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Neural Population Clocks: Encoding Time in Dynamic Patterns of Neural Activity

Shanglin Zhou[1] and Dean V. Buonomano[1, 2]

[1] Department of Neurobiology, University of California, Los Angeles

[2] Department of Psychology, University of California, Los Angeles

The ability to predict and prepare for near- and far-future events is among the most fundamental computations the brain performs. Because of the importance of time for prediction and sensorimotor processing, the brain has evolved multiple mechanisms to tell and encode time across scales ranging from microseconds to days and beyond. Converging experimental and computational data indicate that, on the scale of seconds, timing relies on diverse neural mechanisms distributed across different brain areas. Among the different encoding mechanisms on the scale of seconds, we distinguish between neural population clocks and ramping activity as distinct strategies to encode time. One instance of neural population clocks, neural sequences, represents in some ways an optimal and flexible dynamic regime for the encoding of time. Specifically, neural sequences comprise a high-dimensional representation that can be used by downstream areas to flexibly generate arbitrarily simple and complex output patterns using biologically plausible learning rules. We propose that high-level integration areas may use high-dimensional dynamics such as neural sequences to encode time, providing downstream areas information to build low-dimensional ramp-like activity that can drive movements and temporal expectation.

Keywords: striatum, premotor cortex, neural dynamics, computational model, neural basis of timing

The ability to predict changes in one's environment—for example, anticipate the actions of predators or availability of food—strongly translates into the evolutionary currency of survival and reproduction. For this reason, anticipating and preparing for near- and far-future events are among the most fundamental computations the brain performs. Indeed, the ultimate biological function of memory is to allow animals to learn from past experiences in order to better predict and prepare for the future (Buonomano, 2017; Dudai & Carruthers, 2005; Schacter et al., 2007; Tulving, 2005). Because prediction requires determining both what and when events happen, the brain has evolved the ability to tell and represent time across a large range of time scales from milliseconds to the daily circadian rhythms. Furthermore, in order to interact with a dynamic environment, the ability to tell time is necessary to decode sensory information and generate appropriately timed motor responses. Overall, the brain tells time across over 12 orders of magnitude from microseconds to days and beyond (Figure 1). Across these scales, timing in the range of hundreds of milliseconds to tens of seconds has drawn much attention for its fundamental importance in sensory-motor processing, learning, decision-making, prediction, and cognition (Buhusi & Meck, 2005; Paton & Buonomano, 2018). For instance, catching prey in motion, speech discrimination, playing a musical piece at different speeds, anticipating a reward, all rely on the ability to flexibly tell and encode time on the scale of seconds (Cannon & Patel, 2021; Fung et al., 2021; Issa et al., 2020; Mauk & Buonomano, 2004; Merchant et al., 2013). Similarly, many forms of cognition, such as intertemporal decision-making and temporal attention also rely on timing on the scale of seconds (J. Coull & Nobre, 2008; Namboodiri et al., 2014; Nobre & van Ede, 2018; Sosa et al., 2021).

Given the importance of temporal processing to sensorimotor processing, learning, and cognition, a critical question is how neurons and neural circuits implement timers and clocks. A related question pertains to localization, that is, which brain areas are responsible for the timing of the scale of seconds? For much of the 20th century, it was hypothesized that there might be a single brain area responsible for timing in its many shapes and forms. However, converging evidence over the past two decades indicates that timing relies on a diverse set of mechanisms and brain areas (Figure 1). Specifically, although for any given task, there may be a few brain areas that critically contribute to timing, the role of any given area is likely task-dependent—influenced, for example, by sensory modality, motor requirements, whether the task relies on simple intervals or requires temporal pattern production, as well as temporal scale (Paton & Buonomano, 2018). Indeed, depending on the task, a large number of brain areas have been implicated in timing including striatum, prefrontal cortex, parietal cortex, temporal cortex (including the hippocampus and entorhinal cortex), and

