Early Detection of Alzheimer's Disease: A Computational Approach

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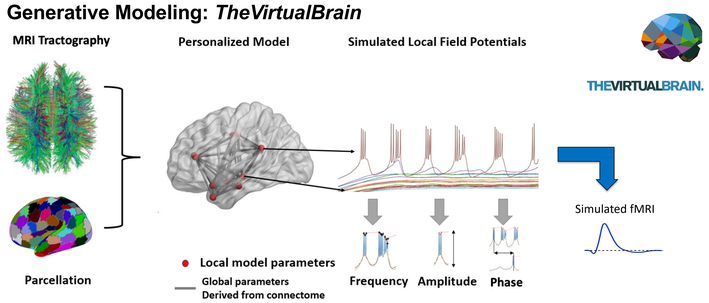
INTRODUCTION

Alzheimer's Disease (AD), the most prevalent form of dementia, is associated with widespread brain degeneration. Although the neuropathological changes have been recognized for a long time, there are no curative therapies. To fill this knowledge gap, new approaches based on generative modeling (*TheVirtualBrain, TVB*) are providing unique mechanistic insights based on brain dynamics[1]. The overarching goal of this study is to use the changes in brain dynamics to predict conversion to AD in prodromal and presymptomatic individuals. For this, we combine complementary biophysical analyses with model-based and model-free approaches. Preliminary observations suggest an increase accuracy assessing converters to AD.

METHODS

Clinical Cohorts

Generative Modeling: *TheVirtualBrain*

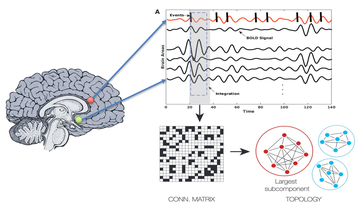


Simulation of LFPs and rs-fMRI: Empirical input: MRI tractography to derive global parameters; Local biophysical model: Stefanescu-Jirsa 3D model including 16 parameters. Forward solution from LFPs to rs-fMRI

Computation: **670** simulations per subject, **74** subjects in total with **49,580** simulations.

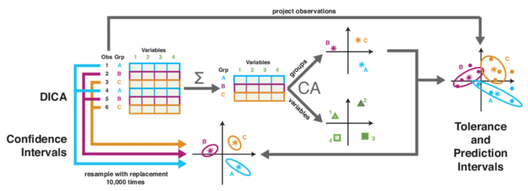
Model-Free Analysis: Measures of Brain Synchrony

Integration and Metastability framework:
Integration: Quantification of the ability of a brain region to synchronize other areas[2]. **Metastability:** Variance on the number of regions synchronized by the target region[2].



Computation: **2** calculations per subject, **74** subjects in total with **148** calculations

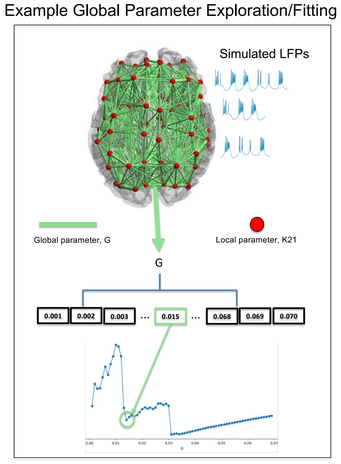
Statistical Analysis: MUDiCA - Prediction



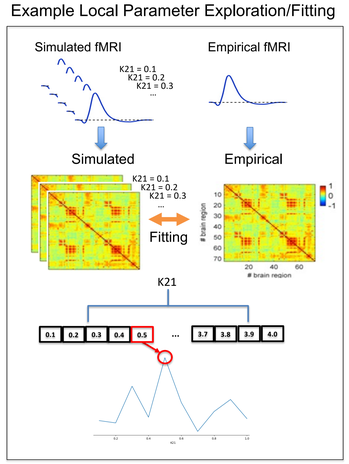
The Multiblock **Discriminant Correspondence Analysis** (MUDiCA): A multivariate categorical statistical analysis. It projects both variables and individuals into a low-dimensional space while maximizing the separation between groups to assign statistical membership for each subject based on measures of brain dynamics.

