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Theoretical Limitations on Functional Imaging Resolution in Auditory Cortex

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Abstract

Functional imaging can reveal detailed organizational structure in cerebral cortical areas, but neuronal response features and local neural interconnectivity can influence the resulting images, possibly limiting the inferences that can be drawn about neural function. Discerning the fundamental principles of organizational structure in the auditory cortex of multiple species has been somewhat challenging historically both with functional imaging and with electrophysiology. A possible limitation affecting any methodology using pooled neuronal measures may be the relative distribution of response selectivity throughout the population of auditory cortex neurons. One neuronal response type inherited from the cochlea, for example, exhibits a receptive field that increases in size (i.e., decreases in selectivity) at higher stimulus intensities. Even though these neurons appear to represent a minority of auditory cortex neurons, they are likely to contribute disproportionately to the activity detected in functional images, especially if intense sounds are used for stimulation. To evaluate the potential influence of neuronal subpopulations upon functional images of primary auditory cortex, a model array representing cortical neurons was probed with virtual imaging experiments under various assumptions about the local circuit organization. As expected, different neuronal subpopulations were activated preferentially under different stimulus conditions. In fact, stimulus protocols that can preferentially excite selective neurons, resulting in a relatively sparse activation map, have the potential to improve the effective resolution of functional auditory cortical images. These experimental results also make predictions about auditory cortex organization that can be tested with refined functional imaging experiments.

Keywords

virtual imaging; computational model; self-organizing feature map; SOFM; topographic map; topography

1. Introduction

Functional neuroimaging has become a powerful tool for evaluating the physiological characteristics of large neuronal populations at high spatial resolution. Functional maps of neocortical sensory areas in particular can often elucidate overall neuronal organization more

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clearly than even dense electrophysiological mapping studies. Modern functional brain imaging technologies include optical imaging of intrinsic signals (OIS) and functional magnetic resonance imaging of blood-oxygen-level-dependent signal (fMRI-BOLD), both of which exhibit high enough spatial resolution to reveal functional maps within individual cortical areas (Cheng et al., 2001; Roe and Chen, 2008; Yacoub et al., 2008). Despite having relatively high spatial resolution, however, both techniques still measure phenomena related to summed neuronal activity rather than the responses of individual neurons (Logothetis, 2008; Logothetis et al., 2001). The neural activity summed within an individual imaged pixel/voxel is influenced by the ongoing neural activity of the neurons contributing to the measured response. In particular, if sparse and non-sparse responding neuron populations both contribute to measured activity, they are likely to contribute disproportionately relative to their population sizes. The possibility exists, then, that more information could potentially be extracted from functional images of primary auditory cortex (A1) if the response properties of different neuronal subpopulations were explicitly taken into account.

Auditory cortex has typically been challenging to study with functional imaging techniques, particularly for functional organization beyond acoustic frequency. Early OIS imaging experiments in A1, for example, followed closely upon successful studies in V1 but did not fully recapitulate organizational features known to exist in A1 from electrophysiological studies. For example, pure tone acoustic stimulation in early OIS studies of primary auditory cortex (A1) revealed stimulus-driven activity with nearly circular areas of activation that shifted across the cortical surface with changes in tone frequency (Harrison et al., 1998; Spitzer et al., 2001). Electrophysiological mapping studies, however, have demonstrated that isofrequency regions in cat A1 are long and band-like instead of circular (Cheung et al., 2001; Merzenich et al., 1973; Merzenich et al., 1975; Schreiner and Mendelson, 1990). Several factors may have contributed to these difficulties, including technical factors that appear to have been successfully addressed in later studies. Recent OIS experiments in rat, cat and ferret A1, for example, have more clearly revealed frequency organization, consistent with the findings from electrophysiology and implying that modern techniques can more closely recapitulate classical electrophysiological findings in A1 (Kalatsky et al., 2005; Nelken et al., 2008; Ojima et al., 2005). Recent fMRI-BOLD experiments in macaque monkey A1 have been able to define tonotopic frequency maps (Petkov et al., 2006), as well as crude bandwidth maps (Kayser et al., 2007).

Beyond technical issues and physiological response properties specific to particular imaging modalities, the physiological properties of the auditory neurons themselves, as well as their microcircuitry and their physical arrangements, are likely to limit the efficacy of functional imaging studies. For example, OIS activity in A1 has been reported to increase monotonically with stimulus intensity (Harrison et al., 1998; Ojima et al., 2005; Sheth et al., 2003; Sheth et al., 2004). Electrophysiology studies, however, have shown that these imaging responses are representative of only a subpopulation of A1 neurons whose rate responses increase monotonically with increasing intensity (Brugge and Merzenich, 1973; Erulkar et al., 1956; Pfingst and O'Connor, 1981; Sadagopan and Wang, 2008; Suga and Manabe, 1982). Functional imaging methods therefore appear to be able to discern some features of A1 that are also observed with electrophysiology and consequently have the potential to extend our understanding of A1 functional organization beyond what is possible with electrode mappings that are relatively sparse in comparison. The contribution of aggregate neuronal responses to functional images in A1 is incompletely known, however, and improved understanding of how this process occurs has the potential to augment the inferences that can be drawn from functional imaging studies.

The existence of specialized circuits repeated across the cortical surface implies the need for precise spatial arrangements of neurons in order to achieve efficient feature space

representations and interconnections (Chklovskii and Koulakov, 2004; Koulakov and Chklovskii, 2001; Kozloski et al., 2001; Watkins et al., 2009). For this reason, we investigated virtual functional images of A1 with plausible maps of characteristic frequency (CF), bandwidth and threshold. These neuronal measures reflect the parameters needed to describe frequency response areas (FRAs) and are nonrandomly distributed in A1 (Bonham et al., 2004; Cheung et al., 2001; Merzenich et al., 1975; Philibert et al., 2005; Schreiner and Mendelson, 1990; Schreiner and Sutter, 1992). Outside of frequency, however, the fundamental principles governing physiological feature organization within A1 have been more challenging to discern with electrophysiology. We have previously proposed plausible topographic structures for functional A1 maps based upon theoretical arguments (Watkins et al., 2009). For the current study we used examples of these maps to construct an array of modeled A1 neurons, which were then probed in virtual imaging experiments to determine how response nonlinearities peculiar to the auditory system may affect the results of functional imaging studies. In particular, some A1 neurons (i.e., Type V neurons) inherit from the cochlea a broadening of frequency sensitivity at increasing sound intensities. We explored how this broadening of frequency sensitivity, and the relatively low stimulus selectivity that accompanies this property, may hinder the ability of imaging experiments to detect the underlying physiological properties in A1. Under many circumstances tested, these broadly tuned neurons dominated the imaged responses and led to results similar to those that have been observed in recent functional images. These results indicate, however, that if the relative proportion of selective versus non-selective neurons responding in a particular stimulus protocol could be manipulated, then the effective imaging resolution could be improved.

