CA1 pyramidal cells have diverse biophysical properties, affected by development, experience, and aging

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Abstract

Neuron types (e.g. pyramidal cells) within one area of the brain are often considered homogenous, despite wide variability in their biophysical properties. We review literature demonstrating variability in the electrical activity of CA1 hippocampal pyramidal cells (PCs), including responses to somatic current injection, synaptic stimulation, and spontaneous network-related activity. We describe how responses of CA1 PCs vary with development, experience, and aging. Our goal is to provide a synthesis of the literature for experimentalists studying CA1 PCs, and also to give theorists an idea of the rich diversity of behaviors their models may need to reproduce to accurately represent these cells. We suggest directions for future research, including the use of text and data mining to systematically study cellular heterogeneity in more depth; dynamical systems theory to understand and potentially classify neuron firing patterns; and mathematical modeling to study the interaction between cellular properties and network output.

1 Introduction

Understanding the brain and the activity of its $\sim$86 billion neurons [1] is a daunting task. To facilitate experimentation and analysis, neuroscientists often group neurons into types [2–5]. However, problems with classification arise. It is not clear what are the ideal groupings. Should we group neurons by function, location, morphology, biophysical properties, or some combination? Are these groupings meaningful? Researchers may erroneously assume that cells in one group are relatively homogeneous [6, 7], but what is the extent and role of biophysical heterogeneity?

Neurons are often classified by their electrical activity [8, 9]. However, neurons in the same brain area or with similar morphology may show different firing patterns [10–13], while neurons in different areas or with distinct morphology may have similar activity [13–15]. Neurons can switch between firing patterns depending on conditions [16–18]. In some cases, compensatory changes in connection strengths or regulation of gene expression may counteract variability in firing patterns to maintain normal microcircuit output [19–21]. In other cases, variability in the
biophysical properties of neurons may alter, and even be vital, for network function [22]. The potential functional significance of cellular heterogeneity suggests it deserves more consideration than it has historically received. The hippocampus provides an ideal structure to consider functional cellular heterogeneity, given the abundance of data from this area, as well as its critical role in learning and memory [23–25]. Hippocampal pyramidal cells (PCs) have been studied extensively using a variety of stimulation protocols and tasks [26–28]. PCs display diverse electrical behaviors, even under seemingly identical experimental conditions [29, 30], leading some to suggest the existence of distinct subpopulations [31].

What are these subpopulations? How should experimental scientists classify PC firing behaviors? How should computational scientists decide which firing behaviors models must reproduce? Are the biophysical properties of PCs relatively stable, or do they vary under different conditions, such as developmental stages, experience, and aging? We review the literature on electrical activity in CA1 PCs. We synthesize information to provide an overview of the behavioral repertoire of CA1 PCs, both intrinsically and in the context of network activity. We describe results, some conflicting, on how the biophysical properties of CA1 PCs change under different conditions. Finally, we suggest several directions for future research, including text and data mining of the literature to further explore and quantify the extent of cellular heterogeneity within and across neuron types [4, 32]; use of dynamical systems theory to study and potentially classify firing behaviors [33]; and use of mathematical modeling to investigate the effects of cellular heterogeneity on network output [34].

2 Responses to somatic current injection

A common experimental protocol to study neuron responses involves injecting pulses of current into the soma to characterize resulting changes in membrane potential. This protocol is advantageous because the precise timing and level of stimulation is known, allowing temporal aspects of responsiveness such as onset, offset, and adaptation to be quantified.

2.1 Spike latency

In response to current injection, CA1 PCs can begin spiking \(\sim 20\) ms after stimulus onset [35–37]. Short spike latencies in PCs have been shown, though not quantified, in several studies [38–46]. However, other studies have recorded PCs with spiking delays lasting from around 100 milliseconds (ms) to seconds [47–52]. In a single study, CA1 PCs were recorded with delays ranging from \(\sim 10-110\) ms [53]. In contrast to studies that report no delay, some studies describe long spike latencies as ‘characteristic’ [49] or ‘typical’ [52] of CA1 PC firing. Some of the variability in spike latency is shown in Fig. 1.

Spike latency depends in part on the amplitude of injected current [29, 30, 35, 48, 55]. Aiken et al. report that delay to first spike decreases from 20 to 5 ms as stimulus amplitude increases by 400 pA. Although their baseline delay is longer, Chu et al. similarly report that spike latency decreases by nearly 100 ms as stimulation amplitude increases by 50 pA [48]. Response latency decreases with increasing stimulation amplitude regardless of whether PCs fire single spikes or bursts [29, 30, 55].
Figure 1: Variability in delayed firing in CA1 PCs. A. CA1 PC with a firing delay of more than 500 ms. The long firing delay is eliminated by an A-type K$^+$ channel blocker. From [52], used with permission. B. CA1 PC with a firing delay of less than 100 ms. The $I_H$ enhancer SKF83959 increases the delay (gray trace). From [48], reused under the terms of the Creative Commons Attribution (CC BY) license. C. CA1 PCs with a short firing delay, which is unaffected by the metabotropic glutamate receptor agonist DHPG. From [54], CC BY. D. Firing delay is reduced in PCs undergoing a conditioning protocol. Unpaired stimuli do not reduce firing delay. From [53], CC BY.

Spike latency also depends on biophysical properties of PCs, such as availability of K$^+$ channels mediating transmembrane currents. Pharmacological studies suggest that slowly-inactivating D-type K$^+$ channels are responsible for producing long firing delays in CA1 PCs [49, 51, 52]. Spike latency decreases from hundreds to tens of ms when $I_D$ is blocked [52]. More recent studies, however, argue that A-type K$^+$ channels, specifically those encoded by Kv4.2, play a crucial role in delayed firing [36, 53, 56]. Average delay to first spike observed in PCs increases by hundreds of ms when Kv4.2 currents are potentiated by active CaMKII [56]. Kv4 channel overexpression results in spike latencies tens of ms longer than in controls [36]. Loss of the accessory protein DPPX causes the voltage sensitivity of Kv4 channels to shift, leaving more channels available for activation at rest and increasing firing delay in PCs [37]. PCs receiving paired somatic depolarization and synaptic stimulation show decreased spike latency mediated by a reduction in A-type channel availability [53].

