combination of more accurate experimental measurements (Kremkow et al., 2016; Lee et al., 2016; Nauhaus et al., 2016) and computational models (Miller, 1994; Paik and Ringach, 2011; Swindale et al., 2000) may soon explain what we thought were complicated parameter relations with some simple connectivity rules.

A better understanding of visual cortical topography is likely to bring important new insights about cortical function. Knowing what and how image parameters are mapped in visual cortex and what parameter combinations are allocated the largest portion of cortical space can help to better understand the building blocks of visual cortical processing. Parameters that are mapped together may be more likely to be wired together in the form of local and long-distance neuronal networks, and knowledge of this topography may help to reveal new rules of cortical connectivity. Visual cortical maps are also closely related to visual

function. For example, humans maximize the visual processing of detail and color by dedicating half of their primary visual cortex to a small fraction of their central retinas while using the rest of the visual cortex to map the binocular visual field. In contrast, rabbits maximize their chances of survival by devoting a large portion of their visual cortex to a horizontal retinal line that help them detect distant predators, while using the rest of their visual cortex to nearly cover a complete visual-field-sphere surrounding their heads. Just as the differences in spatial mapping are closely related to visual function, future research may reveal the functional implications of specific topographic relations that remained hidden by our coarse technical tools.

REFERENCES

Hubel, D.H., and Wiesel, T.N. (1977). Proc. R. Soc. Lond. B Biol. Sci. *198*, 1–59.

Jin, J., Wang, Y., Swadlow, H.A., and Alonso, J.M. (2011). Nat. Neurosci. *14*, 232–238.

Kara, P., and Boyd, J.D. (2009). Nature *458*, 627–631.

Kremkow, J., Jin, J., Wang, Y., and Alonso, J.M. (2016). Nature *533*, 52–57.

Lee, K.S., Huang, X., and Fitzpatrick, D. (2016). Nature *533*, 90–94.

Miller, K.D. (1994). J. Neurosci. *14*, 409–441.

Nauhaus, I., Nielsen, K.J., Disney, A.A., and Callaway, E.M. (2012). Nat. Neurosci. *15*, 1683–1690.

Nauhaus, I., Nielsel, K.J., and Callaway, E.M. (2016). Neuron *91*, this issue, 893–904.

Obermayer, K., and Blasdel, G.G. (1993). J. Neurosci. *13*, 4114–4129.

Paik, S.B., and Ringach, D.L. (2011). Nat. Neurosci. *14*, 919–925.

Swindale, N.V., Shoham, D., Grinvald, A., Bonhoeffer, T., and Hübener, M. (2000). Nat. Neurosci. *3*, 822–826.

Yu, H., Farley, B.J., Jin, D.Z., and Sur, M. (2005). Neuron *47*, 267–280.

Neuronal Mechanisms and Transformations Encoding Time-Varying Signals

Christopher I. Petkov[1,*] and Daniel Bendor[2,*]
[1]Institute of Neuroscience, Newcastle University Medical School, Framlington Place, Newcastle upon Tyne NE24HH, UK
[2]Department of Experimental Psychology, University College London, 26 Bedford Way, London WC1H 0AP, UK
*Correspondence: chris.petkov@ncl.ac.uk (C.I.P.), d.bendor@ucl.ac.uk (D.B.)
http://dx.doi.org/10.1016/j.neuron.2016.08.006

Sensation in natural environments requires the analysis of time-varying signals. While previous work has uncovered how a signal's temporal rate is represented by neurons in sensory cortex, in this issue of *Neuron*, new evidence from Gao et al. (2016) provides insights on the underlying mechanisms.

The song of the cricket and repetitive drumming of a woodpecker are examples of natural time-varying signals created by the periodic repetition of transient acoustic events (Figure 1A). Perceptually, we hear each woodpecker's peck as a discrete event, while the repetitive leg-wing rubbing that produces the cricket song is perceptually fused into a single continuous sound (compare Audio S1 and S2, available online). Why we perceive

slowly repeated sounds as discrete events (flutter perception) and quickly repeated sounds as a continuous acoustic signal (fusion perception) is thought to be a direct result of how these signals are represented by sensory cortical neurons.

