

HIGH PERFORMANCE DECODING OF BEHAVIORAL INFORMATION FROM MEAN BACKGROUND ACTIVITY IN EXTRACELLULAR NEURAL RECORDINGS

M. Okatan, and M. Kocaturk

Abstract— We have previously shown that the standard deviation of background activity in bandpass filtered extracellular neural recording snippets is strongly modulated by behavior such that it can be used to decode behavioral variables with up to 100% accuracy. Here we show that the mean background activity is also strongly modulated by behavior and that it too can be used to decode behavioral variables with up to 100% accuracy. To the best of our knowledge, our method extracts the weakest signal that has ever been extracted from extracellular neural recordings, which can still be used to decode a behavioral variable with very high accuracy. Our results demonstrate that both the standard deviation and the mean of the background activity can be exploited in brain-machine interfaces.

Keywords— *Computational Neuroscience, Truncation Thresholds, Amplitude Thresholding, Brain-Computer Interfaces*

1. INTRODUCTION

Extracellular neural recordings provide a wealth of information about the information encoded in the spiking activity of individual and populations of neurons [1]. In the past several decades this technique has yielded substantial amounts of information about what types of movement-related information are encoded in the activity of individual neurons in the motor cortices [2]. At the turn of this century brain-machine interface systems that use such information to infer behavioral variables have become a reality [3]. Initially, such systems decoded behavioral variables by modeling the spiking activity of populations of neurons. However this approach requires first to recover the spike trains of individual neurons from extracellular neural recordings; a process called spike sorting. In spike sorting extracellular recordings are first bandpass filtered with a pass band that is suitable for spike detection. Bandpass filtered recording is then thresholded and suprathreshold waveforms are clustered in high-dimensional feature spaces to identify the spikes fired by distinct neurons [4]. Usually a high threshold, such as three to five times the standard deviation of the filtered recording ($3-5\sigma$), is used as the threshold to make sure that suprathreshold waveforms are sufficiently well-defined and can form distinct clusters [5, 6, 7]. As the number of electrodes increased in advanced brain-machine interface systems, spike sorting emerged as a

computational bottleneck for real-time decoding of behavioral information from extracellular neural recordings. This led researchers to question whether decoding could be carried out without spike sorting [7]. It was found that decoding could indeed be performed without spike sorting but that thresholds in the range of $3-5\sigma$ were too high for that purpose [7]. This raised the problem of optimizing the threshold. It has been proposed that the threshold that maximizes the signal to noise ratio of the behavioral variable of interest in suprathreshold activity can be used as the amplitude threshold (SNR-threshold) [8]. While this method is more principled and usually yields thresholds smaller than $3-5\sigma$, it does however depend on the behavioral variable of interest. Therefore more information may be available in the filtered recording than what the SNR-thresholds yield. Exploring the nature of that residual information would be informative from the point of view of both basic neuroscience research and brain-machine interface technology. This issue of residual information has been addressed by a method that we developed to automatically compute a pair of amplitude thresholds for filtered recordings using only neural data in a fully data-driven way [9]. Our method computes a pair of thresholds, called *truncation thresholds*, such that the distribution of the subthreshold data obeys a well-defined noise distribution according to Kolmogorov-Smirnov test with a significance level greater than 0.05 and the thresholds are as far away from each other as possible. This method yields thresholds far below $3-5\sigma$ in real data [9], attesting to the fact that there is more information in filtered recordings than what is extracted using $3-5\sigma$ thresholds.

The mean (μ_{tr}) and the standard deviation (σ_{tr}) of the background activity are automatically estimated by maximum likelihood in our method as a byproduct of the computation of the truncation thresholds. We have previously shown using simulated data that σ_{tr} is more accurate than alternative scale estimators, such as the conventional standard deviation formula, robust median estimator, mean absolute deviation, S_n , Q_n , trimmed estimator, winsorized estimator and DATE [9, 10, 11]. Moreover, we have shown that, in extracellular recordings from the rat primary motor cortex, σ_{tr} exhibits significant changes in different periods of a behavioral task where subjects press a right or left lever with their respective front paw in response to a visual stimulus [12]. This modulation is so strong that what lever the subject presses can be inferred with up to 100% accuracy using a logistic regression model where the independent variables are σ_{tr} estimates obtained from filtered recording snippets in the vicinity of the lever pressing time. These results showed for the first time in the literature that samples that would normally be considered

Murat Okatan, is with Sivas Vocational School, Sivas Cumhuriyet University, Sivas, Turkey, (e-mail: muratokatan@cumhuriyet.edu.tr). 