The hyperpolarization-activated cation current ($I_h$) also affects firing delay in PCs. Application of the $I_h$ blocker ZD7288 causes hyperpolarization of the cell and produces a spike latency of hundreds of ms not seen in controls [57]. In contrast, injecting current to counteract ZD7288-
induced hyperpolarization and hold the cell at a normal resting potential eliminates firing delay and causes increased excitability. These results demonstrate the importance of testing various initial conditions when evaluating effects of a given manipulation and the role of different currents. It is likely not one but multiple currents contribute to spike latency, depending on cellular conditions.

2.2 Spike frequency adaptation

Spike frequency adaptation in response to prolonged current stimulation is often hailed as a feature of CA1 PC firing. However, the degree of adaptation seen in these cells varies. In some recordings, PCs adapt strongly and cease firing before the end of a current pulse lasting hundreds of ms [40, 45, 58]. In other recordings, adaptation slows but does not terminate firing [36, 39, 41, 53, 59]. In some PCs, little to no adaptation is seen [47, 51, 60, 61].

The degree of adaptation depends in part on stimulus strength [41, 58, 62]. Bianchi et al. report that PCs fire for the duration of a 1 s pulse and spike number increases linearly for moderate stimulation amplitudes (200-900 pA), but decreases at higher amplitudes (over 900 pA) [62]. Other studies report only an increase in spike number with no firing cessation even up to 1.3 nA [63]. The change in adaptation at higher stimulus amplitudes seen in some PCs can cause early spikes to cluster into burst-like firing [41, 64].

Adaptation in PCs shows both a Ca$^{2+}$-dependent component [38, 58, 65] involving L-type channels [42], and a non-Ca$^{2+}$-dependent component [58]. Adaptation may be divided into early and late phases, with distinct currents contributing to each phase [66–68]. Gu et al. report a role for M and H channels in early adaptation [57]. Large-conductance Ca$^{2+}$-dependent K$^+$ (BK) channels contribute to early adaptation for high- but not low-frequency firing [66]. There is debate about which currents are responsible for late-phase adaptation. Some studies report a role for small-conductance Ca$^{2+}$-dependent K$^+$ (SK) channels [43, 45, 67]. Pedarzani et al. found that the SK channel activator 1-EBIO produces such strong adaptation that PCs go from tonic to single spikers [43]. Gu et al. argue, however, that SK channels can slow firing in PCs if necessary, but are not recruited during typical activity [41]. Instead, they show a strong contribution of M channels to adaptation. Other studies confirm that M channels contribute to late adaptation [35], and underlie stronger adaptation in dorsal versus ventral PCs [69]. It is likely both Ca$^{2+}$-dependent K$^+$ and M currents produce adaptation, depending on conditions [58, 65].

Adaptation in CA1 PCs varies with experience, learning, and aging. Repeatedly stimulating neurons with square-pulse currents leads to a short-term increase in adaptation [39]. Coincident pre- and postsynaptic stimulation decreases adaptation [70]. Firing frequency increases and adaptation decreases in rats exposed to an enriched environment [59, 71]. Rats trained on an inhibitory avoidance task show decreased adaptation for up to 24 hours, while animals exposed to the environment but not trained show a decrease lasting only 1 hour [72]. Similar results are seen in rabbits, where conditioning decreases adaptation 1 hour after training [73]. Adaptation increases with aging [40, 42, 46, 74] and is associated with impaired learning [46, 74].

2.3 Afterhyperpolarizations

AP repolarization and spike frequency adaptation in PCs are mediated by after-hyperpolarizations (AHPs) (see Fig. 2), often divided into fast (1-5 ms), medium (tens to hundreds of ms), and slow
(hundreds of ms to seconds) components [57, 65, 68]. AHPs are distinguished not only by their timescales, but also by their underlying currents and effects on PC firing.

fAHPs

The fAHP is mediated by a Ca$^{2+}$-dependent BK current. Ca$^{2+}$-free medium, Ca$^{2+}$ chelators, and Ca$^{2+}$ channel blockers reduce or eliminate the fAHP [30, 44, 65, 75]. Application of BK channel blockers reduces the fAHP, slows AP repolarization, and produces prolonged spikes in PCs [44, 60, 66, 76]. During high-frequency (e.g. 100 Hz) firing, spike broadening between the first and third spikes of a train in response to current injection is eliminated by BK channel blockers when all spikes become broadened [44]. This slows high-frequency repetitive firing and reduces early adaptation [66]. BK channels play a greater role in the early rather than late phase of the response due to channel inactivation [44, 66]. Interestingly, low-frequency (e.g. 13 Hz) firing does not produce spike broadening and is unaffected by BK channel block [44, 66]. Spike prolongation increases as firing frequency goes from 10 to 150 Hz, indicating the increasing influence of BK currents [44]. Repeated synaptic stimulation decreases the somatically-induced fAHP [60]. In both young and aged rats, learning decreases fAHP amplitude relative to controls [77]. There is no difference between fAHPs recorded in PCs from young versus aged animals.

mAHPs

The currents producing the mAHP in CA1 PCs are under debate. Some studies implicate SK channels [43, 45, 78–80]. Outward currents underlying the mAHP show Ca$^{2+}$ dependence [78, 80, 81], and a single-channel conductance of 17-31 pS [78], similar to SK channels in other systems [82]. SK channel blockers reduce the mAHP [43, 79–81], causing increased PC excitability and improved plasticity and spatial memory [45]. SK agonists augment the mAHP and reduce excitability, converting some PCs from tonic to single spikers [43]. Studies in transgenic mice have identified SK2-encoded channels as mediating the mAHP [83].

