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Large-Scale Dynamical Graph Networks Applied to Brain Cancer Image Data Processing

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ABSTRACT

Brain tumor patients frequently experience tumor-induced alterations in cognitive functions. The early detection of such alterations becomes imperative in the clinical environment and with this the need for computational tools that are capable of quantitatively characterizing functional connectivity changes observed in brain imaging data. This paper presents the application of a novel modern control concept, pinning controllability, to determine intervention points (driver nodes) in the brain tumor-bearing resting-state connectome. The theoretical frameworks provides us with the minimal number of "driver nodes", and their location to determine the full control over the obtained graph network in order to provide a change in the network's dynamics from an initial state (disease) to a desired state (non-disease). Thus we are able to quantify the tumor-induced alterations in different brain regions and the differences in brain connectivity and dynamics. The achieved results will provide clinicians with techniques to identify more tumor-affected regions and biological pathways for brain cancer, to design and test novel therapeutic solutions.

Keywords: Graph Theory, Nonlinear Dynamics, Dynamic Graph, Brain Cancer, Resting-state Connectivity

1. INTRODUCTION

With the increasing amount of available medical data, computing power and network speed, modern brain data image processing is facing an unprecedented amount of data to analyze and interpret. Phenomena such as Big Data-omics stemming from several brain imaging modalities tend to produce almost unmanageable quantities of data. The paper addresses the aforementioned context by assuming that a novel paradigm in massive data processing and automation becomes necessary in order to improve diagnostics of brain cancer and neurodegenerative diseases such as dementia and facilitate personalized and precision medicine for each patient. Static graph networks are unable to capture the fluctuations in brain processing and monitor disease evolution. Temporal graph networks and novel concepts borrowed from modern control have paved the path for a dynamic graph theory that can predict neurodegenerative disease evolution and replace longitudinal studies. Brain data processing in connection with neurodegenerative diseases demonstrates the relevance of these concepts. We believe that these novel paradigms will impact multiple facets of neuroradiology and neurology such as brain cancer research.

Brain tumor patients frequently experience tumor-induced alterations in cognitive functions. The early detection of such alterations becomes imperative and non-invasive techniques such as magnetoencephalography (MEG) and resting-state functional MRI (rsfMRI) provide a wealth of information in terms of qualitative changes. However, this detailed information does not automatically provide a deep insight into how to use this acquired knowledge in reverse engineering and drug design. Therefore, it is very useful to determine the nodes in a network that offer us full access to control the dynamics of the network and represents "key points" of external signals,

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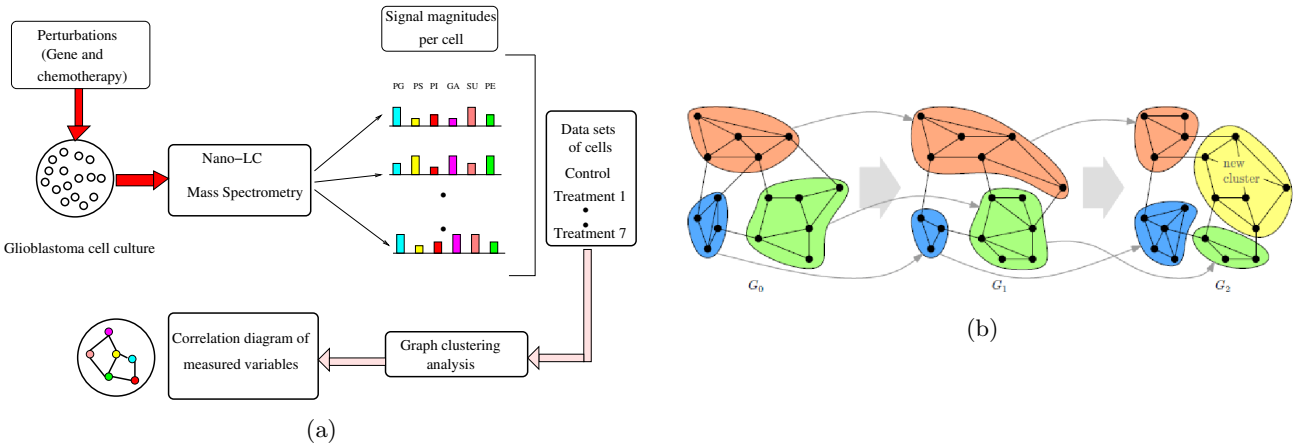

