there are also specific sets of non-synaptic
333 forms of plasticity (in channel densities and properties, for instance) that are concomitant to the
334 synaptic plasticity induced by different activity patterns (Abbott and Nelson, 2000; Abbott and
335 Regehr, 2004; Bi and Poo, 1998; Bliss and Collingridge, 1993; Bliss and Lomo, 1973; Chung *et*
336 *al.*, 2009a; Chung *et al.*, 2009b; Cooper and Bear, 2012; Dittman *et al.*, 2000; Dudek and Bear,
337 1992; Fortune and Rose, 2001; Frick *et al.*, 2004; Jorntell and Hansel, 2006; Lin *et al.*, 2008;
338 Losonczy *et al.*, 2008; Lujan *et al.*, 2009; Magee and Johnston, 1997; Markram *et al.*, 1997;
339 Narayanan and Johnston, 2007, 2008; Shah *et al.*, 2010; Sjostrom *et al.*, 2008). This implies
340 *plasticity profile homeostasis* (Anirudhan and Narayanan, 2015; Mukunda and Narayanan,
341 2017), where synapses of the same subtype respond similarly to analogous afferent activity,
342 thereby resulting in a subtype-dependent rule for synaptic plasticity (Larsen and Sjostrom, 2015).

343 In terms of non-synaptic plasticity, such plasticity profile homeostasis could be generalized to
344 subtypes of cells manifesting specific forms of neuronal plasticity (in intrinsic properties, for
345 instance).

346 Juxtaposed against the considerable variability in different constitutive components
347 across neurons of the same subtype, and given the critical dissociations between different forms
348 of homeostasis (Sec. 2.2), it is easy to deduce that the maintenance of baseline homeostasis of a
349 given measurement (say activity or calcium) does not necessarily imply that the system will
350 respond in a similar manner to identical perturbations (Fig. 3B). As the direction and strength of
351 change in activity or calcium is a critical determinant of the plasticity profile (Lisman, 1989;
352 Lisman *et al.*, 2002; Lisman *et al.*, 2012; Lisman, 2001; Nevian and Sakmann, 2006; Regehr,
353 2012; Shouval *et al.*, 2002; Sjostrom and Nelson, 2002; Sjostrom *et al.*, 2008; Zucker, 1999;
354 Zucker and Regehr, 2002), variable responses to incoming perturbations (physiological or
355 pathophysiological) would translate to very distinct plasticity profiles even in synapses of the
356 same subtype (Anirudhan and Narayanan, 2015; Mukunda and Narayanan, 2017; O'Leary *et al.*,
357 2013; Srikanth and Narayanan, 2015). Therefore, from the perspective of homeostasis in
358 encoding systems such as the hippocampus, it is not just sufficient to ask if baseline homeostasis
359 of a given measurement is maintained. It is also important to ask if the response of the system to
360 identical perturbations is similar to enable plasticity profile homeostasis. The absence of such
361 plasticity profile homeostasis would result in very different adaptations to identical perturbations
362 even under baseline conditions, resulting in the absence of signature plasticity profiles being
363 associated with specific neurons and synapses. Although there is dissociation between the
364 maintenance of baseline *vs.* plasticity profile homeostasis, studies have demonstrated degeneracy
365 in the maintenance of short- and long-term plasticity profiles. Specifically, these studies have

366 shown that disparate combinations of ion channel conductances and calcium-handling
367 mechanisms could yield analogous short- or long-term plasticity profiles (Anirudhan and
368 Narayanan, 2015; Mukunda and Narayanan, 2017). Although we dealt with plasticity profile
369 homeostasis and its dissociation from baseline homeostasis, a related phenomenon that involves
370 plasticity of *plasticity profiles* has been defined as metaplasticity (Abraham, 2008; Abraham and
371 Bear, 1996; Abraham and Tate, 1997; Cooper and Bear, 2012; Hulme *et al.*, 2013; Sehgal *et al.*,
372 2013). Lines of evidence supporting degeneracy in hippocampal metaplasticity and its roles in
373 stable learning will be explored in Sec. 3.3.
374

375 **2.4. Encoding and homeostasis within the degeneracy framework**

376 The function of learning systems extends beyond simple maintenance of physiological or
377 plasticity homeostasis. The functional goal in these systems is rather contrary to *maintenance* of
378 homeostasis, because encoding or learning of new information demands *alteration* in
379 physiology/behavior through continual *adaptation* in an experience-/activity-dependent manner.
380 This presents a paradoxical requirement where components ought to *change* to encode new
381 information, *without* perturbing the overall homeostatic balance of the system. Thus, encoding of
382 a new experience entails a tricky balance between change and homeostasis (James, 1890):

383 "Plasticity, then, in the wide sense of the word, means the possession of a structure
384 weak enough to yield to an influence, but strong enough not to yield all at once.
385 Each relatively stable phase of equilibrium in such a structure is marked by what
386 we may call a new set of habits."
387
388 From the degeneracy and physiology perspectives, this balance poses several tricky questions
389 that the literature does not present definitive answers to. For instance, could learning systems
390 accomplish this balance between encoding of new information *and* maintenance of homeostasis
391 *within* the framework of degeneracy? In other words, could the plasticity mechanisms that define

392 encoding *and* the homeostatic mechanisms that negate the impact of perturbation *together* be
393 realized through disparate combinations of constitutive components (Narayanan and Johnston,
394 2012; Nelson and Turrigiano, 2008; Turrigiano, 2007, 2011; Turrigiano *et al.*, 1994; Turrigiano,
395 1999; Turrigiano and Nelson, 2000)? Would the availability of more routes to achieve encoding
396 or homeostasis be detrimental or be advantageous towards accomplishing these goals together?
397 Would the dissociations between different forms of homeostasis (Sec. 2.2) and between baseline
398 *vs*. plasticity profile homeostasis (Sec. 2.3) translate to severe constraints on accomplishing this
399 balance *within* the framework of degeneracy?

400 Together, there are lines of evidence supporting the formulation that plasticity and
401 homeostasis individually could be achieved through several non-unique routes through disparate
402 combinations of constituent components (Anirudhan and Narayanan, 2015; Mukunda and
403 Narayanan, 2017; Narayanan and Johnston, 2012; Nelson and Turrigiano, 2008; O'Leary *et al.*,
404 2013; Srikanth and Narayanan, 2015; Turrigiano, 2007, 2011; Turrigiano *et al.*, 1994;
405 Turrigiano, 1999; Turrigiano and Nelson, 2000). However, the focus on achieving the *conjoined*
406 goals of effectuating changes in response to new information *and* maintaining robust
407 homeostasis in the face of such changes *within* the framework of degeneracy have been
408 conspicuously lacking. Such focus is especially important because of the seemingly
409 contradictory requirements of the two processes, where one necessitates change and the other
410 works to negate any change, resulting in the possibility where there could be detrimental cross-
411 interference working towards negating each other. Therefore, for the framework of degeneracy to
412 be relevant in learning systems, it is important that future studies assess the twin goals of
413 encoding and homeostasis to be synergistically conjoined rather than treat them as isolated
414 processes that independently achieve their respective goals. Without the recognition of such

synergy between encoding and homeostatic systems, assessing the ability of these two processes to avoid cross-interference becomes intractable.

2.5. Curse-of-dimensionality or evolutionary robustness

Curse of dimensionality, coined by Bellman (Bellman, 1957), refers to the extreme difficulties encountered with the comprehension or solution to a problem that involves exorbitantly large numbers of input variables, their attributes and possible solutions. In biology in general, and in neuroscience in particular, the dimensions of the parametric space is typically large, making dimensions of the interactional space (the space that covers all forms of interactions spanning all these parameters) even larger. The variability of parametric values even in systems exhibiting similar functions and the perpetual adaptation of these parameters in response to external perturbations (or even baseline turnover towards maintaining homeostasis) make it impossible to localize any biological function to a small subspace of this large interactional space. This, as a consequence of the curse of dimensionality, translates to mathematical and computational intractability of biological systems because of insufficiency of collected data towards providing an accurate answer to questions related to comprehending or assessing the system.

The framework of degeneracy on the other hand suggests that biological systems thrive on this parametric and interactional complexity because it provides the ideal substrate for arriving at disparate structural routes to robust functional similarity. Several strong qualitative and quantitative arguments, based on several lines of evidence spanning different scales of analysis across different biological systems, have been placed in favor of synergistic links between degeneracy, complexity, robustness, evolvability and adaptation. Therefore, the dimensionality of the parametric and interactional space of biological systems should not be

438 treated as a curse in terms of our inability to analytically track or comprehend the system, but as
439 a fundamental and necessary feature towards achieving the contradictory yet conjoint goals (Sec.
440 2.4) of functional robustness (Edelman and Gally, 2001; Kitano, 2007; Marder, 2011; Marder
441 and Goaillard, 2006; Rathour *et al.*, 2016; Rathour and Narayanan, 2012a, 2014; Sporns *et al.*,
442 2000; Stelling *et al.*, 2004; Tononi and Cirelli, 2006; Tononi and Edelman, 1998; Tononi *et al.*,
443 1998; Wagner, 2005, 2008), evolvability (Edelman and Gally, 2001; Wagner, 2008; Whitacre
444 and Bender, 2010; Whitacre, 2010) and adaptation (Albantakis *et al.*, 2014; Anirudhan and
445 Narayanan, 2015; Joshi *et al.*, 2013; Mukunda and Narayanan, 2017).

446 Importantly, the recognition of the critical links between complexity, degeneracy and
447 adaptability allows for better design of experimental and analysis techniques for assessing
448 biological systems and their function. Not only do these techniques alleviate the pains of hand
449 tuning in computational models (Prinz *et al.*, 2003), but also recognize the implications for
450 parametric variability to robust functions and the fallacies associated with misinterpretation of
451 results from knockout animals in the face of perpetual biological compensation (Edelman and
452 Gally, 2001; Grashow *et al.*, 2010; Marder, 2011; Marder and Goaillard, 2006; Marder and
453 Taylor, 2011; O'Leary *et al.*, 2014; Taylor *et al.*, 2009; Wagner, 2005). Some classes of
454 techniques developed with the recognition of the strong links between variability, complexity,
455 adaptability, degeneracy and robustness are: (a) the global sensitivity analysis technique (Sec.
456 3.2) that employs a stochastic search algorithm spanning a large parametric space and optimizes
457 for *multiple* physiological objectives (Foster *et al.*, 1993; Goldman *et al.*, 2001; Marder, 2011;
458 Marder and Goaillard, 2006; Marder and Taylor, 2011; Prinz *et al.*, 2004; Rathour and
459 Narayanan, 2014); (b) the theoretical and experimental assessment of the links between
460 quantitative complexity measures and robustness with reference to several physiological and

461 pathophysiological attributes (Albantakis *et al.*, 2014; Edelman and Gally, 2001; Joshi *et al.*,
462 2013; Kitano, 2007; Sarasso *et al.*, 2015; Sporns *et al.*, 2000; Stelling *et al.*, 2004; Tononi and
463 Edelman, 1998; Tononi *et al.*, 1998; Tononi *et al.*, 1996, 1999; Wagner, 2005, 2008; Whitacre
464 and Bender, 2010; Whitacre, 2010); and (c) plasticity models that have accounted for
465 concomitant changes in multiple components (Secs. 3.6–3.7) rather than focusing on a one-to-
466 one relationship between functional plasticity and one specific component that undergoes
467 changes (Abbott and LeMasson, 1993; Anirudhan and Narayanan, 2015; LeMasson *et al.*, 1993;
468 Mukunda and Narayanan, 2017; O'Leary *et al.*, 2013; O'Leary *et al.*, 2014; Siegel *et al.*, 1994;
469 Srikanth and Narayanan, 2015). These analyses have made it abundantly clear that the
470 complexities inherent to biological systems should be considered as substrates for functional
471 robustness through degeneracy (Edelman and Gally, 2001), rather than be viewed from the
472 curse-of-dimensionality perspective.
473

474 **2.6. Error correction mechanisms**

475 A critical requirement in a system that is endowed with degeneracy is an error-correcting
476 feedback mechanism that regulates constituent components in an effort to achieve a specific
477 function. For instance, consider the example where the goal is to achieve calcium homeostasis in
478 a neuron. In this scenario, as the specific regulatory mechanism that is to be triggered is
479 dependent on the current state of the neuron, or more precisely the current levels of calcium, it is
480 important that the regulatory mechanism is geared towards *correcting* the *error* between the
481 target function and the current state (Abbott and LeMasson, 1993; LeMasson *et al.*, 1993;
482 O'Leary *et al.*, 2013; O'Leary *et al.*, 2014; Siegel *et al.*, 1994; Srikanth and Narayanan, 2015).
483 This requires a closed circuit feedback loop that initiates a compensatory mechanism that is

484 driven by the quantitative distance between the target function and the current state. This state-
485 dependent perpetual error correction becomes especially important in a scenario where distinct
486 regulatory mechanisms govern the different constitute components. With the specific example at
487 hand, let's say the error correcting feedback mechanism regulates ion channel conductances by
488 altering their protein expression through several transcription factors (Srikanth and Narayanan,
489 2015). In such a scenario, calcium homeostasis could be achieved by recruiting several non-
490 unique sets of these transcription factors. As each of these transcription factors could be coupled
491 to the regulation of distinct combinations of ion channels, calcium homeostasis could be
492 achieved through several non-unique combinations of ion channels.

493 Within the degeneracy framework, although distinct solutions are possible with weak
494 pairwise correlations between constitutive components, there is a strong synergistic *collective*
495 dependence of these components to achieve a function (Rathour and Narayanan, 2014).
496 Specifically, let's consider two neurons (neurons 1 and 2) with distinct sets of non-unique
497 parametric combinations that yielded very similar function. However, given the nonlinearities of
498 neural systems, it would be infeasible to expect similar function from a third neuron built with
499 one-half of the parameters taken from neuron 1 and the other half taken from neuron 2. This
500 collective cross-dependence is an essential component of systems manifesting degeneracy and
501 should be respected by mechanisms that regulate the constitutive components. Returning to
502 specific example under consideration, the specific *ensemble* of the targeted transcription factors
503 and channel conductances are important in terms of which solution is *chosen* within the
504 degeneracy framework. This places strong requirements on the distinct regulatory mechanisms,
505 transcription factors in this case, that they strongly interact with each other rather than acting

independent of each other (Srikanth and Narayanan, 2015) in a manner that is *driven* by the error that is being fed back in a state-dependent temporally precise manner.

These requirements become especially important in an encoding system such as the hippocampus, whose afferent activity is perpetually variable in a behavioral state-dependent manner, requiring temporally proximal feedback for the continuous maintenance of robust function. A simple solution to account for cross-interacting regulatory mechanisms is to assume the existence of only one regulatory mechanism that governs all constitutive components (*e.g.*, one transcription factors controls all channels and receptors on a neuron (O'Leary *et al.*, 2014)). However, this might not always be valid or possible or feasible (Srikanth and Narayanan, 2015), especially if the complexity of system is enormous (*e.g.*, coexistence of multiple transcription factors in the hippocampus (Alberini, 2009; Bading *et al.*, 1993; Dolmetsch, 2003; Lein *et al.*, 2007). In these scenarios, it is important that the error-sensing and regulatory mechanisms also exhibit degeneracy and are strongly inter-coupled to each other through cross-regulatory mechanisms at that scale as well (*e.g.*, multiple calcium sensors accompanied by a network of transcription factors coupled through feedback loops that regulate each other (Cheong *et al.*, 2011; Kotaleski and Blackwell, 2010; Losick and Desplan, 2008; Thattai and van Oudenaarden, 2001; Yu *et al.*, 2008)). In summary, the ability to achieve functional robustness through degeneracy in any scale of analysis requires continuous correction of functional deficits, without which it is impossible to adjudge the efficacious accomplishment of a desired goal through a chosen route (which is one among the many possible routes). In a system with enormous complexity, this is typically achieved through an error-correcting feedback pathway that recruits multiple cross-interacting regulatory mechanisms towards maintaining collective cross-

528 dependence of constituent mechanisms (Rathour and Narayanan, 2014; Srikanth and Narayanan,
529 2015).

530 3. Degeneracy at multiple scales in the hippocampus

531 The hippocampus is a brain region that has been shown to be critically involved in spatial
532 representation of the external environment and in several forms of learning and memory
533 (Anderson *et al.*, 2007; Eichenbaum, 2012; Hartley *et al.*, 2014; Moser *et al.*, 2008; Neves *et al.*,
534 2008a; Scoville and Milner, 1957). As a region that is involved in encoding of new information
535 and one that is part of the medial temporal lobe that is critically sensitive to excitotoxic insults
536 (Bernard *et al.*, 2007; Dam, 1980; de Lanerolle *et al.*, 1989; Johnston *et al.*, 2016; Sloviter,
537 1991), it is important that the hippocampal cells maintain some form of activity homeostasis to
538 avoid runaway excitation.

539 The hippocampus consists of several subtypes of neurons and glia receiving afferent
540 information from tens of thousands of synapses and expressing distinct sets of a wide variety of
541 ligand-gated receptors and voltage-gated ion channels, each built through complex structural
542 interactions between a number of main and auxiliary subunits (Lai and Jan, 2006; Migliore and
543 Shepherd, 2002; Nusser, 2009, 2012; Vacher *et al.*, 2008; Verkhratsky and Steinhauser, 2000).
544 The regulatory role of glial cells and their constitutive components in synaptic information
545 processing is well established (Allen and Barres, 2005, 2009; Araque, 2008; Araque *et al.*, 2014;
546 Araque *et al.*, 1999; Bazargani and Attwell, 2016; Deitmer *et al.*, 2006; Fields and Stevens-
547 Graham, 2002; Halassa *et al.*, 2007; Halassa and Haydon, 2010; Haydon and Carmignoto, 2006;
548 Pannasch and Rouach, 2013; Pascual *et al.*, 2005; Perea and Araque, 2005; Perea *et al.*, 2009),
549 providing additional structural substrates that could participate in the encoding and homeostasis

550 processes. The basic properties and regulation of these and other membrane and cytoplasmic
551 protein structures, in conjunction with intracellular (including the ER and the trafficking
552 apparatus) and intercellular interaction dynamics (including neuronal synaptic connectivity and
553 the glial syncytium) and morphological characteristics, regulates the intricate balance between
554 encoding and homeostasis within the hippocampal structure. In addition to these, hippocampal
555 structure and function are critically reliant on the afferent and efferent connectivity patterns, the
556 metabolic pathways that drive and interact with the local cellular structures and the several forms
557 of state-dependent modifications to each of these components. Together, the combinatorial
558 complexity of the constitutive components that define hippocampal function is staggeringly
559 astronomical.

560 A fundamental question that is of considerable interest to the research community is on
561 how the hippocampus achieves robust function, especially in accomplishing the apparently
562 contradictory goals of adaptive change and homeostasis (Sec. 2), in the face of such
563 combinatorial complexity that drives its physiology and plasticity. Within the framework of
564 degeneracy, it could be argued that the complexity is an enabler, and not an impediment, towards
565 achieving functional robustness.

566 Does hippocampal physiology manifest degeneracy at multiple scales, whereby similar
567 hippocampal function could be achieved through disparate structural combinations? In this
568 section, we view hippocampal research spanning the past several decades through the lens of
569 degeneracy and present clear qualitative and quantitative lines of evidence arguing for the
570 ubiquitous presence of degeneracy spanning multiple scales of hippocampal function. We review
571 lines of evidence showing multiple routes to achieving several critical hippocampal functions,
572 which in some cases have been considered to be lines of evidence that are in apparent

573 contradiction to each other, triggering expansive debates and arguments within the field. In a
574 manner similar to (Edelman and Gally, 2001), we systematically explore the expression of
575 degeneracy at distinct scales (starting at the molecular scale and moving incrementally to the
576 systems/behavioral scale) of hippocampal function (Fig. 1A), with function(s) or physiological
577 measurements assessed within the specified scale of analysis. We postulate that the recognition
578 of the ubiquitous prevalence of degeneracy would provide an evolutionarily routed framework to
579 unify the several apparently contradictory routes to achieving the same function as necessity,
580 rather than luxury, towards achieving physiological robustness.
581

582 **3.1. Degeneracy in the properties of channels and receptors**

583 Hippocampal neurons are endowed with myriad voltage and ligand dependent ion channels, with
584 well-defined gradients in their expression profiles and their properties (Barnard *et al.*, 1998;
585 Dingledine *et al.*, 1999; Johnston and Narayanan, 2008; Magee and Cook, 2000; Migliore and
586 Shepherd, 2002; Narayanan and Johnston, 2012; Paoletti *et al.*, 2013; Sieghart and Sperk, 2002).
587 The presence of these channels, with their signature characteristics and expression profiles, has
588 been shown to play critical roles in the physiology (Das *et al.*, 2017; Johnston *et al.*, 1996;
589 Johnston and Narayanan, 2008; Magee, 2000; Narayanan and Johnston, 2012), plasticity (Frick
590 and Johnston, 2005; Johnston *et al.*, 2003; Remy *et al.*, 2010; Shah *et al.*, 2010; Sjostrom *et al.*,
591 2008) and pathophysiology (Bernard *et al.*, 2007; Brager and Johnston, 2014; Johnston *et al.*,
592 2016; Kullmann, 2002; Lee and Jan, 2012; Lerche *et al.*, 2013) of hippocampal neurons and their
593 networks. Therefore, it is essential that the biophysical properties and expression profiles of
594 these channels be tightly regulated to ensure functional robustness.

595 The regulation of targeting, localization and properties of these channels at specific
596 levels, however, is a problem that involves several degrees of combinatorial freedom. The
597 reasons behind this complexity are manifold. First, most of these channels are not protein
598 molecules derived from single genes, but are assembled from several possible pore-forming and
599 auxiliary subunits, expressed in different stoichiometry (Catterall, 1993, 1995; Gurnett and
600 Campbell, 1996; Hille, 2001; Isom *et al.*, 1994). The presence or absence of a specific pore-
601 forming or auxiliary subunit, and the specific ratios of their expression are important for
602 trafficking, localization and properties of these channels. For instance, *A*-type K^+ channels in the
603 hippocampus could be assembled by the main subunits from the Kv1 or Kv4 families and
604 auxiliary subunits from the KChIP and DPP families (Amarillo *et al.*, 2008; Birnbaum *et al.*,
605 2004; Jerng *et al.*, 2004; Kim *et al.*, 2007; Kim *et al.*, 2005; Sun *et al.*, 2011; Vacher and
606 Trimmer, 2011), whereas auxiliary subunits MiRP1, KCR1 and TRIP8b have been implicated in
607 regulating trafficking and properties of *h* channels assembled with main subunits from the HCN
608 family of proteins. Additionally, the properties of *h* channels, in terms of their voltage-
609 dependence, their kinetics and modulation by cyclic nucleotides, are critically regulated by the
610 specific isoforms that are expressed in conjunction with the specific stoichiometry of such
611 expression (Biel *et al.*, 2009; He *et al.*, 2014; Lewis *et al.*, 2011; Much *et al.*, 2003; Robinson
612 and Siegelbaum, 2003; Santoro *et al.*, 2000; Santoro *et al.*, 2009; Santoro *et al.*, 2004; Ulens and
613 Siegelbaum, 2003; Ulens and Tytgat, 2001; Zolles *et al.*, 2009).

614 Second, targeting and functional properties of these assembled channels (Trimmer and
615 Rhodes, 2004; Vacher *et al.*, 2008) could be critically modulated by different forms of post-
616 translational modification (Derkach *et al.*, 1999; Derkach *et al.*, 2007; Levitan, 1994; Misonou *et*
617 *al.*, 2004; Much *et al.*, 2003; Shah *et al.*, 2010; Sjostrom *et al.*, 2008), by local pH (Holzer,

618 2009), by interaction with intracellular messengers (Armstrong and Bezanilla, 1974) and by lipid
619 composition of the plasma membrane (Levitan and Barrantes, 2012). For instance, trafficking of
620 *A*-type K^+ channels is phospho-regulated in a manner that is dependent on their main and
621 auxiliary subunits (Birnbaum *et al.*, 2004; Hammond *et al.*, 2008; Lin *et al.*, 2011; Lin *et al.*,
622 2010; Vacher and Trimmer, 2011), and differences between proximal and distal dendritic sodium
623 channels are partly mediated by phosphorylation states of these channels (Gasparini and Magee,
624 2002).

625 Third, distinct channels have been demonstrated to have structural interactions with each
626 other, thereby cross-regulating the functional properties of each other. For instance, structural
627 interactions between Cav3 and Kv4 channel families are known to regulate neuronal activity
628 through efficient transfer of calcium influx from Cav3 channels to bind onto KChIPs that
629 modulate Kv4 channel function (Anderson *et al.*, 2010). Finally, these channels can undergo
630 activity-dependent plasticity and neuromodulation (Biel *et al.*, 2009; Cantrell and Catterall,
631 2001; He *et al.*, 2014; Hoffman and Johnston, 1999; Lee and Dan, 2012; Marder, 2012; Marder
632 *et al.*, 2014; Marder and Thirumalai, 2002; Robinson and Siegelbaum, 2003), which also could
633 result in important changes to their trafficking and functional properties (Sec. 3.6).

634 How do these channels maintain specific location-dependent levels of expression with
635 specific properties despite this staggering complexity that results in their assemblage and specific
636 function? From the description above, it is clear that channels achieve specific properties and
637 localization through multiple structural routes involving several subunits, enzymes associated
638 with post-translational modification, neuromodulators and their receptors and several signaling
639 cascades (also see Sec. 3.4–3.6). This follows the observation that each functional property of the
640 channel, including its localization and targeting, is regulated by multiple mechanisms, each

641 endowed with the ability to bidirectionally modulate the functional property. Therefore, the
642 combinatorial complexity of regulation and the involvement of different structural routes to
643 achieve similar function together provide ample lines of evidence for the expression of
644 degeneracy in achieving specific function for channels and receptors expressed in the
645 hippocampus. In answering the question on how robustness might be achieved, the argument
646 within the framework of degeneracy would be that functional robustness in the assemblage,
647 targeting and function of ion channels is achieved as a *consequence* of the underlying regulatory
648 and interactional complexity.
649

650 **3.2. Degeneracy in neuronal physiological properties**

651 The presence of various ligand and voltage dependent ion channels confers signature
652 neurophysiological properties, such as input resistance, firing rate, frequency selectivity and
653 integration and propagation of potentials across axonal and dendritic processes, upon different
654 hippocampal neurons (Hutcheon and Yarom, 2000; Johnston *et al.*, 1996; Llinas, 1988).
655 Although there is remarkable variability in these measurements even within a single neuronal
656 subtype (Dougherty *et al.*, 2012; Dougherty *et al.*, 2013; Malik *et al.*, 2016), different neuronal
657 subtypes within the same subregion have signature electrophysiological characteristics
658 (Anderson P, 2007; Freund and Buzsaki, 1996; Klausberger and Somogyi, 2008; Spruston, 2008)
659 that are maintained despite the combinatorial complexity of ion channels expressed in these
660 neurons. Additionally, prominent relationships between intrinsic neurophysiological properties
661 and various pathological conditions, including epilepsy and Fragile X mental disorder, have been
662 reported across several neurological disorders (Beck and Yaari, 2008; Bernard *et al.*, 2007;
663 Brager and Johnston, 2014; Johnston *et al.*, 2016; Kullmann, 2002; Lee and Jan, 2012;

664 Lehmann-Horn and Jurkat-Rott, 1999; Lerche *et al.*, 2013; Poolos and Johnston, 2012). Thus,
665 from the maintaining robust physiology and from the perspective of avoiding pathological
666 excitability conditions, it is essential that neurons maintain their signature electrophysiological
667 characteristics.

668 It is now recognized across systems that there is no one-to-one relationship between
669 neurophysiological properties and the channels that regulate them (Sec. 2.1–2.3, Fig. 2–3). It is
670 established that several channels contribute to the emergence and regulation of a specific
671 physiological property, and the same channel could regulate several physiological properties,
672 resulting in a many-to-many mapping between channels and physiological properties. In addition
673 to the example assessing degeneracy in resonance properties (Sec. 2.1–2.2, Fig. 2–3), we could
674 also consider the example of maintaining neuronal firing rates at specific levels. Whereas fast
675 Na^+ and delayed rectifier K^+ channels mediate action potential firing in hippocampal neurons,
676 their firing rate profiles are regulated by an array of ion channels including the *A*-type K^+, HCN,
677 GIRK, *M*-type K^+ and SK channels (Adelman *et al.*, 2012; Gasparini and DiFrancesco, 1997; Gu
678 *et al.*, 2005; Hu *et al.*, 2007; Kim and Johnston, 2015; Kim *et al.*, 2005; Malik and Johnston,
679 2017; Narayanan and Johnston, 2007; Rathour *et al.*, 2016).

680 These observations provide specific insights about the relationship between channels and
681 physiological properties (Sec. 2.1–2.3; Fig. 2–3). First, there is degeneracy in the emergence of
682 neurophysiological properties, where disparate combinations of channels could come together to
683 elicit similar functional properties (Das *et al.*, 2017; Drion *et al.*, 2015; Foster *et al.*, 1993;
684 Goldman *et al.*, 2001; Marder, 2011; Marder and Goaillard, 2006; Rathour *et al.*, 2016; Rathour
685 and Narayanan, 2012a, 2014; Taylor *et al.*, 2009).

686 Second, the dependence of different physiological properties on distinct channels is
687 variable even within the same neuronal subtype, and is a function of the variable expression
688 profiles of these channels (Drion *et al.*, 2015; O'Leary *et al.*, 2014; Rathour and Narayanan,
689 2014; Taylor *et al.*, 2009). For instance, whereas *A*-type K^+ channels might contribute maximally
690 to maintaining firing rates at a specific level in one neuron, in another neuron of the same
691 subtype it could be SK channels.

692 Third, the dependence of different physiological properties in the *same* neuron on distinct
693 channels is differential and variable, where pharmacological blockade of one channel may have a
694 stronger effect on a specific physiological property compared to another (Rathour *et al.*, 2016).
695 As a consequence of these observations, there is a dissociation between robust maintenance of
696 one physiological property and that of another (Srikanth and Narayanan, 2015). Maintenance of
697 only a few physiological properties would not necessarily translate to maintenance of all
698 physiologically relevant properties. All relevant physiological properties ought to be explicitly
699 maintained for overall robustness.

