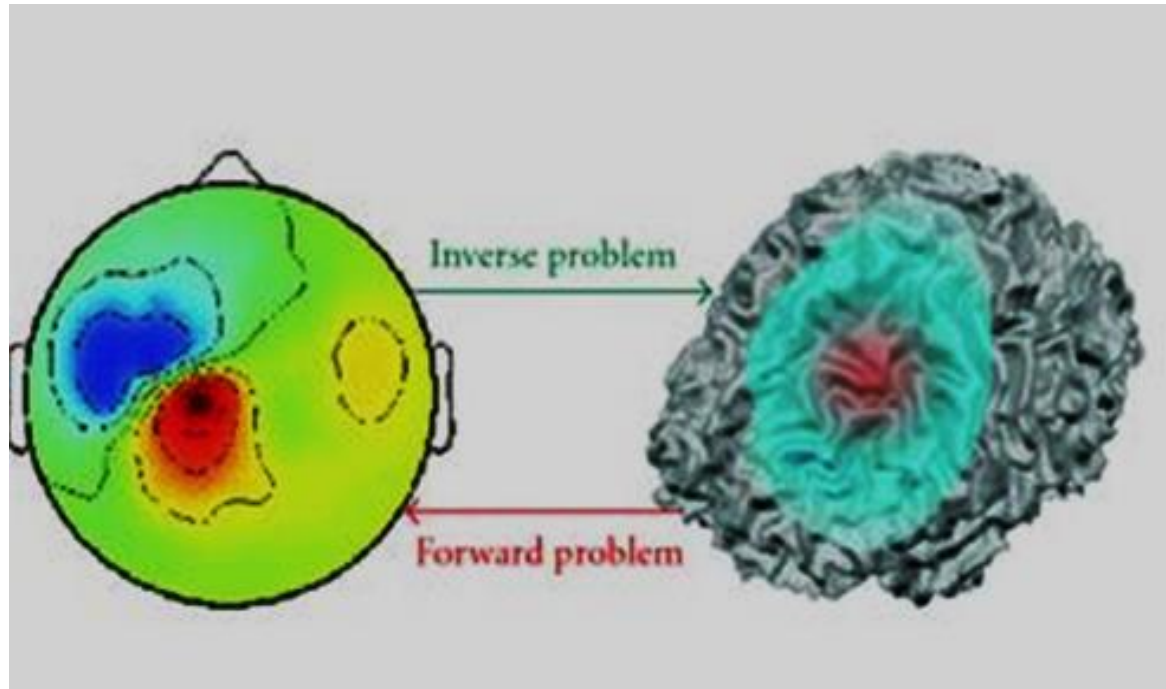


Source localization (inverse problem)



forward-inverse problem [1]

1. Source localization (inverse problem) is to estimate cortical neural source signals from scalp potentials (EEG).
2. Source localization (inverse problem) needs forward problem, i.e. to estimate how cortical source activity transfers to scalp. Forward problem estimates is based on appropriate model for neural source and voltage-current equations in head.

Source localization steps

EEG Neural source model

- The generators of EEG (pyramidal neurons located in gray matter)
- Neural source model : current dipole
- dipole voltage-current equation (Poisson's differential equation)

Head forward problem

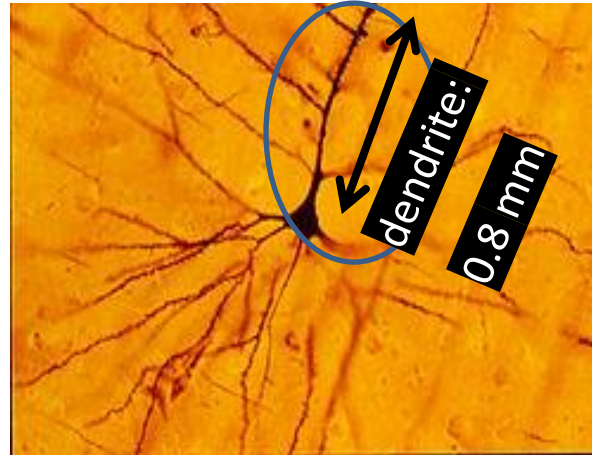
Forward problem purpose: How does cortical source activity transfer to scalp?

- Head model definition (MRI acquisition)
- MRI segmentation (scalp, skull, brain segments)
- Mesh generation (scalp, skull, brain surface triangulated mesh)
- Electrode registration on scalp mesh
- Forward problem: Solving Poisson's differential equation (voltage-current equation for head)
- Output of forward problem (solving Poisson's voltage-current equation for head geometry): for each neuronal current source location, source current to each electrode (sensor) voltage is a coefficient called Lead-field or transfer coefficient.
- Lead-field: the feature for each dipole location on gray matter
- Lead-field coefficient: a function of dipole location, head geometry and conductivity.

Inverse problem

- Estimating amplitude of current sources for each cortex location from EEG and inverse algorithms using Lead-field matrix (forward algorithm)

