Software pipeline from neurophysiological and brain structural connectivity data to individualised TVB model (D1.6 – SGA3)

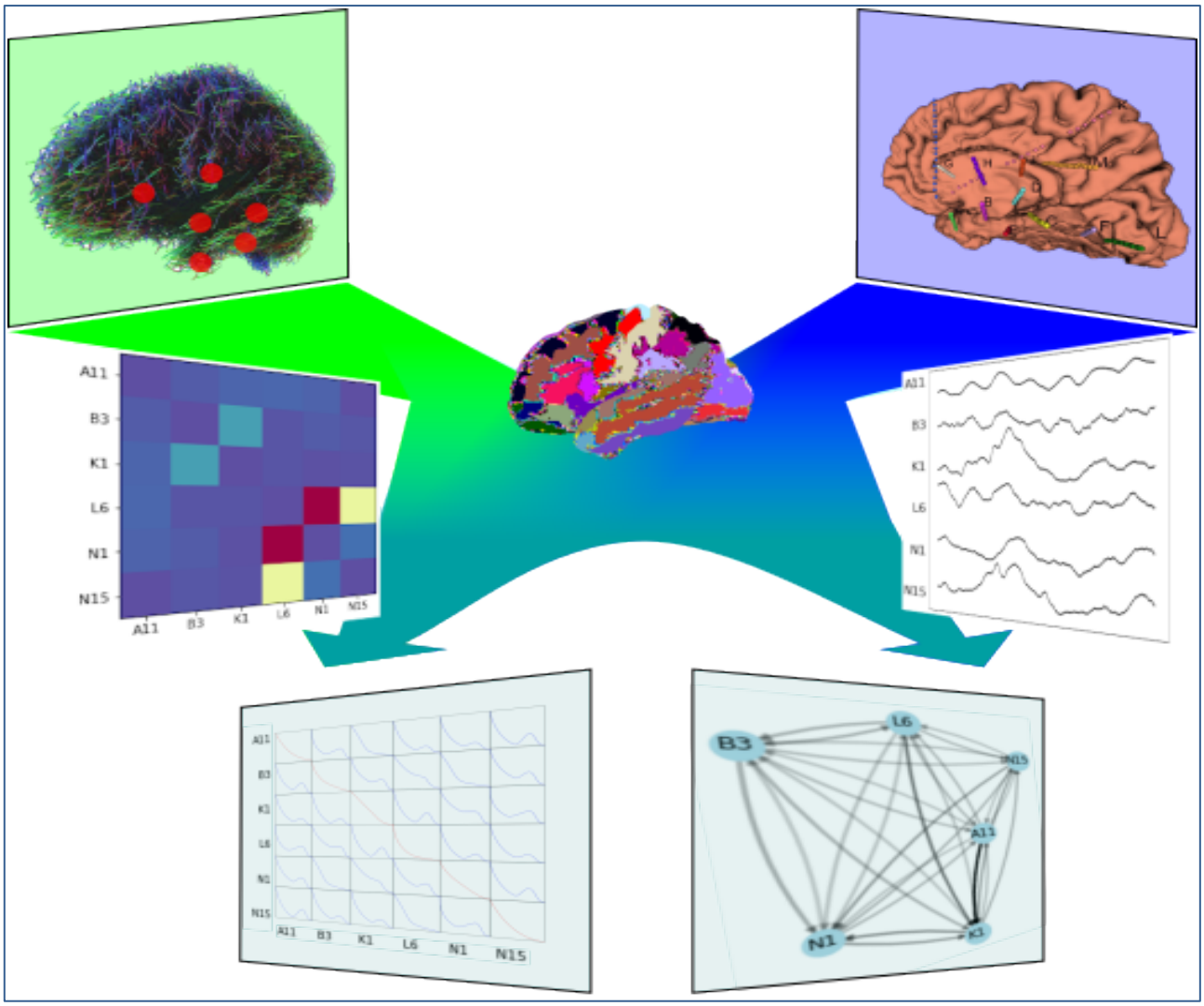

Figure 1: Utilising a dynamic causal modelling framework to create a pipeline for studying effective connectivity using multimodal data