A brief report of these results has appeared previously in abstract form (Chen and Barbour, 2008).

2 Results

2.1 Neuronal subpopulation responses

Virtual imaging experiments were initially conducted using the computational arrays for each neuronal subtype separately, as shown in Figure 1. Five 80 dB tones spaced one octave apart in frequency were delivered consecutively to each of three arrays consisting entirely of Type V, I or O units. These neuronal designations refer to the shapes of the FRAs and distinguish subtypes based upon the behavior of their frequency bandwidths in response to tones as intensity increases from threshold: Type V bandwidths increase with intensity, Type O bandwidths decrease and Type I bandwidths remain unchanged. The response criterion for attributing a driven response to a particular unit was set at either 10% or 50% of maximum firing (top row or bottom row, respectively). All array elements responding at rates greater than the appropriate criterion are color coded according to the frequency of the tone delivered. Overlapping activated regions are shaded with intermediate colors.

Differences between the response types are rather striking. Type V responses (leftmost panels) showed the greatest overall activity and extensive overlap in some activated areas for tones of different frequencies. Units in areas of overlapping activity showed significantly greater mean bandwidth ($t = 49.4$, $p < 0.001$, student's t test) and lower mean threshold than those in nonoverlapping areas ($t = 54.1$, $p < 0.001$, student's t test). These areas corresponded to the upper left and lower right of the Type V array. The combination of high bandwidth and low threshold creates a large FRA for monotonic responses, allowing for a greater variety of stimuli to activate these units than would activate units with a low bandwidth or a high threshold or both. Type O responses (rightmost panels) showed a very different response profile with much smaller, nonoverlapping, punctate areas of activation. A single pure tone at 4 kHz and 80 dB, for example, activated 24% of the Type V array elements above the 10% response criterion but activated only 3.0% of the Type O array elements. These punctate responses are reminiscent

of cat A1 neurons with patchy axonal projections along isofrequency contours (Ojima et al., 1991). Type I responses showed trends between those of Type V and Type O units with no activation overlap for the tones spaced one octave apart (middle panels). Raising the response criterion (e.g., from 10% to 50%) is a manipulation an experimenter could perform in order to attempt to localize frequency responses more accurately, which these virtual imaging experiments demonstrate would yield a visible improvement in frequency map determination. Type V responses to octave-spaced tones are likely to overlap, however, at regions of high bandwidth, even with relatively high response criteria.

The experiments shown so far were conducted with arrays containing only one type of response FRA. Neurons with different FRAs are generally commingled in A1, however, so combinations of units of different types must be evaluated to understand the expected behavior of the entire cortical area. These combination arrays did not explicitly take inhibition into account, but imaging methodologies based upon correlates of neuronal activity such as blood oxygenation should reveal activity regardless if the neurons are excitatory or inhibitory. Furthermore, without simultaneous sounds at multiple frequencies, excitation is likely to be the dominant process affecting the neuronal responses being simulated, particularly as FRAs are measured by pure tones. Figure 2 shows five different relative proportions of the three FRA subtypes within each pixel of the corresponding array. In this case, each pixel can be thought of as a simple average of its constitutive units. If, for example, 100 units contributed to each pixel of the 50:25:25 array, then 50 of them would be Type V, 25 would be Type I and 25 would be Type O. The stimuli and analysis are the same as in Figure 1 with response criteria applied to the mean response for each pixel. At the 10% response criterion (top row), Type V responses tended to dominate the appearance of the population responses when they represented as little as 20% of the total. Their influence can still be seen even when they represent only 10% of the total (upper right), although it diminished dramatically at higher response criteria, as can be seen with the 50% criterion (bottom row). Both Type V and Type I responses lost all influence on the activated area at the 50% criterion when their individual proportions dropped below 25% (bottom right two panels). In those cases only Type O responses can be discerned, and they are relatively robust. This phenomenon occurs because Type O FRAs contribute the most to pixel averages in those situations, and once the response criterion is set below the contribution of Type O FRAs and above the contributions of Type V/I FRAs, the latter disappear from the resulting image. Depending upon the relative proportion of the receptive field subpopulations within A1, therefore, different response criteria are likely to alter the gross appearance of areas activated by tones. In fact, under the conditions used to create our model array, the response criterion at which tone activation areas fracture into multiple noncontiguous regions exactly matches the relative proportion of Type O FRAs. A similar observation in real functional imaging experiments may provide an estimate of the actual Type O prevalence *in vivo*.

Given the unique receptive field dependences of Type V and Type O responses upon stimulus level, one might expect areas of activation to be functions of tone level. Figure 3 shows activated array areas at 10% response criterion for a pure tone at 4 kHz with level stepped from 20 dB through 100 dB in 10 dB steps. As shown in Figure 3A, activated areas for Type V responses generally increased both along isofrequency contours (upper left to lower right) and isobandwidth contours (lower left to upper right) as a function of increasing tone level. Activated areas for Type I responses, on the other hand, increased only along isofrequency contours until a narrow, contiguous band became active (Figure 3B). Type O responses were different still: activated areas migrated along isofrequency contours from a low-threshold region toward a high-threshold region (Figure 3C). While collectively Type V and Type I array response areas increased at higher tone intensities, array response areas remained constant for Type O responses. This result is consistent with sparseness observations made previously in another computational study (Sadagopan and Wang, 2008). Upon combining the three response

classes in equal proportions into a single array, the resulting activation patterns can be seen to mirror Type V responses closely (Figure 3D). This same trend is apparent at other relative unit proportions (data not shown). Smaller population activation areas, as well as more accurate visualization of sound frequency, can therefore be expected in A1 at lower tone intensities.

Neurons isolated within a cortical column of A1 are known to vary somewhat in their response characteristics (Atencio and Schreiner, 2008; Phillips and Irvine, 1981). In other words, individual neurons within a column may have features that deviate from the relevant feature map. This variability may contribute to challenges in discerning functional A1 maps, both electrophysiologically and through functional imaging. To assess the effects of intracolumnar variation in functional imaging experiments, we modified a population array to map features randomly instead of using deterministic values, as was done for the previous experiments. In the modified array, the maps refer to mean CF, bandwidth and threshold at any given point on the cortical surface. The three FRA response type subpopulations were combined in equal proportions. Each subpopulation was further divided into three additional groupings reflecting unique instantiations of the relevant random variables. If, for example, 100 units contributed to the response of each pixel, then (in round numbers) 33 neurons would belong to each of the three responses types, and every 11 neurons would have feature values drawn from different instantiations of the relevant uniform distributions.

