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Dynamic Electrical Source Imaging (DESI) of Seizures and Interictal Epileptic Discharges Without Ensemble Averaging

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Abstract

We propose an algorithm for electrical source imaging of epileptic discharges that takes a data-driven approach to regularizing the dynamics of solutions. The method is based on linear system identification on short time segments, combined with a classical inverse solution approach. Whereas ensemble averaging of segments or epochs discards inter-segment variations by averaging across them, our approach explicitly models them. Indeed, it may even be possible to avoid the need for the time-consuming process of marking epochs containing discharges altogether. We demonstrate that this approach can produce both stable and accurate inverse solutions in experiments using simulated data and real data from epilepsy patients. In an illustrative example, we show that we are able to image propagation using this approach. We show that when applied to imaging seizure data, our approach reproducibly localized frequent seizure activity to within the margins of surgeries that led to patients' seizure freedom. The same approach could be used in the planning of epilepsy surgeries, as a way to localize potentially epileptogenic tissue that should be resected.

I. Introduction

Electrical source imaging (ESI) estimates the locations and magnitudes of electrical sources in the brain from noninvasive electroencephalographic (EEG) measurements by solving an inverse problem. In the context of epilepsy, a chronic neurological disorder marked by recurrent seizures, the goal of ESI is to identify the sources of abnormal electrical activity associated with seizures. This is particularly important for epilepsy surgical planning, since it has been shown that resection of epileptogenic foci localized by ESI may be a good predictor of seizure freedom after surgery [1]. However, conventional ESI methods are still limited in a number of ways that have prevented their more widespread adoption as a technology for guiding epilepsy surgeries.

The current state of the art in clinical ESI for epilepsy uses inverse solution methods on data that has been reviewed and manually processed by at least one expert. The purpose of the expert review of EEG recordings is to precisely identify ictal and interictal discharges (*i.e.*, those occurring during and between seizures, respectively). The expert marks epochs, which are segments of data that each contain a discharge, and aligns them so that the peak of each discharge occurs at the same time within each segment. The data that is supplied as input to conventional ESI methods is an “ensemble average” of these time-aligned epochs, which is a single, representative segment of data obtained by averaging data from corresponding

electrodes and time samples across epochs. One potential problem is that segments selected for analysis can be spread over several days of recording. Another potential problem is that a single, representative segment obtained by ensemble averaging may not be able to provide an adequate summary of the entire time course of discharges due to inter-epoch variability [2], which in turn may result in poor ESI of the sources at those time points. In this paper we propose a new ESI method, Dynamic Electrical Source Imaging (DESI), that may be able to overcome these limitations of conventional ESI by avoiding marking epochs containing individual discharges and ensemble averaging entirely.

DESI models recurrent patterns in EEG data as being generated by an autoregressive linear time-invariant (ARLTI) dynamical system over short time segments. Neural activity at both the cellular and whole brain levels is generally treated as nonlinear, but these nonlinear dynamics may also lie on a manifold [3], which can be modeled as locally linear in time or in space. Therefore, we hypothesize that the generation of epileptic discharges can be modeled by a linear dynamical system over short time segments (~50–100 ms). Moreover, this model may be better for approximating discharges than ensemble averaging them.

The ESI inverse problem is sensitive to noise in the data and an inappropriate model of the data can also lead to errors. Conventional ESI methods are typically applied to an ensemble average of epochs, averaging the signal to reduce noise, assuming it results in improved inverse solutions. However, actually improving the signal-to-noise ratio (SNR) depends on assumptions about what is signal and noise that may not always be valid. Ensemble averaging treats inter-epoch variations as noise and discards them, but in epilepsy they may contain relevant dynamic patterns [2], [4], and discarding them may affect the accuracy of ESI results. Other ESI approaches have modeled inter-epoch covariances statistically [5]. In contrast, the ARLTI model utilized by DESI accounts for signal generation within each epoch or short time segment, and therefore retains more variations across segments of the data (inter-segment variations) than ensemble averaging. We believe that these variations are important for ESI, and we hypothesize that DESI can be used to obtain stable and accurate inverse solutions without ensemble averaging.

By removing the need for ensemble averaging, one can apply an ESI method to data containing arbitrary seizure activity. While conventional ESI methods with ensemble averaging can sometimes be applied to seizure data that consist of rhythmic discharges, not all discharges are sufficiently stereotyped, and only early, sufficiently similar ictal segments can be selected for analysis. We note that ours is not the first ESI method that can be applied to ictal data without ensemble averaging, but previous approaches have generally operated under the assumption that the data contains rhythmic discharges [6] or rhythmic activity limited to a particular frequency band [7], [8] that can be used to separate signal from noise. In our approach, we divide seizure data into a sequence of consecutive, short time segments, and then apply DESI to the collection of segments. The segments do not need to contain rhythmic discharges or activity, since the ARLTI model in DESI accounts for inter-segment variations. Thus we hypothesize that DESI can estimate sources of ictal activity without these assumptions.

The rest of the paper is organized as follows: in Sec. II we present technical background, Sec. III is a description of the DESI method, experimental results are described in Sec. IV, with further discussion of the approach in Sec. V, and conclusions in Sec. VI.

II. Background

In this section we present the background for the method we propose in Sec. III. We first describe the ESI forward and inverse problems, and then describe the theory and methods for dynamical system identification that underpin our approach.

A. ESI Forward and Inverse Problems

The electrical source imaging forward problem models electromagnetic current propagation in the head. In this model, current is assumed to originate from discrete current sources located within cortical gray matter, and to be measured from electrodes at known locations on the surface of the head. A quasi-static approximation to Maxwell's equations results in a system of partial differential equations that can be solved numerically to obtain the ESI forward model [9],

$$y = Ax + \eta. \quad (1)$$

Here A is a matrix that maps a vector of source amplitudes, x , to a vector of potentials at electrodes, y , and η is independent and identically distributed (i.i.d.) noise to account for model errors.

