Real time network modulation for intractable epilepsy

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a scientific curiosity
a scientific curiosity

• How does human brain work?
  • Ancient Egypt and Greece
  • Roman empire
    • the seat of intelligence
a scientific curiosity

• How does human brain work?
  • Ancient Egypt and Greece
  • Roman empire
  • the seat of intelligence
• 19th century
• 90s the “decade of the brain”
• 2013 “the brain initiative”
understanding

- quantum leap

- neuron doctrine
understanding

- quantum leap
  - neuron doctrine
  - electrical circuit
  - electrical excitability
understanding

• quantum leap
  • neuron doctrine

• electrical circuit

• electrical excitability
  • enabler
    • tools
      • microscope
      • electrodes
grand challenges

- ...  

- relation
  
  - neuronal circuit connectivity and behavior
grand challenges

- ... 
- relation
  - neuronal circuit connectivity and behavior
    - transition of neuronal circuits
      - disease state to healthy state
    - learning
  - ...
our research focus

• network modulation as a reparative therapy
  • epilepsy, parkinson, alzheimers

• circuits connectivity—behavior
  • common theme
    • tools
  • influence on network
this talk

• network modulation as a reparative therapy
  • epilepsy, parkinson, alzheimers

• circuits connectivity—behavior
  • common theme
    • tools
  • influence on network
neurological disorders

- human nervous system
  - a gigantic network with nano scale structures
  - 200 billion neurons and trillions of connections
neurological disorders

• human nervous system
  • a gigantic network with nano scale structures
  • 200 billion neurons and trillions of connections
• over 200 identified neurological disorders
• “cost” of neurological diseases
  • $600 billion annually
epilepsy

• unprovoked and recurring seizures

• seizure

  • no standard definition
epilepsy

• unprovoked and recurring seizures

• seizure

  • no standard definition

  • abnormally synchronized hyper-excited neuronal activities

  • variations

    • sub-clinical seizure burst — full blown seizure

    • single focal seizure — multifocal seizure
epilepsy

• effects 3 million patients in the USA
  • medication
  • resection
  • stimulation (modulation)
    • neurons respond to electric signals!
epilepsy

- effects 3 million patients in the USA
  - medication
  - resection
  - stimulation (modulation)
    - neurons respond to electric signals!
recording-stimulation

- deep brain
recording-stimulation

- deep brain

- subdural
recording-stimulation

- deep brain
- subdural
- trans-cranial
recording-stimulation

- deep brain
- subdural
- trans-cranial

tradeoff: invasive versus effective
our methodology

• deep brain

• subdural

• trans-cranial
today’s application

• subdural recording
  • identify epileptic zone
today’s application

• subdural recording
  • identify epileptic zone
• resection!
potential application

- subdural stimulation

epileptic zone
challenges in stimulation

- prevent the network “from going to” hyperexcitable state
- identify seizure zone
- identify temporal markers
  - low frequency stimulation

seizure markers!
subdural recording and stimulation

- wish list
  - real time
  - closed loop
let’s do this!
subdural recording and modulation

• electro-cortico-graphy (ECoG)
  • subdural
  • 154 channels (electrodes)
recording

- electro-cortico-graphy (ECoG)
- subdural
- 154 channels (electrodes)
- recording

Figure 3: Snapshot of ECoG activities in 10 seconds over 4 channels between Temporal and Parietal lobes, referred to as TP.
Epilepsy is a neurological disorder characterized by unprovoked seizures. Surgical resection is only successful in some patients; unfortunately this moderate success rate comes with tremendous risks and potential for negative side effects. Inspired by the success in treating movement disorders like Parkinson's Disease, electrical stimulation using subdural and depth electrodes is considered as a promising technique to treat epilepsy [33].

