Advanced prototype software integrating heterogeneous region models including DEMO2 of Showcases 1 and 2 (D1.2 – SGA3)

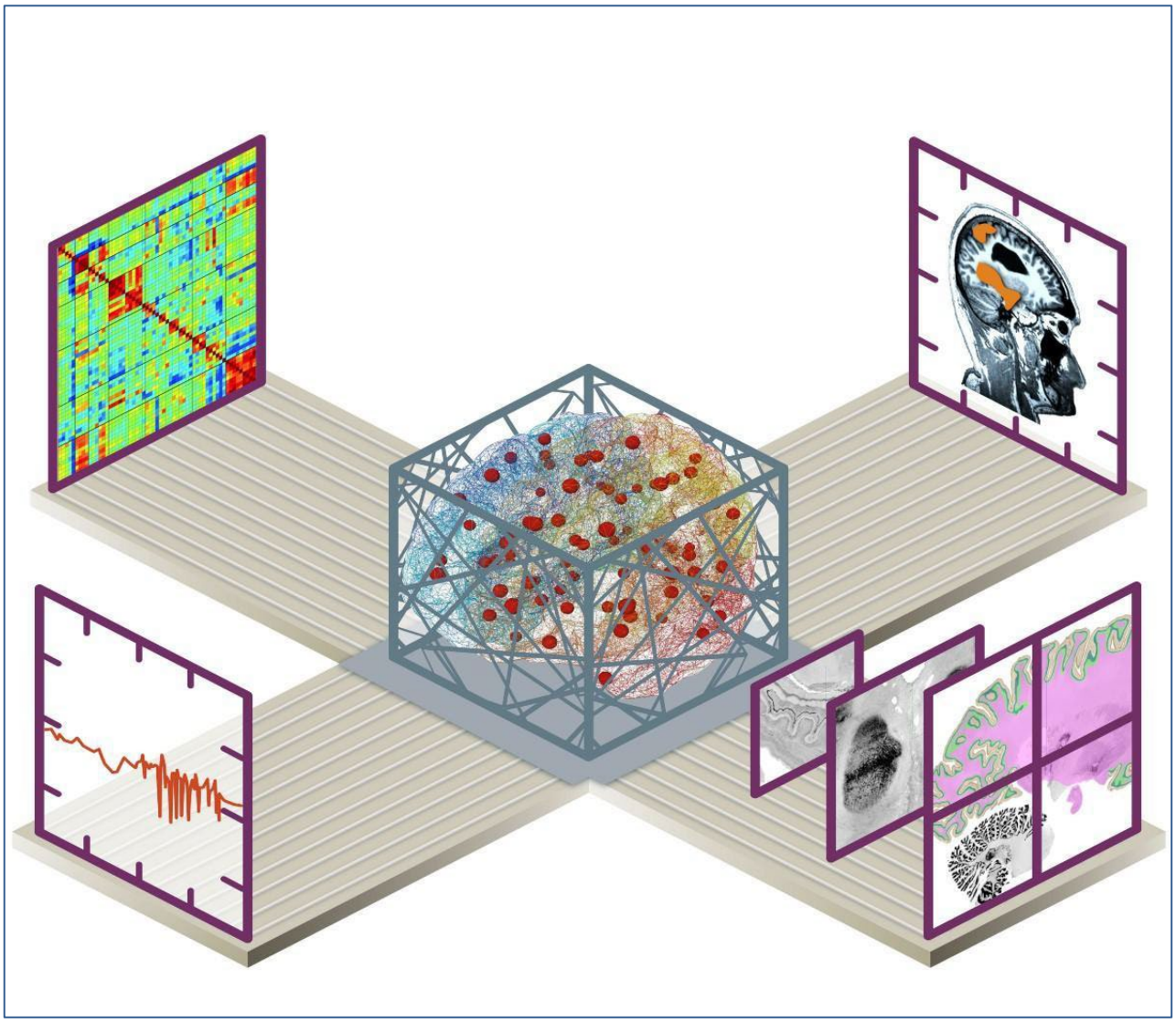

Figure 1: Showcase 1

The Virtual Big Brain is a personalised high-resolution virtual brain model, integrating network modelling with multiscale brain data from connectomics and region-variant architecture in the same reference frame.