In this paper, solutions to the forward problem were obtained using the approaches in [10] and [11]. Specifically, for every case, a volume conductor model of each patient's head was constructed from segmentations of co-registered T1-weighted, T2-weighted, and diffusion-weighted MRI, resampled to the 1mm isotropic resolution of the T1-weighted images. Each model consisted of 5 tissue types: four of them (skin, skull, cerebrospinal fluid (CSF), and gray matter) were assumed to have isotropic conductivities using values from [12], and the fifth tissue type (white matter) was assumed to have spatially-varying anisotropic conductivities derived from diffusion-weighted MRI using the approach described in [13]. Each volume conductor model was solved numerically using a finite differencing approach [14].

Given a forward model of the physics of current propagation in the head, the ESI inverse problem estimates the current sources responsible for actual electrode measurements. This inverse problem is ill-posed, having far fewer electrode measurements than sources to estimate, and therefore also having an infinite number of solutions that equivalently satisfy the forward model [9]. In addition, the actual electrode measurements contain noise, and the least squares solution to Eq. 1 results in unrealistic estimates of cortical activity unless regularized. A classical approach to this is Tikhonov regularization [15], which solves the following optimization problem:

$$\min_x \|y - Ax\|^2 + \lambda \|Rx\|^2, \quad (2)$$

where R is the regularization matrix and λ is a scalar regularization parameter. The minimizer of Eq. 2 is

$$x = (A^T A + \lambda R^T R)^{-1} A^T y. \quad (3)$$

Tikhonov regularization serves as the mathematical basis for several well-known ESI methods, such as low resolution electrical tomography (LORETA) and the minimum norm estimate (MNE) [16].

B. Dynamic Model and System Identification

We model the spatiotemporal dynamics of our data using a discrete-time autoregressive linear time-invariant dynamical system [17]. The general state space form for this model is,

$$s(t+1) = B s(t) \quad (4)$$

$$y(t) = C s(t) + \eta, \quad (5)$$

where t is the discrete time index, $s(t)$ is the state vector at time t , B is a matrix that determines the LTI evolution of the states, $y(t) \in \mathbb{R}^m$ is the vector of measurements, C is an observation matrix that maps from states to measurements, and η is a random noise variable that we assume to be independent and identically distributed (i.i.d.) over time. Eq. 4 is known as the *evolution equation* and Eq. 5 is the *observation equation*.

Estimating the model in Eqs. 4 and 5 from measured data is a well-studied problem known as *system identification* in the control theory literature [17]. The parameters to be estimated are the state space dimension, n , the state vectors, $s(t) \in \mathbb{R}^n$, and the evolution and observation matrices, B and C , respectively. Given n , the optimal solution to this problem is unique up to an invertible transformation [17]. That is, for an optimal set of parameters, $\{n, s(t), B, C\}$, another set of parameters that will generate $y(t)$ identically, $\{n, \tilde{s}(t), \tilde{B}, \tilde{C}\} = \{n, G s(t), G B G^{-1}, G^{-1} C\}$, can be obtained by applying any invertible, linear transformation, G . Parameterizations are equivalent in this sense, and we base the methods in our paper on the Ho-Kalman algorithm, which estimates one such set of ARLTI system parameters [17].

III. Method: Dynamic Electrical Source Imaging

In this section we describe the proposed Dynamic Electrical Source Imaging method. We begin with the dynamic model used by DESI. Then we describe the two steps of the

algorithm: estimating a dynamic model for the measured data, and estimating the electrical sources as observations of this model.

A. Dynamic Model of Electrical Sources and Measurements

The dynamic model used by DESI is based on Eqs. 4 and 5, but includes an additional observation equation. The state space equations for this dynamic model are:

$$s(t+1)=Bs(t) \quad (4)$$

$$y(t)=Cs(t)+\eta \quad (5)$$

$$x(t)=Ds(t)+\gamma. \quad (6)$$

Here η and γ are assumed to be i.i.d. random noise. Eq. 4 describes the evolution of abstract states, $s(t)$, that are not directly related to physical quantities by themselves. However, when they are coupled together, Eq. 5 describes the generation of electrode measurements, $y(t)$, and Eq. 6 describes the generation of source activity in the brain. We refer to C and D as the *electrode observation matrix* and *source observation matrix*, respectively.

An important property of this model is time-invariance, *i.e.*, that the evolution matrix, B , does not change over time. The temporal evolution is deterministic and entirely determined by this matrix, which means that all of the time-varying variables of the system (*i.e.*, $s(t)$, $x(t)$, and $y(t)$) can be generated from an initial state vector, $s(t_1)$. In this paper, we relax this restrictive assumption so that every short time segment can be generated from its own initial state vector. Specifically, it is assumed that every segment shares the same evolution rule and B matrix, but that the model resets to a new initial state at the beginning of each time segment. The resulting ARLTI model is appropriate for modeling segments such as epochs containing marked interictal discharges (~50–100ms each), because the data recorded between discharges is not of interest. It can also be used for modeling a long segment of contiguous data with transient dynamics, such as a seizure, by dividing it into a sequence of short time segments (~50ms each).

Using this dynamic model, DESI estimates source amplitudes from electrode measurements using a two-stage estimation procedure. The diagram in Fig. 1 provides an overview of the flow of the algorithm. It follows from Sec. II-B that the estimation of $s(t)$, B , and C does not depend on Eq. 6, and only depends on Eqs. 4 and 5. We describe how to estimate these variables from time segments with a modified Ho-Kalman algorithm in Sec. III-B. In addition, using Eqs. 5 and 6 together with the forward model, $y(t) = Ax(t) + \eta$, results in the approximate relationship $C \approx AD$. This is an approximate relationship rather than exact one because of the noise variables in Eqs. 1, 5, and 6. In Sec. III-C, we describe how we obtain

an estimate of D given A and C . Finally, given estimates of D and $s(t)$, we can estimate $x(t) = Ds(t)$.