Shanglin Zhou https://orcid.org/0000-0001-7901-615X

Dean V. Buonomano https://orcid.org/0000-0002-8528-9231

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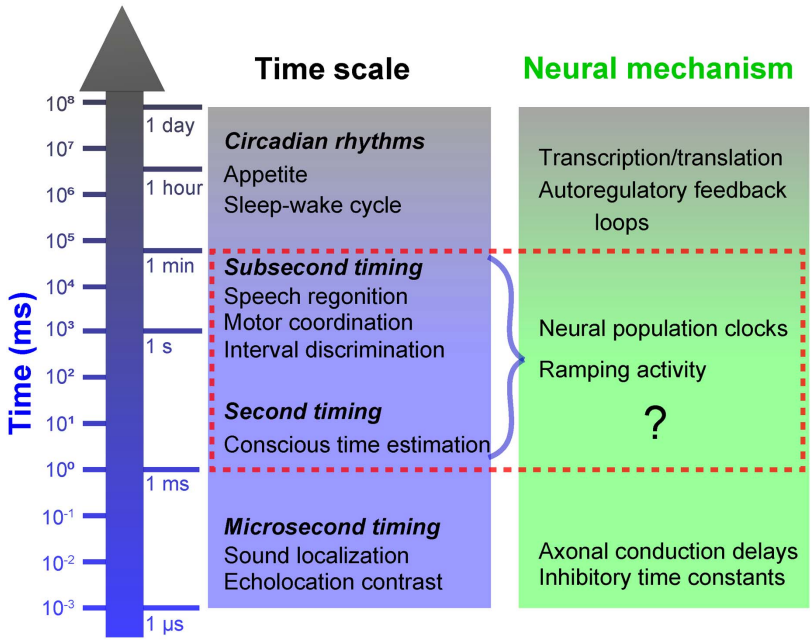
Correspondence concerning this article should be addressed to Dean V. Buonomano, Department of Neurobiology, University of California, Los Angeles, 10833 Le Conte Avenue, Room 73-235 CHS, Los Angeles, CA 90095-1763, United States. Email: dbuono@ucla.edu

Figure 1
Scales and Mechanisms of Timing



Note. Humans can tell time and process temporal information over a scale of at least 12 orders magnitude, ranging from microseconds to circadian rhythms. In contrast to man-made clocks in which a single device can time across many orders of magnitudes, biological systems have evolved fundamentally different mechanisms to tell time across scales. For instance, microsecond discrimination, which is used for sound localization relies on axonal conduction delays, whereas the circadian clock consists of a biochemical oscillator with a period of approximately 24 hr. Timing on the scale of tens of milliseconds to seconds is fundamentally more diverse and complex as it often involves temporal pattern discrimination rather than timing simple intervals and durations. Experimental and computational results indicate that two general strategies for encoding time include neural population clocks and ramping activity. See the online article for the color version of this figure.

the cerebellum (Buhusi & Meck, 2005; J. T. Coull et al., 2011; Giovannucci et al., 2017; Issa et al., 2020; Ivry & Schlerf, 2008; Mauk & Buonomano, 2004; Merchant et al., 2013; Paton & Buonomano, 2018). Additionally, increasing experimental evidence not only suggests that timing information is distributed in different brain areas, but also that it may be the case that temporal information is in a sense transmitted from one area to another and transformed in the process—downstream areas reading out and refining the encoding of time for the task at hand (Bakhurin et al., 2017; Emmons et al., 2017; Zhou et al., 2020).

