Chapter

Integration of Spiking Neural Networks for Understanding Interval Timing

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Abstract

The ability to perceive the passage of time in the seconds-to-minutes range is a vital and ubiquitous characteristic of life. This ability allows organisms to make behavioral changes based on the temporal contingencies between stimuli and the potential rewards they predict. While the psychophysical manifestations of time perception have been well-characterized, many aspects of its underlying biology are still poorly understood. A major contributor to this is limitations of current *in vivo* techniques that do not allow for proper assessment of the di signaling over micro-, meso- and macroscopic spatial scales. Alternatively, the integration of biologically inspired artificial neural networks (ANNs) based on the dynamics and cyto-architecture of brain regions associated with time perception can help mitigate these limitations and, in conjunction, provide a powerful tool for progressing research in the field. To this end, this chapter aims to: (1) provide insight into the biological complexity of interval timing, (2) outline limitations in our ability to accurately assess these neural mechanisms *in vivo,* and (3) demonstrate potential application of ANNs for better understanding the biological underpinnings of temporal processing.

Keywords: interval timing, time perception, neural oscillators, dopamine, basal ganglia, artificial neural networks, spiking neural networks

Highlights

- Examine neural signatures, circuitry dynamics, and neuromodulator pathways related to interval timing behavior
- Address limitations in current *in vivo* techniques in studying timing
- Discuss the use of artificial neural networks for understanding neural dynamics and timing
- Identify properties of thalamocortical dynamics that may be integral to time perception

1. Introduction

When it comes to understanding the neural underpinnings of time perception, the devil is in the details. As all events inevitably unfold in time, there is no shortage of potential "timing" signals. However, behavioral tasks often possess inherent

relationship between time, spatial location, and external signals making it difficult to isolate activity dedicated to timing per se. As a result, timing correlates have been observed across nearly all regions of the cortex [1–4] as well as sub-cortical areas and the cerebellum [5, 6]. Reflecting this anatomical diversity, the number of theoretical models dedicated to timing is also vast, and utilize a diverse range of firing dynamics such as oscillatory [7] ramping [8] or synfire chains [9]. Yet, which of these various timing motifs and to what degree they contribute to a unified perception of time remains unclear [10].

A contributing factor to the multitude of timing theories are the limitations of current *in vivo* techniques, which can be spatially restrictive, produce ambiguous information, and contain representation biases. Though remarkable strides have been made in expanding the scope of techniques used to record, image and modulate neural activity, the capacity to selectively manipulate and/or effectively observe the propagation of activity from a large population of neurons within a particular brain region or across multiple regions, is limited. With theories of temporal processing spanning the microscopic level of intrinsic cellular [11, 12] and network dynamics [13–15] to the macroscopic interplay between multiple brain regions [16], understanding how animals track the passage of time has been an arduous task through reliance on *in vivo* techniques alone.

A promising avenue to help circumvent the aforementioned limitations is the integration of biologically inspired ANNs. While neural networks have been around for over half a century [17], recent years have seen a resurgent interest in their development and application within neuroscience. Spurred by substantial advancements in computational power, the ability for labs to integrate complex, biologically constrained neural networks is more viable than ever before. As the integration and development of biologically inspired ANNs into neuroscience has been steadily growing for many decades, adoption into the field of time and time perception has been comparatively slow.

Though examples do exist, current efforts have remained limited [18–20]. Moreover, these networks often lack characteristics considered vital for biologically realism such as bidirectional activation propagation or Hebbian-based learning [21] - characteristics that see widespread use in other fields. Many of these models utilize rate-based units, applying 'activation functions' and highly simplified network motifs, limiting the temporal dynamics of the network. While these simplified