B. Estimating ARLTI System Parameters from Time Segments

In the first stage of the DESI algorithm, we estimate the unknown parameters of Eqs. 4 and 5 using a modified Ho-Kalman realization algorithm. The inputs are segments of $y(t)$, the ARLTI model order, n , and the number of delay samples, d . The outputs are estimates of $s(t)$, B , and C . Here we provide the steps of the algorithm, including an optional subsampling step that we use when the number of time samples is large.

Let there be M segments of time, $\mathcal{E}_j, j = 1, \dots, M$, from $y(t)$, with a set of N_j time indices in each segment, $\mathcal{E}_j = \{t_1^j, \dots, t_{N_j}^j\}$. Then our modified Ho-Kalman algorithm proceeds as follows.

1) Construct a block Hankel matrix from the input time segments—For each segment, $\mathcal{E}_j, j = 1, \dots, M$, we construct a Hankel matrix of the form:

$$\mathcal{H}_j = \begin{bmatrix} y(t_1^j) & \cdots & y(t_{N_j}^j - d + 1) \\ \vdots & \ddots & \vdots \\ y(t_d^j) & \cdots & y(t_{N_j}^j) \end{bmatrix}. \quad (7)$$

Then we combine them by appending the columns of the resulting matrices into one matrix, $\mathcal{H}_y = [\mathcal{H}_1, \dots, \mathcal{H}_M]$. We note the dependence of the shape and structure of this matrix on the delay samples, d .

2) Compute the singular value decomposition of the block Hankel matrix

(optionally with random subsampling)—The size of $\mathcal{H}_y$ is $md \times \sum_{j=1}^M (N_j - d + 1)$. When this matrix is small, its singular value decomposition (SVD), $\mathcal{H}_y = U\Sigma V'$, can be computed using any available numerical package. For large matrices, a number of strategies exist for estimating an approximate SVD. Our approach has been to employ a random subsampling approach, which is described next.

Optional Random Subsampling: Only the left singular vectors, in the columns of the matrix U , from the SVD are used in the remaining steps of the algorithm. An estimate of U can be obtained by subsampling the columns of $\mathcal{H}_y$ and then computing the SVD of the subsampled matrix instead. To do this, one must specify the number of subsamples as well as a strategy for selecting the subsamples. We choose subsamples randomly, noting that different sets of subsamples could produce different estimates of U . We refer to each such estimate produced by the algorithm as a single *trial*. When the linearity and time-invariance assumptions of the ARLTI model are appropriate, variations across trials are expected to be small. Large variations across trials indicate that model assumptions may be invalid.

3) Extract C from U —The estimated observation matrix, C , is a submatrix of the left singular vector matrix, U . Specifically, we extract C as the $m \times n$ submatrix from the top-left corner of U .

4) Solve for B using U —Let F be the $m \times n$ submatrix in the bottom-left corner of U . Then let P be the submatrix remaining between the C and F submatrices of U , such that the first n columns of U can be written in block matrix form as $[C^T P^T F^T]^T$. Then the matrix B can be obtained as the least squares solution to the equation:

$$\begin{bmatrix} C \\ P \end{bmatrix} B = \begin{bmatrix} P \\ F \end{bmatrix}.$$

5) Estimate the initial conditions for each segment—Given B and C , the ARLTI approximation for each segment, $\mathcal{E}_j$, $j = 1, \dots, M$, of $y(t)$ is:

$$\begin{bmatrix} y(t_1^j) \\ y(t_2^j) \\ \vdots \\ y(t_{N_j}^j) \end{bmatrix} = \begin{bmatrix} CB^0 \\ CB^1 \\ \vdots \\ CB^{N_j-1} \end{bmatrix} s(t_1^j).$$

The initial conditions for each segment, $s(t_1^j)$, can be estimated as the least squares solution to that equation.

6) Propagate the initial conditions to the other states within each segment—We use the evolution equation (Eq. 4) to propagate the initial conditions to the other states,

$$s(t_2^j) = B s(t_1^j),$$

$$\begin{aligned} s(t_3^j) &= B s(t_2^j), \\ &\vdots \\ s(t_{N_j}^j) &= B s(t_{N_j-1}^j), \end{aligned}$$

which concludes the modified Ho-Kalman algorithm.

C. Estimating the Source Observation Matrix and Amplitudes

Given estimates of the parameters $s(t)$ and C from Sec. III-B, the second stage of the algorithm estimates D and $x(t)$ from Eq. 6. We use Tikhonov regularization (Eq. 2) to estimate D from C , and then compute $x(t) = D s(t)$ to estimate the source parameters. Our approach relies on a number of modifications to the classical Tikhonov framework, which we describe below.

We substitute the observation equations from our dynamic model (Eqs. 5 and 6) into the Tikhonov framework in Eq. 2 to obtain the optimization problem:

$$\min_D \sum_t \|Cs(t) - ADs(t)\|^2 + \lambda \|RDS(t)\|^2. \quad (8)$$

Let $S_j = [s(t_1^j), \dots, s(t_{N_j}^j)]$ be a matrix with the states from segment j in its columns, and $S = [S_1, \dots, S_M]$ be a matrix of size $n \times T$ with the states from all M segments in its columns. Then Eq. 8 is equivalent to

$$\min_D \|(C - AD)S\|_{\text{Frobenius}}^2 + \lambda \|RDS\|_{\text{Frobenius}}^2, \quad (9)$$

which can be further simplified to

$$\min_D \left\| \begin{pmatrix} C \\ 0 \end{pmatrix} - \begin{pmatrix} A \\ \sqrt{\lambda}R \end{pmatrix} D \right\|_{\text{Frobenius}}^2 S. \quad (10)$$

The minimizer of Eq. 10 is:

$$D = (A^T A + \lambda R^T R)^{-1} A^T C. \quad (11)$$

Note that although D does not depend on S , the selection of λ using the L-curve method does depend on S .