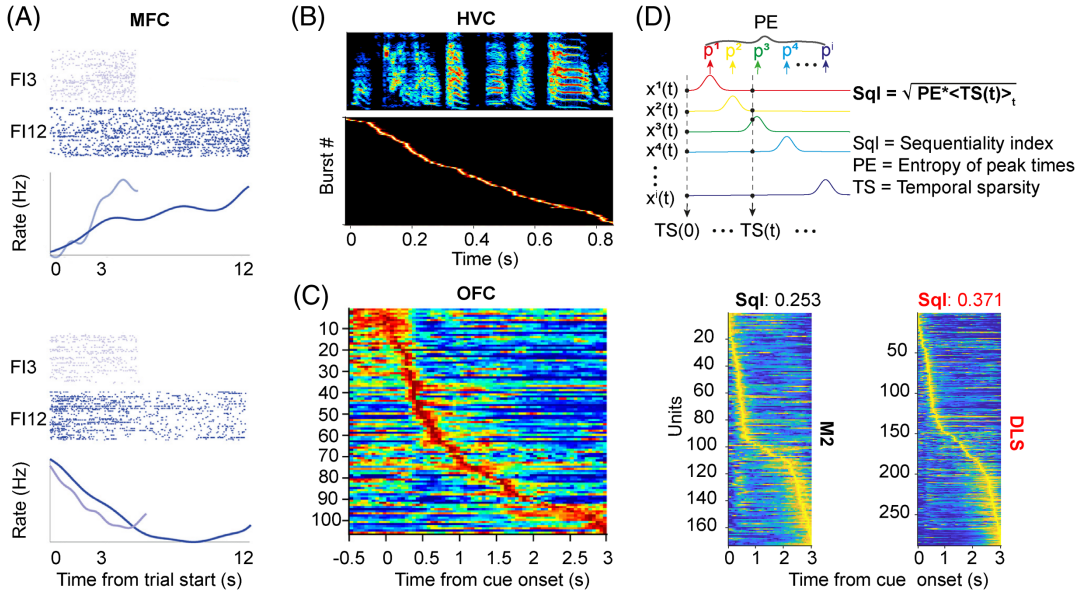
Because of the diversity and required flexibility of timing on the scale of seconds, the neural mechanisms of timing on this scale appear to be more complex than those on the scale of microseconds and days. Fortunately, technological progress and ongoing research over the past two decades have significantly advanced our understanding of how the brain tells time on the scale of seconds. Although early theories of timing focused primarily on oscillator and clock-like mechanisms (Buhusi & Meck, 2005; Creelman, 1962; Gibbon, 1977; Matell & Meck, 2004; Miall, 1989; Treisman, 1963), accumulating experimental and computational evidence indicates that on the scale of seconds, the brain often encodes time through changing patterns of neural activity. Two broad examples of how neurons encode time include *ramping activity* and *neural population clocks* (Figure 2). Ramping activity and neural population clocks represent two distinct dynamic regimes, that is, they require different neural mechanisms to generate them and are characterized by fundamentally different patterns of time-varying neural activity. Below we explore the experimental evidence, neural mechanisms, and computational trade-offs for these two broad timing mechanisms.

Ramping Activity

Experimental research has revealed many instances in which time is encoded in monotonic increases or decreases of firing rates of neurons—that is, ramping activity (Figure 2A). Ramping activity has been observed in a large number of tasks (Brody et al., 2003; Monosov & Hikosaka, 2013; Schultz et al., 1992; Yang & Shadlen, 2007), including timing tasks (Cueva et al., 2020; Emmons et al., 2017; Jazayeri & Shadlen, 2015; Kunimatsu et al., 2018; Leon & Shadlen, 2003; Liu et al., 2019; Narayanan, 2016; Tsao et al., 2018), and can take the form of approximately linear increases or decreases in activity, or exponentially changing firing rates. A key difference between neural population clocks (see below) and ramping activity

