SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Characterizing Dynamic Causal Modelling based neuronal model search algorithms, and application in clinical and preclinical research

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The Examination takes place at the meeting room no.107 at the Faculty of Nuclear Medicine, University of Debrecen
, 2022. July 19. 11:00

Head of the **Defense Committee**:	László Csernoch, PhD, DSc
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	Lajos Rudolf Kozák, MD, PhD
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The PhD Defense takes place at the meeting room no.107 at the Faculty of Nuclear Medicine, University of Debrecen
, 2022. July 19. 13:00

Live online access will be provided. If you wish to join the discussion, please send an e-mail to the aranyi.csaba@med.unideb.hu address until 2 p.m. at latest on the previous day of the defense (18th July, 2022). For technical reasons, after the deadline, it will not be possible to join the defense.

1 Background and Objectives

With the rapid development in neuroimaging many complex methods have emerged to observe and examine brain functions. Beyond the analysis of functional brain images demand arose to understand how functional measurements are created based on responses to neural stimulation, and how the different areas of the brain cooperate to process the received information. The evoked responses may affect many anatomically separable areas in the brain. Despite this "functional segregation" the neuronal processes are more elaborate than the synchronized activity of these areas. Brain regions need to communicate, during which the processed information is transferred optimally to the other regions to elicit the expected behavior. This is called "functional integration".

With non-invasive functional magnetic resonance imaging (fMRI) the difference in magnetic field homogeneity is measurable between oxy- and deoxyhemoglobin. The deoxygenation of blood can be viewed as an indirect measurement of synaptic activity. The increased blood volume in metabolically more active areas might implicate a 2-4% change in image intensity, which is peaked at 4-8 seconds after increased neuronal activity. Nowadays clinically utilized fMRI sequences allow for sampling the whole cranial volume with a 2-3 seconds repetition time (TR). As a result time varying blood oxygen level-dependent (BOLD) signal can be obtained from any part of the brain, which can be used for discovering interactions between brain regions, or connectivity withing brain networks. As an indirect measure of real neural activity, the BOLD-response is not only affected by hemodynamic effects, but known (external stimulation) and unknown (neurophysiological and measurement noise, magnetic field inhomogenity) factors, as well. Thus the imaging time-series need to be temporally and spatially corrected and standardized before analysis to enhance signals of interest.

The dependencies between neural activity and BOLD-signal is thoroughly researched. Brain connectivity reveals patterns of inter-regional connections on differ-

ent levels: structural (neuroanatomical), functional and effective connectivity. The patterns of anatomical connections is described by structural connectivity. The exact definition of structural connectivity is not clear, although, it usually refers to the neural pathways between regions, which coincides with our anatomical knowledge. Information like this can be obtained by diffusion tensor imaging (DTI) technique. With functional connectivity one can investigate statistical dependencies of regional activity. For example, connection strength can be estimated by correlating regional time-dependent changes in neural activity. Although functional connectivity is useful to describe abnormal connectivity patterns, it is unable to to reveal hidden causal effects. In contrast, effective connectivity estimates the effect, that a neural system exerts on another. In other words one can discover causal dependencies between neuron populations, where typically directed inter-regional connections are examined. Most procedures, that estimate connectivity, use time-series data representing brain activity, such as electroencephalography (EEG), local field potentials (LFP) or functional MRI data.

Dynamic causal modelling (DCM) is a widely used effective connectivity method, with which we create models of a brain network dynamically perturbed by external stimuli, and we compare the the output (e.g. BOLD-signal) generated by the model with the real measurement data. This approach fundamentally differs from traditional methodology, and reflects the non-linear and dynamic nature of neural interactions accurately. When creating a model, one needs to specify nodes of the network with the connections between them, and the connection modulatory and the driving effects of experimental conditions or external stimulation as model parameters. The specified model can be represented with a directed cyclic graph structure. From these prior parameters a Bayesian optimization method estimates the posterior densities, which can be used to infer directed connectivity strength (and uncertainty) between nodes. Marginalizing the posterior densities DCM also approximates model evidence for given data, which describes the likelihood of model fit. Mathematically

the model is described by differential state equations. These equations define the dynamics between hidden neural states, or the dynamically changing neural activities, where effective connectivity is expressed by the conditional dependencies between states.

