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Determining Driver Nodes in Dynamic Signed Biological Networks

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ABSTRACT

Leader-follower controllability in brain networks which are affected neurodegenerative diseases can provide important biomarkers relevant for disease evolution. The brain network is viewed as a dynamic system where the nodes interact via neighbor-based Laplacian feedback rules. The network has cooperative connections between the nodes described by positive weights along with competitive connections which are described by negative connection weights. The nodes take the role of either leaders or followers, thus forming a leader-follower signed dynamic graph network. The results of this analysis can be easily generalized on unsigned brain networks. We apply the leader-follower concept to structural and functional brain networks with neurodegenerative diseases (dementia) and show that the found leaders represent important biomarkers for disease evolution. In other words, the leader nodes drive the network towards deteriorating cognitive states.

Keywords: Signed graph, Driver node, Neurodegenerative disease, Alzheimer, Imaging connectomics

1. INTRODUCTION

Novel mathematical concepts such as graph theoretical techniques can capture the connectivity between areas of the brain, and thus the topology of its network graph.[1–3] These graph networks are mostly based on Pearson correlation and are capturing either the structural and/or functional brain connectivity. From these graphs, new descriptors can be derived in order to quantify induced changes in topology or network organization, or to serve as theory-driven biomarkers which can help to predict dementia at the level of the individual subject.

Most graph networks applied to dementia research, even for longitudinal data, are static graph networks. These models cannot capture the dynamical processes which govern the time evolution of the disease. Therefore, a new paradigm in dementia research – dynamical graph networks – is necessary in order to advance this field and overcome the obstacles posed by static graph theoretic models in terms of disease prediction, evolution, and its associated connectivity changes over time.

Several research avenues have been proposed to understand and analyze the temporal evolution of brain networks. One of the first was to employ a simplified method which results in a model of lower complexity. The standard method for model reduction is known as balanced truncation.[4] This method is based on a state-space point of view of employing the canonical observability and controllability Gramian matrices,[5–7] and is related to both the past input energy (controllability) and the future input energy (observability). While for linear systems

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this procedure is pretty straightforward, for nonlinear systems balancing truncation becomes, in general, not a simple task.[8,9] These methods are thus not quite efficient in terms of model reduction for large-scale networks. For brain connectivity models, we require a structure preservation between subsystems, and at the same time, a network topology-preserving mechanism to provide model reduction. In previous work, we addressed this issue by choosing a technique based on an area aggregation and time-scale modeling for sparse brain networks with densely interconnected hubs and externally sparse interconnections between these hubs.[10,11] In[12] it was shown that the neurons in the hubs synchronize on the fast time-scale, and that the aggregated neurons determine the slow dynamics of the neural network. The basic concept of singular perturbation, applied in,[12] has been extensively studied in other neural networks at different time-scales.[13–20]

Another important concept relevant for the analysis of dynamic graph networks is that of synchronization. Synchronization has been an important topic in biological neural networks, and has played a major role in neurodegenerative disease research. Synchronization, however, cannot always be achieved by the whole network. Thus controllers must be be designed in order to force the network to reach a synchronized state. The controllers may only be applied to a restricted number of nodes, and this is achieved by the so-called pinning control.[21,22] Typically, there are both random and specific pinning control algorithms.[23,24] An important theoretical implication is that the number of nodes to be controlled in a large-scale network is in general small. There are different strategies to determine these driver or leader nodes, some exploiting the connectivity values of the graph network[25,26] while others only the architecture.[27–30] For many neurodegenerative diseases, it's very important to obtain some information about some neural states in order to recover the others. Equally relevant is "pinning observability", first proposed in.[31] This refers to observation of a small number of neurons, such that the states of the other neurons can be recovered analytically. Differently from the concept of pinning controllability, in this case the dynamics of the neurons can be heterogeneous.[32–35]

In this paper, we apply the modern paradigm of leader-follower networks to both structural and functional graph networks in brain networks affected by dementia. The nodes in the brain network interact via neighbor-based Laplacian feedback rules. We apply the concept of leader-follower controllability to both structural and functional brain networks with neurodegenerative diseases (dementia) and show that the found leaders represent important biomarkers for disease evolution. In other words, the leaders play a role in "driving" the network towards cognitive deteriorating states.