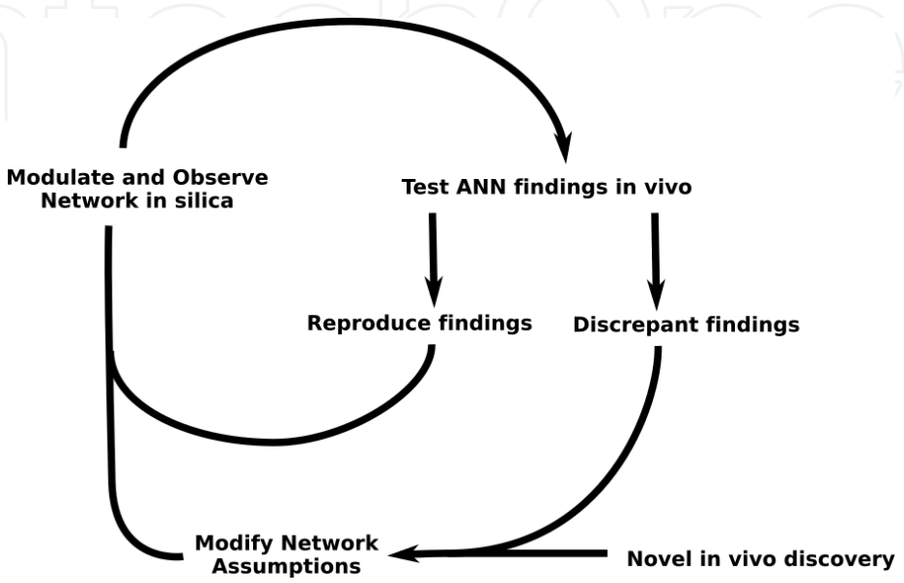

Figure 1.
Proposed cycle for integration of SNNs. Schematic visualization of integrating SNNs into empirical process.

networks provide valuable theoretical insight, the incorporation of spiking neural networks (SNNs) with biologically inspired 'spiking' units and network architectures, allows SNNs to capture neural dynamics more analogous to the biological systems which they are based and a more critical assessment of timing theories. The integration of SNNs can allow researchers to visualize the propagation of temporal information as well as finer control over neuromodulatory systems not possible in other models.

The aim of this chapter is to demonstrate how the field of timing and time perception can benefit from the implementation of biologically constrained SNNs. In so doing, limitations of current *in* vivo recording and imaging techniques will be addressed along with examples of how SNNs can be used to circumvent such constraints and facilitate hypothesis driven research (**Figure 1**). Lastly, specific outstanding questions in the field of interval timing that could most benefit from integration of SNN models will be identified.

2. Interval timing networks and dynamics

Neural correlates of time perception have been observed across nearly the entire cortical mantel. In theory, any pattern that remains consistent for a given duration yet varies across durations is capable of acting as a biological timer. As these requirements are not particularly stringent, electrophysiological recordings have uncovered many candidate patterns. The prefrontal cortex (PFC) alone contains ramping, peaking, and oscillatory activity meeting such criterion [22–26]. In addition to spiking activity, EEG and MEG recordings in humans [27–29] demonstrate a robust relationship between mesoscopic oscillations and timing behavior.

2.1 Cortical spiking and mesoscopic oscillations

Electrophysiological studies in rodent and non-human primates have shown robust correlations between cortical activity and timing behavior across multiple brain regions. Yet, how dynamics within and across cortical regions contribute to these behaviors are still unclear. Though ever expanding, limitations in our current knowledge on how information propagates across interconnected brain regions has made drawing causative relationships between timing behavior and specific neural signals difficult.

One of the most studied neural correlates of timing is 'ramping activity' (**Figure 2A**). These monotonic increases or decreases in firing rate have been observed within the prefrontal [25, 26] primary motor [30] and posterior parietal cortex [31, 32] during various timing tasks. Along with its seemingly ubiquitous presence within the cortex, key observations further indicate ramping as a viable timing mechanism: (i) ramping activity has been demonstrated to occur across multiple timescales from hundreds of milliseconds to multiple seconds (ii) the rate of change can be adjusted through learning different durations (iii) the rate of change during a reproduction task is dependent on the presented duration. Specifically, neuronal activity in the lateral inferior parietal cortex (LIP), recorded in macaques trained on a temporal reproduction task, found changes in firing rate were inversely proportional to the duration being produced. That is, shorter durations had steeper ramping activity therefore reaching threshold sooner [31].

However, pharmacological inactivation of ramping activity within these same regions of the cortex, namely the posterior parietal cortex (PPC), during evidence accumulation tasks has negligible effects on stimulus categorization [33]. Conversely, decreasing prefrontal cholinergic concentrations reduced temporal

