Causal Discovery methods for Effective Connectivity

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Abstract

We propose a new application for causal discovery methods on human brain networks in order to derive effective connectivity. The directive nature of effective brain networks suggest causal methods can be used. As current methods for effective connectivity suffer from computational difficulties and often cannot cope with latent variables, we propose an application of PC-algorithm and the Bayesian BCCD-algorithm [Claassen and Heskes, 2012] to estimate effective connectivity. Both methods will be applied on six healthy subjects of which fMRI data and structural networks are readily available.

Keywords. Effective connectivity, Causal Discovery

1 Introduction

Motivation The brain and particularly the human brain have been studied for hundreds of years. Today, the secrets of our brains still are one of the most sought-after. The techniques however have changed. We have come a long way since the time of Phrenology, the pseudoscience based attempting to derive cognitive ability and personality from measurements of the skull or, post-mortem, the brain. Advanced measurement methods exist that allow scientists to peek inside brains that give a coarse but broad overview without opening a single skull.

Of particular interest are causal relations between brain regions and cognitive and bodily functions. The question if brain region X is functionally or structurally connected to brain region Y and whether these are causally related is still highly relevant; it is the main question of the present-day scientific field of brain connectivity. Understanding brain structure implies understanding more about the brain as a whole.

Not surprisingly, brain connectivity also finds applications in medicine. Neuro-degenerative diseases such as Alzheimer's disease, Parkinson's disease, dementia, Amyotrophic lateral sclerosis (ALS) have all been shown to severely alter brain connectivity. Better methods for analysing connectivity could lead to more insight in these diseases.

The field of brain connectivity finds its roots in the early 1990s [Friston et al., 1993,Friston, 1994], though because of more recent developments in the field of Artificial Intelligence and Machine Learning it is possible to do more thorough analysis [van den Heuvel and Pol, 2010]. One type of connectivity analysis involves finding how brain region X causes what region Y does. This is called *effective connectivity*. More concretely: how does the measured fMRI signal, representing an underlying neuronal process, determine what other neuronal processes are activated. Research regarding effective is relatively new and its application still faces many challenges that require further research [Ramsey et al., 2010]. The directed character in effective connectivity seems similar to traditional causal relations. In what follows, we suggest to use causal discovery methods for deriving effective connectivity.

Problem statement This project seeks to utilise the strengths of current state-of-the-art causal discovery methods by applying them to resting state brain fMRI data in order to find new applicable methods for determining causal patterns in the human brain.

The work by [Ramsey et al., 2010] addresses several problems causal analysis in fMRI analysis suffers from. Methods in causal discovery have high computational costs, making it nearly impossible to calculate networks with more than hundreds of nodes. Another important fact is that fMRI Analysis indirectly measures brain activity. Brain models that do not account for possible latent - indirect - sources within the brain or the shortcomings of fMRI may suffer from noise, fail to capture underlying patterns or draw erroneous conclusions. Solutions to this particular problem have been proposed that do account for latent sources [Ramsey et al., 2010, Waldorp et al., 2011]. Another problem is the strong diversity between subjects. Every brain is inherently different, making it non-trivial to combine subject data or even draw conclusions across subjects. Even within a single brain it changes how different areas react over time.

Several methods for finding effective connectivity already exist [Mclntosh and Gonzalez-Lima, 1994, Harrison et al., 2003, Friston et al., 2003, Roebroeck et al., 2005]. However, using more generally applicable causal discovery methods has not been elaborated on much. Also, none of these provide a measure of uncertainty. It is a fact that there are errors in any graph produced. This is inherent to the methods and the coarseness of the measurements. As there is no standard baseline to compare results with, a measure of uncertainty would be highly preferable. A framework for such a probabilistic approach is introduced in [Claassen and Heskes, 2012].

We would like to know whether applying such methods, such as the approach introduced in [Claassen and Heskes, 2012], or a standard approach such as the PC-algorithm [Spirtes et al., 2000] can solve some of the difficulties effective connectivity suffers from.

In the remainder of this proposal we briefly discuss some necessary background knowledge on connectivity and methods, we then discuss our strategy and finally we present a time-plan overview.

2 Theory

Brain connectivity

Functional connectivity

Functional connectivity describes the statistical dependence of neuronal activity between different brain regions [Friston et al., 1993]. This gives an insight in the organisation of the brain. Functional connectivity is strongly time-dependent, as activity changes rapidly providing and fMRI has a low temporal resolution. This means measured dependencies can be the result of statistical noise. Functional connectivity can be deduced by fMRI measurement of brains in resting-state [Lowe et al., 2000,Doria et al., 2010,Bullmore and Sporns, 2009]. Resting state indicates that subjects are instructed to relax without thinking of anything in particular to stimulate spontaneous brain activity.

Structural connectivity

Structural connectivity is defined as the mapping of anatomical - neural - paths in the brain between different brain regions [Friston, 1994]. This is strongly related with functional connectivity: regions can only be functionally connected if there is a structural relation between them [Cabral et al., 2012]. This intuitive relation can be demonstrated empirically [van den Heuvel et al., 2009]. Structural connectivity is less time dependent as it involves mappings of anatomical connections opposing temporal activity patterns.

