RE: Warnings and Caveats in Brain Controllability

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Abstract

The use of network control theory to analyze the organization of white matter fibers in the human brain has the potential to enable mechanistic theories of cognition, and to inform the development of novel diagnostics and treatments for neurological disease and psychiatric disorders [1]. The recent article [2] aims to challenge several of the contributions of [1], and particularly the conclusions that brain networks are theoretically controllable from single regions, and that brain networks feature no specific controllability profiles when compared to random network models. Here we provide additional theoretical arguments in support of [1] and against the results and methodologies used in [2], thus settling that (i) brain networks are controllable from a single region, (ii) brain networks require large control energy, and (iii) brain networks feature distinctive controllability properties with respect to a class of random network models.

The authors of the recent article [2] revisit and challenge the characterization of controllability of structural brain networks reconstructed from diffusion imaging data, which was first conducted in [1]. Briefly, the topics of disagreement relate to the questions of (i) whether a linear dynamical network is controllable from a single node, where the network structure is akin to those reconstructed from tract tracing data in non-human animals, or from diffusion tensor, diffusion spectrum, and other diffusion-weighted imaging scans in humans, and (ii) whether the structure of the system leads to distinctive controllability profiles (see [1] for a detailed description of the problem). Although the authors in [2] claim to provide contrasting results to the ones published in [1], we respectfully believe that the arguments presented in [2] hardly dispute any of the conclusions of the earlier work. In fact, if anything, the article [2] strengthens the conclusions of [1], as we articulate in the following paragraphs.

(Controllability of brain networks from a single region.) Both [1] and [2] adopt the same standard definition of controllability. In particular, a network with dynamics

$$x(t+1) = Ax(t) + Bu(t) \tag{1}$$

is controllable if and only if the controllability Gramian

$$W = \sum_{\tau=0}^{\infty} A^{\tau} B B^{\mathsf{T}} (A^{\mathsf{T}})^{\tau}$$

is nonsingular [3]. Controllability of (1) implies that, for any states $x(0)$ and x_{f}, there exists a sequence of inputs $u(0), u(1), \ldots, u(T-1)$ such that $x(T) = x_{\mathrm{f}}$, where T is a sufficiently long control horizon. For the study in [1], the matrix A in (1) can be viewed as the symmetric weighted adjacency matrix of a graph where the nodes represent brain regions and the edge weights are proportional to the number of white matter streamlines connecting two different brain regions (see [1] for details). Further, the matrix B equals the i-th canonical vector of appropriate dimension, indicating that only the i-th node is in fact controlled.

In [1] we numerically show that brain networks are controllable from a single brain region, a result that is challenged in [2] using numerical evidence. The source of confusion is due to the fact that assessing controllability via numerical analysis typically leads to ill-conditioned problems, and often generates results that are difficult to interpret; e.g., see [4]. If one knew that the smallest eigenvalue of the Gramian were equal to ε, for any arbitrarily small but positive value of ε, then controllability would follow. Thus, the problem is not the magnitude of the smallest eigenvalue of the Gramian, if computed reliably, and stating that it is statistically compatible with zero, as done in [2], does not constitute reliable or useful evidence in favor or against controllability of the considered brain networks. For instance, the eigenvalues of the controllability Gramian are *always* nonnegative [3], showing that the negative values reported in [2] are certainly incorrect.

To support our conclusion, in [5], which was available before the publication of [2], and also in [6], we follow an alternative theoretically-validated and numerically-reliable approach to assess controllability of brain networks from a single region. Our results show that the considered brain networks are *structurally controllable*[1] from every single

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[1] Structural controllability depends only on the network struc-

region. That is, the papers [5, 6] mathematically prove that the considered brain networks controllable for almost all choices of network weights, with methods that are rigorous and numerically reliable. To clarify further, in [5, 6] we prove that the structure of brain networks is sufficiently rich to allow for controllability from any single brain region. And we also prove with *probability equal to one* that the result in [1] is correct: because brain networks are structurally controllable, they are numerically controllable for any generic choice of network weights. Interestingly, the authors of [2] decided to ignore our results on structural controllability, which we had shared with them, and instead decided to include a similar structural study on networks of C. Elegans connectomes (see below).

