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Linking extracellular electric potential in the brain to neural activity – a review of source localization and component identification methods

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Due to technological advances in electrophysiology, there is renewed interest in the analysis of local field potentials recorded at many sites simultaneously. In this paper the main problems related to the analysis of LFP are presented, and recent developments in the data analysis methods are reviewed. The focus of the paper is on reconstruction of current source density from extracellular recordings and on decomposition of neural activity into meaningful components.

Key words: local field potential, extracellular potential, Current Source Density, Independent Component Analysis, data analysis

INTRODUCTION

Brain activity can be studied using various experimental techniques which allow for imaging in different spatial and temporal scales (Sejnowski et al. 2014). Among those techniques electrophysiology, that is recording of electric fields in neurons and brain tissue, is particularly important when studying information processing in the brain. Electrophysiology offers excellent, sub-millisecond temporal resolution, which is orders of magnitude better than most other techniques (Sejnowski et al. 2014). This allows for precise study of intricate brain phenomena, such as the order of activation of brain structures when processing sensory stimuli. Moreover, electrophysiology allows for studies across many spatial scales, from parts of a single neuron (patch clamp techniques), through the registration of spiking activity of single and multiple units, local field potentials (LFP) reflecting population activity, to the activity of the whole brain (electroencephalography, magnetoencephalography).

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Lately, due to technological advances, there is a new wave of interest in recording and analysis of LFP, that is, the low-frequency part of the electric potential recorded extracellularly, often at multiple sites simultaneously (Einevoll et al. 2013). LFP allows for long-term stable recordings of brain activity at the population level. On the other hand, the interpretation of such recordings is often difficult. Two main problems while interpreting LFP are (1) localizing the sources, and (2) decomposing the signal into functional components which could be attributed to separate cell populations.

The first problem is a direct consequence of the laws governing the propagation of electric field in the tissue. The extracellular field in the tissue is generated by electric currents flowing across cellular membranes (both ionic and capacitive currents), that is, by charges flowing into or out of the cells. The potential from a point source decays as the inverse of distance, hence even a well-localized source (such as a single synapse) generates electric field of large, theoretically infinite, spread. That causes spatial blurring of the active region of the tissue: the activity of cells (that is, locally non-zero net transmembrane current) can be detected even millimeters away, which makes precise localization hard. To deal with this problem one can use Current Source Density (CSD) analysis, which uses

LFP values to estimate the distribution of transmembrane current sinks and sources, that is regions in which charges flowing into the cells and out of the cells, respectively, dominate.

Even if we solve the first problem by reconstructing the underlying configuration of sinks and sources from the LFP, the resulting distribution will still represent a number of different, possibly overlapping cell populations. To understand information processing in the brain we would like to decompose the current source density into meaningful components. There are several methods which allow to do it, and they all rely on supplementing the recorded LFP with additional constraints or information.

This paper is organized as follows: first, the relations between the neural activity and the extracellular electric field are presented. Then I review the various CSD methods for reconstructing the transmembrane currents from the recorded potentials. Finally, methods for decomposing neural activity into components are discussed.

SOURCES OF EXTRACELLULAR POTENTIAL

In the simplest formulation, the extracellular electric potential Φ in neural tissue is related to the volume density C of transmembrane currents *via* the Poisson equation:

$$\sigma \Delta \Phi = -C, \tag{1}$$

where σ is the conductivity of the tissue, and Δ stands for the Laplace operator (which in Cartesian coordinates x, y, z is the sum of second derivatives with respect to all the coordinates). This equation holds under several assumptions: (1) quasi-static approximation, (2) spatial homogeneity and isotropy, (3) purely resistive medium. Some of the assumptions can be relaxed, for example one can consider models of tissue in which the conductivity is neither homogenous nor isotropic. In that case σ becomes conductivity tensor, with components possibly dependent on the position.