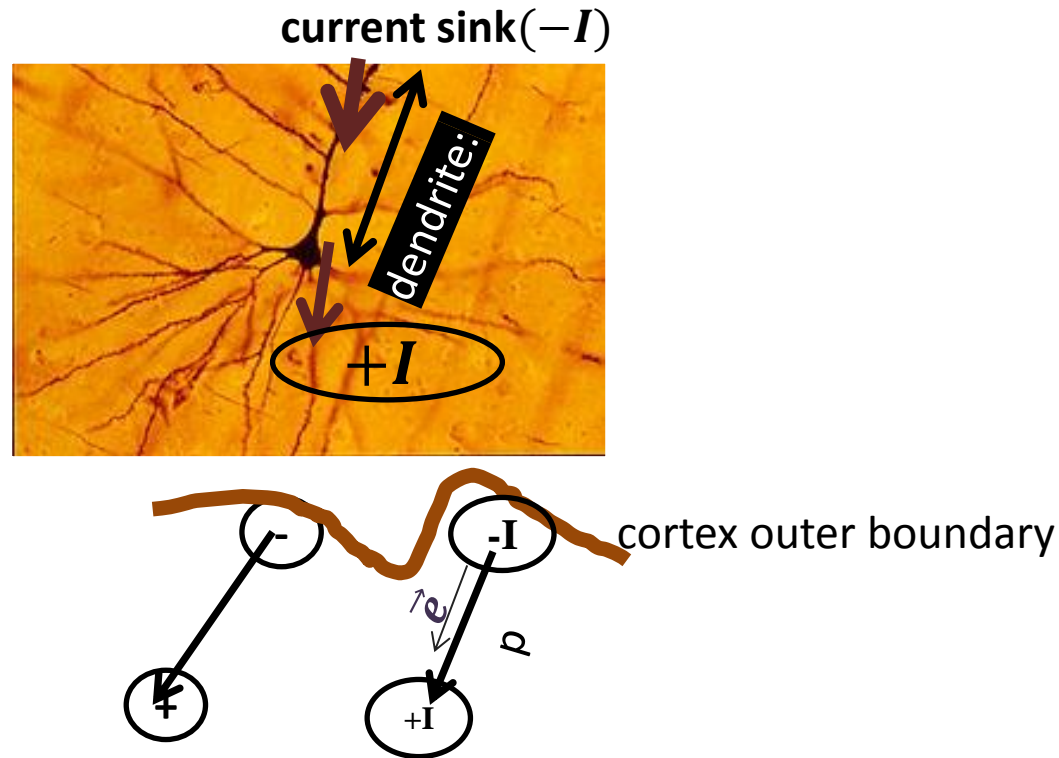
The generators of EEG



pyramidal neurons visualized by light microscopy technique

- Pyramidal neurons located in Neocortex (outer layer of cerebral cortex), 2-4mm width (depth)
- Neocortex: 6 layers numbering from outer layer to depth (0.3-0.6 mm width of each layer)
- Layers 3 and 5 are the probable locations for 10-14 billion pyramidal neurons (depth: 0.9-1.8 mm)

Neural source model (current dipole)



Dipole momentum definition at one point between two monopoles (sink and source)

$$\vec{d} = I \cdot p \cdot \vec{e} = I \cdot p \cdot \vec{e}$$

P : distance between two monopoles (m) usually considered unit (1)

I : current density (A/m^2)

\vec{e} : vector from sink to source (two monopoles), this vector is normal to surface on outer layer of gray matter (cerebral cortex)

dipole voltage-current equation (Poisson's differential equation)

$$\mathbf{J} = \mathbf{J}^p + \sigma \mathbf{E}$$

\mathbf{J} (A/m^2): total current density

σ : conductivity

\mathbf{J}^p : primary current density(in or near to cell)

$\sigma \mathbf{E}$: secondary (volume) current

A small volume around neuron has no net current.

$$\mathbf{J} = \nabla \times \mathbf{B} \rightarrow \nabla \cdot \mathbf{J} = \nabla \cdot (\nabla \times \mathbf{B}) = 0$$

$$\mathbf{J} = \mathbf{J}^p + \sigma \mathbf{E} = \mathbf{J}^p - \sigma \nabla V$$

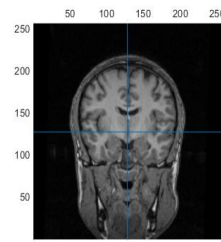
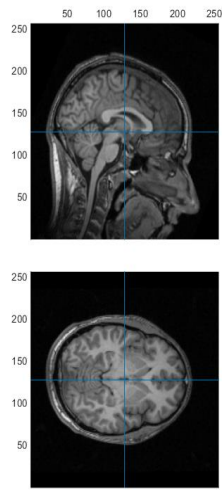
$$\nabla \cdot \mathbf{J}^p = -I\delta(\mathbf{r} - \mathbf{r}_{sink}) + I\delta(\mathbf{r} - \mathbf{r}_{source})$$

$\nabla \cdot (\sigma \nabla V) = \nabla \cdot \mathbf{J}^p$: This is called the Poisson's differential equation

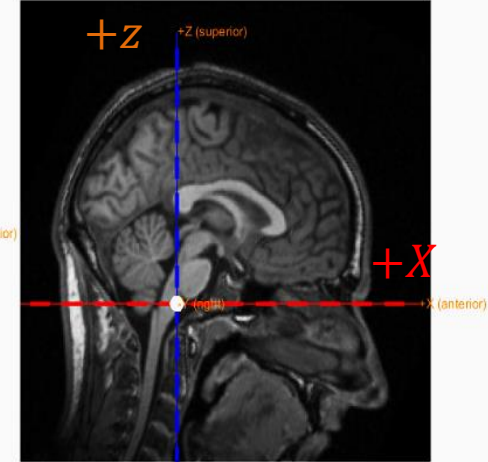
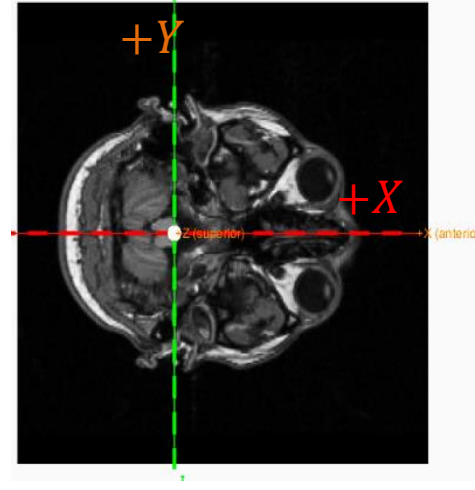
So \mathbf{J}^p , primary current density is the EEG source.