To examine the effects of variations within a cortical column on functional imaging results, we delivered a tone at 4 kHz and 80 dB to a nondeterministic array comprising equal proportions of the three neuronal response classes (i.e., 33:33:33). The resulting responses are shown in Figure 4. The no-variability case (Figure 4A) reflects no randomization, thereby matching the configuration of all the previous arrays. Contour lines representing deciles relative to maximum firing rate can be seen, and the overall structure is noticeably influenced by Type V neurons. As variability is increased to 10%, the response contours are disrupted (Figure 4B), but little overall change in the activated area is evident to the naked eye with one exception: variability appears to have the greatest impact upon regions of the map with the lowest bandwidths and the highest thresholds. This trend continues at 20% variability (Figure 4C) and beyond (data not shown) and implies that even low-resolution functional imaging results may be relatively robust in the absence of a strict cortical columnar structure of functional similarity. To put this finding into perspective, an electrode penetrating a cortical column with 20% variability at a 4000 Hz point in the nondeterministic map would be equally likely to encounter any frequency in the range of 2639 Hz to 6063 Hz—considerably larger than might be expected in catA1 (Atencio and Schreiner, 2008). Even with a clear map of parameter means, such variability could make discerning the structure with sparse electrode penetrations quite challenging, however, while the natural neuronal averaging inherent to imaging could enable a fairly clear depiction of the underlying map.

2.2 Functional Map Extraction

We next examined the feasibility of extracting the original feature maps of frequency, bandwidth and threshold from our virtual imaging results using only pure tone stimuli. For these models, we used a frequency range of 500 Hz to 32 kHz. Figure 5 shows maps extracted using relatively simple procedures (see *Materials & Methods*). CF maps were extracted fairly accurately using only 17 tones (Figure 5A). A small portion of the map in the center of the array (<0.9% of the total map) did not produce any response because the CFs of the units located in these regions fell between the tone frequencies presented, and the bandwidths of these units were very narrow. With a larger number of tone stimuli, these unresponsive areas disappeared (data not shown). Ignoring these areas for the case of 17 tones, the estimated CF was on average 0.048 octaves away from the mapped CF values for arrays with equal

proportions of FRA types and 0.056 octaves for arrays with 10:10:80 proportions of Type V:Type I:Type O responses (data not shown).

Both threshold maps and bandwidth maps were extracted using a large number of pure tones. Mapping both features required tones to be spread out over a variety of sound intensities and frequencies instead of just frequency as in the mapping of CF. For threshold, a large number of tones must be spaced out in frequency to predict an accurate rate-level curve at the CF. If 1377 pure tones are used, threshold maps were also extracted very accurately (Figure 5C). The mean difference between the extracted and the mapped thresholds was 0.84 dB for the arrays with equal proportions of FRA types and 0.68 dB for 10:10:80 arrays. Bandwidth was not so easily predicted, however (Figure 5B). In order to resolve the bandwidth map, the tones must be spaced in frequency no farther apart than at least the lowest neuronal bandwidth.

Furthermore, the intervals of tone amplitudes must be small enough to allow for accurate prediction of the bandwidth at the desired level (in this study, always measured at 10 dB above threshold). With pure tones presented at tenth-octave intervals of frequency and 5 dB intervals of amplitude, the mean difference between the extracted and actual bandwidths was 0.054 octaves for arrays with evenly distributed proportions of FRA types and 0.053 octaves for arrays with 10:10:80 arrays. These errors represent 18% of the range of mapped bandwidths (0.1 to 0.5 octaves), which is considerably higher than the errors for the other two features. While this degree of error does not allow for a fine bandwidth map to be discerned even for large numbers of stimuli, the gross organization of the map can be identified, especially the highest- and lowest-bandwidth regions. Smaller numbers of stimuli may also be just as effective at providing crude estimates of “high-bandwidth” and “low-bandwidth” regions.

Of the three features evaluated for this study, threshold appears to have the least evidence for a consistent map (Cheung et al., 2001). In order to evaluate the effects of threshold mapping on anticipated imaging results, we delivered tones to models of A1 with no threshold map (Figure 6A–C) and observed the resulting activation patterns. Figure 6D–F reveal the tone responses for each subtype in the array with the randomized threshold distribution. Once again, areas with the lowest bandwidth showed the least extent of activation while areas with the highest bandwidth showed the greatest extent of activation. Activation overlap for Type V neurons again occurred in regions with the highest bandwidth. The clearest difference in response to tones relative to the original maps is the lack of punctate activation islands for Type O neurons. In fact, the outline of both Type I and Type O response areas appear to be quite similar to one another, although the Type O response is considerably sparser. Attempting to extract the underlying feature maps with tone stimulation revealed a rather striking finding—the frequency map appears to be rather well estimated by this procedure, and despite obvious errors in the low-bandwidth regions, the bandwidth map was also reasonably well estimated (Figure 6G,H). The frequency and bandwidth maps would therefore be predicted to dominate functional maps of A1 determined by pure tones, particularly if threshold were not mapped in A1 (Figure 6I).

3. Discussion

3.1 Implications of Response Maps on Functional Imaging in A1

Functional imaging studies allow the response properties of large portions of the brain to be analyzed in parallel. These results are achieved by examining combined behavior of many neurons located near one another performing similar functions. Limitations in these studies, however, may stem from technological considerations, such as poor spatiotemporal resolution, from physiological characteristics, such as neurovascular coupling, or from neuronal characteristics, such as lack of a topographic feature map. Functional imaging has traditionally been less successful at inferring novel neuronal behavior in the auditory system than in other sensory modalities. We examined some of the known and postulated functional map properties

of A1 to determine which imaging limitations can be attributed to the neurophysiology and how these limitations might be overcome using modified image acquisition techniques.

