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Brain controllability: Not a slam dunk yet

Samir Suweis [a,b,*], Chengyi Tu [c,d], Rodrigo P. Rocha [b,e,f], Sandro Zampieri [b,g], Marzo Zorzi [h,i], Maurizio Corbetta [b,j,k]

[a] Dipartimento di Fisica e Astronomia, 'G. Galilei' & INFN, Università di Padova, Padova, Italy
[b] Padova Neuroscience Center, Università di Padova, Padova, Italy
[c] Department of Environmental Science, Policy, and Management, University of California, Berkeley, USA
[d] School of Ecology and Environmental Science, Yunnan University, Yunnan, China
[e] Department of Physics, School of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil
[f] Departamento de Física, Universidade Federal de Santa Catarina, 88040-900, Florianópolis, SC, Brazil
[g] Dipartimento di Ingegneria dell'informazione, Università di Padova, Padova, Italy
[h] Dipartimento di Psicologia Generale, Università di Padova, Padova, Italy
[i] Fondazione Ospedale San Camillo IRCCS, Venezia, Italy
[j] Dipartimento di Neuroscienze, Universita' di Padova, Padova, Italy
[k] Departments of Neurology, Radiology, Neuroscience, and Bioengineering, Washington University, School of Medicine, St. Louis, USA

A B S T R A C T

In our recent article [1] published in this journal we provide quantitative evidence to show that there are warnings and caveats in the way Gu and collaborators [2] define controllability of brain networks and measure the contribution of each of its nodes.

The comment by Pasqualetti et al. [3] confirms the need to go beyond the methodology and approach presented in Gu et al.'s original work. In fact, they recognize that *"the source of confusion is due to the fact that assessing controllability via numerical analysis typically leads to ill-conditioned problems, and thus often generates results that are difficult to interpret"*. This is indeed the first warning we discussed in [1]: our work was not meant to prove that brain networks are not controllable from one node, rather we wished to highlight that the one node controllability framework and all consequent results were not properly justified based on the methodology presented in Gu et al. [2]. We used in our work the same method of Gu et al. not because we believe it is the best methodology, but because we extensively investigated it with the aim of replicating, testing, and extending their results. The warning and caveats we have proposed are the results of this investigation.

Indeed, on the basis of our controllability analyses of multiple human brain networks datasets, we concluded: "*The $\lambda_{\min}(W_K)$ are statistically compatible with zero and thus the associated controllability Gramian cannot be inverted*[1]*. These results show that it is not possible to infer one node controllability of the brain numerically*". Hence both groups agree that one node controllability cannot be inferred numerically.

1. Controllability of brain networks from a single region

We appreciate that Pasqualetti et al., stimulated by our article (that we shared with them before publication), developed a new approach (Menara et al., 2017) to measure structural (and not Kalman as in (Gu et al., 2015)[1]) controllability of symmetric networks and we acknowledge that the new method (Menara et al., 2017) is a potential suitable approach to determine if the network is structurally controllable from a single node.

Nevertheless, we note that: *i)* (Menara et al., 2017) does not provide any systematic test of the new method on all nodes and/or the different brain network datasets presented in (Gu et al., 2015); *ii)* (Menara et al., 2017) does not provide any tools to quantify the strength (in terms of controllability) of a node in the network (as supposed for average or modal single node controllability).

Therefore, any conclusion related to the controllability profiles of different brain regions (e.g. densely vs. weakly connected area) or networks (e.g. default vs. visual) is at present unwarranted. Moreover, the computational feasibility and efficiency of the method proposed in (Menara et al., 2017) to infer the structural controllability from each node of large brain networks remains unclear (finding the Hamiltonian path is a NP complete problem).

* Corresponding author. Padova Neuroscience Center, Università di Padova, Padova, Italy.
E-mail address: samir.suweis@unipd.it (S. Suweis).

[1] Finding negative eigenvalues for the Gramian is the consequence of the non-invertibility of the matrix, i.e. when solving the Lyapunov equation to find W, if the linear system is at the edge of instability, then W may have negative eigenvalues. This is what also Gu et al. find, as stated in (Gu et al., 2015): "*These values (smallest eigenvalues of the Gramian) … remained small (mean $2.5*10^{-23}$, standard deviation $4.8*10^{-23}$)*". This result highlights that also (Gu et al. (2015)) Gu et al. (2015) have found negative eigenvalues of W within one standard deviation (i.e. $2.5*10^{-23} - 4.8*10^{-23} < 0$).