Solving Poisson's differential equation= primary current density estimation

Head model definition (MRI)



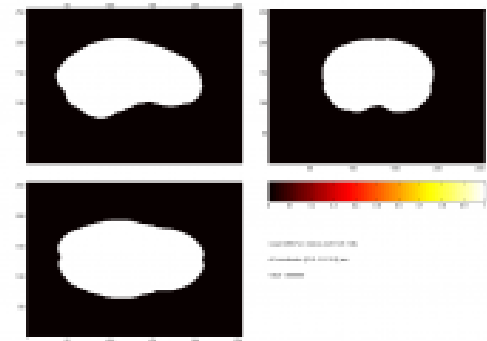
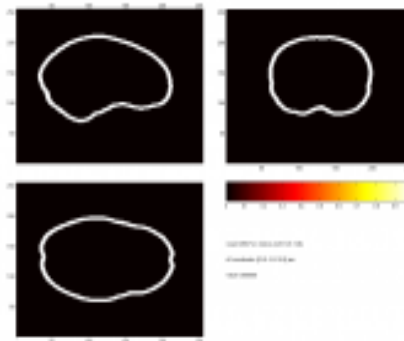
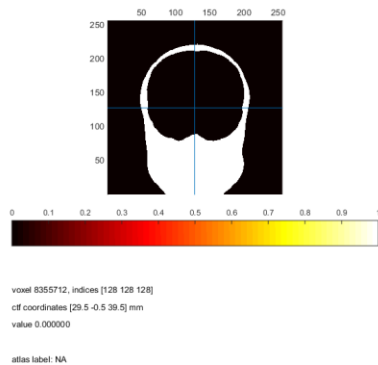
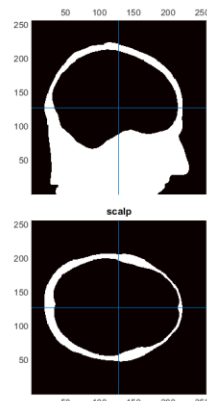
voxel 8355712, indices [128 128 128]
cift coordinates [29.5 -0.5 39.5] mm
atlas label: NA



Left: T1 weighted MRI With 256 slices (plates) of each 256*256 voxels (cubes)

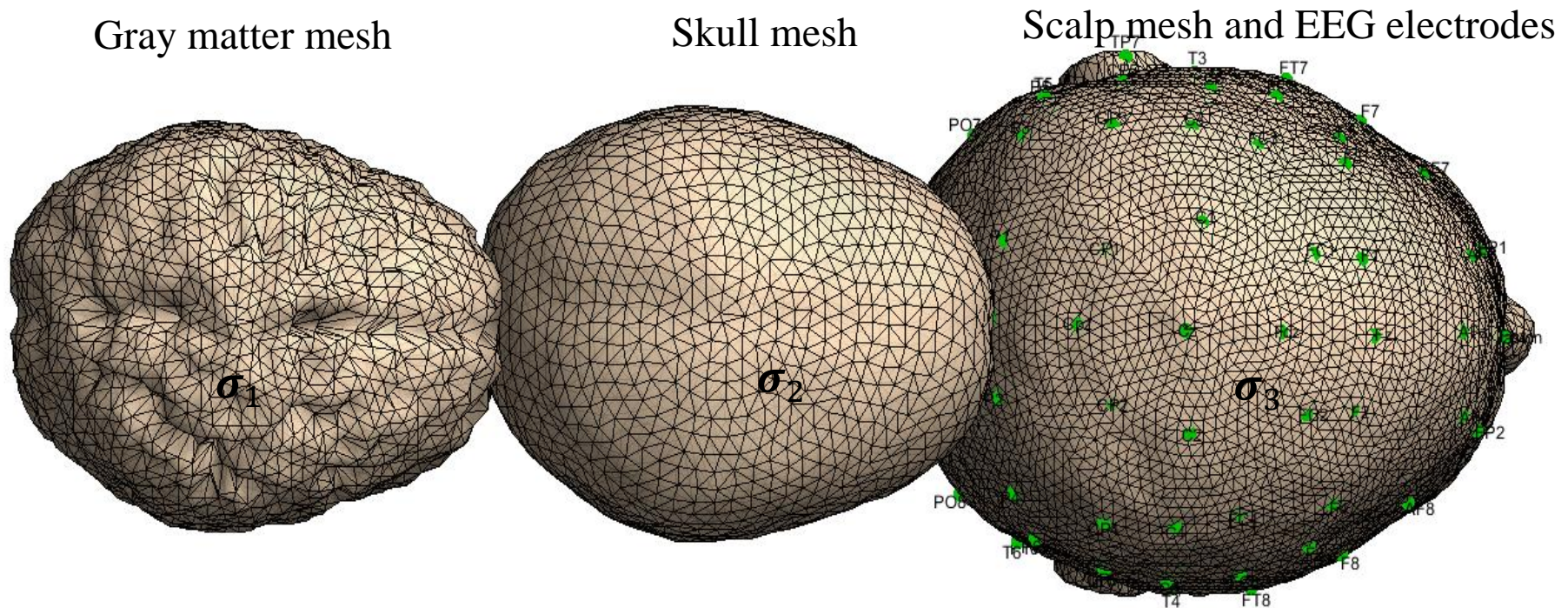
Right: MRI coordinate system, Define +X+Y+Z MRI coordsys corresponding anatomical directions, (A)nterior (nose)/(P)osterior (inion), (S)uperior (vertex)/(I)nferior, (R)ight (ear)/(L)eft. The coordsys is 'ALS' and center of coordsys is inter auricular (between ears)

MRI has a transformation matrix for transforming each voxel (cube) location from voxel space (i, j, k) to 3d (x, y, z) real location in MRI coordsys. Each voxel is discretized by it's location and intensity (gray level)



Segmented MRI (scalp, skull, brain segments). Method: Allocating different gray levels to different tissues (scalp, skull, gray matter) based on tissue probability maps form MRI atlases besides tissue morphology, good tools to segment head tissues [7].

Mesh generation



Surface triangulated meshes (brain, skull, scalp interfaces (boundaries)) [8]
acquired from segmented MRI and their conductivities ($\sigma_1, \sigma_2, \sigma_3$),

$$\sigma_1 \approx \sigma_3 = a \sigma_2$$

$$\sigma_1 \approx \sigma_3 = 0.33, a = 15 - 80, \text{ most reported } a = 25. [2]$$

Conductivities are acquired with different techniques [2] such as electric impedance tomography (EIT, an imaging technique which applies source-sink currents to paired scalp electrodes and images scalp potentials using forward problem and an other concept based reciprocity in electronic circuits).

according to 10-10 standard

3

dipole general directions at one location (1,0,0) (0,1,0) (0,0,1)

 $\vec{e}_{d(3*1)}$: dipole normalized vector direction

A diagram showing a curved surface. A vector labeled \mathbf{e}_n points outwards from the surface, representing the normal direction. Two stress components, σ_1 and σ_2 , are indicated on the surface, representing the principal stresses acting on the surface.

