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Controllability of Structural Brain Networks in Dementia

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ABSTRACT

The dynamics of large-scale neural circuits is known to play an important role in both aberrant and normal cognitive functioning. Describing these phenomena is extremely important when we want to get an understanding of the aging processes and for neurodegenerative disease evolution. Modern systems and control theory offers a wealth of methods and concepts that can be easily applied to facilitate an insight into the dynamic processes governing disease evolution at the patient level, treatment response evaluation and revealing some central mechanism in a network that drives alterations in these diseases. Past research has shown that two types of controllability - the modal and average controllability - are key components when it comes to the mechanistic explanation of how the brain operates in different cognitive states. The average controllability describes the role of a brain network's node in driving the system to many easily reachable states. On the other hand, the modal controllability is employed to identify the states that are difficult to control. The first controllability type favors highly connected areas while the latter weakly connected areas of the brain. Certain areas of the brain or nodes in the connectivity graph (structural or functional) can act as drivers and move the system (brain) into specific states of action. To determine these areas we apply the novel concept of exact controllability and determine the minimum set and the location of driver nodes for dementia 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 show the transition of some driver nodes and the conservation of others in the course of this disease.

Keywords: Neurodegenerative disease, minimum driver set, leader-follower networks, exact controllability

1. INTRODUCTION

A brain network can be mathematically easily described by a graph where the nodes represent brain areas and the edges the strength of connections between these areas emerging when certain tasks are performed. The first known and still most common graphs are static graphs[1] that lack a node or edge dynamics with connections reflecting the correlations between certain brain areas. However these networks can not describe cognitive fluctations nor the functional and structural connectivity or state changes of both. Introducing the concept of dynamical graphs, we are able to model the dynamical behavior and capture the whole temporal and spatial dynamics of cognitive networks based on mathematical coupled differential equations.

It has been shown that cognitive control[2] and the ability to control brain dynamics holds great promise for improving cognitive functions and reverse aging processes. The human brain is thus able to navigate between diverse cognitive states. Its most impressive role is in connecting multiple sources of information in large-scale networks that are required, for example, to solve complex cognitive problems and retrieving information from memory. The classical cognitive theory of control is based on the concept of competitive dynamics in frontal cortices modeled by the early computational neuroscience techniques, while modern studies in functional neuroimaging suggest that control functions are facilitated by a transitory interplay of cooperation and competition patterns between distributed neural systems found in default mode, attention and frontoparietal networks.[3] Modern control theory and graph networks can replace longitudinal studies in dementia research by simply developing models of brain dynamics that mimic disease evolution and different state changes found in dynamic functional MRI representative for many neurodegenerative diseases. An analogy exists between networked systems in the

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brain and modern dynamic graph networks: neural ensembles or regions in the brain are mapped to nodes in graph theory and their structural or functional connections correspond to weights. Adopting from control the concepts of controllability and observability are a further step for understanding operational and dynamical brain networks impacting neural function, disease, development and rehabilitation. Controllability for a linear time invariant system, such as the brain can be modeled is understood as the capability of a dynamical system to reach from any initial state in final time any final state.

In[2] and[4–6] was shown that certain brain areas or nodes in the connectivity graph of structural or functional brain networks can act as drivers and move the system (brain) into specific states of action. These are known to influence the cognitive functions. Further analyzing the topology of a brain network, we find highly connected areas and weakly connected areas. In[2] was shown that two different types of controllability concepts can meaningfully describe this aspect. The so-called "average controllability" quantifies the position of a node in directing a network to easily reachable states. Those nodes are found in highly connected areas (hubs). On the other hand, "modal controllability" refers to nodes found in sparse brain network's areas moving the brain to difficult-to-reach states. A modality to determine the average controllability was proposed in[7] determining a ranking of the best driver sets and thus of the network's hubs. For the modal controllability we employ the method proposed by[8] which operates based on the graph distances to determine controllability.

An open question that remains in the dynamical analysis of brain networks is the minimum driver set representing the nodes that influence the long-term dynamical behavior of the networks and their location on the graph network. To tackle this challenging problem, we propose to apply the exact controllability theory[9] on undirected graph networks and determine based on the algebraic multiplicity of the system's matrix the minimum number of driver nodes and through techniques of elementary column transformation their location.

