Electrode-cell distance estimation method, based on spatial potential patterns of spiking cells

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Introduction

Multi microelectrode array systems rose up the possibility of recording and analyzing spatio-temporal patterns of extracellular electric potential generated by neural cells on spatial scale of a single cell. It is well known, that extracellular potential, caused by an intracellular spike, has different shapes on different electrodes, located in different spatial positions. This phenomenon has played a key role in modern extracellular unit recording and sorting methods, as it improved the reliability of spike sorting, [Gray et al., 1995]. This was the main reason why the tetrode technique became succesfull and widespread. The original intention of introducing multi electrode techniques was, that it would made possible localization of the cells around the recording electrodes [Drake et al., 1988, McNaughton et al., 1983, Recce and O'Keefe, 1989], but this original aim failed.

In this paper, first a new principle for cell-electrode distance estimation was presented, which renewed the possibility of the cell localization. This new method required a reliable model of spiking cells' current source density distribution. Thus, properties of the extracellular potential patterns were discussed - referring to problems with monopole, and other point source models. Instead of point source models, a new model was set up and circumstances of its validity were determined. Finally the precision of the new distance estimation method was examined on simulated data and was applied on in vivo measurements.

The amplitude based localization and its assumptions

This method was based on the idea, that the extracellular potential of a spiking cell is decreasing with the inverse of the distance from the cell. If this would be true, cells could be localized by solving an equation system with four unknown variables: three for position and one for amplitude of the source. Thus four recording site would be enough for localization of a point source in three dimension. But it was turned out that cells could not be localized by this method.

The main assumption behind these calculations was that firing cells behaved as monopole point sources. Additional suppositions were that, extracellular space could be considered as a homogeneous and isotropic electrolytic volume conductor. This meant, that extracellular potential satisfied the Poisson equation with scalar conductance and dielectric constant. The source term on the right hand side was the current source density flowing in and out through the cells' membranes. [Malmvuo and Plonsey, 1995] The effect of dielectric properties of the extracellular space, such as frequency dependency and finite speed of electric wave prop-

agation, were neglected.

Since cells could not be localized by the described method, one or more amongst these assumptions were failed. There was no direct evidence against extracellular homogeneity and isotropy on the single cell level, so these assumptions were kept on. Some pieces of evidence came out referring to the failure of the monopole model. [Llinas and Nicholson, 1971, Stuart et al., 1997] These results showed that both perisomatic and dendritic region took its part in the generation and shaping of the action potential's extracellular signal. And failure of the monopole model could be the main reason of localization's failure.

Distance dependence of the extracellular potential patterns

A spike of a multi compartmental cell model was simulated by using Neuron software. The cell had simplified morphology with cylindrical shape. But as it was shown in this paper, the generated spike had many realistic properties. Extracellular potential generated by this neuron in an extracellular medium, was calculated from the transmembrane currents of compartments. Every compartment were considered as point source of current. Their effect on the electrode were calculated according to the $1/r$ weighting, where r was the distance between the center of the compartment and the electrode. Inward current to the cell was considered to be positive.

It was found, that mot only the amplitude decreased rapidly with distance, but the whole spatial potential pattern (SPP) widened out. This widening rose up the possibility of distance estimation based on a width measure, or with fitting an appropriate model to this SPP. Note, that principles under this widening were the same as those allowing the solution of equation system used in the amplitude based localization. But in this case, the spatial potential pattern was considered as a whole.

Distance dependency of width

In order to obtain a formula for distance dependency of width, we performed theoretical analysis of spatial pattern of the electric potential, generated by a localized current source distribution. Three type of point source models were examined according to the first three terms of multipole expansion.

In monopole case, width was defined as distance between two half amplitude points x_1 and x_2. It was obtained, that width w depended on the cell-electrode distance r linearly: $w = |x_1 - x_2| = 2r\sqrt{3}$.

Let V_{max} denotes the maximum of the measured potential. If distance between V_{max}/q points were considered, instead of half amplitude points, the distance dependency remained linear, but steepness depended on q: $w = |x_1 - x_2| = 2r\sqrt{q^2 - 1}$.