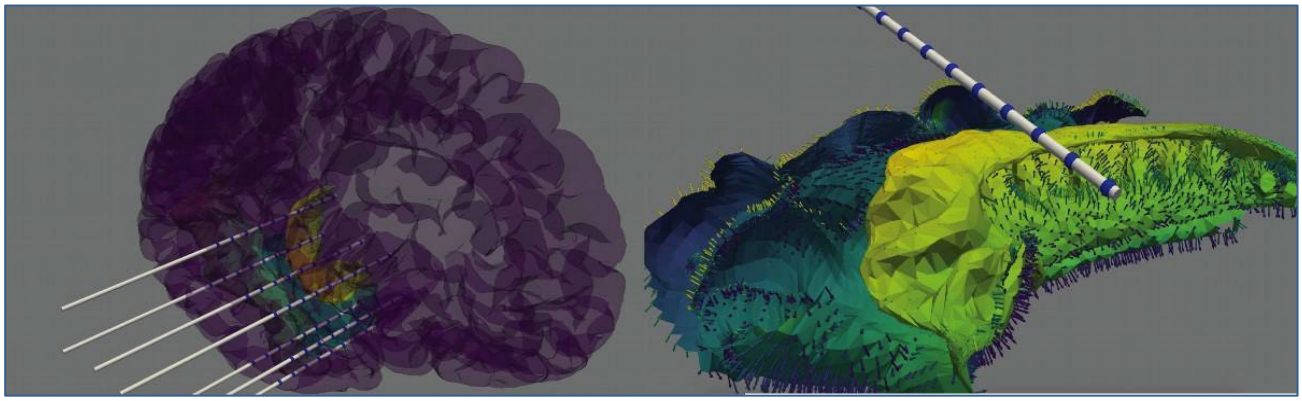

Figure 2: Showcase 2

High-resolution full brain model with implanted SEEG electrodes and detailed human hippocampus model with dipolar neural sources.

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Description in GA:	A more advanced prototype software will be available, in which early drafts of advanced mean field models are integrated in TVB and exchange with EBRAINS atlas services. Showcase demonstrators will be available in the prototype and illustrate functional (but incomplete) workflows including breaking of regional variance in subject-specific brain network models using EBRAINS atlas services, simulation of individual resting fMRI signals and validation against empirical brain imaging signals. Detailed specifications for DEMO3 are provided.
Abstract:	This report is the D1.2 Deliverable (M21) as stated in the DoA. It outlines progress in the development of WP1's Showcases 1 and 2. Showcase 1 develops the workflow for building a virtual brain cohort, which includes data access to the 1000BRAINS cohort, and use of EBRAINS' multilevel human brain atlas and The Virtual Brain (TVB) simulator. Highlights include novel insights into brain aging mechanisms. The

	advanced prototype of Showcase 1 is now available in EBRAINS. Showcase 2 demonstrates how EBRAINS enables advances in personalised medicine through the transition to high-resolution TVB. Highlights include progress in high-resolution and multiscale brain simulation for epilepsy. The first prototype of Showcase 2 is now also available in EBRAINS. The existing functionalities of both demonstrators, including access to the Showcases and a roadmap to the next Showcase Deliverable, D1.5 (D11), in M42 are also described.
Keywords:	Neuroscience, Big Data, Virtual Big Brain, Variability, Cohort, Personalisation, Epilepsy, Modelling
Target Users/Readers:	Clinicians, computational neuroscience community, computer scientists, Consortium members, HPC community, neuroimaging community, neuroinformaticians, neuroscientific community, platform users, scientific community, students, funders, policymakers.

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1. Preamble

Work Package 1 develops two Showcases, which illustrate how EBRAINS enhances the researcher's capacity to interoperate data, methods, models, and theory in digital neuroscience to solve difficult questions in basic and clinical research. Both Showcases make use of data-driven high-resolution virtual brain models, which are rendered subject specific using the individual's anatomical and functional brain imaging data. Showcase 1 illustrates how we can disentangle cause and effect of healthy aging in light of the large intra- and inter-subject variability present in biological systems. Showcase 2 demonstrates how the transition to high-resolution brain models significantly improves the estimation of the epileptogenic zone in drug-resistant epilepsy patients. The Showcases highlight two novel unique dimensions of EBRAINS services, distinguishing the current from preceding modelling efforts, that is the integration of detailed neuroscience data for regional specificity and progress to high-resolution on the sub-mm scale.

