

INVESTIGATING INFORMATION CODING IN THE AUDITORY MIDBRAIN

PhD thesis book

Domonkos Áron Horváth

János Szentágothai PhD School of Neurosciences
Semmelweis University



Supervisor: István Ulbert, D.Sc

Reviewers: László Négyessy, Ph.D.
Bence Rácz, Ph.D, habil.

Head of the Complex Examination Committee: Zoltán Benyó, D.Sc

Members of the Complex Examination Committee: József Pucsok, D.Sc.
Gergely Szabó, Ph.D.

Budapest
2023

Introduction

Detection of events in space is essential for any creature. Interestingly, the notion of space cannot be encoded without using an additional dimension: time. In the avian and mammalian brain, localization of sound direction is based on the added dimension time. The location of a sound source is inferred by the brain using the differences in the neuronal signals transmitted from the two ears upon sensation of a sound. The arrival time of sound in the inner ear depends on the horizontal location of the sound source related to the ears. If a sound source is not exactly in front or behind the animal, sound will reach one of the two ears with a time delay. The temporal evolution of such time-of-arrival differences can be used to localize the sound source. In my thesis work, I investigated the strategies applied by auditory midbrain neurons to maintain the robustness of information coding when facing changes in interaural time difference (ITD) and sound intensity.

1. Objectives

Thorough investigation of the problem outlined in the previous section requires the application of effective quantitative methods that can capture the coding properties of the recorded single neurons and neuronal populations.

My first objective was to prove the effectiveness of genetic algorithm in the optimization of neuronal population decoding. When decoding the responses of neuronal population, it is essential to find optimal weights for each neuron in the population to maximize decoder performance. I show in my thesis that genetic algorithm can be used to find the optimal set of weights for decoder performance maximization.

My second objective was to reveal the effects of interaural time difference and sound intensity on the coding of low frequency sounds in the auditory midbrain of the Mongolian gerbil. In my thesis, I carried out careful analyses to reveal if changes in intensity and ITD affect neural responses in different ways. As a result, I show that at least at moderate intensities, the auditory system employs different strategies at the single neuron and population levels simultaneously to ensure that the coding of sounds is robust to changes in other stimulus features.

2. Methods

To fulfil my first objective, distance metrics was applied on neuronal spike trains for decoding. Distance metrics is a cost-based metric introduced by Victor and Purpura in 1996. In cost-based metrics, the distance of two spike trains is the minimal cost of transforming one spike train to the other. In the most widely used type of this metric, inserting, or deleting a single spike has a cost of 1. The other rule of spike time metrics states that the cost of moving a spike in time (shifting the spike) is proportional to the amount of

time that it is moved. By applying these rules, the distance between two spike trains will be the minimum total cost of the above defined steps transforming one spike train into the other. This distance metrics provide an intuitive method for decoding neural responses, as responses to the same stimulus should be closer to each other, while responses to different stimuli should be farer.

The advent of multiple channel recordings, advanced spike sorting methods and high computational power computers enables researchers to study the influence of multiple identified neurons on decoder performance. After decoding the spike trains for every trial of every stimulus as described above, we measure overall performance as the percent of spike trains that were correctly decoded and denote this quantity as PCp for a single cell p , and $PCP(w)$ for the population P with weights w . The standard approach to finding the optimal set of weights, i.e. the set of weights that maximize $PCP(w)$, is to calculate the gradient $dPCP(w)/dw$ and use it as a guide toward a local, and hopefully global, maximum. However, for the problem considered here, analytical specification of the gradient was not possible and algorithms that calculated the gradient numerically performed very poorly. Fortunately, there is another class of algorithms known as ‘evolutionary’ that do not require knowledge of the

gradient. These algorithms operate iteratively, choosing the best of several candidate solutions on each iteration until performance saturates. Out of the many evolutionary algorithms that may be suitable for this problem, I implemented genetic and particle swarm algorithms. The performance of these two algorithms was similar but genetic algorithm required less computational time and it was easily implemented using the Matlab Genetic Algorithm and Direct Search Toolbox with the following parameters: $y = 25$ initial vectors, $e = 2$ elite vectors, $x = 18$ crossover vectors, $u = 5$ mutation vectors, $V = 100$ maximal number of generations, and less than $\varepsilon = 10^{-5}$ change in best weights in the past $G=25$ generations. To prevent overfitting, it is important to exclude the responses to be decoded when optimizing the weights. For all optimizations, we split the responses into successive training sets (95% of responses) and testing sets (5% of responses) such that all responses were included in the testing set exactly once.

