

# Single neuron and population coding of natural sounds in auditory cortex

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The auditory system drives behavior using information extracted from sounds. Early in the auditory hierarchy, circuits are highly specialized for detecting basic sound features. However, already at the level of the auditory cortex the functional organization of the circuits and the underlying coding principles become different. Here, we review some recent progress in our understanding of single neuron and population coding in primary auditory cortex, focusing on natural sounds. We discuss possible mechanisms explaining why single neuron responses to simple sounds cannot predict responses to natural stimuli. We describe recent work suggesting that structural features like local subnetworks rather than smoothly mapped tonotopy are essential components of population coding. Finally, we suggest a synthesis of how single neurons and subnetworks may be involved in coding natural sounds.

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## Introduction

The auditory system is a fascinating sensory system. It has remarkable spectral and temporal resolutions, even in rodents [1–3]. Hearing is not limited by line of sight considerations, enabling animals to get early warning signals about prey, predators, and conspecifics around them, even in complete darkness when vision is limited and even from a distance when odorous cues may be insufficient. Audition is also central to the communication between individuals of a given species and can promote warning and courtship signals. Auditory disorders, while not lethal, can have devastating effects on life quality of any mammalian species, humans included.

The auditory system has a number of highly specialized circuits in the brainstem, but above the brainstem it has a structure that is highly reminiscent of other sensory system (e.g. the somatosensory system; [4]). Thus, audition is an important model for understanding system-specific as well as general rules of neural coding in the mammalian brain. The functional role that areas like primary auditory cortex (A1) play in auditory coding is still largely a mystery. While we have already a fair amount of understanding regarding the responses of single neurons in A1 to simple stimuli, we still do not know how those responses guide perception and drive behavior.

A prerequisite for a mechanistic understanding of neural coding is to understand how both single neurons and populations of neurons respond to real world stimuli. Here, we will review recent progress in our understanding of responses to natural sounds in the auditory system. We will emphasize computations in auditory cortex, to natural sounds, compare them with the responses to simple sounds, and connect both to what we know about processing of sounds by ensembles of neurons. We will propose a speculative framework to unify some of the still disparate findings in these different facets of stimulus coding by auditory cortex neurons.

## The ‘right’ stimulus

Most physiological studies of the auditory system focused on understanding how simplified stimuli (e.g. pure tones, noises, and clicks) are encoded in the brain. Pure tones are fundamental elements of any sound, and are simple to use and manipulate. Perhaps more importantly, pure tone stimuli can drive auditory neurons robustly, with some responding selectively only to specific frequencies [5,6]. Indeed, pure tones have proven highly successful in studying the function of the auditory system, especially in early brain stations. In the cortex, examples include deciphering the global and local organization of A1 [7], revealing cortical phenomena of short term and long term plasticity [8,9], and providing basic insights into cortical development [10,11]. The success of using pure tones in understanding general mechanisms of auditory processing led to the hope that these may also be instrumental in understanding natural sounds. However, starting with the earliest reports, evidence suggested that except in limited conditions (e.g. [12]), one cannot reliably predict the responses of a neuron to a complex sound based on its response profile to pure tones [13–17]. For example, one way to describe tuning properties of single neurons in the

auditory system is by a two dimensional function of frequency and response time called Spectro Temporal Receptive Field (STRF) [18]. Carruthers and colleagues [14] found that STRF-based models capture only a small percentage (on the order of ~15–20%) of the response variance to sounds as simple as mouse ultrasonic vocalizations (USVs), which are to a large extent just amplitude-modulated and frequency-modulated tones. This low prediction accuracy is supported by earlier experiments showing significant differences between STRFs derived from simple stimuli vs. those derived from natural sounds [19,20].

