Kernel Current Source Density Method

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March 8, 2011

Abstract

Local field potentials (LFP), the low-frequency part of extracellular electrical recordings, are a measure of the neural activity reflecting dendritic processing of synaptic inputs to neuronal populations.

To localize synaptic dynamics it is convenient, whenever possible, to estimate the density of trans-membrane current sources (CSD) generating the LFP.

In this work we propose a new framework, kernel Current Source Density method (kCSD), for non-parametric estimation of CSD from LFP recorded from arbitrarily distributed electrodes using kernel methods. We test specific implementations of this framework on model data measured with one-, two-, and three-dimensional multi-electrode setups. We compare these methods with the traditional approach through numerical approximation of the Laplacian and with the recently developed inverse Current Source Density methods (iCSD). We show that iCSD is a special case of kCSD. The proposed method opens up new experimental possibilites of CSD analysis from already taken or new recordings on arbitrarily distributed electrodes (not necessarily on a grid), which can be obtained in extracellular recordings of single unit activity with multiple electrodes.

1 Introduction

Extracellular recordings of electric potential have great significance in the studies of neural activity in vivo. In the last few years we have witnessed rapid development of technology for large scale electrical recordings. Various types of multielectrodes were devised to simultaneously record extracellular potentials from multiple spatial locations (Normann et al. 1999, Csicsvari et al. 2003, Barthó et al. 2004, Buzsáki 2004, Sher et al. 2007, Imfeld et al. 2008, Frey et al. 2009, Ward et al. 2009, Charvet et al. 2010). The low-frequency part of these recordings, the local field potentials (LFP), typically reflect the dendritic processing of synaptic inputs (Nunez & Srinivasan 2006, Einevoll et al. 2007, Pettersen

et al. 2008, Lindén et al. 2010). Direct interpretation of LFP is difficult as it is a nonlocal measure of the neural activity: it may have contributions from neurons located more than a millimeter away from the electrode (Kreiman et al. 2006, Liu & Newsome 2006, Berens et al. 2008, Katzner et al. 2009, Xing et al. 2009) or even a few milimeters (Hunt et al. 2010). Therefore, if only possible it is convenient to estimate the current source density (CSD), the volume density of net transmembrane currents, generating the LFP (Lorente de No 1947, Pitts 1952, Plonsey 1969, Freeman & Nicholson 1975, Nicholson & Freeman 1975, Mitzdorf 1985). CSD directly relates to the local neural activity and current source density analysis is a convenient tool for analysis of LFP recorded from multielectrodes (Haberly & Shepherd 1973, Mitzdorf 1985, Schroeder et al. 1992, Ylinen et al. 1995, Lakatos et al. 2005, Lipton et al. 2006, Rajkai et al. 2008, de Solages et al. 2008).

Since CSD in a homogeneous and isotropic tissue is given by the Laplacian of the potentials, originally it was estimated by a discrete differentiation scheme from the potentials measured on a regular grid (Freeman & Nicholson 1975, Nicholson & Freeman 1975, Mitzdorf 1985). In the past few years a new method for CSD estimation has been developed, the inverse CSD (iCSD) method (Pettersen et al. 2006, Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007, Wójcik & Łęski 2010, Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011). The main idea behind iCSD is to assume a specific parametric form of CSD generating the measured potentials (e.g. spline interpolated between the grid nodes), calculate the LFP in a forward-modeling scheme to obtain the values of CSD parameters (e.g. CSD values at the nodes) by matching the experimental data with computed values. The iCSD framework requires an assumption of a specific geometry of contacts requiring new calculations for each distribution of electrodes. So far, all the propositions assumed recordings on regular, Cartesian grids.

Here we introduce a new, non-parametric method for CSD estimation. The kernel CSD method (kCSD) uses some basic facts from the theory of reproducing kernel Hilbert spaces used in machine learning (Aronszajn 1950, Vapnik 1998, Schoelkopf & Smola 2002, Shawe-Taylor & Christiani 2004). This method does not require the user to specify the restricted, parametrized form of the admissible CSD distributions. Instead, one specifies an arbitrarily broad family of possible distributions and uniqueness of the solution is guaranteed by the minimum-norm requirement built in the method.

The assumption of regular electrode arrangement is not necessary, kCSD can be applied to recordings from electrodes distributed at any positions on one-, two-, and three-dimensional sets with equal ease. Moreover, we show that kCSD is a general non-parametric framework for CSD estimation including all the previous variants of iCSD methods as special cases.

The article is organized as follows: in Section 2 we introduce the basic framework of the method using reproducing kernel Hilbert spaces (RKHS) (Aronszajn 1950, Vapnik 1998, Schoelkopf & Smola 2002, Shawe-Taylor & Christiani 2004) and show an efficient regression algorithm applicable in RKHS. However, the CSD we want to estimate and the potentials we measure are different physical quantities which normally forces us to solve a linear operator equation. Introducing a cross-kernel between spaces of potentials and sources we can easily obtain estimation of sources. We apply this technique to estimate the most plausible CSD consistent with the measured potentials. We show how to do this in cases where the measurements were taken on sets of different dimensionality, e.g. for laminar multielectrodes, multi-shaft multielectrodes, and in the general three-dimensional case. We also show that the previously introduced iCSD methods are special cases of kCSD introduced here.

To test the viability of the proposed scheme we performed a number of tests on model data where we control the sources to be recovered from potentials. These tests are presented in Section 3. We first consider the case of regular grids, as these are the only cases that were treated by the methods available so far, to show how the new method compares with the readily available alternatives. Then we consider the case of arbitrary distributions of contacts as the proposed methods can easily treat arbitrary geometry of the electrode setup.

Since every measurement is subject to noise it is important to study its effect on the method. Having established the soundness of the basic approach, in Section 4 we study ridge regression as a possible means of avoiding over-fitting and removing almost singularities which might arise for instance in case of atypical setups. The properties of the proposed method, further directions of development, and the significance of the kernel approach are discussed in the final section.

2 The Kernel Current Source Density (kCSD) Method

Consider the following problem: N electrodes are placed in the brain at $\mathbf{x}_1, \ldots, \mathbf{x}_N \in \mathbb{R}^3$ and we measure the extracellular potential V at N locations $(V_1, \ldots, V_N)$. The extracellular potential we sample is generated by transmembrane currents whose density C (current source density, CSD) is what we would like to estimate. The connection between V and C is given by the Poisson equation,

$$\nabla(\sigma\nabla)V = -C. \tag{1}$$

Let us approximate the CSD generated by concerted activity of the myriads of neurons as a sum of M localized sources $\widetilde{b}_i(\mathbf{x})$,

$$C(\mathbf{x}) = \sum_{j=1}^{M} C_j \widetilde{b}_j(\mathbf{x}). \tag{2}$$

Conceptually, we consider each $\widetilde{b}$ as a model of activity of a small population of neurons. In practice we consider sources of constant density within a ball of radius R and 0 elsewhere:

$$\widetilde{b}_i(x, y, z) = \begin{cases} 1 & (x - x_i)^2 + (y - y_i)^2 + (z - z_i)^2 \leq R^2 \\ 0 & \text{otherwise} \end{cases} \tag{3}$$

or Gaussians:

$$\widetilde{b}_i(x, y, z) = \exp\left(-\frac{(x - x_i)^2 + (y - y_i)^2 + (z - z_i)^2}{2R}\right). \tag{4}$$

Each of the sources $\widetilde{b}_i$ generates potential in the whole space consistent with the Poisson equation (1). In what follows we assume homogeneous and uniform conductivity tensor σ and no boundary conditions (we return to discuss this issue in the final section). Then the potential generated by source $\widetilde{b}_i$ is

$$b_i(x, y, z) = \frac{1}{4\pi\sigma} \int dx' \int dy' \int dz' \, \frac{\widetilde{b}_i(x', y', z')}{\sqrt{(x - x')^2 + (y - y')^2 + (z - z')^2}}. \tag{5}$$

The relation between the sources and potentials is different in lower dimensionality and for other models of propagation, boundary conditions etc, but it does not affect the general formulation of the method. In every case, however, we can introduce a linear operator $\mathcal{A} : \widetilde{\mathcal{F}} \mapsto \mathcal{F}$ connecting sources and potentials by

$$V(\mathbf{x}) = \mathcal{A}C(\mathbf{x}) = \sum_{i=1}^{M} a_i b_i(\mathbf{x}) \tag{6}$$

with $b_i = \mathcal{A}\widetilde{b}_i$, where the space of sources is

$$\widetilde{\mathcal{F}} = \left\{ C(\mathbf{x}) = a_1\widetilde{b}_1(\mathbf{x}) + ... + a_n\widetilde{b}_n(\mathbf{x}) : \widetilde{b}_i : \mathbb{R}^d \longrightarrow \mathbb{R} \right\}, \tag{7}$$

and the space of potentials is

$$\mathcal{F} = \left\{ V(\mathbf{x}) = a_1 b_1(\mathbf{x}) + ... + a_n b_n(\mathbf{x}) \ : \ b_i : \mathbb{R}^d \longrightarrow \mathbb{R} \right\}. \tag{8}$$

We assume that $\widetilde{b}_i$ (b_i) are linearly independent and so they constitute bases of the linear spaces $\widetilde{\mathcal{F}}$ and $\mathcal{F}$. We consider $\mathcal{A}$ in one- and two-dimensional cases below.

Let us introduce a kernel function (a kernel for short) $K : \mathbb{R}^d \times \mathbb{R}^d \longrightarrow \mathbb{R}$ by the following equation

$$K(\mathbf{x}, \mathbf{x}') = \sum_{i=1}^{N} b_i(\mathbf{x}) b_i(\mathbf{x}'). \tag{9}$$

With this kernel one can show (see for example Section 1.3, Theorem A in Aronszajn (1950) and Theorem 3.11 in Shawe-Taylor & Christiani (2004)) that the *space of potentials* $\mathcal{F}$ is the feature space of K and as such, $(\mathcal{F}, K)$ is a *Reproducing Kernel Hilbert Space (RKHS)*. That is, one can show that

$$\mathcal{F} = \left\{ \sum_{i=1}^{l} \alpha_i K(\mathbf{x}_i, \mathbf{x}) : l \in \mathbb{N}, \mathbf{x}_i \in \mathbb{R}^d, \alpha_i \in \mathbb{R}, i = 1, ..., l \right\}. \tag{10}$$

and it is a Hilbert space with the inner product of functions $f(\mathbf{x}) = \sum_{i=1}^{l} \alpha_i K(\mathbf{x}_i, \mathbf{x})$, $g(\mathbf{x}) = \sum_{j=1}^{m} \beta_j K(\mathbf{z}_j, \mathbf{x})$ given by

$$\langle f, g \rangle_{\mathcal{H}} = \sum_{i=1}^{l} \sum_{j=1}^{m} \alpha_i \beta_j K(\mathbf{x}_i, \mathbf{z}_j). \tag{11}$$

Note that we have now two representations of every function in $\mathcal{F}$, as sum of kernels or sum of basis elements

$$f(\mathbf{x}) = \sum_{i=1}^{l} \alpha_i K(\mathbf{x}_i, \mathbf{x}) = \sum_{i=1}^{M} a_i b_i(\mathbf{x})$$

where $a_i = \sum_{j=1}^{l} \alpha_j b_i(\mathbf{x}_j)$.