The temporal rate of a sensory signal is initially represented in the sensory periphery by a stimulus-locked temporal firing pattern. However, as signals ascend the

auditory, somatosensory, or visual processing pathways, neurons progressively worsen in their temporal fidelity. In the auditory system, for example, although auditory nerve fibers can synchronize their responses to temporal rates above 1 kHz, this upper cut-off of stimulus synchronization decreases at hierarchically higher auditory areas, falling to around only 30–50 Hz in primary auditory cortex (Joris et al., 2004; Wang, 2007). Moreover,

CrossMark

in the somatosensory cortex, stimulus-locked neural activity evoked by flutter vibration seems to be all but lost downstream of primary somatosensory cortex (Romo and Salinas, 2003).

Without the ability to faithfully represent the temporal pattern of the signal with their spike timing, neurons transform the incoming stimulus-synchronized temporal code (Sync) into a neural code no longer reliant on spike timing, referred to as non-synchronizing (nSync). Non-synchronizing neurons that vary their firing rate with the temporal repetition rate of the sensory stimulus are able to encode temporal information with only their firing rate. In somatosensory cortex, both Sync and nSync response can be observed, with nSync neurons increasing their firing rate with stimulus frequency. Interestingly, in monkeys conducting a frequency discrimination task, S1 neurons have been observed that encode the temporal rate of the stimulus using temporal and rate codes. Although temporal coding is generally more precise than rate coding in these neurons, comparisons of neurometric and psychometric functions suggest that firing rate responses more closely match the monkeys' behavior than temporal response patterns (Romo and Salinas, 2003). Thus, rate coding rather than temporal coding may ultimately be the "language" used by sensory cortex to represent perceptual information.

However, neurons typically need to encode multiple features of the sensory stimulus with their firing rate, which creates the following dilemma. Imagine a neuron increases its firing rate with two distinct acoustic features. If the first

A Examples of natural temporally modulated sounds
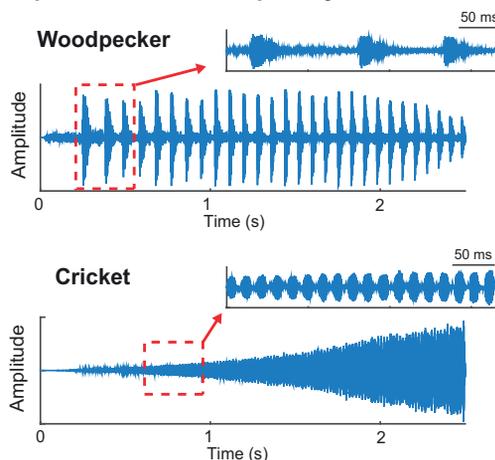
B Types of neuronal responses to temporally modulated sounds
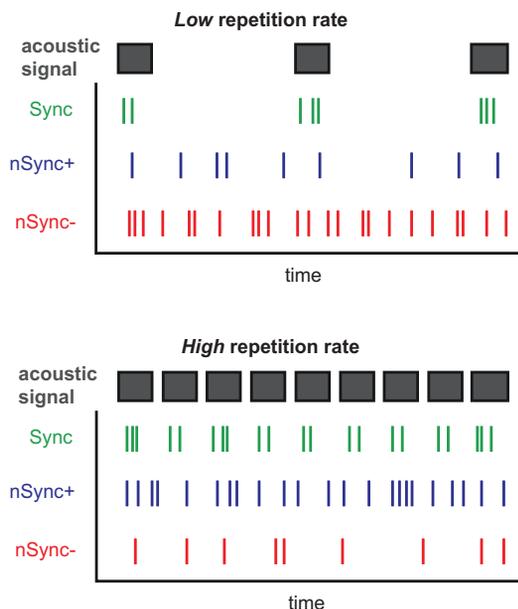

