Measuring & Inducing Neural Activity Using Extracellular Fields I: Inverse systems approach

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Abstract

This project considers the problem of trying to selectively sense and induce activity in individual neurons within a network in a living organism, using a small array of electrodes placed some distance away. We consider a variety of approaches to relate neural behavior to the potential or current at the electrode array. Then we perform a simulation using the simple linear model with uniform conductivity, and demonstrate the ability to resolve axons in the transverse direction. We also demonstrate the use of this same approach to estimate a current at the electrode array to achieve, as best possible, a desired potential difference within the neural tissue.

1 Introduction

The tetrode and related devices such as the multitrode or multielectrode [1], are commonly used for extracellular recording of neural activity. Typically researchers make use of so-called spike sorting algorithms to differentiate neurons by correlating their activity [2]. This project may be considered as an effort to model the interaction of such devices with neurons using an inverse-systems approach, effectively producing an "image" of neural activity in space.

The neuron may be treated as a source of currents, which are what we want to locate. The physics for this problem boils down to a problem in electrostatics, which we will consider in the next section. So we focus on problems that involve relating the current to the potential in a region, where knowledge of either the potential or the current may be limited to measurements at the boundary. We address cases both with constant and varying conductivity. In the simplest case, of uniform conductivity, we have a linear system of equations which we go on to analyze via simulation in the subsequent section. We also demonstrate how the system changes as the assumptions are changed or made more realistic.

2 Theory

We assume extracellular fields fall within the quasistatic regime, where coupling via magnetic fields is insignificant. Further, we assume the neural tissue to be Ohmic, i.e. a pure conductor described by a real conductivity tensor. Under these assumptions, the typical starting point [3] is Eq. (1).

$$\nabla\cdot\left(\sigma(\mathbf{r})\nabla\phi(\mathbf{r})\right)=-\nabla\cdot\rho(\mathbf{r}) \tag{1}$$

Where σ is the conductivity, φ is the potential, and ρ is the charge density. We break the conductivity out into constant and varying parts,

$$\sigma(\mathbf{r})=\sigma_c+\delta\sigma(\mathbf{r}) \tag{2}$$

Then we have

$$\begin{aligned}-\nabla\cdot\rho(\mathbf{r})&=\nabla\cdot\left(\left(\sigma_c+\delta\sigma(\mathbf{r})\right)\nabla\phi(\mathbf{r})\right)\\&=\nabla\cdot\left(\sigma_c\nabla\phi(\mathbf{r})\right)+\nabla\cdot\left(\delta\sigma(\mathbf{r})\nabla\phi(\mathbf{r})\right)\\&=\sigma_c\nabla^2\phi(\mathbf{r})+\nabla\cdot\left(\delta\sigma(\mathbf{r})\nabla\phi(\mathbf{r})\right)\end{aligned} \tag{3}$$

Which we write as a Poisson equation with forcing function,

$$\begin{aligned}\nabla^2\phi(\mathbf{r})&=-\tfrac{1}{\sigma_c}\nabla\cdot\rho(\mathbf{r})-\tfrac{1}{\sigma_c}\nabla\cdot\left(\delta\sigma(\mathbf{r})\nabla\phi(\mathbf{r})\right)\\&=f(\mathbf{r})\end{aligned} \tag{4}$$

The Green's function, which we define as the solution to,

$$\nabla^2G(\mathbf{r})=\delta^3(\mathbf{r}) \tag{5}$$

is well-known for equations of this form. With boundary conditions of zero field at infinity, we get, via Green's theorem,

$$G(\mathbf{r})=\frac{1}{4\pi\|\mathbf{r}\|} \tag{6}$$

Then using the Green's function, we can solve Eq. (4) as

$$\begin{aligned}\phi(\mathbf{r})&=-\int G(\mathbf{r}-\mathbf{r}')f(\mathbf{r})dr'\\&=-\tfrac{1}{\sigma_c}\int G(\mathbf{r}-\mathbf{r}')\left\{\nabla\cdot\rho(\mathbf{r}')+\nabla\cdot\left(\delta\sigma(\mathbf{r}')\nabla\phi(\mathbf{r}')\right)\right\}d\mathbf{r}'\\&=-\tfrac{1}{\sigma_c}\int G(\mathbf{r}-\mathbf{r}')\nabla\cdot\rho(\mathbf{r}')dr'-\tfrac{1}{\sigma_c}\int G(\mathbf{r}-\mathbf{r}')\nabla\cdot\left(\delta\sigma(\mathbf{r}')\nabla\phi(\mathbf{r}')\right)d\mathbf{r}'\end{aligned} \tag{7}$$

Where we have used the fact that the Green's function is shift-invariant. The first term on the right-hand side gives the potential in a constant conductivity, which we call $\phi_0(\mathbf{r})$.

