

Demonstrating causal links between timeseries associated with fMRI data using Granger analysis

Ben J. Smith, Patrice Delmas

Vision Lab NZ

University of Auckland Computer Science Department

Auckland, New Zealand

bsmi080@aucklanduni.ac.nz

Sarina Iwabuchi, Ian J. Kirk

Research Centre for Cognitive Neuroscience

University of Auckland Psychology Department

Auckland, New Zealand

Abstract— Granger analysis, originally an econometric statistical technique, has been applied increasingly in fundamental magnetic resonance imaging (fMRI) for measuring causal connections between brain regions. This paper summarises the possibilities and limitations of applying Granger analysis to fMRI, describes a replication of a previous theoretical study, and an application currently under way. Previous researchers have described methods for detecting time-lagged correlation between region of interest (ROI) activation – primarily variants on, ‘Granger causality’ (GC), originally used in econometrics, as a proxy for causality. With appropriate caveats, GC can draw inferences from temporal precedence about effective connectivity between ROIs in a way other popular methods do not. The current project’s replication uses a different non-linear function, and method of combining an hrf. The project also examines whether time-lag analysis can estimate the direction of causation in frontal and parietal areas known to act together in spatial working memory tasks. Independent Component Analysis (ICA) is used to identify independent spatial components, whose interactions are then examined using the Granger causality method. The method successfully identified causal relationships on replicated, artificially simulated data and in between extracted components in the data. Work is now underway to determine the implications for these relationships.

Keywords—Granger analysis; independent component analysis; effective connectivity; fMRI

I. INTRODUCTION

In neuroscience, “effective connectivity” is defined [1] as “the influence one neural system exerts over another”. Granger analysis, which developed out of econometrics [2], is one method proposed to measure effective connectivity, primarily by measuring the extent to which activity in a brain region can predict future activity in another brain region.

II. GRANGER THEORY

A. MAR Modelling/basic principle

Granger analysis indicates the directionality of influence, predictability, or Granger-causality between two (bivariate) or more (multivariate) regions. The usefulness of a timeseries Y in predicting the behavior of another timeseries X is the ‘Granger-causality’ of Y on X; if Y significantly predicts X, then Y is ‘Granger-causal’ of X.

In Granger analysis, the predictivity of one time series on another is measured by comparing the error r_{AR} of a univariate autoregressive model with the error r_{BAR} of a bivariate autoregressive model, as in

$$F(X, Y) = \log \left(\frac{\text{var}(r_{BAR})}{\text{var}(r_{AR})} \right). \quad (1)$$

B. Multivariate Models

Variations have been developed which can infer causality in the context of more than two timeseries. One such method is Conditional Granger Causality [3], which calculates the causal relationship between two timeseries while controlling for a third.

C. Statistical significance

Statistical significance can be calculated through the bootstrap technique [4], widely employed in fMRI studies [5], particularly in Granger analysis.

D. Inferring causality

‘Granger-causality’ of the kind described above refers to the temporally predictive power that a second timeseries has in predicting the future value of a timeseries of interest. Granger [2, 6] justifies and defines use of the word “causality”, arguing that if all other plausible causes can reasonably be excluded, the one event remaining must be causal. Other plausible causes could be reasonably excluded either by using a multivariate Granger analysis, which tests for causal relationship between two timeseries X and Y given timeseries Z, or by some a priori knowledge that there exists functional connection between two regions and only two of interest.

A single bivariate Granger test, such as that described above, does not itself rule out other causes potential causes; it may only show that time-lagged correlated timeseries Y predicts X rather than necessarily causes it. However, where it is known there exists a functional connection primarily between two, and only two, regions, then such a bivariate Granger test could shed light on the effective connectivity of that region including the directionality of that connection.

III. ADVANTAGES OVER SEM, DCM, AND OTHERS: WHY GRANGER?

Granger analysis offers at least one advantage over both SEM and DCM, two widely-used statistical methods for measuring effective connectivity. Structural equation modelling and DCM require a priori hypothesis about the network nodes and interactions between them [5]. Although the bivariate technique described above cannot be relied upon to describe *causality* without assuming some previous theory regarding interactions, a multivariate Granger technique can do; furthermore, the bivariate approach can still describe predictivity, and can indicate direction of effective connectivity where a connection is known to exist.