In the second case, a dipole source was positioned parallel to the electrode. Width of SPP was defined, as the distance between minimum and maximum of potential distributions. Dependence of extrema's position on source-electrode distance and the distance between them were obtained to be linear: $w = r\sqrt{2} \approx 0.7r$

The third, quadrupole case could appear, when a large current sink was totally compensated by symmetrical counter currents around it. Projecting it onto the axis of the electrode, transmembrane current distribution and extracellular potential became triphasic. Thus the first non-vanishing term of the multipole expansion was the quadrupole term. In this case the width was also defined as the distance between the minimum and maximum of the SPP. Similar to the dipole case, position of extrema and the distance between them depended linearly on the cell-electrode distance: $w = r\sqrt{3/2} \approx 0.8r$

Note, that constant terms in these linear dependencies was 0, thus these lines intersected axes at origo - only their slope was differed.

Finally, the ratio between negative and positive peaks' amplitude was calculated. Difference was found between the biphasic dipole and triphasic

quadrupole situation. In case of a dipole field, the amplitude ratio between minimum V_{min} and maximum V_{max} was -1, but in the triphasic case, this amplitude ratio was found to be: $V_{min}/V_{max} = -2(2/5)^{5/2} \approx 0.2$.

Every current source distribution generated potential could be well approximated with the first few terms of the multipole expansion. On condition that the distance was high enough, comparing to the size of the source. If in an experimental situation, a firing cell's potential could be observed from a distance high enough, one of these point source approximations and the corresponding results should be true. Based on multi microelectrode measurements, it was shown, that point source models were enable to describe the observed cells' SPP.

Problems with the point source models

Results were tested on in vivo measured spikes' spatial potential patterns. A 16 channel silicon probe with 100 μm interelectrode distances was inplanted chronically into a cat primary auditory cortex. Spontaneous and sound evoked potential patterns were recorded with 20 kHz sampling rate and was digitalized with 12 bit precision. Data was band pass filtered from 100 Hz to 6 kHz. Spikes were collected and clustered with Spike-o-matic free software. The optimal model contained 16 spikes, but three of them turned out to be coincidences of spikes, so 13 spike shapes were kept.

Measured minima-maxima ratios

Applying the results from the previous section, first the minima-maxima ratios were examined. If the sources of these potentials would be monopoles, there could not be negative potential values, only at the noise level. In dipole cases, minima and maxima should be on the same level. In quadrupole cases, the minima-maxima ratios should be around -20 percent.

In all spikes, there were also negative potential values in the moment of the peak potential. For eight spikes the amplitude ratios of the minima compared to the maxima were between -1% and -2%. For one spike it was above -1%. For three spikes the negative peaks were higher in their absolute value: $-3\%, -4\%, -12\%$, but only in one case was it comparable to the peak amplitude: -53%. In case of six spikes the minima was significantly more negative than it would expected from the noise. The noise of every spike waveform was calculated as standard deviation of the first twelve time sample points in the spikes' time-windows. It was assumed to be Gaussian white. Note that, the minimum-maximum ratio in case of our simulated spike were distance dependent, grew from -10% towards zero, as the distance increased. These ratios were in good agreement with the measured values.

Except one spike, relatively small absolute value of minimum-maximum ratios were observed. This means, that among the possible three point source distributions, these potential patterns could be close only to the monopole case. But the presence of significant negative values excluded the real monopole sources in those six cases. Although, seven spikes remained, where the monopole source hypothesis were not rejected.

Fitting monopole model

A monopole model was fitted to the measured SPPs to uncover if it could be really generated by a monopole current source or not. The fitted monopole model has three free parameters: the amplitude of the source, the position of the source along the electrode and the distance of the source from the electrode. The numerical fitting was carried out by minimalization of mean square error with conjugate gradient method.