Why are natural sounds important to study in the first place? The main role of the auditory system is to use sounds to drive behavior. Therefore, any sound (either simple or complex, synthetic or natural) which can drive behavior is valid and interesting on its own right. Natural sounds are particularly interesting because, as their name implies, they are what animals encounter in their normal environment. Additionally, natural sounds form the soundscape which shapes auditory circuits during development in an experience dependent manner [21], as well as over evolutionary time scales (e.g. [22]). Natural sounds can be quite complex as they are often mixtures of sounds produced by a number of sources, and may include both narrow and wide spectral components. Unfortunately, the full ‘acoustic biotope’ [23] of any animal has never been characterized. Instead, restricted families of natural sounds that can drive behavior are chosen for specific study. One such family that has been used quite extensively in studies of auditory cortex consists of species-specific communication sounds. Communication sounds (or vocalizations) are thought to be salient to animals in many species across the animal kingdom from singing birds to vocalizing mammals (e.g. whales, bats, rodents, and primates [24–26,27\*,28]). For example, rats are known to emit 22-kHz vocalization in aversive situations and 50 kHz vocalizations in appetitive situations [29,30]. Other rats react to such calls — for example, juvenile rats prefer to interact with rats who commonly emit 50 kHz vocalizations [31].

In mice, several well characterized calls and related behaviors have been studied. A first class of such sounds arise from male mice emitting USVs towards females [32–34], and clearly drive female attraction [35–37]. A second class of vocalizations that has been intensively studied is produced by newborn pups. Pup calls are the main communication means that pups use to actively attract attention of their mothers. The calls are already crisp at birth and continue to develop as the pups mature [38,39]. Mothers perceive the calls and will show preference towards these calls in two alternative force choice bioassays [38,40]. Interestingly, not only females respond to sounds (by males and pups). A recent study shows that males too (in this case fathers), can be ‘called by’ mothers to start caring for their neonates [27\*].

These encouragement calls, identified as 38 kHz USVs, induce parental care behavior by the fathers.

In all examples discussed here, the neural mechanisms connecting the processing of the vocalizations in the auditory system to the behavioral output are unknown. While it has been repeatedly shown that auditory cortex, and earlier stations, shows preferential responses to communication calls [14,21,41–43], the reported differences in neuronal responses were often quite modest. Furthermore, species-specific vocalizations form only a small (although extremely important) part of all auditory inputs in most mammals, and when they occur, they often appear in mixtures with other sounds. Thus, the role of the auditory system in connecting communication calls with behavior may be just a particular case of its role in shaping the ‘auditory objects’ to which animals respond [44]. This argument leads to the prediction that auditory cortex would show preferential responses to any sound that is associated with behavioral consequences.

### Coding of natural sounds

Significant advances have been achieved in recent years in understanding both the phenomenological basis and the biological mechanisms that underlie the complexity of responses to natural sounds in auditory cortex. The weak ability of STRFs to account for the responses of cortical neurons to natural sounds is a good starting point for understanding these issues. This weakness has been traced to at least two factors. The first is the non-linearity of the neuronal responses in auditory cortex (and in some subcortical stations as well; [45]). The non-linear response properties cause biases in the estimation of the STRF [46], making STRFs depend on the sound ensemble used to estimate them [16]. A number of authors tried to get around the problem of non-linearity of spectro-temporal processing in auditory cortex by first calculating sound features that are either non-linear functions of the standard time-frequency representations (such as the instantaneous frequency of a frequency-modulated chirp; [14,47\*]), or are hand-tailored for the task (such as the amplitude and time derivative of the amplitude of an amplitude-modulated noise burst [48\*]). The predictive power of such models may be better than that of the STRF, certainly in inferior colliculus (IC) [47\*], but is still low in cortex [14].

In fact, strong non-linearities in the responses to combinations of narrow-band and wide-band stimuli lead to effects that cannot be even approximated by a linear model based on simple sound features. For example, Nelken and coworkers demonstrated, in a number of studies, very strong occlusion caused by a weak broadband stimulus added to a high-level narrowband stimulus [44,49,50], as well as in the reverse situation of a weak tone added to a high-level broadband noise [51]. Chechik and Nelken argued that such effects are consistent with

the representation of abstract categories rather than the physical structure of the sound, consistent with the notion that auditory cortex represents sounds by their relevance [44].