Hinne et al. [Hinne et al., 2013] proposed a Bayesian method for estimating structural networks based on Diffusion Weighted MRI (DWI) and probabilistic Tractography. The location of white-matter tracts does not become immediately clear from imagery alone. Other methods rely on thresholds to estimate location of said tracts. The proposed method results in a measure of uncertainty about where a hypothesised connection will terminate and so provides a clearly interpretable network structure as result.

Effective connectivity

In contrast to functional and structural connectivity, effective connectivity takes into account the cause and effect of relations. It has been described as “the influence one neural system exerts over another” [Friston, 1994]. Effective connectivity indicates which brain regions stimulate other regions. Time series need to be analysed to infer effective connectivity as cause and effect can be deduced from which event precedes which. It is possible to infer effective connectivity from structural and functional connectivity [Mclntosh and Gonzalez-Lima, 1994, Harrison et al., 2003, Friston et al., 2003, Roebroeck et al., 2005].

Research has been done on inferring effective connectivity directly with several methods. The most renowned methods are Granger causality

[Roebroeck et al., 2005], Structural Equation Modelling [Mclntosh and Gonzalez-Lima, 1994], Multivariate Autoregressive Modeling [Harrison et al., 2003] and Dynamic Causal Modelling [Friston et al., 2003]. These are all methods dedicated to this problem. These methods also suffer from similar problems of which perhaps the most important is scaling. Most of these methods can only handle tens of nodes in reasonable time, which becomes problematic in realistic situations with up to tens of thousands of nodes, ideally.

Causal discovery methods

The first causal method we will apply on brain structure data will be the PC-algorithm [Spirtes et al., 2000]. It is used to find structure, as well as causal relations between vertices in directed graphs. If we already provide a graph skeleton, PC-algorithm can be used to determine directions. An adaptation of PC that is better adapted to finding latent variables is Fast Causal Inference [Spirtes et al., 2000], though this method does not scale well to tens of variables.

Another causal discovery method is the Baysian Constraint-based Causal Discovery (BCCD) algorithm [Claassen and Heskes, 2012], which gives similar results as PC, and is designed in an attempt to improve PC. This algorithm has some useful properties; it is a Bayesian approach and as such, it is more robust against noise. The authors have shown the method to perform as good as or better than other causal discovery algorithms such as PC on representative datasets. As is inherent to Bayesian methods, or approximations of Bayesian methods, the resulting network graph is not a single structure but rather a distribution over possible structures. Concretely, this provides an uncertainty measure over edges in the network, giving additional information compared to PC.

Data acquisition & analysis

We will apply the mentioned methods on structural and functional data gathered from human subjects. For this we are largely dependent on data collected by others. Hinne et al. has provided fMRI time-series data and structural network data as used and derived in [Hinne et al., 2013], of which six subjects were selected at random. We can estimate functional connectivity from fMRI-measurement in combination with structural networks according to a procedure currently submitted by Hinne et al. [Ambrogioni et al., 2013]. To find effective connectivity, both structural networks and functional data is needed.

3 Methods & Strategy

We use an existing implementation of BCCD to infer effective connectivity; PC will be implemented in this project. An implementation of BCCD suitable for this project is made available by the department of Intelligent Systems at the Radboud University Nijmegen.

The first step will be to get the implementations for the algorithms working on the datasets with functional and structural data.

Firstly we will use structural networks as a basis for the algorithms, and use functional information to infer causal relations. Later we will use functional information only, to infer both the network and the causal relations. We will compare this with the previous. As PC is a well-described algorithm [Spirtes et al., 2000] and should not be difficult to implement, so this will be done within this project.

The second step is to apply the BCCD-algorithm, also to be used with and without provided network structure. Both methods provide a connectivity matrix representing effective connectivity.

Results will then be evaluated and compared over

<table>
<tr><th>Week</th><th>41</th><th>42</th><th>43</th><th>44</th><th>45</th><th>46</th><th>47</th><th>48</th><th>49</th><th>50</th></tr>
<tr><td>PC</td><td colspan="2">Make implementation</td><td colspan="2">Structural</td><td>Functional</td><td colspan="4"></td><td></td></tr>
<tr><td>BCCD</td><td colspan="4"></td><td colspan="2">Structural</td><td>Functional</td><td colspan="3"></td></tr>
<tr><td>Analysis</td><td colspan="3"></td><td colspan="2">PC</td><td></td><td colspan="2">BCCD</td><td colspan="2"></td></tr>
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Figure 1: Project time table. 'Structural' implies applying the given method using structural data as a network skeleton. 'Functional' implies inferring structure with the given method first through functional data.

all six subjects to see to which extent obtained networks are consistent across subjects. If so, we will analyse the properties and difficulties presented by Ramsey et al. [Ramsey et al., 2010]. We will conclude whether standard causal discovery methods provide a good direction of research for deriving and evaluating effective connectivity.

4 Time schedule

This project is divided into four main parts: applying the PC-algorithm, applying the BCCD-algorithm, analysing the data (including cross-subject comparison) and writing the article. The schedule for applying the algorithm has been subdivided into applying it with functional connectivity using structural data as a basis, and applying it to only functional data.

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