For my second objective, I recorded the activity of single neurons in the inferior colliculus of anesthetized Mongolian gerbils. The neural responses were evoked by acoustic noise snippets presented with different ITDs and intensities. A total of 5 different ITDs and 3 different intensities were presented, resulting in 15 different stimulus conditions. The same sound stimuli were presented without and with the addition of background noise. Spike train decoding was also performed on the

neural activity recorded in these experiments to determine the tuning significance of the recorded neurons to the different stimulus conditions. To characterize decoder performance between the different stimulus conditions and between the without and with background noise conditions, I applied statistical tests on the recorded data.

3. Results

By applying a genetic algorithm to find optimal decoder weights for the decoding of neural spike trains, I found that genetic algorithm outperforms other methods, such as assigning equal weights to every neuron, determining weights by the response error correlations of the neurons, and applying particle swarm algorithm. This finding was true without and with the addition of background noise, as shown on Figure 1 and Figure 2.

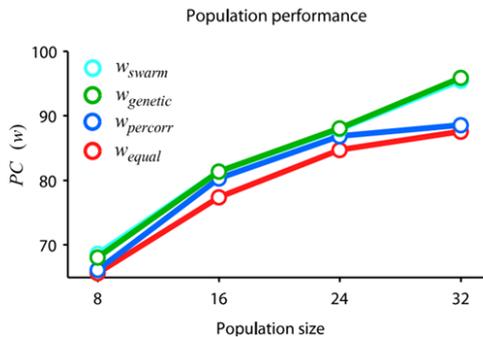


Figure 1. The decoder performance $PC_P(w)$ for subpopulations of increasing size for four sets of weights, without background noise.

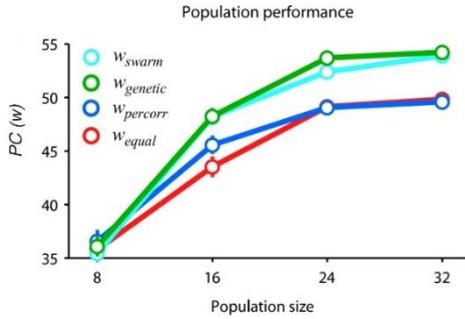


Figure 2. The decoder performance $PC_P(w)$ for subpopulations of increasing size for four sets of weights, with background noise.

For my second objective, I first characterized the firing changes of the recorded neurons in response to the 15 different stimulus conditions.

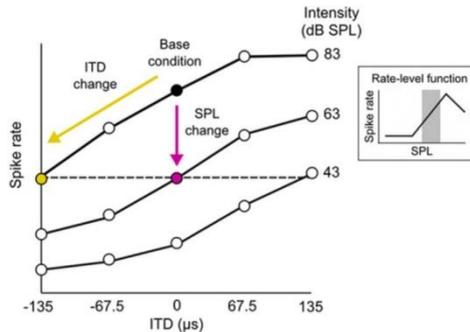


Figure 3. A schematic diagram depicting the relationship between the three stimulus conditions.

As shown on Figure 3, only those cells for which the intensity change condition could be defined by a change in intensity along the positive slope of the rate-level function (RLF) were analyzed. To study the effects of changes in intensity and ITD beyond those

that result from changes in overall spike rate, I analyzed only responses from those neurons for which I found a decrease in intensity and a negative change in ITD that caused approximately the same decrease in spike rate relative to an arbitrary base condition (the base condition could be any intensity/ITD combination and was chosen independently for each cell) (Figure 3.). Because the sampling of the space of possible intensity/ITD combinations was relatively sparse, only 19 neurons satisfied this criterion (the reductions in spike rate for the intensity change (Δ SPL) and ITD change (Δ ITD) conditions relative to the base condition for these neurons were not significantly different; paired Wilcoxon test, $p = 0.08$; median reduction was 29% for Δ SPL and 30% for Δ ITD). By analyzing the responses of these neurons, I found that, relative to the base condition, the change in intensity caused a change in the overall timing of events, reflected by the decrease in correlation coefficients (CCs) between the PSTHs for the base and the intensity change condition, but had little impact on precision of spike timing across trials (Figure 4, left). In contrast, the change in ITD caused a decrease in the precision of spike timing across trials but left the overall timing of spike events largely unchanged, as reflected by decrease of response signal-to-noise ratios (SNRs) between the base and the ITD change conditions, as shown on Figure 4, center. A decrease in spike timing precision when changing ITD is also shown by

