Mental State Transitions and the Role of Polysynaptic Pathways

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Abstract

Brain state transitions are crucial for high order mental processes, but the relationship between the white matter architecture of the brain and its implementation of these transitions remains under study. We address this question using network control theory by first defining a brain state as a pattern of activity across brain regions, and then delineating a model of brain dynamics. From this we can calculate the optimal input signals necessary to shift the brain into states of activity in different cognitive systems, and subsequently assess the contributions made by different brain regions. We can show that these contributions are correlated with regional weighted degrees of control efficiency and network communicability, a measure of connectedness both by direct and longer, indirect pathways between brain regions. Finally, we identify an optimal weighted calculation of communicability in order to improve this correlation, lending insight on the role of longer polysynaptic pathways in facilitating brain state transitions. This insight can subsequently lead to further knowledge of the biological basis by which these longer pathways were formed and maintained, despite an apparent evolutionary disadvantage. We found that scaling the communicability values by weaker functions than the original exponential, such as linear functions, led to an improvement in the correlation between control efficiency and communicability, indicating influences of longer transition pathways which have not been fully accounted for in previous definitions of communicability.
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Introduction

Many studies of the human brain, a uniquely complex and dynamic system, seek to answer a staple question of modern biology regarding the relationship between a system’s physical structure and its function [1]. As complex as the neuroanatomy of the brain is, a structural brain network can be built from diffusion spectrum imaging (DSI) data, where the physical interactions can be represented as a graph in which physical structures or brain regions form the nodes of the network, and anatomical connections form the edges between nodes [2,6]. This model can then be treated as a dynamical system, assessing each brain region as a dynamic element with time dependent internal states. Network control theory offers a mathematical framework for studying and controlling the evolution of these dynamical systems [3].

This framework can be used to identify energy input signals which can most efficiently transition the system between specific brain states with minimal energy cost, along the associated optimal trajectory. The signals are introduced through previously defined control sites, and can be thought of as issuing directly from brain regions acting as local network administrators. Within the model, an intuitive option for defining the initial state or default mode is the brain’s well-known baseline condition [4]. Focus can then be placed on transitioning into target states of high activity in the primary sensorimotor cortex, the brain’s center for processing movement and sensory information, representing the simplest targets for transition to and from the default mode: for example, the shift from rest to action. These transitions are of particular interest in clinical cases of stroke and traumatic brain injury, in which impairment of cognitive functions performed by these target areas severely affect quality of life [5].

This research is primarily interested in how the organization of white matter architecture constrains cognitive states, and the processes that allow the brain to move between them through
finite-time transitions. Given the aforementioned trajectory from a given initial state to the target states with minimal energy cost, brain regions which will be the most energetically efficient in inducing state transitions can be predicted, thus demonstrating that a brain region’s weighted controllability degree is correlated to its control energy. This suggests that regions with many strong connections contribute disproportionately more energy than regions with few or weak connections. The effect of selectively suppressing input to sets of brain regions can also be studied to observe the resultant compensatory interactions among the remaining regions, and can show that the degree to which one region compensates for the removal of another can be predicted with a measure of network communicability, or the strength of direct and indirect pathways between network nodes [7].

Previous studies have shown a correlation between a region’s ranked network communicability with target regions and its control efficiency [2], but the unexplained scatter in the results leaves room for improvement and suggests a more complex calculation of communicability than previously assumed. Communicability calculations currently implement an exponential weighting function to adjust for walks (pathways between communication nodes) of different lengths [8], with the intuitive assumption that longer walks should be weighted less highly due to the material and energy cost inherent of longer structural pathways. However, we question this assumption and hypothesize that an alternative definition of communicability exists through manipulation of the weighting function, which can lead to a stronger correlation between communicability ratings and control efficiency values. Alternative weightings of walks of different lengths would allow for the possibility that longer pathways are either more impactful and efficient in brain state transitions than previously assumed, or ultimately biologically irrelevant, and can lead to a greater understanding of the role of polysynaptic pathways in brain
state transitions, and ultimately new knowledge regarding the impact of overall brain architecture on changes in mental state.