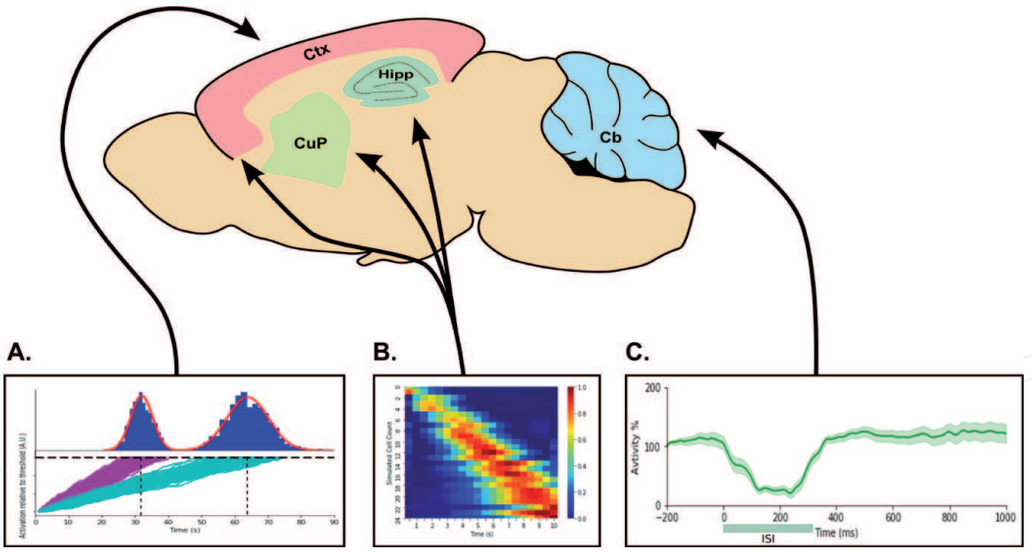

Figure 2.
Distribution of timing correlates and associated activity patterns. (A) Simulation of ramping activity as observed in cortical networks during timing tasks. Parameterized using values from model of neural integration (Simon et al. 2011). Theoretical accumulation of activity (bottom) and distribution of time to threshold (top) (B) Heatmap of simulated activity normalized by max firing rate depicting trajectory dynamics found in the cortex, hippocampus, and striatum. (C) Depiction of pauses in Purkinje cell activity within the cerebellum during 300 millisecond delay (ISI) Pavlovian eye-lid conditioning.

precision without disrupting ramping activity demonstrating a potential dissociation between ramping and timing behavior [34]. Other regions have demonstrated a more causal relationship, namely, ramping in the frontal orienting field (FOF) was found to be necessary for proper performance possibly implicate ramping activity as a general computational motif within cortical circuits of which timing is localized to a particular cortical region.

Recent evidence suggests that neuronal ramping may not, in fact, be ramping at all, but an artifact of bi-stable neuron activity averaged over multiple trials. Analysis of spiking activity within the LIP during individual trials of a motion discrimination task showed 31 of 40 neurons exhibited 'stepping' behavior [35] as opposed to the deterministic gradual increase expected of a truly ramping dynamic (c.f. [36, 37]). These findings parallel human studies which have cast doubt on the role of the contingent negative variance (CNV) – an EEG correlate of ramping activity – in temporal processing due to the poor predictive ability of the CNV and the high temporal accuracy demonstrated even after the resolution of the signal [38]. How ramping activity develops also remains unclear [39, 40].

Larger scale recordings, containing 55–120 simultaneously recorded neurons, have painted a relatively different picture of spiking activity within the cortex during timing. Bakhurin and colleagues [22] found putative projection neurons contained activity patterns in which individual neurons in the orbital frontal cortex (OFC) displayed sequential activity that tiled a 1.5 s delay period following an olfactory cue. This type of firing is reminiscent of "time cell" activity recorded in other brain regions such as the striatum [6, 41] and hippocampus [42, 43] providing a parsimonious representation of timing signals across distinct brain regions (**Figure 2B**).

At the mesoscopic level, oscillatory activity within cortical regions has also been theorized as an underlying mechanism for time perception. As with spiking correlates of timing, neural oscillations are pervasive throughout the brain and implicated in a multitude of cognitive processes such as attention, memory, movement preparation and even consciousness [44]. Yet, their computational role in these processes is generally unresolved [45]. Nevertheless, researchers have long

recognized the potential of rhythmically repeating oscillators to track the passage of time from hundreds of milliseconds to tens of minutes [46, 47].

Increases of delta range (~4 Hz) oscillations in the medial prefrontal cortex (mPFC) were shown to negatively impact the temporal precision of rats performing a 12 s fixed-interval task. Pharmacological attenuation of these increases in delta through blockage of D1 dopamine receptor (D1DR) signaling mitigated the associated deficits in timing [2]. Interestingly, D1DR+ neurons in the prefrontal cortex have strong delta frequency coherence with a subset of neurons exhibiting ramping activity implicating a direct link between microscopic spiking and mesoscopic oscillations during timing [48]. Additional evidence supports the existence of spike phase relationships with the mPFC particularly within the theta frequency (5–10 Hz) [23, 49, 50]. However, Benchenane et al. [23] demonstrated that spike-phase entrainment to theta in the mPFC only occurs during times of high coherence between mPFC and hippocampal (HIPP) theta and is most prominent at times requiring encoding or retrieval of spatial memory. This property likely makes it too transient to track time over multiple seconds. Increases in cortical theta have also been associated with interval timing tasks where sustained increases in cortical theta power occur during the encoding of the standard duration in a temporal comparison task [51, 52], though whether coherence between HIPP and mPFC remains high across this entire duration has not been tested.

