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Structural Target Controllability of Brain Networks in Dementia

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Abstract— **Controlling the dynamics of large-scale neural circuits might play an important role in aberrant cognitive functioning as found in Alzheimer's disease (AD). Analyzing the disease trajectory changes is of critical relevance when we want to get an understanding of the neurodegenerative disease evolution. Advanced control theory offers a multitude of techniques and concepts that can be easily translated into the dynamic processes governing disease evolution at the patient level, treatment response evaluation and revealing some central mechanisms in brain connectomic networks that drive alterations in these diseases. Two types of controllability - the modal and average controllability - have been applied in brain research to provide the mechanistic explanation of how the brain operates in different cognitive states. In this paper, we apply the concept of target controllability to structural (MRI) connectivity graphs for control (CN), mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects. In target controllability, only a subset of the network states are steered towards a desired objective. We show the graph-theoretic necessary and sufficient conditions for the structural target controllability of the above-mentioned brain networks and demonstrate that only local topological information is needed for its verification. Certain areas of the brain and corresponding to nodes in the brain network graphs can act as drivers and move the system (brain) into specific states of action. We select first the drivers that ensures the controllability of these networks and since they do not represent the smallest set, we employ the concept of structural target controllability to determine those nodes that can steer a collection of states being representative for the transitions between CN, MCI and AD networks. Our results applied on structural brain networks in dementia suggest that this novel technique can accurately describe the different node roles in controlling trajectories of brain networks and being relevant for disease evolution.**

I. INTRODUCTION

Modern graph control theory provides a powerful insight into dynamical phenomena that take place in brain imaging connectomics in connection with the progression of neurodegenerative diseases such as dementia. The changes in structural or functional connectivity over time can be captured by the trajectories of the many states of the brain networks. The regions found on brain images can be mapped as graph nodes and their connectivity as edges.

Both concepts of controllability and observability in modern graph theory [1], [2], [3], [4], [5], [6] are of crucial importance for understanding operational and dynamical brain networks impacting neural function, disease, development and rehabilitation. Controllability refers to the capability of driving the network system along a desired trajectory while observability refers to infer the internal states from knowing the external outputs [7]. Finding the leader nodes in such networks is a key requirement for influencing the trajectories of the states towards a desired value [8], [9], [10], [11], [12].

In [13] and [14], [15], [16], [17], [18], [19] was shown that certain brain regions or nodes in the functional or structural connectivity graph can act as drivers and move the system (brain) into specific states of action translating into specific trajectories which are different for certain diseases and affect the cognitive functions. Looking into brain networks' graph architectures, we discover highly connected areas and weakly connected areas, and they both take different roles when influencing disease trajectories. In [13] was shown that two different types of controllability concepts apply to this aspect. The so-called "average controllability" quantifies the position of a node in directing a network to easily reachable states. Those nodes represent highly connected hubs. On the other hand, "modal controllability" refers to nodes in weakly connected areas moving the brain to difficult-to-reach states. The mathematical conditions necessary to fulfill the conditions for these two controllability types were derived.

The driver nodes found in the course of a disease such as AD change over time since the brain network structure and connectivity undergoes alterations. Theoretical tools provide us with the set of those driver nodes ensuring the structural controllability of a brain network. In many neurodegenerative diseases such as dementia, only a subset of states needs to be steered towards desired values, instead of the full set of states. This corresponds to the disease-affected regions in the brain network. Given a subset of states, the ability to steer this subset of states arbitrarily is known as target controllability. We apply this novel concept on CN, MCI and AD networks and determine the subset of regions computationally that are involved in disease progression. The location of the leaders are found to be in clinically relevant areas such as temporal and frontal lobes and are already seen in MCI.

II. METHODS

A. Controllability of Complex Networks

A network of N nodes is described as a linear time invariant (LTI) system:

$$\dot{x}(t) = Ax(t) + Bu(t), \mathrm{y}(t) = Cx(t) \tag{1}$$

where $x(t) \in R^N$ is the state of the system, $u(t) \in R^M$ is the input vector and $y(t) \in R^K$ the output vector. A is an $N \times N$ coupling or adjacency matrix of the system with

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a_{ij} representing the weight between node i and j, and B is an $N \times M$ input matrix identifying the nodes that are being directly controlled. $C \in R^{K\times N}$ is the output matrix. For directed nodes $a_{ij} \neq a_{ji}$ while for undirected nodes the weights' symmetry condition holds.

In the following, we will give the definition of the state and structural controllability [20] and a theorem defining four controllability criteria.