Using the inner product we can define the norm in $\mathcal{F}$ by $\|f\|_{\mathcal{F}}^2 = \langle f, f \rangle$. It is easy to see that in the two representations we have

$$\|f\|_{\mathcal{F}}^2 = \sum_{i=1}^{l} \sum_{j=1}^{l} \alpha_i \alpha_j K(\mathbf{x}_i, \mathbf{x}_j) = \sum_{i=1}^{M} a_i^2.$$

We use $\|f\|^2_{\mathcal{F}}$ to induce a norm in $\widetilde{\mathcal{F}}$ by

$$\|\widetilde{f}\|^2_{\widetilde{\mathcal{F}}} := \|\mathcal{A}\widetilde{f}\|^2_{\mathcal{F}} = \sum_{i=1}^{M} a_i^2. \tag{12}$$

Our goal is to find the current source density $C(\mathbf{x})$ consistent with the measured potentials[1]. We first estimate the potential from data. As there are many more sources than measurements there is an infinite number of solutions. Consider potentials $V(\mathbf{x}) = \sum_{i=1}^{M} a_i b_i(\mathbf{x})$ consistent with the measurements, that is $V(\mathbf{x}_k) = \sum_{i=1}^{M} a_i b_i(\mathbf{x}_k) = V_k$. To find the potential with minimum norm $\|V\|^2 = \sum_{i=1}^{M} a_i^2$ satisfying these constraints, the derivative $\partial\|V\|^2/\partial a_k$ must be a linear combination of constraints derivatives along a_k. That is we have

$$a_i = \sum_{k=1}^{N} \beta_k b_i(\mathbf{x}_k)$$

and the potential we seek takes the form

$$V^*(\mathbf{x}) = \sum_{i=1}^{N} \beta_i K(\mathbf{x}_i, \mathbf{x}) \in \mathcal{M}. \tag{13}$$

Solving the constraints we get the parameters $\beta_1, \ldots, \beta_N$ to be

$$\begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} = \begin{bmatrix} K(\mathbf{x}_1, \mathbf{x}_1) & \cdots & K(\mathbf{x}_1, \mathbf{x}_N) \\ \vdots & \ddots & \vdots \\ K(\mathbf{x}_N, \mathbf{x}_1) & \cdots & K(\mathbf{x}_N, \mathbf{x}_N) \end{bmatrix}^{-1} \begin{bmatrix} V_1 \\ \vdots \\ V_N \end{bmatrix}, \tag{14}$$

which can be written in more compact notation as

$$\boldsymbol{\beta} = \mathbf{K}^{-1} \cdot \mathbf{V}$$

with an obvious definition of terms.

We have also assumed here that the measurements are sufficiently independent (informative) that $\mathbf{K}$ is of full order and so can be inverted. In all the cases we considered $\mathbf{K}$ was invertible and we expect this to be true for all experimentally accessible electrode setups. If this is not the case, for instance if two contacts are too close giving unstable inverse, one can use one of many strategies to stabilize inversion. In particular the regularization which we discuss in Section 4 also overcomes the problem of possible almost singularities of $\mathbf{K}$.

Having V^* given by

$$V^*(x) = \sum_{i=1}^{M} \beta_i K(\mathbf{x}_i, \mathbf{x}) = \sum_{j=1}^{N} a_j b_j(\mathbf{x}), \tag{15}$$

where $a_j = \sum_{i=1}^{M} \beta_i b_j(\mathbf{x}_i)$, we know that there exists exactly one $C^* \in \widetilde{\mathcal{F}}$ generating V^* and it is given by

$$C^* = \sum_{j=1}^{N} a_j \widetilde{b}_j(\mathbf{x}) = \sum_{i=1}^{M} \beta_i \sum_{j=1}^{N} b_j(\mathbf{x}_i)\widetilde{b}_j(\mathbf{x}) = \sum_{i=1}^{N} \beta_i \widetilde{K}(\mathbf{x}_i, \mathbf{x}). \tag{16}$$

[1]Such consistence with data is appropriate when the observations are noise free. In section 4 we discuss a more general treatment of data with noise.

Thus we see that it is convenient to introduce the *cross-kernel function*

$$\widetilde{K}(\mathbf{x},\mathbf{y}) = \sum_{i=1}^{n} b_i(\mathbf{x})\widetilde{b}_i(\mathbf{y}). \tag{17}$$

If we define the *vector* function

$$\widetilde{\mathbf{K}}^T(\mathbf{x}) := [\widetilde{K}(\mathbf{x}_1,\mathbf{x}),\ldots,\widetilde{K}(\mathbf{x}_n,\mathbf{x})],$$

then

$$C^*(\mathbf{x}) = \widetilde{\mathbf{K}}^T(\mathbf{x})\cdot\mathbf{K}^{-1}\cdot\mathbf{V}. \tag{18}$$

From (12) we see that C^* is the current source density consistent with the measured potentials that has the smallest norm in $\widetilde{\mathcal{F}}$.

2.1 kCSD for measurements taken on planes or lines

In lower dimensionality the framework changes because in order to calculate the potentials generated by a source we must assume the structure of the source in the normal (perpendicular) directions to the plane (in 2D) or line (in 1D) of measurements. The need for such models and specific examples were carefully discussed by Pettersen et al. (2006) for the case of laminar recordings and by Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik (2011) for planar recordings (such as multishaft electrodes).

2.1.1 kCSD in 2D

Consider a situation in which LFP is measured by electrodes that are arranged on a flat surface, e.g. as in (Csicsvari et al. 2003). To estimate CSD we need to make assumptions about its profile in the direction perpendicular to the surface. Let's introduce a coordinate system (x, y, z) and assume that the electrodes are arranged on the surface spanned by the x and y axes. In Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik (2011) we proposed to consider the CSD as a product of a two-dimensional profile $\widetilde{f}(x, y)$ and a specific profile H in the perpendicular direction z :

$$\widetilde{f}(x, y, z) = \widetilde{f}(x, y)H(z).$$

For $H(z)$ here we take a simple step function:

$$H(z) = \begin{cases} 1 & -h \le z \le h \\ 0 & \text{otherwise} \end{cases}$$

although other choices such as a Gaussian profile are also possible. Thus we assume that the CSD profile is constant in z direction within a slice of thickness $2h$ centered at the surface with electrodes and 0 elsewhere. It turns out that the specific choice of profile $H(z)$ influences mainly the amplitude of the calculated potentials and so the estimated sources, while their overall shape is reasonably robust (Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011).

The potential measured by an electrode placed in some point $(x, y, 0)$ is in this case given by:

$$f(x,y) = \frac{1}{2\pi\sigma}\int dx' \int dy' \ \text{arsinh}\left(\frac{2h}{\sqrt{(x-x')^2+(y-y')^2}}\right)\widetilde{f}(x',y') =: (\mathcal{A}_2\widetilde{f})(x,y). \tag{19}$$

In this case it is sufficient to estimate the two-dimensional profile $\widetilde{f}(x,y)$ to get an estimate of the overall CSD in the region. Therefore we can define spaces $\mathcal{F}$ and $\widetilde{\mathcal{F}}$ by introducing two-variable basis functions. This can be done similarly as in the 3D case, using simple step basis functions for space $\widetilde{\mathcal{F}}$:

$$\widetilde{b}_i(x,y) = \begin{cases} 1 & (x-x_i)^2 + (y-y_i)^2 \leq R^2 \\ 0 & \text{otherwise} \end{cases} \tag{20}$$

or Gaussians:

$$\widetilde{b}_i(x,y) = \exp\left(-\frac{(x-x_i)^2 + (y-y_i)^2}{2R}\right). \tag{21}$$

The potential basis functions $b_i \in \mathcal{F}$ can be derived by applying equation (19):

$$b_i(x,y) = \frac{1}{2\pi\sigma} \int dx' \int dy' \ \text{arsinh}\left(\frac{2h}{\sqrt{(x-x')^2 + (y-y')^2}}\right) \widetilde{b}_i(x',y'). \tag{22}$$

2.1.2 kCSD in 1D

Assume that the electrodes are arranged along a straight line. As in the previous section we need to make assumptions on CSD profile in the perpendicular plane. Pettersen et al. (2006) proposed to introduce an overall CSD profile of the form:

$$\widetilde{f}(x,y,z) = \widetilde{f}(z)H(x,y).$$

We assume rotational symmetry around z axis and for $H(x,y)$ we take a simple step function on a disk of radius r:

$$H(x,y) = \begin{cases} 1 & x^2 + y^2 \leq r^2, \\ 0 & \text{otherwise.} \end{cases}$$

The potential measured by an electrode placed in some point $(0,0,z)$ is in this case given by:

$$f(z) = \frac{1}{2\sigma} \int dz' \left(\sqrt{(z-z')^2 + r^2} - |z-z'|\right) \widetilde{f}(z') = (\mathcal{A}_1 \widetilde{f})(z) \tag{23}$$

Now the space of CSD $\widetilde{\mathcal{F}}$ can be defined by introducing one-variable basis functions. As in the previous cases, one can use simple step functions

$$\widetilde{b}_i(z) = \mathbb{I}_{[z_i - R; z_i + R]}(z) \tag{24}$$

or Gaussians

$$\widetilde{b}_i(z) = \exp\left(-\frac{(z-z_i)^2}{2R}\right). \tag{25}$$

Finally, the potential basis functions $b_i \in \mathcal{F}$ can be obtained by applying equation (23):

$$b_i(z) = \frac{1}{2\sigma} \int dz' \left(\sqrt{(z-z')^2 + r^2} - |z-z'|\right) \widetilde{b}_i(z'). \tag{26}$$

2.2 Spatial arrangement of the basis elements

In Section 2 we introduced example shapes of the basis functions $\left\{\widetilde{b}_i\right\}_{i=1}^{n}$ which we considered in various dimensions. To implement kCSD we have to specify the number and localization of these sources. Let us denote the area where we want to estimate CSD by $\mathcal{B} \subset \mathbb{R}^d$, where $d \in \{1, 2, 3\}$. In all the tests we carried out $\mathcal{B}$ was a product of intervals, $\mathcal{B} = \cap_{k=1}^{d} I_k$, $I_k = [a_k, b_k] \subset \mathbb{R}$, for example, in Section 3.1:

$$\mathcal{B} = \left\{(x, y) \in \mathbb{R}^2 : x_{\min} - \xi\Delta x \leq x \leq x_{\max} + \xi\Delta x, y_{\min} - \xi\Delta y \leq y \leq y_{\max} + \xi\Delta y\right\}.$$

To generate the basis of sources we always took a spherically symmetric template function $\widetilde{b}(\mathbf{x})$ and translated it to nodes of a regular, rectangular grid $\mathbf{x}_i \in \mathcal{B}$ obtaining the full basis $\widetilde{b}_i(\mathbf{x}) = \widetilde{b}\left((\mathbf{x} - \mathbf{x}_i)^2\right)$ making sure that each point in the estimation area $\mathcal{B}$ belongs to the support of at least two basis sources. It turns out that to get apparently smooth results R should be a multiple of the spacing between the grid nodes, otherwise we observed significant irregularities.