700 Fourth, hippocampal neurons are endowed with complex dendritic arborization with
701 several well-defined functional maps expressing along their somato-dendritic arbor, making
702 proteostasis, or protein homeostasis (Balch *et al.*, 2008), in these neurons a complex problem
703 (Hanus and Schuman, 2013; Narayanan and Johnston, 2012). Despite the strong structural
704 constraint of maintaining robustness of several tightly coupled location-dependent functional
705 measurements, it has been demonstrated that it is not essential to maintain individual channels at
706 specific densities or with specific properties for achieving robust functional homeostasis. Instead,
707 several disparate combinations of channel parameters, spanning properties and densities of
708 several channels, could robustly maintain *concomitant* homeostasis of multiple functions across

709 the dendritic arbor (Rathour and Narayanan, 2014). It is however essential to note that dendritic
710 morphology plays a crucial role in regulating intrinsic properties and their location-dependent
711 characteristics, especially in electrotonically *non*-compact hippocampal pyramidal neurons
712 (Dhupia *et al.*, 2015; Golding *et al.*, 2005; Krichmar *et al.*, 2002; Mainen and Sejnowski, 1996;
713 Narayanan and Chattarji, 2010; Spruston *et al.*, 1994; Spruston *et al.*, 1993), and could contribute
714 to degeneracy in the emergence of single-neuron physiology.

715 Finally, depending on the localization profiles and voltage-dependent properties of
716 different channels they may or may not spatiotemporally interact (Migliore and Migliore, 2012;
717 Mishra and Narayanan, 2015; Rathour and Narayanan, 2012b). For instance, owing to mostly
718 non-overlapping voltage-dependence and localization profiles, *M*-type K^+ and HCN channels
719 mediate complementary somato-dendritic theta filtering in hippocampal neurons (Hu *et al.*,
720 2009; Narayanan and Johnston, 2007, 2008). In contrast, *A*-type K^+ and HCN channels strongly
721 overlap both in their voltage-dependence and localization, resulting in their ability to co-regulate
722 the same form of resonance in hippocampal pyramidal neurons (Rathour *et al.*, 2016; Rathour
723 and Narayanan, 2012a, 2014)

724 These insights are driven by experimental observations coupled with physiologically
725 relevant computational models that allowed greater flexibility in terms of understanding
726 mechanistic basis, importance of ion channel interactions and the degree of contribution of each
727 channel type in regulating neuronal properties. Multi parametric multi objective stochastic search
728 algorithms are a class of algorithms that has been employed as an extremely effective method to
729 explore cellular-level degeneracy in a systematic and rigorous manner through global sensitivity
730 analysis (Anirudhan and Narayanan, 2015; Drion *et al.*, 2015; Foster *et al.*, 1993; Goldman *et al.*,
731 2001; Mukunda and Narayanan, 2017; Rathour and Narayanan, 2012a, 2014; Taylor *et al.*,

732 2009). These algorithms provide a quantitative route to understanding the structure of the global
733 parametric space in any given model, without making explicit assumptions about co-variation of
734 different parameters test the robustness of the system to parametric variability. In this technique,
735 model neurons generated by uniform random sampling of the global parametric space are tested
736 against experimental statistics of several measurements. Model neurons that satisfy *several*
737 experimental constraints are declared as "valid models". The use of multiple measurements to
738 establish the validity of models is essential because of afore-mentioned (Sec. 2.1–2.3)
739 dissociation between different forms of homeostasis and the differential dependence of different
740 measurements on distinct constitutive components (Fig. 2–3). It is well recognized in the design
741 principle of these techniques that establishing physiological equivalence of only a partial set of
742 measurements *does not* necessarily ensure that the other measurements which have not been
743 constrained by the validation process are within the physiological ranges (Achard and De
744 Schutter, 2006; Foster *et al.*, 1993; Goldman *et al.*, 2001; Hobbs and Hooper, 2008; Marder,
745 2011; Marder and Goaillard, 2006; Marder and Taylor, 2011; Prinz *et al.*, 2003; Prinz *et al.*,
746 2004; Rathour and Narayanan, 2012a, 2014; Srikanth and Narayanan, 2015; Taylor *et al.*, 2009;
747 Tobin *et al.*, 2006; Weaver and Wearne, 2008). If such a stochastic search algorithm fails to yield
748 any valid model that satisfies all the physiological objectives, the interpretation should not be
749 that the specified model configuration is incapable of achieving all objectives. This is because
750 the stochastic search does not *entirely* span the global parametric space, thereby allowing for the
751 possibility that valid solutions could exist within the unexamined regions of this parametric
752 space.

753 Once the validity of a (typically small) subset of models through multiple physiological
754 constraints is established, the approach has been employed to explore degeneracy by assessing

755 pair-wise and cross-dependencies across different parameters. Pairwise correlations across valid
756 model parametric values are typically employed to explore such dependencies, where a strong
757 correlation between any two parameters is interpreted as a pointer to potential co-regulation of
758 biological mechanisms defining these parameters (Anirudhan and Narayanan, 2015; Foster *et al.*,
759 1993; Goldman *et al.*, 2001; Mukunda and Narayanan, 2017; Rathour and Narayanan, 2012a,
760 2014; Taylor *et al.*, 2009). These analyses also provide insights about how critically specific
761 parameters should be regulated to achieve the *multiple* objectives imposed by the validation
762 criteria. Importantly, these algorithms provide a quantitative route to finding the relative
763 sensitivities of different measurements to each channel that contributed to the emergence of
764 robust functionality spanning multiple measurements. It is recognized that the dependence of
765 measurements on individual channels would be variable given that different model neurons are
766 endowed with considerable variability in each channel conductance. However, it is still known
767 that the average dependence of a given measurement (say resonance frequency) is higher for one
768 specific channel (say HCN channels), *relative* to the other channels expressed in the system.
769 Different methodologies have been proposed to assess these relative contributions and have been
770 effectively employed to understand the differential and variable dependencies of different
771 measurements on each underlying channel (O'Leary *et al.*, 2014; Rathour and Narayanan, 2014;
772 Taylor *et al.*, 2009).

773 Together, through a confluence of electrophysiological and computational techniques that
774 assessed variability and homeostasis in neuronal and channel properties, the expression of
775 degeneracy in the emergence of single neuron physiology is well established across several
776 systems, including the mammalian hippocampus. It is clear that disparate combinations of
777 morphological and channel parameters could robustly yield analogous single neuron physiology,

778 despite being constrained by *multiple* measurements that span the entire somato-dendritic arbor
779 of the *same* neuron.
780

781 **3.3. Degeneracy in calcium regulation and in the induction of synaptic plasticity**

782 Whereas the ability to maintain baseline physiological measurements at specific levels is
783 important from the homeostasis perspective, the ability to alter responses (through changes in
784 parameters) towards achieving a specific target is important from the perspective of learning or
785 encoding. This ability to undergo long-term plasticity is absolutely critical in an encoding
786 system. One of the most well studied forms of long-term plasticity in hippocampal neurons is
787 plasticity in synaptic structures. There are several lines of evidence for degeneracy in the
788 induction, expression and maintenance of long-term synaptic plasticity and the mechanisms that
789 are associated with each of these distinct phases of synaptic plasticity. As long-term synaptic
790 plasticity is relatively well studied, we will first outline these lines of evidence from the synaptic
791 plasticity perspective and then switch to the implications for *concomitant* non-synaptic plasticity
792 that typically accompanies synaptic plasticity.

793 A popular methodology to study long-term synaptic plasticity in neurons within the
794 hippocampus and other brain structures is the use of specific induction protocols that result in
795 synaptic plasticity. These induction protocols are activity-dependent, and are typically induced
796 by combinations of presynaptic stimulation and/or postsynaptic current injection. There are also
797 several chemical protocols for inducing synaptic plasticity, say through depolarization induced
798 through elevated levels of extracellular potassium or potassium channel blockers (Hanse and
799 Gustafsson, 1994; Huang and Malenka, 1993; Huber *et al.*, 1995; Lin *et al.*, 2008; Otmakhov *et*
800 *al.*, 2004; Roth-Alpermann *et al.*, 2006). These protocols are critically tied to the specific

801 synaptic structures that are studied and show signature profiles across synaptic structures of
802 similar subtypes (Abbott and Nelson, 2000). The protocols required for induction of synaptic
803 plasticity are not unique. Several disparate protocols with very distinct combinations of
804 presynaptic stimulation and/or postsynaptic current injection (Fig. 4) have been shown to elicit
805 long-term potentiation (LTP) or long-term depression (LTD). The cellular mechanisms required
806 for inducing LTP are also very different across these protocols, with differences sometimes
807 manifesting even within a single protocol for synapses at two different locations on the same
808 neuron. For instance, with the theta burst protocol for inducing LTP (Fig. 4A), proximal synaptic
809 LTP requires pairing with backpropagating action potentials, but distal synapses recruit dendritic
810 spikes and do not require backpropagating action potentials (Golding *et al.*, 2002; Kim *et al.*,
811 2015; Magee and Johnston, 1997).

812 The ability of multiple activity protocols (Fig. 4) to elicit similar levels of synaptic
813 plasticity might be an example of multiple realizability, but it could be argued that this does not
814 constitute an instance of degeneracy, which requires that disparate *structural* components elicit
815 similar function. To address this argument, we refer to established answers for one of the
816 fundamental questions on synaptic plasticity: What is the mechanistic basis for these induction
817 protocols to elicit synaptic plasticity? The influx of calcium into the cytosol is considered as the
818 first step that results in the induction of LTP or LTD (Lynch *et al.*, 1983; Malenka *et al.*, 1992;
819 Mulkey and Malenka, 1992). Quantitatively, there have been suggestions for the amplitude,
820 spread and kinetics of cytosolic calcium elevation to be specific attributes that translate to the
821 strength and direction of plasticity (Larkman and Jack, 1995; Lisman, 1989; Lisman, 2001;
822 Shouval *et al.*, 2002). From this perspective, it may be argued that disparate protocols for
823 inducing LTP (or LTD) result in similar amplitude, spread and kinetics of calcium elevation,

824 thereby resulting in similar strength of LTP (or LTD). With calcium elevation established as a
825 mechanistic basis for the induction of synaptic plasticity, the question of degeneracy here should
826 now focus on the structural basis for eliciting similar elevation in cytosolic calcium.

827 The mechanisms that govern the strength, spread and kinetics of neuronal calcium are
828 well studied (Augustine *et al.*, 2003; Berridge, 1998, 2002, 2006; Berridge *et al.*, 2000; Frick *et*
829 *al.*, 2003; Higley and Sabatini, 2012; Jaffe *et al.*, 1992; Miyakawa *et al.*, 1992; Rizzuto and
830 Pozzan, 2006; Ross, 2012; Sabatini *et al.*, 2002; Yasuda *et al.*, 2004). Briefly, synergistic
831 interactions between three prominent sets of mechanisms (Fig. 5) regulate cytosolic calcium
832 levels, especially from the perspective of induction of synaptic plasticity. First, the disparate
833 structural components through which calcium ions flow into the cytosol either from the
834 extracellular matrix or from the endoplasmic reticulum (ER). These are typically receptors or
835 channels expressed on the plasma membrane or the ER membrane. The second set is built of
836 disparate mechanisms that alter postsynaptic excitability, which mediates the conversion from
837 synaptic current to synaptic voltage responses. Changes in excitability modulate voltage-levels,
838 which in turn alter calcium influx through voltage-sensitive synaptic receptors or voltage-gated
839 calcium channels. Finally, the expression of calcium-handling mechanisms such as pumps,
840 exchangers and buffers limit the spatiotemporal spread of calcium thereby maintaining
841 specificity of signaling, apart from regulating the strength and kinetics of calcium influx. Thus
842 there are disparate mechanisms that regulate calcium influx, and non-unique combinations of
843 these mechanisms could yield similar strength and kinetics of calcium influx in response to
844 different induction protocols.

845 Importantly, electrophysiological recordings coupled with pharmacological treatments
846 provide strong lines of evidence that induction of synaptic plasticity could indeed be mediated

847 and regulated by these distinct components. Specifically, there are strong lines of evidence that
848 the induction of bidirectional synaptic plasticity in the hippocampus is mediated by different
849 calcium sources, with certain protocols requiring synergistic activation of multiple calcium
850 sources (Brager and Johnston, 2007; Christie *et al.*, 1996; Golding *et al.*, 2002; Huber *et al.*,
851 1995; Nishiyama *et al.*, 2000; Raymond, 2007). These studies show that plasticity induction is
852 dependent on influx of calcium through NMDA receptors (Christie *et al.*, 1996; Collingridge and
853 Bliss, 1987; Collingridge *et al.*, 1983; Morris *et al.*, 1986; Mulkey and Malenka, 1992;
854 Nishiyama *et al.*, 2000; Tsien *et al.*, 1996; Wang *et al.*, 2003), voltage-gated calcium channels
855 (Brager and Johnston, 2007; Christie *et al.*, 1996; Christie *et al.*, 1997; Johnston *et al.*, 1992;
856 Moosmang *et al.*, 2005; Nicholson and Kullmann, 2017; Wang *et al.*, 2003), store-operated
857 calcium channels (Baba *et al.*, 2003; Garcia-Alvarez *et al.*, 2015; Majewski and Kuznicki, 2015;
858 Majewski *et al.*, 2016; Prakriya and Lewis, 2015) and receptors on the ER activated by
859 metabotropic receptors on the plasma membrane (Huber *et al.*, 2000; Nishiyama *et al.*, 2000;
860 Verkhratsky, 2002). Additionally, voltage-gated channels and their auxiliary subunits
861 (Anirudhan and Narayanan, 2015; Brager *et al.*, 2013; Chen *et al.*, 2006; Chung *et al.*, 2009a;
862 Chung *et al.*, 2009b; Johnston *et al.*, 2003; Jung *et al.*, 2008; Kim *et al.*, 2007; Lin *et al.*, 2008;
863 Lujan *et al.*, 2009; Malik and Johnston, 2017; Nolan *et al.*, 2004; Sehgal *et al.*, 2013; Shah *et al.*,
864 2010; Watanabe *et al.*, 2002) have also been shown to critically regulate the strength and
865 direction of synaptic plasticity. Thus, several structural components that mediate or modulate
866 calcium influx into the cytosol have been demonstrated as critical regulators of the induction of
867 synaptic plasticity, both from the qualitative perspective of expression of plasticity and the
868 quantitative perspective of the specific levels of plasticity attained with an induction protocol.
869 Finally, computational modeling has demonstrated that similar synaptic plasticity profiles could

870 be achieved through disparate combinations of channels and receptors (Anirudhan and
871 Narayanan, 2015; Ashhad and Narayanan, 2013; Narayanan and Johnston, 2010; Shouval *et al.*,
872 2002) and is critically dependent on the state of the synapse (Migliore *et al.*, 2015). In
873 conjunction with the experimental studies reviewed above, these provide very strong lines of
874 evidence for degeneracy in the induction of synaptic plasticity, where similar levels of calcium
875 influx and analogous synaptic plasticity could be achieved through disparate combinations of
876 parameters that synergistically regulate calcium influx (Fig. 4B).
877

878 **3.4. Degeneracy in signaling cascades that regulate synaptic plasticity**
879
880 What follows calcium elevation in the process of inducing synaptic plasticity? Once specific
881 strengths and kinetics of calcium influx are achieved as a consequence of induction protocols
882 activating the several disparate mechanisms, is the route to the expression of synaptic plasticity
883 unique? Could multiple mechanisms be activated in response to similar elevations of cytosolic
884 calcium towards achieving specific levels of synaptic plasticity? In other words, is there
885 degeneracy in terms of distinct pathways involving different constitutive components that could
886 link the induction of synaptic plasticity to its expression?

887 The large body of literature on the signaling cascades involved in synaptic plasticity has
888 presented several lines of evidence that there are several signaling routes, contributing
889 synergistically or differentially, to achieving the translation from the induction of synaptic
890 plasticity to its expression (Fig. 6). Specifically, there is evidence that there are several
891 biochemical species that control synaptic efficacy through a complex network of
892 spatiotemporally interacting signaling cascades (Bhalla, 2014; Bhalla and Iyengar, 1999;
893 Derkach *et al.*, 2007; Kennedy, 2000; Kennedy *et al.*, 2005; Kholodenko, 2006; Kotaleski and
894 Blackwell, 2010; Larkman and Jack, 1995; Manninen *et al.*, 2010; Neves and Iyengar, 2009;

895 Neves *et al.*, 2008b; Regehr *et al.*, 2009; Weng *et al.*, 1999). It is also clear that the dominance of
896 any specific cascade that determines the strength and direction of plasticity is dependent on
897 synaptic state (Migliore *et al.*, 2015), the protocol employed (Kandel *et al.*, 2014; Mayford *et al.*,
898 2012) and on the spatiotemporal dynamics of changes in the postsynaptic calcium concentration
899 (Berridge, 1998; Korte and Schmitz, 2016; Lisman, 1989; Lisman, 2001; Parekh, 2008; Rizzuto
900 and Pozzan, 2006).

901 The biochemical signaling diversity involved in synaptic plasticity spans both the pre-
902 and post-synaptic sides. The signaling cascades involved in the translation of induction to
903 expression include several enzymes that mediate posttranslational modification of disparate
904 protein substrates, protein synthesis regulators, retrograde messengers, protein trafficking
905 regulators and mechanisms mediating structural plasticity. As a specific example, with reference
906 to the diversity of enzymes that are involved in post-translational modifications resulting in the
907 expression of synaptic plasticity, it has been shown that different protocols for inducing LTP in
908 the Schaffer collateral synapses projecting to CA1 are differentially dependent on different
909 kinases (Kandel, 2001; Kandel *et al.*, 2014; Manninen *et al.*, 2010; Mayford *et al.*, 2012;
910 Raymond, 2007; Soderling and Derkach, 2000). Example kinases are the calcium-calmodulin
911 kinase II, CaMKII (Lisman *et al.*, 2002; Lisman *et al.*, 2012; Malinow *et al.*, 1989; Ouyang *et*
912 *al.*, 1997; Ouyang *et al.*, 1999), protein kinase A, PKA (Frey *et al.*, 1993; Lin *et al.*, 2008;
913 Otmakhova *et al.*, 2000; Rosenkranz *et al.*, 2009; Woo *et al.*, 2003) and mitogen associated
914 protein kinase, MAPK (English and Sweatt, 1997; Rosenkranz *et al.*, 2009), which could be
915 activated with the same or different LTP protocols. For instance, the theta-burst pairing protocol
916 activates all of CaMKII, MAPK and PKA (Fan *et al.*, 2005; Lin *et al.*, 2008; Rosenkranz *et al.*,
917 2009), with very different target substrates involving different channels and receptors (see Sec.

3.6). Additionally the expression of synaptic plasticity, or the substrate for altered synaptic efficacy, could be dependent on several factors (Sec. 3.5), each of which could undergo distinct plasticity with reference to the same activity protocols (Sec. 3.6). Together, the possible combinations of mechanisms that could mediate the translation of plasticity induction protocol to plasticity expression, even for a single synaptic subtype, are numerous. There are also lines of evidence that similar strength and direction of synaptic plasticity could be achieved through the activation of disparate combinations of these mechanisms, providing evidence for the manifestation of degeneracy in the signaling cascades that mediate the transition from plasticity induction to expression.

3.5. Degeneracy in the expression of synaptic plasticity

The above analyses establish that hippocampal neurons exhibit degeneracy with reference to the induction of synaptic plasticity and in terms of the mechanisms that mediate the transition from induction to expression. Do these mechanisms act in concert to alter a single target to effectuate the expression of synaptic plasticity? Or are there multiple targets that could be altered to achieve similar strength and direction of synaptic plasticity in a specific synapse?

From the very first study that demonstrated LTP, it has been clear that the protocols employed for inducing synaptic plasticity can recruit different structural components (Bliss and Lomo, 1973):

> "The results suggest that two independent mechanisms are responsible for long-lasting potentiation: (a) an increase in the efficiency of synaptic transmission at the perforant path synapses; (b) an increase in the excitability of the granule cell population."

Several studies that followed up on this landmark study have now clearly shown that there are disparate routes to achieving synaptic plasticity, even with very similar strength and the same

944 direction of plasticity (Fig. 7). It is now well established that the expression of synaptic plasticity
945 could recruit mechanisms spanning pre- and post-synaptic components, including
946 channels/receptors, morphological features and cytoplasmic constituents on either side (Fig. 7).
947 In other words, different combinations of changes in presynaptic channels/receptors, release
948 mechanisms and postsynaptic channels/receptors could mediate the expression of synaptic
949 plasticity.

950 The framework of degeneracy provides an ideal way to reconcile the thorny debates
951 regarding pre- and post-synaptic mechanisms that could mediate synaptic plasticity. Specifically,
952 within this framework, pre- and post-synaptic components would be considered simply as *a*
953 *subset* (see Sec. 3.6) of the broad repertoire of mechanisms that are available to the neural system
954 to alter towards achieving a specific level of synaptic plasticity or accomplishing an encoding
955 task. Disparate combinations of these components could synergistically contribute to the
956 expression of specific levels of plasticity, at times even with temporal differences in the
957 expression of plasticity in different components. The specific combination of changes that are
958 recruited to mediate plasticity for a chosen protocol or for a given behavioral task would then be
959 state-dependent, critically reliant on the specific calcium sources (Sec. 3.3) and signaling
960 cascades (Sec. 3.4) that were recruited in response to the induction protocol or a behavioral task.
961 In addition to these neuronal components, glial cells, through several mechanisms including
962 gliotransmission or transmitter reuptake and recycling mechanisms, have also been shown to
963 play a critical role in synaptic plasticity (Araque *et al.*, 2014; Ashhad and Narayanan, 2016;
964 Halassa *et al.*, 2007; Haydon and Carmignoto, 2006; Henneberger *et al.*, 2010; Pannasch and
965 Rouach, 2013; Perea and Araque, 2007; Perea *et al.*, 2016; Zorec *et al.*, 2012), thereby adding

966 another layer of parameters and another set of interactional complexity to the mechanistic basis
967 for synaptic plasticity.

968 This combinatorial complexity of parameters and associated interactions provide a strong
969 foundation for degeneracy in the emergence of not just the induction and expression of long-term
970 plasticity, but also in the emergence of short-term synaptic plasticity. Specifically, several of the
971 components involved in the induction and expression of long-term plasticity have also been
972 shown to play critical roles in short-term forms of plasticity such as paired pulse facilitation, and
973 on the synaptic filters that they mediate (Atwood *et al.*, 2014; Bouchard *et al.*, 2003; De Pitta *et*
974 *al.*, 2011; Dittman *et al.*, 2000; Emptage *et al.*, 2001; Fioravante and Regehr, 2011; Fortune and
975 Rose, 2001; Regehr, 2012; Siegelbaum, 2000; Zucker, 1989, 1999; Zucker and Regehr, 2002).
976 These observations, in conjunction with quantitative computational models have led to the
977 suggestion for the manifestation of degeneracy in the emergence of short-term plasticity profiles
978 and associated synaptic filters (Mukunda and Narayanan, 2017). Specifically, it has been
979 demonstrated that analogous synaptic filters emerge from disparate combinations of presynaptic
980 parameters (Mukunda and Narayanan, 2017). Together, these observations provide clear lines of
981 evidence for the manifestation of degeneracy in short- and long-term forms of synaptic plasticity
982 in the hippocampus.

983

984 **3.6. Degeneracy in the induction and expression of non-synaptic plasticity**

985

986 It is now widely acknowledged that plasticity protocols and learning paradigms that were once
987 assumed to exclusively recruit or induce synaptic plasticity also induce plasticity in other
988 components (Fig. 8), in a manner that could either be localized or global. Similar to the study of
989 synaptic plasticity, specific activity protocols (most of which are similar, if not identical, to
990 synaptic plasticity protocols) are employed to assess plasticity in other protein molecules and

991 structural changes. Plasticity in voltage-gated ion channels and other neuronal components that
992 result in changes to neuronal intrinsic properties have been dubbed as *intrinsic plasticity*, and is
993 known to occur in the hippocampus with reference to most activity-dependent protocols
994 employed for inducing synaptic plasticity (Brager and Johnston, 2007; Chung *et al.*, 2009a;
995 Chung *et al.*, 2009b; Fan *et al.*, 2005; Frick and Johnston, 2005; Frick *et al.*, 2004; Johnston *et*
996 *al.*, 2003; Johnston and Narayanan, 2008; Kim and Linden, 2007; Lin *et al.*, 2008; Losonczy *et*
997 *al.*, 2008; Magee, 2000; Mozzachiodi and Byrne, 2010; Narayanan and Johnston, 2007, 2008,
998 2012; Nelson and Turrigiano, 2008; Remy *et al.*, 2010; Sjostrom *et al.*, 2008; Spruston, 2008;
999 Wang *et al.*, 2003; Zhang and Linden, 2003). Although it is generally assumed that intrinsic
1000 plasticity refers only to global changes in intrinsic *excitability*, it is important to recognize that
1001 intrinsic plasticity encompasses *all* intrinsic properties that are mediated by neuronal constitutive
1002 components (Llinas, 1988; Marder, 2011; Marder *et al.*, 1996; Marder and Goaillard, 2006),
1003 including neuronal spectral selectivity conferred by specific sets of ion channels (Das *et al.*,
1004 2017; Hutcheon and Yarom, 2000) and calcium wave propagation mediated by receptors on the
1005 endoplasmic reticulum (Ross, 2012). These distinct intrinsic properties, including excitability,
1006 have been shown to undergo bidirectional changes in a manner that is local to specific neuronal
1007 locations or is global spanning all locations (Brager and Johnston, 2007; Das *et al.*, 2017;
1008 Johnston and Narayanan, 2008; Narayanan *et al.*, 2010; Narayanan and Johnston, 2007, 2008).
1009 As the protocols employed for inducing non-synaptic (including intrinsic and structural)
1010 plasticity are at most instances identical to synaptic plasticity induction protocols, the broad
1011 mechanisms involved in the induction and in the translation of induction to expression are very
1012 similar to those for synaptic plasticity (Fig. 8). Specifically, induction of intrinsic plasticity
1013 requires influx of cytosolic calcium with different kinetics and strengths of calcium translating to

1014 distinct strengths and directions of intrinsic plasticity (Brager and Johnston, 2007; Fan *et al.*,
1015 2005; Huang *et al.*, 2005; Sjostrom *et al.*, 2008; Wang *et al.*, 2003). The components that
1016 mediate calcium entry for synaptic plasticity also mediate calcium entry for non-synaptic
1017 plasticity, including NMDA receptors (Chung *et al.*, 2009a; Chung *et al.*, 2009b; Engert and
1018 Bonhoeffer, 1999; Fan *et al.*, 2005; Frick *et al.*, 2004; Huang *et al.*, 2005; Lin *et al.*, 2008;
1019 Losonczy *et al.*, 2008; Matsuzaki *et al.*, 2004; Nagerl *et al.*, 2004; Narayanan and Johnston,
1020 2007; Tonnesen *et al.*, 2014; Wang *et al.*, 2003), voltage-gated calcium channels (Chung *et al.*,
1021 2009a; Chung *et al.*, 2009b; Lin *et al.*, 2008; Wang *et al.*, 2003) and receptors on the ER
1022 (Ashhad *et al.*, 2015; Brager and Johnston, 2007; Brager *et al.*, 2013; Clemens and Johnston,
1023 2014; Kim *et al.*, 2017; Narayanan *et al.*, 2010). This implies that the arguments (Secs. 3.3–3.4)
1024 placed about synergistic interactions between different calcium sources and about degeneracy in
1025 the induction of synaptic plasticity extends to the induction of non-synaptic plasticity as well
1026 (Fig. 8).

1027 As a direct consequence of the similarity in the protocols employed in inducing synaptic
1028 and intrinsic plasticity, the downstream mechanisms that mediate the translation from induction
1029 of non-synaptic plasticity to its expression are also similar (Shah *et al.*, 2010) to those that
1030 mediate a similar transition in synaptic plasticity (Fig. 8). Several signaling cascades that are
1031 present on the pre- and post-synaptic sides mediate this translation, with retrograde messengers
1032 acting as mechanisms that signal the elevation of postsynaptic calcium to the presynaptic
1033 terminals. Specifically, the same set of enzymes and messengers that mediate synaptic plasticity
1034 also mediate non-synaptic plasticity (Fig. 8). Examples to this equivalence include non-synaptic
1035 forms of plasticity that are mediated by CaMKII (Fan *et al.*, 2005; Huang *et al.*, 2005; Lujan *et*
1036 *al.*, 2009; Matsuzaki *et al.*, 2004; Wang and Wagner, 1999), PKA (Lin *et al.*, 2008; Narayanan *et*

1037 *al.*, 2010; Rosenkranz *et al.*, 2009) and MAPK (Rosenkranz *et al.*, 2009; Yuan *et al.*, 2002).
1038 However, there could be dissociation between the mechanisms that are involved in the
1039 translation to the expression of different forms of plasticity that are consequent to the *same*
1040 induction protocol, where different enzymes and messengers mediate different forms of plasticity
1041 (Brager and Johnston, 2007; Fan *et al.*, 2005; Lin *et al.*, 2008; Rosenkranz *et al.*, 2009; Wang *et*
1042 *al.*, 2003). As mentioned earlier (Sec. 3.5), the expression of plasticity in synapses could be
1043 mediated by plasticity in voltage-gated calcium channels that are expressed in the presynaptic
1044 terminal, mediated by retrograde messengers and presynaptic signaling cascades, or by change in
1045 mechanisms that alter postsynaptic excitability, thus blurring the distinction between synaptic
1046 and certain forms of non-synaptic plasticity.

1047 Following the activation of different signaling cascades, akin to the expression of
1048 synaptic plasticity, several molecular processes, including synthesis, trafficking and post-
1049 translational modification of the several membrane and cytosolic proteins, mediate the final step
1050 towards the expression of distinct forms of non-synaptic plasticity (Fig. 8). The mechanisms
1051 behind the trafficking of several ion channels have been studied (Cusdin *et al.*, 2008; Jensen *et*
1052 *al.*, 2011; Lai and Jan, 2006; Lau and Zukin, 2007; Lujan *et al.*, 2009; Shah *et al.*, 2010; Vacher
1053 *et al.*, 2008; Wenthold *et al.*, 2003), and it is now clear that plasticity is ubiquitous (Kim and
1054 Linden, 2007). In addition to these changes in cytosolic and membrane proteins, it has been
1055 shown that hippocampal spines undergo continuous structural changes, apart from
1056 demonstrations of distinct forms of structural plasticity in spines, dendrites and axons (Attardo *et*
1057 *al.*, 2015; Chen *et al.*, 2014; Emoto, 2011; Engert and Bonhoeffer, 1999; Ghiretti and Paradis,
1058 2014; Grubb and Burrone, 2010a, b; Grubb *et al.*, 2011; Ikegaya *et al.*, 2001; Johnston *et al.*,
1059 2016; Luo and O'Leary, 2005; Matsuzaki *et al.*, 2004; Nagerl *et al.*, 2004; Tonnesen *et al.*, 2014;

1060 Yuste and Bonhoeffer, 2001). Finally, the dynamics associated with the various glial functions
1061 and their interactions with neuronal and metabolic pathways could also undergo changes in
1062 response to behavioral experiences and activity (Araque *et al.*, 2014; Baumann and Pham-Dinh,
1063 2001; Fields, 2010; Halassa and Haydon, 2010; Haydon and Carmignoto, 2006; Khakh and
1064 Sofroniew, 2015; Pannasch and Rouach, 2013; Perea *et al.*, 2016; Sierra *et al.*, 2014; Volterra *et*
1065 *al.*, 2014). It is therefore clear that there is no escape from the conclusion that activity- or
1066 experience- or pathology-dependent plasticity does not confine itself to a few constitutive
1067 components, but is rather expansive and even ubiquitous (Kim and Linden, 2007). There are
1068 considerable overlaps in the mechanisms that mediate the induction and expression of these
1069 forms of plasticity, and many-to-one and one-to-many mappings between the induction protocol
1070 (or behavioral experience) and achieving specific levels of plasticity in specific components (Fig.
1071 8).