2. Showcase 1: Degeneracy in neuroscience - when is Big Data big enough? Demo 2

2.1 Introduction

Showcase 1 addresses one of the oldest enigmas in neuroscience, the dichotomy of brain structure and function. Individual brains differ from each other while maintaining full functionality in a given range of "normal" status. Outside of this range, brain function is diminished or lost. The functional loss, however, occurs for different conditions in each brain, and similar structural alterations may be functionally dramatic in one brain, but almost inconsequential to the other. What applies to empirical data, equally applies to mathematical models in neuroscience and is known as degeneracy, i.e. the propensity for multiple subsystems to support similar functions. When applying models to data, increasingly large amounts of data are required to make meaningful statements about mechanisms in the models due to such degeneracy. The objective of this Showcase is to demonstrate that cutting edge datasets on structural variability can be used to formulate causal hypotheses about brain mechanisms and then drive whole-brain modelling to explain functional variability within and across individuals.

Human brain ageing is a well-suited paradigm for this task. A better understanding of aging feeds directly into one of Europe's priority efforts, the maintenance of active and healthy ageing of its population. Aging is, next to sex, the factor that is expressed best in brain imaging data and thus quantifies inter-subject variability well. This is also why aging was used in many brain network studies during SGA1 and SGA2, which generated metrics and paradigms used in SGA3's WP1 and WP2. Although brain aging is well described structurally (e.g. atrophies, micro-lesions, dysconnectivity) and functionally (e.g. adaptations in network architecture and non-efficient recruitment of brain regions), there is, to this day, no established causality between observations, albeit several competing hypotheses exist. The interindividual variability in brain structure, function and cognitive abilities in older subjects is very pronounced and is a key obstacle on the way to a better understanding of aging. The relevant factors influencing this variability, be it genetics or environmental and lifestyle factors, are manifold. Similarly, the different levels within the organisation of the brain, from the molecular, cellular to the systems level, contribute to these effects to varying degrees. To explore the variability and ultimately explain aging mechanisms, large numbers are required, and a cohort approach is the only viable way of doing so. This requirement imposes constraints in terms of data, curation and storage, high performance computation, multiscale modelling, and validation, which today are met only in EBRAINS.

The target paradigm of Showcase 1 is the resting-state brain activity as measured in fMRI. Resting state is the paradigm that has been used most for the development of HBP's full brain network models during SGA1 and SGA2. It is routinely imaged in basic and clinical research and is recognised as a fingerprint of an individual's brain, affected by drugs, disease, age and cognitive factors. In Showcase 1, we integrate detailed multiscale data (brain connectome, region-specific data) in

virtual brain models (see Figure 1), implement the hypothesised ageing mechanisms, and simulate the functional resting-state brain imaging data of a large cohort of individual brains. A novel model inversion process has been developed for the resting-state during SGA3 and independently validates the empirical against the virtual cohort data, demonstrating that neurodegeneration of long interhemispheric fibre tracts is a major causal factor affecting brain activity during healthy aging. Compensation has been previously hypothesised counteracting these adverse effects of neural decline, but not yet demonstrated. In Showcase 1, we provide first evidence of compensatory scaffolding in aging, which we demonstrate within a subject-specific causal inference framework in a large cohort. While the virtual ageing brain links functional variability with structural variability via white matter degeneration, regional variation is captured by the inclusion of neuroreceptor density data, critical for explaining the impact of pharmacological agents on brain regions and thereby modulating the whole-brain dynamics. Demo 2 establishes proof of concept showing the effects of regional variability on brain dynamics. The M21 Deliverable provides the complete workflow comprising data, model, and methods in EBRAINS, making use of two curated cohort data sets, the 1000BRAINS cohort and the HCP cohort.