The creation and refinement of Type O responses locally within primary auditory cortex (A1) by neurons with similar characteristic frequencies but different bandwidths and thresholds (Tan et al., 2007) implies that the mapping of these three neuronal features may be important for constructing local microcircuits in A1 that give rise to these responses. By constructing theoretical maps of these three features, we were able to replicate results from a recent A1 optical imaging study that in turn matched classical electrophysiological findings (Ojima et al., 2005). In that study large portions of cat A1 were activated with relatively few pure tone stimuli, such that overlapping areas of activation were smallest in the center of A1 and greatest dorsally and ventrally. Our virtual imaging experiments showed that the overlapping regions of activation observed in our model arrays when stimulated by octave-spaced tones were associated with high-bandwidth and low-threshold map regions. Electrophysiological bandwidth mapping studies in cat A1 indicate that high-bandwidth neurons are located toward the dorsal and ventral areas of A1 (Bonham et al., 2004; Schreiner and Sutter, 1992). Threshold mapping studies have not yielded consistent maps as threshold seems to be mapped differently between animals (Cheung et al., 2001; Schreiner et al., 1992). Because our computational feature maps were selected based upon their gross similarities to the organization of those features found in physiological mapping studies, at least in terms of frequency and bandwidth (Watkins et al., 2009), the model array reproduced the dumbbell shapes and overlapping activations seen in images from the Ojima study.

As pure-tone stimuli of higher level are presented to the model arrays, the three response classes exhibit different behaviors that translate into different functional mappings. Type V arrays are the only arrays that exhibit expansion along the tonotopic axis as a function of level, which would tend to lower effective frequency resolution of any imaging technique at higher intensities. When the three response types are combined into a single array, Type V responses dominate the resulting functional maps at most relative proportions of the three response types. The influence of Type V responses can be dramatically reduced by adopting a higher response criterion, however. This effect is achieved because the Type I and Type O elements responding at the highest rates are more compactly organized on the cortical surface than the Type V responses, owing partly to their stimulus selectivity.

The percentage of Type O, intensity-tuned, or “nonmonotonic” neurons reported in electrophysiological studies of A1 has ranged from none to as high as 78% in one study of macaque monkeys (Pfingst and O’Connor, 1981), and many values in between (Bonham et al., 2004; Calford and Semple, 1995; Ojima and Murakami, 2002; Schreiner et al., 1992; Sutter and Schreiner, 1995). The true relative proportion of Type O neurons detectable in A1 is likely to be dependent upon species, anesthetic state, neuronal sampling methodology, stimulus selection and possibly other factors. Our own physiological data from awake marmoset monkeys indicate nonmonotonic proportions in excess of 50% in A1 (Watkins and Barbour, 2008). Given uncertainties regarding the true proportion of Type O neurons across different preparations, however, we elected to evaluate model arrays with various relative proportions of the three response types. It may be possible that simple analytic methods applied to functional images derived from tone stimulation of A1 will enable a more accurate estimate of the true proportion of nonmonotonic neurons. One such technique suggested by our virtual imaging results would be to increase the response criterion until responses to pure tones fracture into multiple disconnected islands along the isofrequency axis. The response criterion as a percentage of maximum response should approximately equal the relative proportion of Type O neurons under such conditions (c.f., Figure 2).

While the properties of neurons within a cortical column are similar to one another, they are not identical and can in some cases exhibit variability, even when a topographic map is known to exist (Abeles and Goldstein, 1970; Atencio and Schreiner, 2008; Imig and Adrian, 1977; Phillips and Irvine, 1981). A rather surprising finding of our study is that even with considerable variability in all three mapped features, the gross structure of A1 activation by a single tone remains relatively constant. Indeed, if the spatial resolution of an imaging modality is lower than the resolution of our array (or, presumably, the columnar spacing in cortex), even extensive feature map variability may not alter functional images substantially. The one likely exception to this observation in the present case is in regions of narrow bandwidth (i.e., small receptive field size). Activity in those regions appeared to dilute along the tonotopic axis and diminish in prominence as variability increased. Thus, even if considerable variability exists in the functional map(s) around some “ideal” map, well-designed imaging experiments may be able to discern the ideal map structure more clearly than electrophysiological experiments, which could be misleading should the number of neurons sampled be too low in the face of map variability. Such a situation may have contributed to early observations from single-unit mapping studies that stimulus frequency was not likely to be mapped in A1 (Abeles and Goldstein, 1970).

3.2 Functional Map Extractions

Pure-tone stimulus protocols were used effectively to extract estimated frequency and threshold maps from our model array that closely matched the actual feature topographies. Tone-based protocols elicited the most error for these two features in map regions of lowest bandwidth. Bandwidth itself proved to be an extremely challenging feature to extract with a reasonable number of tone stimuli. Mapping bandwidth requires high-resolution frequency sampling in order to resolve adequately the activity of low-bandwidth neurons, as well as high-resolution threshold mapping in order to attribute the estimated bandwidth to the proper level (e.g., 10 dB above threshold). Since the bandwidth of Type V responses is a function of stimulus level, errors in estimated threshold maps will greatly increase the error in bandwidth estimation for these units in particular. (Note that the threshold map estimates depicted in Figure 6I are reasonably accurate, although the situation depicted represents the limiting case of no threshold map whatsoever.) Furthermore, even with a large number of stimuli (over 1000 pure tones for the estimated map in Figure 5B), the extracted maps of bandwidth were crude. While they revealed the overall shape and the organization of the actual map, the estimated maps had a relatively high degree of error compared with the frequency and threshold maps. Attempts to map bandwidth in A1 based upon functional imaging experiments have generally attempted simply to identify “high-” and “low-” bandwidth regions (Kayser et al., 2007). In our simulations, identifying high-bandwidth regions was relatively straightforward based upon overlapping areas of activation from tones of different frequencies. Low-bandwidth regions can then be identified as active pixels that do not demonstrate overlap at a particular tone frequency spacing and level. We have not been able to devise a practical stimulus protocol that improves upon this procedure. Any method of mapping a distinction between “high-” and “low-” bandwidth regions likely represents a reasonable approach for determining the general structure of the A1 bandwidth map.

While Type V responses may diminish imaging resolution in general, particularly for wideband sounds, they paradoxically appear to aid in the extraction of frequency maps using pure tones. Their large bandwidth in response to high sound level helps decrease the number of stimuli needed to resolve the frequency map for all of A1. Because only the maximum firing rate of the fitted frequency response curve was used to assign a frequency to a given pixel, the saturation from the Type V units did not affect our ability to extract the CF. The increased receptive field size allowed the neuron to respond to a larger number of stimuli, which provided more points on the FRC to create a better curve fit. This finding may be attributable to our

knowledge of the FRC shapes in advance and may not be applicable under physiological conditions where Type V FRCs are not perfect Gaussians. While estimated map accuracy was consistent across all the relative proportions of response types we tested, the absolute firing rates for the equal-proportion arrays were much higher than for the 10:10:80 Type V:Type I:Type O arrays. Physiological accuracy of estimated maps may vary from what we predict, therefore, depending upon noisiness of the neuron activity and the actual response type proportions.