2. PINNING CONTROL IN IMAGING CONNECTOMICS

The most intriguing question when analyzing a dynamic graph network is the role of each node. In order to reach an advanced debilitating neurodegenerative state, we need to "drive" a regulatory network from an existing disease-free to a diseased state. The complexity of the actual networks poses many limitations to traditional analysis tools:[25] (1) most graph networks are directed, (2) the size of the network does not allow testing of several combinations to determine driver nodes, and (3) the weights between nodes are not equal and time-dependent. Modern control theory[31,36] provides many tools to control such a network and thus to successfully implement a therapeutic strategy. In the parlance of control theory, tools are described that are able to identify the set of driver nodes and thus guide the network's entire dynamics.

We define the consensus problem as a modality to reach an agreement or synchronization between a group of autonomous agents, in our case the nodes of a brain network, when the states of the nodes change dynamically.

Mathematically, the consensus protocol in a multi-node system is defined as:

$$\dot{x_i}(t) = \sum_{j \neq i} a_{ij}(x_j(t) - x_i(t)) = -\sum_{j=1}^{N} L_{ij} x_j(t) \tag{1}$$

where $x_i(t) \in R^n$ is the state of the node. $L = L(t)$ is a time-varying matrix when the graph network topology changes over time.

Assuming that the dynamics of the node are nonlinear,[37] the state equation becomes

$$\dot{x_i}(t) = f(x_i(t)) - c\sum_{j=1}^{N} L_{ij}\Gamma x_j(t) \tag{2}$$

with $f() \in R^n$ representing the nonlinearity, c the coupling strength, and $\Gamma = diag(\gamma_1, \cdots, \gamma_n) \in R^{n\times n}$ being a semi-positive definite diagonal matrix with $\gamma_j \geq 0$. If $\gamma_j \neq 0$ means that the nodes can communicate through their jth state.

A desired trajectory to be reached by the system, corresponding to a therapeutic solution, is defined as

$$\dot{s}(t) = f(s(t)) \tag{3}$$

where $s(t)$ is an isolated equilibrium point. To achieve this equilibrium point, the new equation to describe evolution becomes

$$\dot{y_i}(t) = f(x_i(t)) - f(s(t)) - c\sum_{j=1}^{N} L_{ij}\Gamma y_j(t) \tag{4}$$

where $y_i = x_i - s_i$. The pinning control strategy is to guide the network to the desired state $s(t)$. The controllability of the system is evaluated based on the algebraic connectivity. Measures derived from the smallest and largest eigenvalue of the connecting matrix are essential to determine the success of controllability. The number of controlling nodes is smaller than the number of total nodes in the network and a direct control is possible only at these nodes, and then is propagated to the rest of network through vertices.

3. CONTROLLABILITY AND LEADER SELECTION IN SIGNED GRAPHS

3.1 Problem Formulation

We consider undirected connected signed brain networks defined as $\mathcal{G} = (\mathcal{V}, \mathcal{E}, \mathcal{W})$ consisting of a set of nodes $V = \{1, 2, \cdots, n\}$ and a set of edges $\mathcal{E} \subset \{i, j | i, j \in \mathcal{V}\}$, the set of all unordered pairs. The interactions among the nodes are described by an adjacency matrix $\mathcal{W} \in R^{n\times n}$ with $w_{ij} \neq 0$ if $(v_i, v_j) \in \mathcal{E}$ and $w_{ij} = 0$ otherwise. Different from unsigned graphs, the weights can be either positive or negative in order to describe collaborative or competitive relationships between the nodes. Thus we define $w_{ij} : \mathcal{E} \to \{\pm 1\}$ in signed graphs. For two neighboring nodes in the graph, we have either $w_{ij} = 1$ denoting cooperative interactions or $w_{ij} = -1$ denoting noncooperative interactions.

A path in $\mathcal{G}$ is defined as a concatenation of edges while a cycle represents a path with identical starting and end node, i. e. $v_1 = v_k$. The signed graph Laplacian of $\mathcal{G}$ is defined as $\mathcal{L}(\mathcal{G}) = \mathcal{D} - \mathcal{W}$ where $\mathcal{D}$ is a diagonal matrix. It's important to point out that for signed graphs, the Laplacian $-\mathcal{L}(\mathcal{G})$ is no longer a Metzler matrix with non-negative off-diagonal elements.