2.3 Relation between iCSD and kCSD

The main feature of kCSD is efficient estimation in spaces with rich bases: we assumed here that in general the dimension of the space of sources N is much higher that the number of measurements, M. If $M = N$ then kCSD is equivalent to a variant of previously developed inverse Current Source Density method (Pettersen et al. 2006, Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007, Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011), in which we take the basis from the kCSD method as the N-parameter family of sources in the inverse CSD method. Then in both models we have the same space of sources and no degeneracy, hence the solutions have to be the same. To illustrate the connection between the two approaches we show this explicitly in Appendix B.

3 Tests and examples

To test the viability of the kCSD method we performed a number of numerical experiments using model sources and experimentally registered potentials.

The first question is how the kCSD method compares to the other methods (finite-difference approximation, inverse CSD). To answer this we used several configurations of the model CSD to calculate the potentials which would have been measured using multi-contact electrodes. To be able to apply all the different CSD methods we had to use regular grids, that means we calculated the potentials either at equidistant points in 1D or at points which formed a Cartesian grid in 2D or 3D. Then we tested the similarity of the CSD reconstructions to the model CSD for a wide range of parameters of the kCSD method. These tests are described in more detail in Section 3.1 below. The conclusion is that for the electrode grids where all the methods can be applied the kCSD method performs as well as the spline iCSD method or better (which is typically better than the finite difference — 'traditional' — CSD analysis) if we choose basis appropriately.

A major strength of kCSD is its capability to estimate CSD from arbitrary distributions of contacts with equal ease. Thus the second and perhaps the most interesting question is how the kCSD method performs for contacts not forming a regular grid. Though it is sometimes possible to use other CSD methods in such cases, it is usually harder to use

them without the assumption of the regularity and the kCSD method seems to be the most natural choice. We illustrate this below in Section 3.2. First we show how the kCSD method can be easily applied to (model) potentials recorded on a grid used in Wirth & Lüscher (2004). Then we test the quality of reconstruction for electrodes placed randomly within the probed area and check how it changes with increasing number of electrodes.

The intermediate case between regular and irregular grids is when we use a grid of regularly placed contacts but with a small number of contacts missing. This can happen, for example, when one or two contacts are used for stimulation instead of recording. This problem was studied earlier in Wójcik & Łęski (2010) where two approaches based on iCSD were proposed: one was to substitute the missing channels with averages of their neighbors (LA for local averages), the other was to restrict the dimensionality of the possible CSD distributions and use the least-squares fit to all available recordings (LS). Again, the kCSD method seems to be a natural choice here. In Section 3.3 we test the kCSD method on the same experimental data as used in Wójcik & Łęski (2010) and show that it is a substantially better approach than the LS method from Wójcik & Łęski (2010). Comparison of kCSD with the LA method depends on the dataset tested.

3.1 Comparison of CSD methods on regular grids

The kCSD method as defined above has a number of parameters which need to be specified before the method can be applied to data. Specifically, we need to define the basis $\left\{\widetilde{b}_i(\mathbf{x})\right\}_{i=1}^{n}$ of the space of the CSD distributions $\widetilde{\mathcal{F}}$. As an example we will consider a two-dimensional regular, rectangular electrode grid ($z = 0$ for all electrodes). We generate all the basis functions by translating a single reference function of the form $c(x, y)H(z)$ where as in Section 2.1.1 for $c(x, y)$ we take either a two-dimensional Gaussian

$$c_g(x, y) = \exp\left(-\frac{x^2 + y^2}{2R}\right), \tag{27}$$

or a two-dimensional cylindrically symmetric step function

$$c_s(x, y) = \begin{cases} 1 & \text{if} \quad x^2 + y^2 < R^2 \\ 0 & \text{otherwise.} \end{cases} \tag{28}$$

Therefore, each basis function $\widetilde{b}_i$ is a translation of c_s or c_g. The parameter R in the formulae above is the size of the basis sources in the xy plane. As the transverse profile $H(z)$ we take a step function: $H(z) = 1$ for $-h \leq z \leq h$. Let $x_{\min}, x_{\max}$ denote the minimum and the maximum of the x coordinates of the electrodes, similarly for y; the spacing of the grid is $\Delta x, \Delta y$. We assume that the sources can extend beyond the electrode grid, specifically, the central points (x, y) of the basis functions can be in the region $x_{\min} - \xi\Delta x \leq x \leq x_{\max} + \xi\Delta x$, $y_{\min} - \xi\Delta y \leq y \leq y_{\max} + \xi\Delta y$, where ξ is a parameter. We arrange the sources as described along a regular rectangular grid. The final parameter is the number of sources n. We choose such n that it is a product of numbers of equally spaced sources in x and y directions. Summarizing, the parameters we have to specify are n, R, h, and ξ, and the choice between step and Gaussian profiles in the xy plane. The choice of the translation parameters and number of sources was described in Section 2.2.

Let us focus on an eight-by-eight grid with equal spacing in both directions ($\Delta x = \Delta y = 0.2$, all lengths in this section are in mm) spanning the area $0 \leq x, y \leq 1.4$. We chose two sets of test sources, both having product structure $c(x, y)H(z)$ with $H(z) = 1$

for $-0.5 \leq z \leq 0.5$. The datasets are composed of Gaussian sources: in the first set the sources are large compared to the inter-electrode distance (Fig. 1A), and in the second dataset they are small (Fig. 2A). The exact formulae are given in the Appendix A.

We calculated the potentials at the registration points (for that purpose the integration area was $(x, y) \in [-0.5, 1.9] \times [-0.5, 1.9]$). Then we performed a scan over the space of parameters of the kCSD method: we took all possible combinations of $R = 0.05, 0.1, 0.15, \ldots, 0.4$, $n = 90^2, 120^2, \ldots, 240^2$, $h = 0.2, 0.5, 1$, and $\xi = 0, 0.5, 1, 2, 3$. For each combination of parameters, and for both the Gaussian and the step profiles we reconstructed the CSD and calculated the normalized reconstruction error e using the formula

$$e = \frac{\int (c(x,y) - \hat{c}(x,y))^2}{\int c(x,y)^2},$$

where $\hat{c}(x, y)$ is the reconstructed CSD (Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007).

In Figures 1 and 2 we show example reconstructions using the kCSD method with

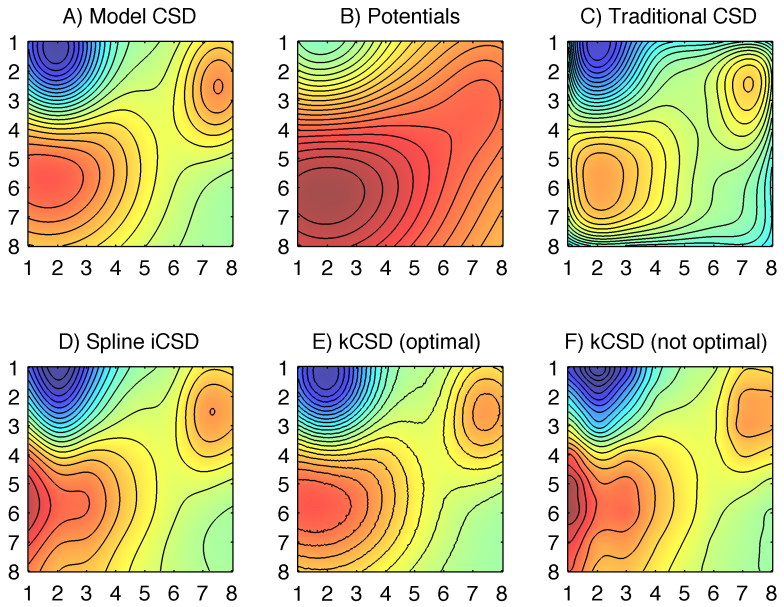

Figure 1: Test results for the first model dataset ('large sources'). A) The model CSD. B) The potentials. C) Reconstruction using traditional CSD. D) Reconstruction using spline iCSD method with D boundary conditions. E) Reconstruction using the kCSD method for $n = 8100$, $\xi = 2$, $R = 0.3$, $h = 0.5$, step basis. F) Reconstruction using the kCSD method for $n = 8100$, $\xi = 1$, $R = 0.1$, $h = 0.5$, Gaussian basis.

parameters close to optimal (Fig. 1E, Fig. 2E) and with parameters farther from optimal (Fig. 1F, Fig. 2F), exact parameter sets given in captions. These are compared with traditional CSD (Fig. 1C, Fig. 2C) and spline iCSD reconstructions (Fig. 1D, Fig. 2D).

By 'traditional CSD' here and in the following we understand the following procedure: *(i)* extend the grid by extra layer in each direction and copy the potential value at extra points from nearest neighbors; *(ii)* calculate the CSD value at the grid points by discrete numerical approximation to the Laplacian; *(iii)* cubic spline interpolate in between. The iCSD with D boundary conditions means the CSD model where the original

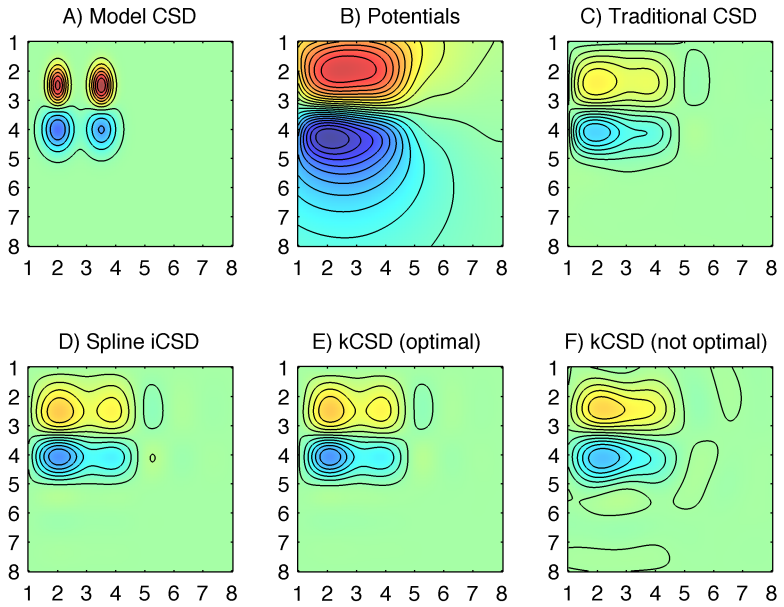

Figure 2: Test results for the first model dataset ('small sources'). A) The model CSD. B) The potentials. C) Reconstruction using traditional CSD. D) Reconstruction using spline iCSD method with D boundary conditions. E) Reconstruction using the kCSD method for $n = 8100$, $\xi = 0.5$, $R = 0.2$, $h = 0.5$, Gaussian basis. F) Reconstruction using the kCSD method for $n = 8100$, $\xi = 0.5$, $R = 0.4$, $h = 0.5$, Gaussian basis.

grid was extended with an extra layer and the same CSD value was assumed as in the nearest neighbor, spline interpolated CSD between the nodes (Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007, Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011).