Definition 1 (State Controllability)

The linear network described in equation 1 is said to be state controllable if, for any initial state $x(t_0) \in R^N$ and any final state $x(t_f) \in R^N$, there is a finite time t_1 and an input signal $u(t) \in R^m, t \in [t_0, t_1]$, such that $x(t_1; x(t_0), u) = x(t_f)$.

There are four equivalent controllability criteria for the system (1) and they are presented in Theorem 1.

Theorem 1 (State Controllability Theorem)

The linear network described in equation 1 is said to be completely state controllable if and only if one of the following conditions is fullfilled:

i) Kalman rank criterion: the controllability $N \times NM$ controllability matrix C

$$Q = (B, AB, A^2B, \cdots, A^{N-1}B) \tag{2}$$

has full rank, that is $rank(Q) = N$.

ii) Popov-Belevitch-Hautus (PBH) rank criterion: rank $[sI_N - AB] = N, \forall s \in Q$.

iii) PBH eigenvector test: the relationship $v^T A = \lambda v^T$ implies $v^T B \neq 0$, where v is the nonzero left eigenvector of A associated with eigenvalue λ.

iv) Gramian matrix criterion: the Gramian matrix

$$W_Q = \int_{t_0}^{t_1} e^{At} BB^T e^{A^T t} dt \tag{3}$$

is nonsingular.

Definition 2 (Structural Controllability)

A structural pair (A, B) is structurally controllable if the controllability matrix $Q(A, B) := (B, AB, A^2B, \cdots, A^{N-1}B)$ has full rank, that is $rank(Q) = N$.

B. Structural Target Controllability

Differently from controllability where we are concerned with steering all states towards a desired final state, in structural target controllability we aim to control the behavior of only a subset of states. More specifically, we consider a set $\mathcal{T} \subseteq [N]$, the so-called *target set*. We then define the pair (A, B) as target controllable with respect to $\mathcal{T}$ and give the definition of structural target controllability below.

Definition 3 (Structural Target Controllability)[21]

Given a structural pair (A, B), and a target set $\mathcal{T} = \{i_1, \cdots, i_K\} \subseteq [N]$. We define a matrix $\mathcal{C}_\mathcal{T} \in R^{K\times N}$ by $[\mathcal{C}_\mathcal{T}]_{l_j} = \begin{cases} 1 & \text{if} j = i_l, i_l \in \mathcal{T}, \\ 0 & \text{otherwise.} \end{cases}$

The structural pair (A, B) is structurally target controllable with respect to $\mathcal{T}$ if the target controllability matrix $Q_\mathcal{T}(A, B) := \mathcal{C}_\mathcal{T}(B, AB, A^2B, \cdots, A^{N-1}B)$ has full rank.

The necessary and sufficient graph theoretic conditions for structural target controllability of the given structural pair (A, B) and target set $\mathcal{T}$ are given below.

Theorem 2 (Structural Target Controllability Theorem)[21]

Consider a structural pair (A, B) with A being a symmetric matrix and a target set $\mathcal{T} \subseteq [N]$. The structural pair (A, B) is structurally target controllable with respect to $\mathcal{T}$, if and only if the following conditions hold simultaneously:

1.) All state vertices in $\mathcal{X}_\mathcal{T}$ are input-reachable;

2.) $|\mathcal{N}(\mathcal{S})| \geq |\mathcal{S}|, \forall \mathcal{S} \subseteq \mathcal{X}_\mathcal{T}$.

$\mathcal{X}_\mathcal{T} \subseteq \mathcal{X}$ represents the set of vertices indexed by $\mathcal{T}$. Let $\mathcal{D} = (\mathcal{V}, \mathcal{E})$ be a a directed graph with a vertex and edge set $\mathcal{V}$ and $\mathcal{E}$, respectively. Given $\mathcal{S} \subseteq V$, we define the in-neighbor set of $\mathcal{S}$ as $\mathcal{N}(\mathcal{S}) = \{v_i \in \mathcal{V} : (v_i, v_j) \in \mathcal{E}, v_j \in \mathcal{S}\}$. A vertex v_i is reachable from vertex j in $\mathcal{D} = (\mathcal{V}, \mathcal{E})$, if there exists a path from vertex v_j to vertex v_i.

C. Determining Driver Nodes Based on Graph Distances

We apply the distance-based structural controllability results from [11] to determine the leader nodes in the structural brain networks. In the context of target control of complex networks, the distance between drivers and target nodes, known as the control distance, plays an important role in the required control energy [22]. In this section, we first utilize such distances to define a tight lower bound on the rank of controllability matrix. The leader selection problem can be stated as finding a minimum number of leaders that render a given network controllable. If edge weights of the graph G are known, one can execute exhaustive search to compute the rank of controllability matrix for any possible subset of leaders and select the minimal set. In addition to computational cost, this method is not possible when edge weights are unknown. In this case, one can convert the leader selection problem to an optimization problem ensuring that the dimension of the controllable subspace is not smaller than a desired value $k \in \{1, 2, \cdots, n\}$.

