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(54) Title: SEIZURE DETECTION DEVICE AND SYSTEMS

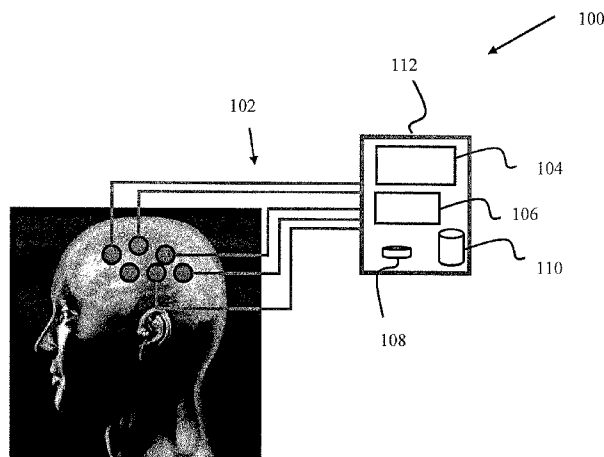


Figure 1

(57) Abstract: A neurostimulation device includes a plurality of electrodes adapted to be electrically connected to a subject to receive multichannel electrical signals from the subject's brain, a multichannel seizure detection unit electrically connected to the plurality of electrical leads to receive the multichannel electrical signals, and a neurostimulation unit in communication with the multichannel seizure detection unit. The plurality of electrodes are at least three electrodes such that the multichannel electrical signals are at least three channels of electrical signals, and the multichannel seizure detection unit detects a presence of a seizure based on multichannel statistics from the multichannel electrical signals including higher order combinations than two-channel combinations.



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SEIZURE DETECTION DEVICE AND SYSTEMS

CROSS-REFERENCE OF RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 61/430,270, filed January 6, 2011, and U.S. Provisional Application No. 61/508,392, filed July 15, 2011, the entire contents of which are hereby incorporated by reference.

BACKGROUND

1. Field of Invention

[0004] The field of the currently claimed embodiments of this invention relates to seizure detection devices and systems.

2. Discussion of Related Art

[0005] Epilepsy has a prevalence of about 1% in children and adults 1-8, and is characterized by chronically recurring seizures without clear precipitants 12. A seizure is a finite-time episode of disturbed cerebral function with abnormal, excessive, and synchronous electrical discharges in large groups of cortical neurons 9. Disturbances may be associated with debilitating phenomena (e.g., convulsions, low responsiveness, etc.) or remain clinically unapparent, have a duration ranging from seconds to minutes 33, and may be followed by post-ictal periods of confusion, psychosis, or sensory impairment which can last up to several hours 14-16. Epilepsy in children is associated with problems including academic achievement, behavioral and emotional adjustment, and social competence 3-5, and contributes to 0.5% of the global economic burden of diseases 12.

[0006] Despite a large variety of medications available to treat epilepsy [9]-[13], 25% of children (30% of adults) are drug-resistant. Furthermore, since medications are administered without any knowledge of an impending seizure, overtreatment is frequent and may lead to increased morbidity, psychosocial handicaps and mortality [1] [15][16].

Children are the most at risk for developing long-term morbidity, as poorly controlled seizures can affect long term cognitive development and function. Alternative treatments for drug-resistant patients include surgical resection of the epileptogenic zone [17][24] and neurostimulation [14]-[28]. Surgical resection is widely accepted but is not always possible and its success mostly depends on the correct localization of the epileptic focus [17] and the specific cortical area to be resected [24]. Chronic open- and closed-loop neurostimulation are still under clinical trials for adults, and although the results are encouraging [47][25], their therapeutic effectiveness critically depends on electrode placement, coverage, morphology of seizure, and most importantly seizure onset detection [14].

[0007] The accurate detection of seizure onsets from sequential iEEG (intracranial electroencephalography) measurements is fundamental for the development of both responsive neurostimulation and effective patient-warning devices. Several OSD (online seizure detection) algorithms have been proposed thus far [47]-[80] and though they are highly sensitive (large number of true positives), these algorithms generally have low specificity (large number of false positives), which limits their clinical use. NeuroPace Inc. has pioneered the development and testing of a closed-loop device, the RNS™ system, which automatically detects an approaching seizure by monitoring two iEEG channels and responds with high frequency periodic stimulation in drug-resistant epilepsy patients [30]. Despite promising results in small populations of patients after short-term follow ups (less than 2 years) [29][30], a recent long-term (5 years) study [31][32] has indicated that the device reduces the number of seizures by 50% in less than 30% of the patients (reduction computed vs. the baseline pre-treatment condition), which is about as effective as a new medication in patients with drug-resistant partial seizures. Although the detection algorithms can be tuned for seizures in a given patient, these simple algorithms lack specificity with many detections of inter-ictal activity that are not destined to evolve into electrical or clinical seizure activity. Since detections result in activation of closed-loop therapy, stimulations are frequently delivered when no seizure occurs. While no significant side effects of stimulation were observed in the RNS trial, increased stimulation frequency can dramatically reduce battery life (typically to 1-2 years [29]). In other studies, there are reports of possible consequences of repetitive stimulation including depression, memory impairment and confusion [49].

[0008] The lack of specificity of current OSD algorithms including the one implemented in the RNS™ system presumably occurs because (i) they compute statistics from 1-2 channels at a time that may not capture network dynamics of the brain, and/or (ii) the detection thresholds are not optimized to maximize OSD performance. By optimally detecting when a seizure occurs, specificity of detection would increase and non-specific closed-loop therapy would decrease.

[0009] Automatic online seizure detection (OSD) in intractable epilepsy has generated great interest in the last twenty years and is a fundamental step toward the development of anti-epileptic responsive neurostimulation [14]-[28]. Pioneering works in the late 1970s and 1980s by Gotman et al. [50][51] showed that seizures can be automatically separated from inter-ictal activity, and since then, several approaches to OSD have been proposed by exploiting either scalp or intracortical EEG recordings, single or multi-channel analysis, linear or nonlinear features.

[0010] Osorio et al. [52]-[55] used a wavelet-based decomposition of selected iEEG recordings to (i) separate the seizure-related component from the background noise, (ii) track the ratio between these components in the time-frequency domain, and (iii) detect a seizure when such a ratio crosses a fixed threshold for a sufficiently long time. Parameters of the detection method (e.g., threshold, duration of the supra-threshold condition, etc.) can be either fixed [52] or adaptive [53][54]. Fixed threshold-based approaches were also proposed in [56]-[58], where the threshold was applied to linear spectral features of the iEEG recordings.

[0011] Gotman et al. [59]-[61] proposed a probabilistic framework for seizure detection using scalp EEG [59][61] and iEEG [60] recordings. For each channel, amplitude and energy measures in multiple frequency bands are computed via wavelet decomposition and the corresponding probability distribution function is estimated. Then, the probability of a seizure is conditioned on the value of such measures and estimated via Bayes' rule. A patient-specific threshold is finally applied on this conditional probability of seizure to decide, for each channel, whether a seizure is likely, and a seizure is detected when that threshold is passed in a sufficient number of channels.

[0012] More recently, this paradigm has been implemented using sophisticated classification tools. In particular, iEEG channels have been processed individually to extract multiple univariate or bivariate features in the time, frequency domain or the wavelet [62]-[78] domain. Then, for each channel, the features have been combined into vectors and classified via support vector machines (SVMs) [67][69][72][75], principal components analysis (PCA) [73][74], artificial neural networks (ANNs) [62][64]-[66][70][76]-[78], fuzzy logics [68], or pattern recognition tools [63]. Finally, decisions made for different channels are combined or ranked to ultimately determine whether or not a seizure has occurred. As a variation to this paradigm, [72][79] merged features extracted from different channels into one vector and applied a classification rule on this vector.

[0013] In the current paradigm, OSD is solved by (i) computing a statistic from a few iEEG measurements at a time, and (ii) then constructing a threshold or classification rule that, based on this statistic, determines whether or not a seizure has occurred (Fig. 2A). The choice of the threshold is traditionally supervised and depends on the fluctuations of the statistic, the specific patient, or the electrode position, and requires long training sessions to be more accurate. Sophisticated classifiers generate unsupervised criteria that separate the feature space into dominant ictal and non-ictal regions but without penalties for specific performance goals (e.g. minimize false positives). All such thresholds trigger too many false alarms when applied to test data. Consequently, all efforts put towards improving OSD algorithms have been in either identifying better statistics with fancy signal processing and/or in implementing more sophisticated classifiers borrowed from the machine learning community. The fundamental problem with this paradigm is that detection performance is not measurable until after implementation (“algorithm defines performance”). There thus remains a need for improved seizure detection devices and systems.

SUMMARY

[0014] A neurostimulation device according to some embodiments of the current invention includes a plurality of electrodes adapted to be electrically connected to a subject to receive multichannel electrical signals from the subject’s brain, a multichannel seizure

detection unit electrically connected to the plurality of electrical leads to receive the multichannel electrical signals, and a neurostimulation unit in communication with the multichannel seizure detection unit. The plurality of electrodes are at least three electrodes such that the multichannel electrical signals are at least three channels of electrical signals, and the multichannel seizure detection unit detects a presence of a seizure based on multichannel statistics from the multichannel electrical signals including higher order combinations than two-channel combinations.

[0015] A multichannel seizure detection system according to some embodiments of the current invention includes a signal interface adapted to receive multichannel electrical signals from the subject's brain, and a data processor configured to receive the multichannel electrical signals and detect a presence of a seizure based on multichannel statistics from the multichannel electrical signals including higher order combinations than two-channel combinations. The multichannel electrical signals are at least three channels of electrical signals.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Further objectives and advantages will become apparent from a consideration of the description, drawings, and examples.

