UNDER REVIEW

RESCIENCE C

Replication / Computational Neuroscience

[Re] Stimulation-Based Control of Dynamic Brain Networks

Nicolas Roth[1], Teresa Chouzouris[1], Cristiana Dimulescu[1], Caglar Cakan[1], Klaus Obermayer[1], and Christoph Metzner[1,2]

[1]Neural Information Processing Group, Institute of Software Engineering and Theoretical Computer Science, Technische Universität Berlin, Berlin, Germany – [2]Biocomputation Group, Centre for Computer Science and Informatics Research, University of Hertfordshire, Hatfield, United Kingdom

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Introduction

Transcranial electrical and magnetic stimulation (TES and TMS, respectively) have been increasingly used in studies over the last decades and have been found to alter and enhance cognitive processes[1,2,3]. Furthermore, deep brain stimulation (DBS) has shown remarkable results in the treatment of tremor symptoms in Parkinsons disease[4] and also great potential in the treatment of psychiatric disorder such as obsessive-compulsive disorder[5]. However, despite this growing success in clinical settings, a principled understanding of the effects of stimulation on the dynamical processes in the brain is still lacking and, hence, stimulation parameters and target areas are currently not being optimized in a systematic fashion.

Therefore, Muldoon et al.[6] develop a framework to explore the effects of targeted transcranial or deep brain stimulation on overall brain dynamics. In their framework they use data-driven computational model based on subject-specific structural connectivity and a nonlinear model of regional brain activity (the so-called Wilson-Cowan model[7]). Furthermore, they demonstrate that structure-based measures from linear network control theory can predict the functional effect of targeted stimulation.

In this work, we present an implementation of the modelling framework from Muldoon et al.[6] writtem im pure Python, where we exchanged the model of regional brain activity to a simpler, phenomenological model, the FitzHugh Nagumo model[8]. We report a *partial/full(?)* replication of their results.

Methods

Overview The original model is, to the best of our knowledge, not publicly available. Therefore, this reimplementation is purely based on the description in the original article and its supplementary material. The reimplementation is written in Python (2.7/3.6? tested with the other?).

We have made two major changes compared to the original article: First, because we did not have access to the DTI data set used in the article, we used publicly available DTI data form the Human Connectome Project. Second, we replaced the Wilson-Cowan model[7] by the simpler and more efficient FithHugh Nagumo model[8]. Both changes will be explained in more detail in the following sections and commented on in the discussion.

Correspondence should be addressed to Christoph Metzner (cmetzner@ni.tu-berlin.de)
The authors have declared that no competing interests exists.
Code is available at https://github.com/ChristophMetzner/Muldoon-Replication.

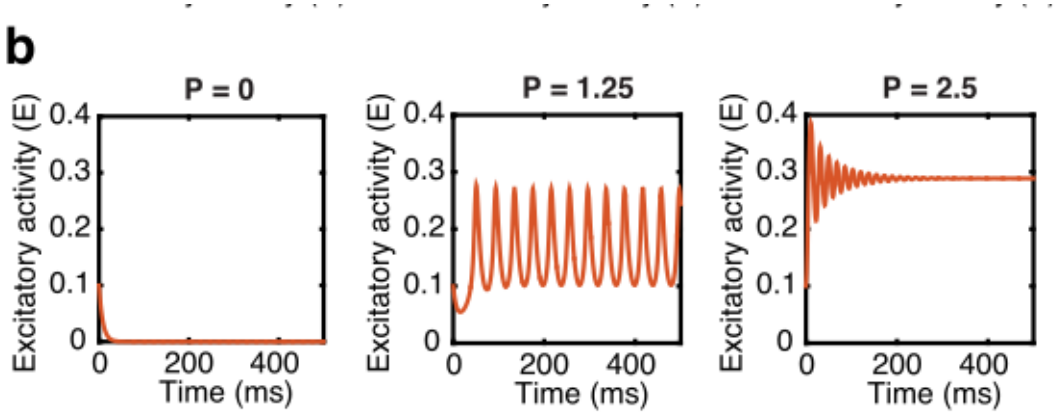


Figure 1. 3 states of the FitzHugh Nagumo (and comparison to the Wilson-Cowan?) *Nico!*

Structural connectivity As explained above, we did not have access to the diffusion tensor imaging (DTI) data form the original article. We thus used DTI data from 10 healthy subjects (mean+std age and gender distribution; possibly even more demographic info *Nico!*) from the publicly available HCP1200 data set of the Human Connectome Project (*link*).