Other studies suggest SK channels do not contribute to the mAHP in CA1 PCs. Gu et al. report that only when other channels are blocked is a SK-related portion of the mAHP revealed [41, 57]. Under control conditions and at normal resting potential, the mAHP is reduced by the M channel blocker XE991[41, 57], which increases firing frequency and converts PCs from tonic spikers to bursters [57]. At hyperpolarized membrane potentials, the mAHP is reduced by the H channel blocker ZD7288. Thus, $I_M$ and $I_h$ may underlie mAHPs, depending on cellular conditions [57]. Additional studies confirm $I_M$ contributes to the mAHP in CA1 PCs [65, 69]. Dorsal PCs are more sensitive than ventral PCs to M current blockers, including a larger reduction in the mAHP current [69]. Chen et al. suggest that SK and M channels serve supporting roles [84], as seen in other hippocampal cells [85].

Effects of experience and aging on mAHPs vary. Some studies show age-related increases in the mAHP, beginning in rats at 12 months of age and worsening at 23 months [40]. Other studies report no age differences in the mAHP [46]. For some tasks, learning in young animals decreases mAHP amplitude, while middle-aged animals classified as learning-impaired show no change [86]. In other tasks, the mAHP does not differ with age, irrespective of learning outcome [46]. In mice, mAHP amplitude varies with genetic background [31]. However, heterogeneity in AHP shape also exists independent of genetic background and is found throughout CA1 [31].
Figure 2: Afterhyperpolarizations (AHPs) in CA1 PCs. A. Responses of CA1 PCs to short, single pulses (left) or a train of pulses (right), showing fast (f), medium (m), and slow (s) AHPs. From [92]. B. In wild-type CA1 PCs, the intermediate \( \text{Ca}^{2+} \)-dependent \( K^+ \) channel blocker TRAM-34 reduces the sAHP. In KCa3.1 null mice, the sAHP is reduced and TRAM-34 has no additional effect. From [93]. C. The sAHP affects cellular excitability. CA1 PCs stimulated by a pulse train cease firing before the end of the train due to a large sAHP. The sAHP is reduced in PCs treated with TRAM-34 and the cells keep firing [93]. D. Aged CA1 PCs show larger AHPs than young cells, which is reduced by the diabetes drug pioglitazone (PIO). E. In contrast to results from [93], [94] found no effects of TRAM-34 on the sAHP. All figures reused under the CC BY license.

**sAHPs**

The sAHP is \( \text{Ca}^{2+} \)-dependent [38, 58, 65, 81, 87, 88], and reduced by L-type \( \text{Ca}^{2+} \) channel blockers [30, 42, 81, 89] and interference with intracellular stores [40, 81, 90]. L-type \( \text{Ca}^{2+} \) channels may be coupled to ryanodine receptors on the stores [40, 91]. The sAHP is likely mediated by \( \text{Ca}^{2+} \)-dependent \( K^+ \) channels, though its molecular identity is still under investigation [92]. sAHP channel conductance is small [92], ruling out BK channels. SK channels are unlikely to be involved either, since the sAHP is unaffected by SK-specific blockers [57, 65, 80, 81]. Transgenic studies in mice have ruled out a role for SK1-3 [83], and suggest the sAHP is mediated by intermediate-conductance \( \text{Ca}^{2+} \)-dependent KCa3.1 channels [93].

Experience, learning, and aging affect sAHPs. Repeated square-pulse stimulation increases sAHP amplitude and duration, producing decreased excitability over time [39]. Aged animals show larger sAHPs than young animals [40, 74, 77, 86, 89, 90, 95, 96]. Environmental enrichment or exercise decreases sAHP amplitude [59, 97], abolishing the difference between aged and young...
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animals [97]. In ventral CA1 PCs in young rats, exposure to an environment reduces sAHPs for up to 1 hour, whereas inhibitory training leads to a 24-hour reduction [72]. Dorsal CA1 PCs show a longer effect latency, with sAHP reduction only after 24 hours. Eyeblink and fear conditioning protocols also decrease sAHPs, but only in successful learners [74, 77, 86]. Aged animals with impaired learning show similar sAHP amplitudes to controls. In mice, sAHP amplitude is larger for some genetic backgrounds [31].

2.4 Afterdepolarizations

In response to brief current pulses (≤ 5 ms), most CA1 PCs fire a single AP, followed by an afterdepolarization (ADP) [30, 38, 64, 98, 99]. Jensen et al. report 35-50% of CA1 PCs show “passive” ADPs lasting ~20 ms and characterized by a smooth decay and a time constant of ~12 ms [29, 98]. The remaining PCs show “active” ADPs lasting ~40 ms, with a period of renewed depolarization before decaying, and a time constant of ~20 ms. Mice from different genetic backgrounds have different-sized ADPs [100]. Some PCs show no obvious ADP [101].

ADPs regulate firing patterns in CA1 PCs. Bursting PCs are more likely to have active and larger ADPs compared to non-bursters [29, 30, 98]. Lowering extracellular Ca\(^{2+}\) increases ADP amplitude, changing spiking cells into bursters [38]. In rats, ADP duration increases from ~5 ms before postnatal day 10 (P10) to a maximum of ~30 ms at P18, then decreases to ~20 ms as animals progress to adulthood, but with large variability across PCs. Changes in ADP duration during development are associated with burst firing [87].