Originally DCM was designed to be a hypothesis-driven method, which is useful to answer neurobiologically relevant questions after estimating a constrained amount of models. Bayesian model selection (BMS) compares the hypothetical models of brain networks to find out which one produces BOLD-signals, that fit measurement data the best with minimal model complexity. Later developments of the DCM framework allowed for comparing sets, or families of models, which alleviate statistical uncertainties regarding comparing single models.

In contrast to hypothesis-driven approach numerous studies follow the strategy of discovering systematically built model-spaces to find the best fitting model and infer connectivity based on that. However, finding the optimal model is not trivial, as the cardinality of the model-space grows hyper-exponentially with the number of regions and external inputs. The Bayesian model reduction (BMR) is a method to efficiently estimate evidence of any reduced model to optimize connectivity. The *post-hoc* model optimization uses a greedy algorithm to remove those connections from the base model, that is not likely to contribute to model evidence. This algorithm is computationally efficient because of BMR, however, it's disadvantage is that model evidence estimation of reduced models is not exact for non-linear models. Furthermore this analytic method ignores the network topology, so that modulations can affect endogenous connections that BMR removed from the optimal model.

One of the most important problems in Bayesian modeling is structure learning. Finding models that most likely explain measured data and exploring large model-spaces is a computationally difficult problem. Numerous data-driven procedures exist for network discovery in the case of Bayesian-nets. However, the literature of search algorithms adapted to DCM is scarce. Structure learning in the DCM

framework is still an open problem due to its high computational demand.

In human studies DCM is one of the most applied method to estimate effective connectivity. Thus far this framework was mostly applied in preclinical small animal studies using EEG measurement data. The priors for the hemodynamic model of DCM (the Balloon-model) is only validated for data of human neurobiology. Since human BOLD-response is different from rat hemodynamic response, it is unusual to apply DCM for rat fMRI data. In our work we would like to demonstrate the application of the DCM framework in a preclinical rat study.

In our work we aimed to explore an entire model-space using topological model search methods adapted to DCM from network science. We finesse the high computational demand of searching through large model-spaces by reimplementing the DCM algorithm optimized for running speed. We present the self-developed ReDCM software, which allows for more rapid estimation of DCM models, aiding the development and testing of model search methods. Finally, we aim to demonstrate the application of the DCM framework in a small animal study. Preliminarily, we aimed to supplement our work by creating a robust workflow for the preprocessing of fMRI images measured in the University of Debrecen. However, these developments are not subjects to this thesis, and can be read in the Appendix. During our research we would like to implement the following methodological developments:

1. Implement an optimized version of dynamic causal modelling for shorter running time, which allows for examination of large model-spaces. During development, our priority is the optimization of the most computationally demanding procedures, and the preparation of the software for high performance computing facilities.

2. Topological model search investigations within the DCM framework.

   2. a) Adapt model search algorithms known from graph theory and network science to DCM, and utilize them in subject- and group-level investiga-

tions.

2. b) Development of a framework for characterizing model search methods to compare search performance based on model evidence and topological properties, as well.

3. Utilize DCM in preclinical environment, and estimate effective connectivity for rat fMRI. DCM effective connectivity is rarely studied in small animal experiments using fMRI data.