[0017] **Figure 1** is a schematic illustration of a neurostimulation device according to an embodiment of the current invention.

[0018] **Figures 2A and 2B** contrast conventional approaches (top) with an embodiment of the current invention (bottom: Multivariate QD approach to OSD).

[0019] **Figures 3A and 3B** illustrate some concepts of the current invention. (A) three-node network with loose connections under 2 measures (2 edges between each pair of nodes) and the corresponding non-square connectivity matrix A , singular values, $\sigma(A)$, and leading singular vector $u_1(A)$. (B) Nodes 1 and 2 of the network are strongly connected under both measures (thick edges). The first 2 singular values of the connectivity matrix B are

much larger than the 3rd one and the first 2 components of first singular vector $\mathbf{u}_1(\mathbf{E})$ are significantly larger in magnitude than the 3rd component.

[0020] **Figures 4A-4D** provide first singular values σ_i and correspondent vectors \mathbf{u}_i around an ictal period (gray background) in patient 1 (seizure s_1 , A), 2 (s_1 , B), 3 (s_3 , C), and 4 (s_3 , D). **Figure 4E** shows \mathbf{u}_i vs. time for patient 4. **Figure 4F** provides average \mathbf{u}_i of the first seizure projected onto subsequent seizures.

[0021] **Figure 5A** is a schematic illustration of a $m = 2$ state HMM according to an embodiment of the current invention. **Figure 5B** shows the sampling probability distribution function of the observations \mathbf{z}_k collected in state $x_k = 0$ (non-ictal) and $x_k = 1$ (ictal). Data collected from Patient 2 in the preliminary dataset. **Figure 5C** shows OSD formulated as a feedback control problem according to an embodiment of the current invention.

[0022] **Figure 6** shows history-dependent values of $q_0(\mathbf{z}_k|H_k)$ and $q_1(\mathbf{z}_k|H_k)$ at the onset of an annotated seizure (gray background).

[0023] **Figures 7A and 7B** provide QD on validation data according to an embodiment of the current invention. The electrographic onset (red line), the correspondent QD estimation (circles), and threshold F_k (green and blue lines for different values of parameter γ which trades off specificity/delay) for Patient 2 (A) and 4 (B). Plots for seizures s_3 in both patients. In bottom plots, horizontal dashed black line is threshold for the BE detector.

DETAILED DESCRIPTION

[0029] Some embodiments of the current invention are discussed in detail below. In describing embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. A person skilled in the relevant art will recognize that other equivalent components can be employed and other methods developed without departing from the broad concepts of the current invention. All references cited anywhere in this specification, including the Background and

Detailed Description sections, are incorporated by reference as if each had been individually incorporated.

[0030] The following defines various abbreviations and terms used throughout the description:

- iEEG: intracranial EEG is an invasive technique based on recording electroencephalography (EEG) signals directly from the human cortex, as opposed to surface recordings in scalp-EEG. This is achieved either by using subdural grids or strips of electrodes placed directly on the surface of the cortex (also known as Electrocorticography), or using multi-lead depth electrodes.
- ECoG: electrocorticography (see iEEG).
- OSD: online seizure detection. An algorithm that measures iEEG activity sequentially and estimates the onset times of each seizure.
- EMU: epilepsy monitoring unit
- ictal: ictal refers to a physiologic state or event, for example, a seizure.
- QD: quickest detection is a change point detection algorithm that minimizes detection delay and probability of false alarm.
- SVD: In linear algebra, the singular value decomposition (SVD) is a factorization of a real or complex matrix, with many useful applications in signal processing and statistics.
- HMM: hidden Markov model. A specific model where the states are unobservable but whose outputs are observable/measurable. It is a statistical Markov model in which the system being modeled is assumed to be a Markov process with unobserved (hidden) states. An HMM can be considered as the simplest dynamic Bayesian network. In a regular Markov model, the state is directly visible to the observer, and therefore the state transition probabilities are the only parameters. In a hidden

Markov model, the state is not directly visible, but output, dependent on the state, is visible. Each state has a probability distribution over the possible output tokens. Therefore the sequence of tokens generated by an HMM gives some information about the sequence of states. Note that the adjective 'hidden' refers to the state sequence through which the model passes, not to the parameters of the model; even if the model parameters are known exactly, the model is still 'hidden'.

- SVM: support vector machine. A support vector machine (SVM) is a concept in computer science for a set of related supervised learning methods that analyze data and recognize patterns, used for classification and regression analysis. The standard SVM takes a set of input data and predicts, for each given input, which of two possible classes comprises the input, making the SVM a non-probabilistic binary linear classifier. Given a set of training examples, each marked as belonging to one of two categories, an SVM training algorithm builds a model that assigns new examples into one category or the other. An SVM model is a representation of the examples as points in space, mapped so that the examples of the separate categories are divided by a clear gap that is as wide as possible. New examples are then mapped into that same space and predicted to belong to a category based on which side of the gap they fall on.
- PCA: Principal component analysis (PCA) is a mathematical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of uncorrelated variables called principal components. The number of principal components is less than or equal to the number of original variables. This transformation is defined in such a way that the first principal component has as high a variance as possible (that is, accounts for as much of the variability in the data as possible), and each succeeding component in turn has the highest variance possible under the constraint that it be orthogonal to (uncorrelated with) the preceding components.
- ANN: An artificial neural network, usually called neural network (NN), is a mathematical model or computational model that is inspired by the structure and/or

functional aspects of biological neural networks. A neural network consists of an interconnected group of artificial neurons, and it processes information using a connectionist approach to computation.

- **DP: Dynamic Programming:** In mathematics and computer science, “dynamic programming” is a method for solving complex problems by breaking them down into simpler subproblems. It is applicable to problems exhibiting the properties of overlapping subproblems which are only slightly smaller and optimal substructure. When applicable, the method takes far less time than naive methods. The key idea behind dynamic programming is quite simple. In general, to solve a given problem, we need to solve different parts of the problem (subproblems), then combine the solutions of the subproblems to reach an overall solution. Often, many of these subproblems are really the same. The dynamic programming approach seeks to solve each subproblem only once, thus reducing the number of computations. This is especially useful when the number of repeating subproblems is exponentially large.

[0031] As described in the background section, according to conventional approaches, OSD is solved by (i) computing a statistic from iEEG measurements that captures changes in brain activity at the seizure onset, and (ii) by constructing a threshold or classification rule that, based on this statistic, determines whether or not a seizure has occurred. The choice of the threshold is typically supervised and depends on the fluctuations of the statistic, the specific patient, and/or the electrode position. Such thresholds trigger too many false alarms when applied to test data because the statistic and/or threshold does not separate ictal (seizure) from non-ictal activity well. Furthermore, true positives may be detected with unacceptably long delays. Consequently, all efforts put towards improving OSD algorithms have been in either identifying better statistics with fancy signal processing and/or in implementing more sophisticated classifiers borrowed from the machine learning community. A problem with this paradigm is that detection performance (e.g. number of false positives) is not measurable until after implementation (“algorithm defines performance”).

[0032] Instead, some embodiments of the current invention take a fresh new approach to OSD. First, we note that classification rules, no matter how fancy, do not account for temporal dependencies and dynamics that exist in neural data. For example, a statistic measured at some time t depends on what values it took on in the past 100-500 ms. Therefore one should *model* this evolution - it is not what the iEEG activity looks like at any given moment, but how it got there. Predictions from this model should then be used to *adapt* the threshold rule. For example, if the dynamics appear to be evolving to an ictal state, then the threshold should drop, making it easier to detect a seizure onset. However, the threshold should adapt in an *unsupervised and optimal* way. Optimality should be defined by maximizing detection performance (“performance defines algorithm!”).

[0033] To address the raised issues, some embodiments of the current invention provide a novel computational framework for OSD that involves (i) constructing multivariate statistics from all electrodes to distinguish between non-ictal vs. ictal states; (ii) modeling the evolution of these statistics in each state and the state-transition probabilities; and, (iii) developing an optimal model-based strategy to detect transitions to ictal states from sequential neural measurements. This strategy is formulated as the Bayesian “Quickest Detection” (QD) of the seizure onset, and is solved via control optimization tools, and explicitly minimizes both the distance between detected and unequivocal onset times and the probability of false alarm. This is a paradigm shift and (i)-(iii) are described in detail below.

[0069] Some embodiments of the current invention may enable more robust detection of seizures for closed-loop intervention. Posthoc review of patient iEEG records (offline seizure confirmation) can also be made more efficient. Overall, the outcomes can lead to more effective treatments, which could potentially avoid fatal accidents thereby saving lives, extending life-expectancy, and improving the administration of anti-seizure drugs.

[0070] Figure 1 is a schematic illustration of a neurostimulation device 100 according to some embodiments of the current invention. The neurostimulation device 100 includes a plurality of electrodes 102 adapted to be electrically connected to a subject to receive

multichannel electrical signals from the subject's brain, a multichannel seizure detection unit 104 electrically connected to the plurality of electrical leads 102 to receive the multichannel electrical signals, and a neurostimulation unit 106 in communication with the multichannel seizure detection unit 104. The neurostimulation device 100 can also include other components, such as a power supply 108 and/or data memory or storage components 110. The power supply can include a battery or other electrical power storage devices, for example. The multichannel seizure detection unit 104 and/or the neurostimulation unit 106 can be at least partially implemented on a data processor encoded with software, or could be implemented on hard-wired devices, for example. The electronics of the neurostimulation device 100 can be packaged together in a case 112 in some embodiments. The electrodes 102 can be attached externally or intracranially, depending on the application. Also, in some embodiments, the case 112 can also be implantable such that the neurostimulation device 100 is an implantable device. However, the general concepts of the current invention are not limited to only implantable devices. In other embodiments, the neurostimulation device 100 can be an external device with electrodes attached to the subject's scalp.