1072 In summary, the lines of evidence provided above point to ample evidence for
1073 degeneracy in the process of their induction and expression of different forms of plasticity and
1074 their combinations, both in terms of their individual strengths and directions. This also implies
1075 that the same functional changes could be achieved through distinct combinations of plasticity
1076 mechanisms, thus pointing to a further dissociation between functional homeostasis and the
1077 plasticity mechanisms that yielded it. In other words, functional equivalence in terms of
1078 transition from one state to another does not necessarily translate to plasticity equivalence (where
1079 the route taken to achieve the transition is always identical). An important class of plasticity
1080 models has recognized the ubiquitous nature of plasticity, with models built within this
1081 framework of plasticity degeneracy. These models account for concomitant changes in multiple
1082 components, also accounting for disparate combinations of plasticity resulting in similar

1083 functional outcomes, rather than assuming plasticity equivalence in the face of functional
1084 equivalence (Abbott and LeMasson, 1993; Anirudhan and Narayanan, 2015; LeMasson *et al.*,
1085 1993; Mukunda and Narayanan, 2017; O'Leary *et al.*, 2013; O'Leary *et al.*, 2014; Siegel *et al.*,
1086 1994; Srikanth and Narayanan, 2015). Future theoretical and experimental investigations into
1087 hippocampal plasticity should therefore account for the truly ubiquitous nature of plasticity in
1088 designing their experiments and addressing outstanding questions, rather than assuming that
1089 plasticity is confined to one single component or the other (Bhalla, 2014; Kim and Linden,
1090 2007).
1091

1092 **3.7. Degeneracy in metaplasticity and in maintaining stability of learning**

1093 Hebbian synaptic plasticity is inherently unstable. In the absence of concomitant homeostatic
1094 mechanisms, Hebbian plasticity would result in runaway excitation (Fig. 9). Several theories and
1095 mechanisms have been proposed as a means to avoid this runaway excitation (Abbott, 2003;
1096 Abraham and Robins, 2005; Korte and Schmitz, 2016; Miller and MacKay, 1994; Nelson and
1097 Turrigiano, 2008; Turrigiano, 2007, 2011; Turrigiano, 1999, 2008, 2017; Turrigiano and Nelson,
1098 2000; van Rossum *et al.*, 2000; Zenke *et al.*, 2017). A prominent theme that spans several such
1099 stability theories is metaplasticity (Abraham, 2008; Abraham and Bear, 1996; Abraham and
1100 Tate, 1997; Hulme *et al.*, 2013), where the profile of plasticity concomitantly changes with the
1101 induction of plasticity (Fig. 9A–B). An extremely useful mathematical treatise that has helped in
1102 the understanding metaplasticity and stability, especially for synaptic plasticity profiles in the
1103 hippocampus, is the Bienenstock-Cooper-Munro (BCM) rule (Bienenstock *et al.*, 1982; Cooper
1104 and Bear, 2012; Shouval *et al.*, 2002; Yeung *et al.*, 2004). This is despite the observation that the
1105 BCM framework and the synaptic plasticity framework in hippocampal synapses are not

1106 completely analogous to each other (Cooper *et al.*, 2004). It should also be noted that not all
1107 synapses follow a BCM-like synaptic plasticity profile, and therefore a stability theory dependent
1108 on this rule is not generalizable to all synapses (Abbott and Nelson, 2000; Jorntell and Hansel,
1109 2006).

1110 Although the utility of BCM-like synaptic rule in understanding stability in synaptic
1111 learning has been invaluable, the exact mechanisms that mediate the sliding modification
1112 threshold and the consequent metaplasticity has remained an open question. Several mechanisms
1113 (Fig. 9*C*) involving changes in morphological characteristics, several receptors, ion channels and
1114 signaling cascades have been proposed as candidates for this role (Abraham, 2008; Abraham and
1115 Bear, 1996; Abraham *et al.*, 2001; Abraham and Tate, 1997; Anirudhan and Narayanan, 2015;
1116 Bear, 2003; Bear *et al.*, 1987; Cooper and Bear, 2012; Hulme *et al.*, 2013; Kalantzis and
1117 Shouval, 2009; Narayanan and Johnston, 2010; Philpot *et al.*, 2003; Philpot *et al.*, 2001; Sehgal
1118 *et al.*, 2013; Triesch, 2007). As any change in mechanisms that regulate the induction or
1119 expression of synaptic plasticity would result in a change in plasticity profiles (Sec. 3.3–3.5), it is
1120 not surprising that mechanisms that regulate synaptic plasticity are candidate mechanisms that
1121 mediate metaplasticity. Similar to the argument placed with reference to the mechanisms that
1122 mediate the expression of synaptic plasticity, the framework of degeneracy provides an elegant
1123 solution to the question on which of these is *the* mechanism that mediates the sliding
1124 modification threshold within a BCM-like plasticity framework. It offers reconciliation to this
1125 conundrum by suggesting that disparate combinations of these distinct mechanisms could result
1126 in similar plasticity profiles (Fig. 9*D–E*), thereby suggesting degeneracy in the emergence of
1127 metaplasticity and stability in synaptic learning (Anirudhan and Narayanan, 2015). Finally, it
1128 was traditionally assumed that stability and homeostatic mechanisms are slower compared to the

1129 encoding mechanisms. However, there are several lines of theoretical and experimental evidence,
1130 spanning several synaptic and intrinsic components as candidate mechanisms, for *concurrent*
1131 emergence of encoding, stability *and* activity homeostasis. These lines of evidence also argue for
1132 prominent advantages when encoding, homeostasis and stability mechanisms are *concurrent*
1133 (Anirudhan and Narayanan, 2015; Honnuraiah and Narayanan, 2013; Ibata *et al.*, 2008; Jedlicka
1134 *et al.*, 2015; Johnston and Narayanan, 2008; Narayanan and Johnston, 2007, 2010; Nelson and
1135 Turrigiano, 2008; O'Leary *et al.*, 2014; Triesch, 2007; Turrigiano, 2011; Turrigiano, 2008, 2017;
1136 Zenke *et al.*, 2017).

1137 Within the framework of degeneracy, the goal of *concomitantly* achieving encoding-
1138 driven plasticity, activity homeostasis and stable learning is achieved through disparate
1139 combinations of synaptic, intrinsic, glial and structural plasticity. With abundant experimental
1140 evidence for plasticity in each of these different components occurring in an activity- or
1141 experience-dependent manner (Sec. 3.6), it is important that the analyses of stable learning
1142 broaden their focus beyond the narrow realm of stable *synaptic* learning. The current theories
1143 implicitly or explicitly assume that encoding is driven by synaptic plasticity, with several
1144 mechanisms contributing to the stability of this synaptic learning system. The metaplasticity
1145 framework also largely focuses on plasticity of *synaptic* plasticity profiles, although the
1146 mechanisms that mediate several forms of plasticity overlap with each other (Sec. 3.6). Future
1147 frameworks should therefore analyze concomitant learning *and* stability as a consequence of
1148 disparate forms of plasticity, also assessing *metaplasticity of intrinsic, glial and structural*
1149 *plasticity*. While plasticity in synaptic structures form *a component* of learning and stability,
1150 given the abundant lines of experimental evidence on ubiquitous plasticity, it is extremely critical

1151 that learning and stability theories broaden their horizon to encompass all forms of plasticity and
1152 degeneracy therein.

1153 **3.8. Degeneracy in the generation and regulation of local field potentials**

1154 Extracellular field recordings are useful readouts of network activity in a given brain region.
1155 Local field potentials (LFP), the low pass filtered version of field recordings have traditionally
1156 been thought to provide information about afferent synaptic activity. LFPs recorded from within
1157 the hippocampus exhibit signature activity patterns that are dependent on the behavioral state of
1158 the animal. For instance, they manifest strong oscillations in the theta frequency range (4–10 Hz)
1159 during exploratory behavior and during rapid eye moment (REM) sleep, and show characteristic
1160 sharp-wave ripple patterns during rest and non-REM sleep. These distinct activity patterns have
1161 been postulated to serve specific functions such as in the consolidation of memory and in neural
1162 encoding of space (Buzsaki, 1986, 1989, 2002, 2006, 2015; Buzsaki and Moser, 2013; Colgin,
1163 2013; English *et al.*, 2014; Grosmark *et al.*, 2012; Hartley *et al.*, 2014; Lisman and Jensen, 2013;
1164 Mizuseki and Buzsaki, 2014; Montgomery *et al.*, 2008; Moser *et al.*, 2008; Moser *et al.*, 2015;
1165 Tononi and Cirelli, 2006; Wilson and McNaughton, 1994; Ylinen *et al.*, 1995a; Ylinen *et al.*,
1166 1995b).

1167 Although these signature patterns of extracellular events manifest as repeating motifs,
1168 there are strong lines of theoretical and experimental evidence that they emerge from very
1169 disparate structures. For instance, theta oscillations in the hippocampus have shown to be
1170 afferent from two reciprocally connected subcortical nuclei that act as pacemakers, the medial
1171 septum-diagonal band of Broca and the supramammillary region. Apart from these two
1172 subcortical nuclei, inputs from entorhinal cortex and CA3 also play an important role in the
1173 generation of theta oscillations in the hippocampus. Furthermore, theoretical modeling and *in*

1174 *vitro* data also suggest that an intact hippocampus could sustain theta oscillations on its own in a
1175 manner that is dependent on intra-hippocampal excitatory and inhibitory synaptic connections
1176 (Buzsaki, 2002, 2006; Colgin, 2013, 2016; Goutagny *et al.*, 2009; Kamondi *et al.*, 1998; Traub *et*
1177 *al.*, 1989). A similar analysis, in terms of disparate underlying sources and mechanisms, holds
1178 for gamma frequency oscillations that are observed in the hippocampus as well (Buzsaki and
1179 Wang, 2012; Colgin, 2016; Colgin and Moser, 2010; Csicsvari *et al.*, 2003; Wang, 2010; Wang
1180 and Buzsaki, 1996). In addition, apart from synaptic contributions to the LFPs, it is now clear
1181 that return transmembrane currents from sub- and supra-threshold somatodendritic ion channels
1182 also alter the LFP in terms of their frequency content, amplitude and phase (Buzsaki *et al.*, 2012;
1183 Einevoll *et al.*, 2013; Ness *et al.*, 2016; Reimann *et al.*, 2013; Schomburg *et al.*, 2012; Sinha and
1184 Narayanan, 2015; Taxidis *et al.*, 2015). In addition, several mechanisms such ephaptic coupling,
1185 heterogeneous extracellular resistivity, glial and axonal transmembrane mechanisms also
1186 contribute and regulate local field potentials, resulting in a complexity that spans almost all
1187 parameters of the local network (Anastassiou and Koch, 2015; Buzsaki *et al.*, 2012; Einevoll *et*
1188 *al.*, 2013; Kajikawa and Schroeder, 2011; Katzner *et al.*, 2009; Linden *et al.*, 2011).

1189 From the complexity involved in the generation and regulation of hippocampal LFPs,
1190 with several brain regions and several constitutive network components contributing to their
1191 emergence, it is easy to discern that similar LFP patterns could be achieved through non-unique
1192 combinations of disparate components. Irrespective of whether it is the manifestation of an
1193 oscillatory pattern in a given frequency range (Buzsaki, 2002; Buzsaki and Wang, 2012; Colgin,
1194 2013; Colgin and Moser, 2010; Csicsvari *et al.*, 2003), or the emergence of sharp wave ripples
1195 (Buzsaki, 2015; English *et al.*, 2014; Taxidis *et al.*, 2015), or the emergence of resonance in the
1196 LFP power spectral density (Ness *et al.*, 2016), or achieving a given phase of single-neuron

1197 firing with reference to an LFP oscillation (Sinha and Narayanan, 2015), the routes are several
1198 and involve several disparate structural components. Thus, there is evidence for degeneracy in
1199 the mechanisms that mediate and regulate local field potentials, implying that extreme caution
1200 should be exercised in making one-to-one relationships between constitutive components and
1201 specific aspects of LFP recordings (Anastassiou and Koch, 2015; Buzsaki *et al.*, 2012; Einevoll
1202 *et al.*, 2013; Kajikawa and Schroeder, 2011; Katzner *et al.*, 2009; Linden *et al.*, 2011).
1203

1204 **3.9. Degeneracy in neural coding**

1205 A particularly thorny debate that has spanned decades is about the codes employed by neurons in
1206 encoding their inputs. The crux of the debate has been about whether neurons encode
1207 information in the rate of or in the precise timing of action potential firing (Buzsaki *et al.*, 2013;
1208 Engel *et al.*, 2001; Engel and Singer, 2001; Fries *et al.*, 2007; Gallistel, 2017; Jaramillo and
1209 Kempter, 2017; London *et al.*, 2010; Panzeri *et al.*, 2017; Shadlen and Newsome, 1994, 1995,
1210 1998; Singer *et al.*, 1997; Softky, 1994; Softky, 1995). Arguments against temporal coding have
1211 raised questions about the ability of neurons to perform millisecond-or-submillisecond
1212 coincidence detection that is essential for decoding a temporal code, about the relevance of
1213 precise timing in the face of noise and variability in neuronal responses to identical stimuli and
1214 about the ability of neuronal networks to reliably propagate synchronous firing (London *et al.*,
1215 2010; Panzeri *et al.*, 2017; Shadlen and Newsome, 1994, 1998). Counterarguments have relied
1216 on the demonstration of millisecond-or-submillisecond coincidence detection in active dendritic
1217 structures, on the dependence of synchrony propagation on neuronal intrinsic properties *and*
1218 input structure and on the existence of temporally precise cell assemblies that could mitigate the
1219 overall background noise in decoding the precise timing of inputs (Buzsaki, 2010; Buzsaki *et al.*,

1220 2013; Das and Narayanan, 2015, 2017; Diesmann *et al.*, 1999; Engel *et al.*, 2001; Engel and
1221 Singer, 2001; Fries *et al.*, 2007; Golding and Oertel, 2012; Hong *et al.*, 2012; Pastalkova *et al.*,
1222 2008; Reyes, 2003; Singer *et al.*, 1997; Softky, 1994).

1223 The expression of *coding* degeneracy in the cellular and network scales (Leonardo,
1224 2005), in terms of the ability of disparate structural components to elicit similar input-output
1225 characteristics, is clear from the lines of evidence presented earlier (Sec. 2.2). In addition,
1226 employing electrophysiological recordings and computational models to assess subthreshold
1227 resonance and spike triggered average (STA) of model neurons, it has been shown that
1228 hippocampal pyramidal neurons are selective to different input features (including spectral
1229 features and temporal coincidence of inputs) depending on the dendritic location of their inputs.
1230 This location-dependent feature encoding is mediated by ion channel expression profiles, and
1231 could be achieved through disparate combinations of different ion channel expression profiles
1232 (Das and Narayanan, 2014, 2015, 2017; Das *et al.*, 2017; Narayanan and Johnston, 2007, 2012;
1233 Rathour *et al.*, 2016; Rathour and Narayanan, 2012a, 2014). Given the well-established strong
1234 relationship between STA and types of coding (Ratte *et al.*, 2013), this location-dependent
1235 scenario argues for location-dependent forms of coding. Specifically, the soma and proximal
1236 dendrites showing class I STA (integrator) and the distal dendrites manifesting class II STA
1237 (coincidence detector) as a consequence of the differential expression of different channels (Das
1238 and Narayanan, 2015). Therefore, it seems reasonable to postulate that the proximal and distal
1239 regions are respectively geared towards rate and temporal coding, with this location-dependent
1240 differential coding strategy extending to cortical and hippocampal neurons (Branco and Hausser,
1241 2010, 2011; Das and Narayanan, 2015). Finally, behaviorally-driven neuromodulatory inputs and
1242 activity-dependent plasticity could markedly alter the operating mode and the class of

1243 excitability of compartments of a single neuron, and the type of coding employed by a neuron is
1244 dependent not just on its operating mode but also the specific characteristics of the input. Thus,
1245 even from the perspective of encoding strategies *within* a single neuron, the arguments that pitch
1246 rate coding *against* temporal coding are oversimplifying the complexity of neural encoding and
1247 decoding. Instead, there are broad lines of evidence pointing to a hybrid rate/temporal coding
1248 system that encompasses degeneracy by achieving encoding goals through disparate
1249 combinations of several cellular and network components in a manner that is strongly dependent
1250 on several spatiotemporal aspects of neuronal and behavioral state (Das and Narayanan, 2014,
1251 2015; Das *et al.*, 2017; Diesmann *et al.*, 1999; Lee and Dan, 2012; Marder, 2012; Marder and
1252 Thirumalai, 2002; Ratte *et al.*, 2013).

1253 With reference to neural codes for features of the external environment, the coding of
1254 spatial location of animal in the hippocampus is an ideal instance of hybrid encoding schema that
1255 expresses degeneracy. Unlike the argument for rate *vs.* temporal coding that seems to drive the
1256 narrative otherwise (Buzsaki *et al.*, 2013; Engel *et al.*, 2001; Engel and Singer, 2001; Fries *et al.*,
1257 2007; Gallistel, 2017; Jaramillo and Kempter, 2017; London *et al.*, 2010; Panzeri *et al.*, 2017;
1258 Shadlen and Newsome, 1994, 1995, 1998; Singer *et al.*, 1997; Softky, 1994; Softky, 1995;
1259 Srivastava *et al.*, 2017), hippocampal physiologists have concurred on the existence of
1260 dual/hybrid encoding schema for place-specific encoding. Specifically, place cells in the
1261 hippocampus elicit higher rates of firing when the animal enters a specific place field. In
1262 conjunction, the phase of action potential firing of place cells with reference to the extracellular
1263 theta rhythm also advances as a function of spatial location of the animal within the place field.
1264 Thus, hippocampal place cells employ a dual code of firing rate *and* phase of firing (temporal
1265 coding involving the precise timing of action potential firing) to represent spatial location of the

animal (Ahmed and Mehta, 2009; Buzsaki and Moser, 2013; Derdikman and Moser, 2010; Hartley *et al.*, 2014; Harvey *et al.*, 2009; Huxter *et al.*, 2003; Lisman, 2005; Lisman and Jensen, 2013; Mehta *et al.*, 2002; Moser *et al.*, 2008; Moser *et al.*, 2015; O'Keefe, 1976, 1979; O'Keefe and Burgess, 1999, 2005; O'Keefe *et al.*, 1998; O'Keefe and Conway, 1978; O'Keefe and Recce, 1993; Skaggs *et al.*, 1996). In certain cases, it has been shown that the two coding schema act independent of each other and could act as the fail-safe mechanisms for each other (Aghajan *et al.*, 2015; Huxter *et al.*, 2003).

Whereas these lines of evidence make a case for employing disparate coding schemas in encoding the same input, the case for disparate mechanisms involved in encoding and maintaining the rate and temporal codes is also strong. Specifically, the role of afferent synaptic drive, local inhibition, several ion channels and receptors, dendritic spikes, spatiotemporal interactions between somatodendritic channels and receptors, and plasticity in each of these components have all been implicated in the emergence and maintenance of these codes (Bittner *et al.*, 2015; Danielson *et al.*, 2016; Geisler *et al.*, 2010; Geisler *et al.*, 2007; Grienberger *et al.*, 2017; Harvey *et al.*, 2009; Lee *et al.*, 2012; Losonczy *et al.*, 2010; Magee, 2001; Nakashiba *et al.*, 2008; Nakazawa *et al.*, 2004; Nolan *et al.*, 2004; Royer *et al.*, 2012; Sheffield and Dombeck, 2015; Skaggs *et al.*, 1996; Tsien *et al.*, 1996; Wills *et al.*, 2005). In addition, there are lines of experimental evidence that suggest that subthreshold afferent synaptic inputs from several place fields arrive onto a single place cell, and that a silent cell could be converted to a place cell for *any* of these place fields by an appropriate plasticity-inducing stimulus (Bittner *et al.*, 2015; Lee *et al.*, 2012), suggesting that disparate cells could achieve the same function of encoding a given spatial location. The expression profiles of several channels and receptors control the overall excitability of a neuron (Sec. 2.2), and there are several mechanisms that regulate the phase of

1289 intracellular voltage oscillations with reference to an external reference or to the overall afferent
1290 current (Geisler *et al.*, 2010; Geisler *et al.*, 2007; Harvey *et al.*, 2009; Narayanan and Johnston,
1291 2008; Rathour *et al.*, 2016; Rathour and Narayanan, 2012a, 2014; Sinha and Narayanan, 2015;
1292 Skaggs *et al.*, 1996). Together, these studies point to the possibility that similar rate *and* phase
1293 spatial codes in a neuron could be achieved through disparate combinations of constituent
1294 components, and several neurons could encode for the same place field with distinct
1295 combinations of these mechanisms. Future studies could further explore the manifestation of
1296 degeneracy in spatial coding in the hippocampus, focusing on the hybrid code involving rate as
1297 well as phase encoding of input features.
1298

1299 **3.10. Degeneracy in learning and memory**

1300 Behavior emerges as a consequence of coordinated activity of multiple brain regions in
1301 conjunction with sensory and motor systems (Bennett and Hacker, 2003; Jazayeri and Afraz,
1302 2017; Krakauer *et al.*, 2017; Tytell *et al.*, 2011; Vetere *et al.*, 2017). The hippocampus has been
1303 implicated in several forms of spatial and non-spatial learning, with strong links to episodic
1304 memory (Anderson *et al.*, 2007; Bird and Burgess, 2008; Bliss and Collingridge, 1993; Bunsey
1305 and Eichenbaum, 1996; Lynch, 2004; Marr, 1971; Martin *et al.*, 2000; Martinez and Derrick,
1306 1996; Mayford *et al.*, 2012; Morris, 1989; Morris *et al.*, 1986; Morris *et al.*, 1982; Moser *et al.*,
1307 2015; Nakazawa *et al.*, 2004; Neves *et al.*, 2008a; Rajasethupathy *et al.*, 2015; Scoville and
1308 Milner, 1957; Squire *et al.*, 2004; Whitlock *et al.*, 2006).

1309 The quest for *the* mechanistic basis for learning and memory in the hippocampus has
1310 spanned several decades, especially since the strong links between the hippocampal lesions and
1311 specific forms of memory were established (Scoville and Milner, 1957). This quest has spanned

1312 several scales of analysis, with efforts to link specific genes, receptors, channels and forms of
1313 cellular plasticity to learning and memory. Several studies have assessed the link between
1314 specific behavioral tasks and cellular/molecular substrates through targeted pharmacological
1315 blockades or genetic manipulations. The existence of divergent and numerous cellular/molecular
1316 components that impair *specific* learning tasks have been unveiled by these efforts, revealing
1317 considerable complexity in the plasticity networks and systems biology of learning and memory.
1318 As is evident from this complexity and associated animal-to-animal and cell-to-cell variability,
1319 which involves the ensemble of mechanisms and interactions discussed above not just from
1320 within the hippocampus but also from other brain regions, demonstrating causality with
1321 reference to learning and memory and *any one specific form of plasticity or cellular/molecular*
1322 *substrate*, has proven extremely challenging (Andersen *et al.*, 2006; Bennett and Hacker, 2003;
1323 Bhalla, 2014; Bhalla and Iyengar, 1999; Bliss and Collingridge, 1993; Collingridge and Bliss,
1324 1987; Jazayeri and Afraz, 2017; Kandel, 2001; Kandel *et al.*, 2014; Kim and Linden, 2007;
1325 Kotaleski and Blackwell, 2010; Krakauer *et al.*, 2017; Lynch, 2004; Manninen *et al.*, 2010;
1326 Martin *et al.*, 2000; Martinez and Derrick, 1996; Mayford *et al.*, 2012; Mozzachiodi and Byrne,
1327 2010; Neves *et al.*, 2008a; Zhang and Linden, 2003).

1328 The complexities of the networks that are involved in learning and memory are only
1329 compounded by the many-to-many mappings that are observed between behavioral observations
1330 and molecular/cellular components, the joint occurrence of several forms of plasticity with the
1331 *same* protocols (Sec. 3.6), the concurrent impairments in different forms of plasticity by
1332 blockade of the *same* signaling cascades (Sec. 3.6), the dissociations between different learning
1333 tasks and the compensatory mechanisms that are associated with the knockout of specific genes
1334 (Bailey *et al.*, 2006; Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017; Mayford *et al.*, 2012;

1335 Tsokas *et al.*, 2016). For instance, the knock out of GluA1 (also referred to as GluR1 or GluRA),
1336 an AMPAR subunit that is important for expression of certain forms of synaptic plasticity,
1337 impaired only some forms of synaptic plasticity and not others at the cellular scale of analysis
1338 (Hoffman *et al.*, 2002; Phillips *et al.*, 2008; Zamanillo *et al.*, 1999). Similarly, at the behavioral
1339 level, although behavioral deficits were observed in certain learning tasks in GluA1 knockout
1340 mice, the knock out did not alter behavior in other learning tasks (Reisel *et al.*, 2002; Zamanillo
1341 *et al.*, 1999). Several examples of such dissociations are reviewed in (Mayford *et al.*, 2012),
1342 further emphasizing the difficulty in assigning a causal link between learning and memory and
1343 *any one specific form of plasticity or cellular/molecular substrate*.

1344 Although this parametric and interactional complexity might seem exasperating if the
1345 goal is to pinpoint *the* cellular/molecular component that is involved in hippocampal-dependent
1346 learning and memory, it is an extremely useful substrate for the effective expression of
1347 degeneracy in achieving the goal of robust learning and memory. The ability to achieve very
1348 similar learning indices through multiple routes involving disparate forms of plasticity in several
1349 constitutive components tremendously increases the ability of the system to achieve robust
1350 learning. As a consequence of the several forms of variability and state-dependence exhibited by
1351 the learning system, in terms of the underlying components, their plasticity and combinatorial
1352 interactions, it is possible that some of these disparate routes may not involve specific
1353 cellular/molecular components or forms of plasticity in the process of achieving certain learning
1354 goals. This also implies animal-to-animal and trial-to-trial variability in the mechanisms that
1355 mediate learning, thereby calling for utmost caution in assigning one-to-one relationships
1356 between behavioral learning and specific forms of plasticity in any single brain region (Bailey *et*
1357 *al.*, 2006; Bennett and Hacker, 2003; Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017; Mayford

et al., 2012; O'Leary and Marder, 2014; Sieling *et al.*, 2014; Tsokas *et al.*, 2016; Vogelstein *et al.*, 2014).

4. The causality conundrum

It is clear from the analyses above that theoretical and experimental evidence exist for: (a) several disparate combinations of distinct constitutive components elicit analogous function; (b) there are forms of animal-to-animal (channel-to-channel, neuron-to-neuron, network-to-network, etc.) variability in terms of the contributions of specific constitutive components that mediate similar function; and (c) the components that mediate similar function, and their relative contributions to the emergence of this function are state-dependent, and could undergo experience-dependent plasticity (towards maintaining robustness of that function or towards learning-dependent alteration of function). Juxtaposed against these observations is the question on whether it is even possible to exclusively assign causal one-to-one relationships between function and specific constitutive components. Evidence for the existence of degeneracy, variability and adaptability have made us acutely aware of the possibility that we could be committing mereological fallacies (Bennett and Hacker, 2003; Varzi, 2016), whereby we assign specific behavioral roles to parts of the animal's brain or to plasticity therein (Bailey *et al.*, 2006; Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017; Mayford *et al.*, 2012; O'Leary and Marder, 2014; Sieling *et al.*, 2014; Tsokas *et al.*, 2016; Vogelstein *et al.*, 2014).

4.1. Inevitable flaws in an experimental plan to establish causality that leaps across multiple scales

Let us chart a hypothetical experimental plan where we are interested in demonstrating that a specific form of learning behavior is dependent on plasticity in one specific component (let's say

component X) in a brain region of our choice (let's say hippocampus). We first measure *in vivo* plasticity in component X along with its time course, and let us say that we find a prominent correlation between this time course and the time course of behavioral learning. Next, we introduce an established blocker of plasticity in component X specifically into the hippocampus, and find that this blocks both the plasticity in component X *in vivo* and impairs learning. We repeat similar experiments with (a) an established pharmacological blocker of component X infused into the hippocampus; (b) transgenic manipulations that take out component X completely in the hippocampus; (c) a pharmacological blocker that leaves component X intact, but impairs its plasticity by blocking a mechanism that induces plasticity in component X; and (d) genetic knockout of mechanisms that mediates plasticity in component X. Let's say that learning was impaired in all four cases, and there was no plasticity in component X in the last two cases (in the first two cases component X was completely abolished). As a final nail in the hypothesis to link plasticity in hippocampal component X to the specific learning behavior, we artificially alter component X and consequently find behavioral signatures related to the learning process. Therefore, we have shown that component X and its plasticity are necessary and sufficient for the specific learning behavior. This experimental plan is broadly similar to that proposed by (Stevens, 1998) to test the hypothesis that auditory synapses in the amygdala become strengthened by LTP during behavioral training that attaches "fear" to the tone, and that he memory of the tone as a fear-producing stimulus resides in the strength of the synapses from the auditory thalamus (Stevens, 1998):

> "How could this idea be tested? It should be that (1) blocking LTP prevents fear learning; (2) the sensory pathways from the thalamus and cortex to the amygdala are capable of LTP; (3) auditory fear conditioning increases the amygdala's postsynaptic response to the tone, and these increases are prevented by blocking LTP pharmacologically or in another way; and (4) inducing LTP in the thalamoamygdaloid pathway attaches "fear" to appropriate sensory stimuli."