2 Materials and Methods

Computational demand of DCM and ReDCM

The variational Laplace (VL) algorithm, which performs estimation of connectivity and physiological parameters, generate regional BOLD-signals based on iteratively updated model parameters to minimize the error of comparison between the simulated and the measured signal. Due to the repeated integration of state equations of the forward model of neural and hemodynamic states, DCM model inversion is computationally intensive algorithm. Profiling running time suggests, that numerical integration of equations takes up most of the computations for DCM (87.2% of total running time). In our work, we aimed to achieve increased estimation speed by using optimized software libraries, while keeping the originally implemented algorithm. We refer to the reimplemented version of DCM as ReDCM.

The aim of ReDCM is to provide an efficient framework for deterministic model inversion, Bayesian model comparison, and development and characterization of model search algorithms. The R programming language is an ideal environment for such work, which can be freely deployed in a computer cluster of arbitrary size to estimate large number of models simultaneously. Based on profiling results, we implemented the methods for integration of state equations in the C programming language, where we utilized the GNU Scientific Library (GSL) to efficiently perform matrix operations. We compared computational performance of ReDCM and DCM12 implementations using simulated time-series data. To simulate BOLD time-series we randomly generated 3x3, 5x5 and 7x7 connections matrices within the interval of [-0.5, 0.5], while we ensured that inhibitory self-connections remain negative. For each model we defined two binary vectors in lengths to correspond with time-series data. These were used as stimulus functions that directly affected each region's neural state. The regional synthetic data were then generated with the `spm_dcm_generate` function from SPM.

Possibilities and requirements of model search in DCM

Finding the best fitting model to measurement data is one of the most important outstanding problem in Bayesian modeling. However, discovering large model-spaces in not trivial in DCM, as the number of model alternatives grow hyper-exponentially with the number of regions and external inputs. In the DCM framework there are multiple possibilities to explore network structure:

- On the individual level we evaluate every possible model alternatives, and select to model with the highest evidence based on fMRI time-series data.
- Apply the *post-hoc* model selection based on BMR, which requires estimation of only one model, and can efficiently approximate free energy (Fe) of any nested model analytically. A heuristic algorithm reduces the connection parameters of initial model until model evidence can not be improved further and reaches a maximal value.
- Perform search among nested models of group-level parametric empirical Bayes (PEB) analysis.

Using model search algorithms requires every model in the model-space to be considered equally likely. In most cases some models are usually neurobiologically more relevant than others, however, we ignore this during Bayesian model comparison. Thus, utilization of model search methods is useful in cases, when no a priori information is available regarding properties of the real network.

A further obstacle is that without any hypothesis on the model generating the data it is difficult to interpret the model found by searching procedures, and may not be reproducible over subjects, or different data. In practice we construct model families, which contain systematically built models around network properties (e.g. the network contains only ”forward” connections, or ”backward” connections, as well). As every model of the families need to be estimated before family-wise inference, model search methods may prove useful to predict the winning family.

Topological model search in DCM

Multiple procedures exists to search Bayesian-nets. Among them there are simple greedy methods and more complex ones, using simulated annealing or genetic algorithms. Depending on the applied search method the number of model alternatives may still be relatively high. To aid development and testing of algorithms adapted to DCM we separated model estimation with database look-ups of the precomputed model-space.

Another way to improve search efficiency is to reduce the population of model alternatives during each iteration of model search by removing models, which contain connection parameters, that are not likely to contribute to model evidence. Thus, we developed an optimized version of each adapted method, that ignores a model that adds or retracts connections to the model, that don't reach or exceed a certain threshold of posterior parameter probability, respectively. Parameter probability is based on the probability of connection parameters in models, that are previously considered during search. With this modification we can ensure to keep parameters with high average probability in all model alternatives, as well as ignore new models with uncertain connections.