Granger analysis is designed to take advantage of temporal precedence, which is a feature of data not captured by SEM, which assumes instantaneous connections, although DCM uses a coupling parameter which describes speed of change of nodes within a model. Furthermore, Granger analysis can work with a large number of ROIs, [5]– another reason that it is a good exploratory method for effective connectivity – although the method does lose power with increasing numbers of ROIs.

Although Granger analysis is not the only way an autoregressive model has been used to measure predictivity in fMRI, it is currently the most widely used.

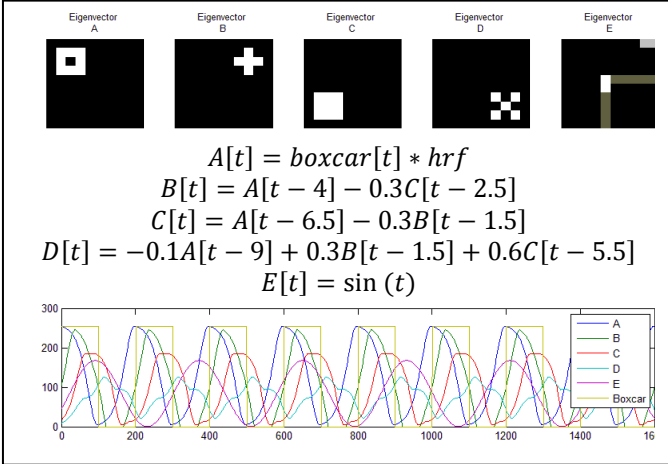


Figure 1. Londei et al. (2006) simulation design, showing the images mixed and time series used to mix each of them.

IV. CURRENT SIMULATED DATA DEMONSTRATION

Londei et al. [7] described a Granger analysis ‘proof of concept’ using simulated fMRI data, which has been replicated with minor changes in the current project. Here, five ground truth ‘independent components’ – activations (Figure 7) have been created. Activation of each over time is described by a set of equations (Figure 1) and random noise is added. The activation of each independent spatial component can be isolated using independent component analysis (Figure 2), specifically the fastICA 2.5 algorithm [11]. In contrast to the Londei et al. [7], a cubic rather than hyperbolic tangent non-linear function was used. A variety of conditions, including

mean centring along each dimension, altering the number of extracted eigenvectors, random or pre-determined initial guesses for the mixing matrix, and different model orders were used. Results here use 20 initial eigenvectors extracted, random initial guesses, and an autoregressive model order of 2. In contrast to the formula shown in Figure 1 for $A[t]$, the hrf convolution was here applied to each pixel in the images after all had been generated, not to the first time series. Each extracted spatial component corresponds to a time series describing the extent to which that component represents the data at any given time. Each time series can be compared to the reference timeseries (Figure 3), and those most closely matching can be chosen for Granger analysis.

We apply the Granger analysis described previously to examine the relationships between each of the timeseries, using a bivariate Granger analysis comparison (Figure 9). Granger causal relationships represent relationships between different components; where these components can be identified with particular regions, ‘Granger-causal’ or predictive relationships are found between those regions (Figure 4).

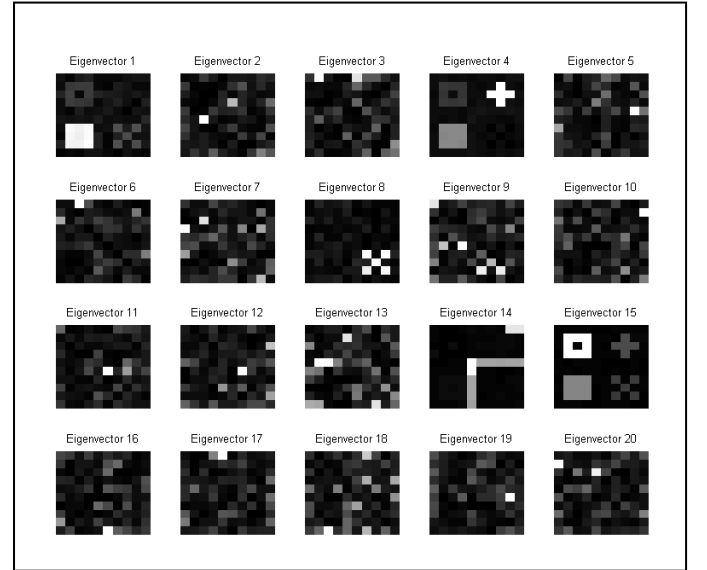


Figure 2. Eigenvectors extracted using ICA.