Figure 2

Experimental Observed Ramping Activity and Neural Population Clocks



Note. (A) Examples of ramping activity consisting of increases (top) and decreases in firing rate (bottom) recorded in medial prefrontal cortex when an animal expected a reward at either a fixed interval of 3 (FI3) or 12 (FI12) s. Adapted from "Rodent medial frontal control of temporal processing in the dorsomedial striatum," by E. B. Emmons, B. J. De Corte, Y. Kim, K. L. Parker, M. S. Matell, and N. S. Narayanan, 2017. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *37*(36), pp. 8718–8733. https://dx.doi.org/10.1523/JNEUROSCI.1376-17.2017. (B) Example of a neuron population clock implemented as a sparse neural sequence. Sequential activation of neurons in area HVC of songbird (bottom), corresponding to the timing of song (top). Each row represents a burst of a neuron. Adapted from "Rhythmic continuous-time coding in the songbird analog of vocal motor cortex," by G. F. Lynch, T. S. Okubo, A. Hanuschkin, R. H. Hahnloser, and M. S. Fee, 2016. *Neuron*, *90*(4), pp. 877–892. https://dx.doi.org/10.1016/j.neuron.2016.04.021. (C) Example of a complex neural population clock. Population activity recorded in orbitofrontal cortex (OFC) sorted by firing rate peak latency in a mouse anticipating a reward to come at 2.5 s after an olfactory cue at time 0. Adapted from "Differential encoding of time by prefrontal and striatal network dynamics," by K. I. Bakhurin, V. Goudar, J. L. Shobe, L. D. Claar, D. V. Buonomano, and S. C. Masmanidis, 2017. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *37*(4), pp. 854–870. https://dx.doi.org/10.1523/JNEUROSCI.1789-16.2016. (D) Top, schematic of the computation of the sequentiality index (SqI), which depends on two terms: peak entropy (PE) that quantifies how uniform the distribution of peak latencies across the population is, and temporal sparsity (TS) that quantifies how sparse the population neural activity is at a given time point. Bottom, population neural activity sorted by peak latency simultaneously recorded in the secondary motor cortex [M2] (left) and dorsal medial striatum (right) in a mouse performing an anticipatory two-interval task, with the corresponding SqIs on top of each plot. Adapted from "Neural sequences as an optimal dynamical regime for the readout of time," by S. Zhou, S. C. Masmanidis, and D. V. Buonomano, 2020. *Neuron*, *108*(4), pp. 651–658. e5. https://dx.doi.org/10.1016/j.neuron.2020.08.020. See the online article for the color version of this figure.

is that in a ramping code, a single neuron can, in principle, encode time across an entire temporal span. For example, the linear change in the firing rate of a single neuron can potentially provide a simple and continuous code for elapsed time—in practice, of course, the precision of this code on a trial-by-trial basis will depend on the cross-trial variability.

Mechanistically, ramping models of timing have relied on intrinsic neuronal properties (Durstewitz, 2003), or network-based mechanisms relying on positive and negative feedback (Gavornik et al., 2009; Lim & Goldman, 2013; Simen et al., 2011). Ramping activity is often observed in parietal and motor areas during tasks in which animals must generate a motor response during a simple interval (Jazayeri & Shadlen, 2015; Merchant & Averbeck, 2017; Murakami et al., 2014; Narayanan, 2016), but it has also been observed in the striatum (Emmons et al., 2017) and prefrontal (J. Kim et al., 2013; Y.-C. Kim et al., 2017) areas.

Critically, ramping activity also provides a potential mechanism to flexibly scale temporal intervals. For instance, as with standard drift-diffusion models, in the ramping model of timing, the slope of the ramp may be controlled by tonic input with different amplitudes, signaling intervals with different durations (Goldman, 2009; Simen et al., 2011). Indeed, in some reports, the slope of the firing rate over time has been shown to increase when a task requires an animal to shift from a long to a short interval (Emmons et al., 2017; Jazayeri & Shadlen, 2015; Leon & Shadlen, 2003).

Neural Population Clocks

One of the earliest models of timing not based on oscillators or integrators was that the dynamically changing population activity of granule cells in the cerebellum encodes time (Buonomano & Mauk, 1994; Mauk & Donegan, 1997; Medina et al., 2000). A notion that

came to be referred to as a neural population clock (Buonomano & Karmarkar, 2002; Buonomano & Laje, 2010; Mauk & Donegan, 1997; Medina et al., 2000; Paton & Buonomano, 2018). The changing pattern of activity of neurons in a network maps out a reproducible trajectory in neural space (a high-dimensional coordinate system in which the firing rate of each neuron represents an axis). Each distinct point along the trajectory is represented by a vector with elements corresponding to the firing rate of each neuron, which defines the state of the network at a specific time point. Thus, there is a one-to-one correspondence between the states in neural space and a moment in time. Two specific criteria for neural population clocks include: (a) any given neuron encodes relatively little information about the passage of time, that is, encoding a span of time requires a population of neurons and (b) the neural dynamics is a product of the local recurrent connections rather than some intrinsic properties or time constant of individual neurons (Paton & Buonomano, 2018).