The result of the fitting showed, that the monopole model could not be fitted well to the measured SPPs. The resulted errors were relatively

high, and they had inhomogenous spatial distribution. The third free parameter of the model, the distance of source from the electrode were set to very little value. This achieved the magnitude of 10^-5 microns during the fitting. The spatial distribution of the error together with those very unrealistic small distances showed, that the measured spikes had narrower SPP-s than the fitted model was able to produce with any parameters. Thus point source models had to be substituted with a finite size current source distribution model.

The counter-current model

The inverse problem of Poisson-equation could not be solved in a general case. So proper restrictions should be found, to reach the balance between solvability and generality. Our counter-current model set up the following restrictions and assumptions: The model was restricted to one dimension, since the electrode measured the potential along one axis. This one dimensional current source density distribution - a line source - was assumed to be parallel to the electrode. This assumption fitted well to the main direction of dendritic branches of cells in the neocortex, parallel to the electrode in our experimental setup. There was a main assumption, for making the model solvable. The line source was a superposition of a point source and a general one dimensional current source distribution with a strictly opposite sign as the point source had. This model assumed, that there was only one main active current sink or source on the cell, but there could be a counter current system through the membrane, with any distribution. Note that the sum of inward and outward currents was not required to be zero.

Fitting the counter current model

Model fitting could be performed only numerically, due to the nonlinear effect of the distance parameter. Conjugate gradient method was used with 1000 step maximally. For numerical solution, the line source distribution was discretised into a chain of point sources. The sign restriction allows the usage of more point sources than the number of recording sites. Both simulated and measured potential record was described by the same model. This consisted of one main point source the position of which was also a free parameter of fitting, and 32 other spatially fixed point source for the counter current system. Thus free parameters were; the line source-electrode distance, the main source position along the line, it's amplitude and the amplitude of 32 counter currents - altogether 35 parameters to fit.

Test of counter-current model on simulated data

Extracellular spatio-temporal potential pattern of a simulated spike was calculated in a distance of 22 μm from the cell, in 325 'recording site'. Distance between the 'recording' sites was 4 μm. Time was sampled with 80 kHz. To test the validity of models on this simulated electric potential, both monopole and counter-current model were fitted onto the whole spatial potential pattern in every time step. This represented the best case, when SPP was known with extremely high precision.

Considering the time course of fitted distance parameters of both models, it is obtained that, in two periods, the counter current model remained very close to the real distance of the cell. The first period started at the onset of the spike and ended at the peak of it. The second period coincided with the hyperpolarization phase of the extracellular spike. The resulted errors of fitting were also very low at these periods, in the magnitude of 10^{-6}. Parallelly, the monopole model had no period, where real distance received back. In the two periods, where the counter current model fitted well to the data, errors of monopole fit were higher with five magnitude.

The small errors and the good results for cell-

electrode distance showed, that in these two periods the counter current model was valid to the current source distribution on the cell. It was also shown, that these periods and the described model fitting method could be used to estimate the distance between the cell and the electrode.

Precision of the distance estimation

In the real experiment, the electric field was measured on 16 channel, with 100 μm interelectrode distances. Naturally, this spatial sampling rate bounded the precision of the distance estimation. To test this effect, the extracellular potential was calculated in 51 different distances, from 10 to 210 μm with 4 μm steps. In every distance the calculated 325 measuring points were 25 times undersampled with different spatial onset. So 25 different records were created, each of them consisted of 13 channel with 100 μm interelectrode distance. The counter current model was fitted to every record, than mean value and standard deviation of the 25 estimated distances were calculated in every distance.

The deviation of estimations' means from the real distance was very small 2-5 μm farther than 80 μm. The standard deviation was in this range. As it was expected, the effect of spatial undersampling was most pronounced at small distances: the jitter and the standard deviation increased under 80 μm up to 10 μm and 15 μm respectively. But still, these increased values marked unexpectedly good performance, compared to the 100 μm interelectrode distances.