$(\sigma_1 \nabla V_1) \cdot \mathbf{e}_n = (\sigma_2 \nabla V_2) \cdot \mathbf{e}_n$, σ_1 and σ_2 inner and outer interface conductivity
 at the surface of scalp: $\mathbf{J}_1 \cdot \mathbf{e}_n = 0$, $(\sigma_1 \nabla V_1) \cdot \mathbf{e}_n = 0$

9

Solving Poisson's equation (for a dipole in infinite homogeneous medium)

$$V_0(\mathbf{r}, \mathbf{r}_{dip}, \vec{\mathbf{d}}) = \frac{\vec{\mathbf{d}} \cdot (\mathbf{r} - \mathbf{r}_{dip})}{4\pi\sigma_0 \|\mathbf{r} - \mathbf{r}_{dip}\|^3}$$

V_0 : potential at any point in infinite homogeneous medium

\mathbf{r} : any point in space

\mathbf{r}_{dip} : dipole location

$\vec{\mathbf{d}}$: dipole moment

σ_0 : medium conductivity (s/m)

Solving Poisson's equation for a dipole in piecewise homogeneous medium (head) Boundary element method (BEM)

$$V(\mathbf{r}) = \frac{2\sigma_0}{\sigma_r^- + \sigma_r^+} V_o(\mathbf{r}) + \sum_{\text{triangles on boundaries}} \text{function (voltage, geometry, conductivity on each triangle)}$$

σ_r^\pm : conductivity (s/m) of outer (+)/inner(-) medium at location \mathbf{r}

Note: \mathbf{r} belongs to one triangle

$$V(\mathbf{r}) = \frac{2\sigma_0}{\sigma_r^- + \sigma_r^+} V_o(\mathbf{r}) + \frac{1}{2\pi} \sum_{k=1}^{R=3} \frac{\sigma_k^- - \sigma_k^+}{\sigma_r^- + \sigma_r^+} \sum_{j=1}^{N_{s_k}} \sum_{i=1}^{N_{s_k}} V_i^k \int_{\Delta_{s_k,j}} h_i(\mathbf{r}) \frac{\mathbf{r}' - \mathbf{r}}{\|\mathbf{r}' - \mathbf{r}\|^3} dS_k$$

σ_k^\pm : conductivity (s/m) on k th outer (+)/inner(-) interface (boundary)
gray/skull interface, skull/scalp interface, scalp/air interface
 σ_0 : *dipole medium* (gray matter) conductivity (equal σ_1^-)

Surface integral is calculated along normal vector (\vec{n}) on each of N_{s_k} triangles (geometry dependent) with unknown voltages V_i^k .

V_i^k : all unknown potentials on N_{s_k} triangles on each boundary, hence the above equation is not solvable.

$h_i(\mathbf{r})$ basis function is defined to simplify the equation by lowering the unknowns and making equation solvable.

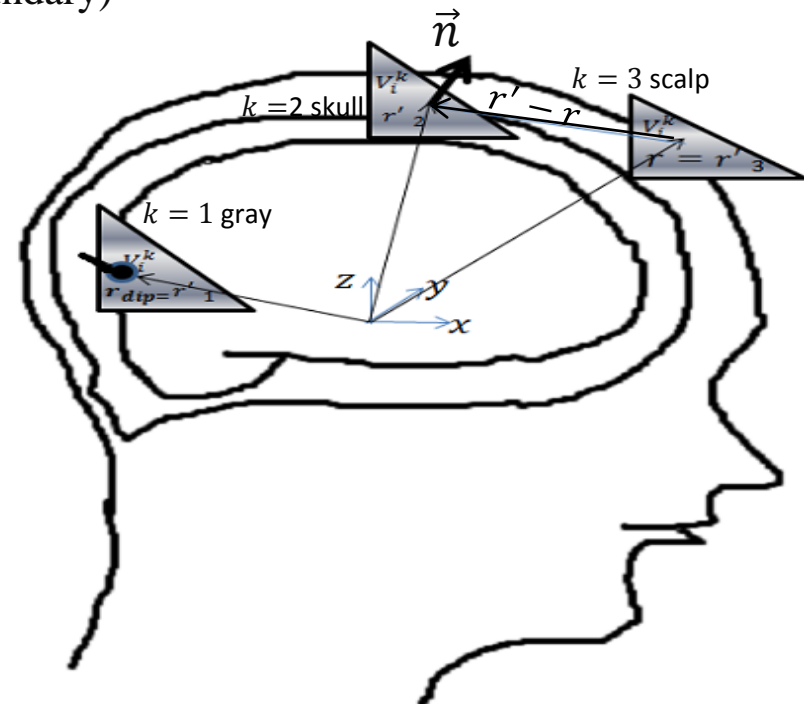
$h_i(\mathbf{r})$: basis function of \mathbf{r} decreasing with increasing distance to \mathbf{r} , a simple definition $h_i(\mathbf{r}) = \begin{cases} 1 & \mathbf{r} \in \Delta_i \\ 0 & \mathbf{r} \notin \Delta_i \end{cases}$, Δ_i is the i -th planar triangle on the tessellated surface.