**Recoding System Model:**
Many patients with intractable epilepsy have been approved to undergo implementation of arrays of electrodes underneath the dura (see Figure 2) and electrocorticographic (ECoG) signals from these arrays are recorded for long periods of time and under a number of different conditions. In addition, epilepsy is a dynamic disease in which brain transitions between different states [23]. The dynamic behavior observed in subdural recordings (i.e., ECoG) makes the selection of optimal temporal and spatial locations for stimulation non-trivial [34]. PI Tandon’s Lab has a substantive track record of the collection and interpretation of ECoG data in the context of cognitive processes and in relating these data to other measures of brain activity and connectivity. These studies have illuminated the neural circuits and mechanisms underlying cognitive control [35], language [36], memory and spatial navigation [37], while pioneering computational techniques for multi-modal data integration [38, 39]. A recent innovation was to show that ECoG data could be used to constrain and validate pathways mediating information transfer revealed by diffusion tensor imaging (DTI) [36, 38, 40–43]. Computational approaches for selecting the optimal electrical stimulation parameters require the complete knowledge of different brain states and the temporal transitions between them. In very preliminary studies, we have developed change point detection algorithms and applied them to ECoG data to identify segments of activity corresponding to the different states of epileptic brain [44].

Data used in that study was an ECoG recording from a patient with epilepsy from Tandon’s Lab and ECoG was recorded from 154 subdural electrodes at 1000 Hz. Figure 3 shows a snapshot of 10 seconds of activity from 4 channels between the temporal (T) and parietal (P) lobes, referred to as TP.
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Leveraging our successful preliminary work with data from Tandon's Lab, our team is uniquely positioned to build a connectivity model for ECoG data exploring their spectral and temporal characteristics. The focus will be on ECoG recording of the activity from the cerebral cortex of the brain. The ECoG electrode grid used for data collection has electrodes and is sampled at 1000 Hz. Let \( x_1: N = x(1), x(2), \ldots, x(N) \) denote the measured ECoG activity, where \( N \) is the number of data samples observed and \( x(n) = [x(1), x(2), \ldots, x(d)]^T \) denotes the vector of activity recorded from the \( d \) electrodes at time index \( n \) with \( x_i^n \) representing the activity at the \( i \)th electrode for \( i = 1, 2, \ldots, d \). We also denote \( x_m:l \) as the data between time indices \( m \) and \( l \), that is, \( x(m), x(m+1), \ldots, x(l) \). As mentioned earlier, the thrusts of the project are to explore spectral, temporal, and spatial characteristics of the ECoG.
recording

- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)
- recording
- stimulation?

![Brain Diagram with ECoG Activity](image)

**Figure 3:** Snapshot of ECoG activities in 10 seconds over 4 channels between Temporal and Parietal lobes, referred to as TP.
stimulation (modulation)

- protocol
  - depress the influence of one population of neurons on another
  - temporally precise low frequency stimulation of selected electrodes
research agenda

- temporally precise low frequency stimulation of selected electrodes

![Block Diagram of the Proposed System](image-url)
research agenda

- temporally precise low frequency stimulation of selected electrodes
- develop a model and protocols—real-time, closed loop,
- build the system
- clinical trial
today’s talk

• develop

• sparse effective connectivity
modeling

- time series of length $N$
- $d$ channels

\[
X_1^N = (x_1, x_2, \ldots, x_N)
\]

\[
x_n = [x_n(1), x_n(2), \ldots, x_n(d)]^T \in \mathbb{R}^d \ \forall n
\]
modeling

- time series of length $N$
- $d$ channels

$$X_1^N = (x_1, x_2, \cdots, x_N)$$

$$x_n = [x_n(1), x_n(2), \cdots, x_n(d)]^T \in \mathbb{R}^d \ \forall n$$

these are not spikes
local field potentials
modeling

• time series of length $N$ --- hours and hours of observations

• $d$ channels --- 154

\[ \mathbf{X}_1^N = (\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_N) \]

\[ \mathbf{x}_n = [x_n(1), x_n(2), \cdots, x_n(d)]^T \in \mathbb{R}^d \quad \forall n \]
modeling

• time series of length $N$ — hours and hours of observations

• $d$ channels — 154

exploit natural sparsity
modeling

- time series of length $N$ — hours and hours of observations
- $d$ channels — 154

exploit natural sparsity

spectral? temporal? spatial?
spectral decomposition

- time-frequency analysis
  - 0.1-4 Hz $\delta$ band
  - 4-8 Hz $\theta$ band
  - 8-14 $\alpha$ band
  - 14-30 $\beta$ band
  - $>$ 30 $\gamma$ band