Specifically, the L-curve method selects λ based on a trade-off between minimizing the two criteria in the objective function of Eq. 9,

$$\varepsilon(\lambda) = \|(C - AD_\lambda)S\|_{\text{Frobenius}}^2 \quad (12)$$

$$\rho(\lambda) = \|RD_\lambda S\|_{\text{Frobenius}}^2, \quad (13)$$

where D_λ denotes the Tikhonov solution for a putative choice of λ . Thus the Tikhonov solution is first computed for a range of λ values, and then the $\varepsilon(\lambda)$ and $\rho(\lambda)$ criteria are computed. The details of the selection of λ can be found in [18]. We note, however, that the computation of $\varepsilon(\lambda)$ and $\rho(\lambda)$ may be inefficient in the forms of Eqs. 12 and 13 when S has a large number of columns (*i.e.*, when T is large). The same criteria can be expressed equivalently as,

$$\begin{aligned}\varepsilon(\lambda) &= \text{tr} \left((C - AD_\lambda)SS^T(C - AD_\lambda)^T \right) \\ &= \text{tr} \left((C - AD_\lambda)^T(C - AD_\lambda)SS^T \right) \quad (14)\end{aligned}$$

$$\begin{aligned}\rho(\lambda) &= \text{tr} \left((RD_\lambda)SS^T(RD_\lambda)^T \right) \\ &= \text{tr} \left((RD_\lambda)^T(RD_\lambda)SS^T \right), \quad (15)\end{aligned}$$

where $\text{tr}(\cdot)$ denotes the trace operator. Since SS^T is an $n \times n$ matrix that does not depend on λ , it can be precomputed and reused in the computation of $\varepsilon(\lambda)$ and $\rho(\lambda)$ for each λ . When $T \gg n$, it is more efficient to compute these criteria as Eqs. 14 and 15 instead of Eqs. 12 and 13.

IV. Experiments and Results

We performed experiments with both simulated and real data to test that: the generation of epileptic discharges can be approximated by an ARLTI model over short time segments; DESI can be used to obtain stable and accurate inverse solutions without ensemble averaging; DESI can be used to estimate sources of seizure activity. We describe these experiments and data in the following sections.

A. Approximation Accuracy and Inverse Solution Stability

DESI works by computing an ARLTI approximation of the EEG data over short time segments, and then computing an inverse solution based on that approximation. Thus we first tested whether the ARLTI model was suitable for approximating the dynamics of epileptic discharges. Then we additionally tested whether DESI was stable with respect to variations in this approximation.

For these experiments, we used EEG recorded at 1000 Hz from 128 electrodes on the scalp of a patient (Patient 1) who was being monitored for epileptic discharges. These recordings were reviewed by an expert neurologist, the fourth author, and several epochs containing interictal epileptic discharges were identified and marked for analysis. The scalp EEG dataset consisted of 433 epochs with 100 time samples in each. Epochs were aligned in time such that each had a spike with its peak amplitude at its center.

1) Approximation Accuracy Tests—The goal of this experiment was to test if discharges generated by sources in the brain, measured indirectly using scalp EEG, could be described accurately by an ARLTI model over short time segments. First, we tested the

dependence of the ARLTI approximation method described in Sec. III-B on its two input parameters: the number of delay samples and the model order. To test for sensitivity to random subsampling, we repeated each approximation over 100 trials, using 1000 subsamples in each trial. We then compared its performance to the ensemble average of the same epochs. Performance was measured using Pearson's correlation¹ between each data approximation and the data itself, which emphasizes similarities between their signal shapes. Pearson's correlation (hereafter referred to as simply "correlation") also avoids penalizing an approximation for having a different mean or magnitude from the original data, which are normal for an ensemble average and are not of concern in this context.

Fig. 2 shows example plots from one electrode of the EEG, with the measured signal from one epoch plotted as a solid black line. The ensemble average is plotted as a dotted black line surrounded by shaded gray area that shows the inter-epoch standard deviation about the ensemble mean at each time point. The ARLTI approximation is plotted as a dashed black line which is also surrounded by a shaded gray area, but this one shows the standard deviation across trials of random subsampling. The ARLTI approximation in this example more closely resembles the original signal than the ensemble average.

More generally, statistical analyses of the accuracy of each approach, summarized in Fig. 3, showed that the ARLTI model more closely approximated these EEG data in terms of correlation with the original signals. Each color corresponds to tests performed with a specific ARLTI model order, and shows how the correlation varies with the number of delay samples for that model order. Colored lines show the means over trials of random subsampling, and error bars show the standard deviations. The details of error bars can be seen more clearly in the magnified view of the colored lines. The correlation of the ensemble average with the data is plotted in the regular view as a dashed line. We note that this line is horizontal and does not have error bars because it is a constant value that does not depend on delay samples and trials. These results show that the ARLTI approximation can be more accurate than the ensemble average for a wide range of model orders and numbers of delay samples.

2) Inverse Solution Stability Tests—Ill-posed inverse problems can be highly sensitive to small perturbations in the data. Since DESI is essentially an inverse solution performed on an ARLTI approximation of the data, the goal of this experiment was to empirically test if DESI was sensitive to approximation variations induced by changing parameters and random subsampling.

These experiments were performed using the same scalp EEG data that were used for the previous approximation accuracy tests. In the first step of the DESI algorithm, the ARLTI

¹Pearson's correlation between two vectors, y_1 and y_2 , can be computed as

$$\rho(y_1, y_2) = (y_1 - \mu(y_1))^T (y_2 - \mu(y_2)) / (\sigma(y_1)\sigma(y_2)),$$

where $\mu(\cdot)$ and $\sigma(\cdot)$ denote the mean and standard deviation over all elements, respectively. When applying this to multivariate time series, we first create a vector from each input that combines spatial and temporal indices.

approximation was computed for a range of model orders and numbers of delay samples, and each approximation was recomputed with 100 trials of random subsampling. The second step of the algorithm, as described in Sec. III-C, was applied to each resulting approximation. An arbitrary solution was selected from the set of trials with model order of 50 and number of delay samples of 40, and used as a reference for comparison to other solutions in terms of correlation.