Figure 1: Graph structures. (a) Graphs excel at hiding their structure. Graph clustering aims at revealing their structure. (b) Time-dependent graph clustering. Three time steps of a dynamic graph: smooth dynamic clustering and cluster tracking over time (gray arrows).[2]

which are applicable to networks, in order to change the dynamic status from an initial (disease) state into a final (disease-free) state.[11,12]

The goal of our paper is to determine the driver nodes in resting-state connectivity graph networks obtained from experimental data from rsfMRI and show quantitatively the differences between tumor-induced changes. New control paradigms become imperative when analyzing and interpreting vast experimental data sets with respect to developing novel therapeutics. Graph theory represents a powerful method to visualize and target in combination with modern control theory relevant nodes in the resulting graph. Previously we applied it in the form of static graph theory to show the differences in treatments in glioma cancer stem cells (GSCs).[6,7] Mathematically, graph networks are defined as relations among a bounded set of nodes with the the typical data model being a graph $G = (V, E)$ with vertices V and edges E representing relations between the nodes. In addition to graph theory, the empirical nature of the field imposes statistical approaches as a complementary tool. While static graphs give a snapshot of a single representation, dynamic graphs describe the temporal evolution of relations among nodes as shown in Figure 1.

2. DYNAMICAL CONTROL STRATEGIES

Network controllability is becoming an important area in molecular therapeutics. The current methods applicable to manipulating signaling pathways are (1) partial mixed-valued control[1] and (2) nonlinear dynamical graph theory to determine driver nodes in networks or reach a consensus.[4,16] In previous work, we have shown that these techniques can be applied to brain imaging data describing functional alterations in Alzheimer's dementia (AD) and that they provide unique biomarkers that are able to discriminate between a healthy control and an AD patient.[8–10]

Traditional quantitative or semi-quantitative studies are not sufficient to understand the dynamic properties of biological networks and to quantitatively predict suitable targets that would alter the responses of the graph networks for therapeutic purposes. To control these dynamic models to achieve desired therapeutic responses, novel concepts from modern control theory can be employed.

2.1 Consensus Dynamics, Pinning Control, and Driver Nodes in Complex Networks

The most intriguing question when analyzing a dynamic graph network is the role of each node. To reach therapeutic efficacy we need to "drive" a regulatory network from an existing disease-state to an optimal disease-free state. The complexity of the networks poses many limitations to traditional analysis tools:[5] (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[4,16] provides many tools to control such a network and thus 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 introduce a weighted directed graph $G = (V, E, A)$ of order N that has a set of nodes $V = \{v_1, \cdots, v_N\}$, a set of directed edges $E \subseteq V \times V$, and a weighted adjacent matrix $A = (a_{ij})_{N\times N}$. The Laplacian matrix $L = (L_{ij})_{N\times N}$ of the graph is defined as $L_{ij} = -a_{ij}$ for $i \neq j$, with $i, j \in \{1, \cdots, N\}$ and $L_{ii} = k_i^{in}$ for $i \in \{1, \cdots, N\}$, and $k_i^{in} = \sum_{j=1, i\neq j}^{N} G_{ij}$, represents the sum of all afferent edges. It's evident that $\sum_{j=1}^{N} L_{ij} = 0$ for all $i = 1, 2, \cdots, N$.

We define the consensus problem as a modality to reach an agreement between a group of autonomous agents, in our case the nodes, when these 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 is nonlinear,[14] then 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 $\gamma_j > 0$. 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 therapeutical 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 evolving equation 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 propagated to the rest of network through vertices.