The challenges in this endeavor are the unknown dependence on frequency, the unknown number of temporal states, the unknown transition times between states, and non-uniform number of observations for each state. One example of a temporal state with few observations is the ictal state, since the ictal state recordings are typically of shorter duration than pre-ictal state recordings. Therefore, the resulting protocols to build connectivity graph must be robust against the uncertainty in all these parameters. Our proposed solution decomposes the problem into three parts. First, we filter the data into different frequency bands using a filter bank, then we describe the transition times between the multiple states, and finally we model the network structure across all these temporal states separately for each frequency band. The change point detection algorithm developed by our team in [44] should be used in conjunction with time-varying graph connectivity estimation algorithms to solve this for each frequency band. The closed-loop and real-time aspects of the proposed solution require development of low complexity algorithms. Thrust 2 will then focus on integrating all the dynamic connectivity graphs to determine the spatio-temporal parameters of LFS.

Spectral Decomposition:
In order to manage complexity of graphical modeling we propose spectral-temporal decomposition of recorded data. To account for the possible variation in connectivity within different frequency bands, we will first band-pass filter the ECoG recordings into different frequency bands and then build the time-varying effective connectivity of the patient during the observation window for each band separately. Spectral decomposition is relatively straightforward. First these recordings are passed through a filter bank consisting of band-pass filters. The band-pass filters separate the recordings into multiple frequency bands given by

- 0.1-4 Hz referred to as $\delta$-band,
- 4-8 Hz referred to $\theta$-band,
- 8-14 $\alpha$ band,
- 14-30 $\beta$ band,
- $>$ 30 $\gamma$ band.
temporal segmentation

- Bayesian change detection
- run length

![Data Samples - $x^{(n)}$](image)

**Figure 5:** (a) Simulated 1000 data samples from Gaussian distribution with different variances. (b) True run-length and the run-length obtained from maximum posterior calculations.

Effective connectivity is usually estimated using the notion of Granger causality [80], transfer entropy [81, 82], dynamic causal modeling (DCM) [83, 84] and directed mutual information [85, 86]. DCM starts from a plausible model of interactions and estimates the exact strength of coupling using the well-known Expectation-Maximization (EM) algorithm. The algorithm has high complexity as the number of nodes increase. Transfer entropy, on the other hand, requires plug-in estimates that do not have convergence properties [87]. Directed mutual information was introduced [85] to analyze neuronal spiking activities. In this work we model the recordings using a MV AR process (1) and estimate the Granger causality using generalized partial directed coherence (GPDC) [88, 89]. In addition to the drawbacks of other techniques, the main reason for this choice is analytical tractability of MV AR processes and they also fit well with the developed probabilistic inference of change points. Also beginning from the work of Granger, autoregressive models are most commonly used to estimate Granger causality [77, 79].

Effective connectivity is calculated from the MV AR model in (1) in two steps: the first step involves calculating the MV AR coupling matrix coefficients and the second step involves computing the Granger causality indices from the MV AR matrices $A_p$, for $p = 1, 2, \ldots, P$ [79, 90]. The non-zero entries in these matrices determine the influence exerted by one neuronal region over another. The number of elements in the matrix is $P^2$, usually a very large number. Generally, the signal at an electrode is only influenced by a small set of regions and therefore most of the elements in $A_p$ are assumed to be zero for $p = 1, 2, \ldots, P$. For that reason, we are only interested in sparse solutions to the problem of fitting MV AR model. We refer to this model as sparse MV AR (SMV AR) model [91].