Application to in vivo data

Distance of 13 spikes' origin were estimated from SPP at their potential peaks. All of them were estimated to be in the 10-50 μm region. These results were more realistic, than 10^{-5} microns with the monopole model, and they were in good agreement with the results of Henze et al., 2000. They found with parallel extra and intracellular recordings, that those clusterable cells, whose extracellular signals were higer than 60 μV were located in 10-50 μm distance from the tetrode. There was no recognizable interconnection between amplitudes and estimated distances, but similar high differences was found by Henze et al., 2000 between extracellular spike amplitudes of cells located in the same distances. This was possibly caused by individual differences between cells.

Discussion and outlook

It was shown that point source models were not able to provide adequate description of measured SPPs. Our counter current model succesfully overcame many difficulties of point source models, and gave a better description of current source density distributions of spiking cells. In possesion of this new description, distance estimation of cells became possible. It turned out, that observable and clusterable cells were in 50 μm surroundings of the electrode. Thus it would be important to increase the precision of estimation on these small distances. This colud be achieved by decreasing the interelectrode distances. Fitting procedure could possibly be developed as well. Direct check of estimation's quality would also be required. Two techniques seemed to be possible: paralell intra and extracellular recordings, as it was performed by Harris et al., 2000, or using multiple electrode probes.

Distance estimation renewed the possibility of determining cells' relative position to the electrode. Since the probe was electrically shilded from one direction, two electrode lines would be enough to position cells in three dimension. Three probes would permit not only localization, but check of estimations' precision. It was required that the electrode lines should be close enough to each other. With multiple electrode probes, the micro imaging of the surrounding brain tissue could be performed.

References

K. L. Drake, K. D. Wise, J. Farraye, D. J. Anderson, and S. L. BeMent. Performance of planar multisite micrprobes in recording extracellular activity. *IEEE Transactions on Biomedical Engineering*, 35:719–732, 1988.

D. Gábor and C. V. Nelson. Determination of the resultant dipole of the heart from measurements on body surface. *Journal of Applied Physics*, 25 (4):413–416, 1954.

C. M. Gray, P. E. Maldonado, M. Wilson, and B. McNaughton. Tetrodes markedly improve the reliability and yield of multiple single-unit isolation from multi-unit recordings in cat striate cortex. *Journal of Neuroscience Methods*, 63: 43–54, 1995.

K. D. Harris, D. A. Henze, j. Csicsvári, H. Hirase, and G. Buzsáki. Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. *Journal of Neurophysiology*, 84:401–414, 2000.

D. A. Henze, Z. Borhegyi, J. Csicsvári, A. Mamiya, K. D. Harris, and G. Buzsáki. Intracellular features predicted by extracellular recordings in the hippocampus in vivo. *Journal of Neurophysiology*, 84:390–400, 2000.

R. Llinas and C. Nicholson. Electrophysiological properties of dendritesand somatea in alligator purkinje cells. *Journal of Neurophysiology*, 1971.

J. Malmvuo and R. Plonsey. *Bioelectromagnetism*. Oxford University Press, 1995.

B. L. McNaughton, J. O'Keefe, and C. A. Barnes. The stereotrode: a new technique for simultaneous isolation of sevenral singel units in central nervous system from multiple unit records. *Journal of Neuroscience Methods*, 8:391–397, 1983.

P. G. Musial, S. N. Baker, G. L. Gerstein, E. A. King, and J. G. Keating. Signal-to-noise ratio improvement in multiple electrode recording. *Journal of Neuroscience Methods*, 115:29–43, 2002.

M. Recce and J. O'Keefe. The tetrode: a new techniqe for mult-unit extracellular recording. *Sociaty for Neuroscience Abstracts*, 15:1250, 1989.

G. Stuart, N. Spruston, B. Sakmann, and M. Häusser. Action potential initiation and backpropagation in neurons of the mammalian cns. *Trends in Neurosciences*, 1997.

P. Varona, M. J. Ibarz, L. López-Aguado, and O. Herreras. Macroscopic and subcellular factors shaping population spikes. *Journal of Neurophysiology*, 83:2192–2208, 2000.