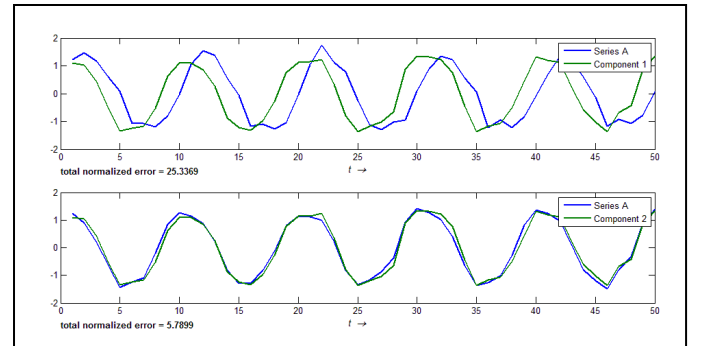
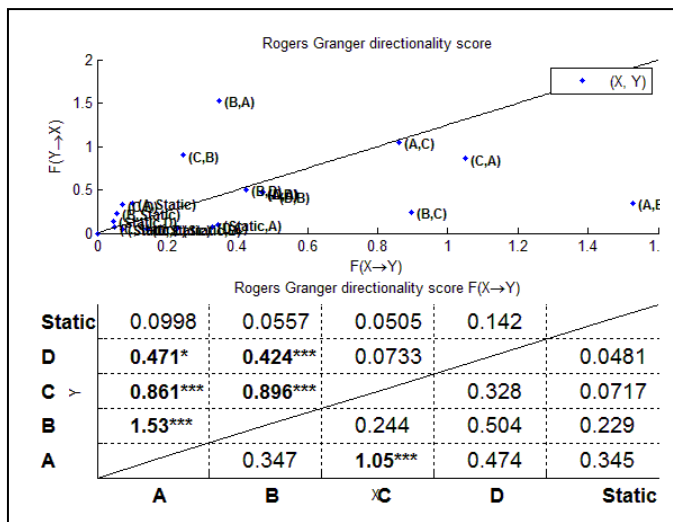


Figure 3. Each component eigenvector is compared to each original series; the closest match eigenvector for each of the original series is chosen for subsequent Granger analysis.



Independent component analysis was applied separately to the data from each subject to extract 80 independent components. The associated time series of those spatial components were compared to the convolution of each of the time series of activation (Figure 5) of each of the two stimulus condition series (Figure 3); the closest 5 matches in each case were selected. The Granger-causal relationships between each of the selected time series were compared. If the matching to stimulus condition series can accurately identify regions

associated with activity in the mental tasks which they represent – respectively, spatial perception and spatial working memory – then causal relationships across those conditions indicate Granger-causal relationships between networks associated with the working memory task and those associated with the spatial perception task.

C. Results

Several significant Granger-causal relationships between components were found for each subject, including relationships between conditions. Exemplars from one subject are shown in Figure X.

It has not been possible to determine whether the independent components extracted are good representations of the regions of interest, or the networks of interest including spatial perception and spatial working memory.