Mehmet Kocaturk, is with Engineering and Natural Sciences Faculty and Regenerative and Restorative Medicine Center (REMERC), Istanbul Medipol University, Istanbul, Turkey, (e-mail: mkocaturk@medipol.edu.tr). 

Manuscript received Jul 15, 2018; accepted Aug 8, 2018.

noise in filtered extracellular neural recordings are actually very informative about the subjects' behavior.

The present study continues along the same lines and explores whether μ_{tr} too depends on behavior and whether it too can be used to decode behavioral variables with high accuracy.

2. METHODS

In this section first the data that are used in the analyses are explained. Next, the estimation of μ_{tr} is presented. Finally, the logistic regression modeling of the lever pressing behavior is explained. All computations were performed in MATLAB (R2015a, MathWorks, Inc., USA) under 64 bit Windows 8.1 Single Language (2013) operating system on a laptop computer with 6 GB RAM and 2.60 GHz Intel® Core™ i5-3230M CPU.

2.1. Data

Neural and behavioral data were recorded from a rat by one of the authors (M.K.) in a previous study. The recording was made using a neuroprosthetic design environment [13] from the primary motor cortex (area M1) of a rat during lever-pressing in response to visual stimuli. In the experimental setup the rat initiates a trial by a nose poke into a port equipped with a photodetector. This triggers a visual stimulus that informs the subject about whether pressing the right or the left lever is the correct response at that trial. The subject responds by pressing the right or the left lever using its ipsilateral front paw. Correct responses are rewarded by approximately a 0.03 ml water reward. The experiment consists of 82 trials. The subject failed to respond at one trial and gave an incorrect response at another trial. The present analysis uses the data obtained in the remaining 80 trials. Neural data were recorded using a 16-channel microelectrode array with a sampling rate of 40 kHz per channel. Eight microelectrodes were implanted in each cortical hemisphere. Data were then digitally bandpass filtered between 400 Hz and 8 kHz using a 4th order Butterworth filter. The responses of the subject were recorded as a binary series in which a 0 represents a left lever-press and a 1 represents a right lever-press.

The length of the time interval between the start of the recording and the initiation of the trial, as well as the response time of the subject, are different at each trial. At each trial there is at least a 2 s recording time before the trial is started by the subject, and at least 0.8 s between the start of the trial and the time of response. At each trial neural recording continues for at least 1 s after the response is given.

To examine the dependency between neural activity and behavior, truncation thresholds, along with σ_{tr} and μ_{tr} , have been computed at each trial for eight recording snippets of 0.5 s duration each (Fig. 1 and Fig. 2). These snippets correspond to the 2 s interval immediately preceding the start of the trial (pre-start; PRS for short), the 0.5 s interval immediately following the start of the trial (post-start; POS for short), the 0.5 s interval immediately preceding the response (pre-response; PRR for short) and the 1 s interval immediately following the response (post-response; POR for short). In this way, the PRS epoch consists of four consecutive snippets, the

POS and PRR epochs consist of one snippet each, and the POR epoch consists of two consecutive snippets (Fig. 2).

2.2. Estimation of μ_{tr}

μ_{tr} is estimated automatically as a byproduct of the computation of truncation thresholds. The source code and standalone executables of the software that computes the truncation thresholds are registered with SciCrunch.org under the name "Truncation Thresholds Software" (RRID:SCR_014637) and are freely available. The algorithm implemented in this software has been explained in detail in our previous work [9, 14]. Briefly, the algorithm uses the bisection method [15] to iteratively compute the truncation thresholds in three steps. The cardinality of the set of candidate solutions is halved at each iteration. For a time series consisting of N samples the algorithm reaches the solution in approximately $\log_2(N^3/4)$ iterations. The algorithm generates approximately $\log_2(N)$ pairs of candidate thresholds and picks the pair that yields the widest interval and for which the distribution of the subthreshold samples is statistically indistinguishable, according to Kolmogorov-Smirnov test at level $P \geq 0.05$, from a truncated normal distribution, truncated at the threshold values. The standard deviation (σ_{tr}) and the mean (μ_{tr}) of the truncated normal distribution are estimated by maximum likelihood from the data.