From an inverse-scattering perspective, ϕ_0 is the "incident field" and the second term is the "scattered field". The incident field we can compute easily given the constant part of the conductivity. The scattered field term, however, depends on the total potential $\phi(\mathbf{r})$, which is unknown.

Using the definition of the current-source density,

$$i(\mathbf{r})\equiv\nabla\cdot\rho(\mathbf{r}) \tag{8}$$

We write ϕ_0 as

$$\begin{aligned}\phi_0(\mathbf{r}) &= -\tfrac{1}{\sigma_c}\int G(\mathbf{r}-\mathbf{r}')\nabla\cdot\rho(\mathbf{r}')\,d\mathbf{r}' \\ &= -\int \frac{i(\mathbf{r}')}{4\pi\sigma_c\|\mathbf{r}-\mathbf{r}'\|}d\mathbf{r}'\end{aligned} \tag{9}$$

The most common approach to solving systems like this is to approximate the potential as resulting from a constant conductivity, i.e.,

$$\begin{aligned}\phi(\mathbf{r}) &= \phi_0(\mathbf{r})+\phi_s(\mathbf{r}) \\ &\approx \phi_0(\mathbf{r}) \\ &\approx -\int \frac{i(\mathbf{r}')}{4\pi\sigma_c\|\mathbf{r}-\mathbf{r}'\|}d\mathbf{r}'\end{aligned} \tag{10}$$

This is a linear system which may either be solved for the potential given known current sources and conductivity, or inverted to get the current sources given a known potential and known conductivity. We can consider the integral over the Greens function as a linear operator (a transfer function here),

$$\phi(\mathbf{r}) \approx -\int \frac{i(\mathbf{r}')}{4\pi\sigma_c\|\mathbf{r}-\mathbf{r}'\|}d\mathbf{r}' = \mathcal{H}i(\mathbf{r}') \tag{11}$$

$\mathcal{H}$ operates on a function over $\mathbf{r}'$ (the region to be imaged) and returns a function over $\mathbf{r}$ (the measured points). If we choose basis functions for these regions (e.g. delta functions spaced on a grid) we may form a linear system as

$$\mathbf{v} = \mathbf{Hi} \tag{12}$$

This is the system we will consider in this report. If we wish to estimate the current density, but the potential is only partly known, for example only at certain points measured by leads, then we have an ill-posed inverse problem.

Next we will derive some better approximations. To improve on the uniform-conductivity approximation we go back to Eq. (7), and now we write it as

$$\phi(\mathbf{r}) = -\int \frac{i(\mathbf{r}')}{4\pi\sigma_c\|\mathbf{r}-\mathbf{r}'\|}d\mathbf{r}' - \int \frac{\nabla\cdot\left(\delta\sigma(\mathbf{r}')\nabla\phi(\mathbf{r}')\right)}{4\pi\sigma_c\|\mathbf{r}-\mathbf{r}'\|}d\mathbf{r}' \tag{13}$$

For the second term we form the operator $\mathcal{K}_\sigma$ which we assume is known to get the system,

$$\phi(\mathbf{r}) = \mathcal{H}i(\mathbf{r}') + \mathcal{K}_\sigma\phi(\mathbf{r}') \tag{14}$$

And we assume the domain and range of the operators is the same (i.e. the operators map the region to itself). If we have known index variations and know the potential everywhere, we can estimate the current via inversion of this equation, forming a linear system as before,

$$(\mathbf{I}-\mathbf{K}_\sigma)\,\mathbf{v} = \mathbf{Hi} \tag{15}$$

If the conductivity variations are unknown, but the potential is known everywhere, we can view the second term in Eq. (13) as a linear operator that depends on ϕ (e.g. $\mathcal{K}_\phi$) acting on $\delta\sigma$, and form a linear system

$$\phi(\mathbf{r}) = \mathcal{H}i(\mathbf{r}') + \mathcal{K}_\phi\delta\sigma(\mathbf{r}') \tag{16}$$

In terms of basis coefficients, the system becomes

$$\begin{aligned}\mathbf{v} &= \mathbf{H}\mathbf{i} + \mathbf{K}_\phi \mathbf{s} \\ &= \begin{pmatrix} \mathbf{H} & \\ & \mathbf{K}_\phi \end{pmatrix} \begin{pmatrix} \mathbf{i} \\ \mathbf{s} \end{pmatrix}\end{aligned} \tag{17}$$

Where **s** is the vector representing the coefficients of $\delta\sigma$ on the basis.