The second factor that renders STRFs a rather weak descriptor of cortical responses is the context-sensitivity of these responses. The same stimulus may evoke different responses when presented in different contexts. For example, Asari and Zador [52] played sounds composed of a number of 1 s segments that could be permuted, and found that the response to the same segment may depend on the sound as far as 4 s back. Forward masking is probably the best documented form of context-dependence in auditory cortex. It has been studied for some time [53,54], and shown to have rather long recovery times (100's of ms). Wehr and Zador demonstrated that recovery times from forward masking in rat auditory cortex are substantially longer than in the thalamus, suggesting a specific role for auditory cortex in this process [55]. While forward masking has been mostly studied with simple sounds (pure tones and white noise), it has obvious relevance to the coding of natural vocalizations, many of which consist of long trains of short sounds. In recent years, longer contextual dependences in the auditory system have been mostly studied in the context of stimulus-specific adaptation (SSA, [56]). These studies uncovered time constants of tens of seconds and possibly longer [57\*]. Such long time constants are obviously important for shaping the responses to a constantly changing acoustic environment.

What are the biological mechanisms underlying these complex effects? A number of recent studies emphasized the role of inhibitory mechanisms in shaping the responses to complex, natural sounds. Already starting in the IC, inhibition shapes the responses of neurons to complex sounds [43], increasing the variability and complexity of the responses [58]. In auditory cortex, inhibitory mechanisms are also important in shaping the responses of neurons in many ways [59–62]. Inhibition by itself need not introduce non-linearities into the neural responses. In fact, STRFs work better in IC than in cortex, in spite of the importance of inhibition in shaping responses to complex sounds in IC. But there may be two specific ways in which inhibition complicates the coding of sounds in auditory cortex. First, the background activity of many neurons in auditory cortex is very low, and inhibition may contribute to the threshold non-linearity in the responses. An elegant example of such effect has been recently demonstrated in IC [63], where an 'iceberg effect' was demonstrated to be controlled by GABA-A receptors that governs the contrast in the responses to standards and deviants in the context of SSA. Second, inhibition may be multiplicative rather than additive. Multiplicative inhibition has been shown in

visual cortex [64], and similar studies in auditory cortex will be very important.

The other mechanism that has been commonly invoked to account for the complexity of responses in auditory cortex is synaptic depression. Synaptic depression is present in auditory cortex, both in thalamocortical and corticocortical synapses. Synaptic depression is an important component of forward masking. Wehr and Zador [17] used intracellular recordings to demonstrate that both excitatory and inhibitory currents depress, and therefore forward masking cannot be accounted for by long-lasting inhibition. Since recovery times in the thalamus were faster than in cortex, they concluded that forward masking in cortex represents mostly synaptic depression of the thalamo-cortical neurons. David and colleagues [65] compared STRFs estimated using speech (as a natural stimulus) and ripple noise (as an artificial stimulus), and showed that much of the difference between the resulting STRFs can be accounted for by rapid depression of the synaptic input to A1. However, synaptic depression may still be insufficient to account for all context-dependence in auditory cortex. For example, Taaseh and colleagues [66] showed that a model based on synaptic depression substantially underestimates the responses to rare sounds when presented over a background of a single repeated tone. Thus, additional mechanisms that shape the responses of cortical neurons to complex sounds, and in particular to species-specific vocalizations, remain to be found.

### Population coding and maps in auditory cortex

While synaptic and cellular response profiles can provide mechanistic views of how single neurons encode stimuli, neuronal computations are eventually carried out by large cohorts of cells. In fact, population codes bear useful information that can go without notice when studying single cells [67,68]. Extracellular recordings from A1 showed how information (of simple stimuli) flows across its laminae [69]. Under spontaneous activity conditions, incoming input spreads upward from thalamocortical-recipient layers to other layers, and then slowly to neighboring columns while evoked activity crosses to neighboring columns sooner. Although the consequences of these observations to the coding of sounds are not fully understood, they emphasize the role of the cortical circuitry in shaping the spatiotemporal structure of the evoked activity. In a separate study from the same group, Luczak and colleagues found that population activity in A1 is highly structured. The highly structured activity was similar when it emerged 'spontaneously' or when it was evoked by sounds. Interestingly, consistent with the hypothesis that stimuli are encoded on the same footing in auditory cortex, no particular differences emerged in structured activity when the cortex was confronted with

simple tones or with natural sounds (voices from animals in a swamp) [70].