In the present analysis μ_{tr} is estimated using the Truncation Thresholds Software (version in English dated 25.01.2018) for each 0.5 s snippet described in Section 2.1. For each of the 16 channels, whether μ_{tr} estimates obtained in the left and right trials differ from each other is tested using the Kruskal-Wallis test separately in the first four (PRS epochs) and the last four (POS, PRR and POR epochs) of the eight epochs considered here.

2.3 Modelling of the response type as a function of μ_{tr}

Response type (0: left; 1 right) has been modelled as a function of the μ_{tr} estimates obtained from the POS, PRR and POR epochs using quadrivariate logistic regression. The parameters of the model have been estimated by maximum likelihood using the `glmfit.m` function of MATLAB (MathWorks, Inc., ABD) under a binomial probability model for the response type. The output $o[d]$ of the model at trial number d is calculated using the `glmval.m` function with a logit link function; $1 \leq d \leq D$, where D is the total number of trials considered, which is 80. If $o[d] > \theta$, then the model is accepted to predict that the right lever was pressed at that trial; otherwise the model is accepted to predict that the left lever was pressed at that trial. The decision threshold θ was determined separately for each electrode by dividing the interval $[\min_d o[d], \max_d o[d]]$ into 99 equal pieces, yielding 100 candidates for θ , and selecting the smallest candidate that maximized the accuracy, where the latter is defined as the total number of true positive and true negative predictions divided by D [16].

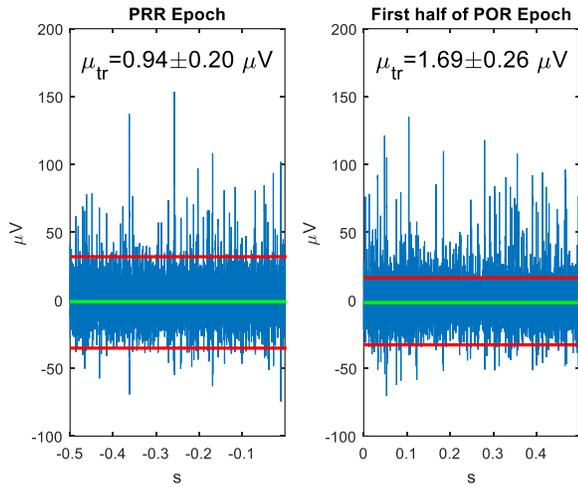


Fig.1. Recording snippets, truncation thresholds (red) and μ_{tr} estimates.

3. RESULTS

Figure 1 shows the filtered recording snippets corresponding to the PRR and the first half of POR epochs at trial 30 collected from electrode 4 (counting from zero) implanted in the left hemisphere, along with the estimated μ_{tr} values and their 95% confidence intervals. Truncation thresholds are shown in red, while μ_{tr} estimates are shown in green. The subject pressed the left lever at this trial and the response time corresponds to 0 s in Fig. 1.

Figure 2 shows μ_{tr} estimates from the same electrode at all trials in different behavioral epochs. The top four graphs show estimates obtained from the last two seconds before the trial is started (PRS). In the bottom row, the leftmost graph shows estimates obtained from the first 0.5 seconds after the trial is started (POS), the next graph shows estimates obtained

TABLE I
PREDICTION ACCURACY

	Electrode	Accuracy (%)	θ
Min.	8, 9	74	0.60, 0.52
Max.	3, 4, 6	100	0.01
Mean \pm s.e.m	-	87.7 \pm 2.5	0.37 \pm 0.06

from the last 0.5 seconds before the response is given (PRR), the last two graphs show estimates obtained from the first 1 second after the response is given (POR).

The difference between the μ_{tr} estimates obtained from the left versus right trials in the PRS epochs was not statistically significant in any of the electrodes ($P \geq 0.05$). By contrast the difference between the μ_{tr} estimates obtained from the left versus right trials in the POS, PRR and POR epochs was statistically significant in eight electrodes ($P < 0.05$).