Evidence suggests that both Ca\(^{2+}\) and persistent Na\(^{+}\) channels participate in ADP generation in CA1 PCs, though the location of the channel populations in each case is different. Blocking persistent Na\(^{+}\) channels with drugs applied to the soma but not the dendrites reduces the ADP [64, 87]. Blocking T/R- and L-type Ca\(^{2+}\) channels with drugs applied to the dendrites but not the soma decreases the ADP and reduces bursting [87], while N/P/Q-type blockers have no effect. K\(^{+}\) currents active during AP repolarization help control ADP size. Increasing extracellular K\(^{+}\) augments the ADP and can trigger bursting [29]. Blocking M channels at the soma but not the dendrites augments the ADP, whereas SK channel blockers have no effect [75, 102]. In contrast, blocking A-type K\(^{+}\) channels at the dendrites but not the soma increases the ADP and leads to bursting [102].

2.5 Burst firing

PCs can burst, rather than fire repetitively [29, 30, 38, 55, 87]. PCs can be grouped into three classes based on firing patterns [29, 30]. Around 80% of PCs are ‘regular spiking cells’ or ‘non-bursters’. The remaining ~20% are either (1) ‘borderline’ / ‘high-threshold’ bursters, which fire single spikes at low stimulation amplitudes but burst at higher amplitudes, or (2) ‘low threshold’ bursters, which burst at low and high stimulation amplitudes. The latter class can be further divided into three grades. Grade I PCs fire single spikes in response to short stimuli but burst with long (hundreds of ms) pulses. Grade II PCs burst in response to both short and long pulses. Grade III PCs burst in the absence of stimulation [29, 30].

The percentage of bursting PCs depends on anatomical location. Only ~10% of proximal PCs burst, compared to over 50% of distal PCs [103]. This difference in bursting likelihood correlates with a similar anatomical variation in ADP amplitude. Changes in both the driving forces for Ca\(^{2+}\)
entry [30, 38, 55] and K+ exit [29] from the cell increase ADPs and promote bursting. Reducing extracellular Ca2+ can induce bursting [30, 55], convert PCs from high- to low-threshold bursters [30], and increase bursting frequency [38, 55]. Increasing extracellular K+ increases the percentage of bursters and can induce spontaneous, rhythmic bursting [29].

The percentage of bursting PCs also depends on developmental stage. In rats, nearly all PCs are non-bursters up to postnatal day 11 (P11) [87]. Subsequently, the percentage of bursters increases, hitting a maximum of 74% between P18 and P19. The percentage decreases again as animals approach adulthood. Changes in bursting tendency correlate with changes in ADP magnitude, which in turn relate to the density of dendritic T/R- and L-type Ca2+ channels and somatic persistent Na+ channels [87]. CA1 PCs in aged rats show a shift towards shorter interspike intervals (ISIs) associated with burst firing during irregular but not theta activity [104].

3 Responses to synaptic stimulation

CA1 PCs receive input from neurons in the CA3 region of the hippocampus via the Schaffer collaterals (SC) terminating in the stratum radiatum, and from neurons in the entorhinal cortex via the perforant path (PP) terminating in the stratum lacunosum-moleculare [105]. Studies have explored SC and PP stimulation to probe responsiveness of CA1 PCs.

3.1 Synaptically-induced afterhyperpolarizations

Synaptic AHPs (synAHPs) are evoked by microsecond pulses delivered to the PP or SCs [79, 88, 96, 106–108]. synAHP size and duration depend on amplitude, location, number, and frequency of the stimulation [88, 96, 107, 108]. Burst firing produces larger synAHPs than single spikes [96]. Suprathreshold stimulation eliciting spikes evokes longer-duration synAHPs than subthreshold stimulation eliciting only EPSPs [88, 107]. synAHPs following single EPSPs are larger when evoked by PP stimulation versus SC stimulation [108]. Around 20% of PCs show no synAHPs and instead show large post-burst ADPs and prolonged spiking, effectively dividing CA1 PCs into two subpopulations [88].

Medium-duration synAHPs in response to subthreshold stimulation are not Ca2+-dependent [88, 108]. Instead, these synAHPs are mediated by $I_H$, but to varying extents depending on the source of stimulation [108]. Those elicited by SC stimulation are nearly abolished by the $I_H$ blocker ZD7288, while those produced by PP stimulation are only reduced by half and depend additionally on GABAergic signaling [108]. Like somatically-generated sAHPs, slow synAHPs following bursts are Ca2+-dependent [79, 106]. The molecular identity of the underlying channels is unclear. Some studies suggest a role for SK channels [79], while others argue against SK involvement based on synAHP kinetics and sensitivity to noradrenaline and $\beta$-adrenergic agonists [106]. Still others have recorded synaptically-stimulated hyperpolarizations which do not respond to $I_{KCa}$ antagonists, but are decreased by enkephalin, suggesting a role for extrinsic input from hippocampal interneurons in generating these potentials [107].

Aging has different effects on slow AHPs stimulated somatically versus synaptically. As discussed in section 2.3, slow AHPs elicited by somatic current injection are larger in aged versus young adult rats, and contribute to spike failure during repetitive stimulation. In contrast,
synaptically-generated AHPs do not affect repetitive spiking, and are smaller in aged than in young adult animals [96].

3.2 Short-term potentiation

Microsecond-pulse trains delivered to the SCs at 1-15 Hz increase EPSP amplitudes and population spikes in CA1 PCs [96, 109–114]. This short-term plasticity, called frequency facilitation (FF) or potentiation (FP), occurs in response to both sub- and suprathreshold stimulation [114]. Potentiation ranges from 20-300% across animals [115], and varies with anatomical location [116]. Dorsal PCs show FP in response to SC stimulation at 1-40 Hz, with the largest potentiation at 10-20 Hz. Higher frequencies result in depressed EPSPs. Ventral PCs instead show minimal FP at 1 Hz but either no response or depression at higher frequencies tested up to 100 Hz [116].

