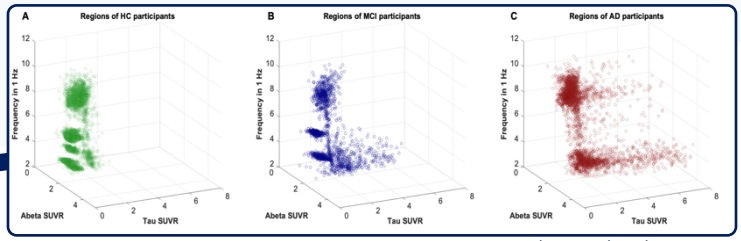
VirtualBrainCloud

Personalized Recommendations for Neurodegenerative Disease



Modified from (Triebkorn, Stefanovski et al. 2022)

www.VirtualBrainCloud-2020.eu

Public deliverable report

D5.6: Workflows established that link progression models and TVB

Date January 2023
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Dissemination level **public**
Website www.VirtualBrainCloud-2020.eu

This project has received funding from the **European Union's Horizon 2020** research and innovation programme under **grant agreement No 826421**

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1. Introduction

The global prevalence of dementia was estimated to be as high as 24 million in 2012, and it is predicted to double every 20 years until at least 2040 as the worldwide population ages (Francis, Palmer et al. 1999, Mayeux and Stern 2012). Among the causes of dementia, Alzheimer's disease (AD) is the most common, reaching about 65% (Sperling, Aisen et al. 2011, Robinson, Corrada et al. 2018). While the estimated annual cost of AD treatment solely in the U.S. rises to $277 billion, it is expected to exceed $1 trillion by 2050. Thus far, there exists no causal treatment for AD (Stefanovski, Triebkorn et al. 2019), while the currently used symptomatic treatment options remain insufficient.

TVB-Cloud provides complex computational models that can reproduce the biological mechanisms that lead to altered neuronal dynamics and brain function related to neurodegeneration. The biological plausibility of such *mechanistic* generative models is increased by informing the models with multimodal data, e.g., electrophysiology, MRI, PET, genetics, protein pathways.

The Virtual Brain (TVB, www.thevirtualbrain.org) is an open-source neuroinformatics platform for brain network simulation (Ritter, Schirner et al. 2013, Sanz Leon, Knock et al. 2013, Sanz-Leon, Knock et al. 2015, Stefanovski, Ghani et al. 2016, Solodkin, Zimmermann et al. 2018). We recently extended TVB with the option for multi-scale co-simulations (Schirner et al. 2022, Meier et al. 2022), i.e. the brain can be simulated at different degrees of detail ranging from brain regions to individual neurons – simultaneously, that is some regions are simulated at greater detail than others through the co-simulation of different simulation frameworks. This interfacing of different neuronal simulators enables to reveal principles of interactions across different scales of brain operation.

AD is associated with two hallmark proteins: Amyloid beta (in the following Abeta) and Tau the presence of which is defining the diagnosis AD (Jack, Bennett et al. 2018). It remains controversial, however, as to which of the two depositing proteins has a driving role upon the other, as well as how their interdependence evolves over time (Jack and Holtzman 2013).

Existing computational models have already proven to predict clinical trajectories of AD to a certain degree (Peng, An et al. 2016, Beheshti, Demirel et al. 2017, Li, Chan et al. 2017, Bhagwat, Viviano et al. 2018, Tabarestani, Aghili et al. 2020). Brain network models have been demonstrated to make the link between gene expression, protein function and the macroscopic changes in MRI reflecting brain structure and function (Costa-Klein, Ettinger et al. 2020). It is stipulated that the simulation inferred neural activity, can disentangle the impact of, e.g., genetic variants on neural function, similar to the intermediate phenotype approach (Meyer-Lindenberg and Weinberger 2006). By combining molecular pathways and large-scale brain simulation, we assess how brain dynamics change when molecular interactions change at the micro-scale.