The change point detection algorithm outputs the change-points in the observed recordings. Let $x_{\tau_m}^{1:n}$ denote the $m$th segment of the data. This segment is modeled with a MV AR process of order $P$ given by (1). This model is equivalent to

$$y_i = Xa_i + z_i,$$

where $y_i = hx_1^{(n)}(\tau_m + 1) \quad x_2^{(n)}(\tau_m + 2) \cdots x_{\tau_m}^{(n)}$ is the vector of recordings from $i$th electrode between $\tau_m$ and $\tau_m + 1$. The change point detection algorithm outputs the change-points in the observed recordings. Let $x_{\tau_m}^{1:n}$ denote the $m$th segment of the data. This segment is modeled with a MV AR process of order $P$ given by (1). This model is equivalent to
temporal segmentation

• Bayesian change detection
  • run length
• seizure markers
  • inter-ictal spikes
• high frequency oscillations

Effective connectivity depends on the model of that influence. Anatomical connectivity is usually determined from diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI). On the other hand, functional and effective connectivity are estimated from different neuro-imaging techniques such as ECoG, EEG, MEG, fMRI, and PET. Of the two, functional connectivity is estimated from the observations directly without assuming any model of connectivity. However, it cannot be distinguish between direct and indirect influences and cannot identify the direction of influence [78, 79]. On the other hand, effective connectivity does not have any of these drawbacks. Effective connectivity is the focus of this proposal since directionality and timing are keys to our network stimulation.

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\[
 y_i = \sum_{a} x_{i, a} + z_i ,
\]

where \( y_i = h x_{\tau_m, 1} + x_{\tau_m, 2} + \ldots + x_{\tau_m, \tau_m} \), \( y_i \) is the vector of recordings from the \( i \)th electrode between \( \tau_m, 1 \) and \( \tau_m, \tau_m \).
spatial connectivity

- graphical model
- connectivity
- causality

![Spatial Connectivity Diagram](image)
Granger causality

- one time series forecasting another
  - economics
  - transportation
  - ...

Granger causality

- one time series forecasting another
  - economics
  - transportation
  - ...
  - Norbert Wiener (1956)
  - Clive Granger (1969)
  - Hans Marko (1973)
  - James Massey (1990)
a little background
a little background

• mutual information

\[ I(X; Y) = \int f_{XY} \log \frac{f_{XY}}{f_X f_Y} \]

• average information about \( X \) provided by \( Y \)
a little background

- mutual information

\[ I(X; Y) = \int f_{XY} \log \frac{f_{XY}}{f_X f_Y} \]

- not directional

- no “temporal” causality
a little background

- directed information and causality

\[ I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n|Y_1^{n-1}) \]

- directional

\[ X_1^N \equiv (X_1, X_2, \ldots, X_N) \quad Y_1^N \equiv (Y_1, Y_2, \ldots, Y_N) \]
a little background

• mutual information of time series

\[ I(\mathbf{X}_1^N; \mathbf{Y}_1^N) = \sum_{n=1}^{N} I(\mathbf{X}_1^N; Y_n | Y_1^{n-1}) \]

• causality?

\[ \mathbf{X}_1^N \equiv (X_1, X_2, \ldots, X_N) \quad \mathbf{Y}_1^N \equiv (Y_1, Y_2, \ldots, Y_N) \]
a little background

- mutual information of time series

\[
I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})
\]

- causality?

\[
I(X_1^N; Y_1^N) = \sum_{n=1}^{N} I(X_1^n, Y_n | Y_1^{n-1})
\]

\[\begin{align*}
X_1^N &\equiv (X_1, X_2, \ldots, X_N) \\
Y_1^N &\equiv (Y_1, Y_2, \ldots, Y_N)
\end{align*}\]
insight

- time series
  
  - Does knowing time series $X$ help with prediction of time series $Y$?
insight

• time series

  • Does knowing time series $X$ help with prediction of time series $Y$?

  • Does knowing time series $Y$ help with prediction of time series $X$? if directionality is not clear.
insight

- time series (specific underlying assumption!!)
  
  - causality
    
    $$X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + z_n$$
    
    ![Diagram of FIR and IIR filters with noise](attachment:image.png)
insight

- time series (specific underlying assumption!!)