Fig. 4 summarizes the results of this experiment, with (a) showing the mean correlation over trials as a function of model order and number of delay samples, and (b) showing the standard deviation. In each of (a) and (b), the location of the black dot represents the parameters that were used for the arbitrarily-chosen reference solution. The other solutions were highly correlated with this reference solution, and the correlations did not vary greatly due to performing random subsampling. Therefore in this experiment, we found that the inverse solutions were very stable with respect to the induced variations.

B. Inverse Solution Accuracy in Simulation Experiments

In this experiment, we tested DESI on simulated data, so that ground truth was available for evaluating accuracy. We also computed inverse solutions with a standard approach, LORETA, to provide a performance baseline for comparisons. Two different types of LORETA solutions were computed: with and without ensemble averaging of epochs. The experiments were repeated under a number of conditions that were made to be progressively more challenging, and were also designed to violate some of the model assumptions made by LORETA with ensemble averaging and DESI.

Source activity was simulated with the sinusoids shown in Fig. 5(a). Sources in cortical gray matter were divided into 1000 parcels (see Fig. 5(b) for a visualization of parcels in an example axial slice), and in each test the sources in either 1, 2, or 3 parcels, which were randomly chosen, were activated simultaneously with these sinusoids. Specifically, source signal 1 from Fig. 5(a) was used in every test, signals 1 and 2 were used when two parcels were active, and signals 1, 2, and 3 were used when three parcels were active. For every test, 120 epochs with 50 time samples each were generated using this approach. In some tests, inter-epoch variability was introduced by randomly phase shifting the signal in each epoch and each parcel independently. Scalp EEG data was simulated from these simulated sources using the forward solution, and adding an average of 5dB Gaussian noise. The resulting epochs were supplied as input segments to DESI. The model order for DESI was 50, the number of delay samples was 40, and 1000 random subsamples were used in each trial. LORETA solutions were computed without ensemble averaging (*i.e.*, on all time points), and, separately, LORETA solutions were computed on the ensemble average of the epochs.

We divided the test conditions into four sets: 1 active parcel and no phase shifts across epochs, 1 active parcel and random phase shifts for each epoch, 2 active parcels and random phase shifts for each epoch and parcel, and 3 active parcels and random phase shifts for each epoch and parcel. None of these test conditions violated the assumptions made by LORETA, but some did violate the model assumptions of DESI and LORETA with ensemble averaging. Having 1 active parcel and no shifts satisfies all of their model assumptions. Having 1, 2, or 3 active parcels with random phase shifts violates the assumptions of

LORETA with ensemble averaging, because the phase shifts introduce inter-epoch variations. Having 1 active parcel with random phase shifts satisfies the assumptions of DESI, because it can still be described by an ARLTI model over short time segments. However, having 2 or 3 active parcels with random phase shifts for each epoch and parcel violates the assumptions of DESI, because this causes the actual ARLTI model order to be much greater than our assumed model order of 50. Tests with each of these four conditions were repeated 1000 times, choosing different parcel locations each time.

Inverse solution accuracy was measured using two criteria: correlation between only the active sources in the ground truth and the inverse estimates of the same sources, and the norm of the difference between normalized distributions,

$$d(x_1, x_2) = \left\| \frac{x_1}{\max|x_1|} - \frac{x_2}{\max|x_2|} \right\|_2,$$

referred to hereafter as the normalized difference between the estimated and ground truth source activity. Whereas correlation was only calculated for the signals in the true active parcels, normalized difference took into account all signals in all parcels. Thus normalized difference was used to more strongly penalize for errors in the locations and spatial extents of active source distributions.

Fig. 5(c) is a scatter plot that summarizes the correlation and normalized difference results from these tests under all of the conditions that were used. Black points mark DESI results, red circles mark LORETA results, and green crosses mark LORETA with ensemble averaging results. Both types of LORETA results had high normalized difference values and a wide range of high and low correlations. The DESI results generally had lower normalized difference values, and had correlations that were higher than both types of LORETA results. This plot shows that DESI has a better overall combination of the two criteria than LORETA and LORETA with ensemble averaging. The tables of correlations in Fig. 5(d) and normalized differences in Fig. 5(e) show how DESI compares the performance of these methods with the same criteria for matching experimental conditions. We report the means and standard deviations of the criteria over these tests (as mean $\pm$ standard deviation).

Comparisons under matching experimental conditions showed that DESI outperformed both LORETA and LORETA with ensemble averaging in terms of both of these criteria. When only 1 parcel was active and no phase shifts were used, LORETA (both with and without ensemble averaging) often estimated either strongly correlated or anti-correlated signals in the true active parcels. When random phase shifts were introduced, the correlation values of LORETA with ensemble averaging got drastically worse, and then continued to get progressively worse as the number of active parcels increased from 1 to 2, and then 3. As the introduction of phase shifts does not violate the model assumptions of LORETA, its correlation values did not drop off as drastically, but they also got progressively worse as conditions became more challenging. As the model assumptions of DESI were not violated with 1 active parcel, whether with or without random phase shifts, its correlation values under these conditions were high and, unlike LORETA solutions, were remarkably consistent, as evidenced by the low standard deviations. When the model assumptions of

DESI were violated by using 2 or 3 active parcels and random phase shifts, its correlation values did get progressively worse but remained relatively high with relatively low standard deviations, as compared with either of the LORETA approaches. We tested this statistically using a two-tailed t-test comparing DESI ($N = 1000$) and LORETA ($N = 1000$), and DESI ($N = 1000$) and LORETA with ensemble averaging ($N = 1000$) for each of the conditions corresponding to the columns of Fig. 5(d) and (e). We found that DESI had greater correlation values than LORETA with ensemble averaging ($p < 0.0001$) and LORETA ($p < 0.0001$). We also found that DESI had lesser normalized difference values than LORETA with ensemble averaging ($p < 0.0001$) and LORETA ($p < 0.0001$). This suggests that DESI was better able to cope with violated model assumptions than LORETA with ensemble averaging, and that it generally did a better job of estimating the source signals in the true active parcels than both LORETA and LORETA with ensemble averaging. Moreover, the consistently large discrepancy between their normalized difference values over all conditions shows that DESI is better able to estimate the spatial locations and distributions of the active parcels than both LORETA and LORETA with ensemble averaging.