We assume $x(t) = [x_1(t), \cdots, x_n(t)]^T \in R^n$ describe the states of the nodes, and that their dynamics are determined by the following Laplacian dynamics:

$$\dot{x}(t) = -\mathcal{L}(\mathcal{G})x(t) \tag{5}$$

We split the node set into a leader $\mathcal{V}_l \subset \mathcal{V}$ and follower set $\mathcal{V}_f \subset V$ with $\mathcal{V}_l \cup \mathcal{V}_f = \mathcal{V}$ defining thus a leader-follower network. Let's assume the first m nodes represent the follower set $\mathcal{V}_f = \{v_1, \cdots, v_m\}$, and the remaining the leader set $\mathcal{V}_l = \{v_{m+1}, \cdots, v_n\}$. The aggregated states of the nodes are given as $x(t) = [x_f^T(t), x_l^T(t)] \in R^n$ with $x_f(t) \in R^{m\times m}$ and $x_l(t) \in R^{n-m}$. The graph Laplacian then is determined to be:

$$\mathcal{L}(\mathcal{G}) = \begin{pmatrix} \mathcal{L}_f(\mathcal{G}) & \mathcal{L}_{fl}(\mathcal{G}) \\ \mathcal{L}_{lf}(\mathcal{G}) & \mathcal{L}_l(\mathcal{G}) \end{pmatrix} \tag{6}$$

with $\mathcal{L}_f(\mathcal{G}) \in R^{m\times m}$, $\mathcal{L}_{fl}(\mathcal{G}) = \mathcal{L}_{lf}^T(\mathcal{G}) \in R^{m\times(n-m)}$, and $\mathcal{L}_l(\mathcal{G}) \in R^{(n-m)\times(n-m)}$. Thus, the followers' dynamics can be described as:

$$\dot{x}_f(t) = -\mathcal{L}_f(\mathcal{G})x_f - \mathcal{L}_{fl}(\mathcal{G})u(t) \tag{7}$$

with $u(t) = x_l(t)$ being the external input signal dictated by the leaders. In leader-follower networks, the leader nodes play a crucial role in influencing the follower nodes, such that the graph network achieves a certain dynamical behavior. Equation 7 shows that the follower nodes are influenced by the leader nodes via the connectivity matrix. The following definition defines the leader-follower controllability.[38]

Definition 1: Assuming that the leaders are fully controllable and dictated by the external input $u(t)$, a leader-follower network with the dynamics shown in Equation 5 is called controllable, if the followers states $x_f(t)$ in Equation (7) can be driven to any state target by properly choosing $u(t)$. The system in Equation (7) is called "controllable" if the controllability matrix, described as:

$$\mathcal{C} = [-\mathcal{L}_{fl} \quad \mathcal{L}_f\mathcal{F}_{fl}\cdots(-1)^m\mathcal{L}_f^{m-1}\mathcal{L}_{fl}] \tag{8}$$

is full rank. Depending on the leader set, the above matrix can be either controllable or non-controllable.

A different set of dynamics for the graph network is given below, where leaders influence indirectly the followers both through the followers' nodes states as well as through their own dynamics.

$$\dot{x}(t) = -\mathcal{L}x(t) + Bu(t) \tag{9}$$

where $B = [b_{ij}] \in R^{n\times(n-m)}$ is a binary matrix with $b_{ij} \neq 0$ if a follower node is connected to a leader node and $b_{ij} = 0$ otherwise. It is also important to mention that the controllability result holds for both equations if they have the same set of leaders.

3.2 Results for Signed and Unsigned Graphs

Define $\mathcal{G}_p = (\mathcal{V}, \mathcal{E}, \mathcal{W})$ as a signed path graph with $\mathcal{V} = \{1, \cdots, n\}$ and $\mathcal{E} = \{(i, i+1)|i \in \{1, \cdots, n-1\}\}$ being the node and edge set, respectively. The weight matrix $\mathcal{W} \in R^{n\times n}$ can have either negative or positive weight values which represent cooperative and competitive/antagonistic connections.

The following theorem[38] gives the controllability result for a signed graph.

Theorem 1: A signed graph $\mathcal{G}_p = (\mathcal{V}, \mathcal{E}, \mathcal{W})$ with followers evolving according to equation (7) is controllable if one of the end nodes (i.e., v_1 or v_n) is selected as a leader.

The proof is given in.[38] As shown in the same reference, the unsigned path graph is controllable if one of the end nodes is selected as a leader.

The above results were extended to multi-leader selection[38] as shown in the following theorem.