If the potential is only known on a limited number of points, and the potential over the region in the integral in (13) is assumed to be completely unknown, but the conductivity is known, we have

$$\mathbf{v}_d = \mathbf{H}\mathbf{i} + \mathbf{K}_\sigma \mathbf{v}_s \tag{18}$$

Where $\mathbf{v}_d$ is the (known) potential at the detector, and $\mathbf{v}_t$ is the (unknown) potential in the neural tissue.

If the conductivity is also unknown we have a quadratic problem. In operator form it would be

$$\phi(\mathbf{r}) = \mathcal{H} i(\mathbf{r}') + \mathcal{K} \delta\sigma(\mathbf{r}') \nabla \phi(\mathbf{r}') \tag{19}$$

Where $\mathcal{K}$ is a new operator which performs the convolution with the Green's function and the divergence, applied to the product of $\delta\sigma(\mathbf{r}')$ and $\nabla\phi(\mathbf{r}')$. Note that a gradient-based solver for this system would, via the product rule for derivatives, solve the above linear systems.

We may form an approximation analogous to the Born approximation of inverse scattering, by assuming the unknown potential values are equal to the potential in constant medium, namely $\phi_0(\mathbf{r})$. Then we have the following variation on Eq. (17), where we use $\mathbf{K}_{\phi_0}$ in place of $\mathbf{K}_\phi$.

$$\mathbf{v} = \begin{pmatrix} \mathbf{H} & \\ & \mathbf{K}_{\phi_0} \end{pmatrix} \begin{pmatrix} \mathbf{i} \\ \mathbf{s} \end{pmatrix} \tag{20}$$

Now we demonstrate simulated results using the system of Eq. (11).

3 Results

We model neurons in tissue as lines of current sources. By considering a typical action potential in a simplified neuron we note that at any given point in time, the signal resulting from a single action potential stretches across hundreds of microns if not millimeters, as depicted in Fig. 1.

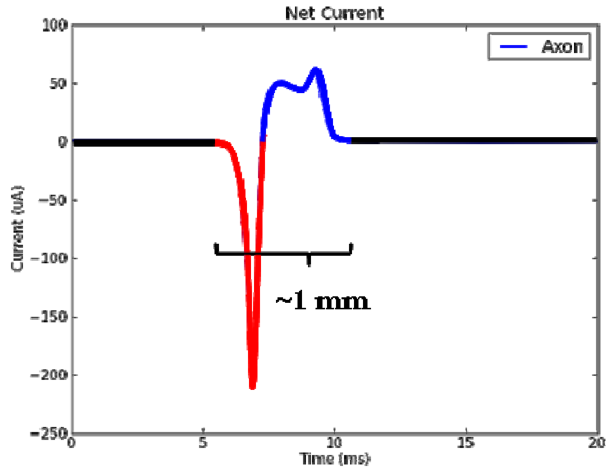

Figure 1: Axon current versus time simulated using NEURON [4].

We also find typical current levels to be in the tens to hundreds of microAmps. Our model of a neuron therefore, will be a line of current sources, which we will assume to be constant over the measurement regime.

First we address the problem of measuring neural activity via extracellular fields. We consider the following geometry, depicted in Fig. 2. The detector is a two-dimensional plate at the y-z plane, with dimensions of 100 by 100 microns. The region to be analyzed is the three dimensional volume adjacent to the plate in the positive x-direction, extending 20 microns deep.

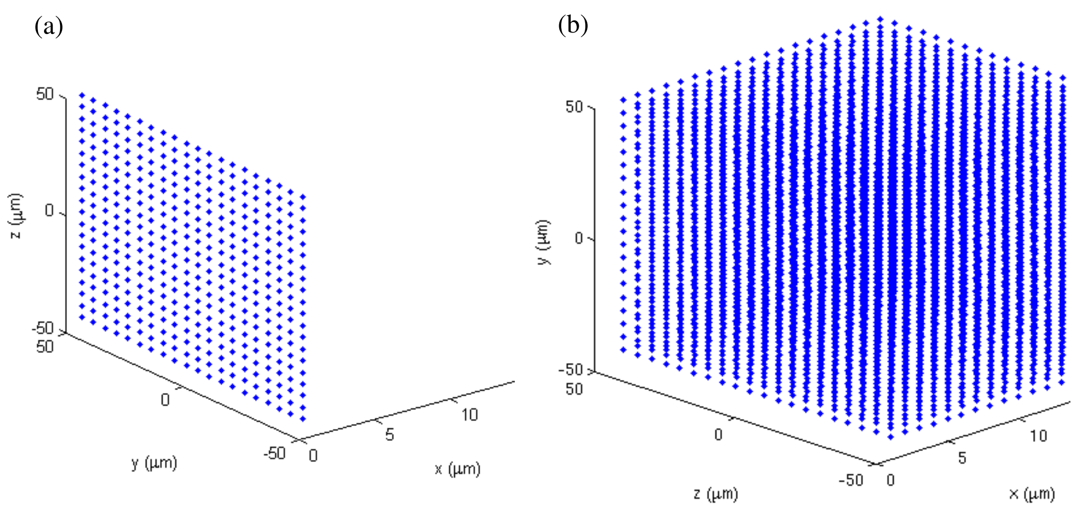

Figure 2: Simulation geometry. (a) Detector points where potential is measured, and (b) variable points where current source density is to be estimated.