Finally, since DESI treats the epochs from this experiment as arbitrary input segments, one could also interpret its performance under these conditions as a test of how it handles segments from contiguous data that have varying rhythmic properties. For example, the segments with 1 active parcel and no phase shifts can be interpreted as coming from contiguous data with ideally rhythmic activity, whereas the other conditions with random phase shifts for each parcel and segment can be interpreted as disrupting that rhythmic activity, with the degree of disruption being proportional to the number of active parcels. Its performance across these conditions shows that DESI can be used to image rhythmic data as well as non-rhythmic data of varying degrees of complexity.

C. DESI Localization of Seizure Activity in Real Patient Data

For this experiment, we used DESI to estimate source distributions during arbitrary stages of seizures in three patients (Patients 2–4) who underwent surgical resection of their suspected epileptogenic zones. Two of these patients (Patients 3 and 4) were rendered completely seizure-free as a result of their surgeries, and these cases were confirmed as Engel Class 1a outcomes at least one year after their surgeries. For one of these patients (Patient 2), surgery was unsuccessful in stopping their seizures, and in this case we analyzed EEG from seizures that were acquired after their surgery. For Patients 3 and 4, we analyzed EEG data of seizures acquired prior to their successful surgeries. First we illustrate how DESI of seizures works on data from Patient 2, and then present results of the same technique applied to data from Patients 3 and 4.

1) Illustrative example—Patient 2 had seizures with left-sided onsets and a suspected epileptogenic zone in the anterior left temporal lobe, which was resected surgically (see Fig. 7 for a visualization). He continued to report having seizures after surgery. Subsequently, the patient was referred to Boston Children's Hospital and several seizures were successfully recorded while undergoing routine clinical video and EEG monitoring for epilepsy. EEG was recorded following the International 10–20 system of electrode placement, with additional electrodes (FT9, TP9, FT10, TP10) to provide better temporal lobe coverage.

After removing bad electrodes, the remaining EEG data had 21 electrodes (see Fig. 6 for electrode labels). Some of these seizures had a long sequence of discharges in the ictal build-up that preceded clinical onset. EEG data from one such sequence lasting 312 seconds is shown in Fig. 6, with an example discharge highlighted and shown magnified on the right side of the figure. These are considered generalized discharges, because they propagate rapidly to nearly all of the electrodes on the scalp, and their spatial origin could not be localized by analyzing EEG data alone. The spectrograms above the EEG data in Fig. 6 show that these discharges did not occur at regular intervals and cannot be isolated to a narrow frequency band. However, these discharges were clearly identifiable, and thus were marked and time-aligned to produce epochs which were then used to compute an ensemble average (see Fig. 7(b)).

LORETA solutions were computed on the ensemble average as well as on the original time series (referred to as “LORETA with ensemble averaging” and “LORETA”, respectively). DESI solutions were computed using the entire set of EEG data shown in Fig. 6 (312 seconds, sampled at 1000 Hz) by dividing the contiguous data into a sequence of segments that were each 50 time samples in length, and then performing the steps of the algorithm described in Secs. III-B and III-C on those segments. As before, the number of delay samples was 40, and the model order was 50. Fig. 7 compares DESI and LORETA solutions at matching time points for an individual discharge (the same one that was highlighted and magnified in Fig. 6), and also shows the results of LORETA with ensemble averaging of all discharges. DESI (Fig. 7(c)–(f)) and LORETA (Fig. 7(g)–(j)) both localized early activity to the same region, adjacent to the resected region of the temporal lobe. A possible reason for this could be that the region was epileptogenic prior to surgery but was not resected, or it may have become epileptogenic after the surgery. LORETA with ensemble averaging localizes early activity to a more mesial region on the inferior surface of the brain.

DESI estimated that activations propagated from an initial region to a broader region over the course of the discharge, which is consistent with its characterization as a generalized discharge. DESI does not impose a spatial propagation model, so the propagation seen in these results occurs because this sequence of spatial patterns was found to be coupled to the dynamics identified in the data. In contrast, LORETA and LORETA with ensemble averaging estimated that the spatial patterns underlying the data did not vary much over the course of the discharge, instead changing mostly in amplitude. Although all three solutions originate from the same location, the DESI solution is the only one that propagates to the spatial extent that is expected for a generalized discharge.

In order to provide a summary of recurrent propagations in DESI solutions, we computed a cumulative activity

$$\mathcal{X} = \sum_{t=1}^T \frac{|x(t)|}{\max_t |x(t)|}, \quad (16)$$

over all 312 seconds of DESI solutions. The summation is over normalized spatial maps in order to weight low-amplitude spatial patterns that appeared earlier during propagation

equally with the higher-amplitude patterns that appeared later during propagation. The cumulative activity map for Patient 2's discharges is shown in Fig. 8. This map shows that the region that was most frequently active over the whole time course was the same region as the one identified at the beginning of the example discharge in Fig. 7(c)–(f).

2) Comparisons with surgical margins that have led to seizure freedom—Two additional patients with focal cortical epilepsy (Patients 3 and 4) were analyzed using this approach. Each one was monitored with clinical EEG prior to surgery, during which they had four seizures each. EEG was recorded at 1000 Hz from electrodes placed according to the International 10–20 system, with additional electrodes to provide better temporal lobe coverage. After removing bad electrodes, Patient 3 had EEG recorded with 19 electrodes, and Patient 4 had EEG recorded with 31 electrodes. All of the seizures were different durations and were analyzed independently from each other. After these seizures were recorded, they subsequently underwent surgeries in which their suspected epileptogenic tissue was resected. Both of these surgeries resulted in seizure freedom, confirmed as Engel Class 1a outcomes after at least one year post-surgery. We compared the cumulative activity maps computed from the DESI solutions for each of these seizures with their surgical resection margins.