[0071] The plurality of electrodes 102 are at least three electrodes such that the multichannel electrical signals are at least three channels of electrical signals. However, the broad concepts of the current invention are not limited to only three electrodes. In some embodiments, there can be up to 10, 20, 30, 50 or even more electrodes, depending on the particular application.

[0072] The multichannel seizure detection unit 104 detects a presence of a seizure based on multichannel statistics from the multichannel electrical signals including higher order combinations than two-channel combinations. In other words, statistics are not determined for only signals within single channels and correlations between pairs of channels. They are also based on triplets of channels, etc.

[0073] In some embodiments of the current invention, multichannel seizure detection unit 104 is configured to model the multichannel electrical signals based on a brain network model. In some embodiments, the brain network model models time-dependent variations of the multichannel statistics. In some embodiments, the brain network model is a Hidden

Markov Model. However, the broad concepts of the current invention are not limited to only Hidden Markov Models. In some embodiments, the multichannel seizure detection unit 104 is configured to detect the presence of the seizure based on a time-dependent threshold. In some embodiments, the multichannel seizure detection unit 104 is configured to detect the presence of the seizure based on optimizing a cost function. The cost function can be dependent on a time delay between an actual seizure and a prediction of the seizure, for example. In some embodiments, the cost function can be further dependent on a probability of a false positive detection. In some embodiments, the neurostimulation unit 106 can be configured to provide an electrical stimulation to the subject's brain. Alternatively, or in addition, the neurostimulation unit 106 can be configured to provide a chemical stimulation. Alternatively, or in addition, the neurostimulation unit 106 can be configured to provide other types of stimulation such as feedback and/or signals. The neurostimulation unit 106 can be responsive to output from the multichannel seizure detection unit 104 in some embodiments. For example, the multichannel seizure detection unit 104 can trigger the neurostimulation unit 106. In some embodiments, the multichannel seizure detection unit 104 can be used alone without a neurostimulation unit 106 and/or in conjunction with other devices.

(i) Multivariate Statistics

[00247] To identify robust multivariate statistics for seizure detection, multi-site iEEG signals can be processed into generalized non-square connectivity matrices that describe the time-varying spectral dependencies between all the channels over multiple frequency bands. The singular value decomposition (SVD), a tool from matrix theory that highlights dependencies within a matrix, can be used to extract multivariate statistics (e.g., leading singular vector) that capture the dynamics of the brain network in non-ictal and ictal states.

[00248] To construct models describing the evolution of multivariate statistics, we note that the network-based statistics evolve over time because of subclinical changes of brain activity that affect iEEG data in time and frequency. To estimate these changes, we can model the evolution of each SVD statistic through a Hidden Markov Model (HMM). The HMMs can be estimated from data for each patient and will characterize (i) neural dynamics

in non-ictal and ictal states, and (ii) the probability distribution of the actual transition (T) from any non-ictal to ictal state.

[00249] For some applications, for each patient, iEEG recordings can be used to (i) construct a time sequence of connectivity matrices, $\{A(k)\}$, (ii) compute the SVD for each matrix, and (iii) track the leading singular value, $\{\sigma_1(k)\}$, and the corresponding singular vector, $\{u_1(k)\}$ to be used for OSD. These statistics, defined below, may significantly modulate during seizure.

[00250] Recent studies have introduced schemes that simultaneously analyze all the available recording channels 86-99106-108. In these schemes, each channel is treated as a node in a graph, and any two nodes are considered *connected* (i.e., an edge exists between them) if the activity at these sites are dependent. The connectivity (topology) of the graph can then be described by a matrix, which is referred to as the “connectivity” or “adjacency” matrix 109). Statistics computed from this matrix can show if the topology changes significantly from non-ictal to ictal states, and significant changes in these statistics can be used to detect a seizure’s onset.

[00251] The connectivity matrix, A , can be computed in several ways. In order to capture linear dependencies between all of the recording sites, we can compute connectivity as the cross-power in different frequency bands (theta, alpha etc.) between all available iEEG channels. That is, for each pair of channels (i, j) the corresponding element of the connectivity matrix in the frequency band F^k is

$$A_{ij}^{F_k} \triangleq \int_{F_k} P_{ij}(f) df, \quad (1)$$

where $P_{ij}(f)$ is the cross-power spectral density of channels i and j at frequency f 110. The frequency bands will include: $F_1 = [4, 7]$ Hz (theta band), $F_2 = [8, 13]$ Hz (alpha band), $F_3 = [13, 35]$ Hz (beta band), and the final non-square connectivity matrix will be (for these bands)

$$A = [A^{F_1} \ A^{F_2} \ A^{F_3}]. \quad (2)$$

[00252] One can compute A over a sliding window, which will result in a sequence of matrices $\{A(k)\}$, one per window. Based on data provided later in this section, one can initially use 5 s-long windows with 1 s slide, which will result in a connectivity matrix $A(k)$ at each time second k .

Singular Value Decomposition (SVD)

[00253] Measures off of the connectivity matrix (2) can be computed to generate multivariate statistics that significantly modulate in the ictal state. Specifically, it has been suggested that the brain enters a more organized, lower complexity state prior to a seizure 33112. As the brain becomes more organized and nodes become more connected, the *rank* (number of linearly independent rows or columns) of the connectivity matrix drops. The SVD of a matrix highlights the rank of a matrix and also generates a weighted set of vectors that span the range space and null space of the matrix 103. Therefore, we can use SVD to measure the time-varying complexity of the brain by tracking the rank and its associated subspaces as a means to characterize non-ictal vs. ictal states. The SVD of the $m \times n$ connectivity matrix A is defined as

$$A = USV^* = \begin{bmatrix} \mathbf{u}_1 & \mathbf{u}_2 & \dots & \mathbf{u}_m \end{bmatrix} \begin{bmatrix} \sigma_1 & & & \\ & \ddots & & \\ & & \sigma_r & \\ \hline & & & 0 \end{bmatrix} \begin{bmatrix} \mathbf{v}_1^* \\ \mathbf{v}_2^* \\ \vdots \\ \mathbf{v}_n^* \end{bmatrix} \quad (3)$$

where U is an $m \times m$ unitary ($UU^* = I$) matrix whose columns, \mathbf{u}_i , are the eigenvectors of the matrix AA^* , V is an $n \times n$ unitary matrix whose columns, \mathbf{v}_i , are the eigenvectors of the matrix A^*A , and $*$ denotes the complex conjugate transpose operator. S is an $m \times n$ matrix whose first r diagonal entries $\sigma_1 \geq \sigma_2 \geq \dots \geq \sigma_r$ are the nonzero singular values of A , with r being the rank of A 103. The first r columns of U span the column space of A and the first r rows of V span the row space of A . When $m = n$ and A is square symmetric ($A = A^*$), the SVD reduces to the conventional eigenvalue decomposition, where the singular values are the square of the eigenvalues of A , $U=V^{-1}$, and the columns of U and V are the eigenvectors of A 103.

[00254] An example is shown in Fig. 3. Here, two 3-node graphs are analyzed. In Fig. 3A, all nodes have similar weak connections (strength < 1) under 2 measures (e.g. cross-power in 2 frequency bands). The SVD of the corresponding non square connectivity matrix, A , reveals that the matrix of this graph has full rank (3 comparable singular values in $\sigma(A)$). More physically, full rank here indicates the activity in the 3 nodes spans a 3 dimensional space, or has 3 degrees of freedom. If the strength between nodes 1 and 2 increases (Fig. 3B), one of the singular values of the corresponding connectivity matrix, B , becomes small in comparison to the other two, indicating that the rank of the matrix has approximately dropped to 2. This means that with the addition of one strong connection, the activity on the graph collapses to two dimensions and has becomes more “ordered”. The singular vectors of graphs in Fig. 3 are given and indicate that the dominant direction of the vectors has also rotated in Fig. 3B.

[00255] The time dependent structure of the first singular vector direction of the connectivity matrix can be used as way to detect seizure onsets.

Example Results

[00256] *Data:* Four subjects with intractable epilepsy were surgically implanted with subdural grid and strip electrodes (26-75 channels, Ad-Tech[®] Medical Instrument Corporation, Racine, WI) for approximately one week before surgical resection of the focal region and monitored by clinicians for seizures and interictal epileptic activity. Electrodes are 4 mm diameter platinum contacts embedded in a silicone sheet with 2.3 mm exposed. Data were digitized and stored using an XLTEK[®] EMU128FS system (Natus Medical Incorporated, San Carlos, CA) with 250-500 Hz sampling frequency. Table I reports patient-specific information, number of electrodes included in this study, and electrode position, respectively. Board-certified electroencephalographers (up to 3) marked the unequivocal electrographic onset (UEO) by consensus of each seizure and the period between onset and termination. UEOs were used as the “Gold Standard” for evaluating the performances of the detection algorithm. Grid electrode recordings (iEEG) included in this study were made available with the written consent of the patients, in accordance with the protocol approved

by the Institutional Review Boards at Brigham and Women's Hospital and Children's Hospital, Boston, MA.