We use the simplified model of Eq. (11), which in terms of the samples values is

$$\mathbf{v} = \mathbf{H}\mathbf{i} \tag{21}$$

$\mathbf{v}$ is a vector containing the potential at the points in Fig. ?? (a), and $\mathbf{i}$ is a vector containing the current density at the points in Fig. 2 (b). $\mathbf{H}$ is a matrix which approximates the linear operation in Eq. (11). In the case depicted here, $\mathbf{v}$ is length 400 (the detector grid is 20x20), while $\mathbf{i}$ is length

7600 (the variable grid is 19x20x20). Therefore **H** is 400x7600 and we have a significantly underdetermined problem.

We can estimate a regularized solution using truncation of the singular-value decomposition (SVD) [6]. If the SVD of **H** is

$$\mathbf{H} = \mathbf{U}\mathbf{S}\mathbf{V}^T \tag{22}$$

Then we can form

$$\mathbf{i} \approx \mathbf{V}\tilde{\mathbf{S}}\mathbf{U}^T\mathbf{v} \tag{23}$$

Where $\tilde{\mathbf{S}}$ is a rectangular diagonal matrix with the inverses of the nonzero singular values of **H** on the diagonal. The singular values of H are plotted in Fig. 3 in decreasing order.

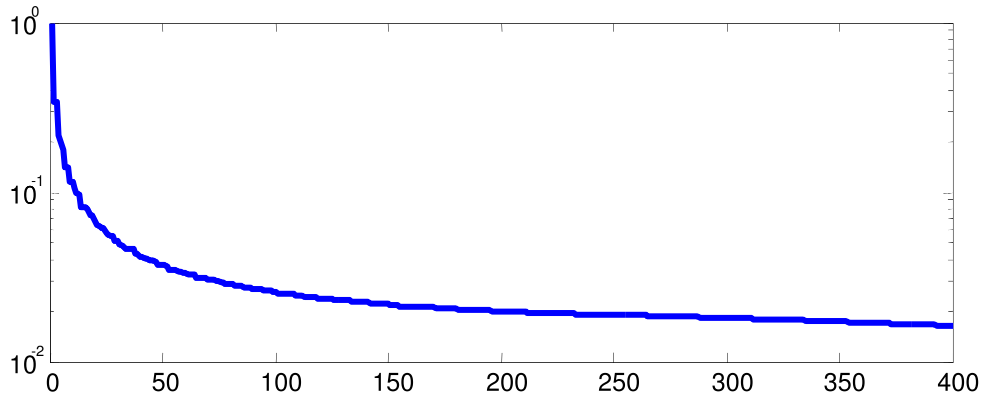

Figure 3: Magnitude of singular values, normalized by largest.

We note that they are all within two orders of magnitude of the largest, meaning that roughly a signal-to-noise ratio of 100 is necessary to collect all available degrees of freedom of the measured data. We assume that we are able to do so in this report.

Next we consider the energy in the collected signal versus depth. In Fig. 4 we have plotted the sum of the energy in the eigenvectors corresponding to the nonzero eigenvalues, integrated over the y-z direction, versus the depth direction.

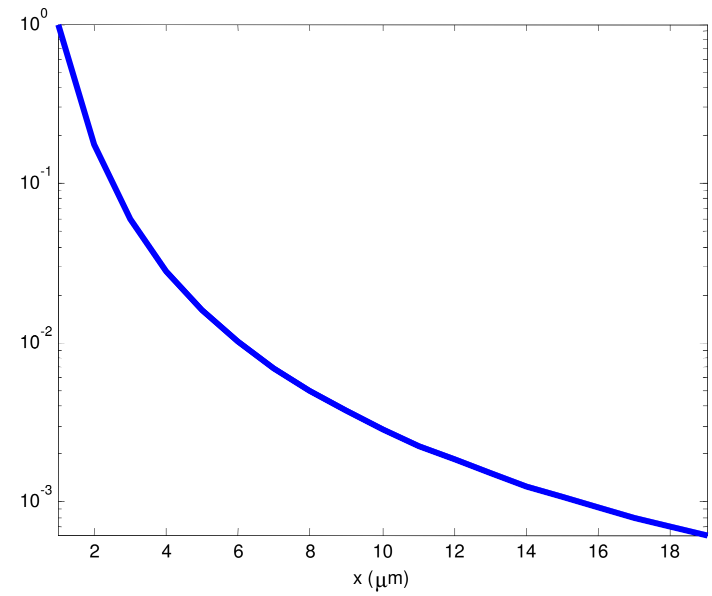

Figure 4: Relative energy in singular values versus depth.