III. RESULTS

We apply the theoretical results on structural (MRI) connectivity graphs for control (CN), mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects. For our application, it's only necessary to fulfill condition i) from Theorem 1. These graphs were extracted from [23] and their data were obtained from the Alzheimer's Disease Neuroimaging

Initiative (ADNI) database (adni.loni.usc.edu). The authors in [23] segmented the MRI images into White Matter (WM) and Gray Matter (GM) tissues but used only the GM images. For the structural data, the connections in the graph show the inter-regional covariation of gray matter volumes in different areas. We considered only 42 out of the 116 from the Automated Anatomical Labeling Atlas (AAL) in the frontal, parietal, occipital and temporal lobes as shown in [23]. The nodes in the graphs represent the regions while the links show if a connection is existing between these regions or not.

Using the distance-based structural controllability results from [11], it is shown in Table I that structural networks would be completely controllable under any weighted consensus-type dynamics if the leaders are selected as follows:

TABLE I

DRIVER NODES FOR STRUCTURAL NETWORKS FOR CN, MCI AND AD GRAPHS.

Controls:	8, 10, 27, 29, 30, 33, 34, 38, 40
MCI:	7, 8, 9, 11, 30, 31, 36, 37, 39, 42
AD:	9, 11, 12, 30, 31, 34, 39, 41

In Figure 1, we visualize all driver nodes (red circles) and see the differences in terms of driver nodes between the CN, MCI and AD networks.

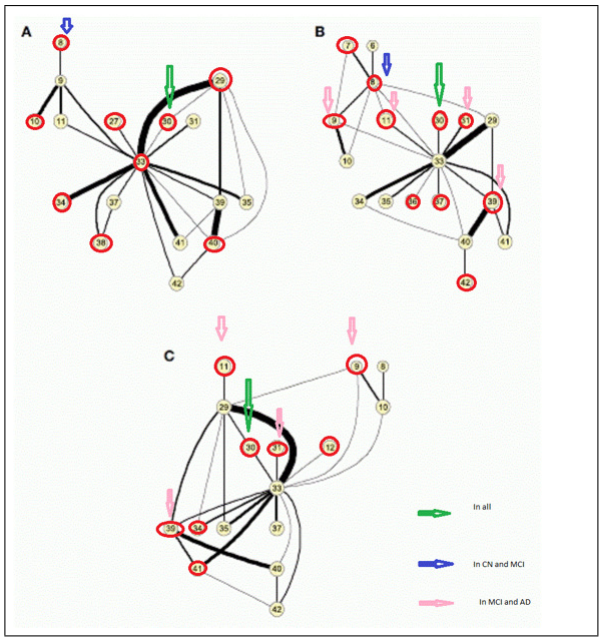

Fig. 1. Identifying the driver nodes in brain network graphs for structural data for (A) controls, (B) MCI and (C) AD as described in [23]. The arrows pointing at the driver nodes show the driver nodes found in all brain networks and those found in CN and MCI or MCI and AD networks.

We select the target set $\mathcal{T}$ for each network in Table II such that it shows the driver nodes found in all brain networks and those found in CN and MCI or MCI and AD networks.

We apply Theorem 3 for determining the structural target controllability for the chosen target set for the CN, MCI and AD networks. We can show that all required conditions are fulfilled and thus the structural target controllability can be achieved for each of the three networks. The common found nodes in the target set for MCI and AD are located in the frontal and temporal lobe, respectively. According to clinical findings, these nodes are a good indicator of the starting neurodegenerative processes in MCI subjects which further continue in AD subjects.

TABLE II

TARGET SET $\mathcal{T}$ FOR STRUCTURAL NETWORKS FOR CN, MCI AND AD.

Controls:	8, 30
MCI:	8, 9, 11, 30, 31, 39,
AD:	9, 11, 30, 31, 39

IV. CONCLUSIONS

In this paper, we applied the novel concept of structural graph controllability on CN, MCI and AD brain networks to obtain a better understanding of the trajectory of the disease progression and the participating regions in dementia. We first determined the leader nodes in these networks but determined mathematically a reduced target set of nodes that are relevant for disease evolution and especially for the transition from MCI to AD. To address this problem, we considered undirected and symmetric graph connectivity matrices. We derived necessary and sufficient conditions for structural target controllability of the brain networks. It is worth to mention that only local topological information was required to verify the structural target controllability. Examples are given to elucidate the theoretical results and are in compliance with clinical findings showing that the target set for MCI and AD are located in the frontal and temporal lobe, respectively.

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