The realisation of Showcase 1 requires the integration of a variety of elements that only the EBRAINS infrastructure can offer in a coordinated and centralised manner. Previous efforts in SGA1 and SGA2 developed the necessary HBP technologies (mean field models, human brain atlas, model inversion and validation) and data (BigBrain, cytoarchitectonic maps and multimodal data features, high-resolution connectomics) needed to build a virtual cohort in SGA3, establish a causal hypothesis and link structural to functional variability. All technologies exist now in EBRAINS and are interoperable. The multilevel Human Brain Atlas, which includes the Julich-Brain probabilistic cytoarchitectonic maps as a microstructural reference parcellation, represent a hallmark that facilitates the integration of datasets by establishing a common reference space, in which data and models can be represented. The integration of The Virtual Brain (TVB) into EBRAINS provides an ecosystem to develop these models in a standardised manner that make code and the workflows easily shareable and re-usable with easy access to High-Performance Computing (HPC) via the FENIX infrastructure. The complete workflow is accessible and executable in Jupyter Python Notebooks in the M21 Deliverable and provides a reusable template for researchers aiming to use EBRAINS infrastructure, services and data in their work.

2.2 Technical Specification

Showcase 1 makes use of the Jupyterlab interactive computing interface available in EBRAINS under lab.ebrains.eu. Concise clients and programmatic interfaces for the EBRAINS services and the Showcase components enable efficient usage for a broad range of users with basic computing and programming skills. The user interacts with the Knowledge Graph and the High-Performance Computing infrastructure with user-friendly programming interfaces. Figure 3 shows a detailed workflow diagram of Showcase 1.

The Showcase is connected with the EBRAINS human brain atlas via the software library siibra-python[1], which is based on the former prototype called 'brainscapes'. The library provides structured access to different parcellations and reference spaces of the human brain, combining the macroscopic scale in MNI and Freesurfer spaces with the microscopic scale of the BigBrain model. Modelling workflows have structured access to spatial properties of brain regions as well as regional data features from different modalities, including regional density measures from different histological experiments, custom sampling of high-resolution image data from the BigBrain model, and access to different forms of connectivity from imaging cohorts (for the use of the EBRAINS human brain atlas in personalised neuroscience see Jockwitz et al., 2021). In the present demonstrator, siibra is used to retrieve spatial maps of neurotransmitter receptor densities.