This result demonstrates that most of the signal that results from deeper sources is not transferred to the detector at deeper distances, i.e. it is projected of the nullspace of **H**.

Now we will perform a simulation using Eq. (23) to estimate the current source density. We use the configuration of Fig. 5 (a) as our unknown source density, consisting of 3 vertical lines at 7 micron depth, and 3 horizontal lines at 14 micron depth. At the detector we see the simulated result of Fig. 5 (b).

(a) (b)

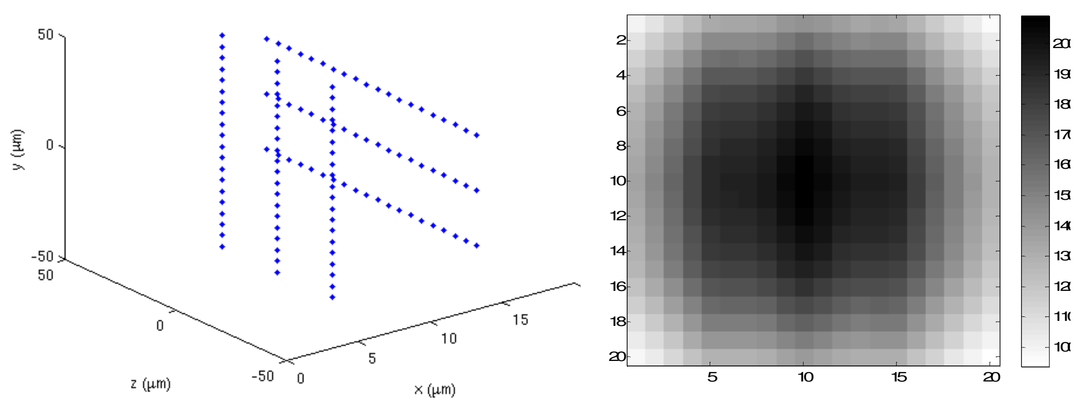

Figure 5: (a) simulated current density, (b) voltage measured at the grid of detector points (in volts).

We solve the inverse system using the SVD approach, and get the estimate of Fig. 5.

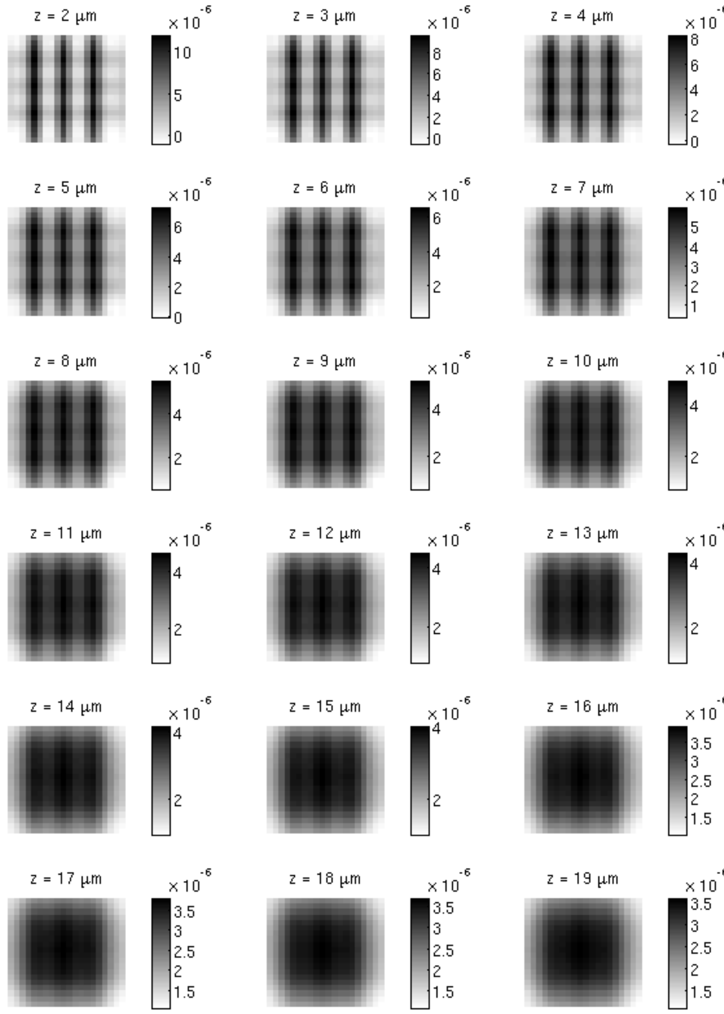

Figure 6: Inversion result, given in cross sections parallel to detector at increasing depth.