In this paper, we determine the location of the minimum set of driver nodes and illustrate in examples of structural brain networks the theoretical analysis.

2. METHODS

2.1 Modal and Average Controllability

In[2] was shown that a simple noise-free linear discrete-time and time-invariant model can be employed to describe the neural dynamics measured by fMRI

$$x(t+1) = Ax(t) + B_{\mathcal{K}} u_{\mathcal{K}}(t) \tag{1}$$

where $x \in R^n$ is the magnitude of the neurophysiological activity (state) of the brain regions over time, $A \in R^{n \times n}$ is the adjacency matrix, $B_K \in R^{n \times m}$ is the input matrix and $u_K \in R^m$ is the input vector. The input matrix identifies the control nodes K in the brain. In[2] was given as the condition for controllability of the network described in equation (1) that the controllability Gramian W_K is invertible with

$$W_K = \sum_{\tau=0}^{\infty} A^{\tau} B_k B_K^T A^{\tau} \tag{2}$$

Two definitions of controllability are used: the average and the modal controllability.

The average controllability is given as the average input energy from a set of control nodes and over all possible target states. In[2] a measure of average controllability[10] is given as $trace(W_k)$. Regions of high average controllability are known to be most influential in the control of the network dynamics.

The modal controllability is employed to identify states that are difficult to control and identifies weakly connected areas. In[11] was stated that the modal controllability is computed from the eigenvector matrix of the network adjacency matrix A.

2.2 Controllability of Complex Networks

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

$$\dot{x}(t) = Ax(t) + Bu(t) \tag{3}$$

where $x(t) \in R^N$ is the state of the system, $u(t) \in R^M$ is the vector of M controllers, A is an $N \times N$ coupling or adjacency matrix of the system with a_{ij} representing the weight between node i and j, and B is an $M \times N$ input matrix identifying the nodes that are being directly controlled. 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 controllability[12] and a theorem defining four controllability criteria.

Definition 1 (State Controllability)

The linear network described in equation 3 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 (3) and they are presented in Theorem 1.

Theorem 1 (State Controllability Theorem)

The linear network described in equation 3 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

$$C = (B, AB, A^2B, \cdots, A^{N-1}B) \tag{4}$$

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

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

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

$$W_C = \int_{t_0}^{t_1} e^{At} B B^T e^{A^T t} dt \tag{5}$$

is nonsingular.

2.3 Analysis of Network Controllability

There are various criteria to determine the controllability of a graph dynamical network for both directed and undirected networks.

2.3.1 Kalman Rank Criterion

In a graph dynamical system, nodes are endowed with state variables and dynamics, and are interconnected in a certain topology. If the nodes represent agents, we talk about a networked multi-agent system and the controllability was shown to be tackled under the leader-follower framework.[13]

Such a networked multi-agent system is described by

$$\dot{x_i}(t) = \sum_{j \in N_i} a_{ij}(x_j(t) - x_i(t)), i = 1, 2, \cdots, N, \tag{6}$$

where $x_i(t) \in R$ is the state vector of the ith node (agent) at time t and a_{ij} the adjacency matrix of an undirected graph. N_i represents the neighbor set of agent i.

The graph network described in (6), can be re-written in the Laplace dynamics form

$$\dot{x_i}(t) = -Lx(t), \tag{7}$$

with $x(t) = [x_1(t), \cdots, x_N(t)]^T \in R^N$ being the aggregated state vector of the agents and $L = (l_{ij}) \in R^{N \times N}$ representing the Laplacian matrix defined by

$$L_{ij} = \begin{cases} -a_{ij} & j \neq i, \\ \sum_{j \in N_i} a_{ij} & i = j \end{cases}$$