We adapted the following algorithms to DCM:

- **Greedy equivalence search (GES):** We initialize the procedure with a randomly selected member of the model-space. Two kind of processes are performed one after the other: a forward, and a backward search. The former we select every model as an alternative to the initial one, that contain exactly one connection less than the initial model. Then, the winning model, based on Fe, is selected to initialize the next iteration of the algorithm. When removing parameters don't improve model evidence further, the forward process stops, and the backward search is initiated. In this phase connections are added to the current best model one at a time. Forward and backward processes alternate each other until we find the optimal model based on Fe. The advantage

of this method is that the initial model determines the local maximum, where the algorithm converges. However, it is unable to improve, and we my never find the best model.

- **Greedy Hamming-distance search (GHD):** A generalized version of GES, which considers model priors as binary vectors. The randomly selected initial model's alternatives are defined as every model that are at most 1 Hamming-distance (Hd) away from the initial one. Next, we select the alternative with the highest evidence and we repeat the procedure until the algorithm converges.

- **Genetikus algoritmus (GA):** The genetic algorithms are a widely used approach for optimization and search problems, which are hard to solve procedurally. The candidates of the solution (often called as individuals or phenotypes) are represented by attribures (chromosomes or genotypes) that define individuals. These attributes are the connections of a DCM model, which can be combined among models by crossovers, or be replaced by mutation operators to produce more viable individuals, with higher Fe, in the following generation. Due to genetic algorithms may cause multiple random alterations in individuals, we can't guarantee search results even for the same initialization of the procedure.

Characterizing model search algorithms

We characterize the adapted graph-based search algorithms by goodness of model fit, or the difference in Fe to the best model (dFe), graph topology (Hamming-distance relative to the best model) and the number of estimates models during search. As GES and GHD procedures are typically deterministic, they reach the same optimum for the same initialization. Randomizing the initial model allows us to measure the efficiency and robustness of the methods. In contrast, the stochastic GA may

converge in a different point each time regardless of the initial model. Thus we measured the performance of the implemented methods 20 consecutive times for data of 10 subjects, and we summarized the average characteristics and their standard deviation for each method.

Currently recommended method to make group-level inference about DCM connectivity is the linear parametric empirical Bayes (PEB) analysis of the full model estimated within the investigated population. Discovery of population level networks uses the same heuristic algorithm as *post-hoc* model selection, and uses BMR to evaluate large number of nested PEB models. As reduced posterior densities can be exactly derived in linear models, BMR can be safely used for PEB models. Thus, we use model evidences computed by BMR as decision criteria for topological search algorithms. We compare model search among PEB models with the results of automatic optimization implemented in the SPM toolbox, then we show connectivity patterns of group-wise networks.

Preclinical application of DCM

In cooperation with the Preclinical Imaging Center of Gedeon Richter Plc. we applied DCM for rat fMRI measurements in preclinical research environment. We investigated the effects of repeated, or lasting nociceptive stimulation, which can sensitize neurons responsible for processing sensory information. Damage in the central pain inhibition system may lead to the development of chronic pain. This central sensitization is an important mechanism of disorders related to neuropathic pain, and may be present in diseases, like fibromyalgia, irritable bowel syndrome, endometriosis or primary head pain. Our study aimed to uncover effects of central sensitization on effective and functional connectivity in rats. Our hypothesis is, that chronic pain resulting in central sensitization changes connectivity within the nociceptive network.

The experiments involved applying chronic inflammatory trigeminal pain model

in 26 adult male Sprague-Dawley rats. In the small animal model we evoked long-lasting pain by injecting complete Freund's adjuvant (CFA) into the rats' whisker pad. Non-noxious "air-puff" stimulation of of the whisker pad was used to evoke BOLD-responses. The measurement started with an initial resting stage for 240 seconds, than a 30 seconds 1 bar air pressure "air-puffs" of 1 Hz frequency stimulation was followed by 60 seconds resting blocks, which alternated 18 times throughout the examination. We investigated effects of central sensitization, and performed fMRI measurements in in three stages: the drug-naive measurements (BASE) were followed by a repeated session after two days in the acute period (CFA2) and after seven days of persistent pain (CFA7).