\mathbf{r}' : any point on triangles of surface meshes of scalp, skull, gray matter ($\mathbf{r}' = \mathbf{r}'_1, \mathbf{r}'_2, \mathbf{r}'_3$),

\mathbf{r} : any point on surface meshes of scalp, skull, gray matter (the purpose location is on scalp, \mathbf{r}'_3),

R : number of interfaces (boundaries) (3 boundaries), N_{s_k} : number of triangles on k -th boundary, ($k = 1, 2, 3$)

A conclusion: $V(\mathbf{r}) = \text{function}(\text{conductivity}, \text{geometry}, \vec{d})$



It is proved: $V \propto V_0 \propto \vec{d}$; $V_0(\mathbf{r}, \mathbf{r}_{dip}, \vec{d}) = \frac{\vec{d} \cdot (\mathbf{r} - \mathbf{r}_{dip})}{4\pi\sigma_0 \|\mathbf{r} - \mathbf{r}_{dip}\|^3}$

$$V(\mathbf{r}) = \text{function}(\text{conductivity, geometry}) * \vec{d} = \text{Lead - field} * \vec{d},$$

leadfield is a constant parameter for each dipole location

for M electrodes and n_d dipoles at time t_i we have:

momentum for dipole location 1

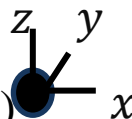
At time t_i

$$\begin{bmatrix} L_1^{1,x} & L_1^{1,y} & L_1^{1,z} & \dots & L_1^{n_d,x} & L_1^{n_d,y} & L_1^{n_d,z} \\ L_2^{1,x} & L_2^{1,y} & L_2^{1,z} & \dots & L_2^{n_d,x} & L_2^{n_d,y} & L_2^{n_d,z} \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ L_M^{1,x} & L_M^{1,y} & L_M^{1,z} & \dots & L_M^{n_d,x} & L_M^{n_d,y} & L_M^{n_d,z} \end{bmatrix} \begin{bmatrix} d^{1,x,t_i} \\ d^{1,y,t_i} \\ d^{1,z,t_i} \\ \dots \\ d^{n_d,x,t_i} \\ d^{n_d,y,t_i} \\ d^{n_d,z,t_i} \end{bmatrix} = \begin{bmatrix} V_1 \\ V_2 \\ \dots \\ V_M \end{bmatrix}$$

Scalp potentials at M electrodes
from n_d dipoles at time t_i

Lead-field for dipole location 1

with 3 general Cartesian directions (x, y, z)



Dipolar sources

+
Head model

(describing conductivity and geometry)

Lead-fields



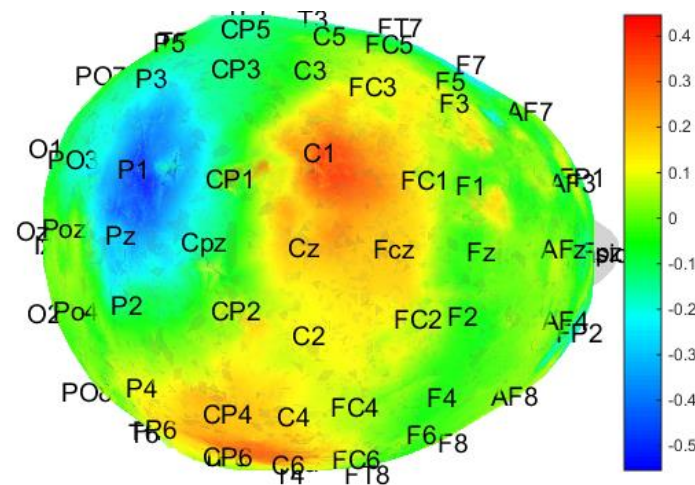
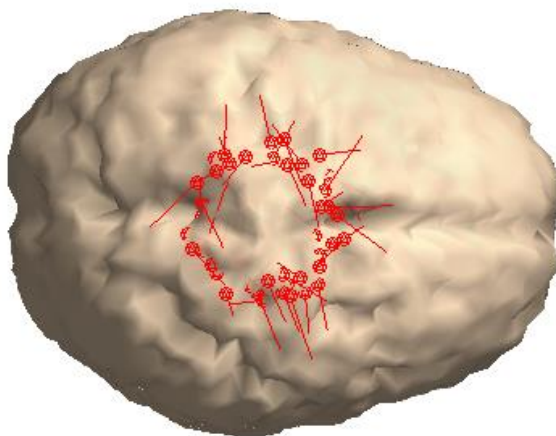
$$\begin{bmatrix} L_1^{1,x} & L_1^{1,y} & L_1^{1,z} & \dots & L_1^{n_d,x} & L_1^{n_d,y} & L_1^{n_d,z} \\ L_2^{1,x} & L_2^{1,y} & L_2^{1,z} & \dots & L_2^{n_d,x} & L_2^{n_d,y} & L_2^{n_d,z} \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ L_M^{1,x} & L_M^{1,y} & L_M^{1,z} & \dots & L_M^{n_d,x} & L_M^{n_d,y} & L_M^{n_d,z} \end{bmatrix} \begin{bmatrix} d^{1,x,t_i} \\ d^{1,y,t_i} \\ d^{1,z,t_i} \\ \dots \\ d^{n_d,x,t_i} \\ d^{n_d,y,t_i} \\ d^{n_d,z,t_i} \end{bmatrix} = \begin{bmatrix} V_1 \\ V_2 \\ \dots \\ V_M \end{bmatrix}$$