Solving equation (1) for a point current source of magnitude I, with the boundary conditions Φ=0 at infinity, yields

$$\Phi = \frac{I}{4\pi\sigma r}, \tag{2}$$

where r is the distance to the source, that is, the potential is inversely proportional to the distance. Because of linearity of the Poisson equation this solution can be used to calculate the extracelluar field stemming from an arbitrary configuration of the sources. This procedure is called 'forward modelling'. One has to simply add a number of terms of the form (2):

$$\Phi = \sum_i \frac{I_i}{4\pi\sigma r_i}, \tag{3}$$

or, in the continuous limit, perform an integral:

$$\Phi = \frac{1}{4\pi\sigma} \int \frac{C}{r} \mathrm{d}V. \tag{4}$$

It is sometimes of interest to study the relation between the extracellular potential Φ and the current-source density C under different assumptions than those leading to Equation 1. For example, the spatial homogeneity assumption has to be relaxed in order to study extracellular field in thin slices of brain tissue (Ness et al. 2015).

It is worth stressing that – once the geometry of the setup and the assumptions are specified – the forward model is well defined and poses no conceptual problems, even if simulating neural activity and calculating Φ may in practice require significant computational power. On the other hand, the 'inverse problem', that is, estimating C from measured Φ, is ill-posed in the sense that there are many CSD distributions compatible with a given set of recorded potentials. To obtain a unique solution to the inverse problem one has to assume (explicitly or not) additional constraints, this is discussed in the next section.

CURRENT SOURCE DENSITY ANALYSIS

In principle to estimate the current source density C from the extracellular potential Φ one only needs to apply the Laplace operator (sum of the second spatial derivatives) to Φ. However, this operation could only be performed if one knew Φ at all points in space. In practice we only measure Φ in several discrete locations (electrode contacts).

Approximations of second spatial derivative

One simple way to estimate the current source density from discrete measurements is to approximate the spatial second derivative using differences between Φ at neighboring recording points (Pitts 1952). In one-dimensional case the resulting formula is:

$$C(z) = -\sigma \frac{\Phi(z+h) - 2\Phi(z) + \Phi(z-h)}{h^2}, \quad (5)$$

where h is the spacing between neighboring recording points. This method has been successfully used to analyze recordings from one-dimensional electrodes (see Mitzdorf 1985 for a review); however, it has certain limitations. First, the underlying assumption is that the potential is constant in infinite z=const. planes, which in case of cortical columns may not be a reasonable approximation (Pettersen et al. 2006). Second, the method can not be generalized in a straightforward way to more complex tissue geometry (e.g. including inhomogeneities) nor to cases with irregular electrode placement. Third, to estimate C in one point z we need the values of Φ also in neighboring points – Φ(z+h) and Φ(z−h) – so points at the boundary are lost.

Inverse CSD

The above mentioned problems with traditional CSD are partially solved in inverse CSD method proposed by Pettersen and coworkers (2006). In this method one assumes that the underlying CSD distribution belongs to a family of dimensionality equal to the number of recording points. That allows for the construction of an invertible linear operator F connecting the CSD distributions to the measured values. By inverting this operator one can in turn estimate the CSD distribution from measurements.

In Pettersen and others (2006) several families of CSD distributions were considered. First, the authors study the δ-source iCSD. In that method the CSD is assumed to be distributed on infinitely thin discs of radius R centered at the electrode contacts and perpendicular to the electrode. The contribution from the disc centered at i-th electrode (located at z_i) to the potential on the j-th electrode is found to be

$$\frac{hC(z_i)}{2\sigma}\left(\sqrt{(z_j - z_i)^2 + R^2} - |z_j - z_i|\right). \quad (6)$$

The total potential at z_j can be written in the form of a linear operator F acting on a vector of CSD values at the electrode points:

$$\Phi(z_j) = \sum_{i=1}^{N} F_{ji} C(z_i), \quad (7)$$

or, in matrix form $\Phi = FC$, with

$$F_{ji} = \frac{h}{2\sigma}\left(\sqrt{(z_j - z_i)^2 + R^2} - |z_j - z_i|\right). \quad (8)$$

The matrix F is non-singular, therefore it can be inverted, leading to the formula for the CSD estimate:

$$C = F^{-1}\Phi. \quad (9)$$

The δ-source iCSD is computationally the simplest iCSD method, and therefore we use it here to present the iCSD. Also, interestingly, δ-source iCSD converges to the traditional CSD in the $R \to \infty$ limit for the N−2 interior electrode contacts. However, for real applications different one-dimensional iCSD methods seem to be more relevant. In the other two methods proposed by Pettersen and colleagues (2006), step iCSD and spline iCSD, the CSD distribution is again parametrized by CSD values at the electrode contacts. However, as opposed to δ-source iCSD, the currents are distributed in the whole volume surrounding the electrode, and not only on discrete discs; between the electrode contacts the density of transmembrane currents is given by interpolating the values at the contacts either using nearest-neighbor interpolation (step iCSD) or spline interpolation (spline iCSD). In that way more physiologically plausible distributions are obtained, as opposed to the unphysiological, discrete distribution assumed in δ-source iCSD.