As with ramping activates relation to timing behavior, the coupling of spikes to oscillations appears to be region specific. Though oscillatory activity has been observed within the cortex across multiple frequency bands, there is limited support for individual neurons firing-rates to entrain to these rhythms. For example, though timing behavior correlates with cortical beta (~15–30 Hz) activity within the dorso- and ventro-lateral prefrontal cortex, premotor cortex, and posterior parietal cortex [28], recent work suggests that spiking activity demonstrates minimal coupling to beta rhythms [53].

2.2 Neuromodulators and time perception

Timing behavior has been shown to be highly susceptible to manipulations of neuromodulators such as dopamine (DA: [54–58]) serotonin (5-HT: [59–61]) and acetylcholine (Ach: [34, 62, 63]). Additionally, patients suffering from disorders involving these pathways [64–66] demonstrate systematic changes in their timing ability.

Dopamine has been the most widely studied neuromodulator in the field of interval timing. Despite this depth of research, many questions still remain as research has produced seemingly paradoxical effects. Early psychopharmacological studies demonstrated bidirectional shifts in timing accuracy (i.e. over- or underestimations of a target duration) after administration of DA agonists and antagonists, respectively [55–57, 67]. This work suggested that DA changes the speed of a subjects internal timing mechanism (i.e. "clock speed" effect). This could manifest itself as changes in the slope of ramping neurons or oscillator frequency. However, other research suggested that administration of dopaminergic drugs such as the selective D_2 and D_3 agonist Quinpirole disrupts timing precision rather than accuracy through modifying attentional processes [58, 68]. While later work using a variation of the peak interval procedure supported the changes in accuracy, the directionality of the peak shifts did not align with the original "clock speed" hypothesis [69]. Subsequent experiments further demonstrated these effects to be sensitive to non-temporal aspects of the task similar to the "attentional modulation" hypothesis.

The wide repertoire of timing behaviors related to DA modulation may be a product of its diffuse circuitry [70, 71]. Alternatively, the complexity may result from interactions with other neuromodulatory pathways. Electrophysiological evidence suggests DA neurons elicit tonic excitatory control over 5-HT neurons within the raphe nucleus [72]. In fact, a mouse model of Parkinson's disease using 6-OHDA lesions lead to increases in spontaneous firing as well as maximum firing rate of 5-HT neurons in the dorsal raphe nucleus [73].

Administration of 5-HT_{1A} receptor agonist 8-OH-DPAT modulated timing precision on retrospective timing tasks, while immediate timing tasks saw changes in accuracy [74]. However, the contribution of 5-HTergic pathways to timing behavior remains precarious as many of these studies were unable to dissociate changes in interval timing from intertemporal choice [60]. In fact, more recent work indicates 5-HT to be more strongly associated with intertemporal choice [75] along with additional factors such as reward rate and temporal uncertainty [76]. This relationship appears to be bidirectional as 5-HT projections from the dorsal raphe nucleus can modulate DA release directly through excitatory synapses onto VTA dopamine neurons [77]. A selective 5-HT_{2c} ligand shown to increase vigor and persistence in goal-directed behavior also leads to increased tonic DA levels in the dorsal medial striatum [78]. The aforementioned interaction within the DMS is likely driven by excitation of striatal cholinergic interneurons which can drive action potentials independent of DA release [79, 80]; thus, linking cholinergic pathways to an already complex system.

Despite considerable work on the role of neuromodulators in timing behavior, dissociating the mechanisms responsible for these effects is yet to be fully understood. These systems contain multiple origins with diffuse and overlapping targets. Moreover, direct as well as indirect connections between these pathways makes it difficult to confidently assign credit to a single pathway and behavioral changes are often dependent on the parameterization of the particular study. As a result, it is likely that non-traditional methods allowing for more systematic modulation of the respective pathways is necessary to fully disentangle their individual roles in timing behavior.

3. Limitations of current *in vivo* techniques

Substantial advancements of *in vivo* techniques are now allowing for exceptional insight into neuronal dynamics. The number of simultaneously recorded single neurons has seen a near doubling every 7 years [81]. Coupled with growth of open-source hardware systems, access to these powerful technologies is becoming more feasible and cost effective [82]. However, these techniques are still limited in the amount of information they are able to reliably produce in relation to the dynamic properties of the brain. This has led to debate into the sufficiency of correlations between firing activity and behavioral output. Additionally, many of the current methods used for manipulating endogenous activity suffer from a lack of specificity. The aforementioned diffuseness of the interval timing network coupled with sensitivity to neuromodulation limit the insight from *in vivo* techniques alone.