Multivariate SVD Statistics

[00257] The connectivity matrix was estimated using the cross-power in a specific frequency band (1) for each patient over consecutive overlapping windows (5 s-long window, 4 s overlap). See Table I. We computed connectivity in one frequency band for simplicity to initially construct our QD framework. The corresponding maximum singular value σ_1 and first singular vector \mathbf{u}_1 are plotted in Fig. 4 for consecutive windows covering an ictal period.

| Patient ID | Seizure origin | Type of seizures | # iEEG channels | hours of recordings | Frequency band for σ_1 |
|------------|----------------|------------------|-----------------|---------------------|-------------------------------|
| 1 | T | CP | 34 | 40 | 13-30 Hz |
| 2 | T | TC | 28 | 47 | 4-7 Hz |
| 3 | F | CP | 44 | 47 | 13-30 Hz |
| 4 | O | SP | 26 | 34 | 13-30 Hz |

Table I. Experimental setup. F = frontal lobe; O = occipital lobe; T = temporal lobe; CP = complex partial; SP = simple partial; TC = tonic clonic. For each patient, the frequency band was chosen by maximizing the distance between ictal vs. non-ictal GLM parameters (training data only).

[00258] The sequence of σ_1 has a consistent pattern across patients during the non-ictal, pre- and post-ictal states. The corresponding singular vector \mathbf{u}_1 shows a leading direction before the seizure onset, which depends on both the patient and the location of the focal region. During a seizure, σ_1 rapidly increases compared to the non-ictal activity in the previous minutes, reaches a local maximum at approximately half of the ictal period (gray boxes, Fig. 4A-D), and then slowly decreases to smaller non-ictal values. The change in the dynamics of σ_1 is observed almost at the beginning of the hand-annotated seizure onset, while the return to the non-ictal condition is usually slower. Interestingly, after every seizure, σ_1 decreased below the average value achieved before the seizure and, then, increased to the pre-ictal values with a long drift (at least 2 hr, data not reported), which may be consistent with the definition of a post-ictal state given in 112.

[00259] The stereotypical dynamics of σ_1 was associated with a sudden change in the direction of the singular vector \mathbf{u}_1 . Furthermore, the new direction remained consistent across different seizures (Fig. 4E,F). Modulo a scaling factor, the dynamics of σ_1 and \mathbf{u}_1 were similar in patients 1-2, and 4 (Fig. 4A,B,D), independently of the connectivity matrix being computed in different frequency bands. These dynamics were less clear in patient 3, where σ_1 showed slow oscillations independently of the seizure occurrence (Fig. 4C, top). However, at the seizure onset, the value of σ_1 first decreased, then rapidly rose to a local maximum, and finally drifted to baseline value, as did occur in the other patients.

[00260] The notion of connectivity (e.g. cross power) and the particular statistic computed from the connectivity matrix (e.g. $\mathbf{\Phi}_1$) may not perform well for all types of seizures or all types of epilepsy. If needed, can use other connectivity measures (e.g. mutual information 111) and/or other matrix measures (e.g. spectral clusters [83]). Furthermore, there may be patients with independent multifocal onsets, which may be reflected by a connectivity matrix that changes periodically over time as seizures ping-pong back and forth between foci. To identify these cases, localization consistency will be measured across all seizures within a patient.

(ii) Modeling **the evolution of multivariate statistics**

[00261] In this example, we model the evolution of the maximum singular value statistic using an HMM. For any given patient, we assume that the maximum singular value computed at each second is generated by an HMM. In particular, at each stage $k \geq 0$, the brain is in one of m subclinical states, i.e., $x_k \in \{0, 1, \dots, m-1\}$, which follows a Markov Chain 113, i.e.

$$\begin{aligned} \Pr(x_{k+1} = j | x_k, x_{k-1}, \dots, x_0) &= \Pr(x_{k+1} = j | x_k = i) \equiv p_{ij} && \text{for all } i, j \\ \sum_{j=1}^{m-1} p_{ij} &= 1 \quad \forall i, \quad \sum_{i=1}^m p_i &= 1 && (4) \end{aligned}$$

where $p_i \triangleq \Pr(x_0 = i)$, $i = 0, 1, \dots, m-1$, is the probability of starting in state i . For a fixed state i , we assume that the observations $z_k \triangleq \sigma_1(k)$, $k = 1, 2, \dots$ are generated according to a known history-dependent probability law $q_i(z | H_k) \triangleq \Pr(z_k = z | x_k = i, H_k)$,

where $H_k \triangleq \{z_0, z_1, \dots, z_{k-1}\}$ denotes the sequence of past observations. Note that the dependency of z_k on previous observations accounts for temporal dependencies that exist in neural data 115116. The HMM is therefore uniquely defined by the triple $\{\mathcal{P}, \Sigma, \mathbf{q}\}$, with $\mathcal{P} \triangleq [\mathcal{P}_0 \mathcal{P}_1 \dots \mathcal{P}_{m-1}]$, $\Sigma_{ij} \triangleq p_{ij}$, $i, j = 0, 1, \dots, m-1$, and $\mathbf{q} \triangleq [q_0 \dots q_{m-1}]$. See Fig. 5A.

[00262] For our QD framework, we may initially fit an $m = 2$ state HMM on each patient, with state $x = 0$ and $x = 1$ denoting the non-ictal and ictal condition, respectively. The ictal state begins and ends with the unequivocal ictal onset and offset determined by clinicians. Early-ictal or pre-ictal conditions are subsumed in the non-ictal state as they may not exist in all patients. Since we will begin monitoring a patient in the non-ictal state 0, we set $\mathcal{P} = [1 \ 0]$. We will also initially assume that the state transition probability matrix is

$$\Sigma = \begin{bmatrix} 1-\rho & \rho \\ 0 & 1 \end{bmatrix}, \quad (5)$$

where ρ will be estimated from training data via maximum likelihood estimation 114-116. The output probability law $q_x(z|H_k), x = 0, 1$ will be estimated by combining generalized linear models (GLM) 117 and maximum likelihood estimation. Training data includes at least 3 hours of non-ictal data well before seizure (min 3 hr, max 12hr before the seizure) and at least 1 ictal period.

[00263] Results. Fig. 5B and Fig. 6 show results for the HMM estimation. Although the mean value and the variance of σ_1 were different in the ictal versus non-ictal state, the sampling probability distribution functions overlap (Fig. 5B), which means that several of the same values of σ_1 were likely to be achieved both during the ictal and non-ictal states.

[00264] To better characterize the distribution of σ_1 in each state, we used a history-dependent model (see 102 for details) to describe the distribution of σ_1 (Fig. 6). At each stage k , this model modulates the probability of observing $\sigma_1(k)$ in each state based on the values of σ_1 in the last 15 s. The functions q_0 and q_1 (i) varied the probability of any given observation σ_1 at each stage k depending on the past observations, and (ii) had opposite dynamics in ictal vs. non-ictal state. For the computed sequence of σ_1 in each patient, $q_1(\cdot)$

was consistently larger than $q_0(\cdot)$ during ictal periods, but decreased during non-ictal periods (Fig. 6). In each patient, $q_0(\cdot)$ and $q_1(\cdot)$ were almost 0 right after every seizure, suggesting a post-ictal period characterized by a resetting of brain activity 112.

[00265] There may be reactivity of iEEG waveforms due to sleeping, moving etc. that impacts how the multivariate statistic evolves over time. To capture reactivity, it may be needed to build an m -state HMM, where $m \geq 2$, for each patient (e.g. $m = 3$: non-ictal sleep, non-ictal awake, ictal). The methodology described above is easily extended to such cases.

(iii) Quickest Detection of Seizure Onsets

[00266] Next, we will (i) implement the QD framework, (ii) test the QD-based strategy on clinical data, and (iii) compare QD to a variety of existing OSD algorithms. We begin by deriving the QD framework and then describe other OSD algorithms that we will also implement for comparison. We then discuss results of the examples according to an embodiment of the current invention.

[00267] Because the state of an HMM is hidden, a Bayesian information state variable $\pi_k \triangleq \Pr(x_k = 1 | z_k, H_k)$ can be introduced 119 in order to estimate how likely the transition from the non-ictal to ictal state is at each stage k . Note that π_k is the *a posteriori* probability of being in state 1 at stage k and depends on the observations up to and including stage k . The evolution equation of π_k is recursive and given by

$$\pi_{k+1} = \frac{L_{k+1}[\pi_k + (1-\pi_k)p_{01}]}{(1-\pi_k)(1-p_{01}) + L_{k+1}[\pi_k + (1-\pi_k)p_{01}]} \triangleq \Phi(\pi_k, z_{k+1}, H_{k+1}) \quad (6)$$

where $q_x(z_0)$ is the probability of observing z_0 in state 0 at time $k = 0$, $L_k \triangleq \frac{q_1(z_k | H_k)}{q_0(z_k | H_k)}$ is the likelihood ratio, and Bayes' rule is applied. See 102 for details. Note that the evolution equation (6) depends on the likelihood ratio, L_k , between q_1 and q_0 . The dependency of q_1 and q_0 on the history H_k contributes to separating their dynamics, thus achieving a larger modulation of L_k in ictal vs. non-ictal states. Consequently, this history-dependency makes π_k more reliable as it achieves high values only around the actual seizure onset.