While subthreshold stimulation produces equivalent FP in young and aged animals [114], the response to suprathreshold stimulation is reduced with aging [109–114]. Gant *et al.* report that FP responses are significantly different between aged and young animals at stimulation frequencies in the theta range (e.g. 7 Hz), but not at lower (3 Hz) or higher (15 Hz) frequencies [96]. Other studies, however, report robust FP differences in young versus aged animals at stimulation frequencies of 10-12 Hz [109, 111]. Landfield *et al.* report that young animals show a multiphase response to stimulation, with early potentiation, followed by depression, and then stronger potentiation [111]. In contrast, FP in aged animals is normal for the first few pulses, but decays and responses depress with no rebound as stimulation proceeds [96]. Response depression in aged animals is stronger and faster with higher frequencies and longer pulse trains [109, 111].

FP in young animals is associated with a decrease in the distal vesicle pool, an increase in the local pool, and a clustering of vesicles at the synapse active zone [109]. Aged animals show a lower density of distal vesicles at rest compared to young animals, and show little change in density with stimulation. The local vesicle pool does increase in aged animals with stimulation, but fewer vesicles are found clustered at the active zone, indicating aged animals may have vesicle release or cycling deficits which lead to impaired FP [109].

Development of FP in young animals is associated with increases in intracellular Ca\(^{2+}\). Aged animals demonstrate similar increases in Ca\(^{2+}\) during the early phase but larger increases during the late phase of repetitive stimulation, compared to young animals [114]. This excess Ca\(^{2+}\) is thought to activate Ca\(^{2+}\)-dependent channels underlying AHPs, which are larger in aged animals and contribute to decreased excitability [96, 114]. Larger AHPs in aged animals can lead to spike failure in response to subsequent synaptic stimulation [96]. Aged rats exposed to high Mg\(^{2+}\) show increased FP and better learning [112].

3.3 Long-term potentiation

One of the most well-studied forms of plasticity in CA1 PCs is long-term potentiation (LTP) [119–123], an increase in synaptic strength in response to high-frequency repetitive stimulation (see Fig. 3) first reported in the dentate [124]. A comprehensive discussion of LTP is beyond the scope of this review. Instead, we focus on variability in LTP due to stimulation at different sites, frequencies, cellular locations, development, and aging.

Regional differences exist in LTP induction. Left CA3 input induces ipsilateral and contralateral LTP in CA1, whereas right CA3 stimulation does not evoke LTP. CA1 synapses receiving left CA3
input show smaller spines with increased expression of the NMDA receptor (NMDAR) subunit GluN2B [125, 126], which evidence suggests is more effective than GluN2A in mediating LTP [121, 127–129]. The relative expression of GluN2B to GluN2A subunits decreases during development [128], but this change may be negligible at left CA3-CA1 synapses, causing them to remain in an “immature plastic state” [121]. NMDAR expression is decreased in the ventral (temporal) compared to dorsal (septal) CA1 [130]. LTP is correspondingly less in ventral relative to dorsal PCs [131–133]. Around 60% of dorsal PCs show robust LTP, while 57% of ventral PCs show no LTP [133]. Ventral PCs that do show LTP show smaller changes in EPSP responses compared to dorsal PCs [131].

A second form of LTP depends not on NMDARs but on voltage-dependent Ca^{2+} channels (VDCCs) [134]. NMDA-dependent LTP is reduced in aged animals, while VDCC-dependent LTP is increased, compared to young controls. When both forms are functional, LTP is equivalent in young and aged animals, demonstrating the compensatory role played by VDCCs [134]. This could explain why some studies find age-related deficits in LTP, while others do not. Some stimulation protocols activate only NMDA-dependent LTP, revealing a deficit in aged animals, while others...
protocols activate VDCC-dependent LTP, allowing compensation [135].

LTP is often induced using high-frequency or tetanic stimulation (HFS). In recent years, theta burst stimulation (TBS) has been used as an arguably more realistic reproduction of endogenous hippocampal activity [136]. Studies report TBS is more effective than HFS in inducing LTP [136], especially if bursts fall on the positive phase of endogenous theta rhythms (see section 4.2). If bursts fall instead on the negative phase, TBS induces depotentiation [137] or long-term depression (LTD) [138]. Young and aged animals show equivalent LTP induced by HFS [139] while aged rats show reduced-magnitude LTP induced by TBS [139, 140]. Learning-impaired aged rats show decreased TBS-induced LTP, but no differences in LTP induced by HFS [141]. Aged rats show equivalent potentiation of dendritic EPSPs but weaker potentiation of somatic population spikes compared to young animals [142]. Deupree et al. speculate this indicates functional plasticity of individual synapses but deficient dendritic integration and somatic signaling in aged animals [142].

4 Spontaneous and network activity

To understand the complete electrophysiological repertoire of neurons, we must see how they respond spontaneously under different behavioral conditions.

4.1 Place field firing

Some CA1 PCs respond as an animal traverses specific areas in an environment [143–146]. These place cells increase their firing rate in defined place fields, which develop when an animal explores either a physical or virtual space [147]. Some studies give the impression that spatial coding is the only function of CA1 PCs. However, Wiener cautions we should not define these cells only by their place-related firing since their activity is “highly plastic” and context-dependent [28].

Not all PCs develop place fields (see Fig. 4). Between 30% and 70% of PCs whose activity is evoked by stimulation, or by select behavioral states, do not show spontaneous activity or place-related firing in a maze environment [145, 147–149]. Spontaneously active place cells have distinct biophysical properties from so-called ‘silent’ cells, including increased excitability and plateau depolarizations [150]. Depolarizing silent cells with somatic current injection during exploration induces the appearance of place fields [150]. Thus, these cells receive spatial input but are unable to respond without a ‘boost’. Around 20% of silent cells spontaneously and abruptly convert into place cells, which correlates with increased interneuron input [151].