There is rather good evidence that neuronal response properties in A1 show columnar organization, at least in some species like monkeys, cats and ferrets. For example, in the cat A1, both selectivity to tone frequency [71] and binaural response properties [72] have long been known to be organized in columns (for more subtle columnar analyses using STRFs see [73]). More complex sound properties have been shown to possess columnar organization as well, including the tendency to show stimulus-specific adaptation in cats [74], and asymmetry of the inhibitory sidebands surrounding best frequency in ferrets [75]. Notably, the temporal response patterns to natural calls also seem to cluster in columns, as was shown for the representation of the purr call in the guinea pig [76]. In other species, like rats, no columnar organization was obviously evident for pure tone responses [77]. Of note, however, in the rat study loose patch recording was used while in the other studies classic extracellular methods were used which may have a bias towards the more active cortical cells.

Is there additional order beyond columnar organization in A1? In recent years there has been a steady increase in advances of novel technologies to study neural circuits with new kind of detail. Specifically, *in vivo* two photon calcium imaging (i2PCI) has been particularly important because of its superb spatial resolution and ability to penetrate optically into scattering tissue [78]. i2PCI continues to develop and cover a wide range of scales from submicron resolution for structural and functional spine imaging [79], to larger volumes for imaging a few dozens of neurons in close proximity [80]. In the auditory cortex, the use of these new techniques is still in its infancy but has already started to produce interesting new insights about how populations of neurons work in concert. For example, imaging local populations of neurons in A1 showed that neighboring neurons could have both similar as well as diverse response profiles [81<sup>•</sup>,82<sup>•</sup>] yet still share common features as shown by a strong correlation between their signal as well as noise correlations and the distance between them [81<sup>•</sup>]. In a recent study, Bathelier and colleagues studied local network dynamics and found that small cohorts of nearby neurons are activated as distinct modules, suggesting the existence of local subnetworks that share common properties. The transitions between the activity of modules responding to different stimuli were shown to be highly non-linear, suggesting that local subnetworks code categorical information [83<sup>••</sup>]. Local subnetworks have been demonstrated in the visual cortex before and may be a general property of neocortical coding [84]. Recently, *in vivo* imaging and slice physiology were combined to directly show that neurons with shared stimulus response profiles were also preferentially connected to each other,

forming local subnetworks [85]. Moreover, it appears that during development, response properties emerge earlier than subnetworks do (at least in the visual cortex of mice), suggesting that subnetworks may develop *ad hoc* to serve the functional demands of the circuit [86<sup>•</sup>]. As suggested by imaging [81<sup>•</sup>,83<sup>••</sup>], there is good evidence that local subnetworks in auditory cortex exist as well, although their nature, especially in the context of natural sounds, remains to be discovered.