1406
1407 Although this experimental plan has shown that component X and its plasticity are
1408 necessary and sufficient for the specific learning behavior, given the complexity that we have
1409 elucidated thus far, this experimental design *does not* provide a causal link between component
1410 X or its plasticity with behavior. First, we were so focused on component X that we implicitly
1411 precluded the change of any other component either in the hippocampus or in other brain region.
1412 Given the rich complexity in the distinct components, their plasticity and interactions among
1413 them, it is infeasible that only component X in the hippocampus was changing in response to the
1414 behavioral stimulus. It is now well established that several cellular components change in
1415 response the same calcium signal or the activation of the same signaling cascade, and there are
1416 several parallel homeostasis mechanisms that also exhibit degeneracy. This implies that altering
1417 component X in the hippocampus *without* altering anything else across the brain is highly
1418 unlikely. Therefore, if we had performed the same set of experiments on another component Y,
1419 we might have arrived at similar conclusions (including correlated time courses). In other words,
1420 it is important not to interpret measurement correlations as evidence for causation, and to
1421 understand that absence of measurements in other forms of plasticity or plasticity in other brain
1422 regions does not mean they don't coexist with the form of plasticity that we are focused on.
1423 Second, when we blocked plasticity in component X, given the complexities elucidated
1424 above, it is highly unlikely that we *specifically* blocked plasticity in component X without
1425 disturbing plasticity in any other measurement or without introducing metaplasticity in some
1426 other form of plasticity (Sec. 3.6–3.7). For instance, from a cellular perspective, theta burst
1427 pairing results in plasticity of synaptic strength and of HCN, *A*-type K^+ and SK channels, and
1428 pharmacologically blocking NMDAR receptors impairs plasticity not just in one of them, but in
1429 *all* of them (Fan *et al.*, 2005; Frick *et al.*, 2004; Lin *et al.*, 2008; Losonczy *et al.*, 2008). Thus if

1430 we had observed impairment of plasticity in only one of these components, we would have
1431 wrongly concluded that to be the only component that changes with TBP. Returning to our
1432 experimental plan on the role of component X, there could several other secondary and
1433 unintended effects of blocking plasticity in component X that spans the hippocampus and other
1434 brain regions (Bhalla, 2014; Jazayeri and Afraz, 2017; Kotaleski and Blackwell, 2010; Krakauer
1435 *et al.*, 2017; Otchy *et al.*, 2015). Thus, it is prudent not to dismiss absence of measurements as
1436 absence of evidence for other components.

1437 Third, when we performed the experiment of artificially altering component X, it is
1438 obvious that it is highly unlikely that we achieved this without disturbing any other component in
1439 some brain region or without introducing metaplasticity in some form of plasticity. Therefore,
1440 the alternate interpretations of our observations (other than the "linear narrative" that concludes
1441 "plasticity in hippocampal component X mediates learning behavior") are innumerable given the
1442 staggering complexity of the underlying system and the degeneracy involved in accomplishing
1443 the learning task. Ruling out *all these* alternate interpretations is essential for convergence to the
1444 linear narrative, but is rather impossible because measurements of all constitutive components in
1445 all brain regions is currently infeasible. From a nonlinear dynamical system perspective
1446 (Guckenheimer and Holmes, 1983; Nayfeh and Balachandran, 1995; Strogatz, 2014), our "linear
1447 narrative" and the associated inference are equivalent to declaring a component to be critically
1448 important for system performance because perturbation to that one component, — which is part
1449 of a high-dimensional, adaptive, non-linear dynamical system with strong coupling across
1450 dimensions, — collapses the system. Additionally, especially given the expression of
1451 degeneracy, in our artificial perturbation experiment, we showed that the system *could* perform a
1452 specific behavior when we introduced a perturbation to component X. However, this observation

1453 does not necessarily imply that the system *does* employ a similar perturbation to component X to
1454 elicit the same behavior under normal ethological conditions (Adamantidis *et al.*, 2015). Given
1455 the degeneracy framework, it is important to appreciate that the existence of *a* solution neither
1456 implies its uniqueness nor does it ensure that the solution is employed by the physiological
1457 system under standard ethological conditions.

1458 **4.2. Degeneracy: The way forward**

1459 It is important to distinguish between understanding functionality that emerges through
1460 interactions between components in an adjacent scale and efforts aimed at causality that leaps
1461 across multiple scales. It is clear that assessing interactions between constitutive components in
1462 the emergence of function in an adjacent scale have provided invaluable insights in neuroscience.
1463 As an example, the question on how different ionic currents at the molecular scale interact to
1464 result in the emergence of an action potential in the cellular scale (Hodgkin and Huxley, 1952)
1465 has revolutionized several aspects of neuroscience over the past several decades. Even within the
1466 framework of degeneracy, the question on whether and how different combinations of disparate
1467 combinations of parameters in a give scale could result in similar functionality in an adjacent
1468 scale have provided deep insights into how the nervous system might be solving the robustness
1469 problem in the face of variability (Anirudhan and Narayanan, 2015; Dhawale *et al.*, 2017; Foster
1470 *et al.*, 1993; Gjorgjieva *et al.*, 2016; Goldman *et al.*, 2001; Katz, 2016; Marder, 2011; Marder
1471 and Goaillard, 2006; Marder *et al.*, 2015; Marder and Taylor, 2011; Mukunda and Narayanan,
1472 2017; O'Leary and Marder, 2014; Prinz *et al.*, 2004; Rathour and Narayanan, 2012a, 2014;
1473 Taylor *et al.*, 2009).

1474 However, causal leaps beyond a single scale of analysis should be treated with extreme
1475 caution. For instance, approaches assuming a unique reductionist solution for a behavioral

1476 observation will invariably end up in apparently contradictory conclusions about *the* mechanism
1477 that mediates behavior. Prominent among the several reasons that result in these apparent
1478 contradictions — such as adaptive compensations and animal-to-animal variability — is inherent
1479 degeneracy, where disparate combinations of components could result in identical behavior in a
1480 manner that is dependent on several factors, including behavioral state. The flaws that emerge in
1481 an experimental plan to establish causality that leaps multiple scales in a nonlinear dynamical
1482 system that expresses degeneracy are obvious from the analysis presented above. Here, it is
1483 critical to ask the impossible question on whether we are sure that *nothing else* has changed in
1484 neurons (and other cells) of the same brain region or the other, which could be
1485 mediating/contributing to the observed behavioral changes *before* declaring a causal one-to-one
1486 relationship between a molecular/cellular component and behavior.

1487 This is especially important because there are several properties that *emerge* at each jump
1488 along the multiscale axis of neuroscience (Fig. 1A), and leaps across multiple scales (like genes
1489 to behavior) traverses several *emergent* properties owing to innumerable nonlinear processes that
1490 exhibit degeneracy. This yields a system that is intractable even at the scale where the
1491 perturbations were introduced because of the complex feedback loops spanning several scales
1492 that mediate homeostasis and adaptation. Consequently, the outcomes of any perturbation at any
1493 scale are critically dependent on several components across scales, the nature of interactions of
1494 these components with the perturbation and importantly on the adaptation that is triggered by the
1495 perturbation in all these components across scales. Therefore, extreme caution should be
1496 exercised in assigning causal one-to-one relationship between components (or manifolds) that
1497 are several scales apart along the multi-scale axis (Bennett and Hacker, 2003; Jazayeri and Afraz,
1498 2017; Krakauer *et al.*, 2017; Otchy *et al.*, 2015).

Together, while degeneracy is an invaluable asset to evolution, physiology and behavior in achieving robust functions through several degrees of freedom, it makes the resultant complex system rather intractable. This intractability makes it nearly impossible to achieve the goals of reductionism, where the pursuit has largely been for causal one-to-one relationships that leap across several scales. Several thorny debates in the field about apparent contradictions involving different components mediating the same function could be put to rest if this requirement of one-to-one relationships is relaxed. Specifically, the ubiquitous expression of degeneracy spanning multiple scales offers an ideal reconciliation to these controversies, through the recognition that the distinct routes to achieve a functional goal are not necessarily contradictory to each other, but are alternate routes that the system might recruit towards accomplishment of the goal. The intense drive to make leaps across multiple scales to establish unique one-to-one relationships should instead be replaced by a steadfast recognition for degeneracy as an essential component in physiology, behavior and evolution. This recognition, apart from precluding one-to-one relationships, would provide clear warnings in assigning causal relationships that leap across multiple scales and multiple emergent properties. Importantly, this recognition would pave the way for a strong focus on integrative and holistic treatises to neuroscience and behavior, arguments for which have only been growing over the years (Bennett and Hacker, 2003; Edelman and Gally, 2001; Jazayeri and Afraz, 2017; Krakauer *et al.*, 2017; Tononi and Edelman, 1998; Tononi *et al.*, 1998; Tononi *et al.*, 1994; Tytell *et al.*, 2011). Future approaches should recognize that behavior emerges from disparate combinations of tightly cross-coupled multi-scale emergent properties, each diverging and converging at each scale of analysis through degeneracy spanning complex parametric and interactional spaces. Large-scale databases related to neuronal morphology, models and physiology — such as the Allen brain atlas (Sunkin *et al.*,

2013), ICGenealogy (Podlaski *et al.*, 2017), Channelpedia (Ranjan *et al.*, 2011), Neuromorpho (Ascoli *et al.*, 2007), ModelDB (Hines *et al.*, 2004) and Neuroelectro (Tripathy *et al.*, 2014) — provide ideal tools for such analyses involving large parametric spaces, and could provide critical insights about the role of degeneracy in the emergence of robust brain physiology and its links to behavior.

5. Conclusions

In this review, we systematically presented lines of evidence for the ubiquitous expression of degeneracy spanning several scales of the mammalian hippocampus. We argued that the framework of degeneracy in an encoding system shouldn't be viewed from the limited perspective of maintaining homeostasis, but should be assessed from the perspective of achieving the twin goals of encoding information and maintaining homeostasis. Within the broad framework of degeneracy, it is extremely important that future studies focus on the fundamental questions on (i) how does the brain change its constituent components towards encoding new information without jeopardizing homeostasis?; and (ii) how do homeostatic mechanisms maintain robust function without affecting learning-induced changes in the brain? Without an effective answer to this overall question on concomitant learning and homeostasis in the face of staggeringly combinatorial complexity, our understanding of the nervous system in terms of its ability to systematically adapt to the environment will remain incomplete. Although the core conclusions on degeneracy reviewed and analyzed here would extend to other mammalian brain regions and functions that they have been implicated in encoding processes, this extrapolation should be preceded by careful assessment of the specifics associated with the constitutive components and specific interactions there. Additionally, although our focus here was on encoding, homeostasis and physiology, it is important that future studies also assess the implications for degeneracy in the emergence of pathological conditions (Edelman and Gally, 2001; O'Leary *et al.*, 2014).

Finally, returning to the distinction between the "structure defines function" and the "form follows function" perspectives, it seems like the distinction also seemingly extends to the methodology that is deemed appropriate for assessing neuronal systems. At one end, a strong emphasis is placed on the requirement for an experimental approach (Buzsaki, 2006):

> "The complexity and precision of brain wiring make an experimental approach absolutely necessary. No amount of introspection or algorithmic modeling can help without parallel empirical exploration."

At the other end, the emphasis, reflecting Richard Feymann's quote "What I cannot create, I do not understand", is on *in silico* approaches (Sakmann, 2017):

> "At present however, it seems that "What we cannot reconstruct *in silico* and model we have not understood"."

Within the degeneracy framework, however, it is starkly evident from existing literature reviewed here that a holistic combination of computational and experimental techniques is indispensible towards understanding structure-function relationships and the associated complexities (Das *et al.*, 2017; Edelman and Gally, 2001; Foster *et al.*, 1993; Marder, 1998, 2011; Marder and Goaillard, 2006; Marder and Taylor, 2011; Rathour *et al.*, 2016; Rathour and Narayanan, 2012a, b, 2014; Sporns *et al.*, 2000; Tononi and Edelman, 1998; Tononi *et al.*, 1998; Tononi *et al.*, 1994, 1996, 1999).

Emphasizing the strong links between biology and evolution, Theodosius Dobzhansky had written "nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973). Given the ubiquitous prevalence of degeneracy and its strong links to evolution (Edelman and Gally, 2001), it is perhaps apt to add a corollary to this quote and state "nothing in physiology makes sense except in the light of degeneracy".

ACKNOWLEDGMENTS

We thank Dr. Peter Jedlicka, Dr. Manisha Sinha and members of the cellular neurophysiology laboratory for useful discussions and for thoughtful comments on a draft of this manuscript. Work reviewed here was supported by the Wellcome Trust-DBT India Alliance (Senior fellowship to RN: IA/S/16/2/502727), Human Frontier Science Program (HFSP) Organization (RN), the Department of Biotechnology (RN), the Department of Science and Technology (RN) and the Ministry of Human Resource Development, India (RKR and RN).

REFERENCES

Abbott, L. F. (2003) Balancing homeostasis and learning in neural circuits. *Zoology (Jena)* **106,** 365-371.

Abbott, L. F. and LeMasson, G. (1993) Analysis of Neuron Models with Dynamically Regulated Conductances. *Neural Comput* **5,** 823-842.

Abbott, L. F. and Nelson, S. B. (2000) Synaptic plasticity: taming the beast. *Nat Neurosci* **3 Suppl,** 1178-1183.

Abbott, L. F. and Regehr, W. G. (2004) Synaptic computation. *Nature* **431,** 796-803.

Abraham, W. C. (2008) Metaplasticity: tuning synapses and networks for plasticity. *Nature reviews. Neuroscience* **9,** 387.

Abraham, W. C. and Bear, M. F. (1996) Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci* **19,** 126-130.

Abraham, W. C., Mason-Parker, S. E., Bear, M. F., Webb, S. and Tate, W. P. (2001) Heterosynaptic metaplasticity in the hippocampus in vivo: a BCM-like modifiable threshold for LTP. *Proc Natl Acad Sci U S A* **98,** 10924-10929.

Abraham, W. C. and Robins, A. (2005) Memory retention--the synaptic stability versus plasticity dilemma. *Trends Neurosci* **28,** 73-78.

Abraham, W. C. and Tate, W. P. (1997) Metaplasticity: a new vista across the field of synaptic plasticity. *Progress in neurobiology* **52,** 303-323.

Achard, P. and De Schutter, E. (2006) Complex parameter landscape for a complex neuron model. *PLoS computational biology* **2,** e94.

Adamantidis, A., Arber, S., Bains, J. S., Bamberg, E., Bonci, A., Buzsaki, G., Cardin, J. A., Costa, R. M., Dan, Y., Goda, Y., Graybiel, A. M., Hausser, M., Hegemann, P., Huguenard, J. R., Insel, T. R., Janak, P. H., Johnston, D., Josselyn, S. A., Koch, C., Kreitzer, A. C., Luscher, C., Malenka, R. C., Miesenbock, G., Nagel, G., Roska, B., Schnitzer, M. J., Shenoy, K. V., Soltesz, I., Sternson, S. M., Tsien, R. W., Tsien, R. Y., Turrigiano, G. G., Tye, K. M. and Wilson, R. I. (2015) Optogenetics: 10 years after ChR2 in neurons--views from the community. *Nat Neurosci* **18,** 1202-1212.

Adelman, J. P., Maylie, J. and Sah, P. (2012) Small-conductance Ca2+-activated K+ channels: form and function. *Annual review of physiology* **74,** 245-269.

Aghajan, Z. M., Acharya, L., Moore, J. J., Cushman, J. D., Vuong, C. and Mehta, M. R. (2015) Impaired spatial selectivity and intact phase precession in two-dimensional virtual reality. *Nat Neurosci* **18,** 121-128.

Ahmed, O. J. and Mehta, M. R. (2009) The hippocampal rate code: anatomy, physiology and theory. *Trends Neurosci* **32,** 329-338.

Albantakis, L., Hintze, A., Koch, C., Adami, C. and Tononi, G. (2014) Evolution of integrated causal structures in animats exposed to environments of increasing complexity. *PLoS computational biology* **10,** e1003966.

Alberini, C. M. (2009) Transcription factors in long-term memory and synaptic plasticity. *Physiol Rev* **89,** 121-145.

Allen, N. J. and Barres, B. A. (2005) Signaling between glia and neurons: focus on synaptic plasticity. *Current opinion in neurobiology* **15,** 542-548.

Allen, N. J. and Barres, B. A. (2009) Neuroscience: Glia - more than just brain glue. *Nature* **457,** 675-677.

Amarillo, Y., De Santiago-Castillo, J. A., Dougherty, K., Maffie, J., Kwon, E., Covarrubias, M. and Rudy, B. (2008) Ternary Kv4.2 channels recapitulate voltage-dependent inactivation kinetics of A-type K+ channels in cerebellar granule neurons. *J Physiol* **586,** 2093-2106.

Anastassiou, C. A. and Koch, C. (2015) Ephaptic coupling to endogenous electric field activity: why bother? *Current opinion in neurobiology* **31,** 95-103.

Andersen, P., Morris, R., Amaral, D., Bliss, T. and O'Keefe, J. (2006) *The hippocampus book*. Oxford University Press: New York, USA.

Anderson, D., Mehaffey, W. H., Iftinca, M., Rehak, R., Engbers, J. D., Hameed, S., Zamponi, G. W. and Turner, R. W. (2010) Regulation of neuronal activity by Cav3-Kv4 channel signaling complexes. *Nat Neurosci* **13,** 333-337.

Anderson, P., Morris, R., Amaral, D., Bliss, T. V. and O'Keefe, J. (2007) *The Hippocampus Book*. Oxford University Press.

Anderson P, M. R., Amaral D, Bliss T, O'Keefe J (2007) *The Hippocampus Book*. Oxford University Press: NewYork.

Andrasfalvy, B. K. and Magee, J. C. (2001) Distance-dependent increase in AMPA receptor number in the dendrites of adult hippocampal CA1 pyramidal neurons. *J Neurosci* **21,** 9151-9159.
Andrasfalvy, B. K. and Mody, I. (2006) Differences between the scaling of miniature IPSCs and EPSCs recorded in the dendrites of CA1 mouse pyramidal neurons. *J Physiol* **576,** 191-196.
Anirudhan, A. and Narayanan, R. (2015) Analogous synaptic plasticity profiles emerge from disparate channel combinations. *J Neurosci* **35,** 4691-4705.
Araque, A. (2008) Astrocytes process synaptic information. *Neuron glia biology* **4,** 3-10.
Araque, A., Carmignoto, G., Haydon, P. G., Oliet, S. H., Robitaille, R. and Volterra, A. (2014) Gliotransmitters travel in time and space. *Neuron* **81,** 728-739.
Araque, A., Parpura, V., Sanzgiri, R. P. and Haydon, P. G. (1999) Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci* **22,** 208-215.
Armstrong, C. M. and Bezanilla, F. (1974) Charge movement associated with the opening and closing of the activation gates of the Na channels. *The Journal of general physiology* **63,** 533-552.
Ascoli, G. A., Donohue, D. E. and Halavi, M. (2007) NeuroMorpho.Org: a central resource for neuronal morphologies. *J Neurosci* **27,** 9247-9251.
Ashhad, S., Johnston, D. and Narayanan, R. (2015) Activation of InsP3 receptors is sufficient for inducing graded intrinsic plasticity in rat hippocampal pyramidal neurons. *Journal of neurophysiology* **113,** 2002-2013.
Ashhad, S. and Narayanan, R. (2013) Quantitative interactions between the A-type K+ current and inositol trisphosphate receptors regulate intraneuronal Ca2+ waves and synaptic plasticity. *J Physiol* **591,** 1645-1669.
Ashhad, S. and Narayanan, R. (2016) Active dendrites regulate the impact of gliotransmission on rat hippocampal pyramidal neurons. *Proc Natl Acad Sci U S A* **113,** E3280-3289.
Attardo, A., Fitzgerald, J. E. and Schnitzer, M. J. (2015) Impermanence of dendritic spines in live adult CA1 hippocampus. *Nature* **523,** 592-596.
Atwood, B. K., Lovinger, D. M. and Mathur, B. N. (2014) Presynaptic long-term depression mediated by Gi/o-coupled receptors. *Trends Neurosci* **37,** 663-673.
Augustine, G. J., Santamaria, F. and Tanaka, K. (2003) Local calcium signaling in neurons. *Neuron* **40,** 331-346.
Baba, A., Yasui, T., Fujisawa, S., Yamada, R. X., Yamada, M. K., Nishiyama, N., Matsuki, N. and Ikegaya, Y. (2003) Activity-evoked capacitative Ca2+ entry: implications in synaptic plasticity. *J Neurosci* **23,** 7737-7741.
Bading, H., Ginty, D. D. and Greenberg, M. E. (1993) Regulation of gene expression in hippocampal neurons by distinct calcium signaling pathways. *Science* **260,** 181-186.
Bailey, K. R., Rustay, N. R. and Crawley, J. N. (2006) Behavioral phenotyping of transgenic and knockout mice: practical concerns and potential pitfalls. *ILAR journal* **47,** 124-131.
Balch, W. E., Morimoto, R. I., Dillin, A. and Kelly, J. W. (2008) Adapting proteostasis for disease intervention. *Science* **319,** 916-919.
Bargmann, C. I. and Marder, E. (2013) From the connectome to brain function. *Nat Methods* **10,** 483-490.
Barnard, E. A., Skolnick, P., Olsen, R. W., Mohler, H., Sieghart, W., Biggio, G., Braestrup, C., Bateson, A. N. and Langer, S. Z. (1998) International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: classification on the basis of subunit structure and receptor function. *Pharmacological reviews* **50,** 291-313.
Basu, J., Zaremba, J. D., Cheung, S. K., Hitti, F. L., Zemelman, B. V., Losonczy, A. and Siegelbaum, S. A. (2016) Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition. *Science* **351,** aaa5694.
Baumann, N. and Pham-Dinh, D. (2001) Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiol Rev* **81,** 871-927.
Bazargani, N. and Attwell, D. (2016) Astrocyte calcium signaling: the third wave. *Nat Neurosci* **19,** 182-189.
Bear, M. F. (2003) Bidirectional synaptic plasticity: from theory to reality. *Philos Trans R Soc Lond B Biol Sci* **358,** 649-655.
Bear, M. F., Cooper, L. N. and Ebner, F. F. (1987) A physiological basis for a theory of synapse modification. *Science* **237,** 42-48.
Beck, H. and Yaari, Y. (2008) Plasticity of intrinsic neuronal properties in CNS disorders. *Nature reviews. Neuroscience* **9,** 357-369.
Bellman, R. E. (1957) *Dynamic programming*. Princeton University Press: Princeton, NJ.

Bennett, M. R. and Hacker, P. M. S. (2003) *Philosophical Foundations of Neuroscience*. Wiley-Blackwell: Malden, MA.

Bernard, C., Shah, M. and Johnston, D. (2007) Dendrites and disease. In: *Dendrites*. Eds. G. Stuart, N. Spruston, M. Hausser. Oxford University Press.

Berridge, M. J. (1998) Neuronal calcium signaling. *Neuron* **21,** 13-26.

Berridge, M. J. (2002) The endoplasmic reticulum: a multifunctional signaling organelle. *Cell Calcium* **32,** 235-249.

Berridge, M. J. (2006) Calcium microdomains: organization and function. *Cell Calcium* **40,** 405-412.

Berridge, M. J., Lipp, P. and Bootman, M. D. (2000) The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1,** 11-21.

Bhalla, U. S. (2014) Multiscale modeling and synaptic plasticity. *Progress in molecular biology and translational science* **123,** 351-386.

Bhalla, U. S. and Iyengar, R. (1999) Emergent properties of networks of biological signaling pathways. *Science* **283,** 381-387.

Bi, G. Q. and Poo, M. M. (1998) Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J Neurosci* **18,** 10464-10472.

Bickle, J. (2015) Marr and reductionism. *Topics in cognitive science* **7,** 299-311.

Biel, M., Wahl-Schott, C., Michalakis, S. and Zong, X. (2009) Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev* **89,** 847-885.

Bienenstock, E. L., Cooper, L. N. and Munro, P. W. (1982) Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J Neurosci* **2,** 32-48.

Bird, C. M. and Burgess, N. (2008) The hippocampus and memory: insights from spatial processing. *Nature reviews. Neuroscience* **9,** 182-194.

Birnbaum, S. G., Varga, A. W., Yuan, L. L., Anderson, A. E., Sweatt, J. D. and Schrader, L. A. (2004) Structure and function of Kv4-family transient potassium channels. *Physiol Rev* **84,** 803-833.

Bittner, K. C., Grienberger, C., Vaidya, S. P., Milstein, A. D., Macklin, J. J., Suh, J., Tonegawa, S. and Magee, J. C. (2015) Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. *Nat Neurosci* **18,** 1133-1142.

Bittner, K. C., Milstein, A. D., Grienberger, C., Romani, S. and Magee, J. C. (2017) Behavioral time scale synaptic plasticity underlies CA1 place fields. *Science* **357,** 1033-1036.

Bliss, T. V. and Collingridge, G. L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361,** 31-39.

Bliss, T. V. and Gardner-Medwin, A. R. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. *J Physiol* **232,** 357-374.

Bliss, T. V. and Lomo, T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* **232,** 331-356.

Bouchard, R., Pattarini, R. and Geiger, J. D. (2003) Presence and functional significance of presynaptic ryanodine receptors. *Progress in neurobiology* **69,** 391-418.

Brager, D. H. and Johnston, D. (2007) Plasticity of intrinsic excitability during long-term depression is mediated through mGluR-dependent changes in $I_{\rm h}$ in hippocampal CA1 pyramidal neurons. *J Neurosci* **27,** 13926-13937.

Brager, D. H. and Johnston, D. (2014) Channelopathies and dendritic dysfunction in fragile X syndrome. *Brain Res Bull* **103C,** 11-17.

Brager, D. H., Lewis, A. S., Chetkovich, D. M. and Johnston, D. (2013) Short- and long-term plasticity in CA1 neurons from mice lacking h-channel auxiliary subunit TRIP8b. *Journal of neurophysiology* **110,** 2350-2357.

Branco, T. and Hausser, M. (2010) The single dendritic branch as a fundamental functional unit in the nervous system. *Current opinion in neurobiology* **20,** 494-502.

Branco, T. and Hausser, M. (2011) Synaptic integration gradients in single cortical pyramidal cell dendrites. *Neuron* **69,** 885-892.

Bunsey, M. and Eichenbaum, H. (1996) Conservation of hippocampal memory function in rats and humans. *Nature* **379,** 255-257.

Buzsaki, G. (1986) Hippocampal sharp waves: their origin and significance. *Brain Res* **398,** 242-252.

Buzsaki, G. (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* **31,** 551-570.
Buzsaki, G. (2002) Theta oscillations in the hippocampus. *Neuron* **33,** 325-340.
Buzsaki, G. (2006) *Rhythms of the brain*. Oxford University Press: New York.
Buzsaki, G. (2010) Neural syntax: cell assemblies, synapsembles, and readers. *Neuron* **68,** 362-385.
Buzsaki, G. (2015) Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus* **25,** 1073-1188.
Buzsaki, G., Anastassiou, C. A. and Koch, C. (2012) The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. *Nature reviews. Neuroscience* **13,** 407-420.
Buzsaki, G., Logothetis, N. and Singer, W. (2013) Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron* **80,** 751-764.
Buzsaki, G. and Moser, E. I. (2013) Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat Neurosci* **16,** 130-138.
Buzsaki, G. and Wang, X. J. (2012) Mechanisms of gamma oscillations. *Annu Rev Neurosci* **35,** 203-225.
Cantrell, A. R. and Catterall, W. A. (2001) Neuromodulation of Na+ channels: an unexpected form of cellular plasticity. *Nature reviews. Neuroscience* **2,** 397-407.
Carlson, J. M. and Doyle, J. (2002) Complexity and robustness. *Proc Natl Acad Sci U S A* **99 Suppl 1,** 2538-2545.
Catterall, W. A. (1993) Structure and function of voltage-gated ion channels. *Trends Neurosci* **16,** 500-506.
Catterall, W. A. (1995) Structure and function of voltage-gated ion channels. *Annual review of biochemistry* **64,** 493-531.
Chen, C. C., Lu, J. and Zuo, Y. (2014) Spatiotemporal dynamics of dendritic spines in the living brain. *Frontiers in neuroanatomy* **8,** 28.
Chen, X., Yuan, L. L., Zhao, C., Birnbaum, S. G., Frick, A., Jung, W. E., Schwarz, T. L., Sweatt, J. D. and Johnston, D. (2006) Deletion of Kv4.2 gene eliminates dendritic A-type K+ current and enhances induction of long-term potentiation in hippocampal CA1 pyramidal neurons. *J Neurosci* **26,** 12143-12151.
Cheong, R., Rhee, A., Wang, C. J., Nemenman, I. and Levchenko, A. (2011) Information transduction capacity of noisy biochemical signaling networks. *Science* **334,** 354-358.
Chevaleyre, V., Takahashi, K. A. and Castillo, P. E. (2006) Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu Rev Neurosci* **29,** 37-76.
Christie, B. R., Kerr, D. S. and Abraham, W. C. (1994) Flip side of synaptic plasticity: long-term depression mechanisms in the hippocampus. *Hippocampus* **4,** 127-135.
Christie, B. R., Magee, J. C. and Johnston, D. (1996) The role of dendritic action potentials and Ca2+ influx in the induction of homosynaptic long-term depression in hippocampal CA1 pyramidal neurons. *Learn Mem* **3,** 160-169.
Christie, B. R., Schexnayder, L. K. and Johnston, D. (1997) Contribution of voltage-gated Ca2+ channels to homosynaptic long-term depression in the CA1 region in vitro. *Journal of neurophysiology* **77,** 1651-1655.
Chung, H. J., Ge, W. P., Qian, X., Wiser, O., Jan, Y. N. and Jan, L. Y. (2009a) G protein-activated inwardly rectifying potassium channels mediate depotentiation of long-term potentiation. *Proc Natl Acad Sci U S A* **106,** 635-640.
Chung, H. J., Qian, X., Ehlers, M., Jan, Y. N. and Jan, L. Y. (2009b) Neuronal activity regulates phosphorylation-dependent surface delivery of G protein-activated inwardly rectifying potassium channels. *Proc Natl Acad Sci U S A* **106,** 629-634.
Churchland, P. and Sejnowski, T. (1992) *The Computational Brain*. MIT Press: Cambridge, MA.
Churchland, P. S. and Sejnowski, T. J. (1988) Perspectives on cognitive neuroscience. *Science* **242,** 741-745.
Clemens, A. M. and Johnston, D. (2014) Age- and location-dependent differences in store depletion-induced h-channel plasticity in hippocampal pyramidal neurons. *Journal of neurophysiology* **111,** 1369-1382.
Cole, K. S. (1968) *Membranes, ions and impulses: A chapter of classical biophysics*. University of California, Berkeley press: Berkeley.
Colgin, L. L. (2013) Mechanisms and Functions of Theta Rhythms. *Annual Review of Neuroscience, Vol 36* **36,** 295-312.
Colgin, L. L. (2016) Rhythms of the hippocampal network. *Nature reviews. Neuroscience* **17,** 239-249.
Colgin, L. L. and Moser, E. I. (2010) Gamma oscillations in the hippocampus. *Physiology* **25,** 319-329.
Collingridge, G. L. and Bliss, T. V. P. (1987) NMDA receptors - their role in long-term potentiation. *Trends Neurosci* **10,** 288-293.