Figure 1. Natural Variation in Sound Rate and Neural Coding Principles
(A) Example sounds with different time-varying features and percepts are the drumming of the woodpecker and the cricket's song; see text and listen to Audio S1 and S2.
(B) Responses of Sync (green), nSync+ (blue), and nSync− (red) neurons to a sequence of acoustic events, repeated at a low repetition rate (top) or a high repetition rate (bottom).

acoustic variable has a low value, causing the neuron's firing rate to decrease, this will also decrease the dynamic range available for encoding the second acoustic feature. The problem is solved if an acoustic parameter is always encoded

with a complementary rate code—one set of neurons increasing their firing rate and one set of neurons decreasing their firing rate—as the acoustic parameter changes. Thus, the neural coding dynamic range is maintained over the entire parameter range, with the relative difference in firing rate between the two populations (rather than absolute firing rate) encoding the acoustic parameter. A complementary rate coding strategy has been observed in both the auditory cortex (Bendor and Wang, 2007) and the secondary somatosensory cortex (Romo et al., 2002) of monkeys. In auditory cortex, this complementary rate code is generated by non-synchronized neurons that increase their firing rate with an increase in stimulus repetition rate (nSync+), and a separate population of neurons that do the opposite by decreasing their firing rate with an increase in stimulus repetition rate (nSync−). Similar neural rate coding strategies have also been reported for spatial localization (Stecker et al., 2005), and thus, opponent coding may be a general property in the brain for rate coding of certain sensory features.

How does auditory cortex transform stimulus-locked thalamic inputs into the variety of response types (Sync, nSync+, nSync−, mixed) that are observed (Figure 1B)? While the existence of these different classes of neuronal responses was first identified by single-unit extracellular recordings in awake marmoset monkeys, this approach could not reveal the underlying mechanisms. In particular, how do nSync neurons "lose" their temporal fidelity? Is this a by-product of competing excitatory and inhibitory dendritic inputs, or the passive biophysical properties of a neuron's membrane potential transforming
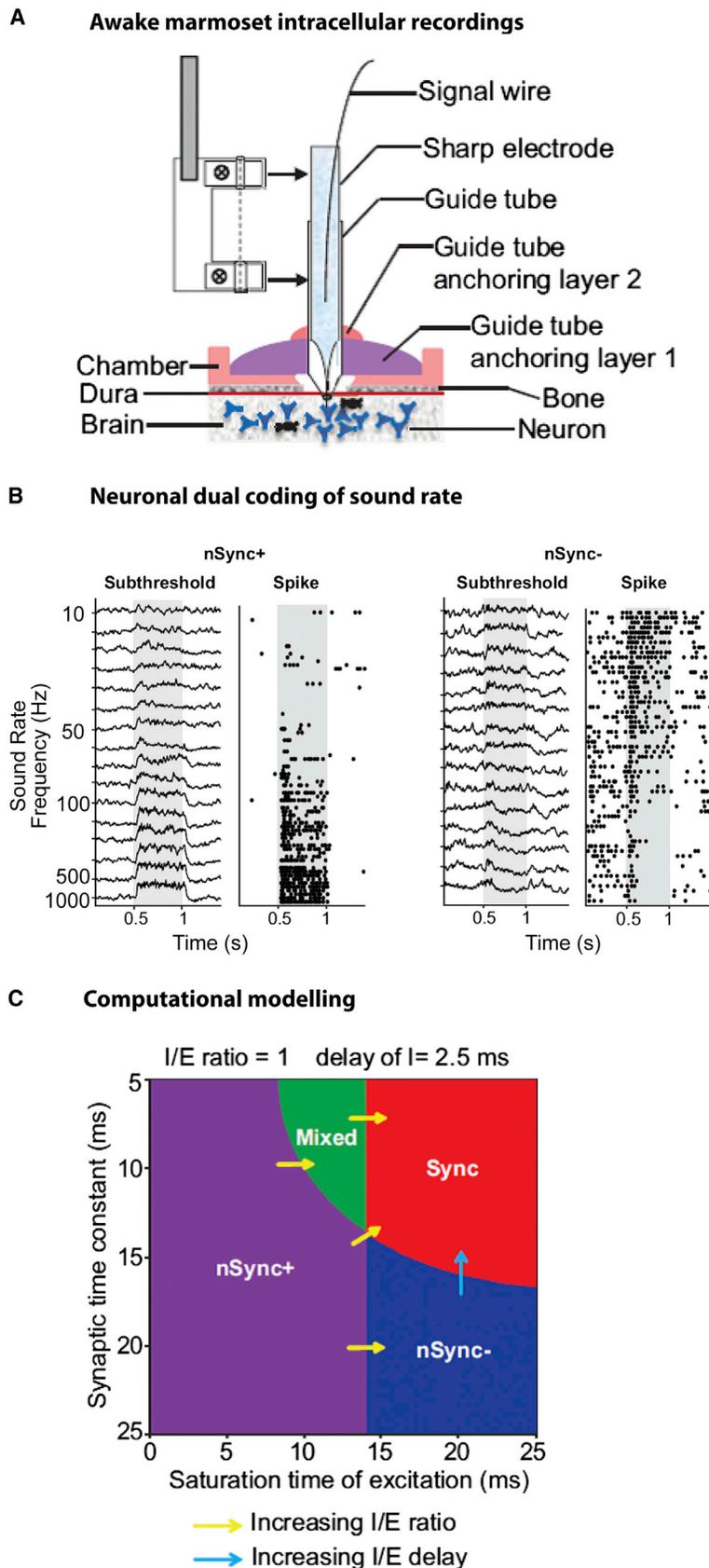
A — Awake marmoset intracellular recordings