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2. Controllability of human brain networks versus the *C. elegans* neuronal network

Beyond the challenging proof that brain networks may be controllable from every single node with finite energy, an important theoretical open question is the relationship between network complexity and controllability. In (Tu et al., 2018) we showed, using a method to detect driver nodes in directed networks (Liu et al., 2011), that the control of the C.elegans connectome, which is precisely known, requires about 7% of the nodes. In particular, in (Tu et al., 2018) we wanted to highlight that the directionality of the network (neglected in (Gu et al., 2015; Pasqualetti et al., 2019; Menara et al., 2017)) plays a crucial role in its controllability profiles.

In (Pasqualetti et al., 2019) Pasqualetti et al. argue that *C. elegans* network control requires more nodes than human networks because they are simpler, and that more complex networks are more easily controllable. The explanation of Pasqualetti et al. on the relative controllability of human vs. C.Elegans connectome based on the complexity of connections is interesting, but unproven, and frankly the example is not convincing. If we define the average density of links in the network with C (i.e., $C = [0,1]$), then the example made in (Pasqualetti et al., 2019) compares the controllability of a network characterized by $C = 0$ (i.e., only nodes without links in the graph), with the fully connected case ($C = 1$). However, this is far from the case we have analyzed in (Tu et al., 2018). In fact, the average density of links in the C. Elegans brains and in the different human brain networks used in (Tu et al., 2018) is comparable ($C = 0.0715$ vs. $C = 0.077$, respectively). Therefore, with respect to this feature (density of links), the two types of networks have the same "complexity". Indeed, network complexity is not easy to define, and it is not simply related to the number of links in the network. For example, one may consider networks with the same C, but different topological structures. For instance, Erdős–Rènyi graphs have a "simple" homogenous random structure, while Barabasi-Albert scale free graphs have a heterogenous architecture. Which of the two types of networks is more complex? One can argue that the latter (scale free) are more complex than Bernoulli random graphs. Yet, it can be proved analytically (Liu et al., 2011) that directed random Erdős–Rènyi graphs can be controlled with fewer driver nodes than directed scale free networks. Thus, the relationship between network complexity and controllability is far from being understood.

3. Difference in the network models

In (Tu et al., 2018) we used a linearization of a Wilson-Cowan model around the quiescent state. In this specific case (linearization around $x^* = 0$) we confirm that our model and the linear model presented in (Gu et al., 2015) are practically equivalent. In other words, it is important to highlight that all results presented in (Tu et al., 2018) hold if the linear model proposed in (Gu et al., 2015) is used instead. As an important sidebar, even though the two models can be practically equivalent, it is quite relevant if the derivation of the model is correct or not. Our model is rigorously derived from linearization procedure of non-linear model describing whole brain activity. How was the linear model of Gu and collaborators derived[2]? There is another important consequence: the linear model *only works* around the linearization point ($x^* = 0$), while in Gu et al. the linear model is considered valid for *any* x^*. These implications are not discussed in (Gu et al., 2015), nor in (Pasqualetti et al., 2019) and (Menara et al., 2017).

4. Controllability as a distinct feature of brain networks

Pasqualetti et al. (2019) claim that in our work we state that "connectivity properties of structural networks estimated from diffusion imaging (DSI/DTI) do not play an important role in brain controllability". We disagree, in fact what we showed, using the methodology proposed in (Gu et al., 2015), is that random networks and empirical networks show similar controllability profiles, although the topological properties of the networks are clearly different. This is one of the reasons for concluding that average and modal controllability are unreliable measures to quantify the controllability strength of a node. The importance of using null random models was the second central warning in our work.

However, Pasqualetti et al. (2019), in their response to (Tu et al., 2018), maintain that the controllability profiles of random null models and empirical brain networks are fundamentally different, as shown in their Fig. 1. Intriguingly, their Fig. 1 is very different from Figs. 1–2 in our work (Tu et al., 2018), in which we found no significant segregation between random and brain networks and a different range in average and modal controllability values, even though– as explained above –the same definition of average and modal controllability was used in the two studies (boundary controllability was not considered, but the results do not change).

Thus, where does such a big difference in results come from?

The difference does not lie in the different linear models used in (Tu et al., 2018) and in (Gu et al., 2015) as discussed above.