momentum for dipole location 1

At time t_i

Lead-field for dipole location 1

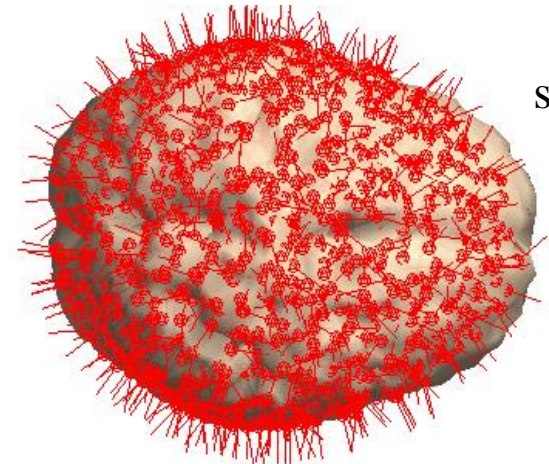
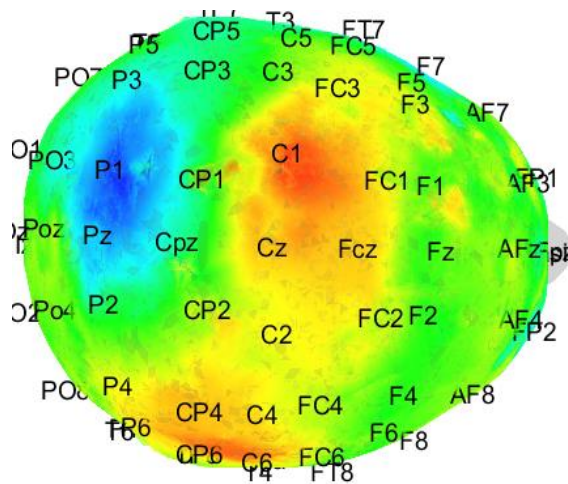
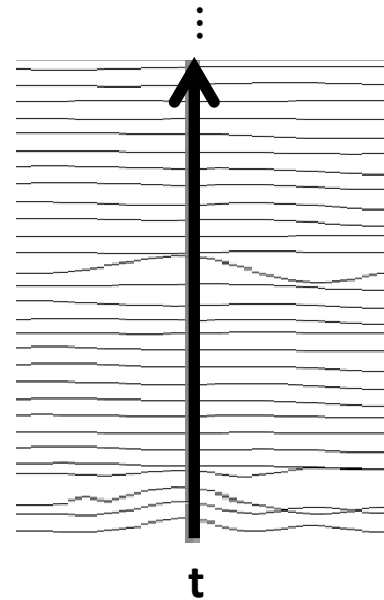
Scalp potentials at M electrodes
from n_d dipoles at time t_i



Mapping lead-fields on electrodes for $n_d=50$

dipolar sources with amplitude=1 and normal directions to gray matter surface mesh

Inverse problem (source estimation)



source grid
 $gd (mm)$

Left: EEG and EEG-map at one time sample (known)

Right: A set of dipole sources (with unknown amplitudes, known lead-fields), predefined and distributed on gray matter. Sources can be distributed on a grid (a set of location points) with a predefined minimum grid distance ($gd (mm)$)

$$L_{forward} \vec{d} = EEG$$

Inverse

$$\vec{d} = L_{inverse}^{\dagger} EEG = (L_{inverse}' L_{inverse})^{-1} L_{inverse}' EEG$$

Each 3 columns of $L_{inverse}$ is Lead-field

corresponding each predefined source location

$L_{forward}$: Lead-field Matrix with $3 \times n_d$ columns corresponding n_d active sources

✓ distributed dipole source over large area of brain (since we don't know exact locations of sources), hence $L_{inverse}$ is a large matrix.

Problems with large $L_{inverse}$:

- Any small change in EEG may cause a large change in \vec{d}
- Reason: eigenvalues / singular values of $L_{inverse}^\dagger$ are largest in the reverse mapping where they were smallest in the forward mapping ($L_{forward}$). High Eigen value causes discontinuous change in \vec{d} with a little change in EEG .
- Condition number: $K(L'L) = \|(L'L)\| \|(L'L)^{-1}\| = \max(eig(L'L)) / \min(eig(L'L))$,
- **eig**: Eigen value $L=L_{inverse}$

Higher Condition number increases the probability for discontinuity of source signal estimations.

Solution for achieving low condition number, well-posed (unique best approximate) solver for \vec{d} :

$$\vec{d} = (L'L + \alpha I)^{-1} L' EEG, (L'L + \alpha I) \text{ has lower Condition number}$$

I : identity matrix, α : Tikhonov regularization number

$$\text{Min } F_\alpha(\vec{d}) = \|L\vec{d} - EEG\|^2 + \alpha \|\vec{d}\|^2$$

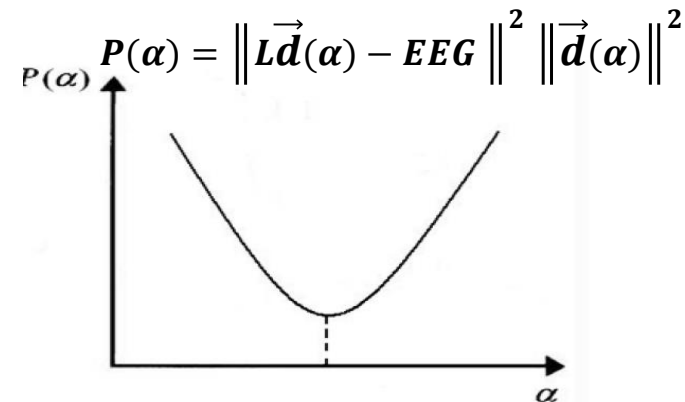
minimum norm inverse solution

General form for minimum norm inverse solution:

$$\text{Min } F_\alpha(\vec{d}) = \|L\vec{d} - EEG\|^2 + \alpha \|W\vec{d}\|^2$$

W : weight matrix, α : Tikhonov regularization number

different weights \equiv different minimum norm inverse methods.



Inverse methods	weight matrix (W)	Output dipole current sources (\vec{d})
MNE (Minimum norm estimate)	W=I (identity matrix)	$\vec{d} = (L'L + \alpha W'W)^{-1} L' EEG$
WMNE (weighted Minimum norm estimate)	W= B B = diag(norm(columns (L))) <i>Diag</i> (...): diagonal matrix with non zero components in diagonal, each component is norm of one column of L This compensates for lower gains of different locations by MNE	$\vec{d} = (L'L + \alpha W'W)^{-1} L' EEG$
LORETA (Low resolution electromagnetic tomography)	W=ΔB, Δ: laplacian operator B = diag(norm(columns (L))) Diag(...): diagonal matrix with non zero components in diagonal, each component is norm of one column of L laplacian of B _i for each source location: $\frac{1}{d} (6B_i - \sum_{i=1}^p B_p)$, ∀p under constraint $\ r_i - r_p\ = d1$ d1: minimum distance between two gridpoints This increases spatial resolution of source localization.	$\vec{d} = (L'L + \alpha W'W)^{-1} L' EEG$