Figure 1: Schematic illustration of the pipeline combining structural connectivity and intracranial EEG data. Structural connectivity information derived from MR-based imaging (top left corner) is combined with electrophysiological recordings of ongoing neuronal activity (top right corner) in the form of generative models of networked neuronal oscillators (bottom). These generative models reproduce features of electrophysiological activity whilst taking into account the constraints given by structural connectivity in the network.

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Description in GA:	Software pipeline from neurophysiological and brain structural connectivity data to individualised TVB model equipped with synaptic and connectivity rate constants, derived from DCM (with supporting academic papers)
Abstract:	Neuroimaging techniques now allow the investigation of structural and functional networks in the human brain in both health and disease through the use of multiple imaging and recording modalities. Linking structure and function in these complex networks is non-trivial. Developing generative models of neuronal interactions with features that map onto the empirically available data is one possible framework that allows for the principled integration of multiple data types for hypothesis testing. Here, we build on recent progress in implementation of such a framework - dynamic causal modelling - to deliver a pipeline that allows a non-trivial mapping between structural and functional connectivity. This pipeline takes macroscopic structural and functional data (e.g. DTI-based structural connectomes, intracranial EEG data) and derives generative neuronal mass models of coupled brain regions. Through a variational Bayesian approach, this pipeline infers coupling parameter estimates conditioned both on functional recordings of individual brain regions and prior information on their structural connectivity, as well as providing free energy-based estimates for the model evidence of a given model inversion. This pipeline therefore allows for (1) estimating effective between-region connectivity that accounts for structural and functional connectivity measures, and (2) testing different hypotheses of how structural and functional connectivity are quantitatively related to be directly compared using Bayesian models selection.

	The pipeline is implemented using Python and standalone Matlab runtimes, making it scalable on cloud computing infrastructure without licensing restrictions. It is computationally efficient, utilising recent advances in Bayeisan model reduction for inferring parameters and model evidence across large families of related models.
Keywords:	Python, Statistic Parametric Mapping, SPM, Dynamic Causal Modelling, Bayesian Model Inversion, Bayesian Model Reduction, Neural Mass Modelling, Canonical Microcircuit Modelling, Dysconnectivity Syndromes, Generative Models, Dynamic Causal Modelling, Effective Connectivity, Bayesian Inference, Epilepsy, Structural Imaging, Multimodal Modelling
Target Users/Readers:	Computational neuroscience community, experts in epilepsy, neuroimaging community, neuroscientific community, platform users, research, students, clinicians in epilepsy

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1. Preamble

Current neuroimaging techniques now allow unprecedented insights into the anatomy and function of distributed brain networks in health and disease, yet often result in distinct representations of brain-networks with non-trivial mappings between them. Allowing for hypotheses regarding individual brain's network features to be tested across structural and functional connectomic data is an essential next step to realise the translational potential of human brain imaging and personalised brain modelling.

One key use case for such individualised brain models can be found in epilepsy surgery. In order to identify epileptogenic areas, patients are extensively investigated through non-invasive neuroimaging, as well as intracranial EEG recordings, with complex, patient-specific datasets that require extensive analysis to allow clinical decision making. There have been several developments that allow for quantitative identification of abnormally connected brain regions in the epileptic brain from several available data modalities. Furthermore, generative models of regional activity are increasingly being used to test different hypotheses regarding epileptogenic networks 'in silico' prior to epilepsy surgery with the aim to support future surgical decision making. Many of these – such as The Virtual Epileptic Patient – are being pioneered in the Human Brain Project.