The results of the regression analysis that modelled the response type as a function of the μ_{tr} estimates obtained from the POS, PRR and POR epochs are summarized in Table 1. The lowest accuracy was obtained as %74 at electrodes 8 and 9 (both in the right hemisphere). High values of the decision threshold (0.52 and 0.60) indicate that the model failed to generate a low probability for a “right response” at left trials in these electrodes. By contrast data from electrodes 3, 4 and 6 (all in the left hemisphere) predicted the response type with 100% accuracy. It is seen that the decision threshold is as low as 0.01 in these electrodes. Namely the output of the regression model is so close to 0 on the left trials that the first non-zero decision threshold candidate succeeds in predicting the response with 100% accuracy. The average accuracy across all 16 electrodes was about 88%. There was no hemispheric difference in prediction accuracy ($P \geq 0.17$;

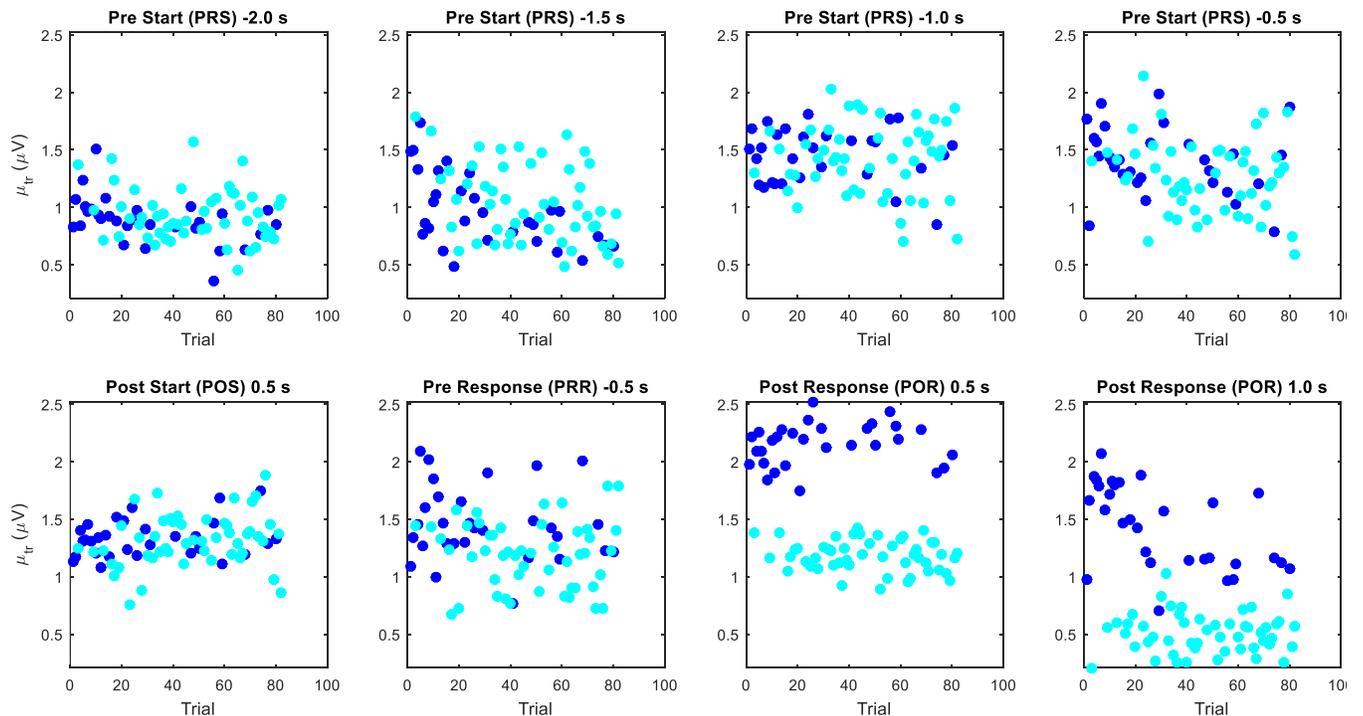


Fig.2. Change in μ_{tr} with behavior. Estimates from left (right) trials are shown in dark (light) blue.

Kruskal-Wallis test).

4. DISCUSSION

Information is usually extracted from extracellular neural recordings by thresholding the amplitude of the filtered recording and using the suprathreshold data. We have previously shown, for the first time in the literature, that the standard deviation of the subthreshold data (σ_{tr}) can also be used to extract behavioral information from these recordings with very high accuracy [12]. The present results show that the mean of the subthreshold data (μ_{tr}) too can be used for this purpose with a similar performance.