Neural population clocks can take the form of many different dynamic regimes, including *neural sequences* and *complex population clocks* (Figure 2B, C). Neural sequences are defined as dynamic regimes in which each neuron is generally only active during a single period within a trial, and the population as a whole tiles the entire time span—resulting in an apparent feedforward chain of neural activity (Figure 2B). In a complex population clock (Figure 2C), neurons can exhibit widely varying patterns of activity, including multiple peaks and a mixture of time fields that potentially include transient ramping.

A diverse set of population clocks has been reported across animals, brain regions, and tasks, including sparse neural sequences (Hahnloser et al., 2002; Long et al., 2010; Lynch et al., 2016), dense neural sequences (Kraus et al., 2013; MacDonald et al., 2011; Mello et al., 2015; Pastalkova et al., 2008; Shimbo et al., 2021; Taxidis et al., 2020; Zhou et al., 2020), and complex population clocks (Bakhurin et al., 2017; Carnevale et al., 2015; Crowe et al., 2014; Jin et al., 2009; Stokes et al., 2013; Wang et al., 2018; Xu et al., 2014; Zhou et al., 2020).

Sparse neural sequences in which a given cell fires a single spike or burst during the entire time span represent one extreme of neural population clocks. Such an extreme code is rare, however, for in most cases, there is significant overlap between the time fields of different neurons, and the peak times of the population are not uniformly distributed across the whole period needed to time. Researchers have developed measures to quantify the sequentiality of the activity of a population of neurons (Orhan & Ma, 2019; Zhou et al., 2020). We have defined a sequentiality index composed of two factors (Figure 2D): (a) peak entropy, which captures the entropy of the peak firing times across the whole population—peak entropy is maximal when the time fields of the neural population uniformly tile the time span; and (b) temporal sparsity, which reflects the number of neurons that are firing at any given moment in time (and is inversely related to the overlap of the time fields). Using this measure, we have contrasted the sequentiality index of simultaneously recorded populations in the secondary motor cortex (M2) and dorsal lateral striatum (DLS) during a timing task. Although both areas encoded time equally well (as quantified by decoders), the sequentiality index was higher in DLS compared to M2 (Figure 2D). These results confirm the notion that multiple brain areas can encode time simultaneously and suggest that different areas rely on different dynamic regimes to encode time.

It is important to note that while in the extreme, neural population clocks such as neural sequences, and ramping activity comprise two distinct time encoding regimes, in practice, the two regimes are not mutually exclusive and can be overlapping. This is in part because all regimes are quite noisy in some instances. Furthermore, in principle, it is possible that apparent ramping can emerge from trial averaging (Latimer et al., 2015; Zoltowski et al., 2019). Additionally, the quantitative methods used to analyze neural population data can also strongly bias conclusions in one direction or another, and many decoding methods are ultimately agnostic to the nature of the underlying code.

To date, the vast majority of experimental studies have focused on decoding time from neural activity while animals perform timing tasks, rather than causally linking the neural activity with behavioral timing. Nevertheless, a number of pharmacological and optogenetic experiments have revealed that inhibiting activity in a number of brain areas, including the striatum and prefrontal cortex impairs (but generally does not eliminate) timing (Emmons et al., 2017; Mello et al., 2015; Murakami et al., 2017; Soares et al., 2016; Wang et al., 2018). More compelling evidence arises from brain cooling experiments, which have shown that cooling specific brain areas can slow or temporally dilate behavioral timing (Long & Fee, 2008; Monteiro et al., 2020; Xu et al., 2014).