3.3 Experimental Techniques Predicted to Improve Imaging Resolution

Our simulations indicate that any stimulation paradigm preferentially emphasizing Type O neurons is likely to improve the observed spatial resolution of functional images in A1. First, raising the response criterion for attributing pixels to a given frequency under pure-tone stimulation is one technique that preferentially emphasizes Type O neurons. Second, because the total number of Type O responses elicited as a function of stimulus level is relatively constant for the total number of Type V/I responses increases, delivering stimuli at lower intensities raises the relative proportion of Type O responses. Finally, the temporal response properties of Type O neurons appear to differ from those of Type V/I neurons (Watkins and Barbour, 2008). Exploiting differential adaptation may allow the creation of stimuli designed in temporal blocks that preferentially activate Type O neurons at a particular point in time.

3.4 Limitations in Virtual Imaging

Several caveats exist regarding the physiological applicability of the virtual imaging model used for this study. First, the feature maps used here were based upon theory rather than specific findings within A1, although under appropriate constraints the theoretical maps match known topographies of A1 (Watkins et al., 2009). While our theoretical maps assume independence of different features mapped within A1, these features may not be mapped completely independently of one another (Cheung et al., 2001; Philibert et al., 2005), which may influence functional images. Furthermore, thresholds are not evenly distributed when the auditory system is adapted to silence and tend to be concentrated toward lower values throughout the auditory system (Watkins and Barbour, 2008). Absolute thresholds are also dependent upon frequency because of the filtering effects of the outer and middle ears, leading to higher neuronal thresholds at lower and higher frequencies. These phenomena could affect the activated areas of the simulated functional images, although of the three features studied, threshold appeared to have the least effect upon observed activation patterns. The trends we have observed are robust under many conditions that we tested, however, and are unlikely to be disrupted by minor variations in the underlying feature distributions. In fact, frequency and bandwidth maps appear to be nearly as easily extracted if threshold has no map structure whatsoever (c.f., Figure 6). In any case, the main goal of this work has been to devise hypotheses about A1 organization that are testable with real imaging experiments, which would represent more convincing validation of refutation of these hypotheses than additional model manipulation.

Although not explicitly taken into account in the computational models, real neurons have responses shaped by inhibition as well as excitation (Ojima and Murakami, 2002; Tan et al., 2007; Wang et al., 2002; Wehr and Zador, 2003), and inhibition has the potential to alter responses to complex stimuli in particular. One likely role of this inhibition is to create selective neuronal responses. All of the virtual imaging experiments described here exploited the delivery of pure tones. The three types of FRAs described reflect canonical compact A1 receptive field behavior in response to pure tones. Neuronal responses to wideband stimuli exhibit more variety than is apparent with the three FRA types presented here, typically manifested as increased selectivity, which is most likely created through inhibitory mechanisms. When activity from selective and nonselective neurons is averaged together, the resulting activity most closely resembles the nonselective neuron. This phenomenon was

exhibited for combinations of Type V (nonselective) and Type O (selective) neurons in Figure 2. Furthermore, imaged activity likely reflects as much subthreshold activity as suprathreshold (or more). Given that Type O neurons can be created and refined by local circuits within A1 (Tan et al., 2007), Type V, I and O neurons are likely to be intermixed physically in A1, leading to the relatively nonselective response behavior that we explicitly modeled, although their distribution does not appear to be entirely uniform (Schreiner et al., 1992).

Inhibition also likely plays a critical role in shaping the responses of A1 neurons to dynamic acoustic stimuli. We deliberately confined our experiments to imaging experiments conducted with pure tones that remain on for a relatively long period of time in order to investigate steady-state neuronal behavior. This approach provides a simpler set of conditions to evaluate than is possible with dynamic stimuli. Furthermore, many imaging technologies have relatively low temporal resolution and cannot resolve rapid neural events, so the virtual experiments described here would be adequate for making predictions relevant to these technologies. The virtual functional imaging approach described here could readily be adapted to more biologically realistic functional topographies and neuronal responses, including the transient responses observed electrophysiologically in response to dynamic stimuli.

Finally, the procedures described here represent idealized imaging experiments. We did not introduce neuronal noise, imaging noise, motion artifacts, etc., into the virtual images of this study. It is possible, though unlikely, that noise sources commonly encountered during functional imaging experiments may systematically bias the resulting images. If that were the case, then real functional images may not recapitulate features of these idealized experiments because of this noise. Instead of modeling noise, we chose to focus upon inferences that could be drawn regarding neuronal maps from noise-free images. The degree to which actual functional A1 images correspond with our predicted findings, given the inevitability of noise in the measurements, are probably best evaluated directly in physiological experiments. It is likely that the results of such experiments will allow refinements of our virtual imaging protocol to extend the hypotheses of neural organization presented here.

4. Materials and Methods

4.1 Frequency Response Area Modeling

Neuronal responses in auditory cortex have long been known to be either monotonically nondecreasing (i.e., increasing or saturating) as stimulus intensity increases or nonmonotonic (i.e., decreases at the highest intensities) (Brugge and Merzenich, 1973; Erulkar et al., 1956; Pfingst and O'Connor, 1981; Suga and Manabe, 1982). When probed with pure tones varied in frequency and amplitude, a portion of the monotonic neurons demonstrate increasing bandwidth as well as increasing rate at characteristic frequency (CF) as intensity increases, consistent with responses observed in the auditory nerve (Kiang et al., 1965; Palmer and Evans, 1980; Sachs and Abbas, 1974). Neuronal responses to individual pure tones can therefore be characterized into three major categories based upon the shapes of their frequency response areas (FRAs): Type V, Type I, and Type O neurons (Phillips et al., 1985; Sadagopan and Wang, 2008). Type V and Type I responses are monotonic and Type O responses are nonmonotonic functions of sound level. Type V responses exhibit wideband receptive fields with increasing bandwidth as stimulus intensity increases, while the Type O and Type I responses exhibit relatively narrowband receptive fields with nearly constant bandwidth across their full dynamic range. Type O receptive fields in A1 have been observed with a variety of circular and oval shapes (Sadagopan and Wang, 2008).

