Joint estimation of regional co-activations and causal interplays with a sparse coupled logistic regression framework

Thomas A. W. Bolton & Dimitri Van De Ville

Chemin des Mines 09, 1202 Geneva

E-mail: thomas.bolton@epfl.ch

November 2019

Abstract. This abstract describes my work.
Essentially, it's awesome.
You have to accept it.

Keywords: dynamic functional connectivity, effective connectivity, logistic regression, ℓ_1 regularisation

Submitted to: *J. Neural Eng.*

1. Introduction

Understanding the structural wiring of the brain at its most global scale, and how information flows between remote processing centres, are essential questions to shed light on higher-order behaviours involving multi-modal integration and associated brain disorders. When it comes to functional magnetic resonance imaging (fMRI), the mapping of brain function is commonly performed from resting-state (RS) recordings through the computation of *functional connectivity* (FC), that is, the statistical interdependence between different time courses reflective of regional activity (Friston 1994), as can be assessed from an array of measures (Smith, Miller, Salimi-Khorshidi, Webster, Beckmann, Nichols, Ramsey & Woolrich 2010). This approach has revealed the presence of a set of RS networks (RSNs) (Damoiseaux, Rombouts, Barkhof, Scheltens, Stam, Smith & Beckmann 2006, Power, Fair, Schlaggar & Petersen 2010), whose properties are critical landmarks of brain function and cognition (Bressler & Menon 2010, van den Heuvel & Hulshoff Pol 2010).

Over the past decade, it has become increasingly clear that quantifying FC between two brain regions as one scalar for a full scanning session is an overly simplistic approach that does not characterise the numerous reconfigurations that occur at the time scale of seconds (Chang & Glover 2010). Accordingly, many methodological pipelines have been developed to dig into time-resolved FC, and map brain function dynamically (see (Preti, Bolton & Van De Ville 2017, Lurie, Kessler, Bassett, Betzel, Breakspear, Keilholz, Kucyi, Liégeois, Lindquist & McIntosh 2018) for contemporary reviews).

The most notorious family of dynamic approaches simplifies the originally voxel-wise fMRI data into a state-level representation: first, FC is computed over successive temporal sub-windows, and the concatenated data across the full subject population at hand is subjected to hard clustering to yield a set of dynamic FC (dFC) states (Allen, Damaraju, Plis, Erhardt, Eichele & Calhoun 2014, Damaraju, Allen, Belger, Ford, McEwen, Mathalon, Mueller, Pearlson, Potkin, Preda, Turner, Vaidya, van Erp & Calhoun 2014). Because spatial Independent Component Analysis (ICA) is typically performed prior to clustering, each state stands for a set of RSNs showing specific correlational relationships.

In other analytical schemes, whole-brain voxelwise activity (Liu, Chang & Duyn 2013), or activity transients (Karahanoğlu & Van De Ville 2015), undergo clustering instead of FC patterns; in this case, each of the retrieved centroids directly stands for an RSN. If temporal ICA is applied after spatial ICA, temporally mutually independent RSNs are retrieved (Smith, Miller, Moeller, Xu, Auerbach, Woolrich, Beckmann, Jenkinson, Andersson, Glasser et al. 2012). Finally, the use of a hidden Markov model (HMM) also enables to derive RSNs, as represented under the form of (sparse) FC patterns (Eavani, Satterthwaite, Gur, Gur & Davatzikos 2013, Vidaurre, Smith & Woolrich 2017) or vectors of activation (Chen, Langely, Chen & Hu 2016).

In all the above cases, there is the underlying assumption that the raw fMRI data can be downscaled to a set of RSNs, and that the dynamics of brain function should be understood from this simplified starting point. Recent results, however, question the validity of this assumption: for instance, some brain regions do not remain attached to the same network throughout a scanning session, but instead adjust their modular allegiance over time in a way that relates to cognitive performance (Chen, Cai, Ryali, Supekar & Menon 2016, Pedersen, Zalesky, Omidvarnia & Jackson 2018). In addition, brain regions or networks also morph spatially over time (Kiviniemi, Vire, Remes, Elseoud, Starck, Tervonen & Nikkinen 2011, Kottaram, Johnston, Ganella, Pantelis, Kotagiri & Zalesky 2018, Iraji, Fu, Damaraju, DeRamus, Lewis, Bustillo, Lenroot, Belger, Ford, McEwen et al. 2019).