The errors for optimal kCSD parameters ($e = 0.06\%$ and $e = 35\%$ for large and small sources, respectively) are smaller than the errors of the traditional CSD ($e = 43\%$ and $e = 38\%$) and spline iCSD ($e = 1\%$ and $e = 36\%$). If the parameters are farther from the optimal set the error of the kCSD method grows ($e = 3\%$ and $e = 66\%$ for the presented examples). Note that for the 'small sources' data set all errors are rather large. This is because the electrodes grid is too sparse to probe the detailed structure of the sources, compare Figure 2C–F with Figure 5 where a denser electrodes grid leads to much better reconstruction. This is intuitively very natural as it resembles the situation in Fourier analysis where it is impossible to recover frequencies higher than half the sampling rate of the signal (Nyquist theorem).

The results of the parameters space scan can be summarized as follows: the most important parameter is the size of the basis sources R. For the first set of model sources ('large sources') it is best to choose large R ($R = 0.4$ or even larger), while for the second set ('small sources') the results are best for small R (~ 0.1). This is not surprising since any CSD estimation method works best if the assumed CSD family matches closely the actual distribution.

Since optimal reconstruction parameters depend on the dataset we further tested the dependence of reconstruction error on R on a large set of randomly placed Gaussian sources of different sizes from small to large. We used 2000 data sets, the details on how the sources

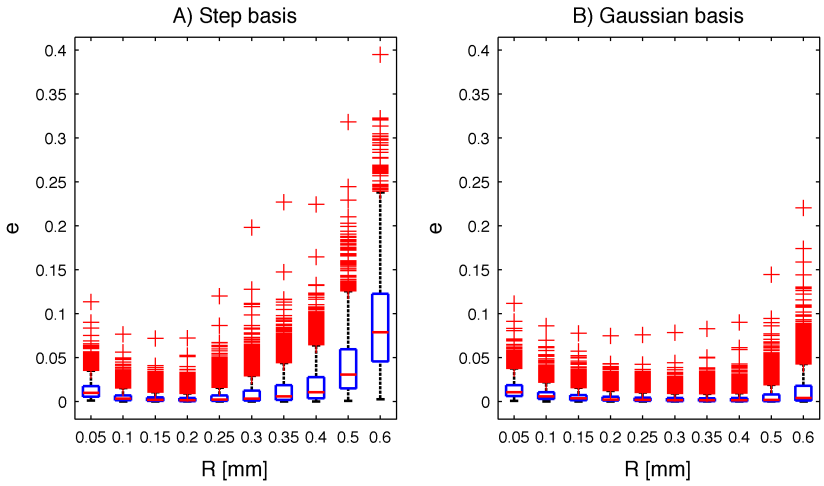

Figure 3: Dependence of reconstruction error on R for step (A) and Gaussian (B) basis sources. The boxes in the 'box and whisker' plots show the median and the lower and upper quartile values; the whiskers extend over the neighboring values up to a maximum of 1.5 times the interquartile range; the values further away are shown as outliers (+ signs, typically less than 10% of the data points).

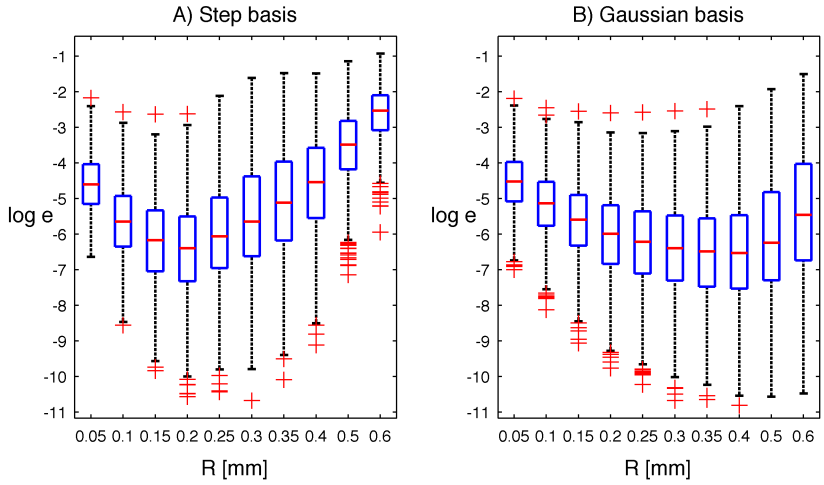

Figure 4: Dependence of (logarithm of) reconstruction error on R for step (A) and Gaussian (B) basis sources. The boxes in the 'box and whisker' plots show the median and the lower and upper quartile values; the whiskers extend over the neighboring values up to a maximum of 1.5 times the interquartile range; the values further away are shown as outliers (+ signs, typically less than 10% of the data points).

were chosen are given in the Appendix A. For each data set we performed reconstructions for different R (other parameters kept fixed). The results for both Gaussian and step bases are presented in Fig. 3 and 4. For this collection of 2000 data sets the optimal R is ~ 0.3 to 0.4 for the Gaussian basis and ~ 0.15 to 0.2 for the step basis. One interesting observation is that the Gaussian basis leads to weaker dependence of the reconstruction error on R. Therefore, the recommendation for this electrode grid would be to use Gaussian basis sources and an intermediate value of R, say $R = 0.35$. For such choice the method should work reasonably well for a wide range of CSD sources.

The conclusions regarding the choice of h are the same as in inverse CSD method (Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011): the closer we are to the actual h, the better; assuming wrong h may have strong influence on the amplitude of the reconstructed sources but the shape of the distribution is roughly preserved. The non-zero values of the parameter ξ dramatically help in cases where the actual activity in the xy plane extends beyond the electrodes grid (the 'large sources' case). The reconstruction error grows with ξ when there is no activity beyond the grid, but this effect is very small, therefore $\xi = 1$ is a safe choice in any case. The number of sources (originally between $n = 90^2$ up to $n = 240^2$) had almost no effect on the reconstructions. We further studied reconstructions with smaller number of sources ($n = 10^2, 11^2, \ldots 15^2, 20^2, 30^2, 45^2, 60^2, 75^2$) and we found that the reconstructions only break for very sparse bases (such as $n = 10^2$); taking $n = 20^2$ yields errors only slightly higher than the optimal values of n. The reason that the method does not work for very small n (especially when used together with small R) is that the character of the cross-kernel functions changes dramatically: for larger n they are 'smooth' functions with a single maximum, whereas for small n the kernels have multiple maxima located at the observation points and are therefore unable to reproduce smooth CSD distributions faithfully. Our recommendation is that n should be such that the basis sources are denser than the observation points (for example $n = 20^2$ for 8 by 8 grid).

3.2 kCSD on irregular grids

One of the strengths of the kCSD method is that it can be easily applied to any configuration of the recording points. As an example let us consider an electrode array used by Wirth & Lüscher (2004), see Fig. 5. The contacts of the array do not form a regular, rectangular grid similar to the ones used in Section 3.1 (although locally they form a square lattice). While it would be possible to apply some form of inverse CSD (or even numerical second derivative), the kCSD method is the most natural method to use in this case. Figure 5 presents the test sources used in this case ('small sources' dataset described in Section 3.1), the potentials resulting from the sources and the reconstructed CSD. Note that this reconstruction is better than the reconstructions obtained in Section 3.1 because the inter-electrode distance, 140μm, is smaller here.

In fact, it is equally easy to apply the kCSD method to regular and irregular grids, which is not the case for other CSD methods such as spline iCSD introduced previously. To demonstrate the strength of this new approach we consider electrodes placed *randomly*. Such irregular placement could occur in real experiments, for example, when many electrodes are positioned independently to record spiking activity and then also the LFP signal is recorded. For the two test datasets defined in Section 3.1 we chose randomly a set of electrodes placed within the area $(x, y) \in [0, 1.4] \times [0, 1.4]$ [2] and calculated the reconstruction error e (example reconstructions shown in Figure 6). For each number of electrodes

[2]The only constraint was that any two electrodes can not be closer than 0.14 mm.

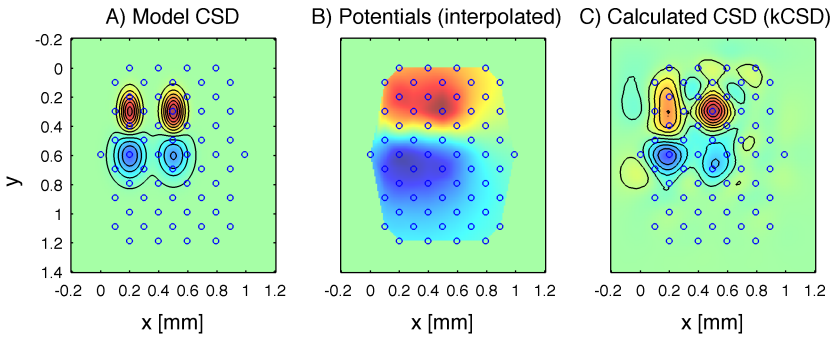

Figure 5: CSD reconstruction on an irregular grid of electrodes (circles). A) The model CSD. B) The estimated potentials. C) CSD reconstructed from potential values at the grid using kCSD method.