One notable feature of one-dimensional iCSD is that the N parameters of the CSD distribution only specify how CSD changes along the line given by electrode contacts. The distribution of CSD in the perpendicular plane has to be assumed. One possibility is to assume homogeneous CSD within each infinitely thin disc of radius R (free parameter of the method), but one could for example assume Gaussian profiles, or include a priori knowledge about the sources. Additionally, one can specify how the CSD distribution along the line behaves outside the first and the last contacts; in Pettersen and colleagues (2006) it was assumed that CSD vanishes one interelectrode distance beyond the edge contacts.

The inverse CSD method can also be applied to two-dimensional (Łęski et al. 2011) and three-dimensional (Łęski et al. 2007) data. The two-dimensional recordings in particular have gained popularity thanks to the availability of multi-shank electrodes. The core idea of iCSD remains unchanged, the CSD distribution is parametrized by the same number of parameters as the number of electrode

contacts. The parameters are typically CSD values at a regular (Cartesian) grid of electrode contacts, and CSD is obtained through interpolation, which especially in 3D leads to rather complex expressions for the F matrix. In 2D iCSD one has to make assumptions regarding the distribution in the perpendicular dimension, notably on the thickness of the tissue region contributing to the signal (Łęski et al. 2011). In 3D there is no need to make such assumptions. However, both in 2D and in 3D one can (and should) specify the behavior at the grid boundary, as this may dramatically improve the method's performance in presence of a distant source located beyond the grid (Łęski et al. 2007, 2011).

One advantage of iCSD over traditional CSD which is especially visible in 2D and 3D is that the boundary points are not excluded from the analysis. This is crucial in 3D, where a large fraction of points may lie on the boundary [in Łęski et al. (2011) 110 out of 140=4×5×7 recording contacts lay on the boundary].

Dealing with missing data in iCSD

The iCSD method in 2D and in 3D is well-suited to regular, Cartesian grid of electrodes. The natural question is whether the method can still be applied if a small number of signals is missing. This problem has been considered in Wójcik and Łęski (2010), where two different ways of dealing with missing data have been studied. The first method is to simply replace the missing data with the average of neighboring signals, the second is to estimate a smaller number of parameters (using a sparser grid) and use the least-squares solution of an overdetermined system of equations. It was shown in Wójcik and Łęski (2010) that the first, simpler approach leads to better and more stable results. Note that this problem disappears in the kernel CSD method described below, as kernel CSD works for arbitrary distributions of electrodes.

Counter-current model and spike CSD

The iCSD methods utilize models of CSD distribution constructed in such a way that the inverse problem (estimating CSD from LFP) becomes well-posed. Similar model-based methods have been devised specifically to analyze extracellular signatures of cortical action potentials (Somogyvári et al. 2005, 2012).

The method described by Somogyvári and others (2005) uses a counter-current model (CCM) of the CSD. The assumption is that the single-cell CSD forms a line source parallel to the electrode. Notably, it is assumed that only one point current sink (negative CSD) is present on the cell, corresponding to the action potential origin, and the remaining line segments contain line current sources (positive CSD). The parameters of the CSD distribution are the position and amplitude of the current sink, amplitudes of the current sources, and the distance between the cell and the electrode. The total number of parameters is smaller than the number of recordings and the model is fit to the data using numerical optimization (direct inversion or pseudo-inversion is not feasible because of non-linear dependence of potentials on the distance parameter).