Collingridge, G. L., Kehl, S. J. and McLennan, H. (1983) Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J Physiol* **334,** 33-46.

Cooper, L. N. and Bear, M. F. (2012) The BCM theory of synapse modification at 30: interaction of theory with experiment. *Nature reviews. Neuroscience* **13,** 798-810.

Cooper, L. N., Intrator, N., Blais, B. S. and Shouval, H. Z. (2004) *Theory of cortical plasticity*. World Scientific Publishing Company: Singapore.

Csicsvari, J., Jamieson, B., Wise, K. D. and Buzsaki, G. (2003) Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* **37,** 311-322.

Cusdin, F. S., Clare, J. J. and Jackson, A. P. (2008) Trafficking and cellular distribution of voltage-gated sodium channels. *Traffic* **9,** 17-26.

Dam, A. M. (1980) Epilepsy and neuron loss in the hippocampus. *Epilepsia* **21,** 617-629.

Dan, Y. and Poo, M. M. (2006) Spike timing-dependent plasticity: from synapse to perception. *Physiol Rev* **86,** 1033-1048.

Danielson, N. B., Zaremba, J. D., Kaifosh, P., Bowler, J., Ladow, M. and Losonczy, A. (2016) Sublayer-Specific Coding Dynamics during Spatial Navigation and Learning in Hippocampal Area CA1. *Neuron* **91,** 652-665.

Das, A. and Narayanan, R. (2014) Active dendrites regulate spectral selectivity in location-dependent spike initiation dynamics of hippocampal model neurons. *J Neurosci* **34,** 1195-1211.

Das, A. and Narayanan, R. (2015) Active dendrites mediate stratified gamma-range coincidence detection in hippocampal model neurons. *J Physiol* **593,** 3549-3576.

Das, A. and Narayanan, R. (2017) Theta-frequency selectivity in the somatic spike triggered average of rat hippocampal pyramidal neurons is dependent on HCN channels. *Journal of neurophysiology* **118,** 2251-2266.

Das, A., Rathour, R. K. and Narayanan, R. (2017) Strings on a Violin: Location Dependence of Frequency Tuning in Active Dendrites. *Front Cell Neurosci* **11,** 72.

de Lanerolle, N. C., Kim, J. H., Robbins, R. J. and Spencer, D. D. (1989) Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. *Brain Res* **495,** 387-395.

De Pitta, M., Volman, V., Berry, H. and Ben-Jacob, E. (2011) A tale of two stories: astrocyte regulation of synaptic depression and facilitation. *PLoS computational biology* **7,** e1002293.

Deitmer, J. W., McCarthy, K. D., Scemes, E. and Giaume, C. (2006) Information processing and transmission in glia: calcium signaling and transmitter release. *Glia* **54,** 639-641.

Derdikman, D. and Moser, E. I. (2010) A manifold of spatial maps in the brain. *Trends Cogn Sci* **14,** 561-569.

Derkach, V., Barria, A. and Soderling, T. R. (1999) Ca2+/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. *Proc Natl Acad Sci U S A* **96,** 3269-3274.

Derkach, V. A., Oh, M. C., Guire, E. S. and Soderling, T. R. (2007) Regulatory mechanisms of AMPA receptors in synaptic plasticity. *Nature reviews. Neuroscience* **8,** 101-113.

Desai, N. S., Cudmore, R. H., Nelson, S. B. and Turrigiano, G. G. (2002) Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat Neurosci* **5,** 783-789.

Desai, N. S., Rutherford, L. C. and Turrigiano, G. G. (1999) Plasticity in the intrinsic excitability of cortical pyramidal neurons. *Nat Neurosci* **2,** 515-520.

Dhawale, A. K., Smith, M. A. and Olveczky, B. P. (2017) The Role of Variability in Motor Learning. *Annu Rev Neurosci* **40,** 479-498.

Dhupia, N., Rathour, R. K. and Narayanan, R. (2015) Dendritic atrophy constricts functional maps in resonance and impedance properties of hippocampal model neurons. *Front Cell Neurosci* **8,** 456.

Diesmann, M., Gewaltig, M. O. and Aertsen, A. (1999) Stable propagation of synchronous spiking in cortical neural networks. *Nature* **402,** 529-533.

Dingledine, R., Borges, K., Bowie, D. and Traynelis, S. F. (1999) The glutamate receptor ion channels. *Pharmacological reviews* **51,** 7-61.

Dittman, J. S., Kreitzer, A. C. and Regehr, W. G. (2000) Interplay between facilitation, depression, and residual calcium at three presynaptic terminals. *J Neurosci* **20,** 1374-1385.

Dobzhansky, T. (1973) Nothing in Biology Makes Sense except in the Light of Evolution. *The Americal Biology Teacher* **35,** 125-129.

Dolmetsch, R. (2003) Excitation-transcription coupling: signaling by ion channels to the nucleus. *Science's STKE : signal transduction knowledge environment* **2003,** PE4.

Dougherty, K. A., Islam, T. and Johnston, D. (2012) Intrinsic excitability of CA1 pyramidal neurones from the rat dorsal and ventral hippocampus. *J Physiol* **590,** 5707-5722.

Dougherty, K. A., Nicholson, D. A., Diaz, L., Buss, E. W., Neuman, K. M., Chetkovich, D. M. and Johnston, D. (2013) Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from dorsal and ventral hippocampus. *Journal of neurophysiology* **109,** 1940-1953.

Drion, G., O'Leary, T. and Marder, E. (2015) Ion channel degeneracy enables robust and tunable neuronal firing rates. *Proc Natl Acad Sci U S A* **112,** E5361-5370.

Dudek, S. M. and Bear, M. F. (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc Natl Acad Sci U S A* **89,** 4363-4367.

Dudek, S. M. and Bear, M. F. (1993) Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. *J Neurosci* **13,** 2910-2918.

Dudman, J. T., Tsay, D. and Siegelbaum, S. A. (2007) A role for synaptic inputs at distal dendrites: instructive signals for hippocampal long-term plasticity. *Neuron* **56,** 866-879.

Edelman, G. M. and Gally, J. A. (2001) Degeneracy and complexity in biological systems. *Proc Natl Acad Sci U S A* **98,** 13763-13768.

Eichenbaum, H. (2012) *The Cognitive Neuroscience of Memory: An Introduction*. Oxford University Press: New York, NY.

Einevoll, G. T., Kayser, C., Logothetis, N. K. and Panzeri, S. (2013) Modelling and analysis of local field potentials for studying the function of cortical circuits. *Nature reviews. Neuroscience* **14,** 770-785.

Emoto, K. (2011) Dendrite remodeling in development and disease. *Development, growth & differentiation* **53,** 277-286.

Emptage, N. J., Reid, C. A. and Fine, A. (2001) Calcium stores in hippocampal synaptic boutons mediate short-term plasticity, store-operated Ca2+ entry, and spontaneous transmitter release. *Neuron* **29,** 197-208.

Engel, A. K., Fries, P. and Singer, W. (2001) Dynamic predictions: oscillations and synchrony in top-down processing. *Nature reviews. Neuroscience* **2,** 704-716.

Engel, A. K. and Singer, W. (2001) Temporal binding and the neural correlates of sensory awareness. *Trends Cogn Sci* **5,** 16-25.

Engert, F. and Bonhoeffer, T. (1999) Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature* **399,** 66-70.

English, D. F., Peyrache, A., Stark, E., Roux, L., Vallentin, D., Long, M. A. and Buzsaki, G. (2014) Excitation and inhibition compete to control spiking during hippocampal ripples: intracellular study in behaving mice. *J Neurosci* **34,** 16509-16517.

English, J. D. and Sweatt, J. D. (1997) A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. *J Biol Chem* **272,** 19103-19106.

Fan, Y., Fricker, D., Brager, D. H., Chen, X., Lu, H. C., Chitwood, R. A. and Johnston, D. (2005) Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I(h). *Nat Neurosci* **8,** 1542-1551.

Fields, R. D. (2010) Neuroscience. Change in the brain's white matter. *Science* **330,** 768-769.

Fields, R. D. and Stevens-Graham, B. (2002) New insights into neuron-glia communication. *Science* **298,** 556-562.

Fioravante, D. and Regehr, W. G. (2011) Short-term forms of presynaptic plasticity. *Current opinion in neurobiology* **21,** 269-274.

Fortune, E. S. and Rose, G. J. (2001) Short-term synaptic plasticity as a temporal filter. *Trends Neurosci* **24,** 381-385.

Foster, W. R., Ungar, L. H. and Schwaber, J. S. (1993) Significance of conductances in Hodgkin-Huxley models. *Journal of neurophysiology* **70,** 2502-2518.

Freund, T. F. and Buzsaki, G. (1996) Interneurons of the hippocampus. *Hippocampus* **6,** 347-470.

Frey, U., Huang, Y. Y. and Kandel, E. R. (1993) Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. *Science* **260,** 1661-1664.

Frick, A. and Johnston, D. (2005) Plasticity of dendritic excitability. *J Neurobiol* **64,** 100-115.

Frick, A., Magee, J. and Johnston, D. (2004) LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. *Nat Neurosci* **7,** 126-135.

Frick, A., Magee, J., Koester, H. J., Migliore, M. and Johnston, D. (2003) Normalization of Ca2+ signals by small oblique dendrites of CA1 pyramidal neurons. *J Neurosci* **23,** 3243-3250.

Fries, P., Nikolic, D. and Singer, W. (2007) The gamma cycle. *Trends Neurosci* **30,** 309-316.

Gallistel, C. R. (2017) The Coding Question. *Trends Cogn Sci* **21,** 498-508.

Garcia-Alvarez, G., Shetty, M. S., Lu, B., Yap, K. A., Oh-Hora, M., Sajikumar, S., Bichler, Z. and Fivaz, M. (2015) Impaired spatial memory and enhanced long-term potentiation in mice with forebrain-specific ablation of the Stim genes. *Frontiers in behavioral neuroscience* **9,** 180.

Gasparini, S. and DiFrancesco, D. (1997) Action of the hyperpolarization-activated current (Ih) blocker ZD 7288 in hippocampal CA1 neurons. *Pflugers Archiv : European journal of physiology* **435,** 99-106.

Gasparini, S. and Magee, J. (2002) Phosphorylation-dependent differences in the activation properties of distal and proximal dendritic Na+ channels in rat CA1 hippocampal neurons. *J Physiol* **541,** 665-672.

Geisler, C., Diba, K., Pastalkova, E., Mizuseki, K., Royer, S. and Buzsaki, G. (2010) Temporal delays among place cells determine the frequency of population theta oscillations in the hippocampus. *Proc Natl Acad Sci U S A* **107,** 7957-7962.

Geisler, C., Robbe, D., Zugaro, M., Sirota, A. and Buzsaki, G. (2007) Hippocampal place cell assemblies are speed-controlled oscillators. *Proc Natl Acad Sci U S A* **104,** 8149-8154.

Ghiretti, A. E. and Paradis, S. (2014) Molecular mechanisms of activity-dependent changes in dendritic morphology: role of RGK proteins. *Trends Neurosci* **37,** 399-407.

Gjorgjieva, J., Drion, G. and Marder, E. (2016) Computational implications of biophysical diversity and multiple timescales in neurons and synapses for circuit performance. *Current opinion in neurobiology* **37,** 44-52.

Golding, N. L., Mickus, T. J., Katz, Y., Kath, W. L. and Spruston, N. (2005) Factors mediating powerful voltage attenuation along CA1 pyramidal neuron dendrites. *J Physiol* **568,** 69-82.

Golding, N. L. and Oertel, D. (2012) Synaptic integration in dendrites: exceptional need for speed. *J Physiol* **590,** 5563-5569.

Golding, N. L., Staff, N. P. and Spruston, N. (2002) Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* **418,** 326-331.

Goldman, M. S., Golowasch, J., Marder, E. and Abbott, L. F. (2001) Global structure, robustness, and modulation of neuronal models. *J Neurosci* **21,** 5229-5238.

Goutagny, R., Jackson, J. and Williams, S. (2009) Self-generated theta oscillations in the hippocampus. *Nat Neurosci* **12,** 1491-1493.

Grant, S. G. (2012) Synaptopathies: diseases of the synaptome. *Current opinion in neurobiology* **22,** 522-529.

Grashow, R., Brookings, T. and Marder, E. (2010) Compensation for variable intrinsic neuronal excitability by circuit-synaptic interactions. *J Neurosci* **30,** 9145-9156.

Grienberger, C., Milstein, A. D., Bittner, K. C., Romani, S. and Magee, J. C. (2017) Inhibitory suppression of heterogeneously tuned excitation enhances spatial coding in CA1 place cells. *Nat Neurosci* **20,** 417-426.

Grosmark, A. D., Mizuseki, K., Pastalkova, E., Diba, K. and Buzsaki, G. (2012) REM sleep reorganizes hippocampal excitability. *Neuron* **75,** 1001-1007.

Grubb, M. S. and Burrone, J. (2010a) Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature* **465,** 1070-1074.

Grubb, M. S. and Burrone, J. (2010b) Building and maintaining the axon initial segment. *Current opinion in neurobiology* **20,** 481-488.

Grubb, M. S., Shu, Y., Kuba, H., Rasband, M. N., Wimmer, V. C. and Bender, K. J. (2011) Short- and long-term plasticity at the axon initial segment. *J Neurosci* **31,** 16049-16055.

Gu, N., Vervaeke, K., Hu, H. and Storm, J. F. (2005) Kv7/KCNQ/M and HCN/h, but not KCa2/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells. *J Physiol* **566,** 689-715.

Guckenheimer, J. and Holmes, P. J. (1983) *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. Springer: New York.

Gurnett, C. A. and Campbell, K. P. (1996) Transmembrane auxiliary subunits of voltage-dependent ion channels. *J Biol Chem* **271,** 27975-27978.

Halassa, M. M., Fellin, T. and Haydon, P. G. (2007) The tripartite synapse: roles for gliotransmission in health and disease. *Trends in molecular medicine* **13,** 54-63.

Halassa, M. M. and Haydon, P. G. (2010) Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annual review of physiology* **72,** 335-355.
Hammond, R. S., Lin, L., Sidorov, M. S., Wikenheiser, A. M. and Hoffman, D. A. (2008) Protein kinase a mediates activity-dependent Kv4.2 channel trafficking. *J Neurosci* **28,** 7513-7519.
Hanse, E. and Gustafsson, B. (1994) TEA elicits two distinct potentiations of synaptic transmission in the CA1 region of the hippocampal slice. *J Neurosci* **14,** 5028-5034.
Hanus, C. and Schuman, E. M. (2013) Proteostasis in complex dendrites. *Nature reviews. Neuroscience* **14,** 638-648.
Hartley, T., Lever, C., Burgess, N. and O'Keefe, J. (2014) Space in the brain: how the hippocampal formation supports spatial cognition. *Philos Trans R Soc Lond B Biol Sci* **369,** 20120510.
Harvey, C. D., Collman, F., Dombeck, D. A. and Tank, D. W. (2009) Intracellular dynamics of hippocampal place cells during virtual navigation. *Nature* **461,** 941-946.
Haydon, P. G. and Carmignoto, G. (2006) Astrocyte control of synaptic transmission and neurovascular coupling. *Physiol Rev* **86,** 1009-1031.
He, C., Chen, F., Li, B. and Hu, Z. (2014) Neurophysiology of HCN channels: from cellular functions to multiple regulations. *Progress in neurobiology* **112,** 1-23.
Hengen, K. B., Torrado Pacheco, A., McGregor, J. N., Van Hooser, S. D. and Turrigiano, G. G. (2016) Neuronal Firing Rate Homeostasis Is Inhibited by Sleep and Promoted by Wake. *Cell* **165,** 180-191.
Henneberger, C., Papouin, T., Oliet, S. H. and Rusakov, D. A. (2010) Long-term potentiation depends on release of D-serine from astrocytes. *Nature* **463,** 232-236.
Higley, M. J. and Sabatini, B. L. (2012) Calcium signaling in dendritic spines. *Cold Spring Harb Perspect Biol* **4,** a005686.
Hille, B. (2001) Ion Channels of Excitable Membranes. *Sinauer Associates, Inc.*
Hines, M. L., Morse, T., Migliore, M., Carnevale, N. T. and Shepherd, G. M. (2004) ModelDB: A Database to Support Computational Neuroscience. *J Comput Neurosci* **17,** 7-11.
Hobbs, K. H. and Hooper, S. L. (2008) Using complicated, wide dynamic range driving to develop models of single neurons in single recording sessions. *Journal of neurophysiology* **99,** 1871-1883.
Hodgkin, A. L. and Huxley, A. F. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* **117,** 500-544.
Hoffman, D. A. and Johnston, D. (1999) Neuromodulation of dendritic action potentials. *Journal of neurophysiology* **81,** 408-411.
Hoffman, D. A., Magee, J. C., Colbert, C. M. and Johnston, D. (1997) K+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* **387,** 869-875.
Hoffman, D. A., Sprengel, R. and Sakmann, B. (2002) Molecular dissection of hippocampal theta-burst pairing potentiation. *Proc Natl Acad Sci U S A* **99,** 7740-7745.
Holzer, P. (2009) Acid-sensitive ion channels and receptors. *Handbook of experimental pharmacology*, 283-332.
Hong, S., Ratte, S., Prescott, S. A. and De Schutter, E. (2012) Single neuron firing properties impact correlation-based population coding. *J Neurosci* **32,** 1413-1428.
Honnuraiah, S. and Narayanan, R. (2013) A calcium-dependent plasticity rule for HCN channels maintains activity homeostasis and stable synaptic learning. *PloS one* **8,** e55590.
Hu, H., Vervaeke, K., Graham, L. J. and Storm, J. F. (2009) Complementary theta resonance filtering by two spatially segregated mechanisms in CA1 hippocampal pyramidal neurons. *J Neurosci* **29,** 14472-14483.
Hu, H., Vervaeke, K. and Storm, J. F. (2002) Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na+ current in rat hippocampal pyramidal cells. *J Physiol* **545,** 783-805.
Hu, H., Vervaeke, K. and Storm, J. F. (2007) M-channels (Kv7/KCNQ channels) that regulate synaptic integration, excitability, and spike pattern of CA1 pyramidal cells are located in the perisomatic region. *J Neurosci* **27,** 1853-1867.
Huang, C. S., Shi, S. H., Ule, J., Ruggiu, M., Barker, L. A., Darnell, R. B., Jan, Y. N. and Jan, L. Y. (2005) Common molecular pathways mediate long-term potentiation of synaptic excitation and slow synaptic inhibition. *Cell* **123,** 105-118.

Huang, Y. Y. and Malenka, R. C. (1993) Examination of TEA-induced synaptic enhancement in area CA1 of the hippocampus: the role of voltage-dependent Ca2+ channels in the induction of LTP. *J Neurosci* **13,** 568-576.

Huber, K. M., Kayser, M. S. and Bear, M. F. (2000) Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. *Science* **288,** 1254-1257.

Huber, K. M., Mauk, M. D. and Kelly, P. T. (1995) Distinct LTP induction mechanisms: contribution of NMDA receptors and voltage-dependent calcium channels. *Journal of neurophysiology* **73,** 270-279.

Hulme, S. R., Jones, O. D. and Abraham, W. C. (2013) Emerging roles of metaplasticity in behaviour and disease. *Trends Neurosci* **36,** 353-362.

Hutcheon, B. and Yarom, Y. (2000) Resonance, oscillation and the intrinsic frequency preferences of neurons. *Trends Neurosci* **23,** 216-222.

Huxter, J., Burgess, N. and O'Keefe, J. (2003) Independent rate and temporal coding in hippocampal pyramidal cells. *Nature* **425,** 828-832.

Ibata, K., Sun, Q. and Turrigiano, G. G. (2008) Rapid synaptic scaling induced by changes in postsynaptic firing. *Neuron* **57,** 819-826.

Ikegaya, Y., Kim, J. A., Baba, M., Iwatsubo, T., Nishiyama, N. and Matsuki, N. (2001) Rapid and reversible changes in dendrite morphology and synaptic efficacy following NMDA receptor activation: implication for a cellular defense against excitotoxicity. *Journal of cell science* **114,** 4083-4093.

Isom, L. L., De Jongh, K. S. and Catterall, W. A. (1994) Auxiliary subunits of voltage-gated ion channels. *Neuron* **12,** 1183-1194.

Jaffe, D. B., Johnston, D., Lasser-Ross, N., Lisman, J. E., Miyakawa, H. and Ross, W. N. (1992) The spread of Na+ spikes determines the pattern of dendritic Ca2+ entry into hippocampal neurons. *Nature* **357,** 244-246.

James, W. (1890) *The principles of psychology*. Henry Holt & Co., NY.

Jaramillo, J. and Kempter, R. (2017) Phase precession: a neural code underlying episodic memory? *Current opinion in neurobiology* **43,** 130-138.

Jazayeri, M. and Afraz, A. (2017) Navigating the Neural Space in Search of the Neural Code. *Neuron* **93,** 1003-1014.

Jedlicka, P., Benuskova, L. and Abraham, W. C. (2015) A Voltage-Based STDP Rule Combined with Fast BCM-Like Metaplasticity Accounts for LTP and Concurrent "Heterosynaptic" LTD in the Dentate Gyrus In Vivo. *PLoS computational biology* **11,** e1004588.

Jensen, C. S., Rasmussen, H. B. and Misonou, H. (2011) Neuronal trafficking of voltage-gated potassium channels. *Molecular and cellular neurosciences* **48,** 288-297.

Jerng, H. H., Pfaffinger, P. J. and Covarrubias, M. (2004) Molecular physiology and modulation of somatodendritic A-type potassium channels. *Molecular and cellular neurosciences* **27,** 343-369.

Johnston, D., Christie, B. R., Frick, A., Gray, R., Hoffman, D. A., Schexnayder, L. K., Watanabe, S. and Yuan, L. L. (2003) Active dendrites, potassium channels and synaptic plasticity. *Philos Trans R Soc Lond B Biol Sci* **358,** 667-674.

Johnston, D., Frick, A. and Poolos, N. (2016) Dendrites and disease. In: *Dendrites*. Eds. G. Stuart, N. Spruston, M. Hausser. Oxford University Press: New York, NY.

Johnston, D., Magee, J. C., Colbert, C. M. and Cristie, B. R. (1996) Active properties of neuronal dendrites. *Annu Rev Neurosci* **19,** 165-186.

Johnston, D. and Narayanan, R. (2008) Active dendrites: colorful wings of the mysterious butterflies. *Trends Neurosci* **31,** 309-316.

Johnston, D., Williams, S., Jaffe, D. and Gray, R. (1992) NMDA-receptor-independent long-term potentiation. *Annual review of physiology* **54,** 489-505.

Jonas, E. and Kording, K. P. (2017) Could a Neuroscientist Understand a Microprocessor? *PLoS computational biology* **13,** e1005268.

Jorntell, H. and Hansel, C. (2006) Synaptic memories upside down: bidirectional plasticity at cerebellar parallel fiber-Purkinje cell synapses. *Neuron* **52,** 227-238.

Joshi, N. J., Tononi, G. and Koch, C. (2013) The minimal complexity of adapting agents increases with fitness. *PLoS computational biology* **9,** e1003111.

Jung, S. C., Kim, J. and Hoffman, D. A. (2008) Rapid, bidirectional remodeling of synaptic NMDA receptor subunit composition by A-type K+ channel activity in hippocampal CA1 pyramidal neurons. *Neuron* **60,** 657-671.

Kajikawa, Y. and Schroeder, C. E. (2011) How local is the local field potential? *Neuron* **72,** 847-858.
Kalantzis, G. and Shouval, H. Z. (2009) Structural plasticity can produce metaplasticity. *PloS one* **4,** e8062.
Kamondi, A., Acsady, L., Wang, X. J. and Buzsaki, G. (1998) Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. *Hippocampus* **8,** 244-261.
Kandel, E. R. (2001) The molecular biology of memory storage: a dialogue between genes and synapses. *Science* **294,** 1030-1038.
Kandel, E. R., Dudai, Y. and Mayford, M. R. (2014) The molecular and systems biology of memory. *Cell* **157,** 163-186.
Katz, P. S. (2016) Evolution of central pattern generators and rhythmic behaviours. *Philos Trans R Soc Lond B Biol Sci* **371,** 20150057.
Katzner, S., Nauhaus, I., Benucci, A., Bonin, V., Ringach, D. L. and Carandini, M. (2009) Local origin of field potentials in visual cortex. *Neuron* **61,** 35-41.
Kennedy, M. B. (2000) Signal-processing machines at the postsynaptic density. *Science* **290,** 750-754.
Kennedy, M. B., Beale, H. C., Carlisle, H. J. and Washburn, L. R. (2005) Integration of biochemical signalling in spines. *Nature reviews. Neuroscience* **6,** 423-434.
Khakh, B. S. and Sofroniew, M. V. (2015) Diversity of astrocyte functions and phenotypes in neural circuits. *Nat Neurosci* **18,** 942-952.
Kholodenko, B. N. (2006) Cell-signalling dynamics in time and space. *Nat Rev Mol Cell Biol* **7,** 165-176.
Kim, C. S., Brager, D. H. and Johnston, D. (2017) Perisomatic changes in h-channels regulate depressive behaviors following chronic unpredictable stress. *Molecular psychiatry*.
Kim, C. S. and Johnston, D. (2015) A1 adenosine receptor-mediated GIRK channels contribute to the resting conductance of CA1 neurons in the dorsal hippocampus. *Journal of neurophysiology* **113,** 2511-2523.
Kim, J., Jung, S. C., Clemens, A. M., Petralia, R. S. and Hoffman, D. A. (2007) Regulation of dendritic excitability by activity-dependent trafficking of the A-type K+ channel subunit Kv4.2 in hippocampal neurons. *Neuron* **54,** 933-947.
Kim, J., Wei, D. S. and Hoffman, D. A. (2005) Kv4 potassium channel subunits control action potential repolarization and frequency-dependent broadening in rat hippocampal CA1 pyramidal neurones. *J Physiol* **569,** 41-57.
Kim, S. J. and Linden, D. J. (2007) Ubiquitous plasticity and memory storage. *Neuron* **56,** 582-592.
Kim, Y., Hsu, C. L., Cembrowski, M. S., Mensh, B. D. and Spruston, N. (2015) Dendritic sodium spikes are required for long-term potentiation at distal synapses on hippocampal pyramidal neurons. *eLife* **4**.
Kitano, H. (2007) Towards a theory of biological robustness. *Molecular systems biology* **3,** 137.
Klausberger, T. and Somogyi, P. (2008) Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* **321,** 53-57.
Koester, H. J. and Johnston, D. (2005) Target cell-dependent normalization of transmitter release at neocortical synapses. *Science* **308,** 863-866.
Korte, M. and Schmitz, D. (2016) Cellular and System Biology of Memory: Timing, Molecules, and Beyond. *Physiol Rev* **96,** 647-693.
Kotaleski, J. H. and Blackwell, K. T. (2010) Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. *Nature reviews. Neuroscience* **11,** 239-251.
Krakauer, J. W., Ghazanfar, A. A., Gomez-Marin, A., MacIver, M. A. and Poeppel, D. (2017) Neuroscience Needs Behavior: Correcting a Reductionist Bias. *Neuron* **93,** 480-490.
Krichmar, J. L., Nasuto, S. J., Scorcioni, R., Washington, S. D. and Ascoli, G. A. (2002) Effects of dendritic morphology on CA3 pyramidal cell electrophysiology: a simulation study. *Brain Res* **941,** 11-28.
Kullmann, D. M. (2002) The neuronal channelopathies. *Brain : a journal of neurology* **125,** 1177-1195.
Lai, H. C. and Jan, L. Y. (2006) The distribution and targeting of neuronal voltage-gated ion channels. *Nature reviews. Neuroscience* **7,** 548-562.
Lamprecht, R. and LeDoux, J. (2004) Structural plasticity and memory. *Nature reviews. Neuroscience* **5,** 45-54.
Larkman, A. U. and Jack, J. J. (1995) Synaptic plasticity: hippocampal LTP. *Current opinion in neurobiology* **5,** 324-334.
Larsen, R. S. and Sjostrom, P. J. (2015) Synapse-type-specific plasticity in local circuits. *Current opinion in neurobiology* **35,** 127-135.
Larson, J., Wong, D. and Lynch, G. (1986) Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res* **368,** 347-350.

Lau, C. G. and Zukin, R. S. (2007) NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nature reviews. Neuroscience* **8,** 413-426.

Lazebnik, Y. (2002) Can a biologist fix a radio?--Or, what I learned while studying apoptosis. *Cancer cell* **2,** 179-182.

Lee, D., Lin, B. J. and Lee, A. K. (2012) Hippocampal place fields emerge upon single-cell manipulation of excitability during behavior. *Science* **337,** 849-853.

Lee, H. Y. and Jan, L. Y. (2012) Fragile X syndrome: mechanistic insights and therapeutic avenues regarding the role of potassium channels. *Current opinion in neurobiology* **22,** 887-894.

Lee, S. H. and Dan, Y. (2012) Neuromodulation of brain states. *Neuron* **76,** 209-222.

Lehmann-Horn, F. and Jurkat-Rott, K. (1999) Voltage-Gated Ion Channels and Hereditary Disease. *Physiol Rev***,** 1317-1372.

Lein, E. S., Hawrylycz, M. J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., Boe, A. F., Boguski, M. S., Brockway, K. S., Byrnes, E. J., Chen, L., Chen, L., Chen, T. M., Chin, M. C., Chong, J., Crook, B. E., Czaplinska, A., Dang, C. N., Datta, S., Dee, N. R., Desaki, A. L., Desta, T., Diep, E., Dolbeare, T. A., Donelan, M. J., Dong, H. W., Dougherty, J. G., Duncan, B. J., Ebbert, A. J., Eichele, G., Estin, L. K., Faber, C., Facer, B. A., Fields, R., Fischer, S. R., Fliss, T. P., Frensley, C., Gates, S. N., Glattfelder, K. J., Halverson, K. R., Hart, M. R., Hohmann, J. G., Howell, M. P., Jeung, D. P., Johnson, R. A., Karr, P. T., Kawal, R., Kidney, J. M., Knapik, R. H., Kuan, C. L., Lake, J. H., Laramee, A. R., Larsen, K. D., Lau, C., Lemon, T. A., Liang, A. J., Liu, Y., Luong, L. T., Michaels, J., Morgan, J. J., Morgan, R. J., Mortrud, M. T., Mosqueda, N. F., Ng, L. L., Ng, R., Orta, G. J., Overly, C. C., Pak, T. H., Parry, S. E., Pathak, S. D., Pearson, O. C., Puchalski, R. B., Riley, Z. L., Rockett, H. R., Rowland, S. A., Royall, J. J., Ruiz, M. J., Sarno, N. R., Schaffnit, K., Shapovalova, N. V., Sivisay, T., Slaughterbeck, C. R., Smith, S. C., Smith, K. A., Smith, B. I., Sodt, A. J., Stewart, N. N., Stumpf, K. R., Sunkin, S. M., Sutram, M., Tam, A., Teemer, C. D., Thaller, C., Thompson, C. L., Varnam, L. R., Visel, A., Whitlock, R. M., Wohnoutka, P. E., Wolkey, C. K., Wong, V. Y., Wood, M., Yaylaoglu, M. B., Young, R. C., Youngstrom, B. L., Yuan, X. F., Zhang, B., Zwingman, T. A. and Jones, A. R. (2007) Genome-wide atlas of gene expression in the adult mouse brain. *Nature* **445,** 168-176.

