Solved problems and remaining challenges for Granger causality analysis in neuroscience: A response to Stokes and Purdon (2017)

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Abstract

Granger-Geweke causality (GGC) is a powerful and popular method for identifying directed functional (‘causal’) connectivity in neuroimaging contexts (Seth et al., 2015). GGC operationalises a statistical, predictive notion of causality in which causes precede, and help predict their effects. When implemented using autoregressive modelling, GGC can be computed in both time and frequency domains, in both bivariate and multivariate (conditional) formulations. Despite its popularity and power, the use of GGC in neuroscience has remained controversial. In a recent paper, Stokes and Purdon (2017) raise two primary concerns: (1) that GGC estimates may be severely biased or of high variance, and (2) that GGC fails to reveal the full structural/causal mechanisms of a system. Here we explain why these concerns are misplaced.

Regarding the first claim, Stokes and Purdon (2017) describe how bias and variance in GGC estimation arise from the use of separate, independent, full and reduced regressions. However, this problem has long been recognised (Chen et al., 2006; Barnett and Seth, 2014) and, moreover, has already been solved by methods which derive GGC from a single full regression. These methods essentially extract reduced model parameters from the full model via factorisation of the spectral density matrix. Well-documented approaches include Wilson’s frequency-domain algorithm (Dhamala et al., 2008), Whittle’s time-domain algorithm (Barnett and Seth, 2014), and a state-space approach which devolves to solution of a discrete-time algebraic Riccati equation (Barnett and Seth, 2015; Solo, 2016). Thus, the source of bias and variance discussed in Stokes and Purdon (2017) has already been resolved.

This is clearly illustrated in Fig. 1, where we plot estimated frequency-domain GGC for the 3-node VAR model in Stokes and Purdon (2017), Example 1, using the single-regression state-space method (Barnett and Seth, 2015; Solo, 2016). We remark that identical results are obtained using the time-domain spectral factorisation method of Barnett and Seth (2014), as implemented in the current (v1.0, 2012) release of the associated MVGC Matlab® software package (Barnett and Seth, 2012). Fig. 1 may be directly compared with Fig. 2 in Stokes and Purdon (2017); we see clearly that all estimates are strictly non-negative, and that exaggerated bias and variance associated with the dual-regression approach are absent. Therefore, Stokes and Purdon (2017) are in error when they state that “Barnett and Seth […] have proposed fitting the reduced model and using it to directly compute the spectral components …”. This is important to note because our MVGC toolbox has been widely adopted within the community, with > 3,500 downloads and a significant number of high-impact research publications using the method (e.g., Yellin et al., 2015; Bruneau et al., 2015; Place et al., 2016; Schmitt et al., 2017; Wilber et al., 2017). Thus, we can reassure users of the toolbox that problems of bias and variance as described by Stokes and Purdon (2017) do not apply.

Sample variance is, of course, still evident, as is bias due to non-negativity of the GGC sample statistic (which may be countered by standard surrogate data methods), but both remain well below their minimum values across all model orders for the dual-regression case (as evidenced by Stokes and Purdon, 2017, Fig. 2). Fig. 2 further compares bias and variance of time-domain GGC for the example system for single

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1We note here that the “partition matrix” solution proposed by Chen et al. (2006) is incorrect; see, e.g., Solo (2016).
Figure 1: Granger-Geweke frequency-domain causalities estimated by the single-regression state-space method (Barnett and Seth, 2015; Solo, 2016) for the 3-node VAR model in Stokes and Purdon (2017), (Example 1, cf. Fig. 2). The true model order of 3 was used for the (single, full-model) VAR estimates. Plots are based on 10,000 time series realisations of 500 observations: red lines plot the exact causality for the model and blue lines sample estimate medians. The shaded areas indicate 90% central confidence intervals, while the green lines plot. The dashed horizontal lines indicate critical thresholds over all frequencies [see Stokes and Purdon (2017), Supporting Information, S9] at 95% significance, derived from simulation of the corresponding null model.
statistical inference, and which also stands as an effect size for directed information flow between components of the system (Barrett and Barnett, 2013). Both approaches address valid questions of interest to neuroscientific analysis.

Concluding, GGC represents a conceptually satisfying and statistically powerful method for (directed) functional connectivity analysis in neuroscience and neuroimaging. Currently available implementations [e.g., Barnett and Seth (2012)] deal appropriately with issues of bias and variance associated with dual regression methods. However, a range of additional challenges remain in further developing this useful technique. These include issues of stationarity, linearity and exogenous influences, as noted by Stokes and Purdon (2017), and in addition the influences of noise, sampling rates and temporal/spatial aggregation engendered by neural data acquisition (Solo, 2016; Barnett and Seth, 2017).