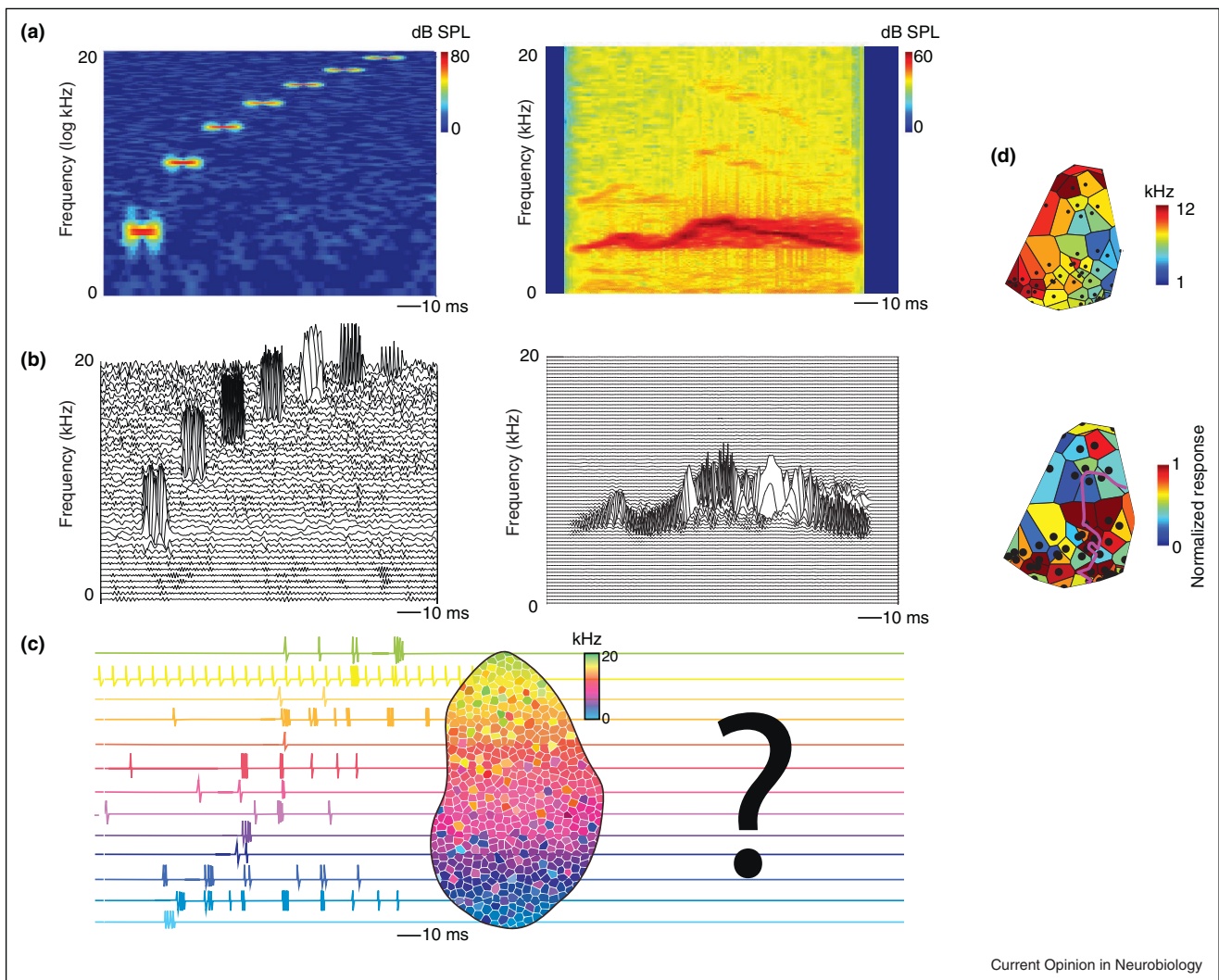
Are functional response properties of neurons in auditory cortex mapped in a continuous way on the cortical surface? The most dominant structural feature in the auditory system is tonotopy. Tonotopy refers to the orderly organization of neuronal responses to pure tones, such that nearby neurons respond to similar tone frequencies. Tonotopy in A1 has been reported in all species that have been examined to date [7]. Nevertheless, recent studies in the mouse auditory cortex reported seemingly contradictory results when tonotopy was measured with high-resolution methods. Two independent imaging studies found rather weak tonotopic order among neurons within <200  $\mu\text{m}$  of each other, suggesting a ‘salt and pepper’ like organization at these short distances [81<sup>•</sup>,82<sup>•</sup>]. Shortly thereafter, two studies (both from the same group) using electrical multiunit recordings argued that tonotopy is robust [87,88]. A closer look at these studies suggests that the differences between these two groups of studies may not be so large despite major differences in measurement techniques and analyses. In both studies coarse-grain tonotopy was clearly present while fine-grain tonotopy was somewhat noisy (as much as 2–3 octaves apart in neurons separated by only 250  $\mu\text{m}$ ).

Regardless of the existence of fine-grain topographical precision, did tonotopy teach us anything new about auditory cortex? The answer is a definite yes — for example, comparing tonotopy under different conditions proved highly useful, particularly in the context of cortical plasticity [7]. For example, Kilgard and colleagues showed that map plasticity is necessary for learning [89<sup>•</sup>]. However, following learning, functional architecture (i.e. map plasticity) returned to baseline. These transient changes strengthen the argument that A1 is highly sensitive to the contingencies of the recent stimulus stream.