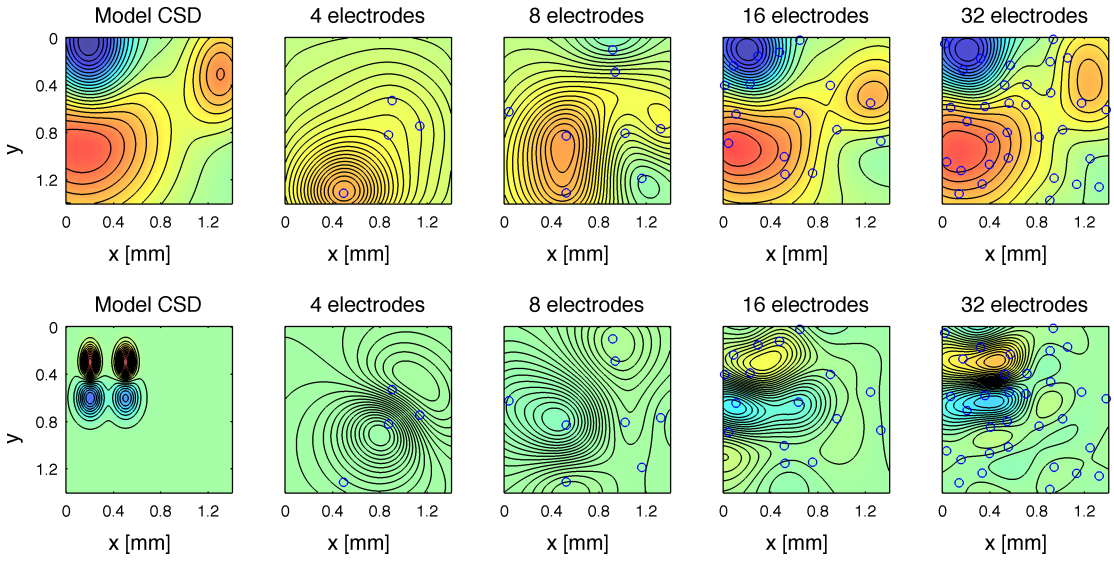

Figure 6: CSD reconstructions from randomly placed electrodes (examples). Top row: 'large sources', bottom row: 'small sources'.

we repeated this procedure 50 times to obtain error bars on e. The results are presented in Figure 7. For 'large sources' the CSD can be reconstructed quite faithfully from as little

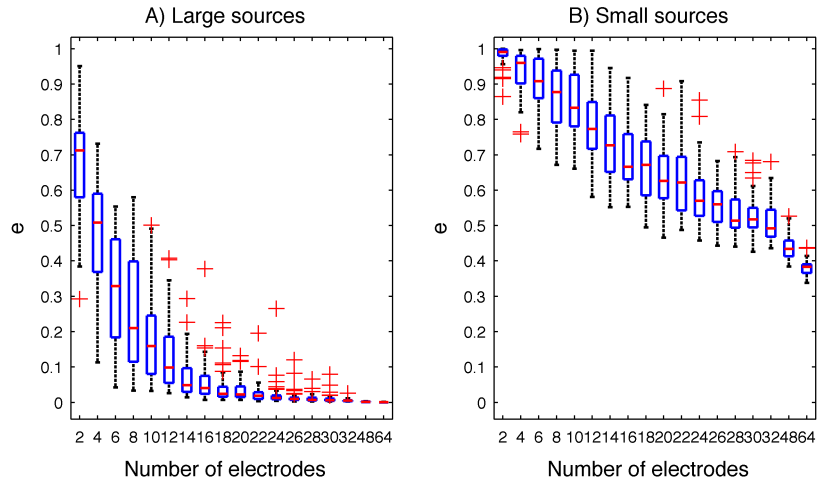

Figure 7: Distribution of errors for reconstruction from randomly placed electrodes. A) Large sources, B) small sources. For the meaning of the 'box and whisker' plots see caption of Figure 3.

as 16 electrodes. Because of small spatial extent of 'small sources', the errors are large ($\sim 40\%$) even for 64 electrodes.

Similar reconstructions from randomly placed electrodes can be performed also in one and three dimensions. Figure 8 shows an example of reconstruction of sources (A) from

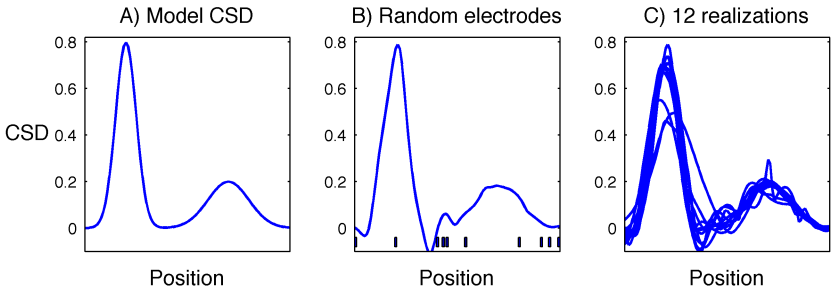

Figure 8: CSD reconstruction from randomly placed electrodes in 1D. A) model CSD; B) single reconstruction, electrodes positions are marked with vertical bars at the x axis; C) reconstructions for 12 different sets of randomly placed electrodes.

9 electrodes placed randomly on a line (B). Fig. 8 (C) shows reconstructed sources for 12 different distributions of nine contacts. The sources used in Fig. 8 and Fig. 9 are described in Appendix A.4.

3.3 Kernel CSD on incomplete regular grids

One interesting case of irregular grids are regular grids with a number of missing contacts. Such situations arise often in real experiments e.g. because of specific experimental setup (Bakker et al. 2009) or hardware failures. In the kCSD framework one can deal with such situations without problems. Figure 9 shows a simple one-dimensional example for the same sources presented in Fig. 8.

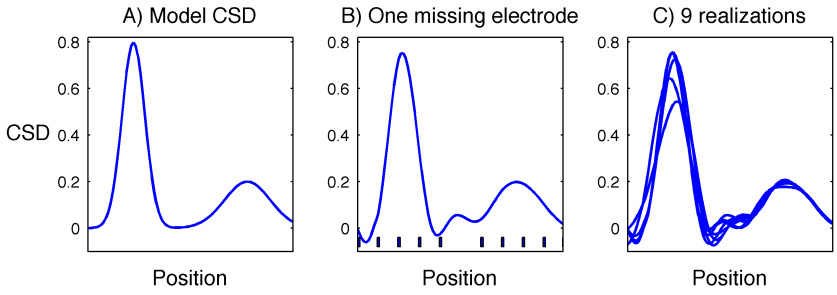

Figure 9: One-dimensional example of reconstructing CSD from a regular grid with one missing electrode. A) Model CSD. B) Reconstruction from all but one channels, electrodes positions are marked with vertical bars at the x axis — note one is missing. C) Realizations for different electrodes removed.

In previous work (Wójcik & Łęski 2010) we studied possible remedies to the 'incomplete grid' problem in the context of the inverse CSD (iCSD) method. We proposed two solutions: either to substitute the missing channels with averages of the neighbors (LA for 'local averaging') or to fit a CSD distribution described by fewer parameters than the number of electrodes using least squares method (LS). Here we treat the same problem in the context of kCSD. The kCSD method is a natural replacement for the LS approach. It can also be applied to the full dataset obtained with the LA method (the results are very close to the LA + spline iCSD method). In this section we compare the two approaches (either kCSD on incomplete grid or LA + kCSD). As the irregularity of the grid is naturally accounted for in the kCSD method without the need to explicitly use least squares fit we expect this method to perform much better than the LS method in the inverse CSD case.

To test the relative performance of kCSD and LA + kCSD methods we first studied the two-dimensional datasets ('large sources' and 'small sources') introduced above in Section 3.1. We set a number n of missing channels ($1 \leq n \leq 8$) and we studied a large number of possible combinations of missing points (for $n = 1$ and $n = 2$ we checked all possibilities, 64 and $(64 \times 63) \div 2 = 2016$, respectively; for each larger n we chose randomly 2000 combinations). For each configuration and each of the two datasets we reconstructed the CSD twice, first using the kCSD method on the incomplete dataset, second using the LA + kCSD approach. The results plotted as the mean of the reconstruction error $e \pm$ standard deviation are presented in Figure 10. The kCSD method applied to the incomplete set yields better results than the LA + kCSD method. The difference is striking in case of 'large sources', Figure 10A, which is not unexpected as we saw before that for this dataset the kCSD reconstructions are very precise even for a much smaller number of available measurements (Figure 7). Evidently in this case local averages of neighbors lead to incorrect approximation of the missing values of potential distorting the data and resulting in bigger reconstruction errors.

To directly compare the new kCSD method to the LA + iCSD and LS methods from Wójcik & Łęski (2010) we performed another numerical experiment, this time using the experimental datasets utilized in Wójcik & Łęski (2010). The data are the extracellular evoked potentials recorded in the rat brain on a three-dimensional grid of $4 \times 5 \times 7$ points and are described in detail elsewhere (Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007, Łęski, Kublik, Świejkowski, Wróbel & Wójcik 2010). For the readers' convenience the spline iCSD reconstruction of the two time frames used here are presented in Figure 11. In Wójcik & Łęski (2010) we concluded that the LA + iCSD method is to be

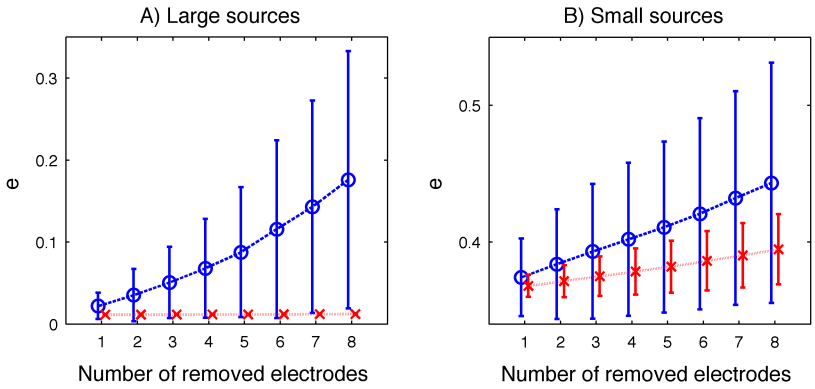

Figure 10: Comparison of two methods (LA followed by kCSD — o's, kCSD on an incomplete grid — x's) to reconstruct CSD from data on a grid with missing points. A) Large sources, B) small sources. The x-axis shows the number of recording points removed from the grid. The values plotted at y-axis are the means of normalized reconstruction error e, error bars are $\pm$ standard deviation.

preferred over the less stable LS approach. Here, similarly as in the two-dimensional case above we calculated the reconstruction error for different electrodes setups using either kCSD or LA + kCSD approach[3]. As expected, the kCSD method is indeed much better than LS combined with spline iCSD: the errors of reconstruction are much smaller and the results are much more robust (there are no cases of huge errors as opposed to the LS method in Wójcik & Łęski (2010)). Still, the LA + kCSD method performs better for this datasets than pure kCSD. This is a result similar to the one obtained in Wójcik & Łęski (2010) and it is different from the result for the two-dimensional case of 'large' and 'small' sources. The results are presented in Figures 12 and 13 (the A and B panels of these figures are direct counterparts of panel C and D of figures 4 and 6 from Wójcik & Łęski (2010)).

Summarizing the two tests described above: the relative performance of the pure kCSD method on an incomplete grid vs. LA + kCSD method depends on the exact geometry of the electrodes. Therefore, we recommend that the decision if missing values should be supplemented with local averages of the neighbors is made based on tests on plausible model data for every particular electrodes setup.