LAURA (local autoregressive averages)	$W_j = (W_m A)' (W_m A)^{\wedge} I_3$ <p>\wedge: kronecker matrix product (each row-element in first matrix multiplied by all row-elements of other matrix)</p> $W_m = \text{diag}(\text{mean}(\text{norm}(\text{3}_{\text{columns}}(\mathbf{L}))))$ <p>Diag(...): diagonal matrix with non zero components in diagonal, each component is mean(average) of norm of 3 column of \mathbf{L}</p> <p>\mathbf{A}: distance matrix, for hexahedral grid</p> $A_{ii} = 26 / \text{num_nearestneighbours} \quad (\sum_{K=1:\text{num_nearestneighbours}} d\mathbf{1}_{ki}^{-3})$ $A_{ki} = d\mathbf{1}_{ki}^{-3}, d\mathbf{1}_{ki}$: distance between k-th and i-th grid point <p>\mathbf{A} is defined based on Physiological constraints from forward problem (based poisson's equation)</p> <p>Reason:</p> $V_o(\mathbf{r}) = \frac{d \cdot (\mathbf{r} - \mathbf{r}_{dip})}{4\pi\sigma \ \mathbf{r} - \mathbf{r}_{dip}\ ^3} = \frac{\ \mathbf{d}\ \cos(\theta)}{4\pi\sigma \ \mathbf{r} - \mathbf{r}_{dip}\ ^2}$ <p>$\mathbf{J} = \vec{\mathbf{d}}$ dipole current, $\mathbf{J} = \sigma \mathbf{E} = \sigma(-\nabla V)$, ∇: gradient</p> $J\alpha \frac{1}{\ \hat{\mathbf{r}}\ ^3}, \hat{\mathbf{r}} = (\mathbf{r} - \mathbf{r}_{dip}), \text{in head volume } J \text{ attenuates with power 3 of distance to source}$	$\vec{\mathbf{d}} = W_j L' (L W_j^{-1} L' \alpha I)^{-1} EEG$
EPIFOCUS	$\mathbf{T} = \mathbf{L} * \mathbf{W} \quad \mathbf{L}$: leadfield matrix, $\mathbf{W} = \mathbf{B}, \mathbf{B} = \text{diag}(1 / \text{norm}(\text{columns}(\mathbf{L})))$ <p>Diag(...): diagonal matrix with non zero components in diagonal, each component is 1/norm of one column of \mathbf{L}</p> $\mathbf{G} = \begin{bmatrix} T_1^{\dagger} \\ T_2^{\dagger} \\ \dots \\ T_{np}^{\dagger} \end{bmatrix}, T_i^{\dagger} \text{: pseudo inverse of each three columns of } \mathbf{T}$ $T_1^{\dagger} = (T_1^T T_1)^{-1} T_1^T$ <p>The idea for dividing by norm: reducing the condition number. The idea behind this method is based on subspace reconstructions of a matrix</p>	$\vec{\mathbf{d}} = \mathbf{G} * EEG$

Inverse problem steps

(source estimation and localization steps at one sample time on EEG)

Source estimation:

$$\vec{d} = (L'L + \alpha W'W)^{-1} L' EEG$$

calculating the magnitude (modulus) of each source after

$$\text{estimation of } \vec{d}, \text{ Magnitude } (\vec{d}) = \sqrt{d_x^2 + d_y^2 + d_z^2}$$

Source detection (localization):

Comparing magnitudes and selecting sources locations with magnitudes more than a threshold