We here provide a summary of workflows that link AD progression models and TVB - established in the European consortium The Virtual Brain Cloud (TVB-Cloud; virtualbraincloud-2020.eu). The approach draws from integrating information from large cohorts of imaging and associated data of healthy human individuals and patients with information from knowledge bases of biological signaling cascades. While the TVB-Cloud project comprises several

technical innovations, including creating a secure environment for sharing and processing personal health data (BIH/Charité secure Virtual Research Environment, VRE[1]), we here focus on the workflows created to systematically explore those multiscale interactions from genes to behavior to come up with generalizable principles. The outlined workflows comprise:

1) Mapping altered subcellular pathways and signaling cascades to brain structures.

2) Creating mathematical models that describe the influence of those changes on the cellular neuronal networks and neuronal population level.

3) Validation of resulting cause-and-effect models.

We demonstrate the use cases of multiscale models in AD that are supported by these workflows. While current AD modeling approaches often consider only few selected aspects of pathogenesis, in future approaches, the cross-modal integration of several such pathological processes in individualized brain models will provide the opportunity to unveil the individual person-specific composition of contributing mechanisms enabling precision medicine.

2. Description of work performed

To link disease progression models of AD – based on molecular disease mechanisms – to TVB, we systematically assessed the existing knowledge and literature (Stefanovski, Meier et al. 2021).

We developed a model of Abeta related excitability changes in AD (Stefanovski, Triebkorn et al. 2019) and investigated whether the resulting simulated data can predict disease progression, i.e., the diagnostic category describing the cognitive state of the patients (Triebkorn, Stefanovski et al. 2022).

Finally, we developed a tool for mapping disease related mechanistic cascades from knowledge graphs to anatomical brain locations to further enrich computational brain network models with disease specific biological constraints (Stefanovski, Bülau et al. 2021).

3. Results

Our review of mechanisms in AD revealed various candidate pathways suitable for disease modeling (Figure 1). The two hallmark proteins, Abeta and Tau, are of particular interest, as they are (1) involved in most of the disease pathways and (2) assessable with state-of-the-art biomarkers.