However, key issues regarding the optimal mapping between structural and functional measures of human brain networks remain unsolved. Dynamic causal modelling (DCM) offers a framework that allows a computationally efficient estimation of parameters of relatively complex networks of neural mass models fitted to empirical recordings of neuronal function. Here, we build on the DCM framework to deliver a pipeline that allows for integration of structural connectivity priors into neural mass network models fitted to intracranial EEG data as used in the context of presurgical evaluation for epilepsy surgery.

This pipeline fits sparsely connected, spatially distributed networked neural masses to cross-spectral density summaries of ongoing intracranial EEG oscillations, conditioned on priors on the structural connections between regions. This allows for the generation of patient-specific models of regional effective neuronal coupling, as well as group-level inference on the optimal quantitative mapping of structural connectomic data onto priors of effective connectivity parameters.

The DCM framework we build on is related to well-developed theories on information processing in the brain and neuronal systems (P4006, P3998, P4007, P4008) and applicable across a wide range of data types and scientific questions (P4009). The pipeline presented here is therefore applicable to multiple brain states, including ictal, preictal and interictal, and can easily be extended to incorporate novel multimodal data components. It therefore complements existing approaches and allows for expansion into novel applications in the near future.

2. Introduction

Dynamic causal modelling (DCM) is a generic Bayesian framework that allows inference on effective connectivity from neuroimaging data ranging from fMRI and fNIRS to MEG, EEG, and local field potentials. The Bayesian formulation of this inference scheme formally integrates likelihood estimates of observed data under certain prior information on the model parameters. This results in full probabilistic estimates of regional effective connectivity measures as well as a free energy-based approximation for the overall model evidence. As such, DCM is well suited to interrogate how specific prior information affects the inference on effective connectivity, and thus whether e.g. additional prior information provides an increase in the overall model evidence. Such increases in model evidence may be because additional prior constraints may restrict spurious parameter values from being inferred or result from an escape from local minima during the parameter inversion. Identifying improvement of model evidence under specific prior constraints therefore provides some evidence that the assumptions encoded in the model priors offer a more parsimonious explanation for the empirical data explained with the model.

Effective connectivity as a concept refers to quantitative descriptions of the causal influence that two regions exert over one another. Conceptually, structural brain networks are the scaffolding on

which causal influences between brain areas unfold; and functional networks are statistical features that can be identified as result of the causal interactions of those brain regions over time. The approach of using DCM to estimate effective connectivity under variable prior constraints has previously been used to identify a non-linear mapping between structural and functional connectivity in diffusion MRI and fMRI data in healthy subjects during cognitive tasks. Identifying the underlying causal networks has particular relevance in brain disorders where abnormal connections (or dysconnectivity) are believed to be a relevant driver of the disorder, such as in epilepsy.

The dynamics of networks are defined both by the dynamic behaviour of individual notes, and their – at times time-varying connectivity. Approaches pioneered by the HBP Consortium already, such as the Virtual Epileptic Patient, seek to identify individual brain regions within a patient's brain that are driving epileptic activity, and derive their effect on the network through patient-specific modelling of structural connectivity and inferring the spatial spread of epileptic activity. Dynamic causal modelling provides a framework that allows inference of both node behaviour and between-node effective connectivity, whilst allowing for computationally efficient implementation of constraints through additional datatype. Furthermore, the framework already allows for the estimation of layered hierarchical models, which can for example identify time varying components in the connectivity as a network transitions between different states (e.g. interictal, preictal and ictal activity). Utilising the dynamic causal modelling framework to infer the time-varying connectivity changes that may underlie epileptic brain dynamics therefore offers a complementary approach to identifying abnormal connection patterns from human brain data. This makes DCM a particularly apt tool for integration into the EBRAINS framework for studying the patterns of connectivity which may give rise to differing states of dysconnection in epilepsy.