DESI was applied independently to data from each seizure. In each case, however, DESI was applied to a single segment of data from before, during, and after a seizure, and thus the dynamics of these stages were modeled together. Patient 3's four segments of data were 695 seconds, 106 seconds, 797 seconds, and 181 seconds long. Patient 4's four segments of data were 59 seconds, 74 seconds, 68 seconds, and 83 seconds long. Each longer segment of data was divided into shorter, consecutive segments of 50 time samples each and supplied to DESI as input. DESI solutions were computed using a model order of 50, and 40 delay samples. Cumulative activity maps were computed over all time samples using Eq. 16. These are shown in Fig. 9(a)–(d) for Patient 3, and Fig. 10(a)–(d) for Patient 4.

Both patients had previous surgeries that had failed to stop their seizures before undergoing their most recent, successful surgeries. The red volume visualized in Fig. 9(e) shows the tissue that was resected from the right temporal lobe of Patient 3 in the most recent surgery. The parts of the right temporal lobe missing in this visualization were resected during the previous surgery. Similarly, the dotted line in Fig. 10 shows the margins of the most recent left temporal lobe resection, and the solid white line shows the adjacent region that was resected during the previous surgery.

The cumulative activity maps for these seizures showed good agreement with the margins of the surgical resections that led to seizure freedom. For Patient 3, the three maps in Fig. 9(a)–(c) show that the most frequent activity estimated by DESI for these seizures was located in the anterior tip of the right temporal lobe that was resected. The fourth map, Fig. 9(d), had a region of frequent activity in the frontal lobe that was not resected, but also had frequent activity in the same region of the right temporal lobe. For Patient 4, all four of the maps in Fig. 10(a)–(d) showed that the most frequent activity estimated by DESI for these seizures was in the anterior tip of the left temporal lobe that was resected. In both cases, DESI was consistently able to localize frequent activity to within the resection margins. Thus DESI is

able to estimate source activity during seizures, and recurring patterns in these can be seen in cumulative activity maps that localize frequent activity to epileptogenic regions.

V. Discussion

The results presented in the previous section suggest that DESI compares favorably to applying LORETA with and without ensemble averaging. The advantage of DESI over these LORETA approaches is that it uses a dynamic model to improve its stability and accuracy. There is a class of previous dynamic source localization techniques based on data matrix decompositions, such as principal component analysis (PCA) [19] and independent component analysis (ICA) [20], [21], which assume the *independence* (geometrical and statistical, respectively) of a small number of discrete sources in the brain. On the contrary, here we describe a distributed source solution technique that seeks to model the *dependencies* between sources as a dynamical system. Along these lines, more recent methods, such as Champagne and Aquavit [22], [23], have sought to model the spatial and temporal statistical dependencies between sources using a hierarchical Bayesian approach. However, Champagne also assumes that sources at different spatial locations are statistically independent over time. Aquavit extends Champagne by allowing some source dependencies, and does so by regularizing the spatial and temporal subspaces of source patterns. The method we presented here can also be interpreted as a decomposition into spatial and temporal subspaces, but the spatial dependencies of temporal behaviors are required to obey a dynamic evolution rule, and this rule is directly estimated from the measured data.

In our approach, we modeled the deterministic dynamic evolution of the recorded data as autoregressive, linear, and time-invariant. Cheung *et al.* also described an approach based on modeling the sources as a linear dynamical system [24]. Their approach differs from ours due to practical model order restrictions arising from the structure imposed on their state evolution matrix, and because their dynamic evolution rule was assumed to be driven by input from a random variable. Our approach begins with the most general state space representation for our deterministic system model, and then imposes *data-driven* constraints on the state evolution matrix by restricting the dynamics to a subspace identified using dimensionality reduction. Cheung *et al.* proposed an expectation-maximization algorithm for maximum likelihood estimation of dynamic model parameters [24]. Instead, we first fit the model parameters of the dynamical system, and then we subsequently estimate the mapping that relates these model parameters to electrical source distributions as a second step.

In contrast to our approach and the one taken by Cheung *et al.* [24], there are also methods that use Kalman filtering to estimate the states and/or electrical source distributions. These methods differ from ours because they assume that the dynamic model parameters are known *a priori* and that only the system's states are unknowns that must be estimated. For example, a recent method by Lamus *et al.* [25] assumes that the dynamics obey a similar linear dynamic model to the one proposed by Cheung *et al.* [24], but they further restrict the solution by specifying its parameters *a priori*. While this type of regularization may be suitable for some applications, the dynamics of the brain are still an on-going topic of research in healthy subjects, which means that the specification of these parameters is an open question even under these circumstances. In order to study seizures in epilepsy, we

have developed a method that estimates (rather than imposes) the dynamic evolution of electrical source distributions.

A potential limitation of DESI is that it uses a linear dynamic evolution rule to model signal generation within each time segment, and this may not provide enough degrees of freedom for adequately describing highly nonlinear EEG. This approach also may not be as useful for conditions outside of epilepsy, and we would need to perform additional tests to determine its suitability.

VI. Conclusions

In this paper we proposed an electrical source imaging method that identifies a dynamical system from EEG data and then uses those dynamics to estimate the source activity underlying seizures and interictal epileptic discharges. The method does not rely on marking individual discharges, and does not rely on averaging them. In our results, we showed that DESI produces both stable and accurate inverse solutions. We showed that DESI of seizures could reproducibly localize frequent seizure activity to within the margins of surgeries that led to patients' seizure freedom. DESI could provide useful new information for epilepsy surgery planning, because localization of activity from before and during the ictal period could help identify the seizure onset zone to be targeted for resection. In future work we will assess the impact that dynamic ESI approaches can have on clinical practice. We will also consider nonlinear dynamical systems that may be able to provide a more parsimonious approximation to epileptic EEG data. We will also compare our approach to those based on phase synchrony [26], and test our localization accuracy with realistic simulations of source activity [27].