Figure 1 and Fig. 2 show that behavioral modulation of μ_{tr} is a very weak but consistent signal. The average difference between the μ_{tr} estimates obtained in the left versus right trials in the first half of the POR epoch is about 1 μ V (Fig. 2). In Fig.1, the μ_{tr} estimates obtained from consecutive 0.5 s intervals intercalating the response time differ by only 0.75 μ V, yet this difference is significant as indicated by the non-overlapping 95% confidence intervals of these estimates. To the best of our knowledge, these results suggest that our method extracts the faintest signal that has so far been extracted from extracellular neural recordings while still being capable of inferring behavioral variables with up to 100% accuracy.

The background activity, which forms the subthreshold data in these analyses, contains information about the ensemble spiking activity of a large number of neurons located far from the recording electrode. Therefore firing rate changes across relatively large cortical areas may result in changes in the statistical structure of the background activity. The present results show that the mean background activity waxes and wanes slightly but consistently as a function of behavior. In bandpass filtered recordings the overall mean is identically equal to zero, since the DC component of the signal has been filtered out. Yet the mean background activity may deviate from 0 when computed in short time windows, as it was done in the present analysis. By using time windows of 0.5 s duration time locked to behavioral events we have been able to show that mean background activity does indeed change with behavior and that this signal can be used to infer behavioral variables with very high accuracy.

The finding that μ_{tr} estimates obtained from time windows occurring before the start of the trial (PRS epoch) were not significantly different in the left versus right trials is not surprising since the subject does not yet have access to information about the correct response at that trial during that epoch. After the trial is started, however, a visual stimulus informs the subject about the correct response at that trial. Our results show that this information affects the mean background activity in some or all of the POS, PRR and POR epochs in some electrodes (Fig. 1, Fig. 2 and Table 1). This effect is so strong in some electrodes that when used in a logistic regression model to predict the response, the subject's response can be predicted with 100% accuracy (Table 1).

Truncation thresholds are a tool for segregating the signal and noise components of filtered extracellular neural recordings in a fully automated and data driven manner [9].

Naturally, more detailed information about the behavior is available in suprathreshold data. That is because suprathreshold data contain spikes fired by neurons located near the recording electrode, as shown in Fig. 1, and it is well known that different motor cortical neurons encode different aspects of the unfolding motor behavior [2]. Therefore it is necessary to use suprathreshold data to extract detailed information about behavior. However such analyses will involve additional computations. By contrast μ_{tr} is estimated automatically as a byproduct of the computation of the truncation thresholds. Our results show that our method can be used to decode coarse-grained behavioral information that is roughly encoded in the activity of large numbers of neurons, such as the right or left lever pressing in the present study, with very high accuracy and without recurring to suprathreshold data analysis.

5. CONCLUSIONS

Our results show that there is practically no *noise* in bandpass filtered extracellular neural recordings, in the sense that even the mean value of the background activity is significantly modulated by behavior. Provided that a clean recording has been obtained, virtually all samples that make up an extracellular neural recording are of neural origin and when taken in the aggregate, their statistics do carry information about the state of the organism. The results show that estimation of μ_{tr} using the truncation thresholds method is capable of detecting signal variations on the order of a microvolt in these recordings. The high sensitivity of our method is due to the computation of truncation thresholds, which are an original and novel tool for amplitude thresholding. Overall, these results suggest that the use of μ_{tr} can increase the performance of brain-machine interfaces when used in conjunction with existing decoding methods.

ACKNOWLEDGMENT

This work is supported by the Scientific Research Project Fund of Sivas Cumhuriyet University under the project number SMYO-023. We thank Eda Dağdevir for critically reading the manuscript.

REFERENCES

- [1] M. E. J. Obien, K. Deligkaris, T. Bullmann, D. J. Bakkum, U. Frey, "Revealing neuronal function through microelectrode array recordings", *Front. Neurosci.* Vol.9, 2015, p.423.
- [2] B. Amirikian and A. P. Georgopoulos, "Directional tuning profiles of motor cortical cells", *Neuroscience Research*, Vol.36, 2000, pp.73-79.
- [3] E. C. Leuthardt, G. Schalk, D. Moran, J. G. Ojemann, "The emerging world of motor neuroprosthetics: a neurosurgical perspective", *Neurosurgery*, Vol.59, No.1, 2006, pp.1-14.
- [4] M. S. Lewicki, "A review of methods for spike sorting: the detection and classification of neural action potentials", *Network: Comput. Neural Syst.*, Vol.9, 1998, pp.R53-R78.
- [5] R. Q. Quiroga et al. "Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering", *Neural Comput.*, Vol.16, 2004, pp.1661-1687.
- [6] C. Vargas-Irwin and J. P. Donoghue, "Automated spike sorting using density grid contour clustering and subtractive waveform decomposition", *J Neurosci Methods*, Vol.164, 2007, pp.1-18.
- [7] S. Todorova et al., "To sort or not to sort: the impact of spike-sorting on neural decoding performance", *J Neural Eng.*, Vol.11, 2014, p.056005.