(Controllability of human brain networks versus C. Elegans.) To support the results of [2], the authors analyze structural controllability of networks representing C. Elegans connectomes. It is found that these networks, which are much simpler than human brain networks, require about 7% of all nodes to be controlled to ensure controllability of the whole system, and this fact is used to challenge the result that a single node is sufficient to control human brain networks. We believe that this conclusion is incorrect. To see this, notice that the simplest network of all, the network with n nodes and no edges, requires n control nodes to ensure controllability, and that the most complex network of all, the complete network with n nodes and n^2 edges, is instead structurally controllable from any single node, even when the edge weights are symmetric. In other words, as we discuss earlier, the structure of the human brain is complex enough to ensure controllability from any single region, as proven in [5, 6].

(Difference in the network model (1)*.)* The papers [1] and [2] used slightly different matrices for the model (1). In particular, while the matrix A in [1] is the weighted adjacency matrix of the considered brain networks, the matrix A used in [2] is derived by linearization from of a general Wilson-Cowan system. From a practical perspective, the main difference between the network matrices used in [1] and [2] is that the diagonal entries of the matrix in [1] are zero, while they are nonzero in the matrix used in [2]. Although we find puzzling that [2] uses a different model to challenge the existing results of [1], and as also argued in [2],[2] we believe that the difference of the used models do not explain the difference in the conclusions of the papers. Importantly, because the controllability results in [5, 6] are valid for almost all choices of network weights, they apply to both the dynamical models used in [1] and [2], showing that the networks used in [2] are also structurally controllable. In fact, it is a known result that self-loops, that is, nonzero diagonal entries, can only facilitate the verification of the conditions for (structural) controllability [7].

(Theoretical versus practical controllability.) Although brain networks are theoretically controllable from a single region, the *energy* needed to fully control the system is extremely large, indicating that brain networks are practically uncontrollable from one region. This property is well recognized and discussed in [1]. For instance, we explicitly say: "These values (smallest eigenvalues of the Gramian) were consistently greater than 0, indicating that the system is theoretically controllable through a single region, but remained small with respect to the largest eigenvalues (always greater or equal to 1), indicating that in practice the system is extremely hard to control through a single region." Thus, the results in [2] do not challenge, but they rather validate what had already been discussed in [1]. Finally, it should be noticed that the above considerations on the control energy of brain networks are expected [8], and compatible with the results on structural controllability in [5, 6], which guarantee that the smallest eigenvalue of the Gramian is greater than zero although possibly small.

To conclude, it should also be noticed that the calculation of the minimum number of control nodes in [2] is based on an *arbitrary* limit on the control energy. Thus, the values in [2, Table 1] should not be regarded as the minimum number of control nodes to control such networks, but rather as the number of control nodes required to control the network with a pre-selected and arbitrary control energy – in fact, as we formally show in [5, 6], one single node is sufficient to control our structural brain networks.

(Controllability as a distinct feature of brain networks.) In [2], it is argued that the connectivity properties of structural networks estimated from diffusing imaging (DSI/DTI) do not play an important role in brain controllability. We respectfully disagree with this statement. For instance, in [5, 6] we show that the connectivity properties of DSI/DTI matrices are such that brain networks are structurally controllable from a single region, while many different real networks require a larger number of driver nodes to ensure controllability [9]. In [10] we show that different network models lead to different controllability profiles. As can be seen in Fig. 1, brain networks occupy a region of the three dimensional space defined by our controllability metrics (average, modal, and boundary controllability) that is far away from the regions covered by classic models of random networks. These data suggest that the structure of brain networks leads in fact to unique controllability features, a conclusion that is also supported by the relations between controllability and the functions that brain regions perform in terms of cognitive control [1] and intrinsic processing [11]. Additional supporting evidence comes from

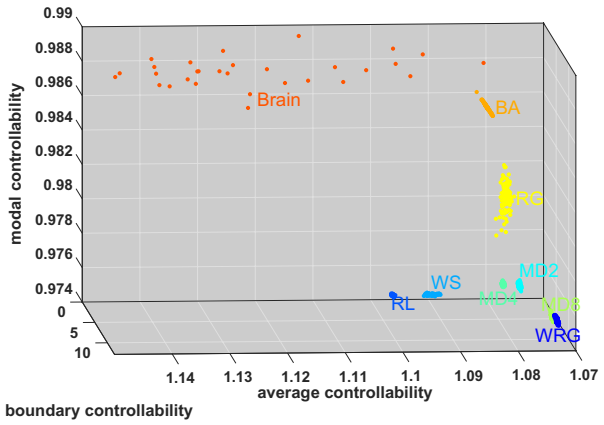
ture and can be assessed reliably and efficiently. When a network is structurally controllable, almost all choices of the edge weights result in a network that is numerically controllable [7]. In our analysis, structural controllability is a proxy to study controllability of brain networks while avoiding ill-conditioned numerical problems.