LeMasson, G., Marder, E. and Abbott, L. F. (1993) Activity-dependent regulation of conductances in model neurons. *Science* **259,** 1915-1917.

Leonardo, A. (2005) Degenerate coding in neural systems. *Journal of comparative physiology. A, Neuroethology, sensory, neural, and behavioral physiology* **191,** 995-1010.

Lerche, H., Shah, M., Beck, H., Noebels, J., Johnston, D. and Vincent, A. (2013) Ion channels in genetic and acquired forms of epilepsy. *J Physiol* **591,** 753-764.

Levitan, I. and Barrantes, F. (2012) *Cholesterol Regulation of Ion Channels and Receptors*. John Wiley & Sons.

Levitan, I. B. (1994) Modulation of ion channels by protein phosphorylation and dephosphorylation. *Annual review of physiology* **56,** 193-212.

Lewis, A. S., Vaidya, S. P., Blaiss, C. A., Liu, Z., Stoub, T. R., Brager, D. H., Chen, X., Bender, R. A., Estep, C. M., Popov, A. B., Kang, C. E., Van Veldhoven, P. P., Bayliss, D. A., Nicholson, D. A., Powell, C. M., Johnston, D. and Chetkovich, D. M. (2011) Deletion of the hyperpolarization-activated cyclic nucleotide-gated channel auxiliary subunit TRIP8b impairs hippocampal Ih localization and function and promotes antidepressant behavior in mice. *J Neurosci* **31,** 7424-7440.

Lin, L., Sun, W., Kung, F., Dell'Acqua, M. L. and Hoffman, D. A. (2011) AKAP79/150 impacts intrinsic excitability of hippocampal neurons through phospho-regulation of A-type K+ channel trafficking. *J Neurosci* **31,** 1323-1332.

Lin, L., Sun, W., Wikenheiser, A. M., Kung, F. and Hoffman, D. A. (2010) KChIP4a regulates Kv4.2 channel trafficking through PKA phosphorylation. *Molecular and cellular neurosciences* **43,** 315-325.

Lin, M. T., Lujan, R., Watanabe, M., Adelman, J. P. and Maylie, J. (2008) SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. *Nat Neurosci* **11,** 170-177.

Linden, H., Tetzlaff, T., Potjans, T. C., Pettersen, K. H., Grun, S., Diesmann, M. and Einevoll, G. T. (2011) Modeling the spatial reach of the LFP. *Neuron* **72,** 859-872.

Lisman, J. (1989) A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. *Proc Natl Acad Sci U S A* **86,** 9574-9578.

Lisman, J. (2005) The theta/gamma discrete phase code occuring during the hippocampal phase precession may be a more general brain coding scheme. *Hippocampus* **15,** 913-922.

Lisman, J., Schulman, H. and Cline, H. (2002) The molecular basis of CaMKII function in synaptic and behavioural memory. *Nature reviews. Neuroscience* **3,** 175-190.

Lisman, J., Yasuda, R. and Raghavachari, S. (2012) Mechanisms of CaMKII action in long-term potentiation. *Nature reviews. Neuroscience* **13,** 169-182.
Lisman, J. E. (2001) Three Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. *J Physiol* **532,** 285.
Lisman, J. E. and Jensen, O. (2013) The theta-gamma neural code. *Neuron* **77,** 1002-1016.
Llinas, R. R. (1988) The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science* **242,** 1654-1664.
London, M., Roth, A., Beeren, L., Hausser, M. and Latham, P. E. (2010) Sensitivity to perturbations in vivo implies high noise and suggests rate coding in cortex. *Nature* **466,** 123-127.
Losick, R. and Desplan, C. (2008) Stochasticity and cell fate. *Science* **320,** 65-68.
Losonczy, A., Makara, J. K. and Magee, J. C. (2008) Compartmentalized dendritic plasticity and input feature storage in neurons. *Nature* **452,** 436-441.
Losonczy, A., Zemelman, B. V., Vaziri, A. and Magee, J. C. (2010) Network mechanisms of theta related neuronal activity in hippocampal CA1 pyramidal neurons. *Nat Neurosci* **13,** 967-972.
Lujan, R., Maylie, J. and Adelman, J. P. (2009) New sites of action for GIRK and SK channels. *Nature reviews. Neuroscience* **10,** 475-480.
Luo, L. and Flanagan, J. G. (2007) Development of continuous and discrete neural maps. *Neuron* **56,** 284-300.
Luo, L. and O'Leary, D. D. (2005) Axon retraction and degeneration in development and disease. *Annu Rev Neurosci* **28,** 127-156.
Lynch, G., Larson, J., Kelso, S., Barrionuevo, G. and Schottler, F. (1983) Intracellular injections of EGTA block induction of hippocampal long-term potentiation. *Nature* **305,** 719-721.
Lynch, G. S., Dunwiddie, T. and Gribkoff, V. (1977) Heterosynaptic depression: a postsynaptic correlate of long-term potentiation. *Nature* **266,** 737-739.
Lynch, M. A. (2004) Long-term potentiation and memory. *Physiol Rev* **84,** 87-136.
Magee, J. C. (2000) Dendritic integration of excitatory synaptic input. *Nature reviews. Neuroscience* **1,** 181-190.
Magee, J. C. (2001) Dendritic mechanisms of phase precession in hippocampal CA1 pyramidal neurons. *Journal of neurophysiology* **86,** 528-532.
Magee, J. C. and Cook, E. P. (2000) Somatic EPSP amplitude is independent of synapse location in hippocampal pyramidal neurons. *Nat Neurosci* **3,** 895-903.
Magee, J. C. and Johnston, D. (1997) A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275,** 209-213.
Mainen, Z. F. and Sejnowski, T. J. (1996) Influence of dendritic structure on firing pattern in model neocortical neurons. *Nature* **382,** 363-366.
Majewski, L. and Kuznicki, J. (2015) SOCE in neurons: Signaling or just refilling? *Biochimica et biophysica acta* **1853,** 1940-1952.
Majewski, L., Maciag, F., Boguszewski, P. M., Wasilewska, I., Wiera, G., Wojtowicz, T., Mozrzymas, J. and Kuznicki, J. (2016) Overexpression of STIM1 in neurons in mouse brain improves contextual learning and impairs long-term depression. *Biochimica et biophysica acta*.
Malenka, R. C., Lancaster, B. and Zucker, R. S. (1992) Temporal limits on the rise in postsynaptic calcium required for the induction of long-term potentiation. *Neuron* **9,** 121-128.
Malik, R., Dougherty, K. A., Parikh, K., Byrne, C. and Johnston, D. (2016) Mapping the electrophysiological and morphological properties of CA1 pyramidal neurons along the longitudinal hippocampal axis. *Hippocampus* **26,** 341-361.
Malik, R. and Johnston, D. (2017) Dendritic GIRK Channels Gate the Integration Window, Plateau Potentials, and Induction of Synaptic Plasticity in Dorsal But Not Ventral CA1 Neurons. *J Neurosci* **37,** 3940-3955.
Malinow, R., Schulman, H. and Tsien, R. W. (1989) Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. *Science* **245,** 862-866.
Manninen, T., Hituri, K., Kotaleski, J. H., Blackwell, K. T. and Linne, M. L. (2010) Postsynaptic signal transduction models for long-term potentiation and depression. *Frontiers in computational neuroscience* **4,** 152.
Marder, E. (1998) From biophysics to models of network function. *Annu Rev Neurosci* **21,** 25-45.
Marder, E. (2011) Variability, compensation, and modulation in neurons and circuits. *Proc Natl Acad Sci U S A* **108 Suppl 3,** 15542-15548.

Marder, E. (2012) Neuromodulation of neuronal circuits: back to the future. *Neuron* **76,** 1-11.
Marder, E., Abbott, L. F., Turrigiano, G. G., Liu, Z. and Golowasch, J. (1996) Memory from the dynamics of intrinsic membrane currents. *Proc Natl Acad Sci U S A* **93,** 13481-13486.
Marder, E. and Goaillard, J. M. (2006) Variability, compensation and homeostasis in neuron and network function. *Nature reviews. Neuroscience* **7,** 563-574.
Marder, E., Goeritz, M. L. and Otopalik, A. G. (2015) Robust circuit rhythms in small circuits arise from variable circuit components and mechanisms. *Current opinion in neurobiology* **31,** 156-163.
Marder, E., O'Leary, T. and Shruti, S. (2014) Neuromodulation of circuits with variable parameters: single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. *Annu Rev Neurosci* **37,** 329-346.
Marder, E. and Taylor, A. L. (2011) Multiple models to capture the variability in biological neurons and networks. *Nat Neurosci* **14,** 133-138.
Marder, E. and Thirumalai, V. (2002) Cellular, synaptic and network effects of neuromodulation. *Neural Netw* **15,** 479-493.
Markram, H., Lubke, J., Frotscher, M. and Sakmann, B. (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275,** 213-215.
Marr, D. (1971) Simple memory: a theory for archicortex. *Philos Trans R Soc Lond B Biol Sci* **262,** 23-81.
Martin, S. J., Grimwood, P. D. and Morris, R. G. (2000) Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu Rev Neurosci* **23,** 649-711.
Martinez, J. L., Jr. and Derrick, B. E. (1996) Long-term potentiation and learning. *Annu Rev Psychol* **47,** 173-203.
Matsuzaki, M., Honkura, N., Ellis-Davies, G. and Kasai, H. (2004) Structural basis of long-term potentiation in single dendritic spines. *Nature* **429,** 761-766.
Mauro, A. (1961) Anomalous impedance, a phenomenological property of time-variant resistance. An analytic review. *Biophysical journal* **1,** 353-372.
Mauro, A., Conti, F., Dodge, F. and Schor, R. (1970) Subthreshold behavior and phenomenological impedance of the squid giant axon. *The Journal of general physiology* **55,** 497-523.
Mayford, M., Siegelbaum, S. A. and Kandel, E. R. (2012) Synapses and memory storage. *Cold Spring Harb Perspect Biol* **4**.
Mehta, M. R., Lee, A. K. and Wilson, M. A. (2002) Role of experience and oscillations in transforming a rate code into a temporal code. *Nature* **417,** 741-746.
Migliore, M., De Simone, G. and Migliore, R. (2015) Effect of the initial synaptic state on the probability to induce long-term potentiation and depression. *Biophysical journal* **108,** 1038-1046.
Migliore, M. and Migliore, R. (2012) Know your current I(h): interaction with a shunting current explains the puzzling effects of its pharmacological or pathological modulations. *PloS one* **7,** e36867.
Migliore, M. and Shepherd, G. M. (2002) Emerging rules for the distributions of active dendritic conductances. *Nature reviews. Neuroscience* **3,** 362-370.
Migliore, M. and Shepherd, G. M. (2005) Opinion: an integrated approach to classifying neuronal phenotypes. *Nature reviews. Neuroscience* **6,** 810-818.
Miller, K. D. and MacKay, D. J. C. (1994) The role of constraints in Hebbian learning. *Neural Comput* **6,** 100-126.
Mishra, P. and Narayanan, R. (2015) High-conductance states and A-type K+ channels are potential regulators of the conductance-current balance triggered by HCN channels. *Journal of neurophysiology* **113,** 23-43.
Misonou, H., Mohapatra, D. P., Park, E. W., Leung, V., Zhen, D., Misonou, K., Anderson, A. E. and Trimmer, J. S. (2004) Regulation of ion channel localization and phosphorylation by neuronal activity. *Nat Neurosci* **7,** 711-718.
Miyakawa, H., Ross, W. N., Jaffe, D., Callaway, J. C., Lasser-Ross, N., Lisman, J. E. and Johnston, D. (1992) Synaptically activated increases in Ca2+ concentration in hippocampal CA1 pyramidal cells are primarily due to voltage-gated Ca2+ channels. *Neuron* **9,** 1163-1173.
Mizuseki, K. and Buzsaki, G. (2014) Theta oscillations decrease spike synchrony in the hippocampus and entorhinal cortex. *Philos Trans R Soc Lond B Biol Sci* **369,** 20120530.
Montgomery, S. M., Sirota, A. and Buzsaki, G. (2008) Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. *J Neurosci* **28,** 6731-6741.

Moosmang, S., Haider, N., Klugbauer, N., Adelsberger, H., Langwieser, N., Muller, J., Stiess, M., Marais, E., Schulla, V., Lacinova, L., Goebbels, S., Nave, K. A., Storm, D. R., Hofmann, F. and Kleppisch, T. (2005) Role of hippocampal Cav1.2 Ca2+ channels in NMDA receptor-independent synaptic plasticity and spatial memory. *J Neurosci* **25,** 9883-9892.

Morris, R. G. (1989) Synaptic plasticity and learning: selective impairment of learning rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5. *J Neurosci* **9,** 3040-3057.

Morris, R. G., Anderson, E., Lynch, G. S. and Baudry, M. (1986) Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* **319,** 774-776.

Morris, R. G., Garrud, P., Rawlins, J. N. and O'Keefe, J. (1982) Place navigation impaired in rats with hippocampal lesions. *Nature* **297,** 681-683.

Moser, E. I., Kropff, E. and Moser, M. B. (2008) Place Cells, Grid Cells, and the Brain's Spatial Representation System. *Annu Rev Neurosci* **31,** 69-89.

Moser, M. B., Rowland, D. C. and Moser, E. I. (2015) Place cells, grid cells, and memory. *Cold Spring Harb Perspect Biol* **7,** a021808.

Mozzachiodi, R. and Byrne, J. H. (2010) More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory. *Trends Neurosci* **33,** 17-26.

Much, B., Wahl-Schott, C., Zong, X., Schneider, A., Baumann, L., Moosmang, S., Ludwig, A. and Biel, M. (2003) Role of subunit heteromerization and N-linked glycosylation in the formation of functional hyperpolarization-activated cyclic nucleotide-gated channels. *J Biol Chem* **278,** 43781-43786.

Mukunda, C. L. and Narayanan, R. (2017) Degeneracy in the regulation of short-term plasticity and synaptic filtering by presynaptic mechanisms. *J Physiol* **595,** 2611-2637.

Mulkey, R. M. and Malenka, R. C. (1992) Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* **9,** 967-975.

Nagerl, U. V., Eberhorn, N., Cambridge, S. B. and Bonhoeffer, T. (2004) Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron* **44,** 759-767.

Nakashiba, T., Young, J. Z., McHugh, T. J., Buhl, D. L. and Tonegawa, S. (2008) Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. *Science* **319,** 1260-1264.

Nakazawa, K., McHugh, T. J., Wilson, M. A. and Tonegawa, S. (2004) NMDA receptors, place cells and hippocampal spatial memory. *Nature reviews. Neuroscience* **5,** 361-372.

Narayanan, R. and Chattarji, S. (2010) Computational analysis of the impact of chronic stress on intrinsic and synaptic excitability in the hippocampus. *Journal of neurophysiology* **103,** 3070-3083.

Narayanan, R., Dougherty, K. J. and Johnston, D. (2010) Calcium Store Depletion Induces Persistent Perisomatic Increases in the Functional Density of h Channels in Hippocampal Pyramidal Neurons. *Neuron* **68,** 921-935.

Narayanan, R. and Johnston, D. (2007) Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability. *Neuron* **56,** 1061-1075.

Narayanan, R. and Johnston, D. (2008) The h channel mediates location dependence and plasticity of intrinsic phase response in rat hippocampal neurons. *J Neurosci* **28,** 5846-5860.

Narayanan, R. and Johnston, D. (2010) The h current is a candidate mechanism for regulating the sliding modification threshold in a BCM-like synaptic learning rule. *Journal of neurophysiology* **104,** 1020-1033.

Narayanan, R. and Johnston, D. (2012) Functional maps within a single neuron. *Journal of neurophysiology* **108,** 2343-2351.

Nayfeh, A. H. and Balachandran, B. (1995) *Applied nonlinear dynamics: analytical, computational and experimental methods*. Wiley-VCH Verlag GmbH: Weinheim, Germany.

Nelson, S. B. and Turrigiano, G. G. (2008) Strength through diversity. *Neuron* **60,** 477-482.

Ness, T. V., Remme, M. W. H. and Einevoll, G. T. (2016) Active subthreshold dendritic conductances shape the local field potential. *J Physiol-London* **594,** 3809-3825.

Neves, G., Cooke, S. F. and Bliss, T. V. (2008a) Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nature reviews. Neuroscience* **9,** 65-75.

Neves, S. R. and Iyengar, R. (2009) Models of spatially restricted biochemical reaction systems. *J Biol Chem* **284,** 5445-5449.

Neves, S. R., Tsokas, P., Sarkar, A., Grace, E. A., Rangamani, P., Taubenfeld, S. M., Alberini, C. M., Schaff, J. C., Blitzer, R. D., Moraru, II and Iyengar, R. (2008b) Cell shape and negative links in regulatory motifs together control spatial information flow in signaling networks. *Cell* **133,** 666-680.

Nevian, T. and Sakmann, B. (2006) Spine Ca2+ signaling in spike-timing-dependent plasticity. *J Neurosci* **26,** 11001-11013.

Nicholson, E. and Kullmann, D. M. (2017) T-type calcium channels contribute to NMDA receptor independent synaptic plasticity in hippocampal regular-spiking oriens-alveus interneurons. *J Physiol*.

Nishiyama, M., Hong, K., Mikoshiba, K., Poo, M. M. and Kato, K. (2000) Calcium stores regulate the polarity and input specificity of synaptic modification. *Nature* **408,** 584-588.

Nolan, M. F., Malleret, G., Dudman, J. T., Buhl, D. L., Santoro, B., Gibbs, E., Vronskaya, S., Buzsaki, G., Siegelbaum, S. A., Kandel, E. R. and Morozov, A. (2004) A behavioral role for dendritic integration: HCN1 channels constrain spatial memory and plasticity at inputs to distal dendrites of CA1 pyramidal neurons. *Cell* **119,** 719-732.

Nusser, Z. (2009) Variability in the subcellular distribution of ion channels increases neuronal diversity. *Trends Neurosci* **32,** 267-274.

Nusser, Z. (2012) Differential subcellular distribution of ion channels and the diversity of neuronal function. *Current opinion in neurobiology* **22,** 366-371.

O'Keefe, J. (1976) Place units in the hippocampus of the freely moving rat. *Experimental neurology* **51,** 78-109.

O'Keefe, J. (1979) A review of the hippocampal place cells. *Progress in neurobiology* **13,** 419-439.

O'Keefe, J. and Burgess, N. (1999) Theta activity, virtual navigation and the human hippocampus. *Trends Cogn Sci* **3,** 403-406.

O'Keefe, J. and Burgess, N. (2005) Dual phase and rate coding in hippocampal place cells: theoretical significance and relationship to entorhinal grid cells. *Hippocampus* **15,** 853-866.

O'Keefe, J., Burgess, N., Donnett, J. G., Jeffery, K. J. and Maguire, E. A. (1998) Place cells, navigational accuracy, and the human hippocampus. *Philos Trans R Soc Lond B Biol Sci* **353,** 1333-1340.

O'Keefe, J. and Conway, D. H. (1978) Hippocampal place units in the freely moving rat: why they fire where they fire. *Experimental brain research* **31,** 573-590.

O'Keefe, J. and Recce, M. L. (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* **3,** 317-330.

O'Leary, T. and Marder, E. (2014) Mapping neural activation onto behavior in an entire animal. *Science* **344,** 372-373.

O'Leary, T., Williams, A. H., Caplan, J. S. and Marder, E. (2013) Correlations in ion channel expression emerge from homeostatic tuning rules. *Proc Natl Acad Sci U S A* **110,** E2645-2654.

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

Otchy, T. M., Wolff, S. B., Rhee, J. Y., Pehlevan, C., Kawai, R., Kempf, A., Gobes, S. M. and Olveczky, B. P. (2015) Acute off-target effects of neural circuit manipulations. *Nature* **528,** 358-363.

Otmakhov, N., Tao-Cheng, J. H., Carpenter, S., Asrican, B., Dosemeci, A., Reese, T. S. and Lisman, J. (2004) Persistent accumulation of calcium/calmodulin-dependent protein kinase II in dendritic spines after induction of NMDA receptor-dependent chemical long-term potentiation. *J Neurosci* **24,** 9324-9331.

Otmakhova, N. A., Otmakhov, N., Mortenson, L. H. and Lisman, J. E. (2000) Inhibition of the cAMP pathway decreases early long-term potentiation at CA1 hippocampal synapses. *J Neurosci* **20,** 4446-4451.

Ouyang, Y., Kantor, D., Harris, K. M., Schuman, E. M. and Kennedy, M. B. (1997) Visualization of the distribution of autophosphorylated calcium/calmodulin-dependent protein kinase II after tetanic stimulation in the CA1 area of the hippocampus. *J Neurosci* **17,** 5416-5427.

Ouyang, Y., Rosenstein, A., Kreiman, G., Schuman, E. M. and Kennedy, M. B. (1999) Tetanic stimulation leads to increased accumulation of Ca(2+)/calmodulin-dependent protein kinase II via dendritic protein synthesis in hippocampal neurons. *J Neurosci* **19,** 7823-7833.

Pannasch, U. and Rouach, N. (2013) Emerging role for astroglial networks in information processing: from synapse to behavior. *Trends Neurosci* **36,** 405-417.

Panzeri, S., Harvey, C. D., Piasini, E., Latham, P. E. and Fellin, T. (2017) Cracking the Neural Code for Sensory Perception by Combining Statistics, Intervention, and Behavior. *Neuron* **93,** 491-507.

Paoletti, P., Bellone, C. and Zhou, Q. (2013) NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nature reviews. Neuroscience* **14,** 383-400.

Parekh, A. B. (2008) Ca2+ microdomains near plasma membrane Ca2+ channels: impact on cell function. *J Physiol* **586,** 3043-3054.

Pascual, O., Casper, K. B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J. Y., Takano, H., Moss, S. J., McCarthy, K. and Haydon, P. G. (2005) Astrocytic purinergic signaling coordinates synaptic networks. *Science* **310,** 113-116.

Pastalkova, E., Itskov, V., Amarasingham, A. and Buzsaki, G. (2008) Internally generated cell assembly sequences in the rat hippocampus. *Science* **321,** 1322-1327.

Perea, G. and Araque, A. (2005) Properties of synaptically evoked astrocyte calcium signal reveal synaptic information processing by astrocytes. *J Neurosci* **25,** 2192-2203.

Perea, G. and Araque, A. (2007) Astrocytes potentiate transmitter release at single hippocampal synapses. *Science* **317,** 1083-1086.

Perea, G., Gomez, R., Mederos, S., Covelo, A., Ballesteros, J. J., Schlosser, L., Hernandez-Vivanco, A., Martin-Fernandez, M., Quintana, R., Rayan, A., Diez, A., Fuenzalida, M., Agarwal, A., Bergles, D. E., Bettler, B., Manahan-Vaughan, D., Martin, E. D., Kirchhoff, F. and Araque, A. (2016) Activity-dependent switch of GABAergic inhibition into glutamatergic excitation in astrocyte-neuron networks. *eLife* **5**.

Perea, G., Navarrete, M. and Araque, A. (2009) Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci* **32,** 421-431.

Phillips, K. G., Hardingham, N. R. and Fox, K. (2008) Postsynaptic action potentials are required for nitric-oxide-dependent long-term potentiation in CA1 neurons of adult GluR1 knock-out and wild-type mice. *J Neurosci* **28,** 14031-14041.

Philpot, B. D., Espinosa, J. S. and Bear, M. F. (2003) Evidence for altered NMDA receptor function as a basis for metaplasticity in visual cortex. *J Neurosci* **23,** 5583-5588.

Philpot, B. D., Sekhar, A. K., Shouval, H. Z. and Bear, M. F. (2001) Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. *Neuron* **29,** 157-169.

Pike, F. G., Goddard, R. S., Suckling, J. M., Ganter, P., Kasthuri, N. and Paulsen, O. (2000) Distinct frequency preferences of different types of rat hippocampal neurones in response to oscillatory input currents. *J Physiol* **529 Pt 1,** 205-213.

Podlaski, W. F., Seeholzer, A., Groschner, L. N., Miesenbock, G., Ranjan, R. and Vogels, T. P. (2017) Mapping the function of neuronal ion channels in model and experiment. *eLife* **6**.

Poolos, N. P. and Johnston, D. (2012) Dendritic ion channelopathy in acquired epilepsy. *Epilepsia* **53 Suppl 9,** 32-40.

Prakriya, M. and Lewis, R. S. (2015) Store-Operated Calcium Channels. *Physiol Rev* **95,** 1383-1436.

Prinz, A. A., Billimoria, C. P. and Marder, E. (2003) Alternative to hand-tuning conductance-based models: construction and analysis of databases of model neurons. *Journal of neurophysiology* **90,** 3998-4015.

Prinz, A. A., Bucher, D. and Marder, E. (2004) Similar network activity from disparate circuit parameters. *Nat Neurosci* **7,** 1345-1352.

Rajasethupathy, P., Sankaran, S., Marshel, J. H., Kim, C. K., Ferenczi, E., Lee, S. Y., Berndt, A., Ramakrishnan, C., Jaffe, A., Lo, M., Liston, C. and Deisseroth, K. (2015) Projections from neocortex mediate top-down control of memory retrieval. *Nature* **526,** 653-659.

Ranjan, R., Khazen, G., Gambazzi, L., Ramaswamy, S., Hill, S. L., Schurmann, F. and Markram, H. (2011) Channelpedia: an integrative and interactive database for ion channels. *Frontiers in neuroinformatics* **5,** 36.

Rathour, R. K., Malik, R. and Narayanan, R. (2016) Transient potassium channels augment degeneracy in hippocampal active dendritic spectral tuning. *Scientific reports* **6,** 24678.

Rathour, R. K. and Narayanan, R. (2012a) Inactivating ion channels augment robustness of subthreshold intrinsic response dynamics to parametric variability in hippocampal model neurons. *J Physiol* **590,** 5629-5652.

Rathour, R. K. and Narayanan, R. (2012b) Influence fields: a quantitative framework for representation and analysis of active dendrites. *Journal of neurophysiology* **107,** 2313-2334.

Rathour, R. K. and Narayanan, R. (2014) Homeostasis of functional maps in active dendrites emerges in the absence of individual channelostasis. *Proc Natl Acad Sci U S A* **111,** E1787-1796.

Ratte, S., Hong, S., De Schutter, E. and Prescott, S. A. (2013) Impact of neuronal properties on network coding: roles of spike initiation dynamics and robust synchrony transfer. *Neuron* **78,** 758-772.

Raymond, C. R. (2007) LTP forms 1, 2 and 3: different mechanisms for the "long" in long-term potentiation. *Trends Neurosci* **30,** 167-175.

Regehr, W. G. (2012) Short-term presynaptic plasticity. *Cold Spring Harb Perspect Biol* **4,** a005702.

Regehr, W. G., Carey, M. R. and Best, A. R. (2009) Activity-dependent regulation of synapses by retrograde messengers. *Neuron* **63,** 154-170.

Reimann, M. W., Anastassiou, C. A., Perin, R., Hill, S. L., Markram, H. and Koch, C. (2013) A biophysically detailed model of neocortical local field potentials predicts the critical role of active membrane currents. *Neuron* **79,** 375-390.

Reisel, D., Bannerman, D. M., Schmitt, W. B., Deacon, R. M., Flint, J., Borchardt, T., Seeburg, P. H. and Rawlins, J. N. (2002) Spatial memory dissociations in mice lacking GluR1. *Nat Neurosci* **5,** 868-873.

Remy, S., Beck, H. and Yaari, Y. (2010) Plasticity of voltage-gated ion channels in pyramidal cell dendrites. *Current opinion in neurobiology*.

Reyes, A. D. (2003) Synchrony-dependent propagation of firing rate in iteratively constructed networks in vitro. *Nat Neurosci* **6,** 593-599.

Rizzuto, R. and Pozzan, T. (2006) Microdomains of intracellular Ca2+: molecular determinants and functional consequences. *Physiol Rev* **86,** 369-408.

Robinson, R. B. and Siegelbaum, S. A. (2003) Hyperpolarization-activated cation currents: from molecules to physiological function. *Annual review of physiology* **65,** 453-480.

Rosenkranz, J. A., Frick, A. and Johnston, D. (2009) Kinase-dependent modification of dendritic excitability after long-term potentiation. *J Physiol* **587,** 115-125.

Ross, W. N. (2012) Understanding calcium waves and sparks in central neurons. *Nature reviews. Neuroscience* **13,** 157-168.

Roth-Alpermann, C., Morris, R. G., Korte, M. and Bonhoeffer, T. (2006) Homeostatic shutdown of long-term potentiation in the adult hippocampus. *Proc Natl Acad Sci U S A* **103,** 11039-11044.

Royer, S., Zemelman, B. V., Losonczy, A., Kim, J., Chance, F., Magee, J. C. and Buzsaki, G. (2012) Control of timing, rate and bursts of hippocampal place cells by dendritic and somatic inhibition. *Nat Neurosci* **15,** 769-775.

Sabatini, B. L., Oertner, T. G. and Svoboda, K. (2002) The life cycle of Ca(2+) ions in dendritic spines. *Neuron* **33,** 439-452.

Sakmann, B. (2017) From single cells and single columns to cortical networks: dendritic excitability, coincidence detection and synaptic transmission in brain slices and brains. *Experimental physiology* **102,** 489-521.

Santoro, B., Chen, S., Luthi, A., Pavlidis, P., Shumyatsky, G. P., Tibbs, G. R. and Siegelbaum, S. A. (2000) Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS. *J Neurosci* **20,** 5264-5275.