This network can be split into two groups, leaders and followers. The external control inputs are injected only into the leaders. Assuming that the leader set forms a disjoint graph from the follower set graph, we can repartition the Laplacian matrix L as

$$L = \begin{pmatrix} L_f & L_{fl} \\ L_{fl}^T & L_l \end{pmatrix},$$

where L_f is the Laplacian matrix related to the followers, L_l to the leaders and L_{fl} denoting the connections between the followers and the leaders. The leaders are in their dynamics independent of the followers. On the other hand, the followers are influenced by the leaders and obey the local nearest-neighbor rule. Their dynamics can be described by the following equation

$$\dot{x}_f(t) = -L_f x_f(t) - L_{fl} x_l(t) \tag{8}$$

where $x_f(t) \in R^{N_f}$ is the state vector of the followers and $x_l(t) \in R^{N-N_f}$ that of the leaders. We assume that the first agents $N_f(1 < N_f < N)$ are the followers and $N_f + 1$ to N the leaders.

The controllability of this system is defined as that the followers can be driven by the leaders from any initial states to arbitrary final states in finite time. There are two theorems regarding the controllability of the system (8) depending whether there is a single or multiple leaders.

Theorem 2[13]

The multi-agent system described in (8) with a single leader is state controllable if and only if the following conditions are fulfilled at the same time:

i) all the eigenvalues of L_f are distinct;

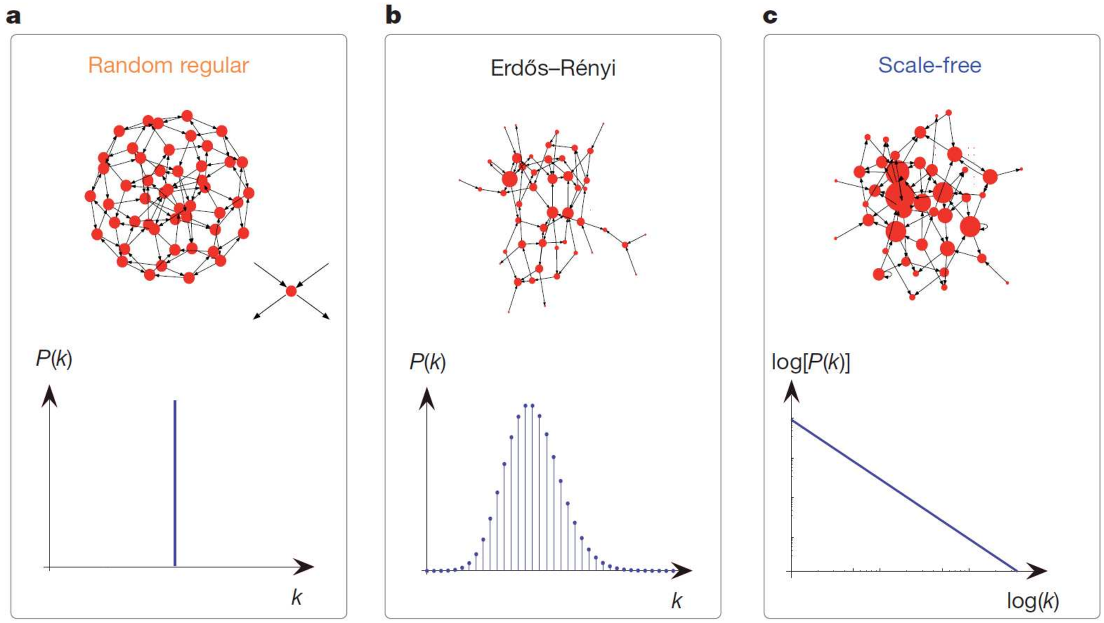
ii) the eigenvectors of L_f are not orthogonal to L_{fl}.

The next theorem states the conditions for the state controllability in case that there are multiple leaders.

Theorem 3[13]

The multi-agent system described in (8) with multiple leaders is state controllable if and only if L and L_f do not share any common eigenvalues.