The theoretical results in[4,16] have shown that: (a) nodes with low degrees should be pinned first and not hubs, which are usually of high degree, and (b) the minimum number of nodes to be selected for control can be theoretically determined. In large real-world networks, however, the detection of controlling regions becomes a constrained optimization problem.[13] These results are valid for both directed and undirected graphs.

2.2 Controllability of Complex Networks

In[4] a different approach was proposed to study the controllability of complex networks.

The networks were modeled as a linear system

$$\dot{x}(t) = Ax(t) + Bu(t) \tag{5}$$

where $x(t) \in R^N$ is the state of the system, $u(t) \in R^M$ is the input, A is an $N \times N$ state matrix, and B is an $M \times N$ input matrix.

The system described in equation 5 is said to be controllable if the controllability $N \times NM$ controllability matrix C

$$C = (B, AB, A^2B, \cdots, A^{N-1}B) \tag{6}$$

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

However, to apply the above theory to a complex network means complete knowledge of the network's weights, which is for most real-world networks almost impossible. To overcome this problem, the number of driver nodes was determined in[4] based on the cavity method. This method computes the number of driver nodes over all network realizations compatible with the input degree distribution. The main hypothesis is that the control of the hubs is essential for the controllability of the network. Hubs are known in static graph theory as nodes of high degree, which are important for structural integrity of network against failures. Summarizing, the most important findings 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.

3. DESCRIBING THE BRAIN-TUMOR ALTERATIONS IN RESTING-STATE NETWORKS BASED ON DRIVER NODES

We apply the theoretical controllability concept and techniques on the cross-correlation matrices describing the resting-state functional connectivity of murine brains from.[3] There the average blood-oxygenation-level-dependent (BOLD) rsfMRI signal was determined for every region-of-interest (ROI) and then the resting-state connectivity between any two ROI pairs was obtained as the cross-correlation coefficient between the BOLD time-courses.

The experimental results from[3] describing the above resting-state functional connectivity graph networks for healthy and tumor-bearing mice in Figure 2 (reprinted with permission from Elsevier) are here further analyzed and the driver nodes obtained from the computational pinning controllability concept are shown in Table 1. Applying the computational concept from,[4] provides us with the minimal number of driver nodes for both graphs showing that twice as many driver nodes are required for the tumor-bearing graph. However their location is determined based on the theoretical framework from.[15]

Table 1: Driver nodes for the healthy mice and tumor-bearing connectivity graph. ROI included: left/ right (L/R) hippocampus (Hi), L/R neocortex (Neo), L/R olfactory bulb (OB), L/R thalamus (Th), L/R striatum (Str), L/R hypothalamus (Hy), brainstem (Stem).

	Healthy mice connectivity graph	Tumor-bearing connectivity graph
Driver nodes	L-Str, R-OB, R-Hy	L-Hi, L-Th, L-Str, L-Hy, R-Hi, R-Th, R-Str, R-Hy, Stem

Table 1 shows the driver nodes and their location for the healthy mice and tumor-bearing connectivity graph. There are more intervention points (drivers) for the tumor-bearing graph than for the healthy one. The location of the driver nodes for the tumor-bearing graph are in (L/R) hippocampus (Hi), L/R hypothalamus (Hy), L/R striatum (Str), L/R thalamus (Th) and the brainstem. The few driver nodes in the healthy brain are located in the L striatum (L-Str), R hypothalamus (R-Hy) and R olfactory bulb (R-OB). Thus being able to control those inputs of the resting-state connectivity network, a desired trajectory in cancer therapeutics can be achieved.