4 Regularization: beyond over-fitting

We have assumed up till now that the data are precise (measured without errors) which is never the case in practice. Measurements from electrodes are always corrupted with noise. To minimize the effect of this noise on inferences one should avoid over-fitting estimations to the data observed. We don't want slight changes in the observations to influence the results. Taking such precautions is known in statistics as regularization.

Regularization can be expressed as reducing the variance of estimators but allowing bias. Until now we have constructed unbiased estimators, that exactly fitted the observa-

[3]Note that here we know only the potentials and not the true sources, therefore the error is the difference between the reconstruction from complete and incomplete data.

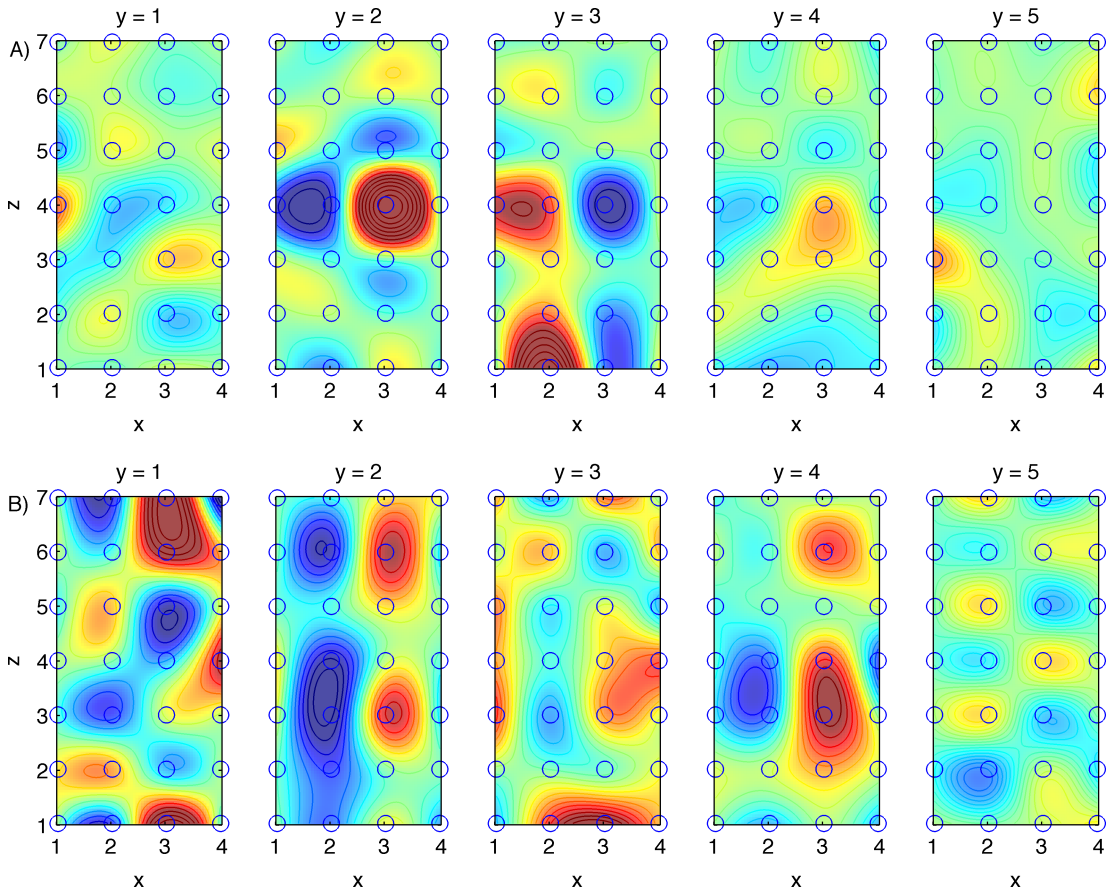

Figure 11: Experimental datasets — CSD reconstructions from complete sets of recordings. Each row presents a three-dimensional volume at a fixed time (top row: $t = 3.5$ ms, bottom row: $t = 15$ ms) after stimulus as a collection of five parallel planes. The electrodes ($4 \times 5 \times 7$ grid) are marked with circles. For details on experiment and full specification of data and procedures used see Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel (2007).

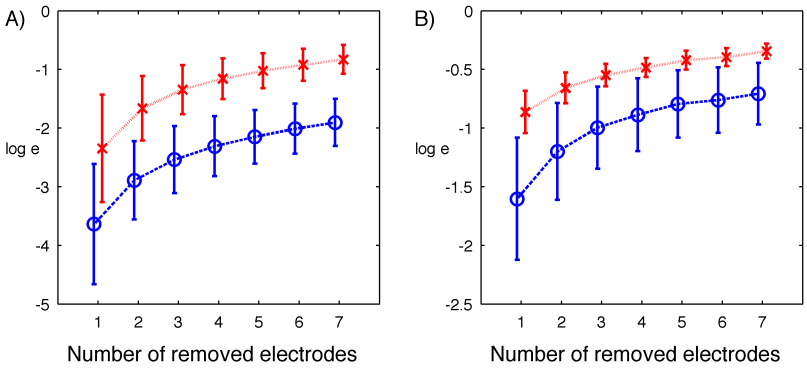

Figure 12: Comparison of two methods (LA followed by kCSD — o's, kCSD on an incomplete grid — x's) to reconstruct CSD from data on a grid with missing points. The x-axis shows the number n of recording points removed from the grid. The values plotted at y-axis are the average logarithm of normalized reconstruction error e, error bars are $\pm$ standard deviation. (A) The best 90% out of 2000 random choices of removed points (except $n = 1$ and $n = 2$ where 90% of all possibilities are used). (B) Same as (A) but for the worst 10% of the cases. The data used here are the same as used in Figures 3 and 4 in Wójcik & Łęski (2010), see also Figure 11A above.

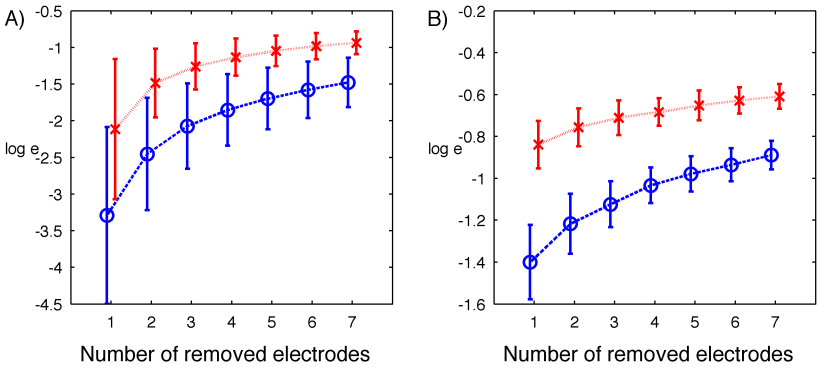

Figure 13: Comparison of methods of reconstructing CSD from incomplete data; see the caption of Figure 12. The data used here are the same as used in Figures 5 and 6 in Wójcik & Łęski (2010), see also Figure 11B above.

tions

$$\sum_{i=1}^{k}\left(\sum_{j=1}^{k}\beta_i K(\mathbf{x}_j,\mathbf{x}_i)-f_i\right)^2=0. \tag{29}$$

We examined a popular method for regularization called ridge regression (Shawe-Taylor & Christiani (2004) p. 31-32) based on a modification of this condition. To make parameters $\{\beta\}_{i=1}^{k}$ less sensitive to noise instead of requiring (29) we minimize:

$$\sum_{i=1}^{k}\left(\sum_{j=1}^{k}\beta_i K(\mathbf{x}_j,\mathbf{x}_i)-f_i\right)^2+\lambda\sum_{i=1}^{k}\beta_i^2, \tag{30}$$

which can be done by the following matrix operations:

$$\beta=(\mathbf{K}+\lambda\mathbf{I})^{-1}\cdot\mathbf{f}. \tag{31}$$

Thus the resulting regularized estimate of CSD is

$$C^*(\mathbf{x})=\widetilde{\mathbf{K}}^T(\mathbf{x})\cdot(\mathbf{K}+\lambda\mathbf{I})^{-1}\cdot\mathbf{V}.$$

Adding a diagonal matrix to $\mathbf{K}$ opposes the bad consequences of an eventual (almost) singularity of $\mathbf{K}$. Increasing the value of λ results in a continous reduction of magnitude of the parameters β which stabilises the model (decreases variation but increases bias) but choosing λ too large eventually ignores the data. Therefore one has to decide on a compromise value for λ.

One possibility to select optimal value of λ using data is to use cross-validation (Hastie & Tibshirani (2001) p. 214 - 215). The idea behind cross-validation is fairly simple. The observations are divided into L subsets which can be of equal size. Next we construct L regressors each time using one of the L subsets as a test set and the rest as a training set. Each time the estimation error on the test set is calculated. This procedure is repeated for a wide range of λ values and each time the average error is calculated. At the end we choose the value of λ which resulted in the smallest average error. In practice we used 'leave one out' cross validation where each test set consists of one element.

To test the viability of ridge regression we performed a test using the model dataset 'large sources'. To the calculated potentials we added Gaussian noise of std equal to

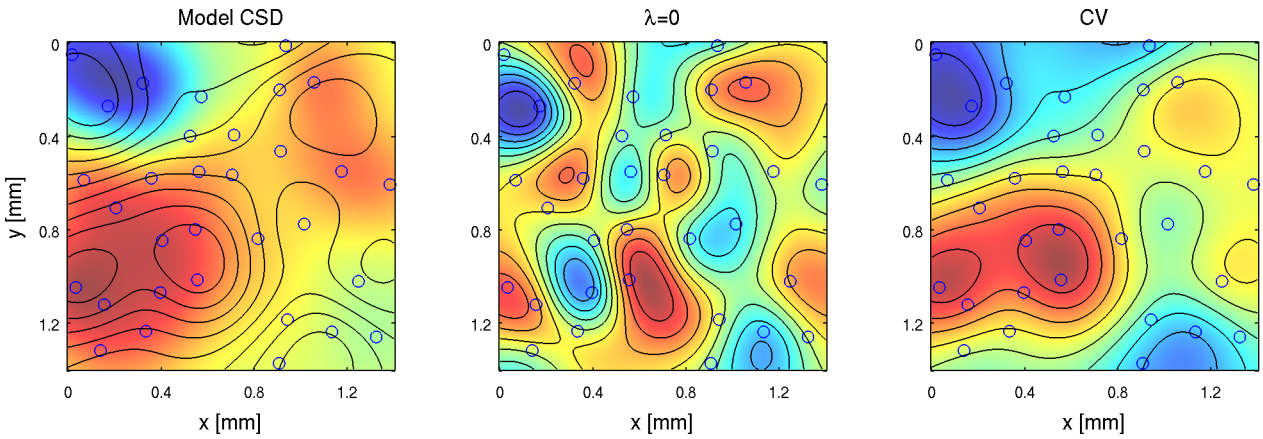

Figure 14: A) Distribution of model sources used to test ridge regression. blue circles indicate positions of simulated electrodes. To the potentials measured there we added Gaussian noise with std equal to 10% of the total variation of the noise-free potential in the studied domain. B) CSD reconstruction without ridge regression C) Reconstruction using ridge regression with λ chosen via cross-validation.