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Fig. 1.

Overview of DESI algorithm: The original data are divided into short time segments, such as the example epochs shown here (blue, red, green, black, and magenta), and then an ARLTI dynamical system over short time segments is estimated using a modified Ho-Kalman algorithm, which produces state space trajectories for each segment. The electrode observation model generates the ARLTI approximation to the original data. The source observation matrix is estimated using Tikhonov regularization, and then it generates source amplitudes.

Fig. 2.

Patient 1: A visualization of inter-epoch variations of time-aligned discharges that are discarded by ensemble averaging, compared with variations induced by approximating with the proposed algorithm in Sec. III-B. We show the signal (solid black line) from one electrode during an example epoch containing a discharge, its ARLTI approximation by the proposed modified Ho-Kalman algorithm (dashed black line), and the ensemble average of this electrode over all epochs (dotted black line). The large shaded area around the dotted line shows the standard deviation about the ensemble average. The smaller shaded area around the dashed line shows the standard deviation over trials of the proposed algorithm.

Fig. 3. Patient 1: Summary plot of correlations between epochs of scalp EEG data containing interictal discharges and their approximations. Magnified views of the means (colored lines) and standard deviations (error bars) show that the correlation of the ARLTI approximation was robust to a wide range of parameter choices and random subsampling (100 trials per pair of parameter choices). These correlation values were also substantially higher than those of the ensemble average (horizontal dashed lines), which shows that a substantial amount of inter-epoch variations are discarded by ensemble averaging.

Fig. 4.

Patient 1: Stability of DESI over approximation variations induced by parameter variations and trials of random subsampling (100 trials per pair of parameter choices). Here we show the (a) means and (b) standard deviations of correlations of DESI solutions with a reference solution computed using parameter choices corresponding to the location of the black dot above (model order of 50, and number of delay samples of 40). High correlations and low standard deviations indicate that DESI inverse solutions are stable with respect to the induced approximation variations in the algorithm.

Fig. 5.

Summary of simulations with DESI, LORETA, and LORETA with ensemble averaging (En. Avg.). The source signals in (a) were applied to either 1, 2, or 3 parcels of cortex, visualized in (b), to generate epochs. Inter-epoch variations were simulated with random phase shifts for each epoch and each parcel. Source activity was estimated from simulated scalp EEG, and each estimate was compared to the ground truth in terms of correlation in the true active parcels, and the norm of the normalized difference between the entire estimate and the ground truth. Simulations for each set of test conditions (*i.e.*, 1–3 active parcels, with or

without phase shifts) were performed $N = 1000$ times. The scatter plot in (c) shows the combined correlation and normalized difference results for all test conditions. For each condition, we also reported (d) correlation and (e) normalized difference (table format: mean $\pm$ standard deviation). A two-tailed t-test determined DESI had a greater correlation than LORETA with ensemble averaging ($p < 0.0001$) and LORETA ($p < 0.0001$), and a lesser normalized difference than LORETA with ensemble averaging ($p < 0.0001$) and LORETA ($p < 0.0001$).

Fig. 6. Patient 2: Plots of scalp EEG from electrodes positioned and labeled according to the International 10–20 system and their corresponding spectrogram. Discharges do not occur at regular intervals and they cannot be isolated to a narrow frequency band. The entire time series was supplied as input to DESI and LORETA. We also ensemble averaged 65 epochs containing generalized discharges, and computed LORETA with ensemble averaging. An example epoch is shown shaded red and magnified. Its detailed DESI and LORETA results are shown and compared to LORETA with ensemble averaging results in Fig. 7.

Fig. 7.

Patient 2: Comparison of DESI and LORETA solutions of the same discharge, and LORETA on the ensemble average of epochs containing discharges. In the top right corner we show three orthogonal volumetric views of brain and the region of the left temporal lobe that was resected prior to EEG recordings. Butterfly plots of (a) the example epoch and (b) the ensemble average of epochs from Fig. 6 show the effects of ensemble averaging these generalized discharges. DESI solutions in (c)–(f), LORETA solutions in (g)–(j), and LORETA with ensemble averaging solutions in (k)–(n) show how the solutions differ in their temporal evolutions. The DESI solution shows propagation of activations originating from a patch of cortex adjacent to the previously resected region of the temporal lobe. The LORETA and LORETA with ensemble averaging solutions localize to similar regions of cortex, but they change very little over time, and do not spread to the spatial extent of activation that is consistent with a generalized discharge.

Fig. 8.

Patient 2: Cumulative activity map computed from DESI solutions for all time points shown in the plots in Fig. 6. This map shows that the DESI solution contained frequent activity in this patch of cortex. This may be due to activations consistently propagating from this initial area, which was shown for an example discharge in Fig. 7(c)–(f).

Fig. 9.

Patient 3: Cumulative activity maps (a)–(d) computed from DESI solutions of four different seizures recorded prior to epilepsy surgery. The margins of the subsequent surgical resection, which resulted in seizure freedom, are visualized as a red volume in (e). The first three seizures (a)–(c) were estimated to have their most frequent activity in the right temporal lobe within the margins of what was later resected. The fourth seizure (d) was also estimated to have frequent activity in the right temporal lobe, but additionally had a broad region of frequent activity in the mesial frontal lobe.

Fig. 10.

Patient 4: Cumulative activity maps (a)–(d) computed from DESI solutions of four different seizures recorded prior to their most recent epilepsy surgery. The colormap is the same as the one used in Fig. 9. The margins of this surgical resection, which resulted in seizure freedom, are visualized as dotted white lines superimposed on each map. The margins of the patient's previous unsuccessful surgery are similarly visualized but with solid white lines. All four seizures were estimated to have their most frequent activity in the remaining anterior tip of the left temporal lobe, within the margins of what was subsequently resected.