In our analysis we focused on the mediator role of the anterior cingulate cortex (Cng) under central sensitization, because this area showed changed BOLD-response in the CFA7 session relative to the BASE measurement. We defined two model families to model two different configuration of connecting Cng to the somatosensory network: 1) Cng transfers central sensitization to the sensory network in a complex system of multiple pathways, and 2) Cng connects to only one of the regions in the network to transfer sensitized state. We compared these "dense" and "sparse" system of Cng connectivity using BMS. Then, we averaged connectivity within the winning family for each session to summarize DCM connectivity parameters on the group-level. To account for variation between subjects, we used random effects (RFX) methods for Bayesian inference.

3 New Scientific Results

ReDCM - The reimplementation of DCM algorithm

To finesse limitations of computational burden by partial reimplementation of DCM in the R programming language, which currently contains the entire VL estimation algorithm for deterministic DCM with the ability to specify single- or two-state, and non-linear neural models. Comparison of models estimated with ReDCM can be performed in the with Bayesian model selection also implemented in the R package for fixed effects (FFX BMS) and for random effects (RFX BMS), as well.

Computational performance of the model estimation procedure implemented in ReDCM shows a significant increase compared to the original algorithm. We compared the running time of VL iterations for each of the 18 synthetic models with variable data length (200, 400, 600, 800, 1 000 and 1 200 time points) and different model sizes (3, 5 and 7 regions). Without any parallelization techniques, or using high performance computing facilities we achieved 296-1 078% increase in performance depending on model size and data length.

We created tools for ReDCM to investigate regional hemodynamic properties. In DCM the neurobiologically informed system of the Balloon-model converts dynamically changing neural states in BOLD-responses. The Balloon-model parameters are estimated in a data-driven environment, and they can be used for statistical inference on each region's hemodynamic attributes. After model inversion in ReDCM one can separate the Balloon-model parametrized with posterior θ^h hemodynamic parameters, and replace the regional neural activity with a Dirac-delta function, so that the input can be substituted with a unit impulse function. Based on the generated response of the Balloon-model to the impulse the attributes of the regional hemodynamic response function (HRF) may be observed: the height of the response, its full width at half-maximum and the time to peak. We developed a web-based R Shiny application built upon ReDCM to demonstrate the connections of HRF and

Balloon-model parameters.

Efficiency of model search algorithms

In individual-level model search the GA slightly outperformed the GES and GHD algorithms in the defined model-space at an average 10.59 difference relative to the best model (dFe). In addition, the stochastic procedure also found models closer to the best model in graph structure in average (3.71 Hd), than the deterministic GES (4.28 Hd) and GHD (4.07 Hd) methods. At the same time, GA needed an average of 202 models to estimate until convergence, which mean around twice as much computations, than in the case of GES (77) and GHD (118). With the modified algorithms we were able to exploit parameter probability estimates of DCM: search performance increased in each implemented search methods after the modifications. By simply fixing parameters the GA' method found the best model multiple times, and reached an average value of 7.37 dFe. Further improvement is that the modified algorithms needed significantly less models to compute. Searching through both DCM and BMR model-spaces we had the opportunity to compare the adapted methods with the *post-hoc* model optimization already available in the SPM toolbox. We found, that GES and GHD performs better then other methods in the BMR model-space, however, optimized versions became unreliable and did not improve search results.

We compared the automatic BMR-based search method among nested group-level PEB models with the three topological search algorithms. For PEB models we initiated GES and GHD methods with the full model, and GA with a random model. BMR only reduced the full model with the modulation of the self-inhibition of right dorsal area of the frontal lobe (rdF) in the "Words" task. The GES and GHD removed this same effect along with the modulation on left ventral (lvF) self-inhibition. After 10 runs the GA method returned the full model as the optimal one in the group-level each time. Graph-theory based network discovery shows their limitations while

searching through hierarchical linear models. The PEB is parametrized to model each higher-level effects (e.g. population mean and group differences) on effective connectivity, and topological methods can search the model structure for only one linear effect at a time. For this reason, BMR is still the recommended reduction method for group-level PEB models.