10% of the total variation of the noise-free potential in the studied domain ($\max V(\mathbf{x}) - \min V(\mathbf{x})$). Figure 14 shows that the kCSD method without ridge regression works rather poorly whereas combining kCSD with ridge regression and cross-validation improves the reconstruction significantly.

Next we tested how well does cross validation perform in choosing the optimal parameter. For a wide range of λ we checked how ridge regression performs on the whole data set. Fig. 15 shows that the λ obtained with cross-validation gives a very good estimate of

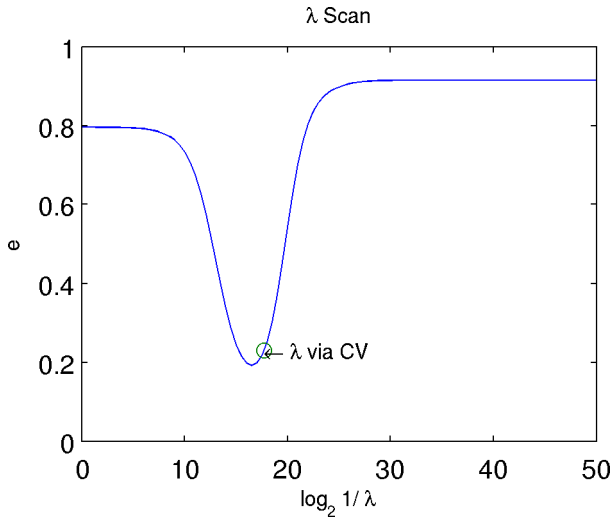

Figure 15: Line: Reconstruction error of kCSD with ridge regression on the whole data set for a wide range of parameters. Circle indicates the value of λ chosen via cross-validation.

the optimal value.

5 Discussion and summary

In this article we have introduced a new framework for estimation of current sources from extracellular potentials using kernel methods. Introduction of kernels in this context opens up new experimental possibilities allowing efficient approximation of the sources from arbitrary distributions of contacts. We discuss here the advantages and limitations of the presented approach indicating possible further directions of development, both in the physical and statistical aspects of the problem.

Advantages of kCSD The main advantages of kCSD compared with the previously developed methods are *(i)* conceptual separation of the model construction (introducing the sources and potentials — the $b_i(\mathbf{x})$ and $\widetilde{b}_j(\mathbf{y})$ basis functions) from the distribution of electrode locations, and *(ii)* ease of reconstructing CSD from arbitrarily located contacts. One immediate benefit is that in cases such as the 3D recordings analyzed in Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel (2007), Łęski, Kublik, Świejkowski, Wróbel & Wójcik (2010), where we know that the potentials where not recorded *exactly* on a grid, in the framework of kCSD we can take the best estimates of electrode position and the cost of calculations does not change, as opposed to the 3D iCSD where we assumed electrode location on a regular grid and neglected possible errors.

This flexibility may lead to new experimental possibilities. One case we see is combining acute experiments, such as the one described in Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel (2007), Łęski, Kublik, Świejkowski, Wróbel & Wójcik (2010), where one can perform precise scans of electrical activation of tissue with high spatial resolution, with chronic experiments, where of necessity, one would restrict oneself to a few precisely positioned electrodes, usually not on a grid. One could then use the information about the activity of CSD obtained in the acute experiments to build optimal model spaces allowing the best possible reconstruction of the sources from the limited number of measurements available in the chronic situation. This may lead to a clearer spatial and temporal separation of functional pathways than possible using methods available so far.

Interplay of modeling and data analysis in CSD reconstruction A question which arises in connection with the above mentioned approach is this: given a specific profile of the sources, including their temporal dynamics or not, assume available N electrodes. How should they be positioned and how should one construct the model RKHS to minimize errors of CSD reconstruction in the studied process? Or alternatively, how many electrodes are needed and how should they be positioned to allow for efficient estimation of CSD with given precision? We expect that the answers to these open questions would significantly depend on the specific activity and structure. To find optimal positions for recording it would probably be necessary to test different arrangements of electrodes on simulated data. This calls for a new optimization scheme and for development of efficient simulations of local field potentials in realistic geometries.

Spectral decomposition We have concentrated here on the estimation of sources from potentials, as the CSD seems to be the main object of interest in terms of physiology. However, the approach through RKHS can give us additional insight through the 'spectral decomposition' (Shi et al. 2008). That is, for a selected representation of sources (given set of basis sources $\widetilde{b}_i(\mathbf{x})$) we can calculate the contribution of every basis source to the

estimated CSD at any time point. We can write Eq. (18) as

$$\widetilde{f}^*(\mathbf{x}) = \sum_{j=1}^{n} \alpha_j \widetilde{b}_j(\mathbf{x})$$

where

$$\alpha_j = \sum_{i=1}^{k} \beta_i b_j(\mathbf{x}_i).$$

It may happen that temporal changes of 'activation' α_j of a source $\widetilde{b}_j(\mathbf{y})$ centered on $\mathbf{x}_j$ are different from the value of estimated CSD at $\mathbf{x}$, as this is a sum of contributions from all the sources $\widetilde{b}_i$ containing $\mathbf{x}_j$ in their support. This could yield additional insight in the analysis of data, especially if the construction of the underlying RKHS is motivated anatomically and the basic sources can be attributed functional meaning.

Parameter choice for kCSD The kCSD framework which we have introduced here is very flexible, one can use many different types of bases. This leads to a question what is the recommended first choice of model space and how to choose parameters for unknown sources. As our numerical experiments in Section 3 show, Gaussian models give smaller errors in a larger range of parameters than the step functions, so we recommend the Gaussians. The optimal value of R for electrodes on regular grid is between 1-2 inter-electrode distances. We expect that even better results can be obtained with basis adapted to problem at hand. Its construction should be motivated by available anatomical and functional information or tests on sources generated in computational modeling, if only possible. Efficient construction of optimal basis for a problem at hand is another direction worth exploring. One possible approach is the use of cross-validation which we demonstrated in Section 4 for selection of the regularization constant λ.

Including time dependence As mentioned in Section 2 time dependence of the potentials was not taken into account in this paper. However, LFP data coming from experiments usually have the form of several time series — one for each electrode. Modeling these time series, relationships between them and incorporating this knowledge in the estimation may reveal more information about the examined region.

A possible way of extending the framework described in this paper would be to add time dependence to the basis functions introduced in Section 2. In the simplest case one could think of basis functions that factorise into the product of two seperate location and time dependent factors:

$$\widetilde{b}_i(\mathbf{x}, t) = \widetilde{b}_{i1}(\mathbf{x})\widetilde{b}_{i2}(t),$$

where $\widetilde{b}_{i2}(t)$ could have a 'step' or a Gaussian shape.

If we calculate the potential generated by $\widetilde{b}_i$ in every moment t, we get a set of potential basis functions $b_i(\mathbf{x}, t)$. We are therefore free to construct kernels as in (9) and (17), run the kCSD method and obtain a time dependent CSD estimator.

Direct kCSD method Up till now we have always derived kernels K and $\widetilde{K}$ from the basis functions via equations (9) and (17). One can also try defining kernel K directly, omitting the introduction of basis functions. It is shown in Shawe-Taylor & Christiani

(2004) (Theorem 3.11) that as long as a kernel function K is positive definite, then there exists an RKHS $\mathcal{H}$ and an equivalent mapping $\phi : \mathbb{R} \longrightarrow \mathcal{H}$ such that:

$$K(\mathbf{x}, \mathbf{y}) = \langle \phi(\mathbf{x}), \phi(\mathbf{y}) \rangle.$$

We are therefore free to model the potentials with kernels typically used in learning algorithms (e.g. a Gaussian kernel), as presented for instance in Schoelkopf & Smola (2002), Chapter 2.3. To model CSD it rests to find the equivalent cross-kernel. This can be done regarding the following equation:

$$K(\mathbf{x}, \mathbf{y}) = \mathcal{A}_{\mathbf{y}} \widetilde{K}(\mathbf{x}, \mathbf{y}),$$

where by $\mathcal{A}_y$ we denote operator $\mathcal{A}$ acting on the second variable, so we can write

$$\widetilde{K}(\mathbf{x}, \mathbf{y}) = [\mathcal{A}_{\mathbf{y}}]^{-1} K(\mathbf{x}, \mathbf{y}).$$

Calculating $\widetilde{K}$ involves inverting operator $\mathcal{A}_{\mathbf{y}}$ which is simple in the three dimensional case where the inverse operator is just the Laplacian. However, in 1D and 2D cases this operator depends on the model of the tissue in the directions normal to the space spanned by the electrodes, so its inversion is more involved.

Our preliminary numerical experiments with the 3D case indicate that this 'direct kCSD' method, as we call it, is even faster, very easy to calculate, and is very stable. A thorough study is underway.

Generalized models of tissue conductivity We have assumed in the analysis constant conductivity. This simplifies the problem and in view of the lack of available data on conductivity in many areas, is a natural approach to start. However, as it is now becoming feasible to measure conductivity more and more precisely and as the changing conductivity seems to influence substantially the fields Goto et al. (2010) it is necessary to develop kCSD to incorporate richer models of sources taking into account space-dependent and perhaps non-scalar conductivity. One important example which calls for a dedicated approach is that of slices on multielectrode arrays (MEA).

Connection to source reconstruction from EEG CSD reconstruction is similar in spirit to reconstruction of sources in EEG (Guljarani 1998, He & Lian 2005, Phillips et al. 2005, Nunez & Srinivasan 2006) and ECoG (Freeman 1980, Zhang et al. 2008), however, since extracellular recordings of LFP are taken much closer to the sources than in the case of EEG, one builds different models (see the discussion in Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik (2011)). Despite the difference in physics, we believe that the same statistical setting can be adapted to the case of human electroencephalography helping in source localization there. The difference would be in the basis elements $b_i(\mathbf{x})$, as for EEG one would naturally consider distributions of dipoles. The connection between the sources and potentials would have to take into account the complication of changing conductivity in the skull, skin, etc and would probably be the most challenging problem. Otherwise, the framework presented here should apply.

Acknowledgements

This work was supported by the Polish Ministry of Science and Higher Education grant PBZ/MNiSW/07/2006/1 and by the infrastructural grant from the Polish Ministry of Regional Development, POIG.02.03.00-00-003/09.

A Specification of the sources used in the tests

In this appendix we provide detailed information about the sources used in testing kCSD method in Section 3.