As with ramping models, population clocks and neural sequences are also able to account for temporal scaling. Specifically, in computational models, if the recurrent weights of a recurrent neural network are tuned appropriately, the same neural trajectory can be traversed slowly or rapidly depending on the amplitude of a tonic input (Hardy et al., 2018; Wang et al., 2018; Zhou et al., 2022). And on the experimental side, similar neural sequences have been reported to unfold at different speeds during the production of different intervals (Mello et al., 2015; Shimbo et al., 2021; Wang et al., 2018; Zhou et al., 2020).

Quantifying and Contrasting Different Neural Codes for Time

As summarized above, experimental results have revealed a range of different neural encoding strategies for time, including neural population clocks and ramping activity. This naturally leads to the question of what is the computational benefit of using one dynamic regime or another to encode time.

In order to answer this question, it is important to note that the information processing in general does not only require the encoding of information, but also the transmission and transformation of that information from one area to the next, and perhaps most importantly, the efficient use and readout of that information by downstream areas. Accumulating evidence has shown that the encoding of time is distributed in different brain areas, and thus that temporal information is presumably transmitted from upstream to downstream areas and transformed or read out in the process. We propose that although neural sequences and ramping activity can both, in principle, encode time equally well, neural population clocks in general and neural sequences in particular, provide a robust and flexible code for downstream areas to read out time. Whereas ramping activity may provide a better code to prepare and generate simple motor responses.

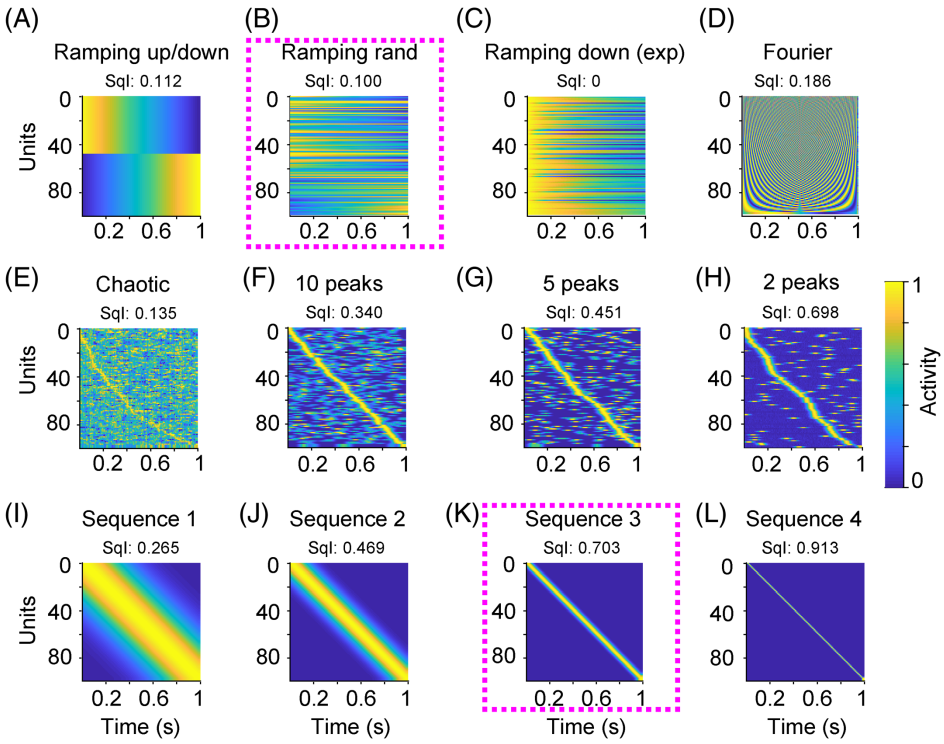
We have previously tested this hypothesis (Zhou et al., 2020) by comparing the ability of downstream neurons to effectively produce