Workflow of TVB Parameter Exploration/Fitting and Model Validation

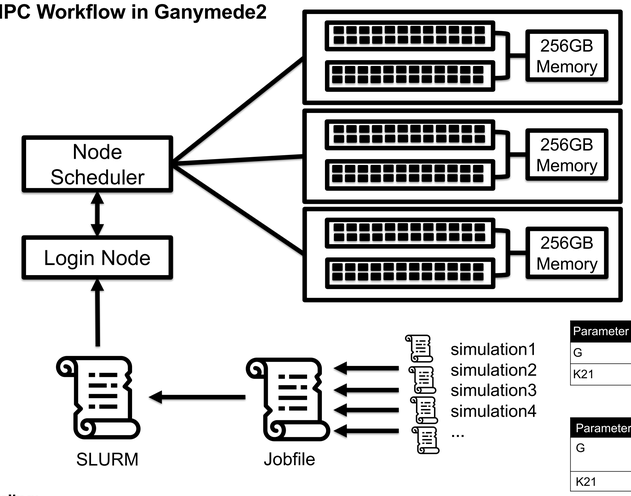
Example Global Parameter Exploration/Fitting



Example Local Parameter Exploration/Fitting



HPC Workflow in Ganymede2



Parameter	Range	Sampling
G	[0.0001, 1]	0.005
K21	[0.1, 4.0]	0.1

Parameter	Range	Sampling
G	[0.0001, 0.07]	0.001
K21	[0.1, 1.0]	0.01

Modeling:
From the 18 parameters, only two were explored and fitted (1 local, 1 global).

- The **parameter exploration** is the determination of possible range of parameter values in a network of 16 nodes. It involves the testing of all potential values starting with small sampling rates. The limits then are tested at higher sampling rates. Typically, this involves **440** simulations/subject.
- The **parameter fitting** is the assessment of a single value per parameter that either, best represents empirical signals or the boundary separating two brain states. This step usually requires **230** simulations per subject.

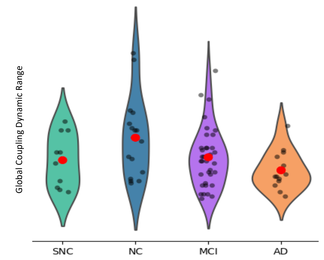
The parallelization is achieved by assigning all possible parameter values of simulations to 3 compute nodes in Ganymede2 system, in total 144 threads with each thread running one simulation independently.

- One simulation requires various time from 1 min to 30 mins. For 74 subjects, the parameter exploration and fitting takes **49,580** simulations, with estimated time **12,395** hours.
- One Integration/Metastability calculation takes 2 mins to finish. For 74 subjects, **148** calculations takes 5 hours.

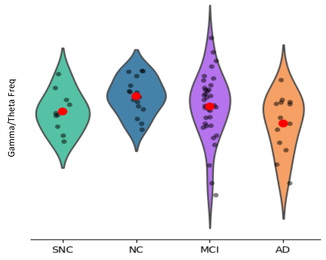
In total, the computation time is **12,400** hours (516 days). Parallelization in Ganymede2 reduces it to **86** hours (3.5 days).

RESULTS

Model-based Analysis: 21 Metrics

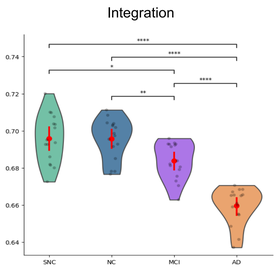


Dynamical range: Reflects the brain state where synchrony between regions occurs. Note the increase of this range in NC and MCI before decreasing in AD

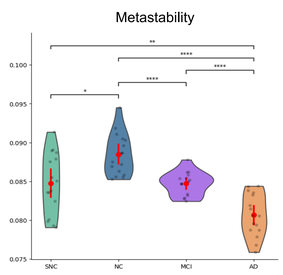


Normalized frequency of Simulated brain signals (LFPs)
A large decrease in frequencies are observed in MCI cases, before diagnosis of AD.

Model-free Analysis: 32 Metrics



Integration is significantly decreased from SNC to AD.



Metastability showed an increase in NC before it decreased in MCI and AD.

Individual Membership Assessment

Latent Variables Map

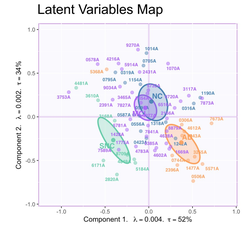


Table: Fixed Confustion Matrix

	SNC.actual	NC.actual	MCI.actual	AD.actual
SNC.predicted	8	1	3	0
NC.predicted	0	10	5	0
MCI.predicted	0	1	15	1
AD.predicted	0	1	7	10

All seven MCI cases classified as AD, were clinically confirmed AD, 4 years later.

Compute time reduced from 12,400 to 86 hours with HPC parallel computing.

SUMMARY

The parallelization of the workflow for both model-free and model-based analysis allows for the careful fitting of parameters in many subjects. This will enable us to validate preliminary results in large, untested cohorts.

REFERENCES

1. Zimmermann, et al., (2018). Differentiation of Alzheimer's disease based on local and global parameters in personalized Virtual Brain models. NeuroImage: Clinical, 19, 240–251.
2. Patow & Deco, G (2024). Whole-Brain Dynamics Disruptions in the Progression of Alzheimer's Disease: Understanding the Influence of Amyloid-Beta and Tau. Preprint.