This document covers the broad technical specifications of the pipeline in Section 3, which is covered in more detail and provided in the Technical Note hosted on EBRAINS (https://wiki.ebrains.eu/bin/view/Collabs/structurally-informed-dcm/). Section 4 shows how to access the pipeline, test data set and how to interpret the pilot study methods and results presented in the technical note and EBRAINS documentation. Section 5 addresses future and current avenues of development for integration of other data modalities into the pipeline.

3. Technical Specifications

Figure 2 shows an overview of our structurally informed DCM pipeline for electrophysiological epilepsy data. The pipeline includes both structural and SEEG data extraction steps in which channels are selected based on an iterative Spectral Principal Component Analysis (SPCA) method. In this procedure, channels are selected by selecting the spectral modes that best align to the spectral axes of maximum variability. This is followed by a data extraction step for model training using brief trials to fit Dynamic Causal Models (DCMs) to empirical channel cross spectral densities using a subject-specific parcellation and structural data produced from Diffusion Tensor Imaging (DTI). Models trained assuming a variety of structure-function relationships parameterised by a specific set of hyperparameters are then compared using a Bayesian free energy criterion. This allows identification of a structure-function mapping for the core epileptogenic network at the level of individual patients.

These methods have been developed building on the core framework established in MATLAB, and provided with an executable version accessible through a Python interface for further integration into EBRAINS. This use case is outlined in Figure 3 and specified further in the siDCM EBRAINS collab, where both the standalone matlab app and the relevant matlab scripts are provided (https://data-proxy.ebrains.eu/structurally-informed-dcm?prefix=02_Code%2Fpackages%2F) with the use of Matlab runtime environment outlined in the 'readme.txt'. The Python package together with the standalone matlab app can be run independently of MATLAB licenses on workstations and cloud computing architecture, as the Python code exposes relevant parameters including individual structural connectivity networks (if desired), SEEG trial data and SEEG metadata (such as the sampling frequency and frequency band of interest) to be specified by the user as demonstrated in the example Jupyter notebook on EBRAINS (https://data-proxy.ebrains.eu/structurally-informed-dcm?prefix=#). This allows users to determine the structural network and network features that are

most relevant to their investigation through a generic pipeline for structural network construction, and interface with relevant pipelines (e.g. TVB) on EBRAINS.