- Acquisition information from HCP
- Preprocessing: software tool, steps and parameters *Nico! Maybe Cristiana?*
- Structural connectivity matrices: Parcellation scheme, thresholding, normalization *Nico!*

Do we have repeated scans of the same individuals? If not, we cannot look at Reproducibility and the within subject variability (see Figure 2 d). Not a big problem, but should then be mentioned here!

Model of regional brain dynamics The second part that is necessary to model the dynamic evolution of brain activity across the entire brain, is a computational model of the regional brain dynamics. In the original article, Muldoon et al.[6] use the Wilson-Cowan model[7]. The Wilson-Cowan model describes the interaction between a local excitatory and a local inhibitory neural population by two coupled differential equations. However, due to the different parameters describing the coupling of the populations and the synaptic interactions, the Wilson-Cowan model has more then ten free parameters and, thus, a high degree of unconstrained variability. Therefore, we opted to exchange the Wilson-Cowan model by the FitzHugh Nagumo (FHN) model[8], which only has six (*correct?**Nico!***) free parameters and, additionally, is computationally slightly more efficient than the Wilson-Cowan model.
The FHN is given by... *FHN equations and parameters (plus explanation)* ***Nico!***
Importantly, the FHN model displays the same three dynamical states depending on the strength of its input than the Wilson-Cowan model (see Figure 1): First, for weak input the FHN resides in a stable fixed point with low activity. Second, for stronger inputs the FHN then transitions into an oscillatory regime and, last, for even stronger inputs it then settles into a stable fixed point again, however, this time with a very high activity.

Individual oscillatory transition paramters *Nico!*

Linear network control theory Muldoon et al.[6] utilize the control theoretic notion of controllability to get theoretical insight inot the effect stimulation might have. They choose two different measures based on a linear control setting: *average controllability* and *modal controllability*. Average controllability is given by the average input energy to the control nodes over all possible target states. Typically, nodes with high average controllability can control networks dynamics over nearby target states in an energy efficient way. On the other modal controllability decribes how well a node can control all network modes. High modal controllability means that such a node is able to reach all modes of a network and, thus, can force the dynamics into hard-to-reach target states.

Functional and structural effect, and fractional activation We calculate functional connectivity matrices as pairwise cross-correlation between the x_1 components of the FHN model of each node. Throughout, we use a 1s time window. As in the original article, the stimulation trials consist of three phases each comprising 1s: the first phase, without any external input, allows the model to stabilise its activity, the second phase, again without external input, is used as a baseline and, lastly, in the third phase the stimulation is applied, i.e. the external input parameter of a single node i is set to $I_i(t) = 0.52$? *Nico* while all others remain 0.

Reproduction of experiments

Regional controllability

- Replicate Figure 2 (c) and (d) and for c) our box plots for all subjects, and d) bar plots with our data
- Replicate Figure 5 b)-d) (plot avg controllability vs. functional effect; calculate structural effect and plot vs avg/modal controllability)
- Replicate Figure 6 (?) (calculate fractional activation and plot against functional/structural effect; plot fraction activation FCs for node 25 and 70)

I don't think we need to replicate Figure 7 (Structure-function landscape)