To capture these spatially more subtle reconfigurations, novel methodologies have attempted to operate at the regional scale, and the assessment of *causal* relationships (*i.e.*, from time t to $t + 1$) between distinct areas showed particular merits as an alternative conceptualisation of RS functional brain dynamics, be it through autoregressive models (Liégeois, Laumann, Snyder, Zhou & Yeo 2017, Lennartz, Schiefer, Rotter, Hennig & LeVan 2018) or Ornstein-Uhlenbeck processes (Gilson, Moreno-Bote, Ponce-Alvarez, Ritter & Deco 2016).

At present, there are thus two conceptually discrepant ways to view RS dFC: on the one hand, expressing it as sets of simultaneously activating regions that make networks, and on the other hand, viewing it as effective connectivity between individual areas. It remains to be determined which of these two viewpoints offers the best representation of RS dynamics, and whether they describe overlapping or distinct facets of the data.

In this work, we have attempted to progress in answering these questions by developing a novel methodological framework that jointly estimate sets of co-activations, and causal couplings, between individual brain regions. A dedicated parameter also enables to modulate the trade-off in data fitting between these two viewpoints.

Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T. & Calhoun, V. D. (2014). Tracking whole-brain connectivity dynamics in the resting state, *Cerebral Cortex* **24**(3): 663–676.

Bressler, S. L. & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles, *Trends in Cognitive Sciences* **14**(6): 277–290.

Chang, C. & Glover, G. H. (2010). Time-frequency dynamics of resting-state brain connectivity measured with fMRI, *Neuroimage* **50**(1): 81–98.
URL: *http://dx.doi.org/10.1016/j.neuroimage.2009.12.011*

Chen, S., Langely, J., Chen, X. & Hu, X. (2016). Spatiotemporal modeling of brain dynamics using resting-state functional magnetic resonance imaging with Gaussian hidden Markov model, *Brain Topography* **6**(4): 326–334.

Chen, T., Cai, W., Ryali, S., Supekar, K. & Menon, V. (2016). Distinct global brain dynamics and spatiotemporal organization of the salience network, *PLOS Biology* **14**(6): 1–21.
URL: *https://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.1002469&type=printable*

Damaraju, E., Allen, E. A., Belger, A., Ford, J. M., McEwen, S., Mathalon, D. H., Mueller, B. A., Pearlson, G. D., Potkin, S. G., Preda, A., Turner, J. A., Vaidya, J. G., van Erp, T. G. & Calhoun, V. D. (2014). Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia, *Neuroimage: Clinical* **5**: 298–308.
URL: *http://dx.doi.org/10.1016/j.nicl.2014.07.003 http://linkinghub.elsevier.com/retrieve/pii/S2213158214000953*

Damoiseaux, J. S., Rombouts, S. A. R., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M. & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects, *Proceedings of the National Academy of Sciences* **103**(37): 13848–13853.
URL: *http://www.pnas.org/content/103/37/13848.short*

Eavani, H., Satterthwaite, T. D., Gur, R. E., Gur, R. C. & Davatzikos, C. (2013). Unsupervised learning of functional network dynamics in resting state fMRI, *Lecture Notes in Computer Science* **7917**: 426–437.
URL: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3974209/pdf/nihms-504470.pdf*

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis, *Human Brain Mapping* **2**(1): 56–78.

Gilson, M., Moreno-Bote, R., Ponce-Alvarez, A., Ritter, P. & Deco, G. (2016). Estimation of directed effective connectivity from fmri functional connectivity hints at asymmetries of cortical connectome, *PLOS Computational Biology* **12**(3): e1004762.

Iraji, A., Fu, Z., Damaraju, E., DeRamus, T. P., Lewis, N., Bustillo, J. R., Lenroot, R. K., Belger, A., Ford, J. M., McEwen, S. et al. (2019). Spatial dynamics within and between brain functional domains: A hierarchical approach to study time-varying brain function, *Human Brain Mapping* **40**(6): 1969–1986.