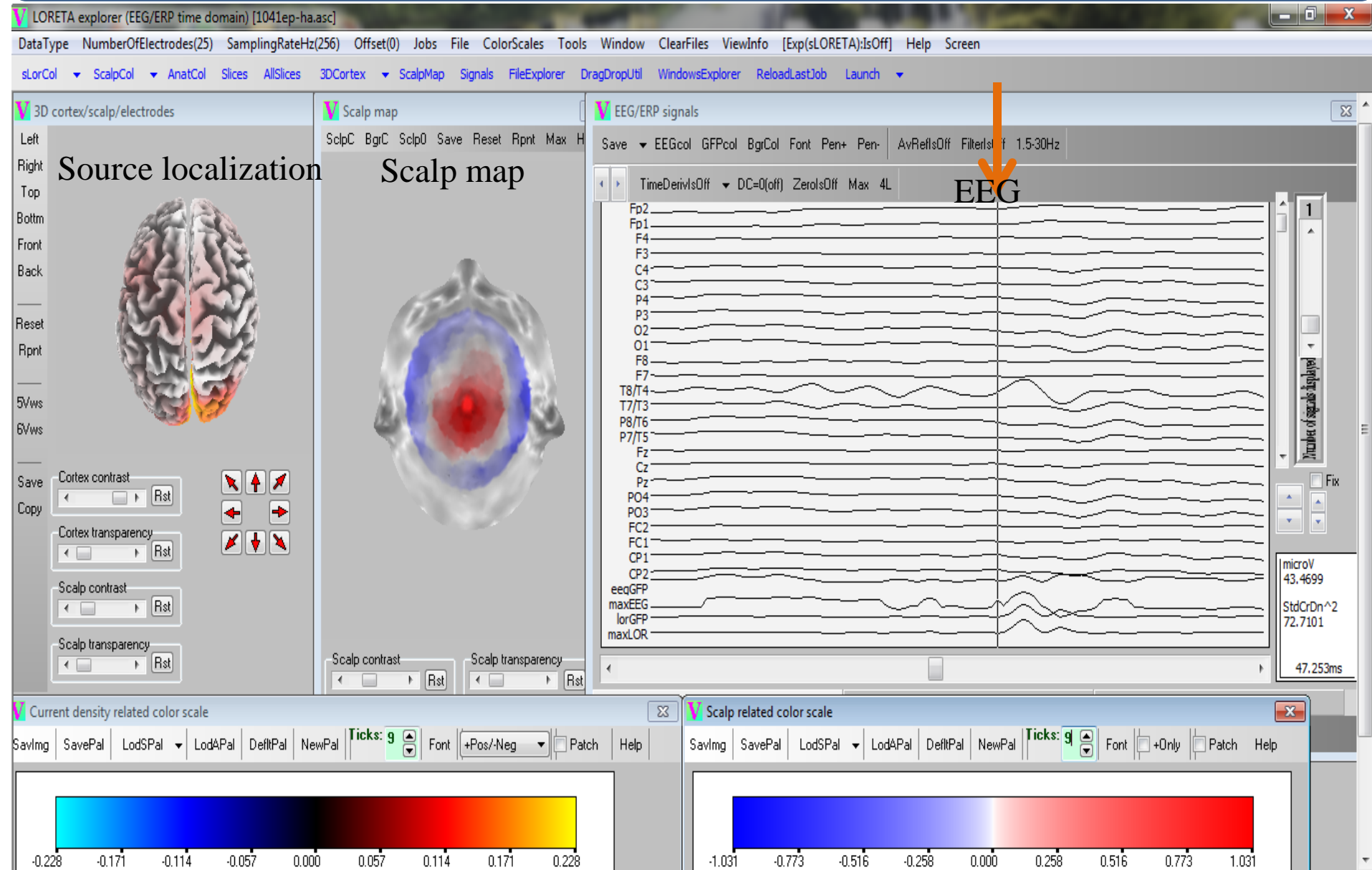


Distance Error:

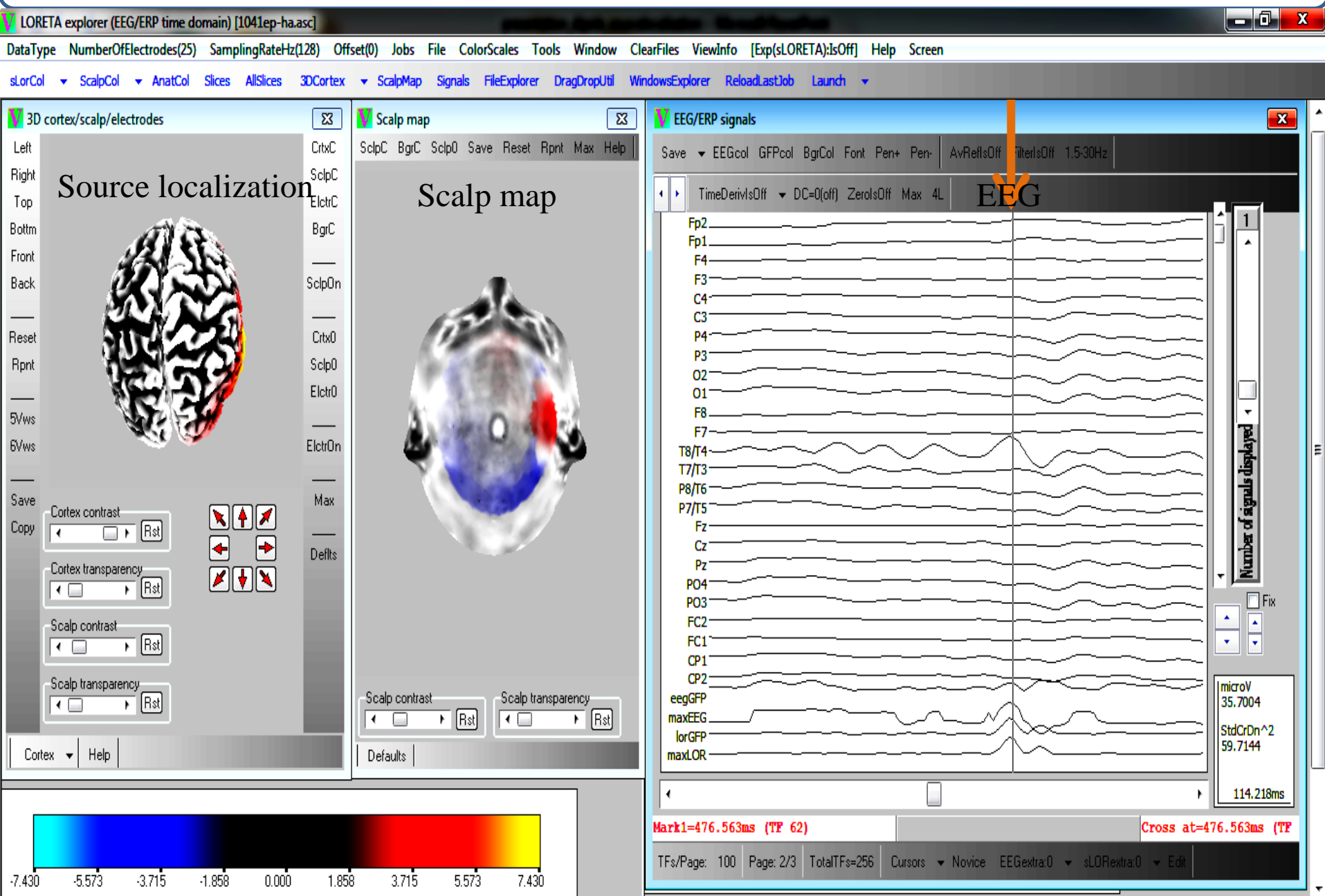
$$\vec{a} = \text{location}_{\text{detected source}} - \text{location}_{\text{real source}}, \text{ distance} = \sqrt{a_x^2 + a_y^2 + a_z^2}$$

1. For each real source location (from intracranial recordings) distance to all detected source locations (from inverse algorithm) is computed and the *minimum_distance* (nearest one) is selected.
2. *Average – Distance – Error* = Average of *minimum_distance* for all real sources
3. *Average – Distance Error – in grid – unit* = *Average – Distance – Error* / *gd*
 - Lower *Average – Distance – Error* is an evaluation number for accuracy of an inverse method
 - Real sources are often concentrated in a region in source grid with minimum grid distance *gd*(mm).
1. for each detected source location (from inverse algorithm), distance to all real source locations is computed and the *minimum_distance* is selected for each detected source.
2. Percentage of detected sources located with *minimum_distance* to real source region in the range [0 1) grid-unit(*gd*(mm)), [1 2) grid-unit (*gd*(mm)),... is an other evaluation parameter for accuracy of an inverse method. Higher percent in [0 1) grid-uni shows more accurate source localization.

Inverse problem (LORETA source localization)



Inverse problem (LORETA source localization)



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