[1] https://github.com/FZJ-INM1-BDA/siibra-python

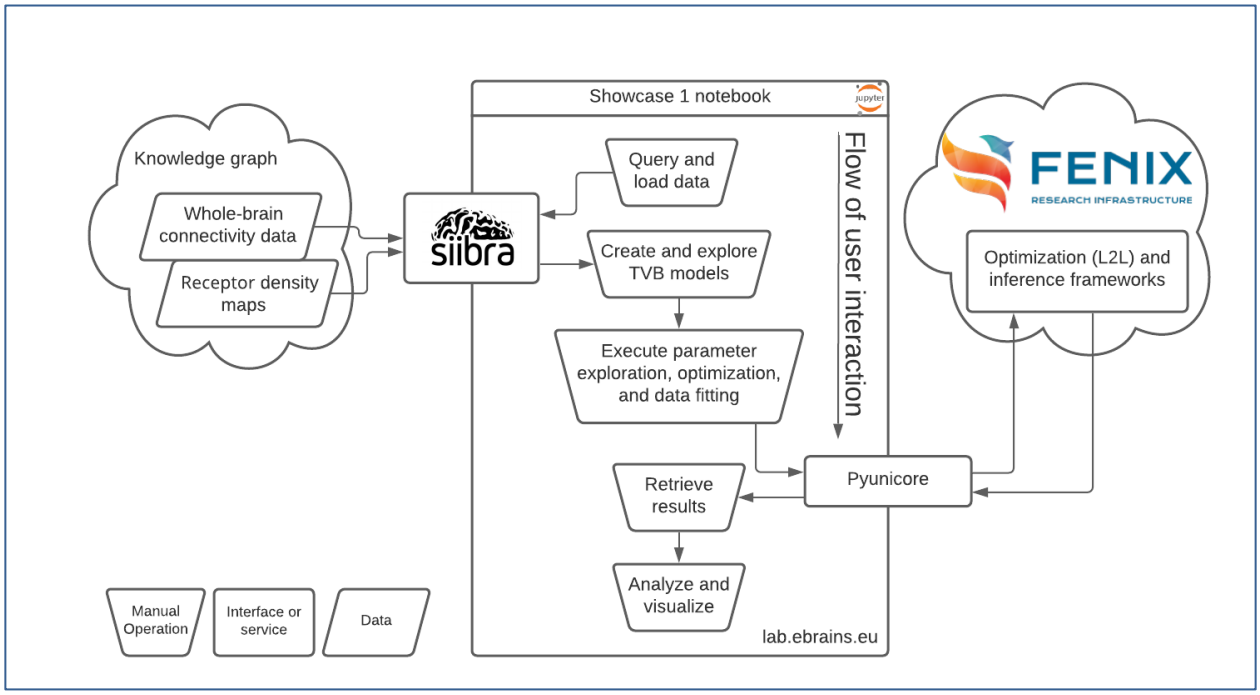

Figure 3: Showcase 1 workflow diagram

Showcase 1 addresses the structure-function link through variability across subjects (inter-subject variability parametrised by age) and across brain regions (intra-subject variability parametrised by neuroreceptor density). The study of inter-subject variability is built on the calculated connectivity data from the 1000BRAINS study[2] (Caspers et al., 2014) available in the Knowledge Graph as a dataset with protected access available to EBRAINS users. The access to protected datasets is provided in EBRAINS through the Human Data Gateway[3] (HDG) which allows full access once the user has validated the terms of use. In the implementation of the study on intra-subject variability, we are using the N=294 ROIs (Regions of Interest) parcellation, with the available receptor density datasets linked to the Julich-Brain cytoarchitectonic atlas (Amunts et al., 2020). Receptor density measurements are available for 33 brain regions at the time of writing, January 2022. For the remaining regions, their values were extrapolated to the nearest neighbour where the corresponding information is defined. In terms of connectivity data, we have used the connectivity matrices in the same parcellation as above from the Parcellation-based structural and resting-state functional brain connectomes of a healthy cohort[4] available in the Knowledge Graph as a public dataset. The connectivity datasets mentioned above are already accessible via the development version siibra-python at the time of writing, using recently developed support for the new Knowledge Graph API (v3) and Human Data Gateway API. Results of the empirical connectivity analyses are shown in Figure 4, where a decline in the inter-hemispheric white matter connections is shown in Figure 4A. In the functional data in Figure 4B, an important quantifier of brain flexibility is captured quantitatively by the variance of interhemispheric Functional Connectivity Dynamics (FCD), which declines with age. FCD is a metric capturing the temporal variation of Functional Connectivity, the latter of which is computed by the usual Pearson correlation. FCD represents intuitively a form of fluidity in the brain signals and has been found during SGA2 to be particularly informative for studies of intra- and inter-subject variability (Battaglia et al., 2020). FCD variations also capture subtle and task-specific variations of cognitive performance (Lombardo et al., 2020) and are linked to the perturbational complexity index in the WP2 Showcase 3.

The second major component of the Showcase is The Virtual Brain (TVB) simulation platform, originally developed outside of HBP (Sanz-Leon et al., 2013), but then heavily expanded during SGA1-SGA3 (Schirner et al., 2021). TVB is a simulation platform that uses empirical structural and functional data to build whole brain models of individual subjects. For convenient model

[2] https://search.kg.ebrains.eu/instances/Dataset/83407c06-b494-4307-861e-d06a5aecdf8a
[3] https://wiki.ebrains.eu/bin/view/Collabs/data-proxy/Human%20Data%20Gateway/
[4] https://search.kg.ebrains.eu/instances/Dataset/d61fc54a-7cc1-4126-93c0-9b6d97775421

construction, the system is based on a processing pipeline for structural, functional, and diffusion-weighted magnetic resonance imaging (MRI) data. The pipeline combines several state-of-the-art neuroinformatics tools to generate subject-specific cortical and subcortical parcellations, surface-tessellations, structural and functional connectomes, and region-wise aggregated blood oxygen level-dependent (BOLD) functional MRI (fMRI) time-series. The output files of the pipeline can be directly used as input for TVB to create and simulate individualised large-scale network models that incorporate intra- and inter-cortical interaction on the basis of cortical surface triangulations and white matter tractography. For regional variation, the simulation is based on a network of nodes that represent brain ROI, each running the BEI (Balanced Excitation-Inhibition) model, which defines two neuronal subpopulations, an excitatory and an inhibitory one, both interacting through neurochemical (e.g. AMPA, GABA, NMDA, etc.) currents. The objective is to demonstrate the precise mechanism through which regional neurotransmitter density affects the excitation-inhibition balance and expresses itself in the full brain network dynamics. Numerically, the goal is to minimise the difference in sliding window FCD (swFCD) between a reference empirical signal and a simulated one. The swFCD subdivides the time-series into successive windows and, for each one, computes its corresponding Functional Connectivity, resulting in a series of NxN matrices. Two swFCD can be compared by means of the Kolmogorov-Smirnov statistics.