**Background**

i. **Brain regions and function**

The brain’s default mode network (DMN) or resting state was studied and explicitly defined by Raichle, et al. as consisting of “the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices of the human brain.”[9] The DMN is primarily active during such nonspecific brain activities as pondering information regarding oneself, contemplating others, or remembering past or imagining future events.[10] This categorical designation proved significant and useful in our study of brain state transitions, as it presented an intuitive and natural starting point from which to transition into different centers of activity in the brain, such as the visual and/or sensorimotor regions. The primary visual cortex, located in the occipital lobe of the brain, is primarily responsible for the processing of visual information, and signifies a prime target state of activity from the default network, since many of the brain’s transitions from rest to interactions with its environment begin with a visual stimulus. Similarly the motor cortex, a region situated in the frontal lobe, works to execute movements and provided another natural target for brain activity in our research, a transition exemplified in any movement from rest to action in daily life.

ii. **Brain controllability**

A precursor to our applications of network control theory in studying brain state transitions is the presumption that the brain is theoretically controllable. Controllability is
here defined as the ability to drive a system along a desired trajectory through manipulation of individual network components, and appears to present itself analogously in higher order mental processes. The brain’s ability to perform complex cognitive functions such as deductive problem solving, inhibition of inappropriate behavior, and selective memory retrieval is known as cognitive control [11], and necessitates the ability of neural systems to alter their dynamics in response to task demands. It has thus been shown that cognitive control, in which critical brain regions act as drivers to modulate the brain system into specific modes of action or cognitive function, is conceptually analogous to mathematical definitions of control, and that the brain is indeed theoretically controllable through individual regions, although difficult since many dynamic processes impact several neural circuits rather than a single brain region [12].

iii. **Diffusion Spectrum Imaging and Network Construction**

Diffusion Spectrum Imaging (DSI) is a technique which generates contrast in magnetic resonance (MR) images through the diffusion of water molecules, allowing for the mapping of biological tissues, in this case the white matter architecture of the brain. In the imaging of white matter, DSI allows for delineation of both the location and orientation of the tracts being measured. The architecture of actions and myelin sheaths facilitate diffusion especially along their main direction, a preferentially oriented diffusion known as anisotropy. As previously reported in related research, performing diffusion tractography on DSI data can allow for estimation of quantitative anisotropy along streamlines linking large scale brain regions [12]. These estimates can be summarized in a weighted adjacency matrix, the entries of which signify the number of
connections between different regions. This adjacency matrix can then in turn aid in defining a model of brain state dynamics which we can use to systematically study the system as a controllable network \cite{12}.

Fig. 1: **Conceptual Schematic.** \cite{12}

(A) Diffusion imaging data, used to infer structural connectivity through diffusion tractography algorithms. (B) Example weighted network constructed from tractography, delineating the connective interactions between 234 brain regions. (C) Schematic of optimal control problem in which brain starts from initial state at time $t = 0$ and through multiple control points arrives at a target state at time $t = T$.

**Materials and Methods**

**Data Acquisition and Network Construction**

Diffusion Spectrum Imaging (DSI) data was acquired from 30 healthy human adults with ages ranging from 18-50 (mean 26 years), of which 14 were female and 16 male. Streamlines were constructed for each individual using a modified Fiber Assignment by Continuous Tracking (FACT) algorithm, and consistent with previous work \cite{12, 13, 14, 15, 17, 18} we used the streamlines to define structural brain networks linking $N = 129$ large-scale brain regions extracted from the Lausanne atlas \cite{19}. These networks can then be summarized in a weighted adjacency matrix $A$, whose entries signify the structural connectivity between each pair of regions.
Optimal Control Trajectories

Given a previously defined model of neural dynamics [12], along with the structural networks constructed from the diffusion imaging data, we can define an optimization problem to calculate the optimal trajectory between a pair of brain states to minimize the corresponding cost function as delineated in the methods of Gu et al. [12]. The cost function is defined as the weighted sum of the energy cost of the transition and the integrated square distance between the two states, after which we can determine the trajectory from some initial state $x_0$ to a target state $x_T$. To compute an optimal control $u$ to induce this transition, the Hamiltonian can be defined as

$$H(p, x, u, t) = x^T x + \rho u^T u + p^T (Ax + Bu). \quad [1]$$

If $u$ is an optimal solution to the energetic minimization problem corresponding to a given trajectory $x$, then there exists a $p$ such that

$$\frac{\partial H}{\partial x} = -2(x_T - x^*) + A^T p^* = -\dot{p}^*, \quad [2]$$

$$\frac{\partial H}{\partial u} = 2\rho u^* + B^T p^* = 0. \quad [3]$$

$$\begin{bmatrix} \dot{x}^* \\ \dot{p}^* \end{bmatrix} = \begin{bmatrix} A & -(2\rho)^{-1} BB^T \\ -2I & -A^T \end{bmatrix} \begin{bmatrix} x^* \\ p^* \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} 2x_T \quad [4]$$

which reduces to

We can then denote

$$\hat{A} = \begin{bmatrix} A & -(2\rho)^{-1} BB^T \\ -2I & -A^T \end{bmatrix}, \quad [5]$$