While spectral responses in A1 as a function of sound level can reveal a great deal of variety (Sutter, 2000; Sutter and Schreiner, 1991), we have focused our model initially upon the stereotypical responses observed around the major frequency input for any given neuron. FRAs

of the three canonical response types described above represent receptive field characteristics as a function of frequency and sound level and were modeled in the current study as combinations of Gaussian functions. Cross-sections of FRAs at fixed intensities demonstrate neuronal tuning properties and are referred to as frequency responses curves (FRCs). These curves were created with a Gaussian density function for all FRA types, and the increasing bandwidth of the Type V responses were modeled by increasing the standard deviation of the Gaussian as the stimulus intensity increased:

$$FRC(F) = \frac{1}{\sigma \sqrt{2\pi}} e^{-(F-\mu_f)^2/2\sigma_f^2},$$

where μ_f is the mean frequency of the FRC, σ_f is the standard deviation, F represents frequency, and FRC represents the frequency response curve. For Type I and Type O responses, σ_f is a constant while for Type V responses, $\sigma_f(I)$ increases proportionally with intensity.

Level response curves (LRCs) were created with a Gaussian density function for Type O responses and a cumulative Gaussian distribution function for Type V and Type I responses:

$$LRC_o(L) = \frac{1}{\sigma \sqrt{2\pi}} e^{-(L-\mu_i)^2/2\sigma_i^2} \text{ and } LRC_{v/I}(L) = \frac{1}{2} \operatorname{erfc}\left(\frac{-(L-\mu_i)}{\sigma_i \sqrt{2}}\right),$$

where μ_i represents the mean level of the LRC, σ_i represents the standard deviation, L represents the stimulus level and LRC represents the level response curve for either Type O responses or Type V/I responses. The complementary error function is given by

$$\operatorname{erfc}(x) = \frac{2}{\sqrt{\pi}} \int_x^{\infty} e^{-t^2} dt.$$

For Type I and Type O responses the outer product of the appropriate LRC and FRC was computed to obtain a template FRA. For Type V responses a unique FRC was computed at each level and scaled by the appropriate value of the LRC. The resulting FRA was normalized to take on rate values between 0 and 100 in order to normalize the overall receptive field activity for each unit regardless of its response subtype. Our own data collected from 544 well-isolated single neurons in awake marmoset monkey A1 reveal no significant difference in maximum firing rate between monotonic and nonmonotonic neuron populations, and while maximum rates are typically less than 100 spikes/s, that number represents a convenient value for standardized quantification. The FRA parameters for any given unit in the model array (CF, threshold, frequency bandwidth, and dynamic range) were set to desired values by scaling and shifting the FRCs and LRCs appropriately. The frequency was scaled to define the frequency bandwidth and shifted to set the CF to its desired value:

$$F = f_c \cdot 2^{F_0 \frac{b}{b_0}},$$

where F and F_0 denote new and initial frequencies, respectively, f_c represents the characteristic frequency, and b and b_0 refer to the new and initial bandwidths. The level was shifted and scaled differently between the monotonic and the nonmonotonic responses. For the monotonic responses, the level was scaled to define the responsive range of the rate-level response, then shifted to set the threshold and saturation point to the desired values:

$$L=(L_0 - s_0)\frac{(s - t)}{(s_0 - t_0)} + s,$$

where L and L_0 represent the new and the initial levels, respectively, s and s_0 represent the new and initial level maxima, and t and t_0 represents the new and initial level thresholds. The responsive range of a unit was considered to extend between its threshold and level maximum (i.e., best level). For Type I and Type V responses, the response at the point of saturation (threshold + dynamic range at the CF) was then obtained and was set to the maximum response:

$$R=\frac{0.9(R_0 - 0.1)}{(R_s - 0.1)} + 0.1,$$

where R and R_0 represent the new and initial response rates, respectively, and R_s is the response at the point of saturation. Any responses greater than 100 were set to 100 after scaling.

For Type O responses, the level was scaled to set the dynamic range appropriately and shifted to set the threshold and peak level:

$$I=(I_0 - t_0)\frac{a}{2a_0} + t + a,$$

where I and I_0 represent the new and the initial intensities, respectively, t represents threshold, and a represents the dynamic range. The maximum modeled level for Type V and Type I responses was set to 100 dB. The threshold was defined as the sound level that produces 10% of the maximum firing rate at the CF. The bandwidth was calculated at 10 dB above the threshold at CF by finding the frequency range in octaves between upper and lower frequencies that elicit 10% of the maximum firing rate.

In our model, the dynamic range was defined as the range between threshold and best level of the response for Type O responses, and the range between threshold and saturation for Type V and Type I responses. For Type V and Type I responses, the dynamic range was normally distributed with a mean of 30 dB and a standard deviation of 20 dB, and for Type O responses, the dynamic range was normally distributed with a mean of 20 dB and a standard deviation of 10 dB. If the actual dynamic range for a particular unit was randomly set to a value below 10 dB, that dynamic range was redefined as 10 dB. If the sum of the threshold and the dynamic range was greater than the maximum modeled level, the dynamic range was set to the difference of the maximum modeled level and the threshold. These dynamic ranges approximated our awake marmoset recordings where the dynamic ranges yielded a mean of 29.9 dB and 17.3 dB for monotonic and nonmonotonic neurons, respectively. These numbers were slightly higher than the average 80% dynamic ranges (i.e., 10% of maximum firing to 90% of maximum firing) for these monkeys (Watkins and Barbour, 2008) and somewhat higher than the average 80% dynamic ranges for barbiturate anesthetized cats, where mean dynamic ranges fell between 12 and 19 dB (Phillips and Hall, 1986; Schreiner et al., 1992). Overall, the total range of dynamic ranges in our model match well the total range of values that has been reported physiologically. Note that the above discussion does not explicitly take into account the response range of type O neurons for levels above best level, which is randomized for each unit and is not mapped in the model.

Simulated firing rates were obtained from the model by delivering individual pure tones to the modeled FRAs. The firing rate was obtained directly from the point on the FRA corresponding

to the frequency and level of the stimulus. The responses were then normalized, so that the maximum response of each FRA type equaled 100 spikes/s. The responses modeled are the simplest that capture the desirable response characteristics likely to be reflected in functional images of A1, although more complex FRA shapes do exist in A1 (Sutter and Schreiner, 1991).