Most PCs have place-related firing in only one environment, but decrease their firing or go silent in others [148, 153]. Just 1-3% of PCs have place-related activity in all environments tested [148, 153]. While overall representation of an environment is relatively stable, with 30% of PCs showing place firing, individual PCs drop in or out of the group of active cells, showing only a 15-25% overlap between recording sessions and demonstrating a “a day-to-day dynamism at the cellular level” [153]. PCs can drop in or out of the spatial representation in response to rotation of environmental cues [149]. Many PCs increase their firing rate during place field traversal (‘on’ response), but some decrease their firing (‘off’ response) [148]. ‘On’ and ‘off’ responses in a single PC are occasionally seen in the same environment.

PCs in different hippocampal areas show distinct spatial coding. While dorsal and ventral PCs show similar firing during resting and sleep, a larger percentage of dorsal than ventral cells show
Figure 4: Firing variability in CA1 PCs. Recordings from CA1 PCs in mice while running on a linear track treadmill. Simultaneous intracellular (black traces) and extracellular (local field potentials; green traces) showed that cells could be characterized by their firing patterns as silent, non-place, or place cells. From [152], used with permission.

place fields during exploration [154]. Dorsal PCs show high spatial specificity. In contrast, ventral place fields are so much larger that some researchers suggest calling these “context” instead of “place” cells [155]. PCs in the middle hippocampal region have place fields intermediate in size, half that of ventral fields but larger than dorsal ones [155]. The percentage of PCs forming place fields is higher closer to the stratum oriens versus the stratum radiatum [156].

Place fields increase in size with increasing exploration [157–159]. Place field expansion occurs on the first day of multiple runs through an environment, but not on subsequent days [160]. Firing rates within place fields also increase and the center of mass of the firing rate distribution shifts backwards in space [157–160]. Place field shape also changes with experience. Mehta et al. report that 78% of place fields are asymmetric and negatively skewed, with firing rates ~35% higher in the second versus the first half of activity [158]. Place field asymmetry is not present when animals are first introduced into an environment, but develops with increasing exploration. This progression from symmetric to asymmetric place fields occurs daily, even in previously explored
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environments [158]. Huxter et al. also report changes in place field shape, but in contrast to Mehta et al., they find that place fields are initially positively skewed and become symmetrical with increasing experience [159]. Experience-related changes in place cell firing are impaired in old animals. Aged rats have smaller place fields than young ones, and show little to no expansion with experience [161]. Increases in firing rate with experience are also smaller in aged animals [161].

4.2 Theta rhythm and phase precession

Rhythmic oscillations in theta frequency (6-12 Hz) are recorded at cellular and population levels in CA1 [162, 163]. While several studies demonstrate the importance of CA3 input in theta rhythm generation, other studies show that CA1 is capable of sustaining an intrinsic rhythm when isolated [164]. Dendritic depolarization in CA1 PCs occurs during the positive phase (peak) of extracellularly-recorded theta [165]. In contrast, somatic depolarization occurs primarily during the negative phase (trough) of theta [165]. The temporal relationship of PC firing to theta is variable and depends on cellular properties and behavior. Buzsáki and colleagues report that while most PCs fire on the negative phase [156, 165–168], a small percentage of weakly-activated cells fire on the positive phase of theta [162, 166]. They also report that a large percentage of PCs are slow-spiking or silent during theta and argue this could bias analysis of PC activity [162, 169, 170].

PC theta firing preference depends on cell location and behavioral state [156]. During exploratory behavior, PCs throughout the CA1 sublayers tend to phase-lock their firing with the trough of theta. During REM sleep, however, while stratum radiatum neurons fire around the trough, ∼50% of stratum oriens neurons fire instead during the peak. CA1 PCs in distinct sublayers show other biophysical differences, leading Mizuseki et al. to classify them as subpopulations [156].

PC theta firing preference can shift during exploratory behavior. O’Keefe and Recce report that as rats traverse a place field, CA1 PCs fire progressively earlier with respect to extracellular theta [171]. This phenomenon, referred to as phase precession, has been studied extensively and established as a characteristic feature of place cell activity [157, 165, 172]. The extent of phase precession depends on experience. At the population level, PCs show a 2-fold increase in the correlation between phase and spatial location after multiple trial runs through an environment [173]. There is a dissociation between the emergence of theta-related firing at the single cell versus population level. While phase precession is present in single CA1 PCs from the first trial run through a novel environment, coordination of population-level neural activity with respect to theta is not recorded until the second trial [174].

Stimulation during theta activity results in different types of plasticity depending on when it is delivered. Huerta and Lisman report that a single burst delivered at the peak of extracellular theta results in LTP, while the same stimulation delivered near the trough leads to depotentiation [175]. Like Huerta and Lisman, Hölscher et al. found that stimulation on the positive phase of theta leads to LTP, while stimulation on the negative phase depotentiatates, but does not depress, synaptic responses [137]. Stimulation on the zero phase of theta does not change synaptic responses. In contrast, Hyman and colleagues found the same results for positive phase stimulation, but report depression, not just depotentiation, after negative-phase stimulation [138]. They argue their results may differ due to the temporal precision of their stimulation, hitting exactly at the trough rather than elsewhere on the negative phase.