Theorem 2: A signed graph $\mathcal{G}_p$ with followers evolving according to equation (7) is controllable if multiple adjacent nodes in $\mathcal{G}_p$ are selected as leaders.

The proof is given in.[38]

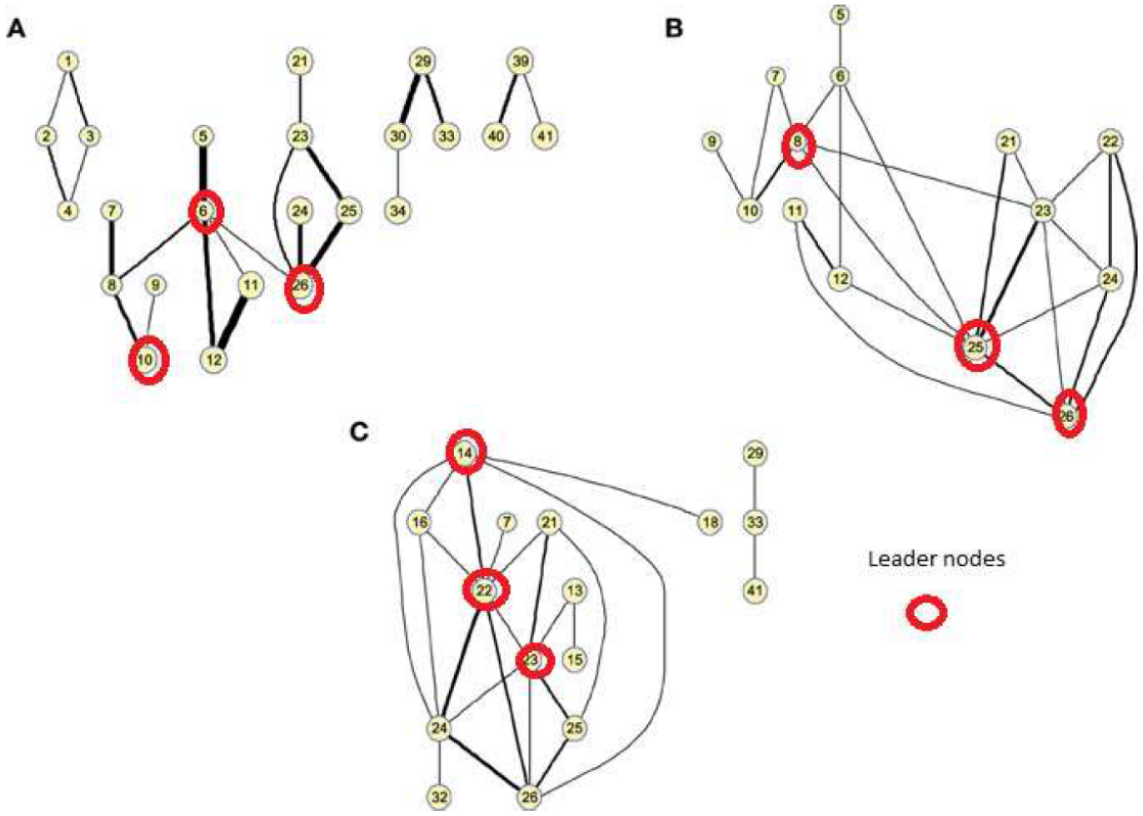

Figure 1. Controllable functional brain networks with the leader set for (A) controls, (B) MCI and (C) AD. The primary leader nodes are situated for (B) and (C) networks in the occipital lobe. Figure adapted from.[39]

4. ALZHEIMER'S DISEASE DIAGNOSIS

We now apply the theoretical results for driver nodes on functional (FDG-PET) and structural (MRI) connectivity graphs[39] 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, while in the case of functional data, the connections do not show the correlation in activity, with links instead describing correlation in the glucose uptake between the different regions. In,[39] these were only 42 out of the 116 considered from the AAL in the frontal, parietal, occipital and temporal lobes. The nodes in the graphs depict the regions, while the edges show if a connection exists between these regions or not. The connections are all positive, meaning we have an unsigned graph, and we apply Theorem 2 assuming the dynamics of the graph are given by equation (7). We define as leaders the hubs found in both functional and structural brain networks.

The functional graphs and their leaders are shown in Figure 3.1. The first leader node lies in the left middle temporal pole while the frontal lobe seems not to be affected. Thus, this first driver node represents an important biomarker of the disease.