The spike CSD method (sCSD), presented in Somogyvári and coauthors (2012), builds upon CCM. Because of the constraints imposed by CCM on the distribution of transmembrane currents, the CCM method is valid only until the largest extracellular amplitude of the action potential (Somogyvári et al. 2012). The sCSD method aims to remove this restriction and to allow for analysis of extracellular spikes throughout their whole duration. The idea is the following: with distance d between the cell and the electrode fixed, an invertible forward model $\mathbf{T}(d)$ is constructed assuming point current sources and sinks located along the cell, as in 1D iCSD method. Next, one takes the time point in the recorded potentials corresponding to the highest amplitude of the negative peak of an action potential. CSD is then reconstructed using $\mathbf{T}^{-1}(d)$ inverse matrices for d ranging from 1 to 200 microns. The optimal distance d_{opt} is then chosen as that for which the reconstructed CSD is a sharp peak surrounded by smooth background (technically, this is done by maximizing a goal function $\mathrm{S}(d)$ which is a measure of 'spike-likeness' of the CSD). Finally, $\mathbf{T}^{-1}(d_{\mathrm{opt}})$ is used to calculate the CSD at every time point.

Kernel CSD

The kernel Current Source Density (kCSD) (Potworowski et al. 2012) is a method based on kernel

techniques known in machine learning. Similarly as iCSD, the kCSD method looks for solutions in a predefined space of functions. However, the dimensionality M of this space need not be equal to the number N of recordings, but is typically much larger. The uniqueness of solution in such a broad family is guaranteed by a minimum-L^2-norm constraint (Potworowski et al. 2012, p. 546), which also results in 'smoothing' the solution.

From practical point of view the main advantage of kCSD over iCSD is that kCSD does not require the recording points to be arranged in a Cartesian grid. In fact, it is equally easy to use kCSD for any configuration of electrodes of given spatial dimensionality.

Another advantage is that kCSD – thanks to the method being rooted in well-studied kernel theory – requires little modifications to deal with noisy data.

The kCSD methods works in the following way. First, we choose a basis, $\widetilde{b}_i(\mathbf{x})$=1…$M$, in the space of possible CSD distributions. The basis is usually chosen so as to admit a large family of functions, that is, with large M. Then, we construct a corresponding basis $b_i(\mathbf{x})$ in the space of voltage distributions (potentials). In the space of potentials we perform kernel interpolation of the measurements. Such an interpolation is given as

$$\Phi^*(\mathbf{x}) = \sum_{i=1}^{N} \beta_i K(\mathbf{x_i}, \mathbf{x}), \tag{10}$$

where K is the kernel function, $K(\mathbf{x}, \mathbf{y}) = \sum_{i=1}^{M} b_i(\mathbf{x}) b_i(\mathbf{y})$, x_i are the positions of the electrode contacts, and β_i are the coefficients obtained from Φ_i, i = 1…N, the N measurements of extracellular potential Φ:

$$\beta_i = \sum_{j=1}^{N} \mathbf{K}^{-1}_{ij} \Phi_j. \tag{11}$$

In the final step we go back from the space of potentials to the space of CSD distributions and obtain the estimated CSD as

$$C^*(\mathbf{x}) = \sum_{i=1}^{N} \beta_i \widetilde{K}(\mathbf{x_i}, \mathbf{x}), \tag{12}$$

where $\widetilde{K}$ is the cross-kernel function, $\widetilde{K}(\mathbf{x}, \mathbf{y}) = \sum_{i=1}^{M} b_i(\mathbf{x}) \widetilde{b}_i(\mathbf{y})$.

For the case with noisy measurements we want to avoid overfitting, so we no longer require the estimated potential function $\Phi^*(\mathbf{x}_i)$ to match the measurements Φ_i exactly. Instead, we minimize the cost function

$$\sum_{i=1}^{N} (\Phi^*(\mathbf{x}_i) - \Phi_i)^2 + \lambda \sum_{i=1}^{N} \beta_i^2, \tag{13}$$

where λ controls how much the solution will be regularized. The estimated CSD is in given by the same formula as in the noise-free case, but now $\beta_i = \sum_{j=1}^{N} (\mathbf{K} + \lambda \mathbf{I})^{-1}_{ij} \Phi_j$. The regularization constant λ can be chosen for example through cross-validation.

Recently, in Ness and coworkers (2015), the kCSD method has been adapted to a setup where activity from a slice of brain tissue is recorded using (two-dimensional) micro-electrode array. That variant of kCSD employs a modified forward model, which takes into account the geometry of the slice. However, the conclusion of Ness and others (2015), was that while the correct forward model is crucial for forward modeling of the extracellular potentials, its inclusion in the kCSD method results in only a very minor correction.