Reimplementation

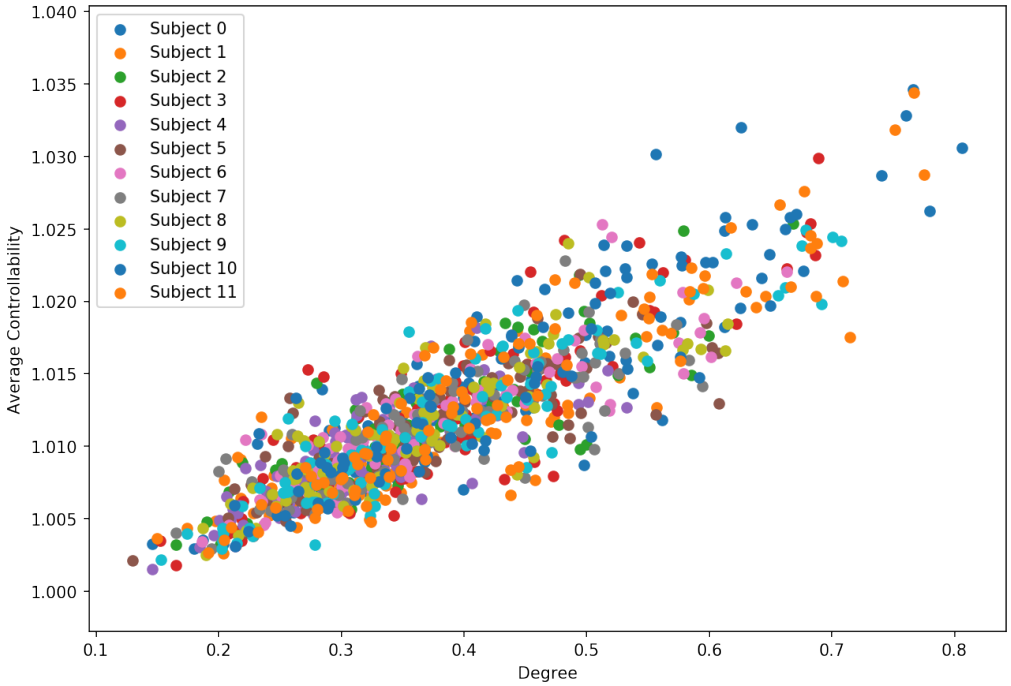
- Details on the new implementation (packages/dependencies, other stuff?, maybe just a paragraph in the methods section)

Discussion

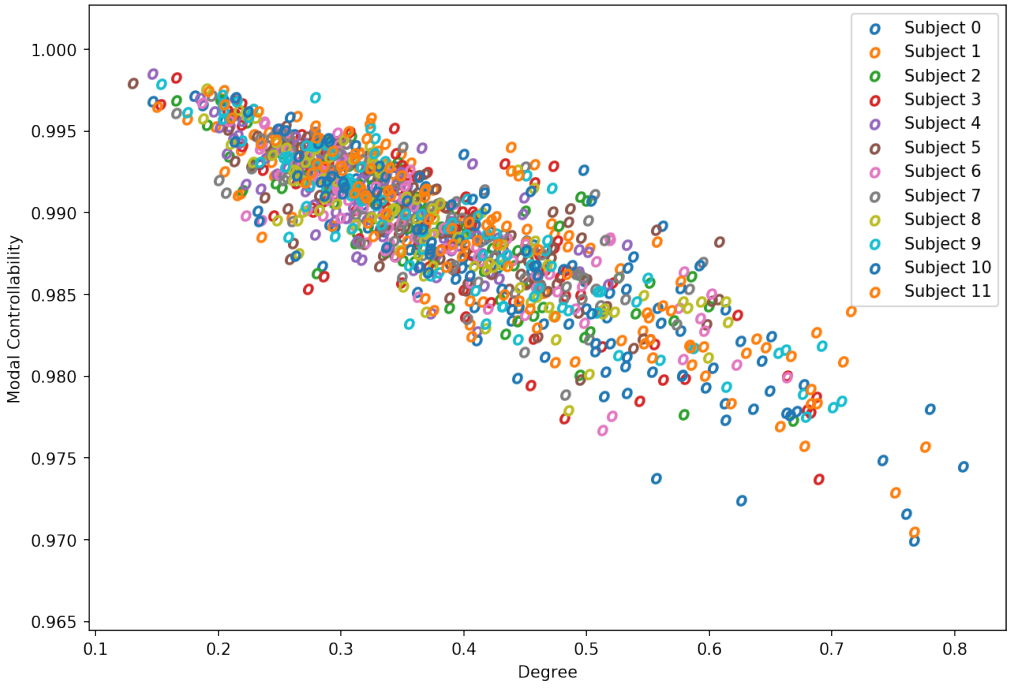
- Main similarities and differences between our and original results. Replication: full, partial or not at all?