The crucial difference is instead in how null models are generated. Pasqualetti et al. (2019) assign the weights of different random networks drawing them "from an empirically-estimated fractional anisotropy distribution". In (Tu et al., 2018), using standard procedures to build null models in network science (Newman, 2003; Maslov and Sneppen, 2002), we use the same weights of the empirical networks. Although we wish more details were available on the randomization procedure (Pasqualetti et al., 2019), and we encouraged Pasqualetti et al. to share their data for replicability, we can safely show that the edge weights have a remarkable impact on the relation between modal and average controllability for different networks. In Fig. 1 (top panels) we show the results by using a Pareto distribution for the edge weights: in this case we can discriminate among different network structures. However, if we change the parameters of the distribution, we found no difference in controllability between brain and random networks (bottom panels). This clearly shows that edge weights are a crucial factor for discriminating between controllability profiles of different networks, and thus they need to be cautiously and properly discussed.

In summary, the procedure for assignment of weights to the random network models proposed by Pasqualetti and collaborators is different from the one proposed by Tu et al., and this explains the different results. The reweighting scheme proposed by Pasqualetti et al. is very unusual in network science, where null models are obtained by keeping the same size and density of links, and just rewiring the links (null model 1 in (Tu et al., 2018)), or keeping also the same degree distribution of the data (null model 2 in (Tu et al., 2018)).

5. Theoretical versus practical controllability

It is crucial to understand, especially for potential users in clinical applications, that only practical controllability matters. In fact, for a structurally controllable network, one node controllability is achievable only if an unrealistically enormous amount of energy is available, when the network dimension is large. This fact has two important consequences. One regards the relevance of one node controllability of the brain network for potential users in clinical applications. Indeed, the huge amount of energy needed to control the system should have engendered some caution in the interpretation of the results. Single-node controllability is a core concept in the theoretical framework of Gu et al.

[2] In their work, Gu et al. correctly state that "Decades of research demonstrate that neural dynamics are nonlinear … Indeed, ref (Galán, 2008). proposes a linearized model for the nonlinear neural dynamics described by Wilson Cowan model … linear models of a system accurately approximate nonlinear models in a neighborhood of the operating point". This is exactly the procedure that we employed in (Tu et al., 2018), while in (Gu et al., 2015) the statement is not followed by implementation.