Theta activity is altered, albeit in small ways, during aging. Middle-aged rats show lower theta amplitude relative to young rats during waking and at multiple running speeds [159, 176]. Theta
frequency is higher in middle-aged rats during running, though this change may be specific to early aging [159], as older animals show decreased theta frequency [161, 177–179]. In young rats, theta frequency [161] and amplitude [159] increase at higher running speeds. These speed-related increases are smaller in aged animals. Likewise, increases in theta power seen in young animals as they transition from resting to active states [179] or due to exercise [176] are smaller in aging animals. Novel environments induce smaller increases in theta power for aged versus in young rats [179]. In contrast to differences seen during activity, there is no difference in theta recorded from young or aged animals during REM sleep [161]. Theta phase precession is also not different in aging animals [159, 161].

4.3 Gamma oscillations

CA1 displays spontaneous oscillations in the gamma frequency (∼25-160 Hz) [180–183]. Gamma oscillations are nested within theta cycles, and larger during theta-related activities, such as exploratory behaviors and REM sleep [184–186]. Changes in the frequency [184] and amplitude [179, 184, 187] of gamma oscillations correlate with changes in corresponding theta measures.

Gamma oscillations can be divided into three distinct bands [188, 189]: (1) slow gamma (∼30-50 Hz), (2) mid gamma (∼50-90 Hz), and (3) fast gamma (90-150 Hz), sometimes called the epsilon band [180, 188, 189]. Each frequency band shows a different theta phase preference, though reports vary. Belluscio et al. report that slow gamma power is largest on the descending phase of theta, mid gamma largest near the peak, and fast gamma largest near the trough [188, 189]. Scheffer-Teixeira et al. find that fast gamma is instead largest on the descending phase of theta [190]. Colgin et al., who collapse mid and fast gamma into one band (65-140 Hz), report that the largest power is near the trough of theta [191]. Theta phase preference can change depending on behavioral state. The peak power of fast gamma shifts from theta trough to peak during exploratory behavior versus REM sleep, respectively [188].

CA1 gamma oscillations vary with depth. Slow gamma is largest in the stratum (s.) radiatum, while mid gamma is largest in the s. oriens/pyramidale and s. lacunosum-moleculare [188]. Fast gamma dominates a small section of the s. pyramidale. While slow gamma power in the s. radiatum decreases during REM sleep, mid gamma power in the s. lacunosum-moleculare increases [189]. Gamma-theta coupling also varies by layer, but results differ across studies. Scheffer-Teixeira et al. report that mid gamma-theta coupling is strongest in the s. pyramidale and theta rhythms. In contrast, Schomburg et al. report slow gamma-theta coupling exists and is strongest in the s. radiatum [189]. Gamma frequency bands and their layer preferences relate to different CA1 inputs. Slow gamma in CA1 correlates with oscillations recorded from CA3, while mid to fast gamma correlates with oscillations in the entorhinal cortex [189, 191].

The percentage of CA1 PCs phase-locking their firing to gamma varies with behavioral state, recording distance, and gamma frequency. Senior et al. report that during waking ∼32% of PCs phase lock their firing to 30-80 Hz gamma, versus only 4% during REM sleep [192]. Mizuseki et al. report that ∼27% of PCs gamma phase lock during maze runs, but only 10% do so during REM sleep [156]. Csicsvari et al. report that ∼43% of PCs phase lock to locally recorded 30-80 Hz oscillations but only 13% to distal fields [186]. Belluscio et al. show that 18% of PCs phase lock to

1Gamma range is typically ∼30-80 Hz, but upper and lower limits vary depending on the reference.
slow gamma, 36% to mid-range gamma, and 75% to fast gamma [188]. Other studies also report
that CA1 PCs preferentially phase lock to fast gamma [189].

CA1 PCs vary with respect to gamma phase preference. During exploratory activity, some PCs
fire during the rising phase of gamma, while others fire at the trough [156, 188, 192]. PCs firing on
the rising phase during active states shift their preference during REM sleep, while the majority
of the population fires at the trough [156, 192]. Rising-phase versus trough-phase PCs are also
different with respect to firing rate, interspike interval, bursting propensity, action potential shape,
magnitude of afterpotentials, theta phase preference, and activity during theta phase precession
[156, 192]. Rising-phase PCs are most likely to be found close to the s. oriens, while trough-phase
PCs are located closer to the s. radiatum [156].

Gamma-related activity can vary with experience and in a task-dependent manner. PCs
preferentially phase lock their firing to either familiar or novel environments [192]. Relative gamma
power increases after learning, but only on certain types of task [193]. For some tasks but not
others, PCs increasingly phase lock their firing to gamma oscillations, particularly those occurring
seconds before reward delivery [193]. Subtle effects of aging on gamma oscillations have been
reported. In middle-aged rats, the increase in normalized gamma amplitude peaks at larger running
speeds than in younger animals [159]. In old rats, gamma amplitude changes little during the theta
cycle, in contrast to the stronger modulation seen in young rats [179]. The increase in gamma
power seen when young rats transition from resting to running occurs but is less prominent in old
rats [179]. Gamma coherence between adjacent recording sites is lower in aged versus young rats,
both within and across CA1 layers [194].

5 Discussion

CA1 pyramidal cells demonstrate an incredible diversity in their responses to somatic current
injection, synaptic stimulation, and spontaneous network-related activity. PCs can be divided into a
variety of different subpopulations, depending on the type of electrical activity considered.