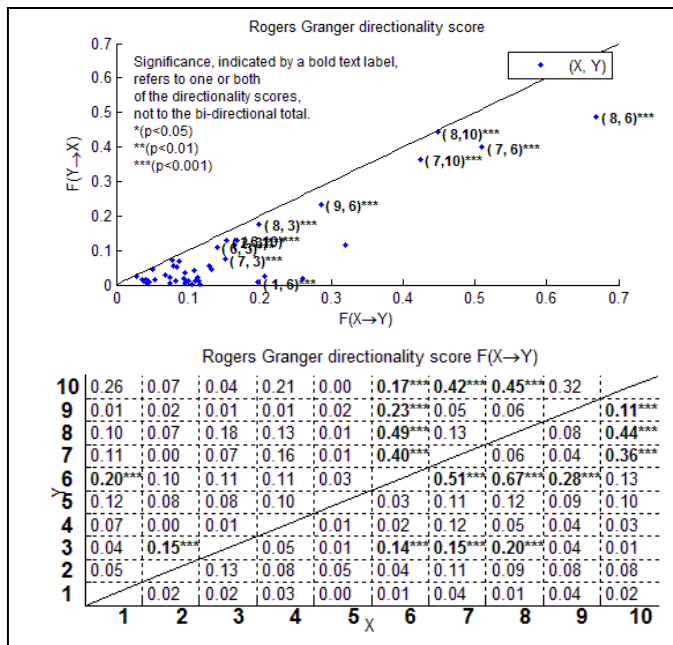


Figure 6. The directionality of extracted components is shown above as a comparison between two axes (a high x-axis value indicates X is predictive of Y; a high y-axis value indicates Y is predictive of X); those scores are shown numerically in the table below. Components 1-5 are associated with the working memory condition; components 6-10 are associated with the spatial perception + working memory condition.

D. Discussion and further work

A number of significant causal relationships were observed between the independent components extracted (Figure 6). Identifying the independent components with particular brain networks would enable inferences about the causal connectivity of those brain networks.

Paired-sample t-tests counting the number of significant Granger analysis scores across all 20 subjects showed that ICs in the perception and memory conditions were each better predicted by other ICs in their own conditions; but there was not a significant difference between number of significant predictive relationships between the perception and memory conditions, yielding no evidence that neural networks

associated with one condition are causal of those associated with another.

Significant functional MRI results more frequently emerge from data combined from a collection of subjects using statistical analyses such as the generalized linear model. Work is currently under way to combine data from different subjects; this could be done either prior to the ICA or subsequent to it, with the extracted time series. The “control” stimulus time series which is used to extract data could be associated with *both* the test conditions instead of only the control test condition, as at present.

VII. SUMMARY

Distinct time series can be extracted from fMRI-like data using ICA to separate the data into different components. These time series can be compared using Granger analysis to detect time-lagged predictive relationships [7]. These predictive relationships could even be described as causal relationships, where influences to external areas can be ruled out with prior knowledge of a system, or the use of Conditional Granger Causality. Finding causal relationships – effective connectivity – in fMRI data can help determine how brain systems are structured and work together. Currently, more work is needed to determine whether Granger-causal relationships between spatial perception and spatial working memory can be detected using Granger causality, and the extent to which Granger causality is able to detect delays between regions.

REFERENCES

- [1] K. J. Friston, C. D. Frith, and R. S. J. Frackowiak, "Time-dependent changes in effective connectivity measured with PET," *Human Brain Mapping*, vol. 1, pp. 69-79, 1993.
- [2] C. W. J. Granger, "Investigating Causal Relations by Econometric Models and Cross-spectral Methods," *Econometrica*, vol. 37, pp. 424-438, 1969.
- [3] M. Ding, Y. Chen, and S. L. Bressler, *Granger causality: basic theory and application to neuroscience*. Wiley-VCH Verlag, 2006.
- [4] B. Efron and R. Tibshirani, *An introduction to the bootstrap*. New York: Chapman & Hall, 1993.
- [5] H. Chen, Q. Yang, W. Liao, Q. Gong, and S. Shen, "Evaluation of the effective connectivity of supplementary motor areas during motor imagery using Granger causality mapping," *NeuroImage*, vol. 47, pp. 1844-1853, Oct 2009.
- [6] C. W. J. Granger, "Testing for causality," *Journal of Economic Dynamics and Control*, vol. 2, pp. 329-352, 1980.
- [7] A. Londei, A. D'Ausilio, D. Basso, and M. O. Belardinelli, "A new method for detecting causality in fMRI data of cognitive processing," *Cognitive Processing*, vol. 7, pp. 42-52, Mar 2006.
- [8] Q. Gao, X. Duan, and H. Chen, "Evaluation of effective connectivity of motor areas during motor imagery and execution using conditional Granger causality," *NeuroImage*, vol. 54, pp. 1280-1288, Jan 2011.
- [9] A. Londei, A. D'Ausilio, D. Basso, C. Sestieri, C. Del Gratta, G. L. Romani, and M. O. Belardinelli, "Brain network for passive word listening as evaluated with ICA and Granger causality," *Brain Research Bulletin*, vol. 72, pp. 284-292, May 2007.
- [10] S. Graham, E. Phua, C. S. Soon, T. Oh, C. Au, B. Shuter, S.-C. Wang, and I. B. Yeh, "Role of medial cortical, hippocampal and striatal interactions during cognitive set-shifting," *NeuroImage*, vol. 45, pp. 1359-1367, May 2009.
- [11] J. R. Sato, A. Fujita, E. F. Cardoso, C. E. Thomaz, M. J. Brammer, and E. Amaro, Jr., "Analyzing the connectivity between regions of interest:

An approach based on cluster Granger causality for fMRI data analysis," *NeuroImage*, vol. 52, pp. 1444-1455, Oct 2010.

- [12] L. Q. Uddin, A. M. C. Kelly, B. B. Biswal, F. X. Castellanos, and M. P. Milham, "Functional connectivity of default mode network components: Correlation, anticorrelation, and causality," *Human Brain Mapping*, vol. 30, pp. 625-637, Feb 2009.
- [13] M. Wilke, K. Lidzba, and I. Krageloh-Mann, "Combined functional and causal connectivity analyses of language networks in children: A feasibility study," *Brain and Language*, vol. 108, pp. 22-29, Jan 2009.
- [14] W. Liao, D. Mantini, Z. Zhang, Z. Pan, J. Ding, Q. Gong, Y. Yang, and H. Chen, "Evaluating the effective connectivity of resting state networks using conditional Granger causality," *Biological Cybernetics*, vol. 102, pp. 57-69, Jan 2010.
- [15] B. B. Biswal, D. A. Eldreth, M. A. Motes, and B. Rypma, "Task-dependent individual differences in prefrontal connectivity," *Cerebral Cortex*, vol. 20, pp. 2188-2197, Sep 2010.
- [16] C. A. Seger, E. J. Peterson, C. M. Cincotta, D. Lopez-Paniagua, and C. W. Anderson, "Dissociating the contributions of independent corticostriatal systems to visual categorization learning through the use of reinforcement learning modeling and Granger causality modeling," *NeuroImage*, vol. 50, pp. 644-656, Apr 2010.
- [17] M. C. Stevens, G. D. Pearlson, and V. D. Calhoun, "Changes in the interaction of resting-state neural networks from adolescence to adulthood," *Human Brain Mapping*, vol. 30, pp. 2356-2366, Aug 2009.
- [18] J. B. Rowe, "Connectivity analysis is essential to understand neurological disorders," *Frontiers in Systems Neuroscience*, vol. 4, pp. 1-13, 2010.
- [19] S. T. Witt and M. E. Meyerand, "The effects of computational method, data modeling, and TR on effective connectivity results," *Brain Imaging and Behavior*, vol. 3, pp. 220-231, 2009.
- [20] S. M. Smith, K. L. Miller, G. Salimi-Khorshidi, M. Webster, C. F. Beckmann, T. E. Nichols, J. D. Ramsey, and M. W. Woolrich, "Network modelling methods for FMRI," *NeuroImage*, vol. 54, pp. 875-971, 2011.
- [21] B. P. Rogers, S. B. Katwal, V. L. Morgan, C. L. Asplund, and J. C. Gore, "Functional MRI and multivariate autoregressive models," *Magnetic Resonance Imaging*, vol. 28, pp. 1058-1065, 2010.
- [22] G. Deshpande, K. Sathian, and X. Hu, "Effect of hemodynamic variability on granger causality analysis of fMRI," *NeuroImage*, vol. 52, pp. 884-896, Sep 2010.
- [23] C. Lycke, K. Specht, L. Ersland, and K. Hugdahl, "An fMRI study of phonological and spatial working memory using identical stimuli," *Scandinavian Journal of Psychology*, vol. 49, pp. 393-401, 2008.