3.1 Recording and imaging

Extracellular *in vivo* recordings have long been the technique of choice for linking neural activity to ongoing behavior through monitoring action potentials (APs) along with more mesoscopic neural activity in the form of local field potentials (LFP). Though Advancements in recording techniques has been able to mitigate

some of the uncertainty in isolating an individual cell's activity, a sizeable degree of error still exists. Though quantification of this error, referred to as the 'spike sorting problem', is difficult due to the lack of 'ground truth' data, estimates suggest semi-automatic clustering error with tetrodes to be on the order of 5–10%, and substantially higher (upwards of 30%) for manual cluster cutting, a process still popular in many labs [83]. Furthermore, the uncertain origin of signals such as gamma range oscillations makes interpretations speculative [84].

A second class of errors that can lead produce specious conclusions is 'selection bias'. Combined intra- and extracellular recordings within CA1 of the hippocampus demonstrated that despite an estimated 140 neurons within the recording distance of a single tetrode, rarely are more than a dozen signals ever detected [85]. While innocuous contributions such as acute edema and glial encapsulation can lead to significant decreases in signal strength and subsequent cell counts [86], other causes such as under classification of cells with low firing rates can skew researcher's interpretation of genuine network dynamics. Furthermore, differential firing rates between regions, such as higher firing rates in deep-layers of the cortex in comparison to pyramidal cells of the superficial-layer [87, 88], may bias researchers toward studying areas with high spiking and subsequently overestimating a regions role in the overarching circuit. Recent attempts at addressing and quantifying the quality of *in vivo* recordings is a step toward lessening the effect of electrical artifacts [89, 90], though further work in this direction is still needed.

In addition to classic recording techniques, calcium imaging has become a popular tool for visualizing activity. Imaging permits precise spatial mapping of activity [91, 92] and mitigates many of the limitations in recording such as the "spike sorting problem" and "cell selection bias'" [93]. Further improvements in fluorescent indicators [94, 95] and scanning techniques [96] have been able to overcome past limitations in sampling rate allowing for detection of somatic calcium transients evoked during action potentials.

However, in non-laminar low cell density brain regions the number of cells that can be simultaneously observed is highly restricted. Sub-cortical areas such as the striatum can be limited to less than 40 cells [97] and require significant damage to regions dorsal to those being imaged. Paired with the inability to sufficiently account for dynamic interactions within a single brain region imaging technique are even more limited when attempting to study interactions across multiple regions. In all, while *in vivo* techniques are one of the most valuable tools for understanding the relationship between neural signals and behavior, alternative methods in conjunction can provide richer insight into not only regional dynamics, but also interregional interactions.

3.2 Pharmacological, chemogenetic, and optical manipulations

While electrophysiological recording and imaging provide insight into endogenous activity, much of our knowledge into how the brain senses the passage of time has arisen from the manipulation of timing networks. Yet, there are often deviations between a researcher's intent and the actual alterations within the brain. The main contributors are lack of specificity or incomplete knowledge of the technique being used.

While the foundation of many theories in time perception, pharmacological manipulations are the most susceptible to confounding interactions. Even drugs touted as selective can display affinity for non-target receptors. Concretely, the commonly used D1-antagonist SCH-23390 also demonstrates high affinity for serotonin receptor subtypes 5-HT_2 and 5-HT_{1C} [98]. While its affinity for D1 receptors is much higher than that of 5-HT, the expression of both receptor types

within this region could explain why timing behavior following local infusions of SCH-23390 into the DMS has been difficult to interpret [99]. As 5-HT_2 activation within the striatum has been shown to indirectly reduce striatal MSN activity [100]. Conversely, timing effects attributed to serotonin could be mediated through or in conjunction with indirect increases in DA, which has been demonstrated in 5-HT_2 agonists such as Psilocybin [101].

In an effort to minimize off-target effects there has been a renaissance in the development of chemogenetic and optogenetic techniques. Vaunted for their ability to mitigate the confounds of pharmacological methods, a growing literature is revealing these approaches come with their own set of drawbacks. While chemogenetic approaches such as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) has helped alleviate some of the uncertainty from pharmacological manipulations, recent work shows that CNO (clozapine N-oxide), the most commonly used agonist in DREADDs, can back metabolize into clozapine and has the potential to accumulate in amounts capable of activating endogenous receptors [102]. Importantly, clozapine has been demonstrated to affect temporal accuracy as well as the flexible use of timing mechanisms [103, 104]. While this limitation can be addressed through the use of proper CNO controls in addition to transitioning to low-dose clozapine, these steps constrain DREADDs extended duration of action, likely its greatest advantages over optical techniques.

As with chemogenetic approaches, optogenetic methods have not been immune from technical setbacks, even after widespread implementation. Despite over a decade of use in neuroscience, new caveats in the effectiveness of microbial opsins are still being discovered. pH-dependent calcium influxes from sustained activation of inhibitory proton pump opsins such as eArch3.0 can increase spontaneous neurotransmitter release during terminal stimulation [105]. Inhibitory Cl- channels (i.e. eNpHR3.0 & GtACR1), on the other hand, can drive axonal spiking through positively shifted chloride reversal potentials leading to unintended spiking at the onset as well as offset of stimulation [105, 106].