5.1 Text and data mining to explore cellular heterogeneity

There is a wealth of information on cellular heterogeneity in the existing literature. However, finding
all the relevant articles, extracting key information, and comparing results across multiple studies is
a task not easily or efficiently done by hand. With text and data mining (TDM), researchers are now
automating these tasks to perform large-scale meta-analyses [195]. A recent study by Tripathy
et al. [32] used TDM to examine variation in biophysical properties, such as resting membrane
potential and input resistance, across multiple neuron types, including CA1 PCs. Much of the
variation they observed could be explained by methodological differences, while significant variation
was unexplained and could be due to cellular heterogeneity. Cluster analysis of six biophysical
measures confirmed known neuron classes, but also revealed new classes based on previously
unidentified similarities between cells [32]. Wheeler et al. mined the hippocampal literature and
identified 122 neuron types based on biochemical, electrophysiological, and morphological features
[4]. These studies demonstrate the power of TDM approaches and suggest there are more
discoveries to be made by mining the neuroscience literature [196].
We propose mining the literature for phrases related to different types of electrical activity, such as "delayed firing" or "spike latency". Automated download of all figures with electrical traces from articles including these phrases will facilitate large-scale comparisons within and across neuron types. Mining can be expanded beyond just the text to data within figures in published articles, made possible with tools developed by projects like Content Mine (contentmine.org). Electrical traces can be extracted from figures and transformed into raw time and voltage data to perform new analyses not done in the original work.

A limitation to this approach is the possible bias present in published articles. Researchers select a few examples from their electrophysiological data to include in the final paper. These recordings may be representative of the majority of recordings, but may exclude some of the diversity found in the sample. In extreme cases, researchers may even remove recordings with different firing patterns from their analysis, assuming they are outliers or possibly different cell types. Proper large-scale meta-analyses of firing pattern diversity will require access to complete, original data sets, confirming the importance of data sharing initiatives for TDM research [197, 198]. Copyright and article licensing reform is also crucial for TDM research, as certain laws restrict the mining of data from the published literature [199–202].

5.2 Dynamical systems theory to study firing patterns

Dynamical systems theory can increase our understanding of neuron electrical diversity. Neurons are dynamical systems, which evolve over time according to specific rules [33, 203]. Neurons can be minimally represented by two differential equations, one describing the change in voltage \(v\) and the other the change in activation of \(K^+\) channels \(w\) [204, 205]. Setting both equations equal to zero and solving gives the fixed points (FPs) of the system where neither variable is changing [33, 203]. Local dynamics around these FPs determine the system’s behavior in response to perturbations. FPs can be stable attractors such that the system tends to return to these points after a perturbation (e.g. the resting potential of a neuron). Instead, FPs may be unstable repellers, in which case trajectories of the system tend to move away from this point. The type of FP is also important for understanding the behavior of the system. For example, if the system is near a stable focus, it will return to the FP after some perturbation in a spiral trajectory, causing subthreshold oscillations. In neurons this is important because it means the system can resonate with different frequency inputs. In contrast, if the FP is a stable node, the system returns after a perturbation without oscillating and the neuron is not capable of resonance [33].

Dynamical systems may also have periodic solutions called limit cycles that describe closed trajectories as the system evolves through the space defined by the two variables (phase space) [33]. For example, an action potential can be described by changes in \(v\) with respect to \(w\); the initial depolarization phase is characterized by an increase in \(v\) with little change in \(w\), while repolarization is characterized by an increase in \(w\) and a decrease in \(v\). If the limit cycle is unstable, a perturbation will lead to a single spike and a return to a resting state (a stable FP). However, if the limit cycle is stable, a perturbation can lead to repetitive spiking [33].

We can explore how a dynamical system changes in response to variation in one parameter, e.g. the amplitude of current injected into a neuron. Does increasing stimulus amplitude affect the number, type, or stability of the FPs? Does it lead to the emergence of stable limit cycles, producing repetitive spiking? Qualitative or topological changes in dynamical systems resulting from a change in parameter value are called bifurcations. Studying the bifurcations that neurons undergo when
transitioning between rest and spiking states can reveal the full spectrum of firing patterns a neuron is capable of producing [33]. In 1948, Hodgkin grouped neurons into classes based on the frequency of their firing in response to a range of current amplitudes [206]. In 1989, Rinzel and Ermentrout showed that these firing classes related to distinct bifurcations [207]. Previous work by one of the present authors (ECM) has shown that the type of bifurcation producing the transition into spiking is related to whether long firing delays are observed in a model motor neuron [208]. The bifurcation structure of the model neuron in [208] depends in part on the expression of delayed rectifier K\textsuperscript{+} channels. Such analysis can demonstrate under what cellular conditions certain firing patterns may emerge, as well as show us the functionally equivalent combinations of channels that produce the same spiking transitions.

5.3 Mathematical modeling to study effects of cellular heterogeneity on network function

While differences in firing patterns may be subtle, or the percentage of PCs deviating from what are considered classical firing behaviors may be small, this variability could have important effects on network function [22]. Unfortunately, it is difficult to properly test the effects of cellular heterogeneity in intact networks. First, characterizing the full range of biophysical properties displayed by cells within a network is often not possible. Second, it is difficult to know the percentage of cells in a network demonstrating specific biophysical properties, thus limiting our ability to determine the number of critical cells required to see an effect. Third, manipulating cells with a given property is difficult without also affecting other players in the network.

Mathematical modeling allows the targeted perturbation of select biophysical properties in single neurons. Since there is no homeostatic compensation, as often observed in real neural networks [19], simulations can be compared to experimental results to determine whether a change in a given parameter is sufficient to produce specific firing patterns. While historically most models have assumed neurons within a population to be relatively homogeneous, heterogeneity can be made a model feature to explore effects [209]. Model networks can be assembled with a known percentage of cells displaying a given biophysical property to determine the critical mass necessary to produce a given output. Synaptic partners and the strength of their connections can be varied to explore how cellular heterogeneity interacts with network organization to produce circuit output, or compensate in cases of altered cellular excitability. In particular, PCs can be modeled to represent cells in juvenile, adult, or aged animals to explore how changes in biophysical properties during developmental stages may affect circuit output. Stimulation protocols used experimentally to induce short-term frequency potentiation (section 3.2) and long-term potentiation (section 3.3) can be simulated to systematically test the effects of cellular heterogeneity on network plasticity.

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