comparing the decoder performance for each of the three different stimulus conditions. As shown in Figure 4, right, decoder performance is significantly reduced for the ITD change condition compared to the other two conditions.

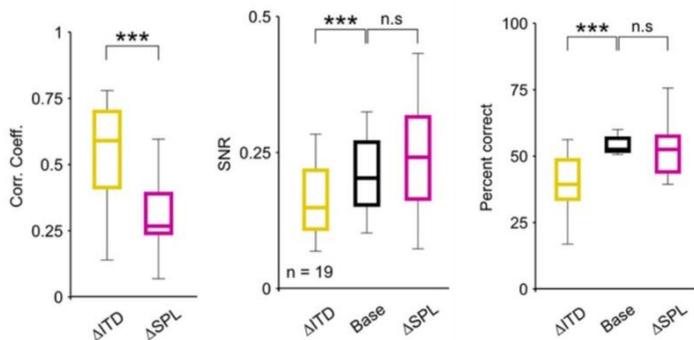


Figure 4. Left: Boxplots showing the distribution of CCs between the PSTHs for the base condition and each of the two change conditions for a sample of 19 neurons. Center: Boxplots showing the distribution of response SNRs for each of the three stimulus conditions. Boxplots showing the distribution of decoder performance at the optimal timescale for each of the three stimulus conditions. n.s., Not significant., ***p < 0.001

All these effects are the same, when background noise is added to the stimulus with 0 dB SNR, as shown in Figure 5.

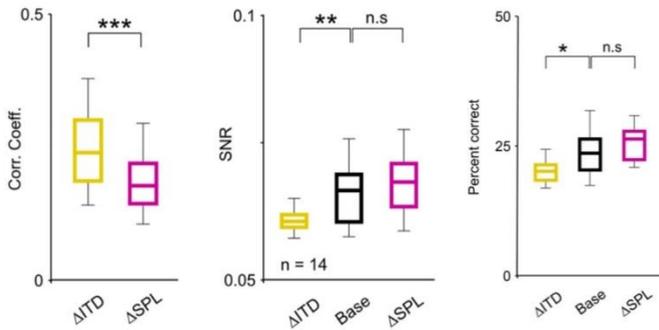


Figure 5. Left: Boxplots showing the distribution of CCs between the PSTHs for the base condition and each of the two change conditions for a sample of 19 neurons. Center: Boxplots showing the distribution of response SNRs for each of the three stimulus conditions. Boxplots showing the distribution of decoder performance at the optimal timescale for each of the three stimulus conditions. n.s., Not significant., *** $p < 0.001$

The results described above demonstrate that changes in intensity and ITD have different effects on the coding of low-frequency sounds in the responses of single neurons. However, these changes also have different effects on the overall spike rates of the entire population. In contrast, because most binaural neurons with low preferred frequencies (including all in this study) respond most strongly to sounds located on the side contralateral to the brain hemisphere that they are in, a change in the ITD of a sound will cause, on average, an increase in spike rate for neurons

in one hemisphere and a decrease in spike rate for neurons in the other hemisphere. To determine how changes in intensity and ITD influenced the coding of sound content at the population level, I decoded the responses of many different random subpopulations of neurons. As shown in Figure 6, when all of the cells in the population were taken from a single hemisphere, the change in ITD caused a decrease in decoder performance similar to that observed in single cells. However, when half of the population was drawn from each hemisphere, the performance of the decoder was independent of ITD.