timed responses based on the activity of an upstream network composed of a wide spectrum of different time-varying population activity. The population dynamics of the upstream area included different ramps, sparse and dense neural sequences, complex population clocks, and oscillators (Figure 3). Mathematically speaking, all the prototypical regimes in Figure 3 can be used to encode time perfectly. However, our results showed that when producing complex outputs under biological constraints (e.g., positive weights from the upstream to downstream output units), activity patterns with higher sequentiality performed best. Here, we extend these findings by comparing the ability of two different upstream patterns of population activity to produce simple and complex output without any constraint of the readout weights. The network was comprised of two layers—corresponding to an upstream area that encoded time and a downstream area that decoded time in order to generate a temporal pattern (Figure 4). The dynamics in the upstream area was composed of a population of 100 units that exhibited either a neural sequence regime as an instance of population clock or ramping activity composed of a diverse population of "up" and "down" ramps with different slopes. The goal was to train the feedforward readout weights on the dynamics of the upstream area to generate the output (downstream area) to best match two different targets using a standard least square regression (and allowing positive and negative weights). One target was composed of a series of timed outputs with each composed of a Gaussian-shaped firing rate—one can interpret this target as appropriately timed finger presses on a keyboard. The second target was a simple ramp composed of a single unit that linearly ramped from the start to the end of the whole duration—we can interpret this output as the temporal expectation, or motor preparation, for a reward. The readout performance was quantified as the root mean square error (RMSE) between the generated output and the targets. As shown in Figure 4, although both neural sequence dynamics and ramping activity can generate an output matching the ramping target (RMSEs for both being very low), only the neural sequence can accurately generate a series of time outputs.

From the results of this simple readout model, neural sequences, compared to ramping, provide a more flexible and efficient code to readout time in the sense that they can be flexibly read out by a downstream area to generate either output pattern. Mathematically, the readout units can be viewed as using a set of basis functions (the temporal profile of each upstream unit corresponding to a basis) to regress to a target through readout weights. A clear advantage of the neural sequences is that each neuron in the neural sequence is uncorrelated with the other, providing a high-dimensional set of nearly orthogonal basis functions. Such high-dimensional and orthogonal dynamics can be used to regress to any target, including ramping activity and neural sequences—even when only allowing positive readout weights. In other words, and not surprisingly, the

Figure 3

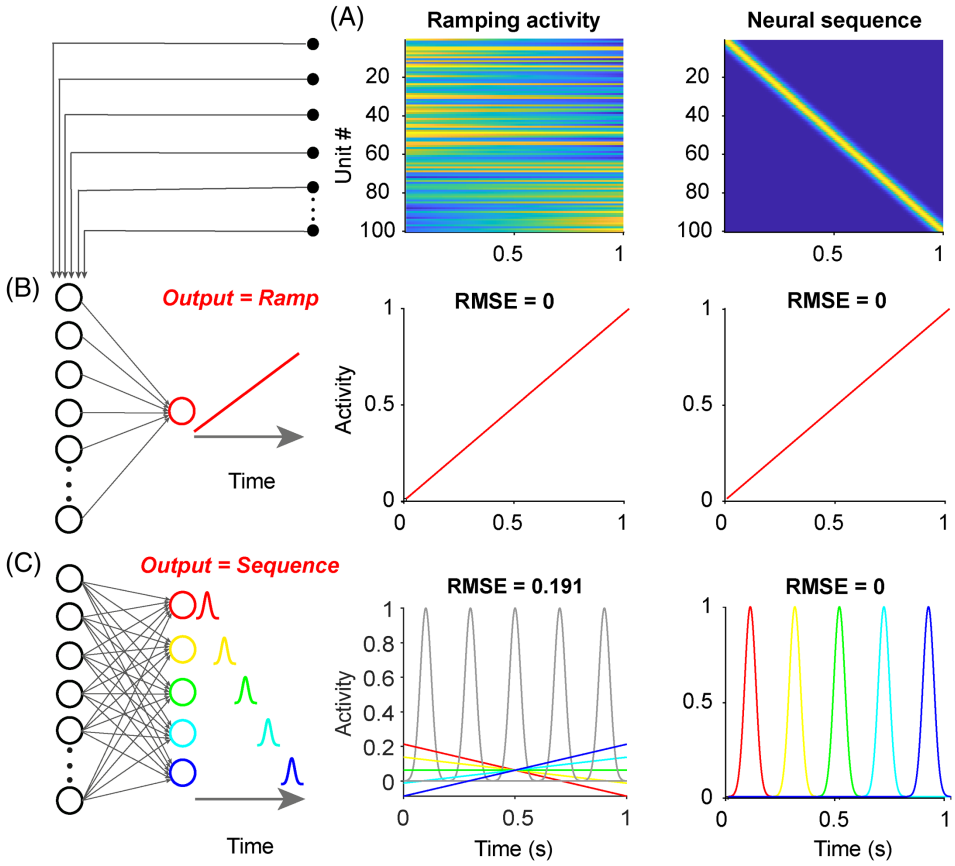
Prototypical Dynamical Regimes for Encoding Time