4.2 Self-Organizing Feature Maps

The self-organizing feature map (SOFM) is a dimensionality-reduction algorithm that projects n feature dimensions—in this case physiological features—onto the two anatomical dimensions of the cortical surface. For example, SOFMs can generate spatial arrangements of neuronal properties well-matched to topographies observed in functional imaging studies of primary visual cortex (V1) (Farley et al., 2007; Obermayer and Blasdel, 1993; Obermayer et al., 1992; Yu et al., 2005). Similar studies have not been made for A1, likely because of the lack of an A1 organizational structure as clear as that in V1. Our SOFM inputs were adapted to create reasonable models of A1 topographies for neuronal CF, bandwidth and threshold. These features are sufficient to determine the previously described FRA shapes derived from individual pure tones and have been determined to be nonrandomly distributed in A1 (Cheung et al., 2001; Philibert et al., 2005; Recanzone et al., 1999; Schreiner and Mendelson, 1990; Schreiner et al., 1992; Schreiner and Sutter, 1992). Higher weightings of a feature lead to greater preservation of mapping uniformity and compactness of that feature. The relative weighting can be interpreted as representing the relative importance of a particular feature in the coding strategy of a given cortical area (Swindale, 2004; Yu et al., 2005). For the 10:2:1 weighting of this study, a uniform distribution of CF (in log units) across frequency space is emphasized five times more in the SOFM algorithm than bandwidth mapping and ten times more than threshold mapping. The properties of SOFMs relevant to functional topographies in A1 are evaluated more thoroughly in (Watkins et al., 2009).

4.3 Model of Primary Auditory Cortex

A1 was modeled by three fully overlapping arrays representing the three different canonical FRA classes. An SOFM was used to define the position and the FRA properties (i.e., CF, bandwidth and threshold) of each unit in each array. All arrays were square with 150×150 units. The particular SOFM selected for this study had relative feature weightings of 10:2:1 for CF, bandwidth, and threshold, respectively because these weightings created CF and bandwidth maps that demonstrate similarity to those seen in sparse electrophysiological recordings in A1 of anesthetized cats (Schreiner and Mendelson, 1990; Schreiner et al., 1992; Schreiner and Sutter, 1992). Frequency is mapped smoothly in the resulting SOFM with the tonotopic axis running along the diagonals of the underlying grid. CFs ranged from 500 Hz to 32 kHz and were distributed uniformly on a logarithmic scale. Bandwidths (measured at 10 dB above threshold) ranged from 0.1 to 0.5 octaves with a median of 0.3 octaves, and thresholds measured at 10 spikes/s ranged from 0 to 75 dB with a median of 35.8 dB, which are values consistent with those observed in awake marmoset A1 (Sadagopan and Wang, 2008). The functional maps used for this study can be seen in Figure 7.

Units in the arrays were assigned FRAs using two different methods for different experiments: the combined method and the variable method. Both methods yielded multiple independent map instantiations indexed by the same grid coordinates. Each instantiation contained a single type of FRA with an SOFM defining the locations and characteristics of the units. Stimulus response for each instantiation was normalized to the maximum firing rate of its corresponding type. Each instantiation was then weighted to adjust for differing relative numbers of units belonging to each of the response types. Activity of all of the instantiations at the same index point (pixel) in response to a given stimulus were summed together to create an overall response. The combined method included three instantiations, each containing only one of the

three different FRA response classes and without randomization of CF, bandwidth and threshold maps.

The variable method used nine total unit instantiations with three different instantiations for each FRA type. Variability was added to the CF, bandwidth, and threshold maps to create pixel-by-pixel misalignment between each instantiation in terms of functional properties. This procedure was intended to simulate the variability in neuronal FRA characteristics observed within individual cortical columns. We quantified variability at a single array location for each feature as a percentage of the total feature range. Each of the three mapped features (CF, bandwidth, and threshold) at each point in the SOFM grid was remapped from the values indicated in the map to a random value within $[m - \frac{1}{2}(v \cdot r), m + \frac{1}{2}(v \cdot r)]$, where m is the mapped feature value, v is the percentage variability and r is the feature range. For frequency and bandwidth the variability was calculated in terms of octaves. For threshold the variability was calculated in terms of level in dB. If any response feature was randomized outside the absolute lower or upper limits of the relevant defined values, then that feature was assigned the limit value. For both combined and variable responses, the sum of all the response rates at each pixel was assigned to that pixel in the resulting population map. The summed responses across all pixels of the array were then normalized to a maximum spiking rate of 100 spikes/s.

To examine the response characteristics of the model, we delivered five separate logarithmically spaced pure tones (1, 2, 4, 8, and 16 kHz) and examined the resulting areas of activation in the model array. Areas of activation were identified by visualizing all pixels with response rates above criterion values of either 10% or 50% of the maximum rate. The average firing rate of the array was obtained by calculating the arithmetic mean of all the pixels. The mapped bandwidth and threshold values for the regions with overlapping areas of activation at the 10% response criterion (i.e., pixels activated by two or more tones) were compared to the bandwidth and threshold values for the activated regions without overlapping activation. Statistical comparisons between the bandwidths and the thresholds in the overlapping and the non-overlapping areas of activation were made using a student's *t*-test.

4.4 Functional Map Extraction

Functional maps with CF range [500 Hz, 32,000 Hz] were extracted using pure tones. To extract frequency, seventeen pure tones ranging from 250 Hz to 64 kHz were delivered at 80 dB and half-octave frequency intervals to combined arrays with either 33:33:33 or 10:10:80 relative weightings of Type V:Type I:Type O. For each point on the array, a Gaussian was fitted to the FRC resulting from the tone delivery. The mean of the Gaussian was designated as that point's CF. Bandwidth and threshold maps were extracted using 1377 pure tones at tenth-octave frequency intervals ranging from 250 Hz to 64 kHz and at 5 dB level intervals ranging from 0 to 80 dB. To extract the threshold maps for each indexed point, the maximum response for each stimulus level was obtained to create a rate-level response curve. This curve was then linearly interpolated and 10% of the maximum response was set as the threshold. Using the extracted threshold maps, the bandwidth at each point in the array was estimated at 10 dB above the threshold previously estimated for that point. The bandwidth was calculated by finding the frequency distance in octaves between the lower and upper frequencies that activated the unit at least 10% of the maximum firing rate. The values were then capped with lower and upper limits of 0.1 and 0.5 octaves.

To quantify the accuracy of the extracted maps, the error between the SOFM maps and the extracted maps was calculated. For frequency, the error at each pixel was calculated by taking the difference in octaves between the mapped and the extracted frequency. For bandwidth and threshold, the pixel error was calculated by taking the difference between the mapped and the extracted values. The mean error was then obtained by averaging the error for each pixel over the entire array.