Tools for Current Source Density analysis

A number of software tools is available for performing the CSD analysis. CSDplotter, a tool accompanying the paper by Pettersen and colleagues (2006), is a graphical application for MATLAB and allows for iCSD analysis of one-dimensional data, possibly with a conductivity jump in the tissue (e.g. at cortical surface), and is available through the INCF Software Center (http://software.incf.org). MATLAB scripts have been made available for 3D and 2D iCSD, together with a GUI tool for 2D iCSD (also available from the INCF Software Center as 'iCSD 2D'). The software for kCSD method includes MATLAB tools for 1D and 2D cases (INCF Software Center, 'kCSD'), and recently a Python implementation for 1D, 2D, and 3D has been developed as a project in Google Summer of Code 2014 (https://github.com/INCF/pykCSD).

DECOMPOSITION OF NEURAL ACTIVITY INTO COMPONENTS

Several different techniques have been used to extract components from multielectrode recordings of

neural activity. In general, to decompose LFP into meaningful parts one has to supplement the recordings with some additional information, or to make assumptions about the origin of the signals. In case of Independent Component Analysis (ICA) the assumption is that the signals generated by individual populations are statistically independent, and one looks for components which maximize a chosen measure of their independence. In Laminar Population Analysis the LFP is supplemented with recordings of spiking activity (Multi Unit Activity, MUA), and the assumption is that the recorded LFP is the post-synaptic response evoked by the recorded firing. Finally, the method presented by Gratiy and coauthors (2011) assumes that the morphology of the cells contributing to the LFP is known, and LFP templates obtained through forward modeling using these morphologies are used to extract activity of populations.

Independent Component Analysis

Independent Component Analysis (ICA) is an algorithm for decomposing a multichannel signal into components. ICA is often introduced as a solution to the 'cocktail-party problem': imagine several audio sources active at the same time, such as several people speaking simultaneously at a party. How can you separate the different sources? ICA can perform this task if the composite signal (mixture of voices) is recorded through several microphones scattered in the room. Each of the signals contains the original voices weighted with different mixing coefficients depending on the distance between the source and the microphone (assuming no propagation delays). The core idea, and the basic assumption of ICA, is that the composite signals – being mixtures of statistically independent sources – are more Gaussian than the originals. ICA scans the possible unmixing coefficients trying to maximize non-Gaussianity of the recovered signals. The situation where multiple neural sources are recorded through a number of electrode contacts resembles this canonical presentation very well, hence the idea to use ICA for analysis of neural recordings.

ICA was used in Łęski and others (2010) to separate components in LFP evoked by whisker deflection and recorded in thalamus of anesthetized rat. The data consisted of average evoked potentials recorded at 140 spatial locations on a three-dimensional grid. After low-pass filtering of potentials CSD analysis was performed (using 3D iCSD) and ICA was further performed at the level of CSD. In result we were able to identify two components repeating across animals, corresponding to two pathways conveying the sensory information; the components had consistent spatial locations (in five out of seven animals), and consistent time delay between them.

The workflow (CSD estimation followed by ICA) was tested in Łęski and colleagues (2010) on simple artificial data. More thorough study of the properties of this approach has been recently published (Głąbska et al. 2014). There the method is applied to simulated activity of a large-scale model of thalamocortical column (Traub et al. 2005), and iCSD is replaced by kCSD. The study confirmed that the recovered components actually correspond to the activity of specific populations of model cells. However, it also showed that the activity of a population is not always well described by a product of a spatial distribution of sources and a time-dependent activation function, which is a standard assumption in ICA. Some populations exhibit clearly non-product spatiotemporal activation pattern and need more product components to be represented faithfully. In such cases the components obtained with ICA correspond well to principal components of the population's activity.

ICA was also used to analyze extracellular activity in CA1 (Makarov et al. 2010). In contrast to Łęski and coworkers (2010) ICA was applied to voltages, not CSD, but still the volume-conducted potentials coming from extrinsic sources were first filtered out. The recorded spiking activity turned out to have higher coherence with the extracted independent components than with the raw signal, which suggests that the components correspond to different synaptic activation patterns of a population of pyramidal cells. The results were supported by a model of a single population of pyramidal cells driven by three differently distributed inputs.

Laminar Population Analysis

This method has been presented by Einevoll and coauthors (2007). The premise is that in addition to the LFP, the low-frequency component of extracellular field assumed to represent synaptic input to neuronal populations, we also know the total spiking activity by extracting the MUA (high-frequency) signal from the recordings.