[1] https://www.re3data.org/repository/r3d100014127

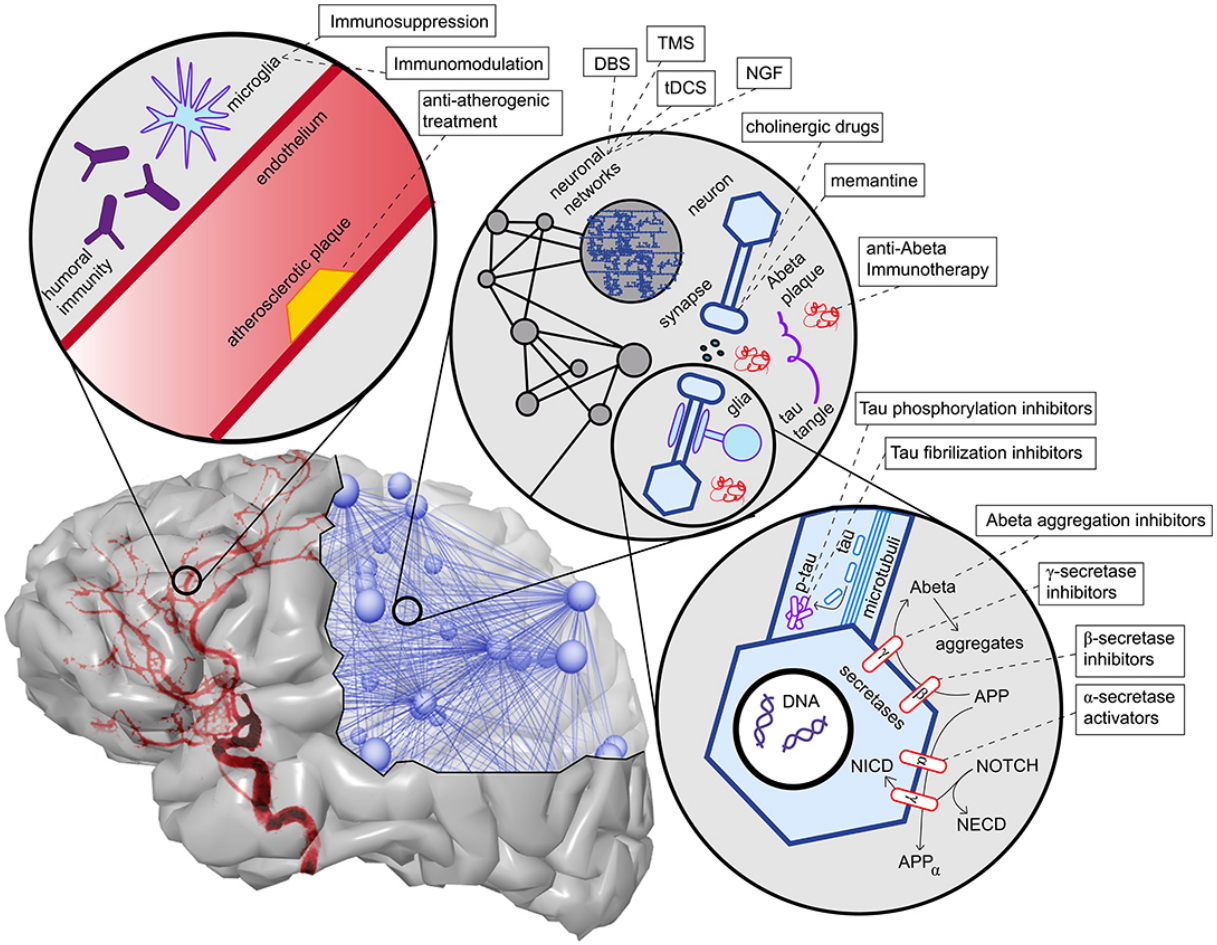

Figure 1: Contributing factors of Alzheimer's Disease. Figure taken from (Stefanovski, Meier et al. 2021) with permission (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/) Of significant interest is the holistic implementation of the two hallmark proteins Abeta and Tau together with the essential co-factors, in particular, network dysfunction as a large-scale feature of the disease.

To assess these proteins' role, we used publicly available data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Since 2004, ADNI has been collecting and sharing longitudinal, multisite data that comprise several AD biomarkers from over 1000 participants between the ages of 55-90. The primary aim of ADNI has been to investigate the progression of MCI and early AD employing a combination of MRI, PET, and other biological markers, as well as clinical and neuropsychological assessments. Results based on ADNI between 2004 and 2018 have been summarized elsewhere (Weiner, Aisen et al. 2010, Weiner, Veitch et al. 2012, Weiner, Veitch et al. 2015, Weiner, Veitch et al. 2017, Weiner, Veitch et al. 2017, Chandra, Valkimadi et al. 2019).

We then used an AD model that links Abeta PET to excitability (Stefanovski, Triebkorn et al. 2019) (Figure 2).