[00268] The quickest detection problem is an *online* decision problem, where at each stage k , we test the hypothesis $\mathcal{H}_0 \triangleq \{\text{a seizure onset has occurred}\}$ conditioned on the observations (H_k, z_k) . We introduce the decision variable $u_k \in \{0,1\}$, where $u_k = 0$ ($u_k = 1$) denotes that the hypothesis \mathcal{H}_0 is rejected (accepted) at stage k . In this way:

$$\pi_{k+1} = f(\pi_k, z_{k+1}, H_{k+1}, u_k) \triangleq \begin{cases} \Phi(\pi_k, z_{k+1}, H_{k+1}) & u_k = 0 \\ \text{terminate \& restart} & u_k = 1 \end{cases} \quad (7)$$

where the “*terminate & restart*” state implies that we restart the detection algorithm after a seizure is detected. With this setup, QD boils down to *deciding when* to switch from $u_k = 0$ to $u_k = 1$, thus claiming that a seizure has occurred. We will design a decision strategy that minimizes the following cost function, which weighs average detection delay and probability of a false positive:

$$\mathcal{J}_0 \triangleq (1 - \gamma) E_{\bar{T} | T_{QD} < \bar{T}} \{T - T_{QD}\} + \gamma E_{\bar{T} | T_{QD} > \bar{T}} \{(T_{QD} - T)^2\} \quad (8)$$

where T and T_{QD} are the actual and estimated seizure onset, respectively. T is unknown but its probability distribution is defined by the HMM transition probabilities, i.e., $P(T = k) = (1 - p_{01})^{k-1} p_{01}$. $E_{\bar{T} | T_{QD} < \bar{T}} \{\cdot\}$ and $E_{\bar{T} | T_{QD} > \bar{T}} \{\cdot\}$ denote the expected values of the distance between T_{QD} and \bar{T} for false positive ($T_{QD} < T$) and delayed detection ($T_{QD} > T$), respectively. Finally, the parameter $\gamma \in [0,1]$ allows the tradeoff of false positives and delayed detection, while the expected value $E_{\bar{T}} \{\cdot\}$ accounts for the average temporal distance between actual and estimated seizure onset.

[00269] We then design the cost (8) as a function of the information state π_k and decision variable u_k . Details are given in 102. Then, the optimal decision deals with choosing the stage $T_{QD} > 0$ such that the policy $(u_1 = 0, u_2 = 0, \dots, u_{T_{QD}-1} = 0, u_{T_{QD}} = 1)$ minimizes the overall cost (8). One can interpret the minimization of (8) with respect to the variable u_k given the evolution model (7), as an *optimal feedback control problem* where u_k is the control variable (Fig. 5C). This formulation can be solved recursively via Dynamic Programming 83, and leads to the optimal quickest detection (QD) policy

$$T_{QD} = \min\{0 < k < M | \pi_k > F_k(\pi_k, z_k, H_k)\} \quad (9)$$

where $F_k(\pi_k, z_k, H_k)$ is an adaptive threshold that depends on the current observation, history, and information state variable. The threshold $F_k(\cdot)$ is computed recursively and has no closed form and it decreases over time non-monotonically. Details can be obtained in 100102.

Example Results

[00270] For each patient, we compare the QD policy to a classical Bayesian estimator (BE) 119, which is widely used in the field of change point detection 33119, and a heuristic threshold based detector (HT), where the threshold is chosen heuristically. The formulae for the estimated seizure onset with each of these predictors are: $BE: T_{BE} \triangleq \min\{k > 0 | \pi_k > 0.5\}$ and $HT: T_{HT} \triangleq \min\{k > 0 | z_k > \bar{h}\}$, where the threshold \bar{h} is fixed heuristically. For each detection policy, we measure the delay between each estimated seizure onset time and the unequivocal electrographic onset 120, which will be annotated by the epileptologists. We can also evaluate the number of true positives (TP), false positives (FP), and false negatives (FN) per patient, where each decision can be classified as TP or FP if an unequivocal onset occurs within a window W from the detection time or not. W was initially be set to 20 s to be comparable to 60. An onset not detected is classified as FN. Finally, given TP, FP, and FN, two measures can be evaluated for each patient: (i) the false positive rate (FPR), which is the number of FP/hr, and the “sensitivity” (S), which is the ratio between TP and TP+FN. For each of these measures, we determine whether the results achieved with the QD policy and any other method are significantly different from the chance-level detection (i.e., random generator of warnings as in 121) and whether FPR and S with QD are significantly lower than with the other methods (t-test). We can finally evaluate the sensitivity to changes of W as well as QD performance for different trade-off gains γ in (10).

| | Patient | Seizure | QD | | | | | BE | | | | | HT | | | | |
|------------|---------|---------|-------------|------------|----|-------------|-----------------|-------------|------------|----|-------------|-----------------|-------------|------------|----|-------------|-----------------|
| | | | Specificity | | | Sensitivity | | Specificity | | | Sensitivity | | Specificity | | | Sensitivity | |
| | | | FP | FPR (FP/h) | FN | TP | $ T_s - T $ (s) | FP | FPR (FP/h) | FN | TP | $ T_s - T $ (s) | FP | FPR (FP/h) | FN | TP | $ T_s - T $ (s) |
| Training | 1 | 1 | 0 | 0 | 0 | 1 | 18 | 0 | 0 | 0 | 1 | 16 | 8 | 2.67 | 0 | 1 | 14 |
| | 2 | 1 | 0 | 0 | 0 | 1 | 19 | 0 | 0 | 0 | 1 | 16 | 8 | 2.67 | 0 | 1 | 20 |
| | 3 | 1 | 3 | 1 | 0 | 1 | 10 | 3 | 1 | 0 | 1 | 7 | 8 | 2.67 | 1 | 0 | n.a. |
| | 4 | 2 | 0 | 0 | 0 | 2 | 9 | 0 | 0 | 0 | 2 | 7 | 0 | 0 | 0 | 2 | 5 |
| Validation | 1 | 1 | 6 | 0.16 | 0 | 1 | 15 | 6 | 0.16 | 0 | 1 | 14 | 42 | 1.14 | 0 | 1 | 12 |
| | 2 | 2 | 7 | 0.16 | 0 | 2 | 31 | 11 | 0.25 | 0 | 2 | 33 | 13 | 0.30 | 0 | 2 | 14.5 |
| | 3 | 3 | 130 | 2.95 | 0 | 3 | 13.7 | 320 | 7.27 | 0 | 3 | 10.7 | 75 | 1.71 | 3 | 0 | n.a. |
| | 4 | 22 | 71 | 2.29 | 0 | 22 | 11.8 | 138 | 4.45 | 0 | 22 | 9.7 | 277 | 8.94 | 0 | 22 | 5.8 |

Table II. Performance Analysis. FP = false positive; TP = true positive; FN = false negative; FPR = false positive rate; n.a. = not

[00271] Table II and Fig. 7 report results for the QD policy vs. the BE and HT detectors. QD achieved significantly fewer false positives than the Bayesian and threshold-based detector (min. 36% less; max. 85% less; mean: 58% less), while achieving 100% sensitivity in every patient. QD delays were comparable and in some cases slightly larger than delays of other detectors. However, Fig. 7A shows that for patient 2, by increasing the penalty for detection delay in (11) (i.e., increasing γ), QD reduced delays to values achieved by BE (16 s, green lines), while maintaining a lower number of FPs (7 vs. 11). For patient 4, by decreasing γ , QD achieved higher robustness to early modulations in the probability π_k , due to abrupt spikes in the sequence of σ_1 , and QD decreased the number of FPs and detect a seizure with less anticipation (Fig. 7B).

[00272] QD results in significantly fewer FPs than other OSD methods, however, the detection delays, are comparable to those produced by other OSD methods. One can also explore penalizing other functions of the detection delay ($T_{QD} - T$) in the cost function (8) to reduce these delays according to other embodiments of the current invention. For example, one can allow this penalty to grow exponentially ($e^{(T_{QD} - T)}$) and as long as the function is a non-decreasing function of the delay, the QD method will hold.

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[00274] The embodiments discussed in this specification are intended to explain concepts of the invention. However, the invention is not intended to be limited to the specific terminology selected and the particular examples described. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

WE CLAIM:

1. A neurostimulation device, comprising:
 - a plurality of electrodes adapted to be electrically connected to a subject to receive multichannel electrical signals from said subject's brain;
 - a multichannel seizure detection unit electrically connected to said plurality of electrical leads to receive said multichannel electrical signals; and
 - a neurostimulation unit in communication with said multichannel seizure detection unit,wherein said plurality of electrodes are at least three electrodes such that said multichannel electrical signals are at least three channels of electrical signals, and
 - wherein said multichannel seizure detection unit detects a presence of a seizure based on multichannel statistics from said multichannel electrical signals including higher order combinations than two-channel combinations.
2. A neurostimulation device according to claim 1, wherein said plurality of electrodes are at least ten electrodes such that said multichannel electrical signals are at least ten channels of electrical signals.
3. A neurostimulation device according to claim 2, wherein said multichannel statistics are based on all combinations of said multichannel electrical signals.
4. A neurostimulation device according to claim 1, wherein said multichannel seizure detection unit is configured to model said multichannel electrical signals based on a brain network model.
5. A neurostimulation device according to claim 4, wherein said brain network model models time-dependent variations of said multichannel statistics.
6. A neurostimulation device according to claim 4, wherein said brain network model is a Hidden Markov Model.

7. A neurostimulation device according to claim 1, wherein said multichannel seizure detection unit is configured to detect said presence of said seizure based on a time-dependent threshold.
8. A neurostimulation device according to claim 1, wherein said multichannel seizure detection unit is configured to detect said presence of said seizure based on optimizing a cost function.
9. A neurostimulation device according to claim 8, wherein said cost function is dependent on a time delay between an actual seizure and a prediction of said seizure.
10. A neurostimulation device according to claim 9, wherein said cost function is further dependent on a probability of a false positive detection.
11. A neurostimulation device according to claim 1, wherein said neurostimulation unit is triggered by said seizure detection unit to provide an electrical stimulation.
12. A neurostimulation device according to claim 1, wherein said neurostimulation unit is triggered by said seizure detection unit to provide a chemical stimulation.
13. A neurostimulation device according to claim 1, wherein said neurostimulation unit is triggered by said seizure detection unit to provide at least one of a visual or auditory warning.
14. A neurostimulation device according to claim 1, wherein said neurostimulation device is an implantable device.
15. A multichannel seizure detection system, comprising:
 - a signal interface adapted to receive multichannel electrical signals from said subject's brain; and

a data processor configured to receive said multichannel electrical signals and detect a presence of a seizure based on multichannel statistics from said multichannel electrical signals including higher order combinations than two-channel combinations,

wherein said multichannel electrical signals are at least three channels of electrical signals.