$$\hat{x} = \begin{bmatrix} x^* \\ p^* \end{bmatrix}, \quad [6]$$

$$\hat{b} = \begin{bmatrix} 0 \\ 2x_T \end{bmatrix}. \quad [7]$$

after which Eqn [4] can be written as

$$\dot{\hat{x}} = \hat{A} \hat{x} + \hat{b}, \quad [7]$$
from which follows

\[ \ddot{\mathbf{x}} + \mathbf{A}^{-1}\mathbf{b} = e^{\mathbf{A}t}\mathbf{c}, \]  

where \( \mathbf{c} \) is a constant fixed from the boundary conditions. Letting \( \mathbf{b} = \begin{bmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{bmatrix} = \mathbf{A}^{-1}\mathbf{b} \), \( e^{-\mathbf{A}T} = \begin{bmatrix} \mathbf{E}_{11} & \mathbf{E}_{12} \\ \mathbf{E}_{21} & \mathbf{E}_{22} \end{bmatrix} \), and plugging in \( t = 0, T \) we have

\[ \begin{bmatrix} \mathbf{x}(0) \\ \mathbf{p}(0) \end{bmatrix} + \begin{bmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{c}_1 \\ \mathbf{c}_2 \end{bmatrix}, \]  

\[ \begin{bmatrix} \mathbf{x}(T) \\ \mathbf{p}(T) \end{bmatrix} + \begin{bmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{E}_{11} & \mathbf{E}_{12} \\ \mathbf{E}_{21} & \mathbf{E}_{22} \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{c}_1 \\ \mathbf{c}_2 \end{bmatrix}. \]

From Equation [9], we can solve for \( \mathbf{c}_1 \), where

\[ \mathbf{c}_1 = \mathbf{x}(0) + \mathbf{b}_1 \]

with which we can compute \( \mathbf{p}(T) \), where

\[ \mathbf{p}(T) = \mathbf{E}_{12}^{-1}(\mathbf{c}_1 - \mathbf{E}_{11}\mathbf{b}_1 - \mathbf{E}_{12}\mathbf{b}_2 - \mathbf{E}_{11}\mathbf{x}(T)) \].

With this we can now find \( \mathbf{c}_2 \), where

\[ \mathbf{c}_2 = \mathbf{E}_{21}\mathbf{x}(T) + \mathbf{E}_{22}\mathbf{p}(T) + \mathbf{E}_{21}\mathbf{b}_1 + \mathbf{E}_{22}\mathbf{b}_2 \]

And subsequently \( \mathbf{u}(t) \) and \( \mathbf{x}(t) \) from Equation 8.

After calculating the optimal trajectories, the energy cost of a specific trajectory can be computed as an integral over time \( T \) as

\[ E(\mathbf{K},x_0,x_T) = \int_0^T \mathbf{u}_{\mathbf{K},x_0,x_T}^2 dt \]

and the spatial cost integrated over time \( T \) as

\[ S(\mathbf{K},x_0,x_T) = \int_0^T \mathbf{x}_{\mathbf{K},x_0,x_T}^2 dt \]

where \( \mathbf{u} \) is the control input with the given control set \( \mathbf{K} \), initial state \( x_0 \), and target state \( x_T \).

**Control Efficiency**
The control efficiency quantifies each region’s efficiency in affecting the transition from a given initial to a desired target state. Mathematically, given N randomly chosen control sets $K_1, \ldots, K_N$, for given target states, the corresponding optimal trajectory with respect to $K_k$ for each target states is defined as set forth in Gu et al. as

$$t_{kj} = \sum_{l=1}^{N} 1(E(K_l, x_0, x_T^l) > E(K_k, x_0, x_T^l))$$  \[16\]

where lower energy costs yield higher tiered values. The control efficiency is then defined as the average of these tiered values:

$$\zeta_{ij} = \frac{\sum_{k=1}^{N} 1(i \in K_k) \cdot t_{ij}}{\sum_{k=1}^{N} 1(i \in K_k)}.$$  \[17\]

**Network Communicability**

For the given weighted connectivity matrix $A$, the network communicability $G$ signifies the level of connectivity among nodes of brain regions, and is standardly defined \[20\] as $G = \exp(D^{-1/2}AD^{-1/2})$, where $D$ is the diagonal matrix. The communicability to the target state (GT) is then quantified as the sum of communicability to all of the target regions, $GT_i = \sum_{j \in \mathcal{I}_T} G_{ij}$ after which the normalized network communicability to the target regions is defined as

$$C_i = \frac{GT_i}{\sum_j GT_j}.$$  \[17\]

Results reported in this work are based on normalized network communicability as defined above.