4. Artificial neural network in timing (ANNs)

Despite being inspired largely by neuroscience, ANNs were initially touted for their powerful computational versatility rather than reliable models of neural or cognitive phenomena. Since their conception, the emergence of conductance-based units, biologically inspired architectures and learning rules has made them an invaluable tool for elucidating how the brain works.

4.1 Importance of spiking neural networks (SNNs)

The 'neuronal' unit embodies the fundamental computational element of an ANN and plays a vital role in the overall capacity of the network. As such, computational neuroscientists have dedicated substantial work transforming early 'neuronal' units, based on the binary threshold unit (i.e. McCulloch-Pitts neurons) into conductance-based 'spiking' models [107–111] that include both detailed biophysical models and simple phenomenological models. Implementation of SNNs allows for rate and temporal dynamics nearly equivalent to those found in biological systems [112].

However, with the increased biological complexity comes an increase in computational cost (i.e. number of floating-point operations per 1-ms of simulation). This has led many to opt for computationally simpler units with continuous 'activation-functions' rather than spiking dynamics. While these 'rate-based' networks have

proven successful in revealing network architectures conducive to timing [113] as well as how shifts in excitability drive timing activity [114], they remove temporal components of neural signaling related to that limit their explanatory power. Electrophysiological evidence from neural recordings within the superior temporal sulcus (STS: [115]) and motor cortex (M1: [116]) indicates the brain relies heavily on temporal coding (i.e. coherent inputs). Importantly, increases in coincident spiking correspond with temporally relevant timepoints independent of changes in firing rate [117].

SNNs thalamocortical [118] and corticostriatal [119] networks, both implicated in proper timing behavior, found sharp transitions in spiking activity are important for normal functioning within the network. This speaks to the diversity of spiking patterns present in the brain that can be captured by spiking units [120], yet absent in rate-based networks. The strongest advocates for SNNs question whether any evidence exists for rate-coding with in the brain [121]. Thus, placing the onus on those who utilize rate-based networks for not choosing SNNs.

Additionally, SNNs allow for implementation of both Hebbian and error-based learning rules. This is of note as the network learning rule can have dramatic effects on the connectivity and dictate whether it develops a feedforward topology scarce in both closed and unique loops or strong reciprocal connectivity motifs like those found in the neocortex [122, 123]. Implementation of these spiking neuron models can lead to dramatic improvements in network performance [124]. The effects of neuromodulators on plasticity also contain tight temporal windows (0.3–2 s) between glutamate release and the presence of DA [125, 126], which is difficult to properly model in rate-based models.

4.2 Current use of SNNs in timing research

Generally absent from earlier ANNs, implicit and/or explicit representations of time within neural network models have been relativity recent [127]. Despite this late adoption, there has been a recent surge in research devoted to elucidating the neural substrates of temporal processing, with a myriad of distinct network motifs being proposed [128]. These models vary in biological realism as it pertains to unit dynamics, network structure, and learning capabilities (**Table 1**), influencing not only the dynamical repertoire of the network, but also the ability to extrapolate findings into the biological systems they are looking to study. That being said, even in their most simplistic form, with little adherence to known biology, network models can provide theoretical insight [132], but these models are highly limited.

Adherence to the underlying neurobiology, allows network models to provide deeper understanding into neural substrates of temporal processing. As interpreting *in vivo* pharmacological manipulations must be done with caution, with many drugs acting on multiple neuromodulatory systems, the ability to isolate these neuromodulatory systems in SNNs allows for uniquely systematic approach. Specifically, a cortico-striatal network model allowed researchers to isolate the effects of changing DA concentrations, free of potential 5-HT confounds, and replicating DA's effect on 'clock speed' [130]. In this same model, modulation of Ach produced the accuracy changes found from systemic injections of drugs acting on the cholinergic pathway [67]. Interestingly, Ach modulation in a hippocampal network produced variations in task precision [134] rather than accuracy. Taken together, these networks may provide evidence indicating dissociated networks for these effects. More recent work has also helped elucidate the potential topographical mapping of duration length across the dorsal-ventral axis of the hippocampus [129, 135].