16. A multichannel seizure detection system according to claim 15, wherein said multichannel electrical signals are at least ten channels of electrical signals.

17. A multichannel seizure detection system according to claim 16, wherein said multichannel statistics are based on all combinations of said multichannel electrical signals.

18. A multichannel seizure detection system according to claim 15, wherein said data processor is further configured to model said multichannel electrical signals based on a brain network model.

19. A multichannel seizure detection system according to claim 18, wherein said brain network model models time-dependent variations of said multichannel statistics.

20. A multichannel seizure detection system according to claim 18, wherein said brain network model is a Hidden Markov Model.

21. A multichannel seizure detection system according to claim 18, wherein said brain network model is a two-state model.

22. A multichannel seizure detection system according to claim 18, wherein said brain network model is a multi-state model.

23. A multichannel seizure detection system according to claim 15, wherein said multichannel seizure detection unit is configured to detect said presence of said seizure based on a time-dependent threshold.
24. A multichannel seizure detection system according to claim 15, wherein said multichannel seizure detection unit is configured to detect said presence of said seizure based on optimizing a cost function.
25. A multichannel seizure detection system according to claim 24, wherein said cost function is dependent on a time delay between an actual seizure and a prediction of said seizure.
26. A multichannel seizure detection system according to claim 25, wherein said cost function is further dependent on a probability of a false positive detection.

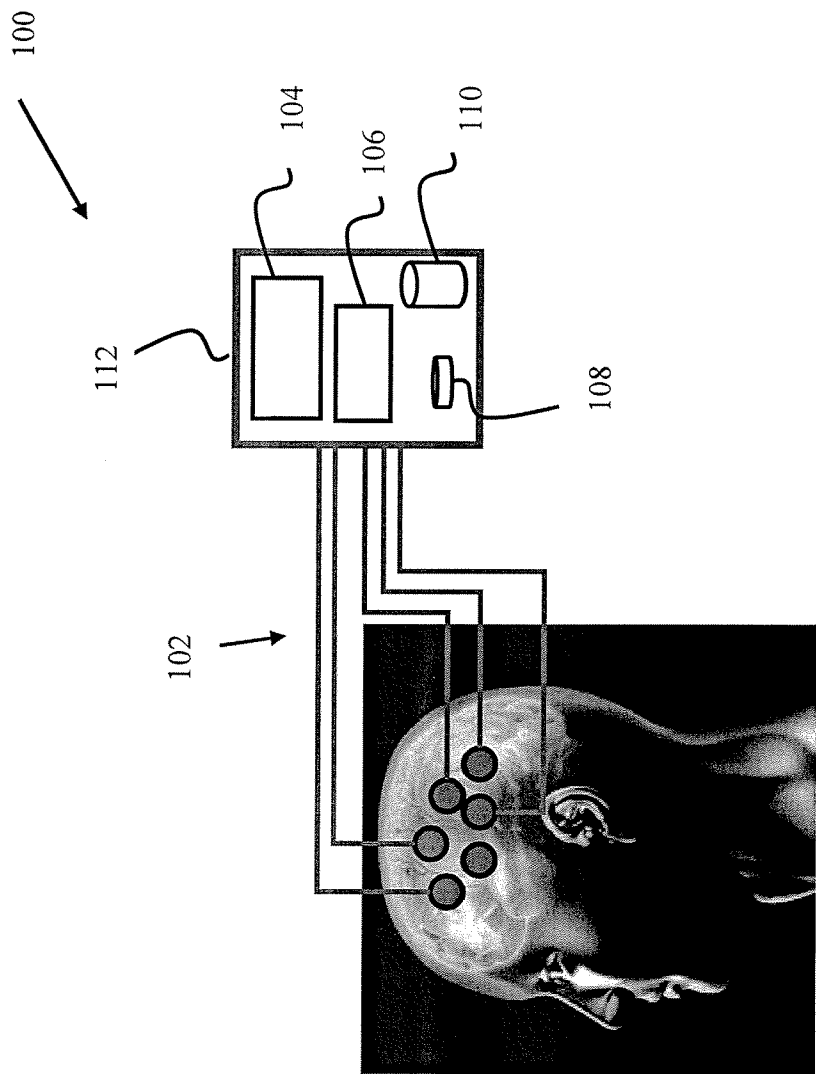
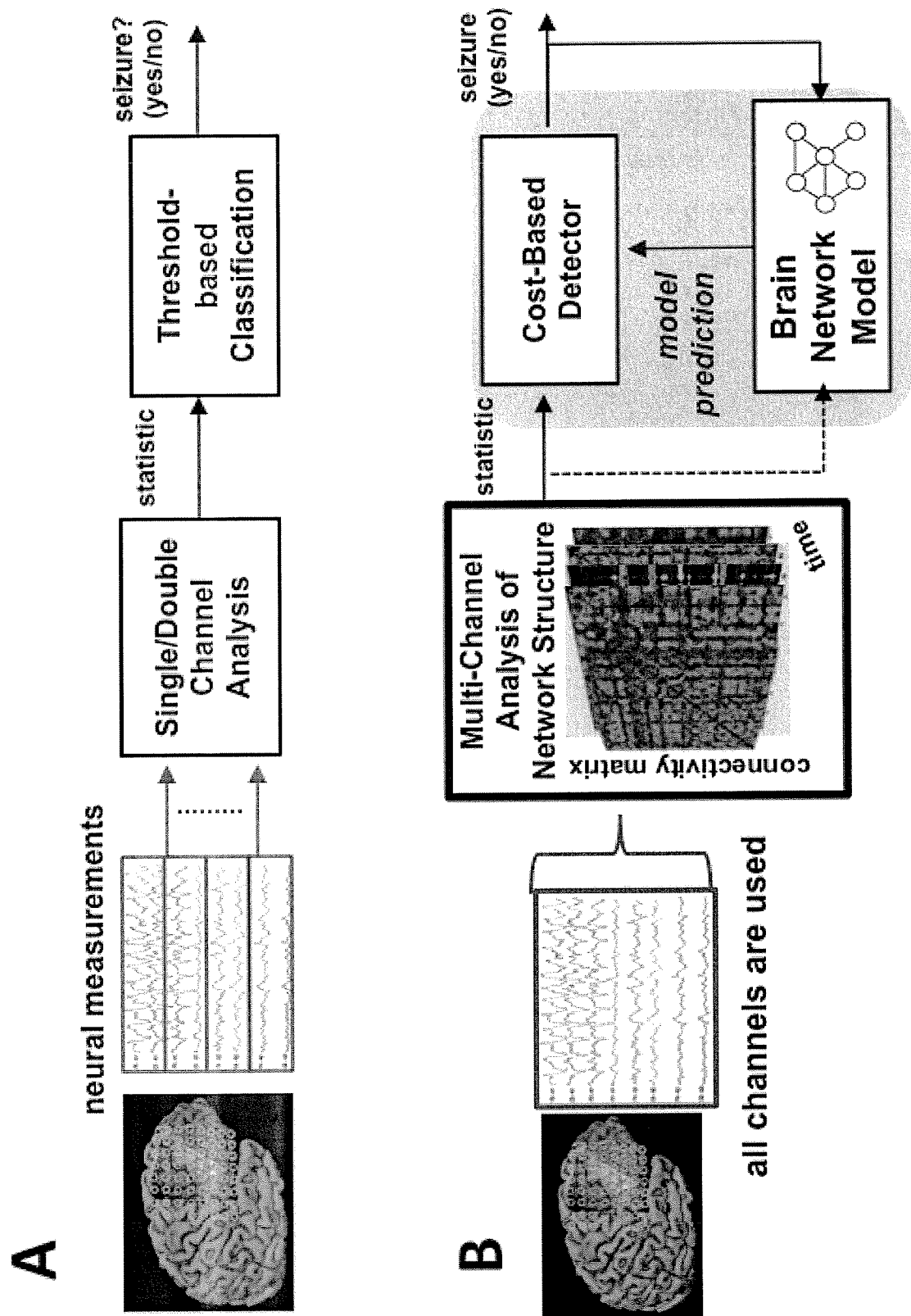