APPENDIX

Autoregressive models [7, 21] can predict the behaviour of a timeseries X at time t based on the values of the timeseries at previous times $X[t-1]$, $X[t-2]$, and so on, and error can be calculated as a measure of how accurate the model is (Figure 7). A typical autoregressive model is

$$Y[t]_{AR} = a_1 Y[t-1] + a_2 Y[t-2] + \dots + a_m Y[t-m] + r_{AR} \quad (2)$$

Error can be calculated as the variance of the residuals for an autoregressive model, over all timesteps. A bivariate autoregressive model,

$$Y[t]_{BAR} = a_1 X[t-1] + a_2 X[t-2] + \dots + a_m X[t-m] + b_1 Y[t-1] + b_2 Y[t-2] + \dots + b_m Y[t-m] + r_{BAR} \quad (3)$$

can predict the behaviour of a timeseries Y at time t , based on the values of the same timeseries Y , as well as another timeseries X , at $X[t-1]$, $X[t-2]$, and so on. Error can also be calculated for the bivariate autoregressive model in the same way as for the autoregressive model (Figure 8). Then, errors between the autoregressive model (based on T), and the bivariate autoregressive model (based on X and Y) can be compared (1), and the result describes causal or predictive power of X on Y . The causal or predictive power of the reverse relationship, Y on X can then be calculated and compared to the causal power of X on Y to find the directionality of causality between timeseries X and Y (Figure 9).

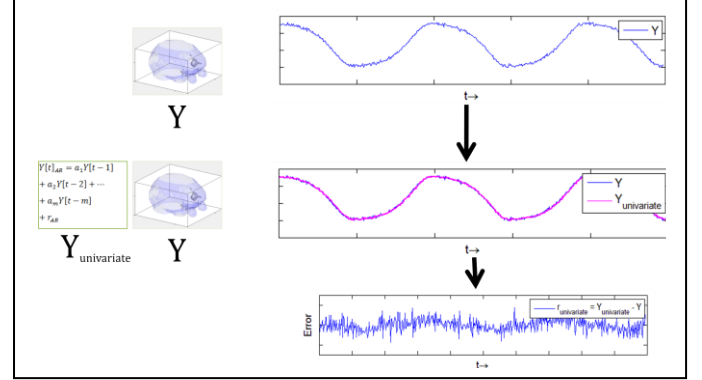


Figure 7. Calculating the error in the univariate autoregressive model.

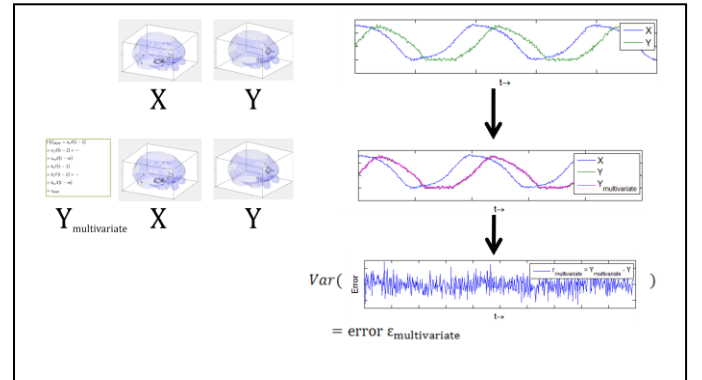


Figure 8. Calculating the error in the multivariate autoregressive model.

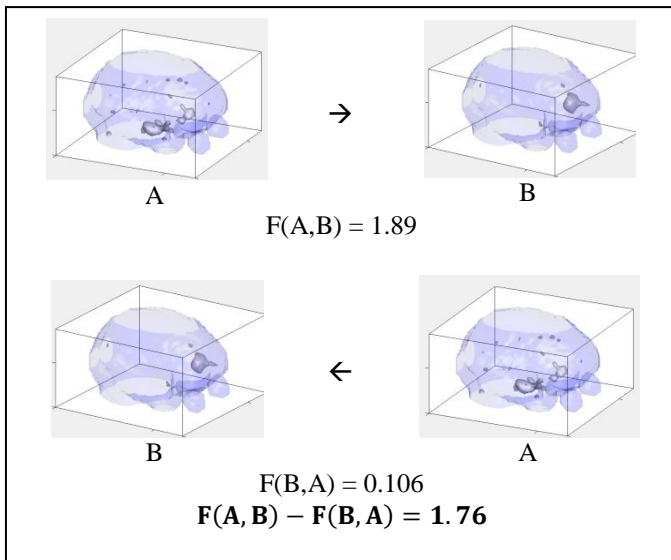


Figure 9. Calculating directionality from a Granger score (see Equation (2)).