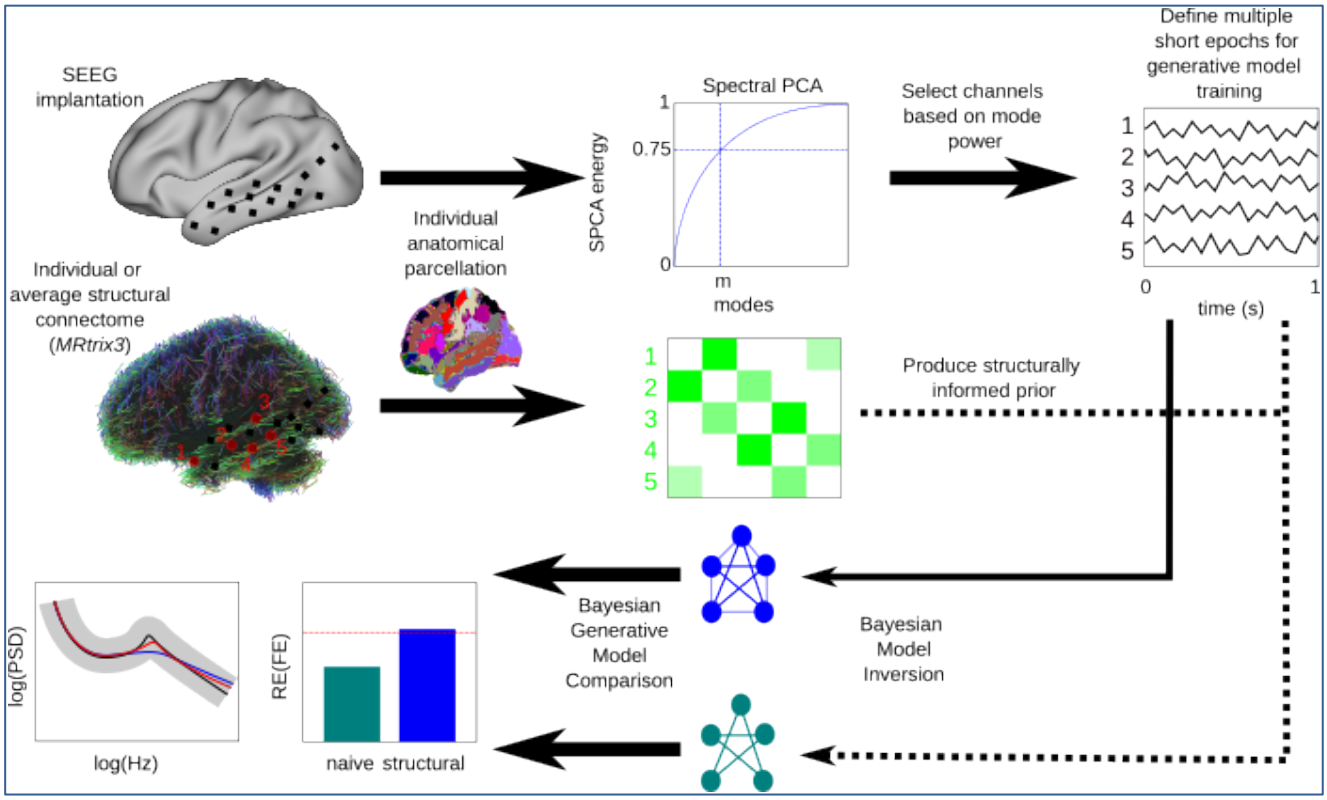

Figure 2: Theoretical overview over structurally informed DCM analysis.

SEEG data and individual structural MRI are used as input for the modelling. Dimensionality is reduced using spectral PCA. Reduced networks of interest are then fitted using a Dynamic Causal Modelling approach allowing model comparison between competing models. (adapted from Wilsenach et al. 2023 https://doi.org/10.17605/OSF.IO/K4P8S)