We find that we are able to resolve the sources in the transverse directions (y-z), but that depth information is basically gone.

Assuming that the reconstruction always makes the mistake of attributing the source to the plane nearest the detector, we now consider the image only at that plane, as we vary the source depth. In Fig. 7, we show the potential measured at the detector as we vary the depth of a vertical line source.

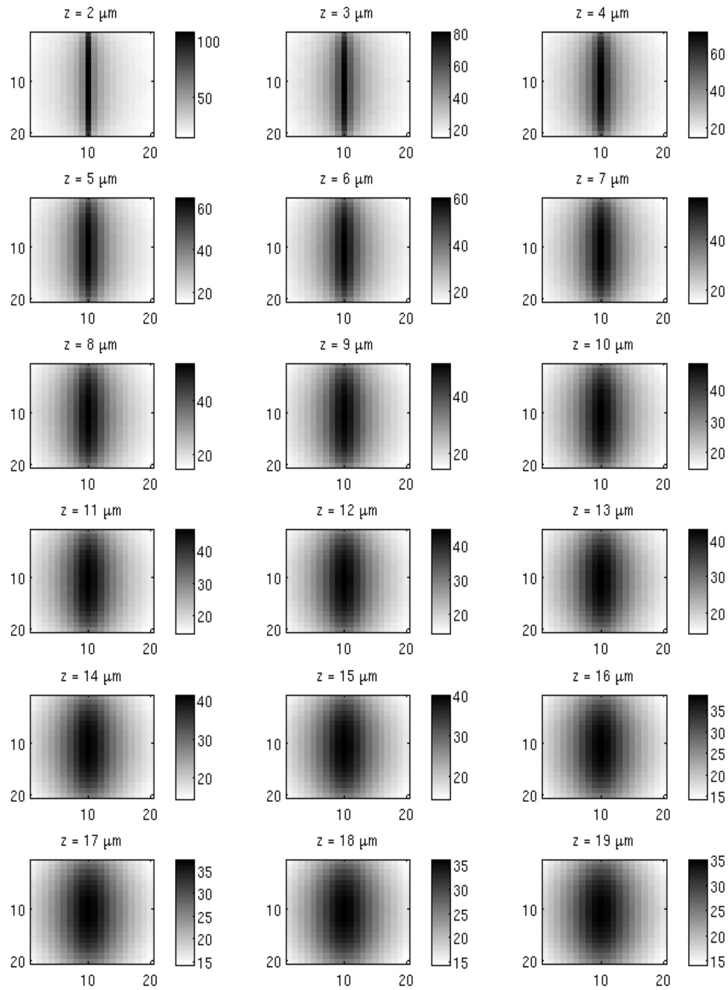

Figure 7: Potential measured at detector for vertical line sources at increasing depth.

In Fig. 8 we find that we are able to reliably resolve the source in the y-z direction by simply looking at the first plane of the inverse estimate.