Study unit	Unit type	Network properties			Learning rule		Findings
		Lateral inhibition	Recursive	Modulators	Hebbian	Error driven	
Oprisan et al. [129]	Spiking* (ML)	No	No	N/A	No	No	Hipp. Topology; K*
Oprisan and Buhusi [130]	Spiking* (ML)	No	No	Ach, DA	No	No	Modulator in SBF framework
Reutimann et al. [131]	Spiking (LIF)	No	No	N/A	Yes (rate)	No	FR adaptation accounts for 'ramping' activity
Hilton and Parter [132]	Spiking (prob. threshold)	No	No	N/A	No	No	Connectivity motifs for efficient timing;
Mikael and Gershman [113]	Gaussian 'state' activity	No	No	DA	No	Yes	Bidirectional DA modulation through RPE framework
Laje and Buonomano [19]	Rate units	Yes	Yes	N/A	No	Yes	Intrinsic timing framework; neural trajectories
Simen et al. (2011)	Rate units	Yes	No	N/A	No	Yes	Temporal integration framework; skewness
Perez and Merchant [133]	Spiking (LIF)	Yes	Yes	N/A	Yes	No	Bias property; scalar property

While a spiking model, membrane potential not spikes where used as unit output.

Table 1.
Recent publications of ANN models in the study of interval-timing.

At the synaptic level, computational work using leaky-integrate and fire neurons demonstrated hallmarks of temporal processing such as the 'bias property' and 'scalar property' are strongly influenced by GABAb receptor dynamics [133]. While outside the field of interval timing, work looking at the relationship of pre-post spike pairings to spike-time dependent plasticity (STDP) has shown LTP/LTD dynamics are better explained by 'nearest-neighbor' inputs rather than an 'all-to-all' motif [136]. Together, these finding place limits on theories utilizing temporal integration as a potential mechanism for tracking the passage of time, such as those relying on ramping dynamics. Additional theories relating synaptic plasticity to motor-timing, a sub-field of interval timing, are grounded heavily in computational work due to the difficulty of assessing these ideas *in vivo* [137].

These results align with animal work demonstrating how important biophysical features of neuron signaling such as receptor kinetics directly influence the timing of durations up to 100 s of milliseconds [12]. Therefore, researchers must be

vigilant in selecting the appropriate level of biological complexity for the question they are looking to address. In this way that time perception may be more sensitive than other senses such as vision, where retention of the biological computations can often be sufficient for producing similarities between representations in higher order processing regions [138].

While the above examples have focused on the ability of SSNs to provide support for particular theories, these models have proven to be equally useful in excluding alternative theories as well. For example, ramping activity in the cortex, a potential neural manifestation of timing, can arise from various network architectures. Two such networks employ either recurrent synaptic facilitation or firing-rate adaptation. Yet, additional firing properties seen during delay response tasks, namely equivalent responding to matching and non-matching stimuli is only evident in networks based on firing-rate adaptation [131]. Additionally, it had been postulated that time perception could evolve from sequentially firing populations of neurons [139] and may underlie temporal pattern formation in song birds - a subset of motor timing [140]. However, recent work demonstrated this architecture is incapable of producing fundamental properties of interval timing such as scale invariance [141]. The ability to cast doubt on proposed timing mechanisms is an important quality of computational models. If the technique was flexible enough to validate all theories, it would be of little value.

4.3 Future directions for SNNs in timing research

Integration of SNN models has proven to be an exciting and fruitful avenue for better understanding neural dynamics related to interval-timing. However, there is still ample room for growth. With the implementation of SNNs still in its early stages, the vast majority of these models lack the biological realism necessary to address open questions in the field. Three areas that have either received little attention or would benefit from greater focus are (1) recurrent interactions between timing circuits (2) Neuromodulator effects on timing signals and (3) biologically based model of temporal learning.

As previously mentioned, time perception is supported by an expansive network of brain regions. However, the vast majority of network models aimed at understanding interval timing are at odds with the multi-regional, recurrent nature of the brain. Models of visual processing have shown recursive networks capture multi-regional cortical dynamics absent in strictly feed-forward models [142] as well as behavioral interactions between reaction time and uncertainty [143]. Recurrent connections may also aid in spontaneously developing high degrees of sparseness within a network like that seen in neocortical circuits [144], which allows for larger networks without compromising effectiveness [145]. In addition to being recursive, connection probabilities vary within and between brain regions. Specifically, cortical areas tend to form 'small world' motifs, connecting more often with nearby cells [146, 147].

In other branches of neuroscience, SNNs have shown promise is their ability to selectively manipulate interactions between as well as distinct activity within neuromodulatory pathways. One of particular interest to understanding time perception is phasic and tonic DA signaling. These methods of DA release are believed to be differentially regulated [148] as well as serve different behavioral purposes [149], though our knowledge is still limited. A SNN of the basal ganglia aimed at understanding PD pathology demonstrates, through methodical control of either phasic or tonic activity, that each system differentially contributed to Parkinsonian akinesia and tremors [150]. As tonic-phasic interactions have been shown to have paradoxical effects in drug-seeking behavior [151], SNNs

may provide invaluable for understanding how individual modulation of these two DA dynamics may contribute the paradoxical effects seen in interval timing studies of DA.