The controllability of large-scale graph networks becomes a complex issue. The theory for structural controllability for these type of networks considering structured matrices A and B was developed by.[14] It was shown that the ability to drive a complex graph network toward any desired states can be measured by the minimum number of driver nodes that need to be driven by input signals such that a complete control of the graph network is achieved. The backbone of the theoretical framework for directed graph is given by the minimum inputs theorem. In[14] was shown that the minimum number of driver nodes is determined by the degree distribution of the network, with the driver nodes avoiding hubs. Sparse and heterogeneous networks are more difficult to control than dense and homogeneous networks which require only a few driver nodes. This relationship is shown in Figure 2.3.1.



a
Random Regular:
degree homogeneous network

b
Erdos-Renyi:
heterogenous,
Poisson degree distribution
$n_D \approx e^{-\bar{k}/2}$

c
Scale free:
heterogenous,
power law degree distribution
$n_D \approx e^{\left[-\frac{1}{2}\left(1-\frac{1}{\gamma-1}\right)\bar{k}\right]}$

Figure 1. Network structure and number of driver nodes.[14] n_D represents the number of driver nodes, $\bar{k}$ the average node degree and γ is the degree exponent. Reprinted from[14] with permission from Nature Publishing Group.

Summarizing, the most important findings from[14] are: (a) the denser a network, the fewer driver nodes are necessary to control it, (b) sparse and heterogeneous networks require the most driver nodes, and (c) not every network is controllable.

2.4 Selection of Driver Nodes

The classical PBH rank criterion from Theorem 1 is shown to connect the state controllability of (A, B) to the maximum multiplicity of the eigenvalues of the system matrix. This condition forms the basis for solving the minimum inputs problem. For directed graphs we apply the maximum multiplicity theorem and for undirected graphs the algebraic multiplicity theorem.

Theorem 4[9]

For an undirected graph with arbitrary weights, the minimum number of driver nodes N_D is equal to the maximum algebraic multiplicity of the eigenvalues of A, i. e.,

$$N_D = max_i[\rho(\lambda_i)], \tag{9}$$

where $\rho(\lambda_i)$ is the algebraic multiplicity of λ_i. This condition is valid for general undirected networks when A is a diagonalizable matrix.

Regarding the controllability of graph networks there are two paradigms to be applied: structural controllability for directed networks characterized by their structured matrices[12] and exact controllability for undirected networks.[9] In undirected graph networks, the matrix A is symmetric and this yields mutual dependencies between the parameters, and the structural controllability will give misleading resultsin this case regarding the minimum numbers of driver nodes. The exact controllability developed in[9] is based on the PBH rank criterion and represents a useful alternative to the structural controllability.

The approach to find the driver nodes is guided by the minimum inputs theorem. In a directed network they are identified via the maximum matching. Another technique applicable to undirected networks is the elementary column transformation.[9] It's important to mention that the set of driver nodes is not unique since it's dependent on the order in generating the elementary column transformation and by the way the linearly dependnet rows are chosen. However the number of driver nodes is unique since it depends on the value of the algebraic multiplicity. The control signals injected via the driver nodes and the matrix B should be applied on the identical rows to eliminate all linear correlations and not jeopardize the full-rank condition.

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 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 AAL in the frontal, parietal, occipital and temporal lobes as shown in.[15] The nodes in the graphs represent the regions while the links show if a connection is existing between these regions or not.

The results of the in-depth dynamical analysis for controllability based on elementary column transformations for structural networks are shown in Figure 2.4. The figure depicts the driver nodes found on the structural data for (A) controls, (B) MCI and (3) AD.

The results show that the nodes thirty and thirty-one represents driver nodes in all three networks located in the temporal lobe. For controls, MCI and AD all but one driver node are located in the temporal lobe with the remaining being located in the frontal lobe. Both MCI and AD brain networks share four common driver nodes located in the temporal lobe.

The found leaders based on this method avoid the central hub. It is important to mention that these are the smallest set of leaders that ensures the controllability of those networks. The results show that it is a valid method for determining the modal controllability.

3. CONCLUSIONS

In this paper, we introduced some novel dynamic graph theory techniques for determining the exact controllability of structural brain connectivity networks. This concept plays an important role in dynamic imaging connectomics since they describe the dynamical behavior of areas in the brain with respect to the role of nodes or brain regions in influencing disease trajectories. We applied the new concepts of choosing the minimum driver set and determining their location on structural dementia graphs. This new paradigm provides us with important disease descriptors showing changes over the disease trajectory such as the hubs of the dynamic system and the weakly connected areas. Examples are given to elucidate the theoretical results and are in compliance with clinical findings.

4. CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5. ACKNOWLEDGMENTS

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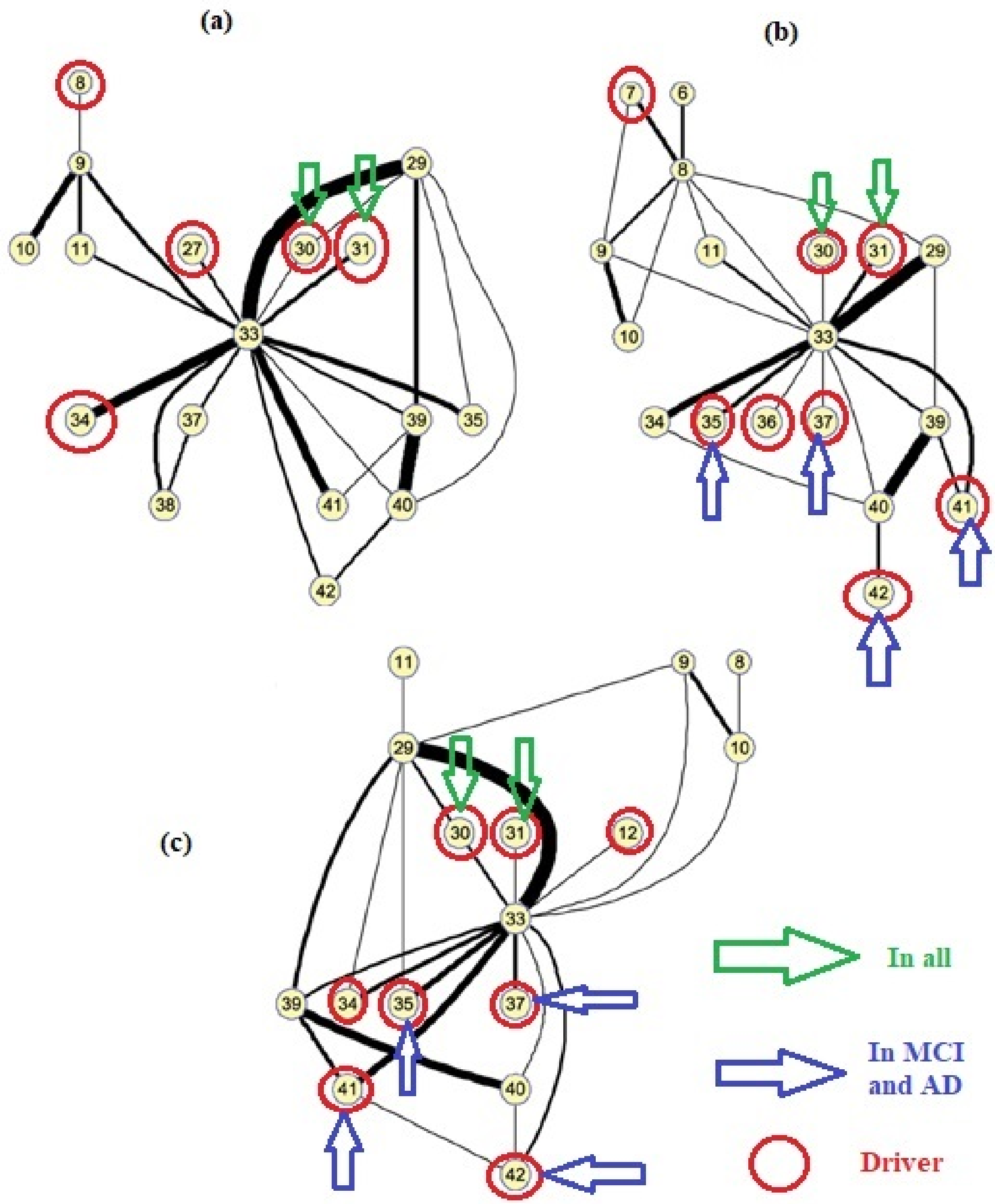

Figure 2. Identifying the driver nodes in brain network graphs for structural data for (A) controls, (B) MCI and (C) AD as described in.[15]

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