Review of: "Big Data, Granger Causality Analysis, and the Undecidability Property of Neuroimaging"

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In this paper, the author argues that an End-Of-Theory (EOT) approach to interpreting the results of a standard Granger Causality (GC) analysis in Neuroscience, has serious shortcomings. They propose that interpreting results from a GC analysis in Neuroscience in a biological sense, also requires a model of how information is encoded at the transmitting end, and decoded at the receiving end. Further, they propose novel terminology, *i.e.* “Undecidability Property of NeuroImaging” or UPN, to convey that information on the encoding/decoding model requires experimental work outside of neuroimaging. I found the paper interesting, relevant and thought-provoking. Below, I ask some questions and make suggestions which I believe will improve the organisation and argumentation of the paper.

Organisation of the paper

I am sure the author knows that the key elements of the paper would be 1.) Background, 2.) Knowledge gap, 3.) Specific research question, 4.) Approach taken to address the research question, 5.) Results of applying the chosen approach, 6.) Meaning of the results, and key contributions of the study to advancing understanding of the chosen topic.

However, the content of these elements for this paper are not always clear to me:

- The Introduction would benefit from the placing the Big Data approach to science in the context of more traditional approaches, such as the ‘Experimental science’, ‘Theoretical science’ and ‘Computational science’ mentioned in Kitchin (2014) and originally in Hey et al. (2009). Providing the reader this background would help them understand the significance of the Big Data approach.

- It is not completely clear to me what the knowledge gap and research question are - Is the research question to 1.) investigate if the EOT approach to applying GC analysis is tenable in Neuroscience, or is it to 2.) study the topic of how the “data-driven science” approach proposed in for e.g. de Wit et al. (2016) can be applied in the context of GC analysis of Neuroscience data, and to begin to flesh out epistemological tenets of the same? It would be good to

provide more clarity on this, toward the end of the Introduction.

- What is the method used to answer the research question? Is it the argument/insight that results from GC analysis cannot be interpreted in a biological sense, in the absence of a hypothesised model of how information is encoded at the transmitter end and decoded at the receiver end?

- How is this method employed to answer the research question? Is it by demonstrating how the insight about encoding/decoding can resolve misunderstandings about the use of the 'model' term in the Stokes & Purdon (2017), and Barnett et al. debate? Is it also by demonstrating how the insight about encoding/decoding can guide how GC analysis should be applied in Neuroscience, using a practical example from a hypothetical study on working memory?

- What is the need for the UPN terminology? Further, does UPN imply that information on the encoding and decoding models can only be gained using methodologies outside of neuroimaging? More on this below (see sub-section "Is UPN necessary?").

- What is the new understanding/contribution gained from the paper? Is it that the paper argues and demonstrates the need for an encoding/decoding model to interpret results from GC analysis in a biological sense? Or, does the paper provide guidance on how the "data-driven science" mentioned in for example de Wit et al. (2016) can be applied in in the context of GC analysis of Neuroscience data? Or is the contribution the introduction of the UPN term, to illuminate what can and cannot be gained from applying GC analysis to Neuroscience data?

Is UPN necessary?

Is data from neuroimaging methods always insufficient to provide information about the encoding and decoding models? I can understand that one would need information from single-neuron recordings if the "neural code" is contained in for *e.g.* spike rates, spike timings etc. However, what if relevant information was contained in amplitudes or phases of neuronal oscillations? In such a case, would not studies with EEG/MEG be able to provide information on the encoding and decoding models? If so, am I correct in thinking that UPN would only hold in some cases but not in others?

On a related note, assume a biologically plausible computational model of *e.g.* EEG or MEG data, which embodied specific assumptions about encoding and decoding. This model could then be used to make predictions of results from applying GC analysis to EEG and MEG data, which could then be tested by comparing to results of GC analysis on

experimental EEG and MEG data. In this case, isn't there no need for other non-neuroimaging methodologies to help interpret the results of the GC analysis on experimental data? One might say that the computational model is from "outside neuroimaging" and hence supports UPN, but every experimental methodology in Neuroscience requires a biologically plausible computational model to help interpret the results of any analysis in a biological sense. Hence, I would argue this situation is not unique to neuroimaging. Finally, de Wit et al. (2016) also argue that information on decoding models can be obtained by comparing trial-trial variation in *e.g.* oscillation amplitudes, to behavioural performance, or by demonstrating that the pattern of results from a particular decoding model, is similar to that of humans. In these cases also, the interpretation of GC results can be done within neuroimaging itself, rather than using non-neuroimaging methodologies? Hence, I am unsure about the need for the UPN term.

Some final points

1.) Page 16, paragraph 4, speaks about a hypothetical situation when GC is observed between two regions X and Y in a particular frequency band, in line with a hypothesis. I understand why in this case, the observed GC can be considered a confirmation of the hypothesis. However, I do not understand why observed GC in a different frequency band between the same two regions X and Y can be regarded as reason for extending the previous hypothesis while GC between for e.g. X and Z should be regarded as a null finding - is this not a bit arbitrary? For example, could observed GC between X and Y also not be reason for extending the previous hypothesis, in some cases?

2.) The paper assumes throughout that Granger Causality (GC) falls within Information Theory, but is this accurate? For example, a strength of information-theoretic measures is considered their ability to detect nonlinear relationships, while GC is only used to model linear relationships (Timme & Lapish (2018)). Hence, is it accurate to describe GC as an information-theoretic method?

3.) Both standard GC and Granger Geweke Causality (GGC) have been used in Neuroscience - the author seems to imply that GGC rather than standard GC is somehow particularly well-suited to Neuroscience data - is that what the author implies and if so why?

4.) The author seems to imply that Tranfer Entropy is the same as conditional Mutual Information. However, is it not the case that Transfer Entropy relates past values of e.g. signal Y to present values of signal X (over and above the past values of signal X), while conditional Mutual Information compares present values of signals X and Y (see page 24 in Timme & Lapish (2018))

5.) Equation 1 could be expressed more concisely.

6.) A glossary of philosophy of science terms e.g. induction, deduction, abductive inference, would help the reader better understand the text.

The paper deals with an interesting, relevant topic, and effectively convey some important points and insights. I wish the author well as they refine the organisation and argumentation of the paper further, and I hope these comments were useful toward that purpose.

References

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