SNNs also offer deeper insight into how different neuromodulatory pathways interact in order to produce learned behaviors. Investigating the computational roles of neuromodulated STDP in the hippocampus, researches demonstrated the importance of DA and Ach interactions on learning during a navigation task [134]. Of particular interest was the ability of Ach to enhance precision in navigation, while DA dominated learning overall. This provides insight into a potential mechanism for increases in temporal precision seen from perinatal choline supplementation [152] and dissociates these from changes in accuracy that can accompany increases in precision when Ach is pharmacologically increased [153]. This result expands upon a growing literature dedicated to better understanding synaptic plasticity through spiking neural models [154–156]. Unfortunately, up until this point SNNs dedicated to time perception that have addressed the role of neuromodulators have done so through implementation of their proposed effects, rather than plasticity directly. Additionally, very few models have used a Hebbian learning rule of any type.

5. Limitations of SNNs

The innate connectivity pattern between neurons plays an important role in shaping the trajectory of neural activity within the brain. To this end, biological models can only be as good as our knowledge of the underlying biology. Within the striatum, slight deviations from the biologically relevant range for recurrent connectivity between MSNs is sufficient to suppress the regular sequential firing patterns of coherent cell assemblies found from *in vivo* recordings [157, 158]. While previous neural network models investigating temporal processing within the cerebellum have benefited from its well-characterized, highly conserved cytoarchitecture [159–161], this is not a luxury afforded to those attempting to construct models of other brain regions such as the striatum. Constituting 1.3% of total brain volume in humans [162] and 4% in rodents [163], the dorsal striatum lacks clear internal divisions making it difficult to model accurately. In response, the past decade has witnessed a prodigious effort in mapping the brain's connectivity.

Benefited by advancements in microscopy and neuroanatomical tracing techniques, recent endeavors have uncovered functional domains within regions of the dorsal striatum based on innervation from cortical afferents [164], which can be a valuable tool for modeling timing networks [165]. Further work at the synaptic level will allow for connectivity parameters within neural network models to be tuned more closely tuned to that seen in the brain. However, as this chapter has demonstrated, it is not only through *in vivo* work that our knowledge of the underlying biology can be expanded. Though confirmation inevitably relies on such techniques, theoretical in addition to computational breakthroughs can be done elsewhere.

Along with biological limitations, implementation of many large-scale models – whether in neuron count or complexity – rely on high-speed supercomputers or computing clusters. In labs where computational modeling is not their primary focus, it is impractical to invest the time or money into such resources and therefore places a ceiling on the size and complexity of their simulations. While cost reductions in hardware dedicated to simulating the highly parallel nature of the brain will inevitably address the largest barrier to widespread use of SNNs, providing intuitive software is vital. Along with closed-source options such as MATLAB's,

a fervent movement is currently underway in provide highly versatile packages in Python - an open-source, high-level, dynamic programming language. Simulators such as Nengo [166], NEST [167], and Brian [168] provide varying degrees of control over network properties allowing users to model neurons and circuits at various levels and permitting detailed models on general purpose computing hardware [169].

6. Conclusion

The ubiquity of temporal structure within the brain has made identifying the exact neural processes an arduous task. Single- and multi-unit recordings, along with more recent imaging techniques, have revealed a myriad of neural activity profiles which may underlie temporal processing. Despite technical advancements, the complex interactions between neuromodulators, neuronal activity, and timing behavior has left our current understanding of how the brain tracks durations across multiple seconds decidedly unclear. A promising avenue for overcoming the limitation of current *in vivo* methods is the incorporation of practices form outside the field, such as integration of SNNs. Specifically, through observing how temporal information flows in biologically constrained networks as well as how systematic manipulation of individual neuromodulatory systems changes timing behavior.

Though ANNs are already a staple in other domains of neuroscience, their integration into the field of time and time perception has remained relatively rudimentary with limited attention being paid to biological constraints. It is important to note that the use of these models is not for deciding the exact neural mechanism as that is not possible, but only for providing insight into potentially fruitful options. While ANNs relying heavily on algorithmic abstractions can proliferate theoretical models of timing, a prefect digital recreation of the brain exchanges one black-box for another. In this way the use of SNN for understanding time perception is neither truly top-down not bottom up, but best approximated as 'middle-out'.

We are now at a time where widely available computational resources possess the power necessary for construction of SNNs that retain much of the complexity in biological neural networks. The ability to visualize activity profiles and connectivity patterns across thousands of modeled neurons within and across brain regions provides a level of analysis unavailable through current *in vivo* recording and imaging techniques. Furthermore, simulations of potential avenues for future studies can assess the robustness of competing models in their ability to predict behavioral changes from *in vivo* modulation. Deeper integration of SNNs within the field of timing will provide a powerful resource in both understanding the plausibly neural underpinnings of timing within the brain.

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