Note. Examples are based on a number of experimentally observed dynamical regimes, for example, ramping up and down or neural sequence with different temporal sparsity, and a high-dimensional periodic regime ("Fourier"). The corresponding sequentiality index (SqI) is displayed on top. The general regimes reflect ramping (A–C), oscillators (D), complex population clocks (E–H), and dense and sparse neural sequences (I–L). Magenta squares mark the dynamic regimes used in Figure 4. See the online article for the color version of this figure.

Figure 4

Performance of Readout Units Trained to Produce Either a Ramp or a Series of Timed "Taps"



Note. (A) Example of the prototypical ramping (left) and sparse neural sequence dynamics (right, reflecting the magenta squares in Figure 3). (B) Left, schematic of the readout model trained to produce an output ramp driven by the ramping or neural sequence upstream network. The model is composed of the time encoding upstream network and an output layer connected by feedforward positive weights. The output layer is composed of one unit with a ramping target. The goal is to fit the output response to the output target (ramp), allowing for positive or negative weights. Performance is quantified by the root mean square error (RMSE) between the fitted output and the target. Output trace (red) for ramping dynamics (middle) and neural sequence (right) to the ramping target (grey, covered by the output trace) with RMSE on top. Whether the upstream dynamics was a neural sequence or a ramp, the output could be trained to produce a ramp. (C) Same as in B but with a desired output pattern comprised of a series of five timed outputs. Note that the desired output pattern cannot be learned when the upstream activity consists of a population of ramping units. Color lines denote the generated outputs, and the gray lines denote the targets. Note that targets are covered by the output lines due to the perfect match for neural sequence (left). See the online article for the color version of this figure.

high-dimensional neural dynamics of neural sequences allow for readout neurons to form complex output and high-dimensional patterns. In contrast, the low-dimensional dynamics of ramping activity can easily generate low-dimensional outputs (which can be used to time simple intervals or durations) but cannot be used (without additional layers) to generate high-dimensional outputs, such as tapping the keys of a piano without fairly sophisticated decoding schemes.

Conclusions

Over the past two decades, it has become clear that the brain does not have a single area or neural mechanism underlying timing in its many shapes and forms. Converging experimental and computational studies indicate that the major neural mechanisms underlying timing include neural population clocks and ramping activity—although it remains unclear if each relies on dependent or interdependent circuitry. Here, we propose that although both neural population clocks and ramps coexist with the brain, they have distinct computational trade-offs and functions.

Ramping activity and neural sequences can, in principle, encode time equally well. However, neural sequences can provide a high-dimensional set of basis functions, which allow downstream areas to decode time and generate both simple and complex spatiotemporal output patterns using biologically plausible constraints and learning rules. Ramping activity, in turn, provides a means to flexibly encode

simple intervals and durations and is well suited for motor preparation and anticipatory responses. Critically, however, we argue that a key difference regarding neural population clocks and ramping codes for time is that the latter are generally ill-suited to account for the generation of complex temporal patterns such as those that are used in temporal reproduction tasks or Morse code generation (Hardy & Buonomano, 2016; Hardy et al., 2018; Slayton et al., 2020). Thus, we predict that high-level integration areas may use high-dimensional dynamics such as neural sequences to encode time, providing downstream areas information to build low-dimensional ramp-like activity that can drive movements and temporal expectation.

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