Santoro, B., Piskorowski, R. A., Pian, P., Hu, L., Liu, H. and Siegelbaum, S. A. (2009) TRIP8b splice variants form a family of auxiliary subunits that regulate gating and trafficking of HCN channels in the brain. *Neuron* **62,** 802-813.

Santoro, B., Wainger, B. J. and Siegelbaum, S. A. (2004) Regulation of HCN channel surface expression by a novel C-terminal protein-protein interaction. *J Neurosci* **24,** 10750-10762.

Sarasso, S., Boly, M., Napolitani, M., Gosseries, O., Charland-Verville, V., Casarotto, S., Rosanova, M., Casali, A. G., Brichant, J. F., Boveroux, P., Rex, S., Tononi, G., Laureys, S. and Massimini, M. (2015) Consciousness and Complexity during Unresponsiveness Induced by Propofol, Xenon, and Ketamine. *Current biology : CB* **25,** 3099-3105.

Schomburg, E. W., Anastassiou, C. A., Buzsaki, G. and Koch, C. (2012) The spiking component of oscillatory extracellular potentials in the rat hippocampus. *J Neurosci* **32,** 11798-11811.

Schreiner, C. E. and Winer, J. A. (2007) Auditory cortex mapmaking: principles, projections, and plasticity. *Neuron* **56,** 356-365.

Schulz, D. J., Goaillard, J. M. and Marder, E. (2006) Variable channel expression in identified single and electrically coupled neurons in different animals. *Nat Neurosci* **9,** 356-362.

Schulz, D. J., Goaillard, J. M. and Marder, E. E. (2007) Quantitative expression profiling of identified neurons reveals cell-specific constraints on highly variable levels of gene expression. *Proc Natl Acad Sci U S A* **104,** 13187-13191.

Scoville, W. B. and Milner, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of neurology, neurosurgery, and psychiatry* **20,** 11-21.

Sehgal, M., Song, C., Ehlers, V. L. and Moyer, J. R., Jr. (2013) Learning to learn - intrinsic plasticity as a metaplasticity mechanism for memory formation. *Neurobiology of learning and memory* **105,** 186-199.

Shadlen, M. N. and Newsome, W. T. (1994) Noise, neural codes and cortical organization. *Current opinion in neurobiology* **4,** 569-579.

Shadlen, M. N. and Newsome, W. T. (1995) Is there a signal in the noise? *Current opinion in neurobiology* **5,** 248-250.

Shadlen, M. N. and Newsome, W. T. (1998) The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J Neurosci* **18,** 3870-3896.

Shah, M. M., Hammond, R. S. and Hoffman, D. A. (2010) Dendritic ion channel trafficking and plasticity. *Trends Neurosci* **33,** 307-316.

Sheffield, M. E. and Dombeck, D. A. (2015) Calcium transient prevalence across the dendritic arbour predicts place field properties. *Nature* **517,** 200-204.

Shouval, H. Z., Bear, M. F. and Cooper, L. N. (2002) A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. *Proc Natl Acad Sci U S A* **99,** 10831-10836.

Siegel, M., Marder, E. and Abbott, L. F. (1994) Activity-dependent current distributions in model neurons. *Proc Natl Acad Sci U S A* **91,** 11308-11312.

Siegelbaum, S. A. (2000) Presynaptic facilitation by hyperpolarization-activated pacemaker channels. *Nat Neurosci* **3,** 101-102.

Sieghart, W. and Sperk, G. (2002) Subunit composition, distribution and function of GABA(A) receptor subtypes. *Curr Top Med Chem* **2,** 795-816.

Sieling, F., Bedecarrats, A., Simmers, J., Prinz, A. A. and Nargeot, R. (2014) Differential roles of nonsynaptic and synaptic plasticity in operant reward learning-induced compulsive behavior. *Current biology : CB* **24,** 941-950.

Sierra, A., Tremblay, M. E. and Wake, H. (2014) Never-resting microglia: physiological roles in the healthy brain and pathological implications. *Front Cell Neurosci* **8,** 240.

Singer, W., Engel, A. K., Kreiter, A. K., Munk, M. H., Neuenschwander, S. and Roelfsema, P. R. (1997) Neuronal assemblies: necessity, signature and detectability. *Trends Cogn Sci* **1,** 252-261.

Sinha, M. and Narayanan, R. (2015) HCN channels enhance spike phase coherence and regulate the phase of spikes and LFPs in the theta-frequency range. *Proc Natl Acad Sci U S A* **112,** E2207-2216.

Sjostrom, P. J. and Nelson, S. B. (2002) Spike timing, calcium signals and synaptic plasticity. *Current opinion in neurobiology* **12,** 305-314.

Sjostrom, P. J., Rancz, E. A., Roth, A. and Hausser, M. (2008) Dendritic excitability and synaptic plasticity. *Physiol Rev* **88,** 769-840.

Skaggs, W. E., McNaughton, B. L., Wilson, M. A. and Barnes, C. A. (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* **6,** 149-172.

Sloviter, R. S. (1991) Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the "dormant basket cell" hypothesis and its possible relevance to temporal lobe epilepsy. *Hippocampus* **1,** 41-66.

Smith, M. A., Ellis-Davies, G. C. and Magee, J. C. (2003) Mechanism of the distance-dependent scaling of Schaffer collateral synapses in rat CA1 pyramidal neurons. *J Physiol* **548,** 245-258.

Soderling, T. R. and Derkach, V. A. (2000) Postsynaptic protein phosphorylation and LTP. *Trends Neurosci* **23,** 75-80.

Softky, W. (1994) Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* **58,** 13-41.

Softky, W. R. (1995) Simple codes versus efficient codes. *Current opinion in neurobiology* **5,** 239-247.

Sporns, O., Tononi, G. and Edelman, G. M. (2000) Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Netw* **13,** 909-922.

Spruston, N. (2008) Pyramidal neurons: dendritic structure and synaptic integration. *Nature reviews. Neuroscience* **9,** 206-221.

Spruston, N., Jaffe, D. B. and Johnston, D. (1994) Dendritic attenuation of synaptic potentials and currents: the role of passive membrane properties. *Trends Neurosci* **17,** 161-166.

Spruston, N., Jaffe, D. B., Williams, S. H. and Johnston, D. (1993) Voltage- and space-clamp errors associated with the measurement of electrotonically remote synaptic events. *Journal of neurophysiology* **70,** 781-802.

Squire, L. R., Stark, C. E. and Clark, R. E. (2004) The medial temporal lobe. *Annu Rev Neurosci* **27,** 279-306.
Srikanth, S. and Narayanan, R. (2015) Variability in State-Dependent Plasticity of Intrinsic Properties during Cell-Autonomous Self-Regulation of Calcium Homeostasis in Hippocampal Model Neurons. *eNeuro* **2,** e0053-0015.2015.
Srivastava, K. H., Holmes, C. M., Vellema, M., Pack, A. R., Elemans, C. P., Nemenman, I. and Sober, S. J. (2017) Motor control by precisely timed spike patterns. *Proc Natl Acad Sci U S A* **114,** 1171-1176.
Staubli, U. and Lynch, G. (1990) Stable depression of potentiated synaptic responses in the hippocampus with 1-5 Hz stimulation. *Brain Res* **513,** 113-118.
Stelling, J., Sauer, U., Szallasi, Z., Doyle, F. J., 3rd and Doyle, J. (2004) Robustness of cellular functions. *Cell* **118,** 675-685.
Stevens, C. F. (1998) A million dollar question: does LTP = memory? *Neuron* **20,** 1-2.
Strogatz, S. H. (2014) *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemisty and Engineering*. Westview Press: Boulder, CO.
Sun, W., Maffie, J. K., Lin, L., Petralia, R. S., Rudy, B. and Hoffman, D. A. (2011) DPP6 establishes the A-type K(+) current gradient critical for the regulation of dendritic excitability in CA1 hippocampal neurons. *Neuron* **71,** 1102-1115.
Sunkin, S. M., Ng, L., Lau, C., Dolbeare, T., Gilbert, T. L., Thompson, C. L., Hawrylycz, M. and Dang, C. (2013) Allen Brain Atlas: an integrated spatio-temporal portal for exploring the central nervous system. *Nucleic acids research* **41,** D996-D1008.
Takahashi, H. and Magee, J. C. (2009) Pathway interactions and synaptic plasticity in the dendritic tuft regions of CA1 pyramidal neurons. *Neuron* **62,** 102-111.
Taxidis, J., Anastassiou, C. A., Diba, K. and Koch, C. (2015) Local Field Potentials Encode Place Cell Ensemble Activation during Hippocampal Sharp Wave Ripples. *Neuron* **87,** 590-604.
Taylor, A. L., Goaillard, J. M. and Marder, E. (2009) How multiple conductances determine electrophysiological properties in a multicompartment model. *J Neurosci* **29,** 5573-5586.
Thattai, M. and van Oudenaarden, A. (2001) Intrinsic noise in gene regulatory networks. *Proceedings of the National Academy of Sciences of the United States of America* **98,** 8614-8619.
Titley, H. K., Brunel, N. and Hansel, C. (2017) Toward a Neurocentric View of Learning. *Neuron* **95,** 19-32.
Tobin, A. E., Van Hooser, S. D. and Calabrese, R. L. (2006) Creation and reduction of a morphologically detailed model of a leech heart interneuron. *Journal of neurophysiology* **96,** 2107-2120.
Tonnesen, J., Katona, G., Rozsa, B. and Nagerl, U. V. (2014) Spine neck plasticity regulates compartmentalization of synapses. *Nat Neurosci* **17,** 678-685.
Tononi, G. and Cirelli, C. (2006) Sleep function and synaptic homeostasis. *Sleep medicine reviews* **10,** 49-62.
Tononi, G. and Edelman, G. M. (1998) Consciousness and complexity. *Science* **282,** 1846-1851.
Tononi, G., Edelman, G. M. and Sporns, O. (1998) Complexity and coherency: integrating information in the brain. *Trends Cogn Sci* **2,** 474-484.
Tononi, G., Sporns, O. and Edelman, G. M. (1994) A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci U S A* **91,** 5033-5037.
Tononi, G., Sporns, O. and Edelman, G. M. (1996) A complexity measure for selective matching of signals by the brain. *Proc Natl Acad Sci U S A* **93,** 3422-3427.
Tononi, G., Sporns, O. and Edelman, G. M. (1999) Measures of degeneracy and redundancy in biological networks. *Proc Natl Acad Sci U S A* **96,** 3257-3262.
Traub, R. D., Miles, R. and Wong, R. K. (1989) Model of the origin of rhythmic population oscillations in the hippocampal slice. *Science* **243,** 1319-1325.
Triesch, J. (2007) Synergies between intrinsic and synaptic plasticity mechanisms. *Neural Comput* **19,** 885-909.
Trimmer, J. S. and Rhodes, K. J. (2004) Localization of voltage-gated ion channels in mammalian brain. *Annual review of physiology* **66,** 477-519.
Tripathy, S. J., Savitskaya, J., Burton, S. D., Urban, N. N. and Gerkin, R. C. (2014) NeuroElectro: a window to the world's neuron electrophysiology data. *Frontiers in neuroinformatics* **8,** 40.
Tsien, J. Z., Huerta, P. T. and Tonegawa, S. (1996) The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell* **87,** 1327-1338.
Tsokas, P., Hsieh, C., Yao, Y., Lesburgueres, E., Wallace, E. J., Tcherepanov, A., Jothianandan, D., Hartley, B. R., Pan, L., Rivard, B., Farese, R. V., Sajan, M. P., Bergold, P. J., Hernandez, A. I., Cottrell, J. E., Shouval, H. Z.,

Fenton, A. A. and Sacktor, T. C. (2016) Compensation for PKMzeta in long-term potentiation and spatial long-term memory in mutant mice. *eLife* **5**.

Turrigiano, G. (2007) Homeostatic signaling: the positive side of negative feedback. *Current opinion in neurobiology* **17,** 318-324.

Turrigiano, G. (2011) Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Annu Rev Neurosci* **34,** 89-103.

Turrigiano, G., Abbott, L. F. and Marder, E. (1994) Activity-dependent changes in the intrinsic properties of cultured neurons. *Science* **264,** 974-977.

Turrigiano, G. G. (1999) Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. *Trends Neurosci* **22,** 221-227.

Turrigiano, G. G. (2008) The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* **135,** 422-435.

Turrigiano, G. G. (2017) The dialectic of Hebb and homeostasis. *Philos Trans R Soc Lond B Biol Sci* **372**.

Turrigiano, G. G. and Nelson, S. B. (2000) Hebb and homeostasis in neuronal plasticity. *Current opinion in neurobiology* **10,** 358-364.

Turrigiano, G. G. and Nelson, S. B. (2004) Homeostatic plasticity in the developing nervous system. *Nature reviews. Neuroscience* **5,** 97-107.

Tytell, E. D., Holmes, P. and Cohen, A. H. (2011) Spikes alone do not behavior make: why neuroscience needs biomechanics. *Current opinion in neurobiology* **21,** 816-822.

Ulens, C. and Siegelbaum, S. A. (2003) Regulation of hyperpolarization-activated HCN channels by cAMP through a gating switch in binding domain symmetry. *Neuron* **40,** 959-970.

Ulens, C. and Tytgat, J. (2001) Functional heteromerization of HCN1 and HCN2 pacemaker channels. *J Biol Chem* **276,** 6069-6072.

Vacher, H., Mohapatra, D. P. and Trimmer, J. S. (2008) Localization and targeting of voltage-dependent ion channels in mammalian central neurons. *Physiol Rev* **88,** 1407-1447.

Vacher, H. and Trimmer, J. S. (2011) Diverse roles for auxiliary subunits in phosphorylation-dependent regulation of mammalian brain voltage-gated potassium channels. *Pflugers Archiv : European journal of physiology* **462,** 631-643.

van Rossum, M. C., Bi, G. Q. and Turrigiano, G. G. (2000) Stable Hebbian learning from spike timing-dependent plasticity. *J Neurosci* **20,** 8812-8821.

Varzi, A. (2016) Mereology. In: *The Stanford Encyclopedia of Philosophy*. Ed. E. N. Zalta. Metaphysics Research Lab, Stanford University: Pala Alto, CA.

Verkhratsky, A. (2002) The endoplasmic reticulum and neuronal calcium signalling. *Cell Calcium* **32,** 393-404.

Verkhratsky, A. and Steinhauser, C. (2000) Ion channels in glial cells. *Brain Res Brain Res Rev* **32,** 380-412.

Vetere, G., Kenney, J. W., Tran, L. M., Xia, F., Steadman, P. E., Parkinson, J., Josselyn, S. A. and Frankland, P. W. (2017) Chemogenetic Interrogation of a Brain-wide Fear Memory Network in Mice. *Neuron* **94,** 363-374 e364.

Vogelstein, J. T., Park, Y., Ohyama, T., Kerr, R. A., Truman, J. W., Priebe, C. E. and Zlatic, M. (2014) Discovery of brainwide neural-behavioral maps via multiscale unsupervised structure learning. *Science* **344,** 386-392.

Volterra, A., Liaudet, N. and Savtchouk, I. (2014) Astrocyte Ca(2)(+) signalling: an unexpected complexity. *Nature reviews. Neuroscience* **15,** 327-335.

Wagner, A. (2005) Distributed robustness versus redundancy as causes of mutational robustness. *Bioessays* **27,** 176-188.

Wagner, A. (2008) Robustness and evolvability: a paradox resolved. *Proceedings. Biological sciences / The Royal Society* **275,** 91-100.

Wang, H. and Wagner, J. J. (1999) Priming-induced shift in synaptic plasticity in the rat hippocampus. *Journal of neurophysiology* **82,** 2024-2028.

Wang, X. J. (2010) Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol Rev* **90,** 1195-1268.

Wang, X. J. and Buzsaki, G. (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J Neurosci* **16,** 6402-6413.

Wang, Z., Xu, N., Wu, C., Duan, S. and Poo, M. (2003) Bidirectional changes in spatial dendritic integration accompanying long-term synaptic modifications. *Neuron* **37,** 463-472.

Watanabe, S., Hoffman, D., Migliore, M. and Johnston, D. (2002) Dendritic K+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. *Proc Natl Acad Sci USA* **99,** 8366-8371.

Weaver, C. M. and Wearne, S. L. (2008) Neuronal firing sensitivity to morphologic and active membrane parameters. *PLoS computational biology* **4,** e11.

Weng, G., Bhalla, U. S. and Iyengar, R. (1999) Complexity in biological signaling systems. *Science* **284,** 92-96.

Wenthold, R. J., Prybylowski, K., Standley, S., Sans, N. and Petralia, R. S. (2003) Trafficking of NMDA receptors. *Annual review of pharmacology and toxicology* **43,** 335-358.

Whitacre, J. and Bender, A. (2010) Degeneracy: a design principle for achieving robustness and evolvability. *J Theor Biol* **263,** 143-153.

Whitacre, J. M. (2010) Degeneracy: a link between evolvability, robustness and complexity in biological systems. *Theoretical biology & medical modelling* **7,** 6.

White, L. E. and Fitzpatrick, D. (2007) Vision and cortical map development. *Neuron* **56,** 327-338.

Whitlock, J. R., Heynen, A. J., Shuler, M. G. and Bear, M. F. (2006) Learning induces long-term potentiation in the hippocampus. *Science* **313,** 1093-1097.

Wills, T. J., Lever, C., Cacucci, F., Burgess, N. and O'Keefe, J. (2005) Attractor dynamics in the hippocampal representation of the local environment. *Science* **308,** 873-876.

Wilson, M. A. and McNaughton, B. L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* **265,** 676-679.

Woo, N. H., Duffy, S. N., Abel, T. and Nguyen, P. V. (2003) Temporal spacing of synaptic stimulation critically modulates the dependence of LTP on cyclic AMP-dependent protein kinase. *Hippocampus* **13,** 293-300.

Yasuda, R., Nimchinsky, E. A., Scheuss, V., Pologruto, T. A., Oertner, T. G., Sabatini, B. L. and Svoboda, K. (2004) Imaging calcium concentration dynamics in small neuronal compartments. *Science's STKE : signal transduction knowledge environment* **2004,** pl5.

Yeung, L. C., Shouval, H. Z., Blais, B. S. and Cooper, L. N. (2004) Synaptic homeostasis and input selectivity follow from a calcium-dependent plasticity model. *Proc Natl Acad Sci U S A* **101,** 14943-14948.

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'Shea, D. J., Sohal, V. S., Goshen, I., Finkelstein, J., Paz, J. T., Stehfest, K., Fudim, R., Ramakrishnan, C., Huguenard, J. R., Hegemann, P. and Deisseroth, K. (2011) Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* **477,** 171-178.

Ylinen, A., Bragin, A., Nadasdy, Z., Jando, G., Szabo, I., Sik, A. and Buzsaki, G. (1995a) Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J Neurosci* **15,** 30-46.

Ylinen, A., Soltesz, I., Bragin, A., Penttonen, M., Sik, A. and Buzsaki, G. (1995b) Intracellular correlates of hippocampal theta rhythm in identified pyramidal cells, granule cells, and basket cells. *Hippocampus* **5,** 78-90.

Yu, R. C., Pesce, C. G., Colman-Lerner, A., Lok, L., Pincus, D., Serra, E., Holl, M., Benjamin, K., Gordon, A. and Brent, R. (2008) Negative feedback that improves information transmission in yeast signalling. *Nature* **456,** 755-761.

Yuan, L.-L., Adams, J. P., Swank, M., Sweatt, J. D. and Johnston, D. (2002) Protein kinase modulation of dendritic K+ channels in hippocampus involves a mitogen-activated protein kinase pathway. *J Neurosci* **22,** 4860-4868.

Yuste, R. and Bonhoeffer, T. (2001) Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu Rev Neurosci* **24,** 1071-1089.

Zamanillo, D., Sprengel, R., Hvalby, O., Jensen, V., Burnashev, N., Rozov, A., Kaiser, K. M., Koster, H. J., Borchardt, T., Worley, P., Lubke, J., Frotscher, M., Kelly, P. H., Sommer, B., Andersen, P., Seeburg, P. H. and Sakmann, B. (1999) Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning. *Science* **284,** 1805-1811.

Zemankovics, R., Kali, S., Paulsen, O., Freund, T. F. and Hajos, N. (2010) Differences in subthreshold resonance of hippocampal pyramidal cells and interneurons: the role of h-current and passive membrane characteristics. *J Physiol* **588,** 2109-2132.

Zenke, F., Gerstner, W. and Ganguli, S. (2017) The temporal paradox of Hebbian learning and homeostatic plasticity. *Current opinion in neurobiology* **43,** 166-176.

2723 Zhang, W. and Linden, D. J. (2003) The other side of the engram: experience-driven changes in neuronal
2724 intrinsic excitability. *Nature reviews. Neuroscience* **4,** 885-900.
2725 Zolles, G., Wenzel, D., Bildl, W., Schulte, U., Hofmann, A., Muller, C. S., Thumfart, J. O., Vlachos, A., Deller, T.,
2726 Pfeifer, A., Fleischmann, B. K., Roeper, J., Fakler, B. and Klocker, N. (2009) Association with the
2727 auxiliary subunit PEX5R/Trip8b controls responsiveness of HCN channels to cAMP and adrenergic
2728 stimulation. *Neuron* **62,** 814-825.
2729 Zorec, R., Araque, A., Carmignoto, G., Haydon, P. G., Verkhratsky, A. and Parpura, V. (2012) Astroglial
2730 excitability and gliotransmission: an appraisal of Ca2+ as a signalling route. *ASN neuro* **4**.
2731 Zucker, R. S. (1989) Short-term synaptic plasticity. *Annu Rev Neurosci* **12,** 13-31.
2732 Zucker, R. S. (1999) Calcium- and activity-dependent synaptic plasticity. *Current opinion in neurobiology* **9,**
2733 305-313.
2734 Zucker, R. S. and Regehr, W. G. (2002) Short-term synaptic plasticity. *Annual review of physiology* **64,** 355-405.
2735
2736

FIGURE LEGENDS

Figure 1. Degeneracy in the emergence of a function and its robustness to external perturbation across multiple scales of analysis. (A) Representation of multiple scales of analysis in neuroscience. The size (large and small) of the scale of analysis is representative of size of the constitutive components in that scale (Churchland and Sejnowski, 1992; Churchland and Sejnowski, 1988). (B) Disparate combinations of parameters in a specified scale of analysis could result in similar function in a larger scale of analysis. Each red circle in the smaller scale of analysis represents a combination of parameters that results in a specified function in large analysis scale, also represented by red circles there. The enclosing black circle in the larger scale represents experimentally observed variability in the function that is being assessed. On the other hand, the black circle in the smaller scale illustrates that robust functionality in the larger scale could be achieved even with small local perturbations in the parametric space. Larger perturbations beyond the black circle, however, would not yield robust functionality. The presence of multiple clusters of red circles in the smaller scale represents degeneracy, where similar functionality is achieved if parameters are within any of those multiple clusters. (C) Disparate combinations of parameters could compensate for functional impairment caused by external perturbation. *Left*, External perturbation results in the observed function in the larger scale of analysis switching from the baseline (red circles) to a perturbed state (blue circles). *Center*, In response, parameters in a smaller scale of analysis could undergo any of the several transitions, represented by green arrows, towards achieving functional homeostasis. Red circles represents the valid baseline parameters before perturbation, and green circles represent the state after the homeostatic response. *Right*, As a consequence of this homeostatic response involving

2760 any of the several disparate combinations of parameters, the system returns back to its baseline
2761 functionality (red circles).
2762
2763 **Figure 2. Qualitative *vs.* quantitative degeneracy.** (A) Qualitative degeneracy, where the
2764 functional goal on which degeneracy is assessed is the expression of resonance, which could be
2765 achieved by the presence of one or more resonating conductances. Depicted are voltage traces
2766 obtained in response to a chirp current injection into neurons containing none, one or two
2767 resonating conductances. The hyperpolarization activated cyclic-nucleotide gated (HCN) and *T*-
2768 type calcium (CaT) are employed as the two example resonating conductances. In a neuron that
2769 expresses two or more resonating conductances (at sufficient densities), resonance ceases to
2770 express only when both resonating conductances are eliminated. The impedance amplitude (left
2771 bottom) and phase profiles (right bottom) are also shown for each color-matched chirp response.
2772 It may be noted that resonance in the amplitude profile and lead in the phase profile are observed
2773 when resonating conductances are expressed individually or together, and synergistically interact
2774 when they are expressed together. (B) Quantitative degeneracy, where the functional goal on
2775 which degeneracy is assessed is the ability to specify a target value of resonance frequency in the
2776 neuron, when a resonating conductance is expressed. Shown are some examples of the disparate
2777 possible routes to achieve quantitative changes to resonance frequency. One set of possibilities
2778 involves altering the properties of the channel mediating resonance (taken to be HCN in this
2779 example) such as its density (Δg_{HCN}), its gating properties (*e.g.*, half-maximal activation voltage,
2780 $\Delta V_{1/2}$) or its kinetics (*e.g.*, activation time constant, $\Delta\tau_{HCN}$). The other set involves introducing
2781 (*e.g.*, *T*-type calcium channels, Δg_{CaT} or *A*-type potassium channels, Δg_{KA}) or altering (e.g.,
2782 change in leak channels Δg_{leak}) other channels that modulate the resonance mediated by the
2783 resonating conductance (whose removal would abolish resonance, $-g_{HCN}$, unless compensated by

the expression of another resonating conductance). (C) In different neurons, the contribution of different channels to any measurement (shown here is resonance frequency, f_R) could be variable. The size of each sphere scales with the quantum of contribution of a given channel (one among HCN, CaT, KA and leak) to f_R in a given neuron (11 neurons are depicted). Traces presented here and associated conclusions are drawn from previous studies (Hutcheon and Yarom, 2000; Narayanan and Johnston, 2007, 2008; Rathour *et al.*, 2016; Rathour and Narayanan, 2012a).

Figure 3. Dissociation between different forms of homeostasis. (A) In different neurons, the contribution of different channels to different measurements (shown here are resonance frequency, f_R, and input resistance, R_{in}) is differential and variable. The size of each sphere scales with the quantum of contribution of a given channel (one among HCN, CaT, KA and leak) to f_R in a given neuron (11 neurons are depicted). It may be noted that in any given neuron, it is not necessary that the contributions of any given channel to f_R and R_{in} need not be equal, even when both f_R and R_{in} are similar across all neurons. Cartoon illustrations are derived from data presented in previous studies (Rathour *et al.*, 2016; Rathour and Narayanan, 2012a, 2014; Srikanth and Narayanan, 2015). (B) Although baseline homeostasis is efficaciously maintained in five different neurons, their responses to an identical perturbation need not necessarily be identical or even similar. The perturbation could be a plasticity-inducing stimulus driven by behavioral experience or by pathological conditions. Cartoon illustration was derived from analyses presented in previous studies (Anirudhan and Narayanan, 2015; O'Leary *et al.*, 2014; Srikanth and Narayanan, 2015).

2808 **Figure 4. Disparate activity-dependent protocols have been employed for the induction of**
2809 **long-term potentiation or depression in hippocampal synapses.** (A–B) Disparate activity-
2810 dependent induction protocols yield long-term potentiation (A) or depression (B) in Schaffer
2811 collateral synapses connecting CA3 pyramidal neurons to CA1 pyramidal neurons. Individual
2812 panels depict cartoon illustrations of induction protocols employed in previous studies (Bi and
2813 Poo, 1998; Christie *et al.*, 1996; Dudek and Bear, 1992; Huber *et al.*, 2000; Larson *et al.*, 1986;
2814 Magee and Johnston, 1997). AP: action potential; STIM: stimulation leading to postsynaptic
2815 potentials; IPI: inter pulse interval. A subset of similar or additional protocols that have been
2816 employed in the induction of potentiation or depression in hippocampal synapses may be found
2817 here: (Basu *et al.*, 2016; Bittner *et al.*, 2015; Bittner *et al.*, 2017; Bliss and Collingridge, 1993;
2818 Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973; Chevaleyre *et al.*, 2006; Christie *et al.*,
2819 1994; Dan and Poo, 2006; Dudek and Bear, 1992, 1993; Dudman *et al.*, 2007; Larkman and
2820 Jack, 1995; Lynch *et al.*, 1983; Lynch *et al.*, 1977; Malenka *et al.*, 1992; Mulkey and Malenka,
2821 1992; Raymond, 2007; Regehr *et al.*, 2009; Staubli and Lynch, 1990; Takahashi and Magee,
2822 2009).
2823
2824 **Figure 5. Disparate cellular and molecular mechanisms govern the strength and kinetics of**
2825 **cytosolic calcium influx.** (A) Different protocols have been employed for the induction of LTP
2826 in hippocampal synapses. Whereas references for the first four of these protocols are provided in
2827 Fig. 4, the last three are derived from protocols in these references (Basu *et al.*, 2016; Bittner *et*
2828 *al.*, 2015; Bittner *et al.*, 2017; Dudman *et al.*, 2007; Hanse and Gustafsson, 1994; Huang and
2829 Malenka, 1993; Huber *et al.*, 1995; Lin *et al.*, 2008; Otmakhov *et al.*, 2004; Roth-Alpermann *et*
2830 *al.*, 2006; Takahashi and Magee, 2009). (B) Protocols shown in (A) typically elicit postsynaptic
2831 calcium influx through synergistic interactions between disparate constitutive components.

2832 Although only postsynaptic components are depicted here, it should be noted that presynaptic
2833 components, including excitability-, calcium- and release-regulating mechanisms, also would
2834 control the postsynaptic calcium influx through regulation of release dynamics and short-term
2835 plasticity. Additionally induction could also be presynaptic. (C) In different neurons, the
2836 contribution of different components to achieve similar strength and kinetics of cytosolic calcium
2837 influx could be variable. The size of each sphere scales with the quantum of contribution of a
2838 given component to cytosolic calcium influx in a given neuron (11 neurons are depicted).
2839 Cartoon representations depicted here are drawn from conclusions arrived in previous studies
2840 (Anirudhan and Narayanan, 2015; Mukunda and Narayanan, 2017).