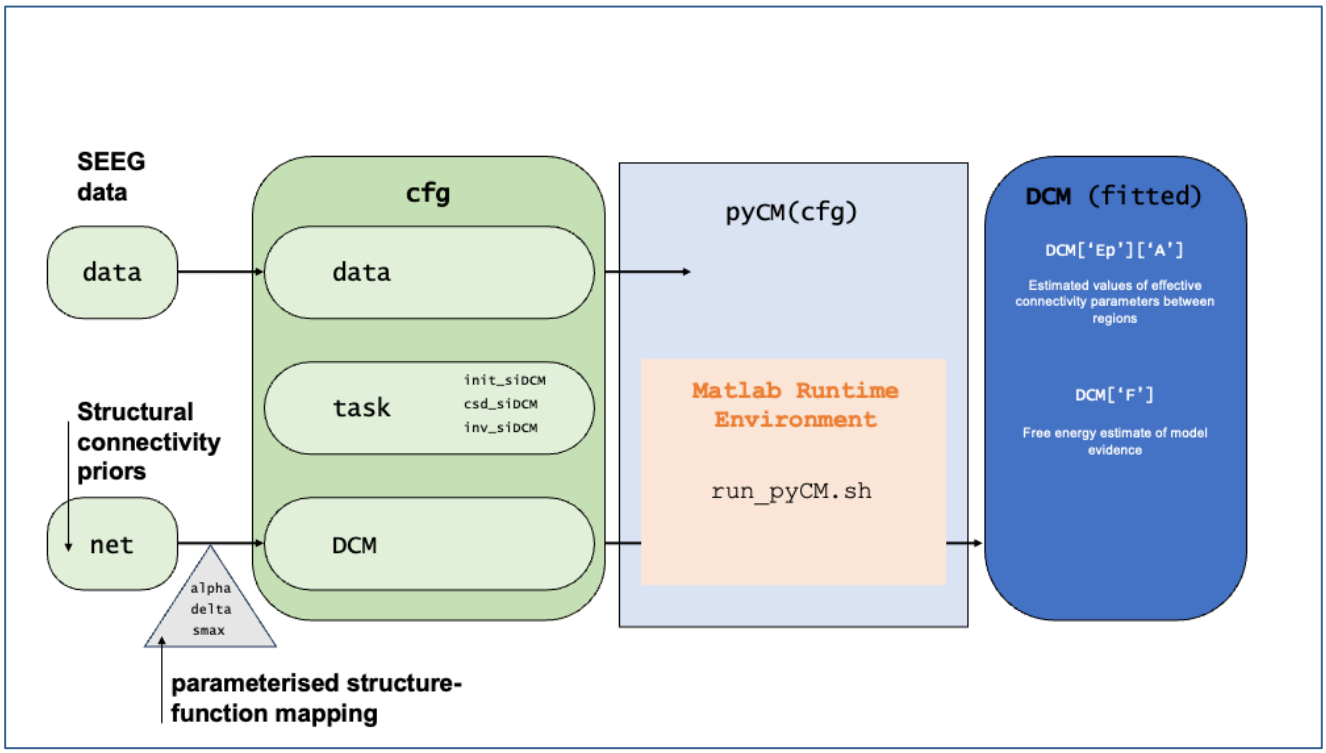

Figure 3: Implementation of structurally informed DCM.

SEEG and structural connectivity data are used to specify a dynamic causal model, which is subsequently inverted within the Matlab Runtime Environment, yielding parameter estimates as well as measures for model evidence. Structural priors are passed through a parameterised structure-function mapping function. Individual steps are specified using the 'task' variable in the configuration 'cfg' structure.

For the specific use case presented, the data recommended for this pipeline include T1 and diffusion weighted images weighted registered to a post-implantation CT scan with SEEG provided as a matrix including a subset of channels of interest. Structural connectome estimation is performed in MRtrix3 using a high-resolution subject-specific atlas based on the Lausanne atlas (Hagman et al. 2018 https://doi.org/10.1371/journal.pbio.0060159) or other relevant cortical atlas registered to subject space. Channels can be selected, using the aforementioned Spectral PCA approach which is available as a stand-alone method, or determined by a hypothesis or research question of interest.

Dynamic causal modelling is then used to estimate the between-region and within-region parameters of a network of neural masses, where each region of interest is modelled as a 4-population network capturing key features of cortical organisation, i.e. the canonical microcircuit (CMC). These models are defined as part of the DCM package within the SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and as such are implemented in MATLAB. These models include detailed intrinsic models of excitatory and inhibitory neuronal cell populations, with additional extrinsic forward and backward connections between each region of interest. All these parameters specifying both the intrinsic and extrinsic features of model are estimated during the model inversion step, which will fit model output to the cross-spectral densities measured empirically using icEEG within each region of interest. Model inversion (or training) follows a Bayesian free energy minimisation approach that assumes a set of reasonable prior values.

These model estimates are based on the neurophysiological recordings, but can be further constraint through prior knowledge – e.g. from normative population data, from multimodal measurements within individual patients, or derived from distinct, competing hypotheses. DCM allows computationally efficient integration of different priors and quantifies an approximation of the model evidence under different prior assumptions. These prior assumptions are specified quantitatively as prior estimates on the model parameters and may therefore encode relative strength of different connections; the absence or presence of certain connections; or the modulation of certain connectivity strengths by conditional effects. This allows direct model comparison regarding the specific hypotheses encoded through such priors. In the use case demonstrated, priors on the effective connections between regions – i.e. the extrinsic connections – are informed by structural connectivity measures, and the optimal mapping between structural connectivity values and effective connectivity parameters is estimated through Bayesian model comparison (for further details see the related preprint Wilsenach et al. 2023 https://doi.org/10.17605/OSF.IO/K4P8S).