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References

Barnett, L., Barrett, A.B., Seth, A.K., 2009. Granger causality and transfer entropy are equivalent for Gaussian variables. Phys. Rev. Lett. 103, 0238701.
Barnett, L., Seth, A.K., 2011. Behaviour of Granger causality under filtering: Theoretical invariance and practical application. J. Neurosci. Methods 201, 404–419.
Barnett, L., Seth, A.K., 2012. The MVGC Multivariate Granger Causality Matlab toolbox. http://users.sussex.ac.uk/~lionelb/MVGC/
Barnett, L., Seth, A.K., 2014. The MVGC multivariate Granger causality toolbox: A new approach to Granger-causal inference. J. Neurosci. Methods 223, 50–68.
Barnett, L., Seth, A.K., 2015. Granger causality for state-space models. Phys. Rev. E (Rapid Communications) 91, 040101(R).
Barnett, L., Seth, A.K., 2017. Detectability of Granger causality for subsampled continuous-time neurophysiological processes. J. Neurosci. Methods 275, 93–121.
Barrett, A.B., Barnett, L., 2013. Granger causality is designed to measure effect, not mechanism. Front. Neuroinform. 7, 6.
Barrett, A.B., Barnett, L., Seth, A.K., 2010. Multivariate Granger causality and generalized variance. Phys. Rev. E 81, 041907.
Bruneau, E.G., Jacoby, N., Saxe, R., 2015. Empathic control through coordinated interaction of amygdala, theory of mind and extended pain matrix brain regions. Neurolmage 114, 105–119.
Chen, Y., Bressler, S.L., Ding, M., 2006. Frequency decomposition of conditional Granger causality and application to multivariate neural field potential data. J. Neurosci. Methods 150, 228–237.
Dhamala, M., Rangarajan, G., Ding, M., 2008. Estimating Granger causality from Fourier and wavelet transforms of time series data. Phys. Rev. Lett. 100, 018701.
Friston, K., Moran, R., Seth, A.K., 2013. Analyzing connectivity with Granger causality and Dynamic Causal Modelling. Curr. Opin. Neurobiol. 23, 172–178.
Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. NeuroImage 19, 1273–1302.
Hannan, E.J., Deistler, M., 2012. The Statistical Theory of Linear Systems. SIAM, Philadelphia, PA, USA.
Place, R., Farovik, A., Brockmann, M., Eichenbaum, H., 2016. Bidirectional prefrontal-hippocampal interactions support context-guided memory. Nature neuroscience 19, 992–994.

Figure 2: Granger-Geweke time-domain causality bias (left column) and variance (right column) for estimation by the single-regression state-space method (red lines) and dual-regression method (blue lines), plotted against time series length, for the example 3-node VAR model in Stokes and Purdon (2017). Bias is measured as the difference between the sample median and true causality, while variance is measured as the mean absolute deviation of the sample causality (we use non-parametric measures, as the GGC sample estimators are non-negative, non-Gaussian, and potentially highly skewed). The true model order of 3 was used for all VAR estimates. Plots are based on 10,000 time series realisations for each number of observations.
Schmitt, L.I., Wimmer, R.D., Nakajima, M., Happ, M., Mofakham, S., Ha-
lassa, M.M., 2017. Thalamic amplification of cortical connectivity sustains
attentional control. Nature 545, 219–223.
Seth, A.K., Barrett, A.B., Barnett, L.C., 2015. Granger causality analysis in
neuroscience and neuroimaging. J. Neurosci. 35, 3293–3297.
Seth, A.K., Chorley, P., Barnett, L., 2013. Granger causality analysis of fMRI
BOLD signals is invariant to hemodynamic convolution but not downsam-
pling. NeuroImage 65, 540–555.
Solo, V., 2016. State-space analysis of Granger-Geweke causality measures
with application to fMRI. Neural Comput. 28, 914–949.
Stephan, K.E., Penny, W.D., Moran, R.J., den Ouden, H.E.M., Daunizeau, J.,
Friston, K.J., 2010. Ten simple rules for dynamic causal modeling. Neu-
roImage 49, 3099–3109.
Stokes, P.A., Purdon, P.L., 2017. A study of problems encountered in Granger
causality analysis from a neuroscience perspective. Proc. Natl. Acad. Sci.
USA 114, 7063–7072.
Valdes-Sosa, P.A., Roebroeck, A., Daunizeau, J., Friston, K., 2011. Effective
connectivity: Influence, causality and biophysical modeling. NeuroImage
58, 339–361.
Wilber, A.A., Skelin, I., Wei, W., McNaughton, B.L., 2017. Organization of
encoding and memory reactivation in the parietal cortex. Neuron 95, 1406–
1419.e5.
Yellin, D., Berkovich-Ohana, A., Malach, R., 2015. Coupling between pupil
fluctuations and resting-state fMRI uncovers a slow build-up of antagonistic
responses in the human cortex. NeuroImage 106, 414–427.