Central sensitization-related changes in rat effective connectivity

To describe changes in effective connectivity related to central sensitization we analysed the differences between BASE and CFA7 connectivity. During Bayesian model selection of model families we selected the winning model by their exceedance probability, which describes how probable any given family (or model) is than any other one in the analysis to describe data. BMS revealed the ”dense” models significantly exceed ”sparse models” in the BASE (with 0.981 and 0.019 exceedance probability for the two families, respectively), as well as the CFA7 (0.928 and 0.072) measurements.

Comparing single models we also found, that dense model types performs better for DCM. In case of BASE models the M11 (deleted Cng - BF connections) and M15 (deleted Cng - M1 connections) models have lower relative probability among dense models with 0.072 and 0.078 exceedance probability. In contrast, seven days after CFA treatment these two models are the most substantial with 0.198 and 0.185 exceedance probability. Regarding sparse model types the only models to exceed 0.01 probability were the M41 (only Cng - BF connections) in CFA7 and the M45 (only Cng - M1 connections) in BASE sessions with 0.069 and 0.022 exceedance probability, respectively.

To infer group-level effective connectivity, parameters of the winning model family were averaged with BMA for each subject separately. Then we aggregated individual averaged models with RFX-BMA to create averaged BASE and CFA7 models, and used Student’s T-test to reveal differences between baseline and post-

treatment connectivity, corrected to false discovery rate (FDR). Both averaged models showed the strongest effective connectivity between BF, M1 and Cng regions. The analysis also support the role of the striatum in pain processing. The results confirm the hypothesis, that striatral dopamine D2 receptors significantly affects responses to pain.

4 Summary

Our aim was to create a workflow for DCM-based effective connectivity computations, that incorporates the unified and up-to-date preprocessing of functional MRI images, the automated and data-driven adjustment of regions defined in literature and the exploration of large DCM model-spaces to find the best fitting neuronal model. Our conclusions are as follows:

1. The main obstacle for developing model search methods is the high computational demand of DCM. To relieve this problem we developed the ReDCM R package, that is optimized for running speed. With ReDCM we have to possibility to evaluate large model-spaces. At the moment, model inversion is available only for deterministic time-series models. Further developments aim to include stochastic models and the scheme to fit spectral densities.

2. In DCM finding the models most likely explaining imaging data is not trivial. We examined the possibilities to apply search methods known from network science in the DCM framework, where we consider models to be directed acyclic graphs, and changing graph topology iteratively we look for the best model. We adapted three model search algorithms for DCM. Our research showed, that on the subject-level the topological methods slightly outperform analytic *post-hoc* model optimization. However, searching through nested PEB models on the group-level the graph theoretical methods show their limitations.

3. We demonstrated, that DCM can be applied on small animal data in preclinical studies, assessing differences in effective connectivity under different conditions. Furthermore, out developments have been successfully applied in research studies in the University of Debrecen, as well as during collaborations with other institutes.

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List of publications related to the dissertation

1. **Aranyi, S. C.**, Nagy, M., Opposits, G., Berényi, E., Emri, M.: Characterizing Network Search Algorithms Developed for Dynamic Causal Modeling.
Front. Neuroinform. 15, 1-14, 2021.
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3. Gecse, K., Dobos, D., **Aranyi, S. C.**, Galambos, A., Baksa, D., Kocsel, N., Szabó, E., Pap, D., Virág, D., Ludányi, K., Kökönyei, G., Emri, M., Bagdy, G., Juhász, G.: Association of plasma tryptophan concentration with periaqueductal gray matter functional connectivity in migraine patients.
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IF: 3.234

Total IF of journals (all publications): 29,443
Total IF of journals (publications related to the dissertation): 7,463

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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