A workbook demonstrating the effects of model hyperparameters and application of the pipeline in an example dataset of interictal data is included. This workbook shows how a DCM model of SEEG activity informed by structural data can be trained in Python 3.8 and the output used to determine important features of the network including estimates of effective connectivity and spectral coherence between channels.

4. Data and Prototype Availability

The python implementation of the structurally-informed-DCM (si-DCM) pipeline for SEEG activity is available at the project's dedicated Collab page:

https://wiki.ebrains.eu/bin/view/Collabs/structurally-informed-dcm

The outline of the notebook and set up instructions can be seen in the README: https://object.cscs.ch/v1/AUTH_7e4157014a3d4c1f8ffe270b57008fd4/structurally-informed-dcm/README.md

The notebook in this collab, siEEG.ipynb, demonstrates the application of this pipeline to a subject dataset (provided here as reduced test data set of non-identifiable reduced and preprocessed data matrices containing short segments of EEG data from small subset of SEEG contacts, and corresponding between region connectivity from the corresponding brain regions estimated in MRtrix3 https://www.mrtrix.org/) The reduced dataset provided here illustrates the pipeline. All metadata regarding SEEG channel locations or events have been removed. The data set is available as a single 'testdata.mat' file with relevant packages, including those for reading and executing MATLAB code and data files imported by the notebook. The notebook also demonstrates how various

hyperparameters for the structural priors affect prior estimates of feedback and feedforward connectivity. The notebook shows how the prior estimates of extrinsic and intrinsic model parameters give rise to estimates of interchannel coherence. Lastly, the model inversion is performed and posterior coherence and directed effective connectivity estimates are shown, which are contrasted with the underlying, undirected structural connectivity network. The notebook and underlying code can also be easily adapted to start with naive priors (fixed, non-structural) by simply leaving the connectivity network argument empty.

Theoretical justification for this pipeline framework and investigation of a small multisubject pilot data set is given in the Technical Note. The pilot study provides a preliminary exploration of structurally informed DCM and contrasts it with models informed by standard (fixed, non-structural) priors. It also references an approach for generating structural connectivity networks from dMRI data using MRtrix3. In addition, details of the suggested channel selection procedure used in the pilot study based on Spectral Principal Component Analysis (SPCA) are given. This is an optional extension of the core pipeline for selecting subnetworks from whole-brain data based on data features alone. Alternatively, hypothesis-driven channel selection could be employed. Code for performing this SPCA-based channel selection procedure is available at

https://github.com/jameswilsenach/SEEG_Channel_Selection

5. Future Directions

In future work, we intend to extend the functionality of the si-DCM pipeline with greater integration into EBRAINS and improved model efficacy. The steps are as follows:

- Extend interface between python wrapper and SPM functions: Expose additional SPM functions used for DCM specifications parameter choices made in python. This can be implemented by adding additional matlab scripts that can be called with parameter sets specified in the ‘cfg’ variable in python. This will expose siDCM to more user-driven modelling specifications (such as defining priors for all intrinsic and extrinsic parameters).
- Provide a means for users to investigate the effects of interventions on the model such as stimulation or task performance. Alternatively, resection may be simulated by removal of one or more nodes.
- Broader exploration of the effectiveness of siDCM for clinical hypothesis testing by applying an expanded set of patients form the extensive historic paediatric epilepsy surgery cohort at Great Ormond Street Hospital (London, United Kingdom; total of 100 patients, with future inclusion in the EBRAINS knowledge graph planned).
- Produce improved model priors by incorporating intrinsic priors based on spatially specific receptor density information or subject-specific data aggregated across multiple SEEG channels.
- Investigate the effects of more complex, information diffusion-based structure-function relationships on model performance.

6. References

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