- [8] E. R. Oby et al., "Extracellular voltage threshold settings can be tuned for optimal encoding of movement and stimulus parameters", *J Neural Eng.*, Vol.13, 2016, p.036009.
- [9] M. Okatan and M. Kocatürk, "Truncation thresholds: a pair of spike detection thresholds computed using truncated probability distributions", *Turk J Elec Eng & Comp Sci.*, Vol.25, 2017, pp.1436-1447.
- [10] M. Okatan, "A comparative study on the estimation of noise standard deviation using DATE and Truncation Thresholds", presented at the Signal Processing and Communications Applications Conference (SIU), 26th. pp: 1-4, 2018, (in Turkish with English abstract), DOI: 10.1109/SIU.2018.8404155.
- [11] M. Okatan, "Comparison of Truncation Thresholds with four different robust scale estimators", presented at the Signal Processing and Communications Applications Conference (SIU), 26th. pp: 1-4, 2018, (in Turkish with English abstract), DOI: 10.1109/SIU.2018.8404387.
- [12] M. Okatan and M Kocatürk, "High performance decoding of behavioral information from background activity in extracellular neural recordings" (Turkish), presented at the 2018 Medical Technologies National Conference (TIPTEKNO). pp:1-4, DOI: 10.1109/TIPTEKNO.2018.8597114.
- [13] M. Kocaturk, H. O. Gulcur, R. Canbeyli, "Toward building hybrid biological/in silico neural networks for motor neuroprosthetic control", *Frontiers in Neurobotics* 2015; Vol.9, 2015, p.8.
- [14] M. Okatan, "Truncation thresholds: a new method for separating signal and noise and its application in biomedical signal processing", (In Turkish). presented at the EEMKON 2015. Biomedical Engineering Symposium, Istanbul, Proc. ISBN: 978-605-01-0922-1, 2016.
- [15] W. H. Press, B. B. Flannery, S. A. Teukolsky, W. T. Vetterling, *Numerical Recipes in C: The Art of Scientific Computing*. 2nd ed. Cambridge: Cambridge University Press, 1992.
- [16] P. Eusebi, "Diagnostic accuracy measures", *Cerebrovascular Diseases* Vol.36, 2013, pp.267-72.

B IOGRAPHIES

Murat Okatan received BSc. degrees in electrical and electronics engineering and physics (double major) from Boğaziçi University in 1995. He completed his MSc. in Neuroscience at Syracuse University in 1997, and his Ph.D. in Cognitive and Neural Systems at Boston University in 2002. During his postdoctoral work at Massachusetts General Hospital (2003-2007) and Boston University (2007-2011) he conducted computational and experimental work on explaining the information encoded in neural spike trains using point-process likelihood models and explaining the hippocampal neural activity patterns observed during reinforcement learning as a function of reward. He returned to Turkey with TÜBİTAK's 2232 Postdoctoral Reintegration Fellowship in 2011. He conducted research in computational neuroscience as a TÜBİTAK 2232 Fellow at Ankara University Medical School, Biophysics Department between 2011 and 2013. He continues his research in this field at Sivas Cumhuriyet University as an assistant professor since 2013. His research interests are in cognitive and neural systems, computational neuroscience and statistical signal processing.

Mehmet Kocatürk received a B.S. degree in electronics and communication engineering from Istanbul Technical University in 2004 and his M.S. and Ph.D. degrees in biomedical engineering from Boğaziçi University in 2007 and 2015, respectively. In addition to his academic activities, he worked in MobiArts Co. as an embedded system design engineer and Nortel Networks Netas Co. as a software design engineer between 2005 and 2008. He is currently an assistant professor in the Department of Biomedical Engineering at Istanbul Medipol University and affiliated with Regenerative and Restorative Medicine Center (REMER) at the same university. His research interests focus on the physiology of the motor system and motor neuroprosthetics.