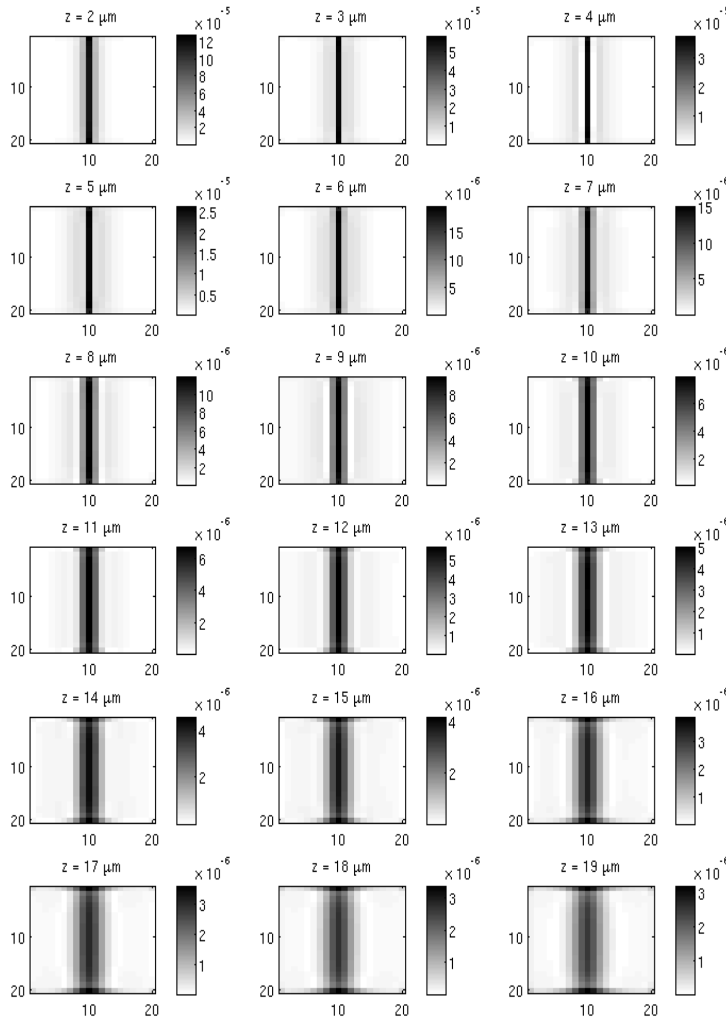

Figure 8: Estimate of Current source density at plane adjacent to detector, for sources at increasing depth.

Next we consider the problem of trying to induce currents rather than measure them. The problem is essentially the same as above, but now the plate detector is the unknown current source, and the imaged region is the desired potential. Our goal is to create a small potential difference. We presume a rapid change in the depth direction would be practically impossible given the system's invariance with depth, so as our target we use a pair of points of opposite voltage adjacent in the z-direction.

In Fig. 9, we show the current source density needed at the source plate to achieve the best possible approximation to a small dipole at different distances.

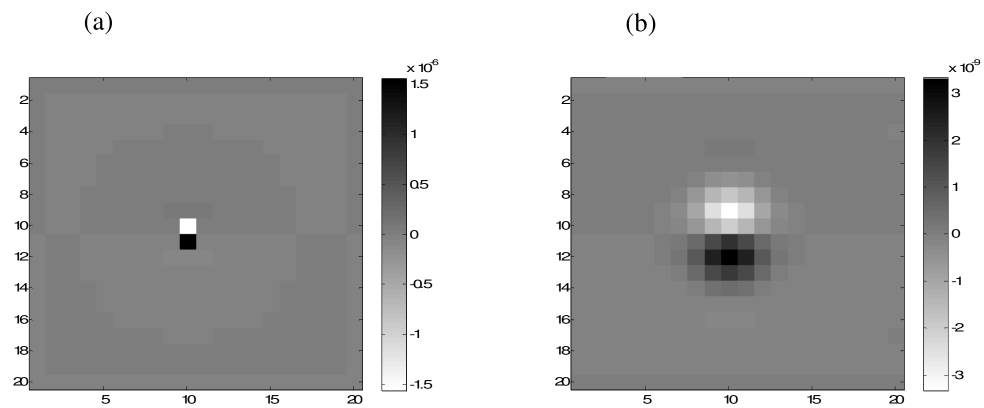

Figure 9: Needed current source densities to achieve desired potential. (a) at 2 micron depth, (b) at 18 micron depth.

To find what we actually expect to achieve, we solve the forward system of Eq. (21) with the above current sources, and get the results in Figs. 10 and 11.