[2] "Although we do not agree on this procedure that neglects the differences between the linearized system dynamics given by the matrix A and the brain connectivity structure given by the matrix M, we note that, for the case of the Wilson-Cowan modeling framework, in practice there is no relevant difference between the two approaches on the final results."

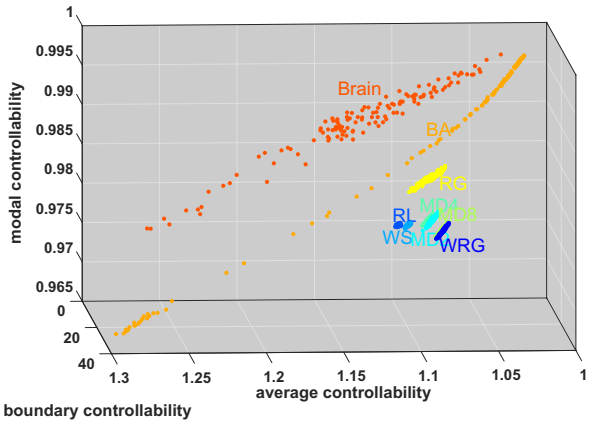
[12], where we show that controllability of random networks is significantly different from that observed in brain networks estimated from diffusion imaging data across 882 humans, and that controllability profiles differ across individuals of different ages, corresponding with individual differences in cognitive ability. Moreover, in [13] we show that controllability profiles are different in individuals who have suffered from mild traumatic brain injury, suggesting that changes of the brain structure affect its controllability properties, and in [14] we show that controllability profiles differ across the structural brain networks of different species. Finally in [15] we show that a different controllability metric, the controllability radius, is also consistently different in brain networks and random network models.

The analysis in [2] of centrality measures and corresponding rankings to compute the number of control nodes and their properties is interesting, but besides the point of challenging the results in [1]. To do so, brain and random networks should have been compared using the same metrics used in [1] as in Fig. 1, which shows that different networks can indeed be distinguished by their controllability properties. Finally, the fact that certain random networks may feature controllability properties similar to brain networks cannot invalidate the direct analysis conducted in [1], which numerically characterizes the controllability properties of given brain and random networks, and does not argue that such controllability properties are unique across different classes of random network models.

In conclusion, we believe that [2] contains interesting ideas, including the comparison of brain and random network models based on controllability and centrality measures, and we agree with [2] that the use of network control theory to model, analyze, and treat the human brain is still in its infancy. Yet, based on the discussions provided in [1] and in the supplementary material, the results of several follow-up studies, and the additional evidence and arguments discussed in this response, we believe that the results and the conclusions in [1] are accurate and correct.



(a)



(b)

Figure 1: This figure shows that different network models may feature inherently different controllability profiles. Brain networks can be uniquely identified in this 3-dimensional controllability space, suggesting that their structure differs from classic random network models and can be uniquely distinguished through a controllability analysis. To compare different network models, the weights of the edges of all networks have been drawn from an empirically-estimated fractional anisotropy distribution, which describes typical weight distributions in large-scale human brain structural networks estimated from diffusion imaging tractography [11]. For each network model, we generate a number of networks (100 for the synthetic network models and 30 for brain networks) with the same cardinality (128 nodes), assign the edge weights, and compute the controllability metrics by varying the control node over all nodes. Then, in panel *(a)* we report the average values computed over all possible control nodes, while in panel *(b)* we report the average values computed over all network instances. Thus, a data point in panel *(a)* represents a network, while a data point in panel *(b)* represents a network node. We use the following random networks: WRG: Weighted Erdős-Rényi model; RL: Ring Lattice model; WS: Watts-Strogatz model; MD2: Modular Network with 2 communities; MD4: Modular Network with 4 communities; MD8: Modular Network with 8 communities; RG: Random Geometric model; BA: Barabasi-Albert model. See also [10], which contains a detailed description of the network models used here.

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