B — Neuronal dual coding of sound rate

C — Computational modelling

Figure 2. Neuronal Mechanisms of Rate Coding in Awake Marmoset Auditory Cortex
(A) Illustrated assembly showing approach for sharp electrode intracellular recordings in awake marmoset auditory cortex.
(B) Subthreshold and spiking responses for two categories of non-synchronizing (nSync) neuronal responses representing sound rate with an increase in firing rate (more spikes or greater membrane depolarization for higher sound frequency rates; nSync+) or with a decrease in firing rate for higher frequencies (nSync−).
(C) A biologically informed computational model of excitatory and inhibitory neuronal interactions that give rise to the subpopulations of Sync or nSync+/− neuronal responses. Images from Gao et al. (2016).

neuronal spiking responses? Gao and Wehr (2015) tested this using whole-cell patch-clamp recordings in awake rats and found that the membrane potential of nSync+ neurons stimulus locked at temporal frequencies significantly higher than observed in their spiking responses. In addition, steady-state levels of depolarization increased as the pulse frequency of the stimulus was increased. The authors proposed that push-pull interactions between excitation and balanced, delayed inhibition disrupted stimulus-locked spikes, while overall firing rates increased as the magnitude of excitation increased.

While these exciting results in murine models provide an explanation for how nSync+ responses were generated, the other half of the dual coding model, nSync− neurons, had remained unaccounted for. How auditory cortical neurons generate nSync− responses is rather counterintuitive, because firing rates must increase as the rate of a repeated sound decreases. Since nSync− neurons have thus far only been reported in awake marmosets, understanding how these responses are generated would require a tour de force: intracellular recordings from awake monkeys. Although the difficulties in obtaining stable intracellular neuronal recordings are reduced by anesthesia, this approach could not be used, as it would unfortunately wipe out nSync neuronal responses (Lu et al., 2001). Recent efforts have made it possible to attain high-quality intracellular recordings from awake primates (Tan et al., 2014), and Gao and colleagues (Gao et al., 2016) took this methodology further, developing a novel approach for repeated acute intracellular recordings

from the auditory cortex of awake marmoset monkeys. They designed a recording chamber and guide tube assembly that allowed them to stabilize a sharp recording pipette and achieved an impressive yield of intracellular recorded neurons from each awake marmoset (Figure 2A). These recordings provided the first glimpse of intracellular potentials for the two types of nSync neuronal responses (Figure 2B). For nSync+ neurons, they observed sustained depolarization and an increase in non-synchronized spiking responses at higher stimulus repetition rates (Figure 2B). For nSync− neurons, they noted hyperpolarization of the membrane potential at high repetition rates, coupled with suppressed firing. By contrast, at low stimulus repetition rates these neurons showed sustained depolarization and an increase in spiking. By developing a new approach, this study achieved a cellular-level explanation of the opponent rate-coding model.