Figure 1



Figures 2A and 2B

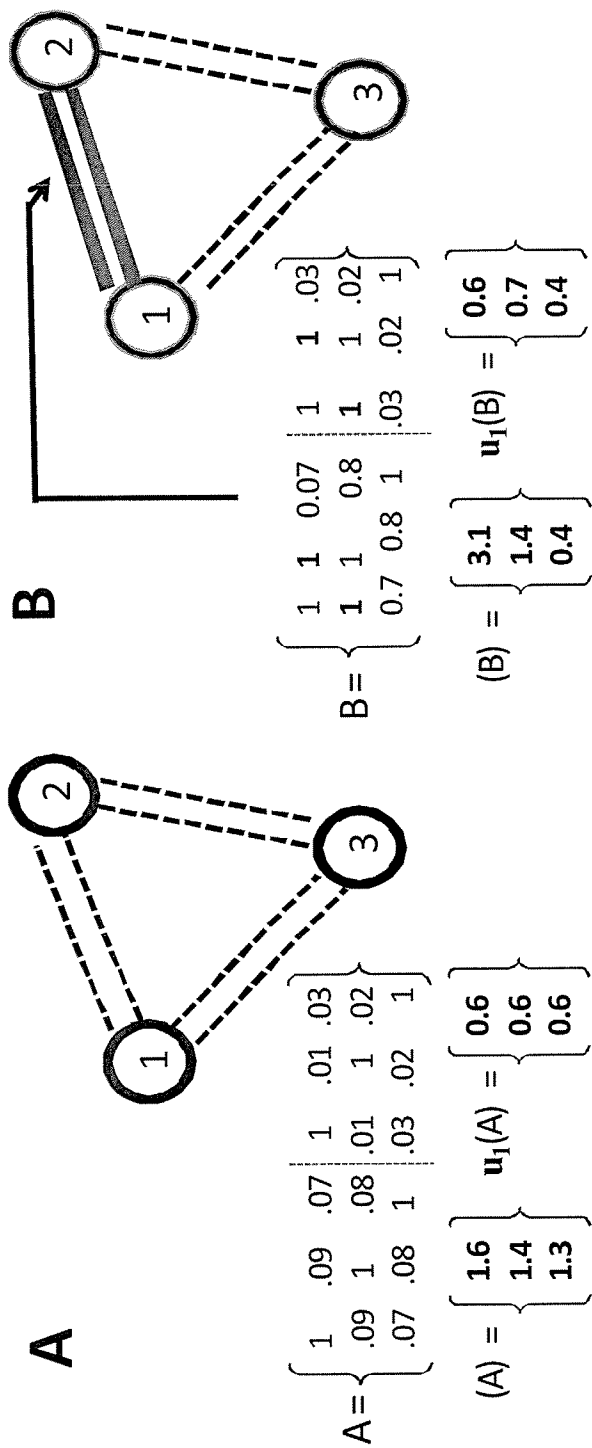
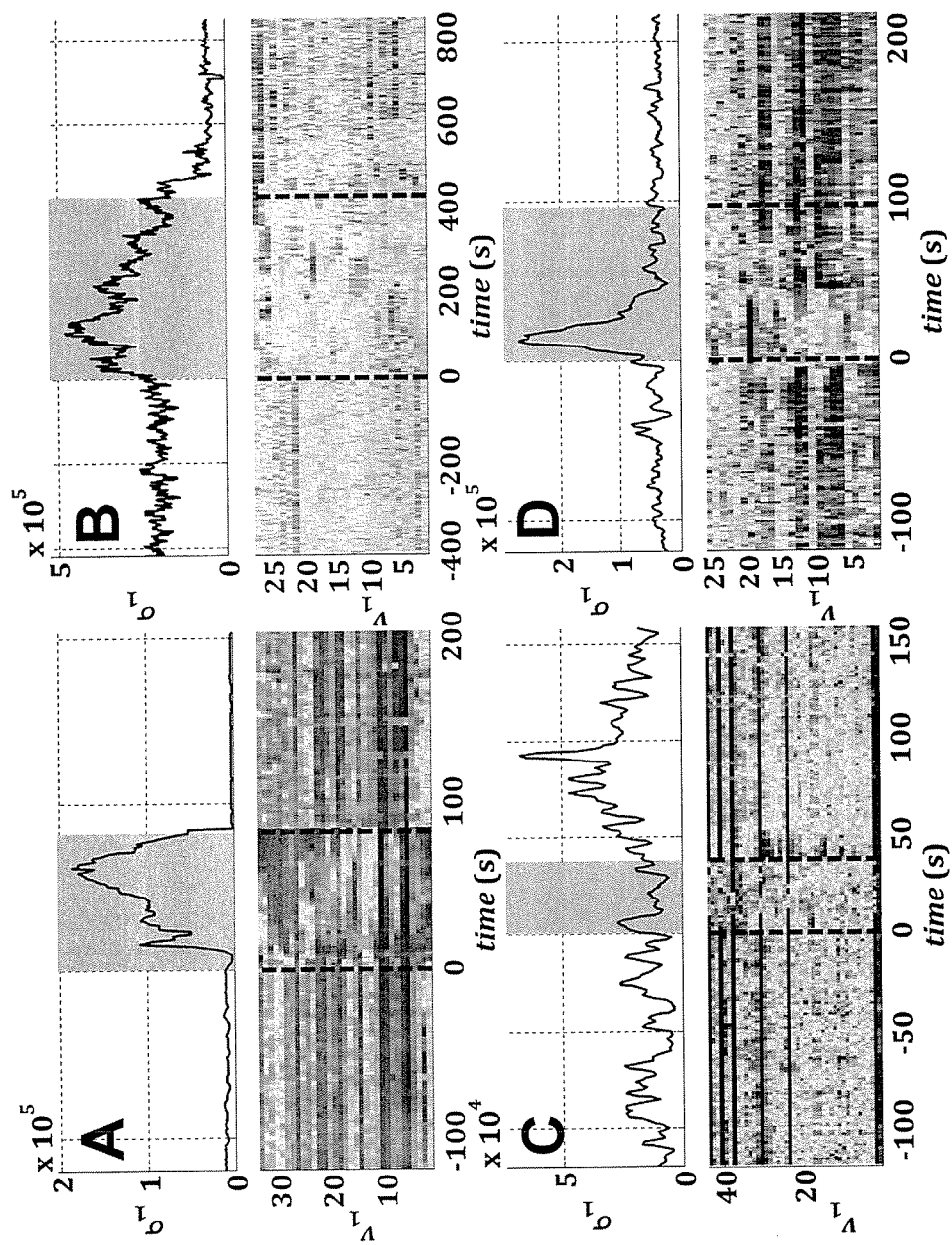
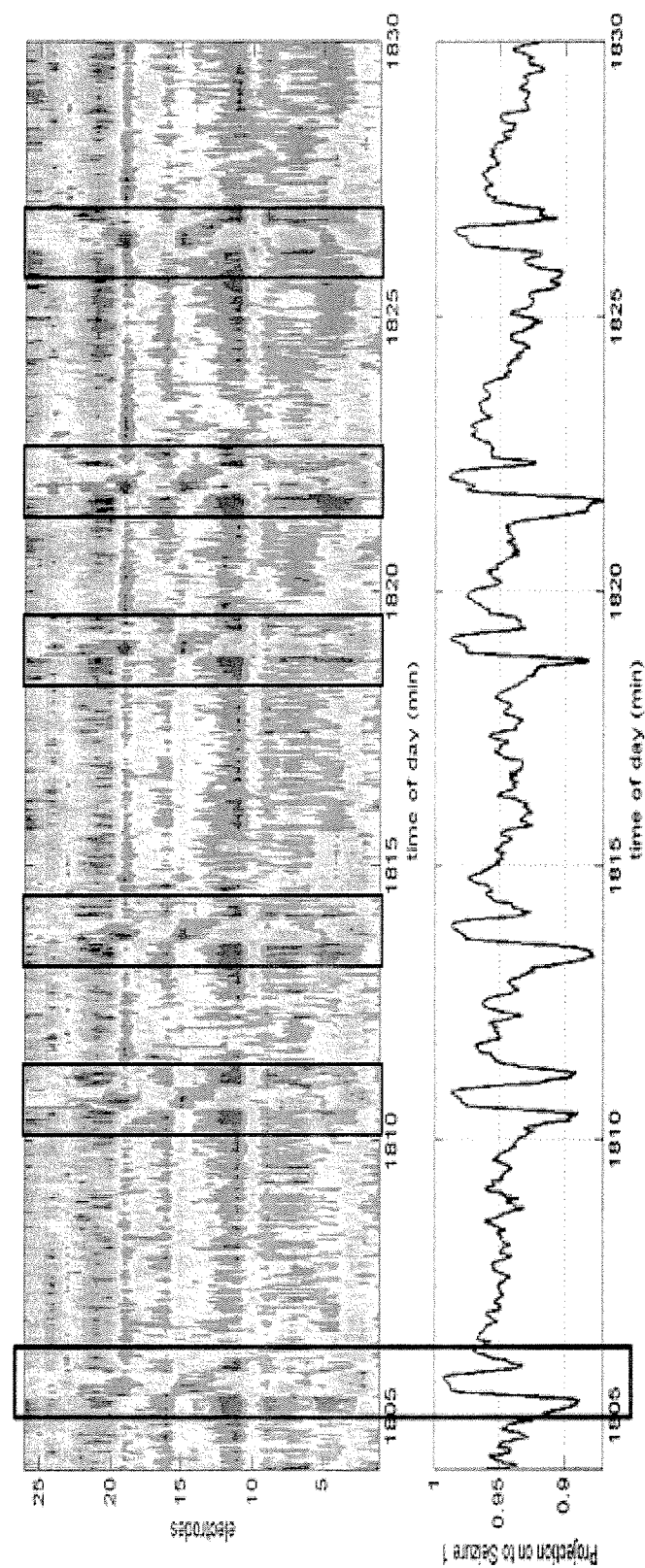