A.1 'Large sources'

The 'large sources' were generated using the following MATLAB function:

```
function f = test_csd(x,y,z)

zz = [0.4; -0.3; -0.1; 0.6];
zs = [0.2; 0.3; 0.4; 0.2];

f1 = 0.5965*exp((-(x-0.1350).^2 - (y-0.8628)^2)/0.4464)*...
 exp(-(z-zz(1))^2/zs(1))/exp(-(zz(1))^2/zs(1));
f2 = -0.9269*exp((-2*(x-0.1848).^2 - (y-0.0897)^2)/0.2046)*...
 exp(-(z-zz(2))^2/zs(2))/exp(-(zz(2))^2/zs(2));
f3 = 0.5910*exp((-3*(x-1.3189).^2 - (y-0.3522)^2)/0.2129)*...
 exp(-(z-zz(3))^2/zs(3))/exp(-(zz(3))^2/zs(3));
f4 = -0.1963*exp((-4*(x-1.3386).^2 - (y-0.5297)^2)/0.2507)*...
 exp(-(z-zz(4))^2/zs(4))/exp(-(zz(4))^2/zs(4));

f= f1+f2+f3+f4;
```

Note that the sources used in this paper have product structure which means that the above function was evaluated only for $z = 0$ and we assumed a step profile in z variable. More general sources were considered in Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik (2011).

A.2 'Small sources'

Let a, μ_1, μ_2 and $\mathbf{C}$ be the parameters (amplitude, mean, covariance matrix) of the following Gaussian function:

$$G_{a,\mu_1,\mu_2,\mathbf{C}}(x,y) = \frac{a}{2\pi\sqrt{\det \mathbf{C}}} \exp\left[-\frac{1}{2}\begin{pmatrix} x-\mu_1 \\ y-\mu_2 \end{pmatrix}^{\mathbf{T}} \mathbf{C}^{-1} \begin{pmatrix} x-\mu_1 \\ y-\mu_2 \end{pmatrix}\right].$$

The 'small sources' dataset was generated by a sum of four such Gaussians with parameters given in the table below:

Number	a	μ_1	μ_2	$\mathbf{C}$
1	0.2	0.2	0.3	$\begin{pmatrix} 0.002 & 0 \\ 0 & 0.008 \end{pmatrix}$
2	-0.25	0.2	0.6	$\begin{pmatrix} 0.005 & 0 \\ 0 & 0.01 \end{pmatrix}$
3	0.24	0.5	0.3	$\begin{pmatrix} 0.0024 & 0 \\ 0 & 0.008 \end{pmatrix}$
4	-0.2	0.5	0.6	$\begin{pmatrix} 0.005 & 0 \\ 0 & 0.01 \end{pmatrix}$

A.3 Random Gaussian sources

The random Gaussian sources were constructed according to the following algorithm (all probability distributions are uniform):

1. choose randomly $r_{\min}$ between 0.1 and 0.2, let $r_{\max} = 2r_{\min}$,
2. choose number n of Gaussian sources, $4 \leq n \leq 8$,
3. for each source choose amplitude a between -1 and 1, angle ϑ between 0 and 2π, position of the source (x_0, y_0) in the square $[0, 1.4]^2$, and σ_x, σ_y between $r_{\min}$ and $r_{\max}$,
4. the test CSD distribution is equal to the sum of n terms, each of the form

$$G(x, y) = a \exp\left[-\mathbf{x}^{\mathbf{T}}\mathbf{A}\mathbf{x}\right],$$

where $\mathbf{x} = \begin{pmatrix} x - x_0 \\ y - y_0 \end{pmatrix}$, and $\mathbf{A} = \begin{pmatrix} \frac{\cos^2\vartheta}{2\sigma_x^2} + \frac{\sin^2\vartheta}{2\sigma_y^2} & -\frac{\sin 2\vartheta}{4\sigma_x^2} + \frac{\sin 2\vartheta}{4\sigma_y^2} \\ -\frac{\sin 2\vartheta}{4\sigma_x^2} + \frac{\sin 2\vartheta}{4\sigma_y^2} & \frac{\sin^2\vartheta}{2\sigma_x^2} + \frac{\cos^2\vartheta}{2\sigma_y^2} \end{pmatrix}$.

(see http://en.wikipedia.org/wiki/Gaussian_function).

A.4 1-D sources

The one-dimensional sources were constructed in the following manner as a mixture of two Gaussians:

$$G_{A_1,\mu_1,\sigma_1,A_2,\mu_2,\sigma_2} = A_1 \exp\left(-\frac{(x-\mu_1)^2}{2\pi\sigma_1}\right) + A_2 \exp\left(-\frac{(x-\mu_2)^2}{2\pi\sigma_2}\right).$$

The parameter values were:

A_1	μ_1	σ_1	A_2	μ_2	σ_2
1	2	0.5	0.5	7	1

B iCSD is a special case of kCSD

To set the stage let us rewrite iCSD in the language used here. We start from a set of k LFP measurements: $(\mathbf{x}_i, V_i)_{i=1}^N, \mathbf{x}_i \in \mathbb{R}^d$. Then a model of CSD is assumed in the form of N-parameter distribution

$$C(\mathbf{x}) = \sum_{j=1}^{N} C_j \widetilde{b}_j(\mathbf{x}).$$

In all the work so far $\mathbf{x}_i$ were assumed to form a regular rectangular grid and C_i were the values of CSD at the nodes of the grid which were to be estimated from the given potentials. The spatial profiles $\widetilde{b}_i(\mathbf{x})$ and the associated potentials $b_i(\mathbf{x})$ are set by the dimensionality of the problem and the variant of the method used (step, linear spline, cubic spline, etc.). For example, in three dimensional spline method $\widetilde{b}_i(\mathbf{x})$ would be spline interpolated three-dimensional function between grid points, taking values 1 at $\mathbf{x}_i$ and 0 at $\mathbf{x}_{j\neq i}$ with appropriate boundary conditions (Łęski, Wójcik, Tereszczuk, Świejkowski, Kublik & Wróbel 2007). The potential generated by source $\widetilde{b}_i(\mathbf{x})$ is given by Eq. (5). In

lower dimensionality one has to add a model of sources in the directions not probed by the electrodes. Thus in the two-dimensional step method (Łęski, Pettersen, Tunstall, Einevoll, Gigg & Wójcik 2011), for example, assuming $\mathbf{x}_i \equiv (x_i, y_i, 0)$ with interelectrode distance Δ and step profile in the perpendicular direction of the depth H we would have

$$\widetilde{b}_i(x,y,z) = \begin{cases} 1 & x \in (x_i - \frac{\Delta}{2}, x_i + \frac{\Delta}{2}), y \in (y_i - \frac{\Delta}{2}, y_i + \frac{\Delta}{2}), z \in (-\frac{H}{2}, \frac{H}{2}) \\ 0 & \text{otherwise} \end{cases}$$

with the potentials given by Eq. (22).

In any iCSD variant, the potentials according to the assumed model of sources are given by $V(\mathbf{x}) = \sum_j C_j b_j(\mathbf{x})$ with the values measured at a grid point i equal to $V(\mathbf{x}_i) = \sum_j C_j b_j(\mathbf{x}_i) = V_i$. To find the model sources we first solve for parameters C_j given the potentials:

$$V \equiv \begin{bmatrix} V_1 \\ \vdots \\ V_N \end{bmatrix} = \begin{bmatrix} b_1(\mathbf{x}_1) & \dots & b_N(\mathbf{x}_1) \\ & \vdots & \\ b_1(\mathbf{x}_N) & \dots & b_N(\mathbf{x}_N) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_N \end{bmatrix} = \begin{bmatrix} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_N \end{bmatrix}$$

with obvious notation $\mathbf{b}(\mathbf{x}) = [b_1(\mathbf{x}), \dots, b_N(\mathbf{x})]^T$. Inverting this relation we obtain

$$C = \begin{bmatrix} C_1 \\ \vdots \\ C_N \end{bmatrix} = \begin{bmatrix} \mathbf{b}^T(x_1) \\ \vdots \\ \mathbf{b}^T(x_N) \end{bmatrix}^{-1} V.$$

Then the source are given by

$$C_{\mathrm{iCSD}}(\mathbf{x}) = \sum_{j=1}^{n} C_j \widetilde{b}_j(\mathbf{x}) = \widetilde{\mathbf{b}}^T(x) \begin{bmatrix} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{bmatrix}^{-1} V. \tag{32}$$

In kCSD framework we have (Eq. (15)):

$$\begin{aligned} \begin{bmatrix} V_1 \\ \vdots \\ V_N \end{bmatrix} &= \begin{bmatrix} K(\mathbf{x}_1, \mathbf{x}_1) & \dots & K(\mathbf{x}_1, \mathbf{x}_N) \\ & \vdots & \\ K(\mathbf{x}_N, \mathbf{x}_1) & \dots & K(\mathbf{x}_N, \mathbf{x}_N) \end{bmatrix} \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} \\ &= \begin{bmatrix} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{bmatrix} \begin{bmatrix} \mathbf{b}(\mathbf{x}_1) & \dots & \mathbf{b}(\mathbf{x}_N) \end{bmatrix} \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} \end{aligned}$$

which gives

$$\begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} = \begin{bmatrix} \mathbf{b}(\mathbf{x}_1) & \dots & \mathbf{b}(\mathbf{x}_N) \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{bmatrix}^{-1} V. \tag{33}$$

Then the sources $C_{\mathrm{kCSD}}(\mathbf{x})$ according to Eq. (16) are given by

$$C_{\mathrm{kCSD}}(\mathbf{x}) = \sum_{i=1}^{k} \beta_i \sum_{j=1}^{n} b_j(\mathbf{x}_i) \widetilde{b}_j(\mathbf{x}) = \widetilde{\mathbf{b}}^T(\mathbf{x}) \begin{bmatrix} \mathbf{b}(\mathbf{x}_1) & \dots & \mathbf{b}(\mathbf{x}_N) \end{bmatrix} \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_N \end{bmatrix} \tag{34}$$

Using (33) and (34) we obtain

$$
\begin{aligned}
C_{\mathrm{kCSD}}(\mathbf{x}) &= \widetilde{\mathbf{b}}^T(\mathbf{x}) \left[\begin{array}{cccc} \mathbf{b}(\mathbf{x}_1) & \dots & \mathbf{b}(\mathbf{x}_N) \end{array} \right] \left[\begin{array}{cccc} \mathbf{b}(\mathbf{x}_1) & \dots & \mathbf{b}(\mathbf{x}_N) \end{array} \right]^{-1} \left[\begin{array}{c} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{array} \right]^{-1} V \\
&= \widetilde{\mathbf{b}}^T(\mathbf{x}) \left[\begin{array}{c} \mathbf{b}^T(\mathbf{x}_1) \\ \vdots \\ \mathbf{b}^T(\mathbf{x}_N) \end{array} \right]^{-1} V = C_{\mathrm{iCSD}}(\mathbf{x}). \qquad (35)
\end{aligned}
$$

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