2841

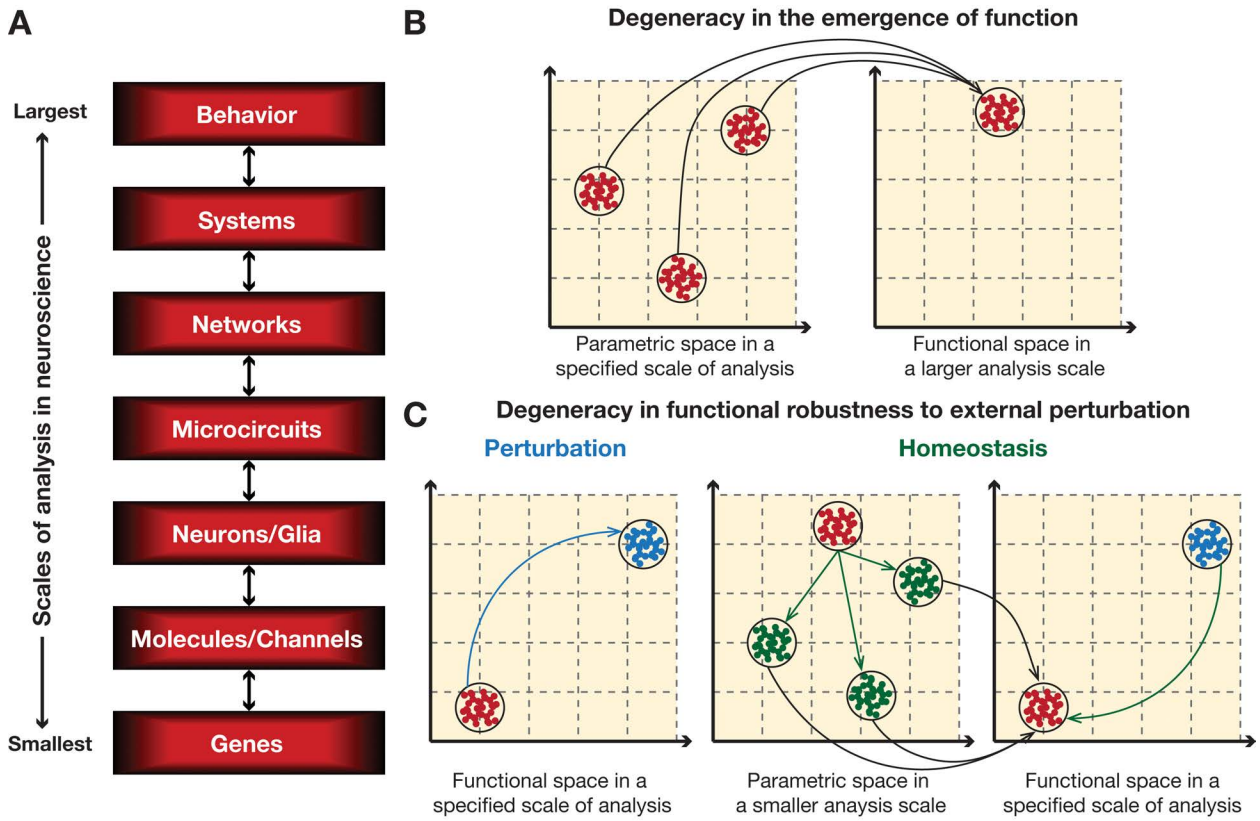
2842 **Figure 6. Disparate signaling cascades with diverse downstream targets are activated**
2843 **following postsynaptic calcium elevation.** Depicted is a tripartite synapse that includes a
2844 presynaptic terminal, a postsynaptic structure and a glial cell. Following the influx of calcium
2845 through disparate sources (see Fig. 5; shown here is only NMDAR for simplicity), several pre-
2846 and post-synaptic signaling cascades could be activated with very different downstream targets.
2847 Retrograde messengers are responsible for intimating the presynaptic terminal about postsynaptic
2848 calcium elevation. Illustration incorporates conclusions from previous studies (Bhalla, 2014;
2849 Bhalla and Iyengar, 1999; Kotaleski and Blackwell, 2010; Manninen *et al.*, 2010; Regehr, 2012;
2850 Regehr *et al.*, 2009).

2851

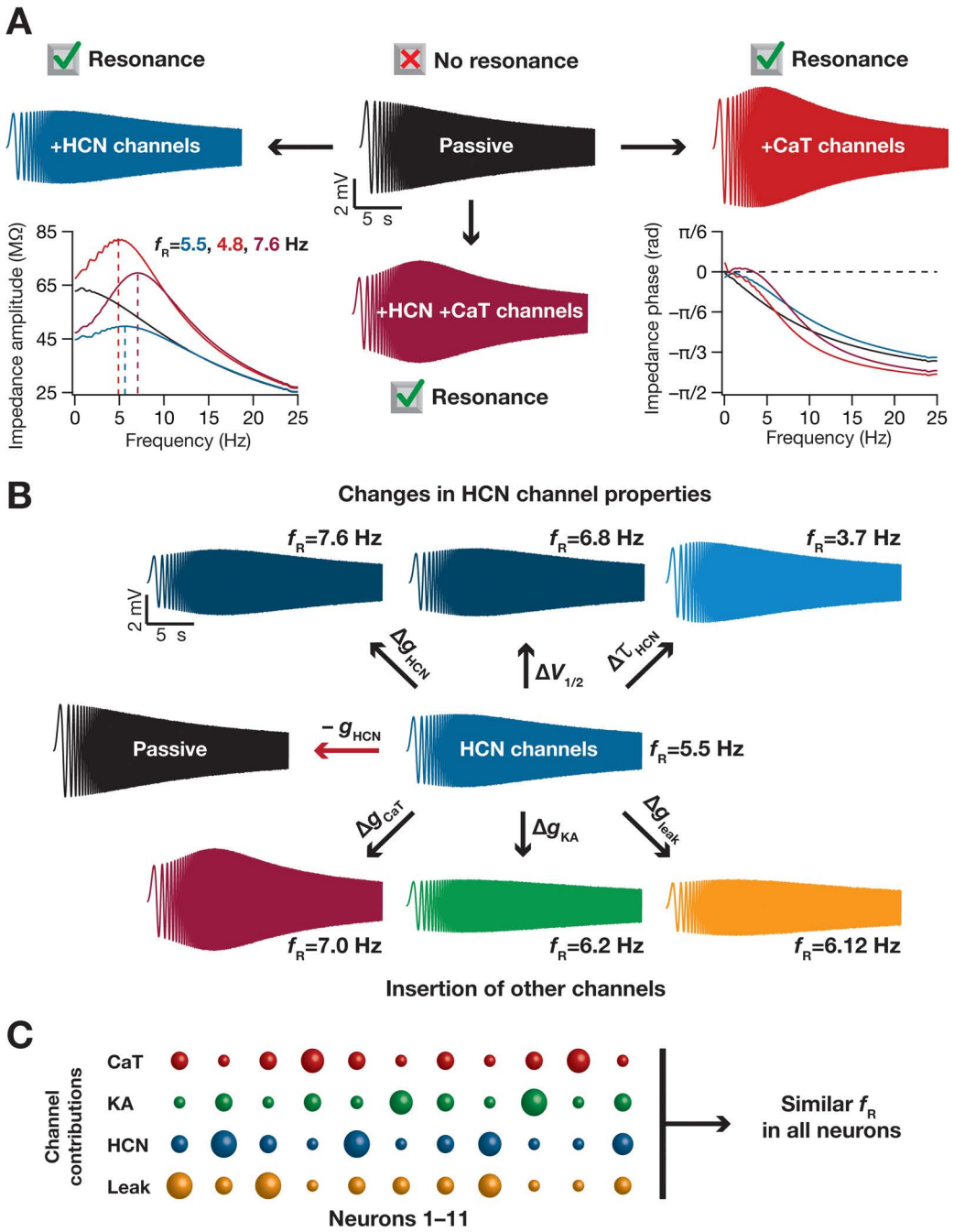
2852 **Figure 7. Disparate mechanisms mediate the expression of short- and long-term synaptic**
2853 **plasticity.** *Left,* Depicted is a tripartite synapse that includes a presynaptic terminal, a
2854 postsynaptic structure and a glial cell. *Right,* Several pre- and post-synaptic mechanisms regulate
2855 synaptic strength, and independent or concomitant long-term changes in any of these

2856 components would result in the expression synaptic plasticity. Plasticity is known to potentially
2857 span all these components and more (Kim and Linden, 2007).
2858
2859 **Figure 8. Disparate forms of synaptic and non-synaptic plasticity are induced through the**
2860 **activation of different signaling cascades triggered by calcium influx regulated by several**
2861 **mechanisms, resulting in multiscale degeneracy in plasticity induction through expression.**
2862 *Left,* Synergistic interactions between several components results in cytosolic calcium influx
2863 following plasticity induction through activity protocols or behavioral experience of pathological
2864 insults. *Center,* Disparate signaling cascades with diverse downstream targets are activated
2865 following postsynaptic calcium elevation. *Right,* The activation of signaling cascades and their
2866 impact on their targets are not just limited to synaptic components, but span a large span of
2867 neuronal and network components. Several forms of synaptic and non-synaptic plasticity express
2868 concomitantly in response to the same protocols or perturbations (Beck and Yaari, 2008;
2869 Johnston *et al.*, 2016; Kim and Linden, 2007; Narayanan and Johnston, 2012).
2870
2871 **Figure 9. Disparate mechanisms with distinct time courses could mediate stability in**
2872 **synaptic learning through metaplasticity.** (A–B) Hebbian synaptic plasticity is inherently
2873 unstable leading to runaway excitation in synaptic structure (A; orange boxes). The Bienenstock-
2874 Cooper–Munro (BCM) rule envisages the existence of a sliding threshold mechanism (B) which
2875 provides a negative feedback loop (B; green boxes) that would preclude runaway excitation by
2876 altering the rules for plasticity. Alteration of plasticity rules has been referred to as metaplasticity
2877 in the literature (Abraham and Bear, 1996; Bienenstock *et al.*, 1982; Cooper and Bear, 2012). (C)
2878 Bidirectional metaplasticity could be mediated by any of the several mechanisms discussed in
2879 Fig. 7–8 with reference to the expression of synaptic and non-synaptic plasticity. (D–E) Similar

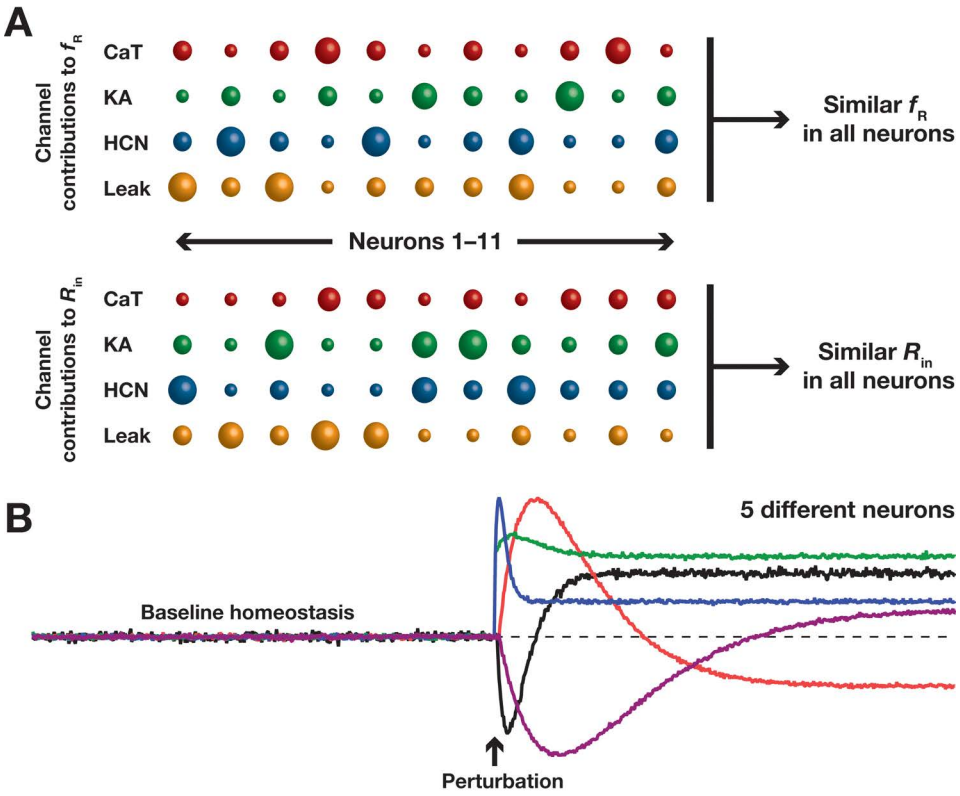
2880 plasticity profiles (D) could be achieved through disparate combinations of constituent parameter
2881 values (E). Cartoon illustrations are derived from conclusions drawn in previous studies
2882 (Abraham, 2008; Abraham and Bear, 1996; Anirudhan and Narayanan, 2015; Hulme *et al.*, 2013;
2883 Sehgal *et al.*, 2013).
2884



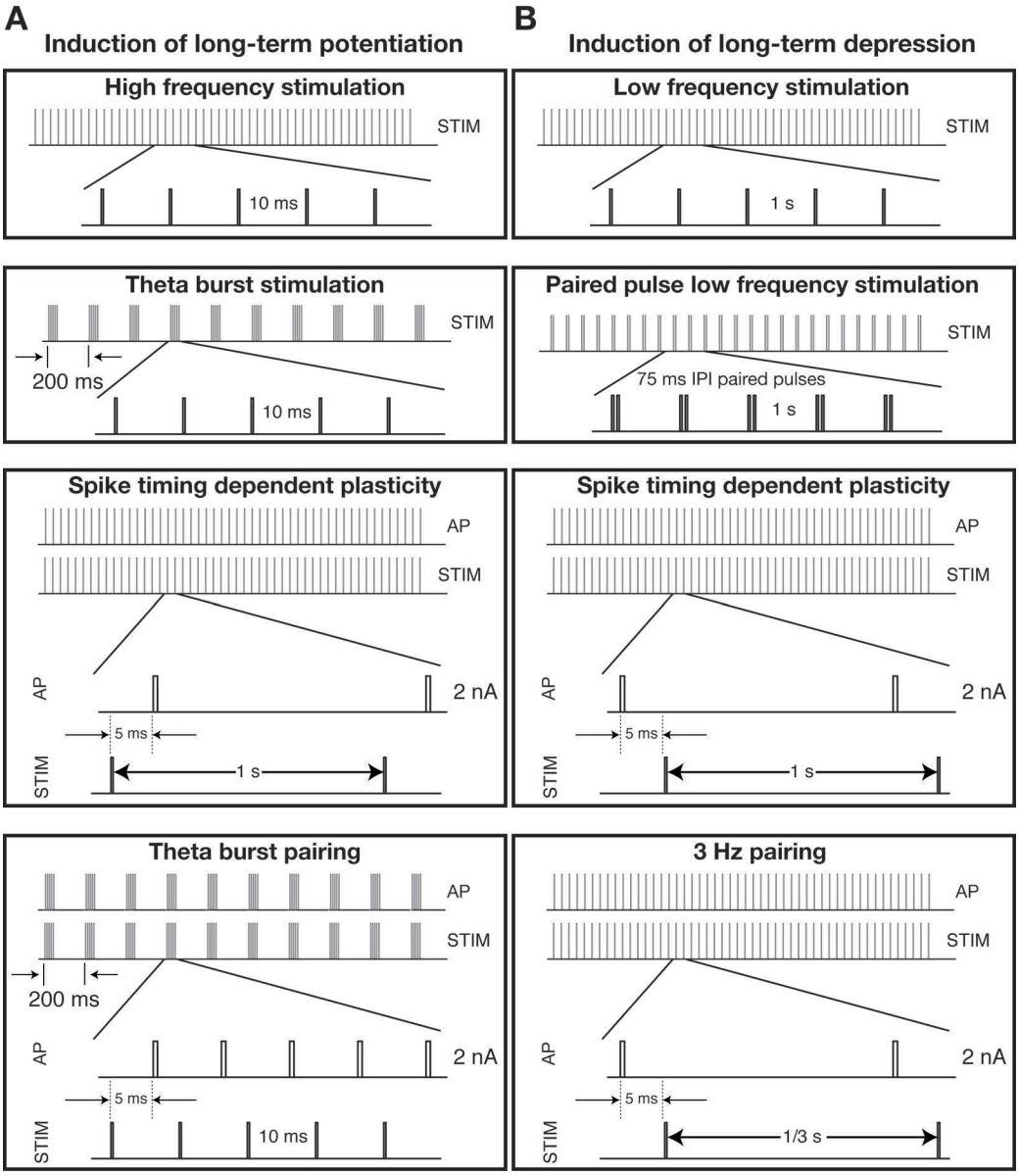
Rathour and Narayanan: Figure 1



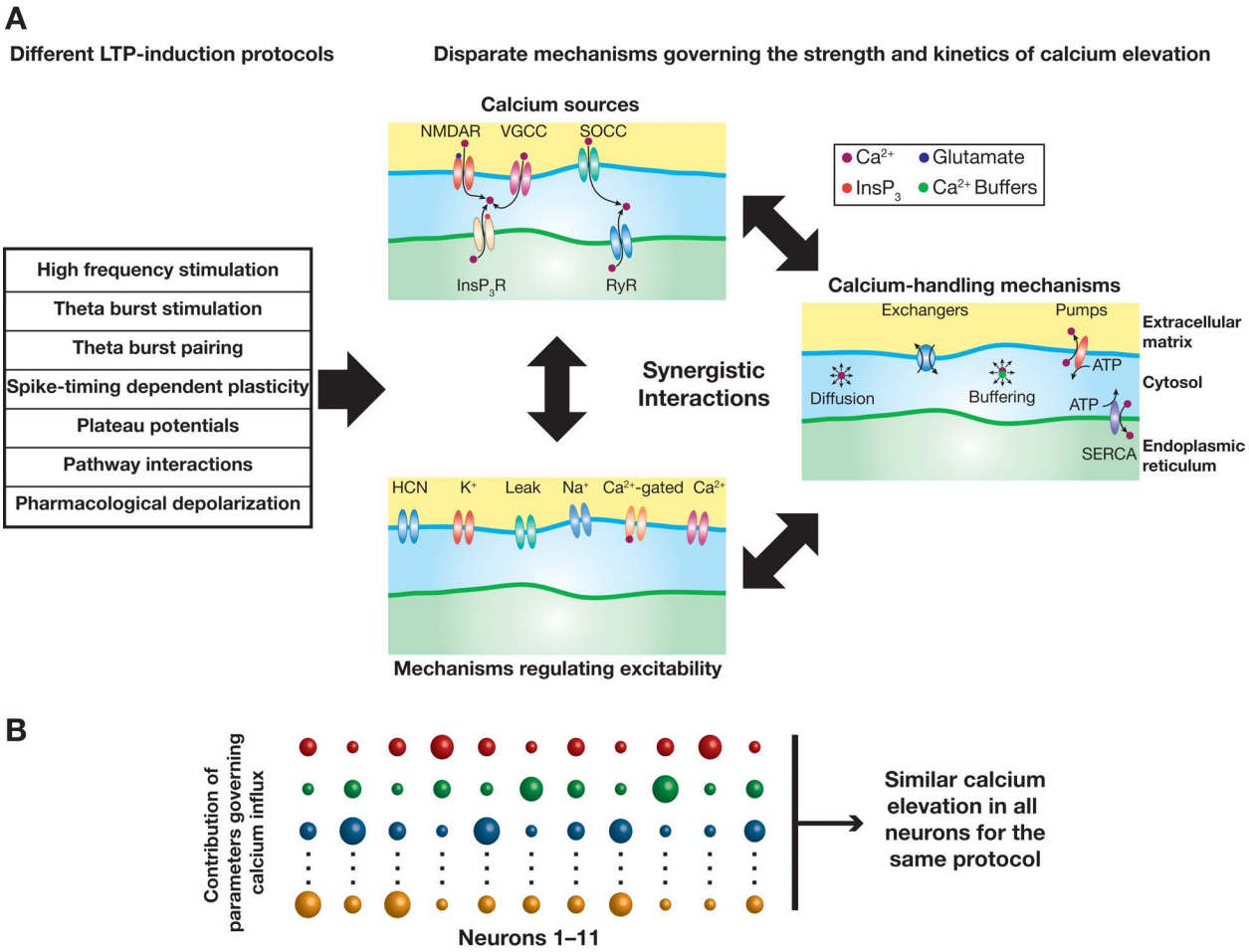
Rathour and Narayanan: Figure 2



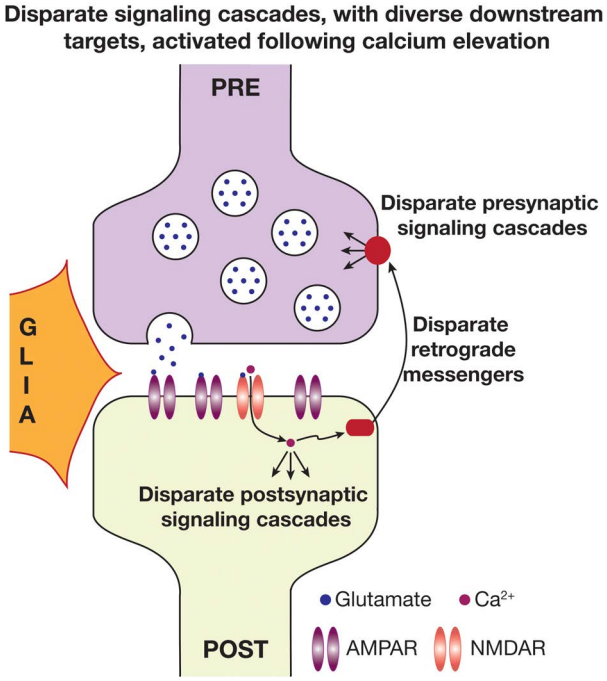
Rathour and Narayanan: Figure 3



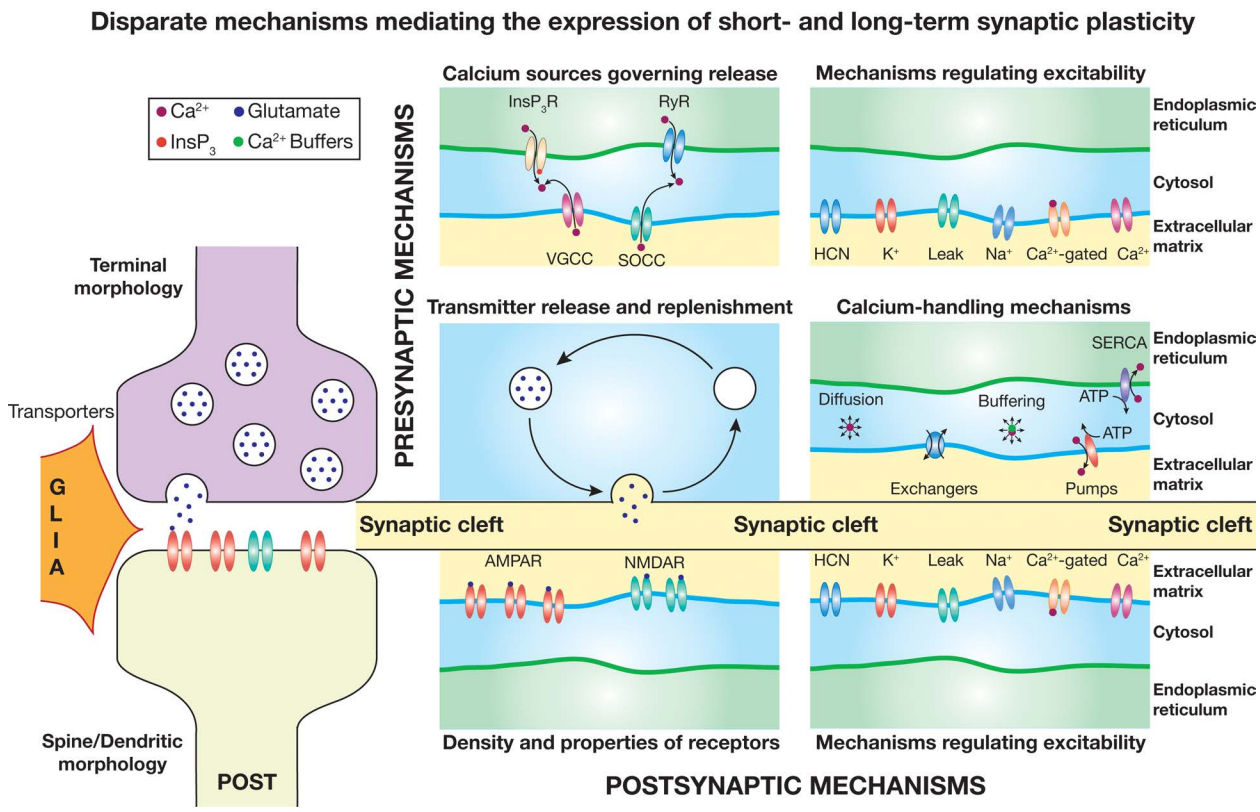
Rathour and Narayanan: Figure 4



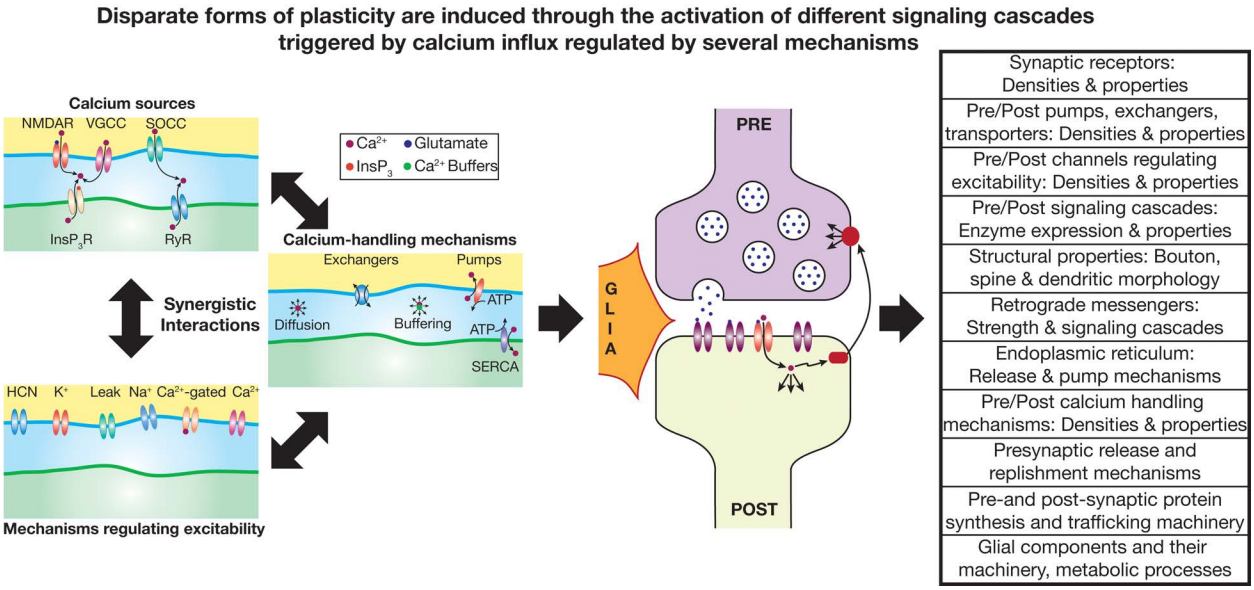
Rathour and Narayanan: Figure 5



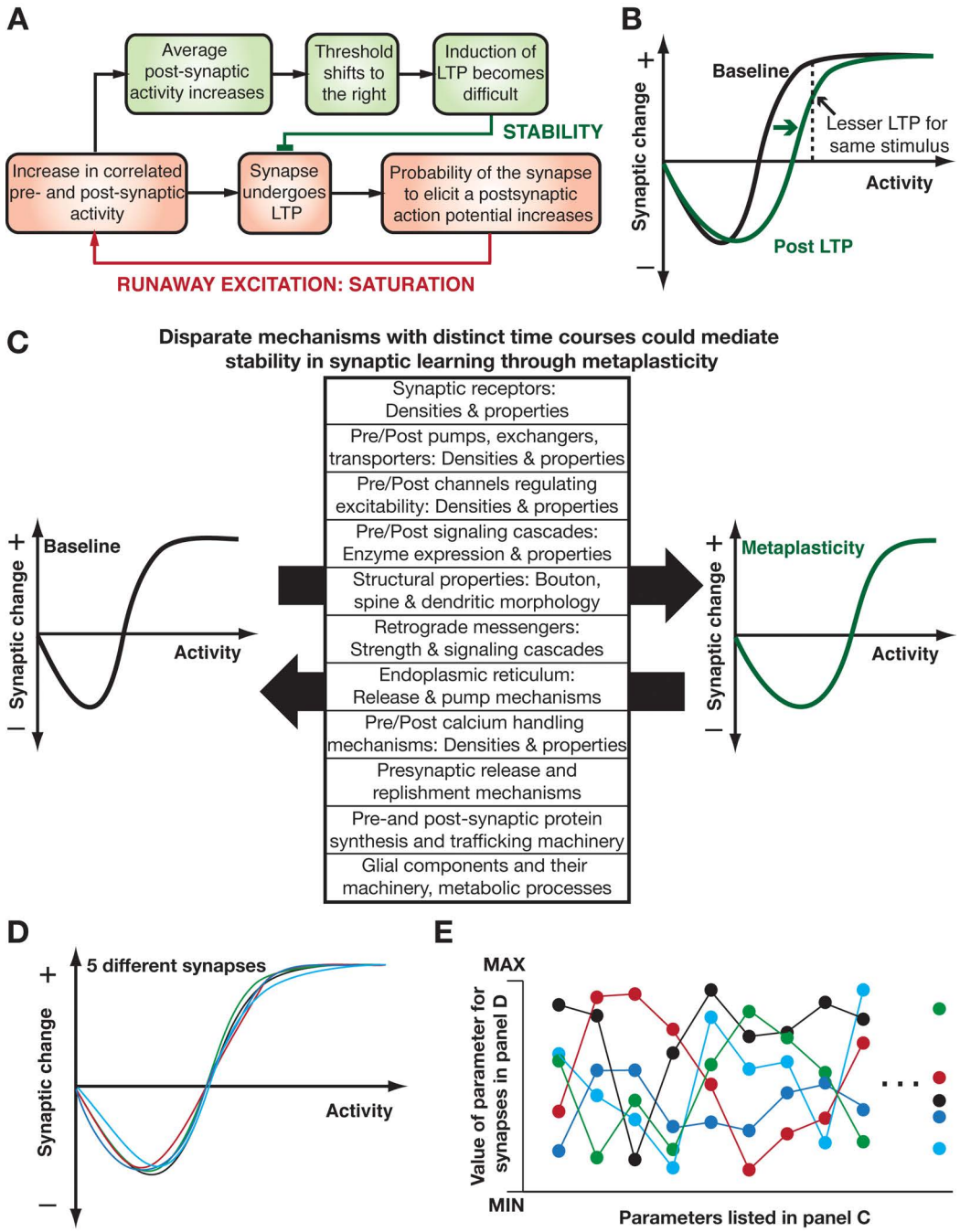
Rathour and Narayanan: Figure 6



Rathour and Narayanan: Figure 7



Rathour and Narayanan: Figure 8



Rathour and Narayanan: Figure 9