- causality

\[ X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + \varepsilon_n \]

- what is

\[ I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1}) \]
2 examples
example 1

\[ X_n = Y_{n-1} + z_n \]

• with i.i.d.

\[ Y_n \sim \text{Gaussian}(0, \sigma_Y^2) \]

\[ z_n \sim \text{Gaussian}(0, \sigma_z^2) \]
example 1

\[ X_n = Y_{n-1} + z_n \]

- with i.i.d.

\[ Y_n \sim \text{Gaussian}(0, \sigma^2_Y) \]

\[ z_n \sim \text{Gaussian}(0, \sigma^2_z) \]
example 1

\[ X_n = Y_{n-1} + z_n \]

Then

\[ I(Y \rightarrow X) = \frac{1}{2} \log(1 + \frac{\sigma_Y^2}{\sigma_z^2}) \]

\[ I(X \rightarrow Y) = 0 \]
example 2

\[ X_n = Y_n + z_n \]

- with i.i.d.

\[ Y_n \sim \text{Gaussian}(0, \sigma_Y^2) \]

\[ z_n \sim \text{Gaussian}(0, \sigma_z^2) \]
example 2  

\[ X_n = Y_n + z_n \]

\begin{itemize}
  \item with i.i.d.
  \end{itemize}

\[ Y_n \sim \text{Gaussian}(0, \sigma_Y^2) \]

\[ z_n \sim \text{Gaussian}(0, \sigma_z^2) \]
example 2

\[ X_n = Y_n + z_n \]

\[ Y_n \sim \text{Gaussian}(0, \sigma_Y^2) \]
\[ z_n \sim \text{Gaussian}(0, \sigma_z^2) \]

- then

\[ I(Y \rightarrow X) = I(X \rightarrow Y) = I(X; Y) = \frac{1}{2} \log\left(1 + \frac{\sigma_Y^2}{\sigma_z^2}\right) \]
insight

- time series
  - Gaussian
  - moving average autoregressive
  - Granger causality = directed information

\[
X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + z_n
\]

\[
I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})
\]
back to real data!

- subdural recording from epileptic patients
  - left hippocampus region
  - 151 channels
  - sampling rate 1kHz
  - focus
    - 6 channels
    - 100 seconds
real data

Time (s)

LAH6
LAH5
LAH4
LAH3
LAH2
LAH1
real data

- Gaussian?
- linear moving average autoregressive model?
real data

- model order in the range $P, Q \in [75, 125]$
- electrodes labeled LAH1-LAH6

$$X_{n}^{(6)} = \sum_{p=1}^{P} U_p X_{n-p}^{(6)} + \sum_{q=0}^{Q} V_q X_{n-q}^{(5)} + z_n$$
real data

- directed information

\[
\{I(X^{(i)} \rightarrow X^{(j)})\}_{6 \times 6} = \begin{pmatrix}
- & 0.11 & 0.05 & 0.05 & 0.06 & 0.08 \\
0.08 & - & 0.07 & 0.09 & 0.09 & 0.10 \\
0.07 & 0.31 & - & 0.86 & 0.48 & 0.32 \\
0.05 & 0.20 & 0.84 & - & 0.85 & 0.47 \\
0.05 & 0.16 & 0.43 & 0.82 & - & 0.91 \\
0.06 & 0.14 & 0.25 & 0.41 & 0.89 & - \\
\end{pmatrix}
\]
strong connections

- directed information
strong connections

• directed information?

\[ I(X^{(3)} \rightarrow X^{(6)}) = 0.32 \]
strong connections

- conditional directed information

\[ I(X^{(3)} \rightarrow X^{(6)} | X^{(5)}) = 0.0 \]
strong connections

• conditional directed information \( I(X^{(3)} \rightarrow X^{(6)} | X^{(5)}) = 0.0 \)
strong connections

- eliminating indirect influence
a broader view—all the electrodes

- not sparse
a broader view

• eliminating indirect influences
a broader view

- not sparse
- temporal variations
a broader view

• eliminating indirect influences
a broader view

• not sparse

• spectral variations?
a broader view

• not sparse

• spectral variations

• 4-8 Hz θ band
a broader view

• eliminating indirect influences
final thoughts

• closed loop stimulation

  • markers

    • spectral

    • temporal

    • spatial
final thoughts

- closed loop stimulation
- markers
- real time

low frequency stimulation to depress the excitable state
final thoughts

• develop protocols
  • temporal markers
  • directed connectivity

• build the system

• clinical trial !!!!!