References

1. V. Walsh and A. Cowey. "Transcranial magnetic stimulation and cognitive neuroscience." In: **Nature Reviews Neuroscience** (2000).
2. C. Lage, K. Wiles, S. S. Shergill, and D. K. Tracy. "A systematic review of the effects of low-frequency repetitive transcranial magnetic stimulation on cognition." In: **Journal of Neural Transmission** 123.12 (Dec. 2016), pp. 1479–1490.
3. W. Paulus, M. A. Nitsche, and A. Antal. "Application of transcranial electric stimulation (tDCS, tACS, tRNS)_ From motor-evoked potentials towards modulation of behaviour_." In: **European Psychologist** 21.1 (2016), pp. 4–14.
4. A. Collomb-Clerc and M.-L. Welter. "Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review." In: **Clinical Neurophysiology** 45 (2015), pp. 371–388.

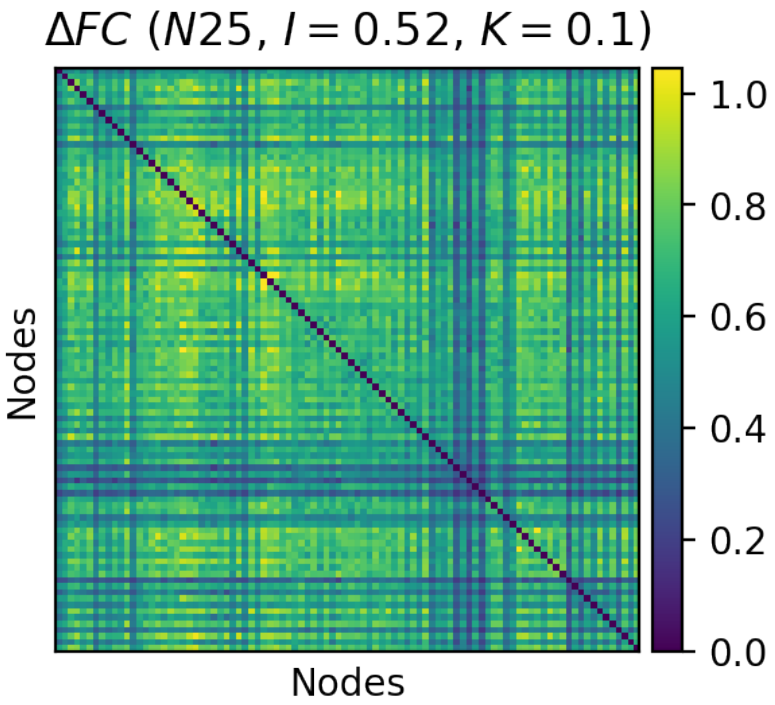


(a)

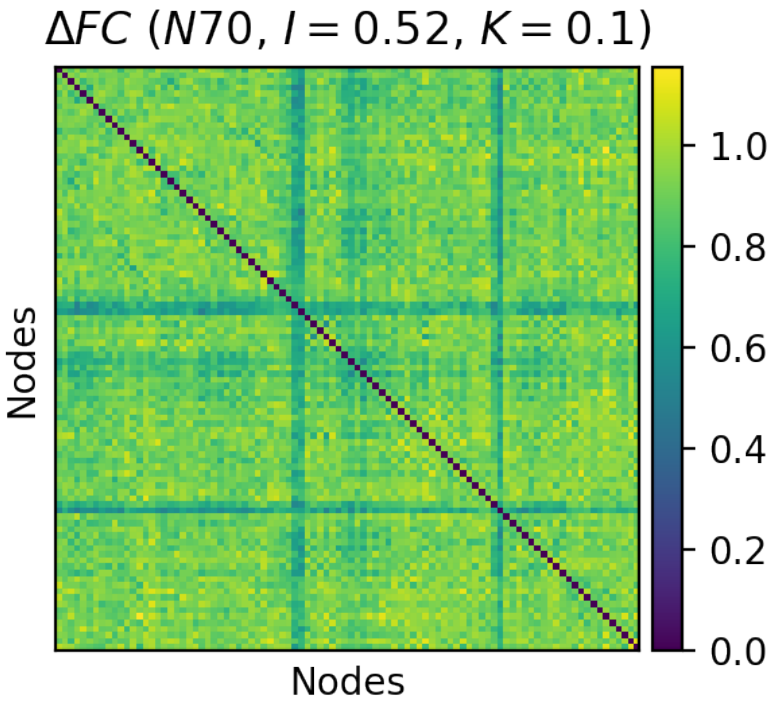


(b)