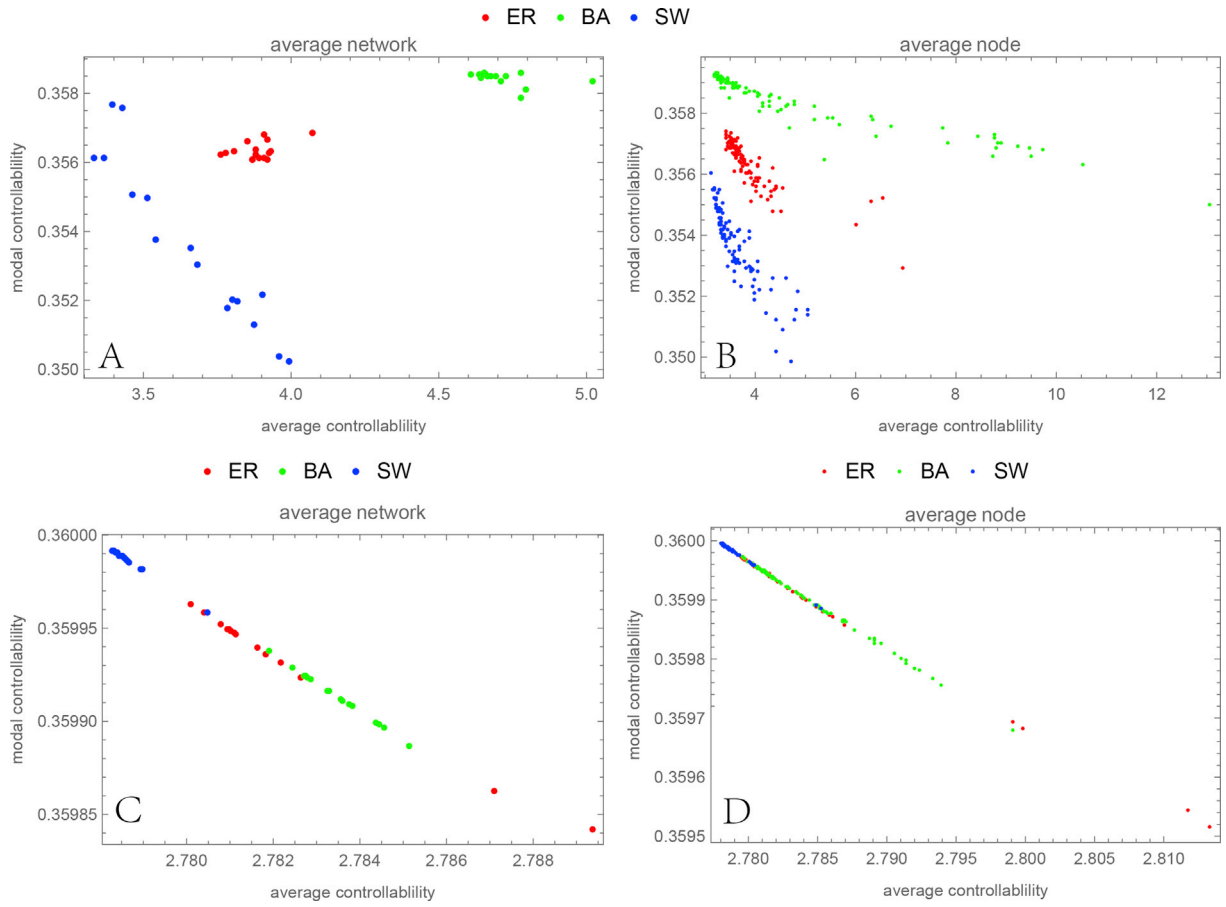

Fig. 1. Controllability profiles for 100 realizations of random networks (Barabasi-Albert (BA), Small-World network (SW) and Erdős–Rènyi network (ER)) of size 100, C = 0.1 and edge weights drawn from Pareto distribution with: Panels A,B) minimum value parameter 2 and shape parameter 3 without normalizing edge weights; Panels C,D) Pareto distribution with minimum value parameter 0.005 and shape parameter 2 after normalization of edge weights). Left panels represent average values computed over all possible control nodes, while in the right panels we report the average values computed over all network instances.

(2015) and given the potential for clinical applications also widely discussed in the paper, and in following ones (e.g., predicting how transcranial magnetic stimulation would affect brain dynamics (Muldoon et al., 2016)), it would seem that a more cautionary interpretation of the findings is warranted. Nevertheless, the one-node controllability framework is already making its way into the empirical neuroscience literature. For example, a recent study concluded that controllability (measured using the methods of (Gu et al., 2015)) modulates the effect of neurostimulation on cognitive performance (Medaglia et al., 2018). It remains unclear how a theoretical construct (one-node controllability) that has little practical significance (because control requires a huge amount of energy) would provide an adequate account of experimental results.

The second reason of concern is that the linear model in Gu et al. is, at best, the linearization of a more realistic nonlinear model (see above). Hence, in case of large signals (such as the signal needed for high energy one node control), the two models would behave in completely different manners. In other words, in the presence of large signals, the linear and the nonlinear models give, in general, different answers to the same question, such as of being one node controllable or not. Also, it is worth highlighting that controllability measures (assuming they are reliable) are meaningful and useful in practice only if they can be disentangled from simpler measures of network structure (i.e., we need to be sure that the empirical effect can only be attributed to controllability; ideally one should assess its effect using other network measures as covariates). In this regard, it is useful to remind the reader that modal and average controllability show near-perfect correlations with node degree (see (Tu et al., 2018; Gu et al., 2015; Medaglia et al., 2018)).

In conclusion, this exchange further highlights the need of carefully assessing 'warnings and caveats' of the controllability framework in network neuroscience. We strongly disagree with Pasqualetti et al. conclusions that the argument is settled with regard to single node (Kalman) controllability, especially in regard of using average and modal controllability to asses brain regions and networks controllability profiles (Gu et al., 2015). We also show that the relationship between topology and controllability depends on how edges weights are assigned, and null models properly built give the same controllability profiles of real brain networks (Tu et al., 2018), highlighting how the methodology proposed in (Gu et al., 2015) on which many other subsequent papers are based is unreliable. Our work is not intended to diminish the potential importance of theoretical tools based on control theory that hopefully will be useful to clinical neuroscientists, and indeed Gu et al. have greatly contributed in putting this framework at center stage. However, difficult work lays ahead in bridging theoretical brain controllability and possible applications in translational neuroscience.

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