Karahanoğlu, F. I. & Van De Ville, D. (2015). Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks, *Nature Communications* **6**: 7751.
URL: *http://www.nature.com/doifinder/10.1038/ncomms8751*

Kiviniemi, V., Vire, T., Remes, J., Elseoud, A. A., Starck, T., Tervonen, O. & Nikkinen, J. (2011). A sliding time-window ICA reveals spatial variability of the default mode network in time, *Brain Connectivity* **1**(4): 339–347.
URL: *http://www.liebertonline.com/doi/abs/10.1089/brain.2011.0036*

Kottaram, A., Johnston, L., Ganella, E., Pantelis, C., Kotagiri, R. & Zalesky, A. (2018). Spatio-temporal dynamics of resting-state brain networks improve single-subject prediction of schizophrenia diagnosis, *Human Brain Mapping* **39**(9): 3663–3681.

Lennartz, C., Schiefer, J., Rotter, S., Hennig, J. & LeVan, P. (2018). Sparse estimation of resting-state effective connectivity from fmri cross-spectra, *Frontiers in Neuroscience* **12**: 287.

Liégeois, R., Laumann, T. O., Snyder, A. Z., Zhou, J. & Yeo, B. T. T. (2017). Interpreting temporal fluctuations in resting-state functional connectivity mri, *Neuroimage* **163**: 437–455.

Liu, X., Chang, C. & Duyn, J. H. (2013). Decomposition of spontaneous brain activity into distinct

fMRI co-activation patterns, *Frontiers in Systems Neuroscience* **7**: 1–11.
URL: *http://journal.frontiersin.org/article/10.3389/fnsys.2013.00101/abstract*

Lurie, D., Kessler, D., Bassett, D., Betzel, R. F., Breakspear, M., Keilholz, S., Kucyi, A., Liégeois, R., Lindquist, M. A. & McIntosh, A. R. (2018). On the nature of resting fmri and time-varying functional connectivity, *PsyArXiv* .

Pedersen, M., Zalesky, A., Omidvarnia, A. & Jackson, G. D. (2018). Multilayer network switching rate predicts brain performance, *Proceedings of the National Academy of Sciences* **115**(52): 13376–13381.

Power, J. D., Fair, D. A., Schlaggar, B. L. & Petersen, S. E. (2010). The Development of Human Functional Brain Networks, *Neuron* **67**(5): 735–748.
URL: *http://dx.doi.org/10.1016/j.neuron.2010.08.017 http://ac.els-cdn.com/S0896627310006276/1-s2.0-S0896627310006276-main.pdf?_tid=530b28c0-358b-11e7-8056-00000aacb35d&acdnat=1494425996_7e5fc23be3ab984395a36c2a6fa42bfb*

Preti, M. G., Bolton, T. A. W. & Van De Ville, D. (2017). The dynamic functional connectome: State-of-the-art and perspectives, *Neuroimage* **160**: 41–54.
URL: *https://ac.els-cdn.com/S1053811916307881/1-s2.0-S1053811916307881-main.pdf?_tid=740fef8f-835b-4993-86d3-a6f60b841679&acdnat=1523360042_29ea611d8892cbd9e44c8ac92ff16e62*

Smith, S. M., Miller, K. L., Moeller, S., Xu, J., Auerbach, E. J., Woolrich, M. W., Beckmann, C. F., Jenkinson, M., Andersson, J., Glasser, M. F. et al. (2012). Temporally-independent functional modes of spontaneous brain activity, *Proceedings of the National Academy of Sciences* **109**(8): 3131–3136.

Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., Ramsey, J. D. & Woolrich, M. W. (2010). Network modelling methods for fMRI, *NeuroImage* .

van den Heuvel, M. P. & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity, *European Neuropsychopharmacology* **20**(8): 519–534.

Vidaurre, D., Smith, S. M. & Woolrich, M. W. (2017). Brain network dynamics are hierarchically organized in time, *Proceedings of the National Academy of Sciences* **114**(48): 201705120.
URL: *http://www.pnas.org/lookup/doi/10.1073/pnas.1705120114*