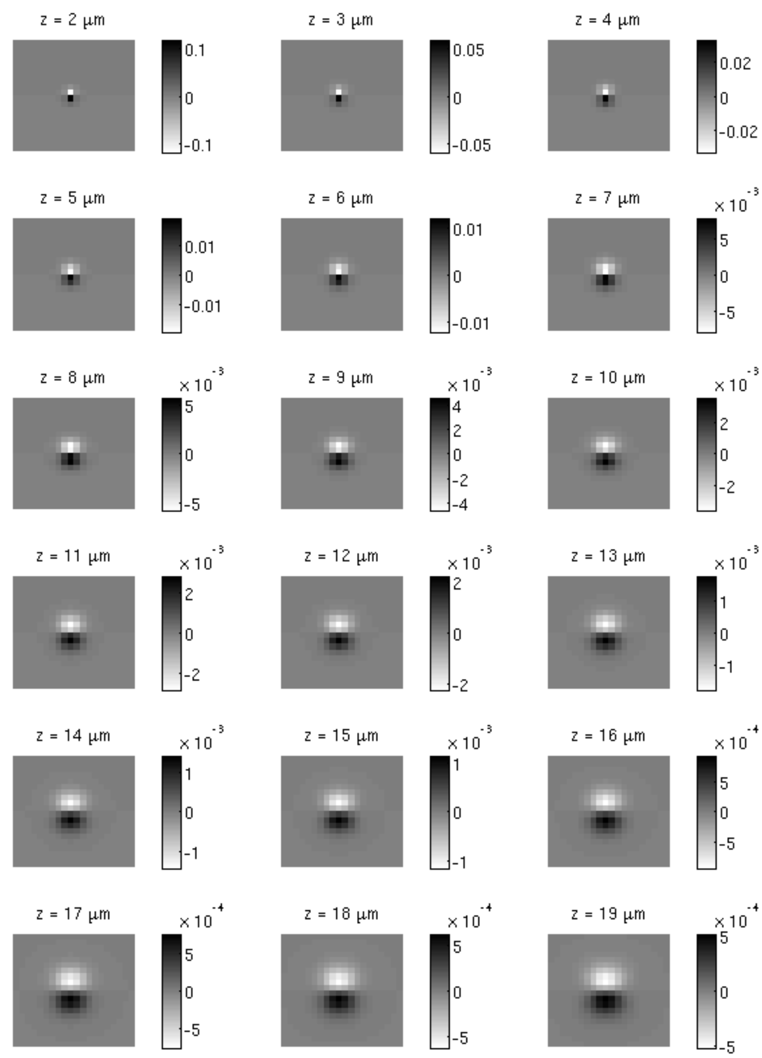

Figure 10: Potential resulting from current source of Fig. 8 (a) at source plate, displayed in cross-sections at increasing depth.

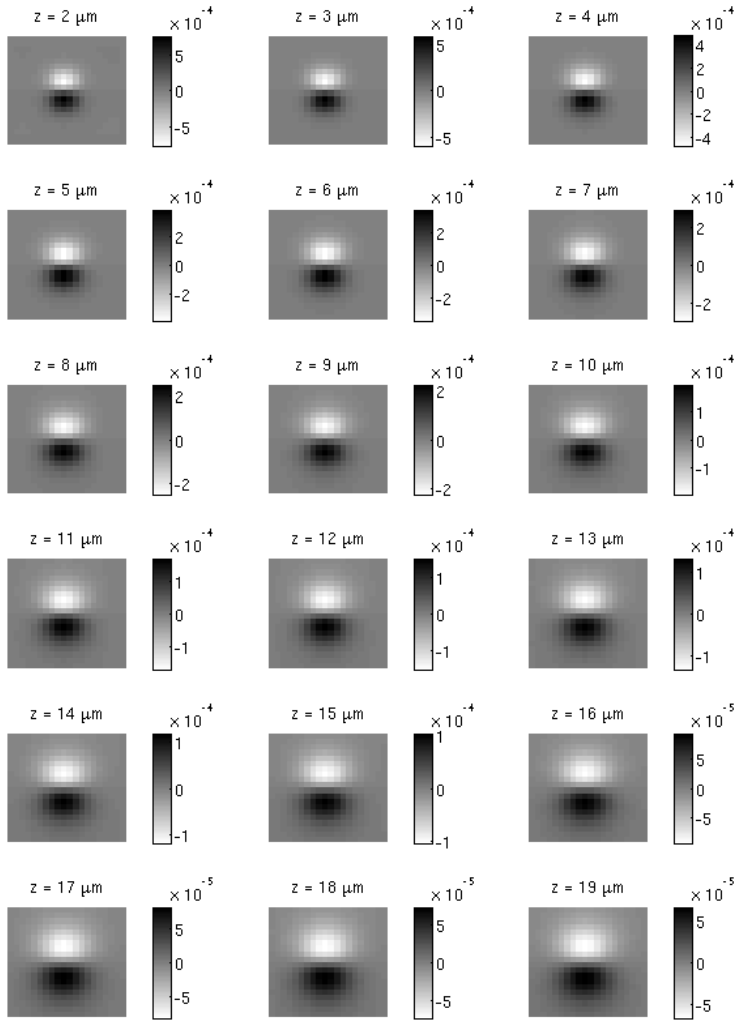

Figure 11: Potential resulting from current source of Fig. 8 (b) at source plate, displayed in cross-sections at increasing depth.

As we should have expected, we find we have minimal ability to control variation in depth.

4 Discussion

We found promising results in our ability to resolve current sources in the transverse direction, with basically zero resolution in the depth direction. Effectively we have a projection of the current source density in the depth direction. This suggests a form of tomography, whereby we might perform this imaging process over a range of angles and combine the results to reconstruct in three dimensions.

The “design problem” of producing as close to possible a desired potential appears more challenging. Our preliminary results suggest we may be able to provide a better resolution of the effect in the transverse directions, over some depth. But the effect in a more realistic scenario may be lost. Further, our real interest is in inducing current into a neuron which means we must consider the lower conductivity of the membrane versus the extracellular medium. Both these issues can perhaps be addressed by using the more sophisticated model of Eq. (20).

References

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