Did tonotopy teach us anything about the coding of natural sounds in auditory cortex? The answer to this question seems to be not much. Neither strict tonotopy on the one hand, nor ‘salt and pepper’ (implying more random local connectivity) on the other hand, provide satisfactory explanations for the unique attributes of cortical responses to sounds as discussed above. In fact, it may be puzzling that tonotopy still exists in A1. Unlike earlier auditory stations where tonotopy is a result of frequency decomposition or used for computing



Figure 1



How are simple and complex sounds represented early and late along the auditory hierarchy? **(a)** Spectrograms of 2 sounds. Left: synthesized sequence of 7 short pulses of pure tones from 2 to 20 kHz with low background noise. Right: a recorded bird chirp [13]. **(b)** Basilar membrane responses simulated with AIM-MAT [95]. Left: simulated response of the membrane to the sequences of pure tones from 'a'. Right: simulated response of the membrane to the bird chirp from 'a'. Note that responses are near perfect reflection of the frequency domain of the stimulus. **(c)** Left: illustrated spiking responses of single neurons in auditory cortex. Each line represents the activity of one neuron, in one trial when playing all the pure tone stimuli (from 'a'). The location in the y-axis corresponds to the approximate location of the neuron in A1, according to the map in the center and color indicates the best frequency of the neuron. Center: an illustration of large scale tonotopy of A1 where each polygon represents the best frequency of its region. Right: how single neurons and networks respond to natural sounds may, but probably may not be (hence the question mark) a reflection of the frequencies of the stimulus nor the underlying tonotopic organizations of A1. **(d)** Topographical distributions of responses in A1 from the cat. Top: tonotopic map of A1 that was depicted using pure tone stimuli. Bottom: responses of the same electrode locations to a natural bird chirp (the one shown in 'a'). The magenta line represents the 7 kHz isofrequency contour where most energy of the chirp resides. The panel is a variation of Figure 7, from Bar Yosef and Nelken [13].

attributes which depend on frequency, A1 is different. Intuitively, A1 seems more involved in combining different frequencies that belong to given contexts rather than keeping frequencies apart.

In summary, early in the auditory stream single neurons behave as expected by a mechanism of frequency

decomposition; be it simple or complex sounds (Figure 1a,b). By the time information has arrived to the cortex, the simple frequency decomposition mechanism is no longer the only computation that has occurred, as the stimulus has gone further processing (Figure 1c). Notably, even for simple stimuli like pure tones, the cortex is not a simple reflection of the cochlea as tonotopic

maps are no longer faithful [7]. In fact, A1 seems to be one of last tonotopic regions along the auditory hierarchy. Recently, tonotopy has been suggested to break in the transition from L4 to other cortical layers [90]. However, it may be expected that when complex sounds are used to describe A1s functional architecture, smooth tonotopic mapping is no longer dominant and new patterns of organization will emerge (Figure 1c, question mark). Indeed, in a small number of studies where responses to natural sounds have been mapped in A1, the resulting topographic patterns showed little similarity to the underlying tonotopic map (Figure 1d; [50]).

### Synthesis and speculation

While a full synthesis of all of these results is not feasible at this point, we risk offering a highly speculative peek into what may be a more complete picture of the responses of auditory cortex to natural stimuli. As early as primary auditory cortex, neuronal responses are categorical, presumably linked to the behavioral meaning of the sounds. They are determined by the joint activity of multiple neurons simultaneously and are strongly constrained by single neuron biophysics as well as the network modes that the sensory inputs can evoke. These population properties could be yet another source of non-linearity in the cortical responses, and a major reason for the weakness of STRFs as a link between the responses to simple and complex stimuli. Furthermore, the network properties that determine the responses in this view are the result of plastic mechanisms that are partially developmental but could also occur during adulthood, for example, in processes of learning or other natural life experiences such as recently studied during pregnancy and following birth [91–93,94\*]. This view suggests a mechanistic explanation for the possibility that all sounds, simple as well as complex, artificial as well as natural, are treated on equal footing in auditory cortex — the responses to all of them are determined eventually by factors that are, to some extent, not purely auditory.

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