The maps of CF, bandwidth, and threshold that we used in our virtual imaging experiments can be seen in the top row of Figure 7. Each point in the array (also referred to as a pixel or a unit) represents a single frequency, bandwidth, and threshold combination used to determine the properties of the three relevant types of receptive fields, depicted as FRAs. Examples indicated by A, B, and C in Figure 7 depict nine units divided into classes by column, but with identical features in each row. Differences in FRA shapes across each row derive solely from the nature of the receptive fields themselves while the differences down each column derive solely from different parameter values.

This model system was used to explore a common experimental observation from functional imaging studies of A1: extensive activation of large areas of cortex by pure tones. A pure tone represents the stimulus at a particular sound level that activates the smallest proportion of sensory epithelium in the cochlea. Equivalent stimuli in the visual and somatosensory systems would be a point of light or a pinprick, respectively. As seen in Figure 8, OIS experiments reveal that a single pure tone can activate a sizable portion of A1 (Harel et al., 2000; Harrison et al., 1998; Ojima et al., 2005; Spitzer et al., 2001), which contrasts with imaging results from other sensory modalities (Das and Gilbert, 1995; Grinvald et al., 1994). Even tones spaced an octave apart still elicit overlapping areas of A1 activation. Collectively, the four tones depicted in this figure activate most of A1. We wanted to evaluate if this extensive spread of activation could be attributed to the underlying physiology of A1.

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Figure 1.

Virtual imaging experiments reveal distinct patterns of primary auditory cortical activity for each of the three canonical receptive field categories. Five pure tones delivered sequentially to an array of Type V neurons at 80 dB and spaced one octave apart in frequency collectively activate a large proportion of the underlying area, including substantial overlapping activity (left column). This pattern is evident both when the neuronal response criterion for inclusion is set at 10% of the maximum response for each pixel (top row) or 50% (bottom row). Similar patterns are seen for Type I neurons, although with less overlap and overall activation at map areas of higher bandwidth (middle column). In contrast, smaller isolated patches of cortex are activated by pure tones for Type O neurons (right column).

Figure 2.

When the overall neuronal population contains a mixture of receptive field types, the resulting functional maps depend upon the relative activity of the subpopulations. Relative proportion of Type V/I responses decrease from left to right, while relative proportion of Type O responses increases. At the lower detection criterion of 10% (top row), Type V responses tend to dominate the maps even when they represent a minority of responses. At the higher detection criterion of 50% (bottom row), the contribution of Type V/I responses to the overall functional map diminishes as their relative proportions diminish.

Figure 3.

Stimulus amplitude predominantly affects the maps of Type V responses. **A.** As the amplitude of a pure tone at 4 kHz increases, Type V subpopulation responses increase in area parallel to the frequency axis. **B.** Type I response areas increase orthogonally to the frequency axis. **C.** Type O response areas do not increase. **D.** Population responses comprising equal proportions of the three subtypes demonstrate increasing activation area parallel to the frequency axis as tone amplitude increases because of the Type V contribution. For all large plots, each pixel is assigned the gray value of the lowest level to which its underlying array element responded. Insets show array responses to a tone at one level with grayscale values corresponding to response rate.

Figure 4.

Variability in map fidelity predominantly affects regions of low receptive field bandwidth. A pure tone at 4 kHz and 80 dB was delivered to an array with equal proportions of the three neuronal subtypes. The value of each of the three mapped stimulus features was mapped to each element of the array (i.e., pixel) as uniformly distributed random variables whose means were the feature values for the exact map. Variability in the random maps is presented as a percentage of the total feature range. Results from stimulating the exact (deterministic) map are shown on the left (**A**) and standard deviations of the random variables increase toward the right with 10% variability (**B**) and 20% variability (**C**). Deciles of rate response are depicted in grayscale. The map areas most clearly affected by randomized mappings correspond to the narrowest receptive fields and, secondarily, the highest thresholds.

Figure 5.

Feature maps can be extracted using sequentially delivered pure tones. **A.** Seventeen pure tones were delivered at half-octave frequency intervals at 80 dB, and the fitted frequency eliciting the greatest response at a given pixel was assigned to that pixel as its characteristic frequency (CF). CF extraction using pure tones produced an accurate estimation of CF, except for small regions in the center of the map where receptive field bandwidth was narrower than the frequency spacing. **B.** Bandwidth maps were extracted using many pure tones at tenth-octave frequency intervals and 5 dB amplitude intervals. Using the extracted threshold maps, the bandwidth was measured at 10 dB above the estimated threshold. Relatively large errors were generated with this technique. **C.** Threshold maps extracted using the same tone stimuli as in B produced relatively accurate map estimates. Each pixel in the extracted threshold map was assigned the lowest stimulus level that elicited a spiking rate above the response criterion.

Figure 6.

Frequency and bandwidth maps affect the virtual images the most. **A–C.** Revised feature maps identical to that shown in Figure 7 except that the threshold map has been randomized. **D–F.** Virtual images in response to sequential tones as in Figure 1 but with the randomized threshold map. The type V responses exhibited more activation overlap and greater dispersion at the narrowest bandwidths, similar to the effect observed with map variability (Figure 4). Type I responses exhibited little change while Type O responses lost their punctuated appearance. **G–H.** The same map extraction procedure applied in Figure 5 is effective at extracting the new map features, including as robust an estimate of frequency and bandwidth as was obtained previously.

Figure 7.

Self-organization of primary auditory cortex functional properties. In the model, three relevant neuronal receptive field features are mapped: center frequency, bandwidth and threshold. Candidate maps for each of these features are presented in the top row. Each map reflects the same physical array of artificial cortical neurons. Three different sites in the array are labeled A, B and C, reflecting three different values for each of the three features. Below, each of these feature values is applied to the three major types of receptive fields observed in auditory cortex. Even at the same frequency, bandwidth and threshold, Type V neurons have larger receptive fields than Type I neurons, which in turn have larger receptive fields than Type O neurons.

Figure 8.

Sample intrinsic optical imaging experiment from cat primary auditory cortex. In this experiment pure tones were delivered sequentially to the animal at a sound level of 60 dB and over a total frequency range of about 2.5 octaves. The areas with statistically significant change in absorbance with respect to baseline are shown in color. Tones separated even by an octave of frequency can activate overlapping regions. Collectively, these four simple stimuli activated nearly all of primary auditory cortex. Adapted from (Ojima et al., 2005) by permission of Oxford University Press.