LPA is performed in two steps. In the first step the MUA Φ_M is assumed to be a sum of contributions from neuronal populations:

$$\Phi_M(z,t) = \sum_{n=1}^{N_{\mathrm{pop}}} M_n(z) r_n(t), \tag{14}$$

where M_n are parametric, trapezoidal spatial profiles, fully described by three parameters per population, and r_n stand for the population firing rate relative to baseline. The parameters are obtained through a numerical optimization procedure which minimizes the deviation from experimental data.

In the second step, which employs the population-specific firing rates from the first step, the LFP Φ_L is cast in the following form:

$$\Phi_L(z,t) = \sum_{n=1}^{N_{\mathrm{pop}}} L_n(z)(h_n \otimes r_n)(t), \tag{15}$$

where L_n are non-parametric LFP spatial profiles, and h_n are temporal coupling kernels which describe the temporal and spatial profiles of synaptic response. The assumption here is that all the recorded LFP is caused by firing of the recorded populations. Again, the parameters are obtained through numerical optimization. The spatial profiles L_n can further be subject to CSD analysis.

The application of LPA to stimulus-averaged data from rat barrel cortex allows to estimate the pattern of synaptic connections between cortical populations from extracellular recordings.

Decomposition using prior knowledge of cell morphology

The paper by Gratiy and coworkers (2011) uses a model of LFP generation based on known morphologies of cells in an attempt to replace mathematical constraints (such as in ICA) with biophysical knowledge. First, the authors choose specific populations of cortical cells (layer 4 spiny stellate cells and two populations of pyramidal cells, layer 2/3 and layer 5). Then, for each population a single representative reconstructed morphology is used to calculate laminar LFP Green's functions, that is, spatiotemporal LFP responses to unit current inputs delivered at specific time and depth. The Green's functions are obtained through numerical simulations of these morphologically-detailed models. Only passive properties of neuronal membrane are considered (no voltage-dependent channels) and synaptic inputs are modeled as currents, not conductivities. As a result the model is linear in synaptic inputs. The total LFP is assumed to be a sum of contributions from the three populations and noise.

This forward LFP model is then inverted to estimate the population-specific and depth-resolved frequency spectrum of input currents from the recordings of the LFP. Because the number of recordings is typically smaller than the number of points at which the synaptic inputs are to be estimated, the solution is found by using regularized inverse operators taking into account the correlation structure of synaptic currents and noise. Such a procedure was found to perform well on model data, and applied to somatosensory evoked potentials in rat [same data as in Einevoll et al. (2007)] gave results consistent with predictions of LPA.

Possible future extensions of this method include: considering active conductances through linearizaton, adding more cell populations, combining LFP recordings with voltage-sensitive dye (VSD) data.

CONCLUSIONS

The recent years has seen a new wave of interest in the analysis of LFP, and a number of new data analysis methods have been developed, usually in response to the needs of specific experiments or experimental setups. The methods reviewed above fall into two categories: source localization methods, that is, variants of Current Source Density analysis, and signal decomposition methods, which aim to interpret the experimental signals in terms of activity of neural populations. In the latter case the methods rely on extra information to decompose the LFP signal into components: either statistical assumptions are made regarding the properties of the signals, or the morphology of the cells is assumed to be known, or spiking activity is included in the analysis.

A common trend in all these studies is to first verify the methods on model data where the ground truth is known. This is a necessity if we are to believe the results of applying a new data analysis method to experimental data. In case of extracellular potential the link between neural activity and the measured signals is known, therefore modeling studies can provide insights into the properties of LFP (Lindén et al. 2011,

2013, Łęski et al. 2013, Hagen et al. 2015). While the studies reviewed in this paper aim to give quantitative estimates on the precision of the used methods, no standard set of test data has emerged which would allow straightforward comparison of different approaches. One of the reasons might be that the different methods are tailored with specific and different experimental situations in mind.

As the technology continues to progress one may expect that new data analysis methods will continue to be proposed, for example methods which would allow for practical analysis of data coming from arrays of not tens or hundreds, but thousands of electrodes. Another likely trend is the emergence of methods combining different imaging modalities, for example extracellular recordings of electric potentials and optical methods employing voltage-sensitive dyes.

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