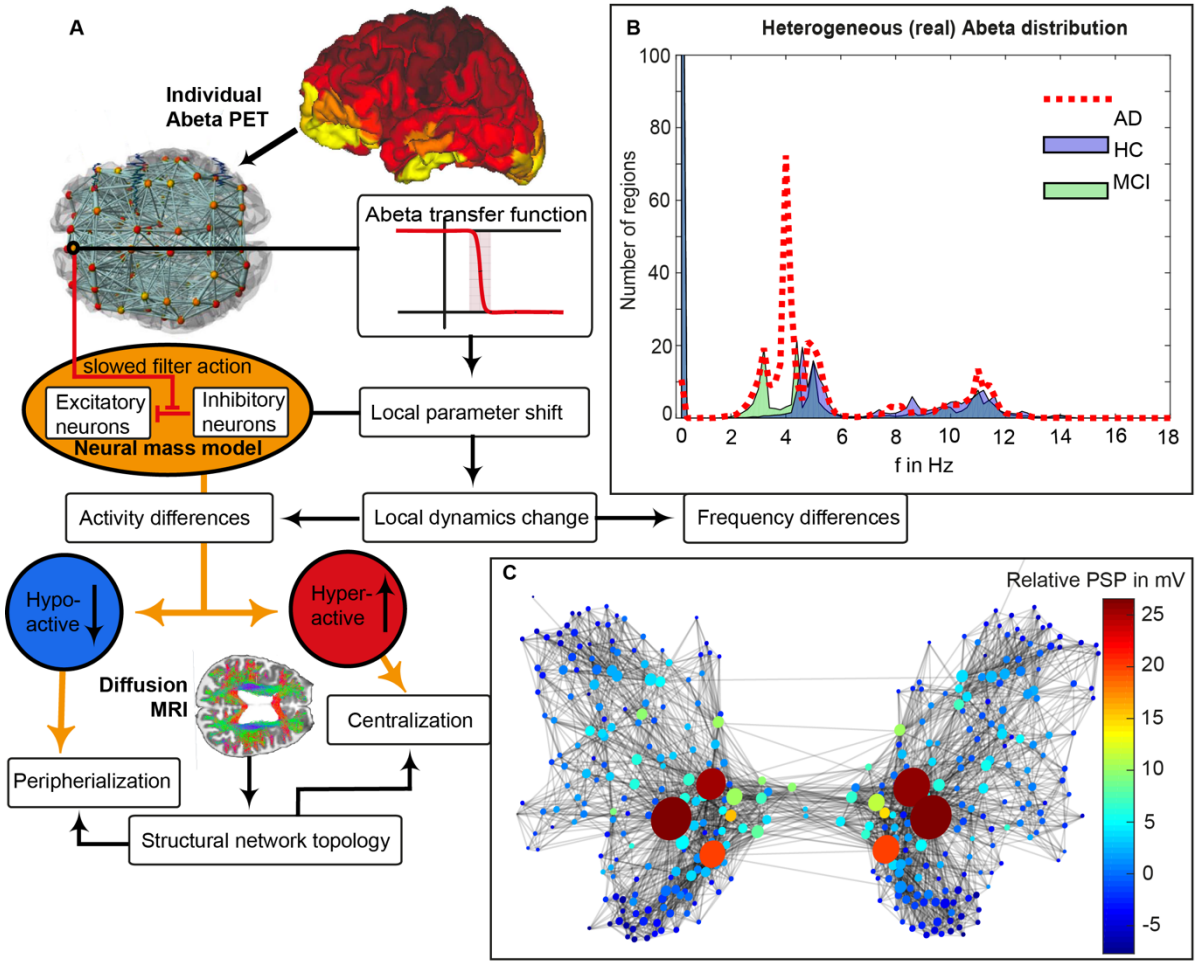

Figure 2: Mechanistic model of Alzheimer's Disease linking Abeta and excitability (Stefanovski, Triebkorn et al. 2019). Figure taken from (Triebkorn, Stefanovski et al. 2022) with permission (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). By linking a higher local burden of Abeta to an impaired inhibitory function, we reproduced electrophysiological slowing in simulated EEG of AD patients. This was linked to a hyperexcitation of particular network hubs, although the Abeta distribution did not predominantly affect these hubs. The model, therefore, explains a potential mechanism of how Abeta's peripheral distribution can affect the brain network's core structures.

As an extension of this study, we investigated whether the simulated (artificial) signals can increase predictive accuracy of the disease progression, i.e., whether classification based on imaging data that were augmented with simulation features between the three stages 1) AD, 2) mild cognitive impairment (MCI), and 3) cognitively unimpaired improves. Our work demonstrated that a machine-learning classifier based on empirical imaging data (Abeta and Tau PET and structural MRI) performed worse than a classifier that considers additionally the simulated local field potential (LFP) frequency data (Figure 3). By this, we have demonstrated that the disease model in TVB can (1) link microscale mechanisms of AD to the actual clinical progression of the disease and (2) potentially outperforms the underlying empirical biomarker data by complementing it with additional "hidden variables".