5. CONCLUSION AND DISCUSSION

This paper presents a new method for leader selection on signed and unsigned brain networks such that controllability of the brain network is ensured. The graph-inspired topological characterizations of network controllability are applied to brain networks describing neurodegenerative diseases. These techniques found leaders in both structural and functional brain networks which represent important disease biomarkers that can be employed to identify the disease and monitor its temporal evolution.

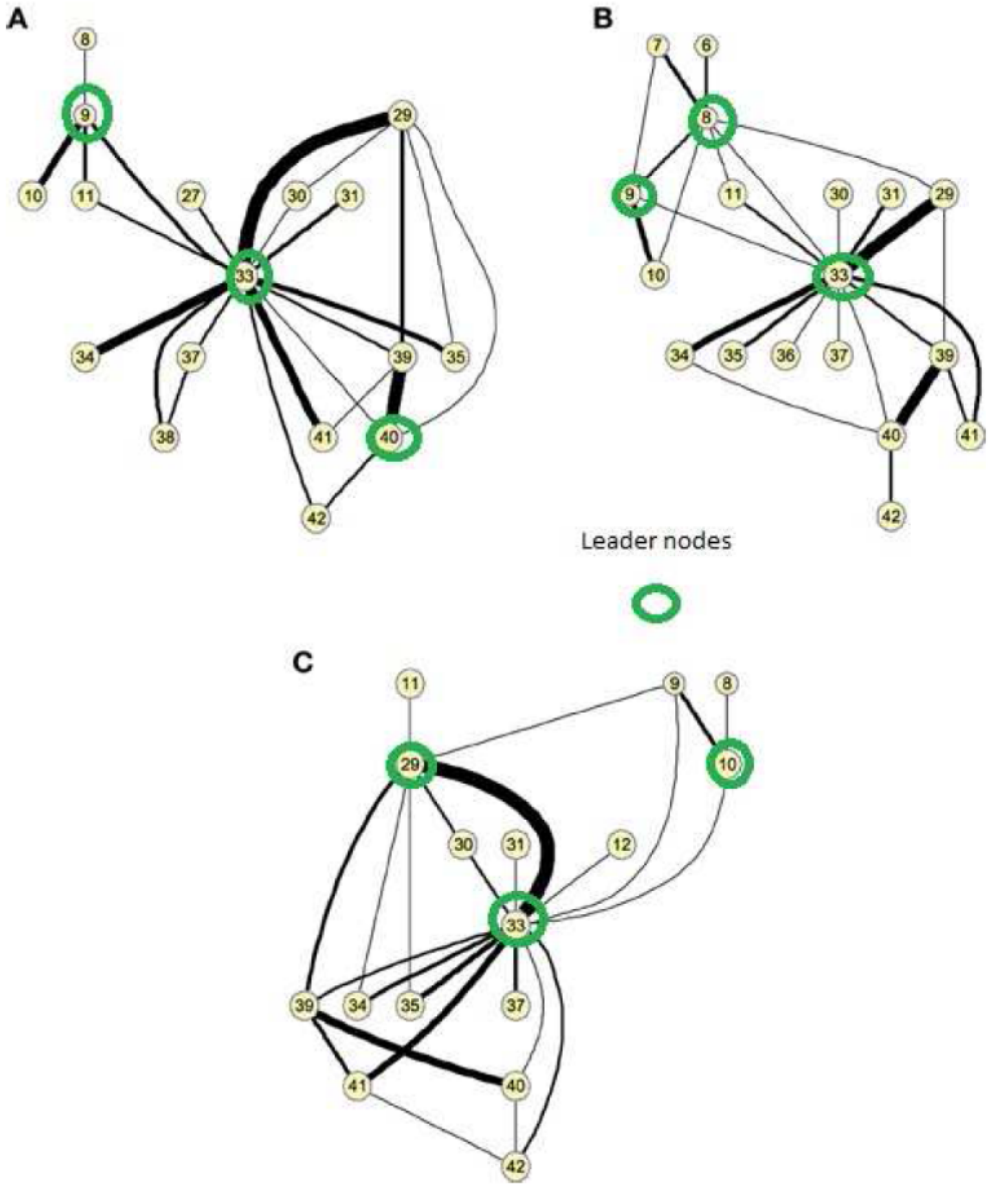

Figure 2. Controllable structural brain networks with the leader set for (A) controls, (B) MCI and (C) AD. The first leader node lies in the left middle temporal pole for all three networks. Figure adapted from.[39]

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