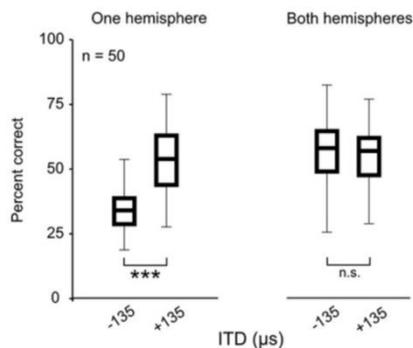


Figure 6. Boxplots showing the distribution of decoder performance for 50 randomly chosen populations of 10 cells with either all cells from the same hemisphere or half of the cells from each hemisphere.. n.s., Not significant. *** $p < 0.001$.

These effects were the same with added background noise, as shown in Figure 7.

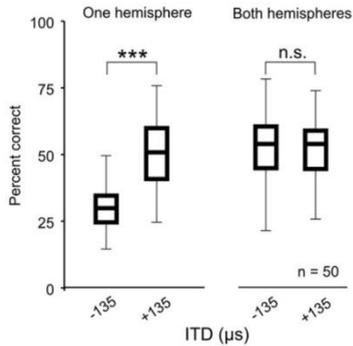


Figure 7. Boxplots showing the distribution of decoder performance for 50 randomly chosen populations of 10 cells with either all cells from the same hemisphere or half of the cells from each hemisphere.. n.s., Not significant. *** $p < 0.001$.

4. Conclusions

In my thesis, I have shown that an optimal set of weights that maximizes decoder performance can be found with genetic algorithm when decoding neural population responses with distance metrics. I have also shown that the change in ITD and intensity have different effects on spiking properties of single neurons in the IC. On the one hand, ITD changes do not change overall spike timing within trials, while intensity changes do. On the other hand, ITD changes reduce spike timing precision across trials, while intensity changes do not alter spike timing precision. As an effect on the coding performance of IC neurons, changes in ITD also result in a significantly reduced decoder performance, while intensity changes do not alter decoder

performance. However, these changes are not present on the population level, as shown by the analysis of neural activity from both hemispheres. I have also shown that these effects are the same with and without the addition of background noise to the stimulus.

5. Bibliography of the candidate's publications

Related to the thesis:

- Hofer, S. B., Mrcsic-Flogel, T. D., Horvath, D., Grothe, B., & Lesica, N. A. (2010). Optimization of population decoding with distance metrics. *Neural Networks*, 23(6), 728–732.
- Horvath, D., & Lesica, N. A. (2011). The Effects of Interaural Time Difference and Intensity on the Coding of Low-Frequency Sounds in the Mammalian Midbrain. *Journal of Neuroscience*, 31(10), 3821–3827.

Not related to the thesis:

- Dombovari B, Fiath R, Kerekes B, Toth E, Wittner L, Horvath D, Seidl K, Herwik S, Torfs T, Paul O, Ruther P, Neves H, Ulbert I. In vivo validation of the electronic depth control probes. *Biomedizinische Technik* 59 : 4 pp. 283-289. , 7 p. (2014)
- Fiath R, Kerekes BP, Wittner L, Toth K, Beregszaszi P, Horvath D, Ulbert I. Laminar analysis of the slow wave activity in the somatosensory cortex of anesthetized rats. *European Journal of Neuroscience* 44 : 3 pp. 1935-1951. , 17 p. (2016)
- Fiath R, Beregszaszi P, Horvath D, Wittner L, Aarts AA, Ruther P, Neves HP, Bokor H, Acsady L, Ulbert I. Large-scale recording of thalamocortical circuits: in vivo electrophysiology with the two-dimensional electronic depth control silicon probe. *Journal of Neurophysiology* 116 : 5 pp. 2312-2330. , 19 p. (2016)
- Fiáth R, Raducanu BC, Musa S, Andrei A, Lopez CM, van Hoof C, Ruther P, Aarts A, Horváth D, Ulbert I. A silicon-based neural probe with densely-packed low-impedance titanium nitride

microelectrodes for ultrahigh-resolution in vivo recordings. *Biosensors & Bioelectronics* 106 pp. 86-92. , 7 p. (2018)

- Fiáth R, Hofer KT, Csikós V, Horváth D, Nánási T, Tóth K, Pothof F, Böhrer C, Asplund M, Ruther P, Ulbert I. Long-term recording performance and biocompatibility of chronically implanted cylindrically-shaped, polymer-based neural interfaces. *Biomedizinische Technik* 63 : 3 pp. 301-315. , 15 p. (2018)