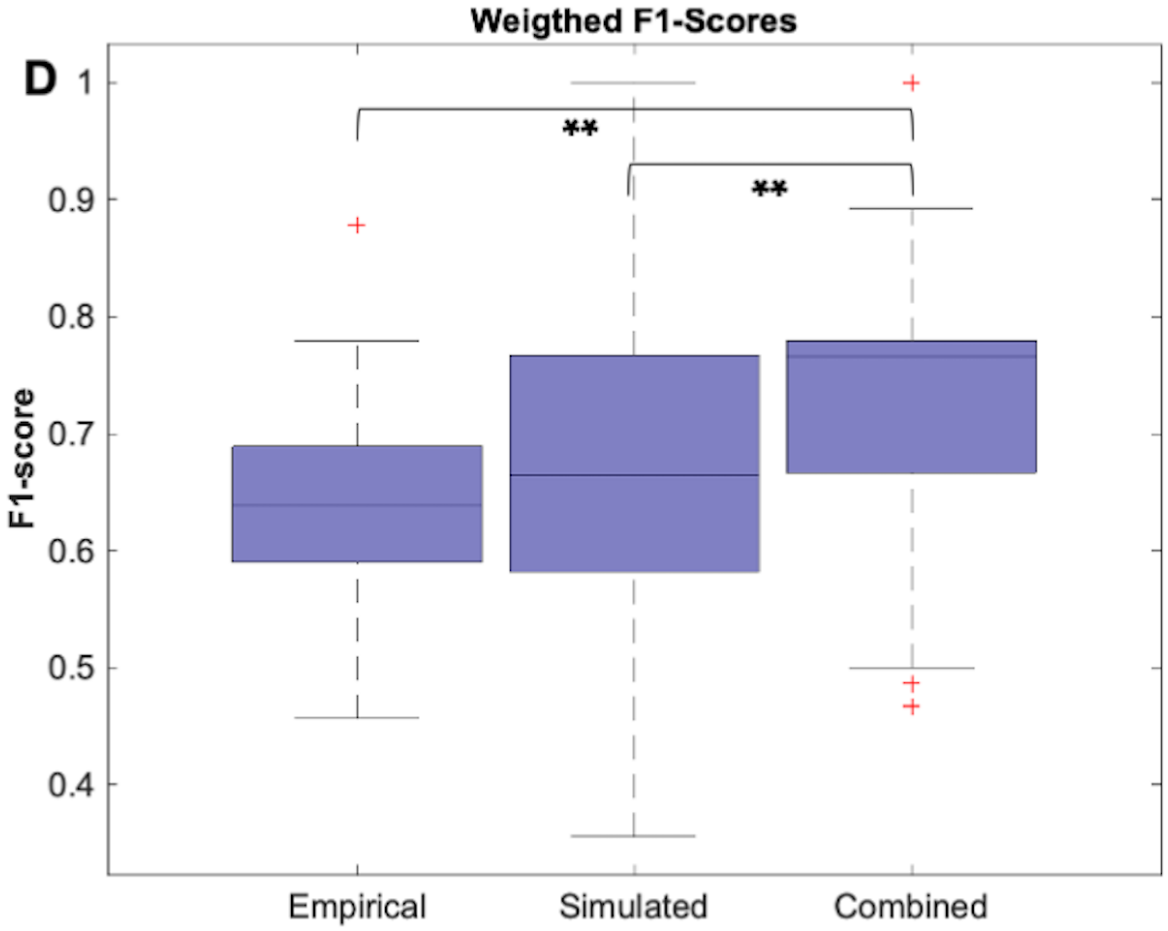

Figure 3: Classification performance based on empirical data and simulated data between Alzheimer's Disease, mild cognitive impairment, and healthy controls. Figure modified from (Triebkorn, Stefanovski et al. 2022) with permission (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). While no difference is observable between empirical features and simulated features alone, the combined dataset outperforms the empirical classification significantly. We used the weighted F1-score to assess the accuracy of the classification approach.

4. Conclusion, next steps

We have demonstrated a workflow that links AD progression models and TVB. As a next step, we aim to generalize this approach by systematically exploring applications for diseases other than AD.

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