Figure 3B

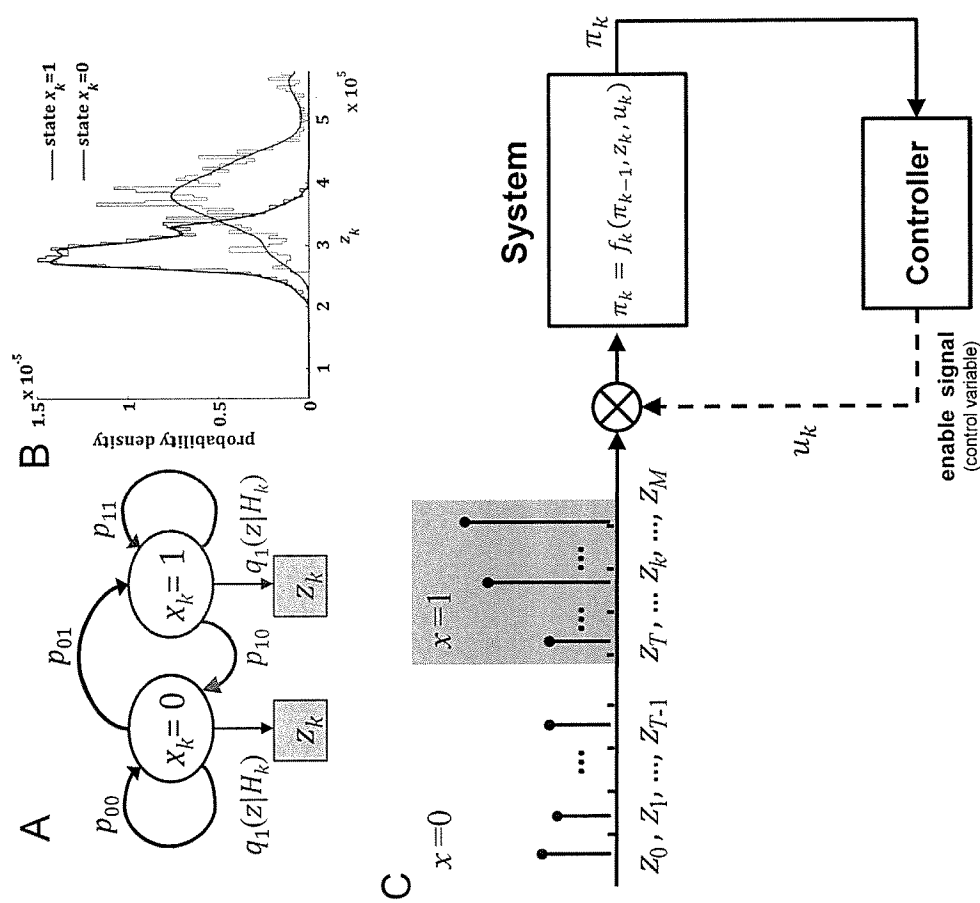
Figure 3A



Figures 4A-4D



Figures 4E and 4F



Figures 5A-5C

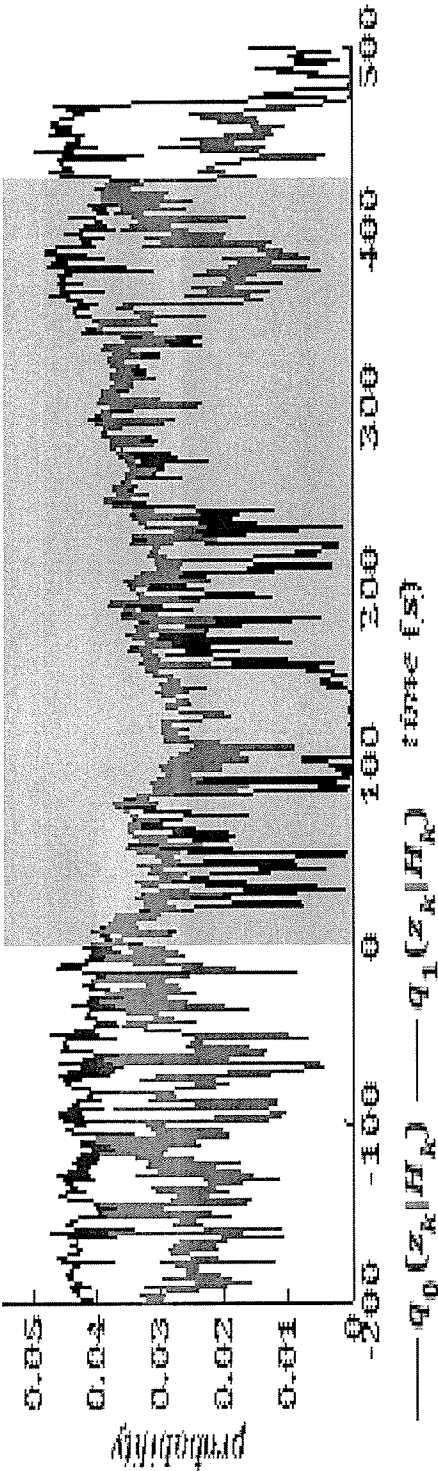


Figure 6

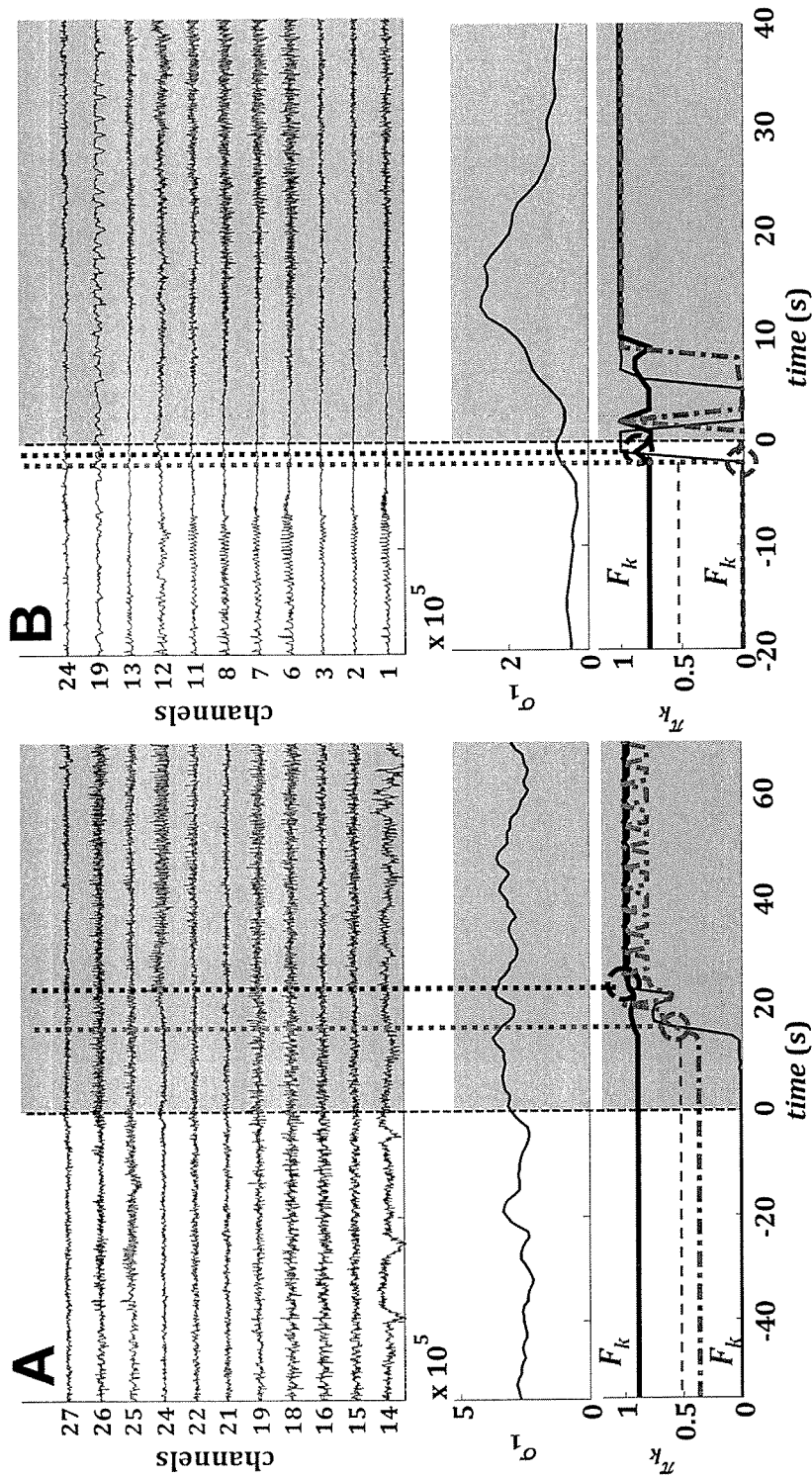


Figure 7A

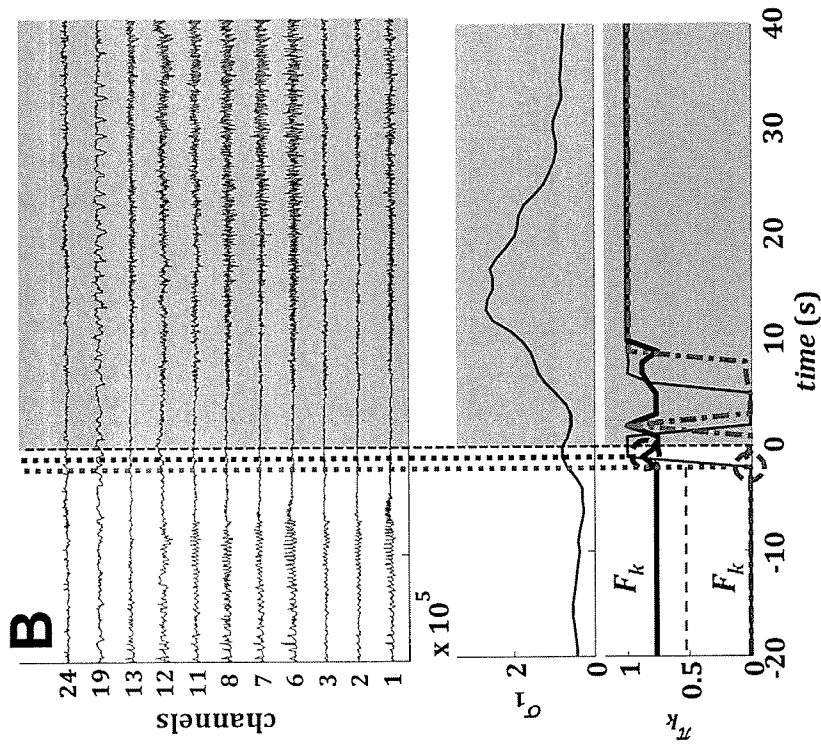


Figure 7B