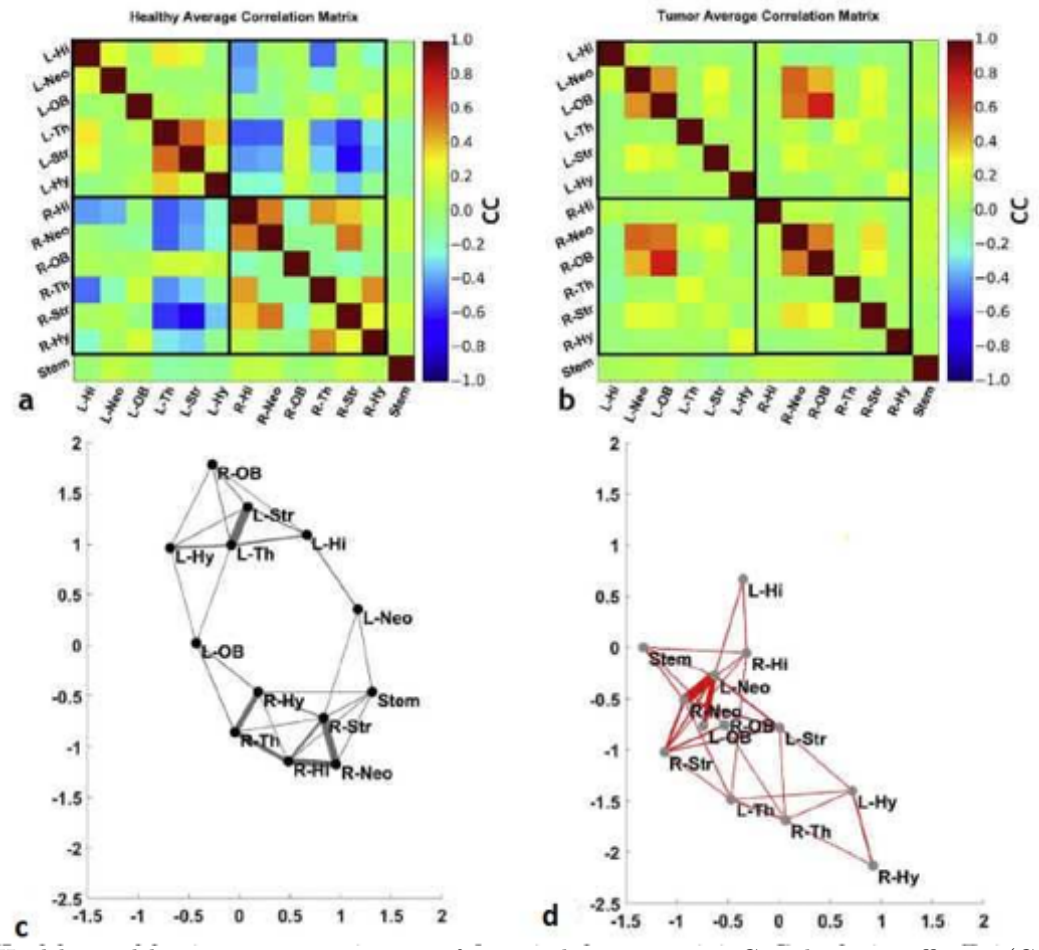

Figure 2: Healthy and brain tumor resting-state functional connectivity. Correlation coefficient (CC) matrices illustrating the average resting-state functional connectivity for: (a) ROI from healthy mice; (b) ROI from tumor-bearing mice. (c-d) Kamada-Kawai (KK) plots corresponding to the CC matrices in (a) and (b). Figure adapted from.[3] Reprinted from[3] with permission from Elsevier.

4. CONCLUSION AND DISCUSSION

We have shown that many aspects of pinning controllability of dynamical systems can be applied analytically to the resting-state connectivity networks in brain cancer. Specifically, our goals were to develop and implement control theory for networks as an alternative to traditional models, to identify the nodes in a graph network that are relevant for controlling the dynamics of the network in order to achieve a desired "therapeutic trajectory". We determined theoretically important driver nodes that are different in healthy and tumor-bearing resting-state connectivity graphs and crucial in influencing the disease. The location of these driver nodes represents an important biomarker in patients with brain cancer. In summary, we have shown that by combining graph network theory with control theory, we open new avenues to enhance our understanding of brain cancer.

5. 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.

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