**Weighting Adjustment**

After first determining the relationship between control efficiency and network communicability based on the generalized definition of communicability, where

$$G = \sum_{k=1}^{\infty} \frac{A^k}{k!}$$
we redefined communicability as simply \( G = A^k \) where \( k = \text{integers from 1-50} \), to individually investigate walks of lengths from 1 to 50. This range was chosen since walks of length \( \infty \) are impractical in the context of a biological organ with finite size, and few changes were expected beyond walks of length 50.

**Experimental Results**

**Reproducing Previous Work**

We first began by attempting to replicate the predictability shown in previous work \cite{12} between regional communicability values and control efficiency. We set the initial state such that the regions of the default mode network were activated while all other regions were suppressed, and the target states as the regions of the dorsal attention, control, visual, limbic, somatomotor, ventral attention, or subcortical regions tested individually. As delineated in the aforementioned work by Gu et al., \cite{12} control sets were generated randomly, and the corresponding optimal control trajectory for each of the state transitions and for individual subjects was computed separately. The random control sets were then ranked in descending order according to the energy cost associated with their respective trajectories, and every region associated with a particular ranking control set was assigned the value of that rank. The control efficiency of the brain region was then defined to be the average of its rank values, such that a region with high control efficiency could intuitively be said to assert significant control with relatively little energy consumption. We then observed that a region’s network communicability, a measurement of the strength of connectivity between regions, was indeed generally positively correlated with that region’s control efficiency (Spearman correlation \( r = 0.18, p = 0.04 \); see Fig. 2A). Individual
region testing showed slight variation but maintained signification correlations in all cases (see Fig. 2B).

Fig. 2: Controllability as Predictor of Network Communicability. (A) Scatterplot of average network communicability with control efficiency for one example subject. (B) Regional comparison of predictability between control efficiency and communicability.

Redefining Communicability

The trends viewed above arise from the assumption that walks (pathways) of increasing lengths contribute exponentially less to the communicability of regions, as implemented by the standardly accepted exponentially decreasing weighting function. We sought to expand this view of communicability and improve the results by instead evaluating individual walk lengths, and observing their impact on the above correlations between control efficiency and network communicability. An interesting trend presented itself in which walks of longer lengths appeared to offer significant value as predictors, particularly contributions from walks of length N = 10-30 (see Fig. 3), although beyond a certain degree (around N = 45) the curve plateaus and longer walks cease to significantly differ from each other in predictive value. This observed relationship
supports the hypothesis that walks of longer lengths may be greater contributors to a region’s communicability to target regions than previously assumed.

Fig. 3: Correlation Dependence on Walk Length. Varying correlation coefficient (r) between control efficiency and communicability as dependent on walk length (N) for combined target regions.
Dependence on target state

We finally sought to investigate how the observed dependence on walk length persisted or varied with respect to individual target regions. In comparison to the combination target regions, in assessing individual regions, walks of length 5 were even more significant and served as the best predictors overall (see Fig. 4). This also supports the hypothesis regarding the greater contribution of polysynaptic pathways or walks of longer lengths to network communicability.

Discussion and Conclusion

In this work we pursued further the question of the relationship between the brains structural connectivity and its ability to move between diverse cognitive states. We built upon existing research [12] showing a relationship between brain regions’ control efficiency and network
communicability, and sought to strengthen this relationship through manipulation and improvement of the existing mathematical definition of communicability. Using structural brain networks estimated from diffusion imaging data from 30 healthy subjects, we replicate a previous finding illustrating a positive correlation between a brain region’s connectivity to surrounding regions and its ability to assert control with minimal energy cost. We then further this knowledge by observing how the correlation changes with connective pathways of varying lengths, and show that the relationship is indeed dependent on walks of different lengths, with preference shown for the particular length of $N = 5$ across all individual brain regions. Altogether, these results offer insight into the importance and contribution of pathways of longer lengths in the connectivity of brain regions, in contrast to previous assumptions regarding the preference for shorter pathways.

**Future work**

Many more variations of the communicability weighting function exist uninvestigated and could bear further study. Replacing the exponential weighting with linear, quadratic, or irregular functions could further improve the correlation between communicability and control efficiency, after which the impact of walks of different lengths can continue to be tested in each new context. Other work may include investigating the cause behind the walk-length preference observed in this research, devising a systematic method of testing and optimizing alternative weighting functions, or comparing the results of data from healthy individuals with that of individuals sustaining brain injuries.
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References