Figure 2. Regional controllability. (a) Relationship between node degree and (a) average controllability and (b) modal controllability, respectively, for all regions and subjects.*replicates Figure 3*



(a)



(b)

Figure 3. Effect of regional stimulation. Effect of stimulation of two example regions: (a) Region 25 (name?) with a low average controllability (value?), (b) Region 70 (name?) with a high average controllability (value?). *replicates Figure 4c*

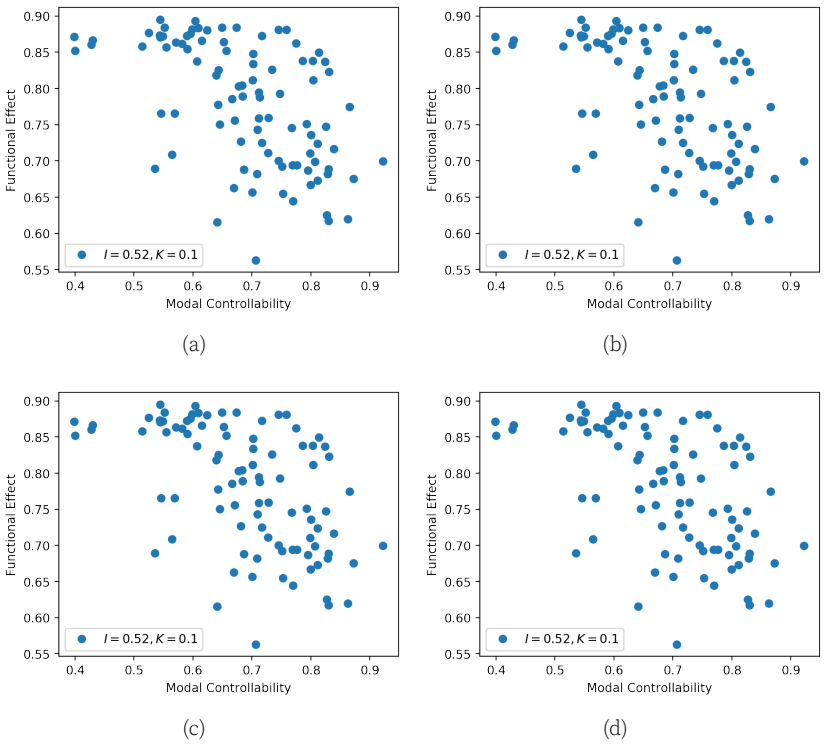


Figure 4. Functional effect and controllability. (a-b) Functional effect of nodal stimulation plotted against average (a) and modal (b) controllability. *replicates Figure 5; change b-d; redo all figures with individual subject resolution* ***Question: Why do we have modal controllability ranging from 0.4 to 1 while Muldoon from 0.965 to 1?***

5. P. Alonso et al. "Deep brain stimulation for obsessive-compulsive disorder: A meta-analysis of treatment outcome and predictors of response." In: **PLoS ONE** 10.7 (July 2015).
6. S. F. Muldoon, F. Pasqualetti, S. Gu, M. Cieslak, S. T. Grafton, J. M. Vettel, and D. S. Bassett. "Stimulation-Based Control of Dynamic Brain Networks." In: **PLoS Computational Biology** 12.9 (Sept. 2016). arXiv: 1601.00987.
7. H. R. Wilson and J. D. Cowan. "Excitatory and Inhibitory Interactions in Localized Populations of Model Neurons." In: **Biophysical Journal** 12.1 (1972), pp. 1–24.
8. R. FitzHugh. "Impulses and Physiological States in Theoretical Models of Nerve Membrane." In: **Biophysical Journal** 1.6 (1961), pp. 445–466.