To further extrapolate these new results, and previous intracellular and extracellular recordings of neuronal responses to temporally modulate acoustic signals, we turn to computational modeling. A recent computational modeling study based on earlier marmoset extracellular data suggested that Sync responses arise from strong excitation and temporally delayed inhibition, whereas nSync+ responses result from weak excitation, or excitation combined with balanced inhibition (Bendor, 2015). Other computational models also point to the temporal interplay of excitatory and inhibitory activity, but rely on alternative mechanisms, such as push-pull dynamics (Gao and Wehr, 2015) or synaptic depression and facilitation (Rabang and Bartlett, 2011). However, these models fail to explain how nSync− responses can be generated. Armed with their new intracellular

recording results, Gao and colleagues (Gao et al., 2016) were able to model the most extensive set of biophysical processes available to date, modeling Sync, nSync+, nSync−, and mixed neuronal response types. Parameters related to the temporal windows of excitation and inhibition seemed to better model the neurobiological data obtained with the fewest assumptions. Namely, the synaptic time constant and the saturation time of excitation were two crucial parameters; increasing these two parameters in the model gave rise to nSync− responses. The synaptic time constant might reflect integration at AMPA and GABA$_A$ receptors with short time constants, or NMDA receptors for longer time constants. These computational models also help to identify how excitatory and inhibitory balance might shift a neuronal response from nSync+/− to a mixed or Sync response (Figure 2), which has interesting implications for the development of Sync and nSync responses as well as how one type might convert into another.

In conclusion, our understanding of the neuronal mechanisms and biophysical properties regulating how cortical neurons respond to a sound's temporal rate has experienced a recent resurgence. New advances in computationally modeling different response types in auditory cortex beg for another round of hair-raising, challenging technological developments, such as the use of pharmacological agents or optogenetics to manipulate excitatory and inhibitory inputs to determine their causal role in generating Sync, nSync+ and nSync− responses. Alongside these developments, we continue to need approaches that can better bridge the animal model work to that in humans, where, although mechanistic details are largely out of reach, complex forms of rate coding

and entrainment can be studied using speech or other types of rate-varying sensory stimulation (Ding et al., 2016). More complete basic science knowledge of these processes is also likely to be relevant for understanding disorders of sensory processing, especially when transformations of neural codes are disrupted and our ability to extract the environment's dynamic structure is compromised.

REFERENCES

Bendor, D. (2015). PLoS Comput. Biol. *11*, e1004197.

Bendor, D., and Wang, X. (2007). Nat. Neurosci. *10*, 763–771.

Ding, N., Melloni, L., Zhang, H., Tian, X., and Poeppel, D. (2016). Nat. Neurosci. *19*, 158–164.

Gao, X., and Wehr, M. (2015). Neuron *86*, 292–303.

Gao, L., Kostlan, K., Wang, Y., and Wang, X. (2016). Neuron *91*, this issue, 905–919.

Joris, P.X., Schreiner, C.E., and Rees, A. (2004). Physiol. Rev. *84*, 541–577.

Lu, T., Liang, L., and Wang, X. (2001). Nat. Neurosci. *4*, 1131–1138.

Rabang, C.F., and Bartlett, E.L. (2011). PLoS ONE *6*, e29375.

Romo, R., and Salinas, E. (2003). Nat. Rev. Neurosci. *4*, 203–218.

Romo, R., Hernández, A., Zainos, A., Lemus, L., and Brody, C.D. (2002). Nat. Neurosci. *5*, 1217–1225.

Stecker, G.C., Harrington, I.A., and Middlebrooks, J.C. (2005). PLoS Biol. *3*, e78.

Tan, A.Y.Y., Chen, Y., Scholl, B., Seidemann, E., and Priebe, N.J. (2014). Nature *509*, 226–229.

Wang, X. (2007). Hear. Res. *229*, 81–93.