The third component establishes the distributed execution of systematic parameter exploration and optimisation on the High-Performance Computing (HPC) infrastructure available in the FENIX RI[5]. The unified access to the federated infrastructure is enabled by the pyunicore[6] library providing a concise API to the common tasks such as compute job submission and management. Simplified interfaces for the jupyterlab environment are created for the user to run the parameter explorations. For the inter-subject variability, we have implemented a custom library for distributed simulations compatible with the controlled data access through the Human data Gateway. For the intra-subject variability, we make use of the “Learning to Learn” (L2L), which is a gradient-free optimisation framework that contains well-documented and tested implementations of various gradient-free optimisation algorithms. It also defines an API that makes it easy to optimise (hyper-) parameters for any task (through a construct called an “optimizee”). All the implementations in this package are parallel and can run across different cores and nodes (but equally well on a single core). The basic idea behind L2L is a multi-tiered optimisation process, in which an “outer loop” optimiser optimises the parameters of an “inner loop” optimizee. This framework is developed for the case where the cycle starts when the outer-loop optimiser generates an instance of a set of parameters and provides it to the inner-loop optimizee. Then, the inner-loop optimizee evaluates how well this set of parameters performs and returns a “fitness” vector for each parameter in the set of parameters. Lastly, the outer-loop optimiser generates a new set of parameters using the fitness vector it got back from the inner-loop optimizee. As a consequence, the outer-loop Optimiser works only with parameters and fitness values and doesn’t have access to the actual underlying model of the optimizee. The optimizee evaluates only the fitness of the given parameter. In our implementation, this fitness function is defined to minimise the distance between empirical and simulated BOLD signals through the swFCD observable, as described above. Once properly configured, L2L allows running the simulation for a “mean” subject signal built as an average of all individual subjects in the dataset, or for each such individual subject. This execution is distributed on top of the computing capabilities of the Jülich Supercomputing Centre, which allows computing in a matter of minutes which otherwise would take several days. In the current implementation, a systematic parameter sweep was used to guarantee accurately finding a global minimum of the parameters to fit. For the example of the 1000BRAINS cohort, optimising the virtual brain model for each subject for maximal fluidity, the same behaviour of FCD variation is found in simulations in Figure 4C as in the empirical data.

The fourth component integrates a Bayesian framework for inference of the full posterior values of the parameters. For this we have employed Simulation Based Inference (SBI; Gonçalves et al., 2020), in which a deep neural estimator is trained to provide a relationship between the parameters of a model (black box simulator) and selected descriptive statistics of the observed data. Neurotransmitter modulation is quantified by the working point G and is estimated independently

[5] https://fenix-ri.eu/infrastructure
[6] https://github.com/HumanBrainProject/pyunicore

using SBI. Individual fluidity increases with age for all subjects in the cohort (Figure 4D). As numerous repeated simulations are at the core of the training phase of SBI (sampling of the prior parameter distributions), the implementation can reuse the infrastructure for the systematic parameter sweeps on the HPC infrastructure. Specifically for inter-subject variability, an estimator was trained on 2,000 simulations per subject to independently retrieve the parameters linked to neuromodulation (in particular dopaminergic subsystems) hypothesised to provide compensation mechanisms in healthy aging. Virtual aging of a young individual brain is simulated by gradual degeneration of inter-hemispheric connectivity in Figure 4E. The inference of coupling strength G in Figure 4F independently validates the increase of G with age for each individual subject when maximising the fluidity in Figure 4D and E. The empirical fMRI time series data haven't been made publicly available yet at time of writing, and the procedure is thus demonstrated in the Jupyter notebooks on simulated data only.

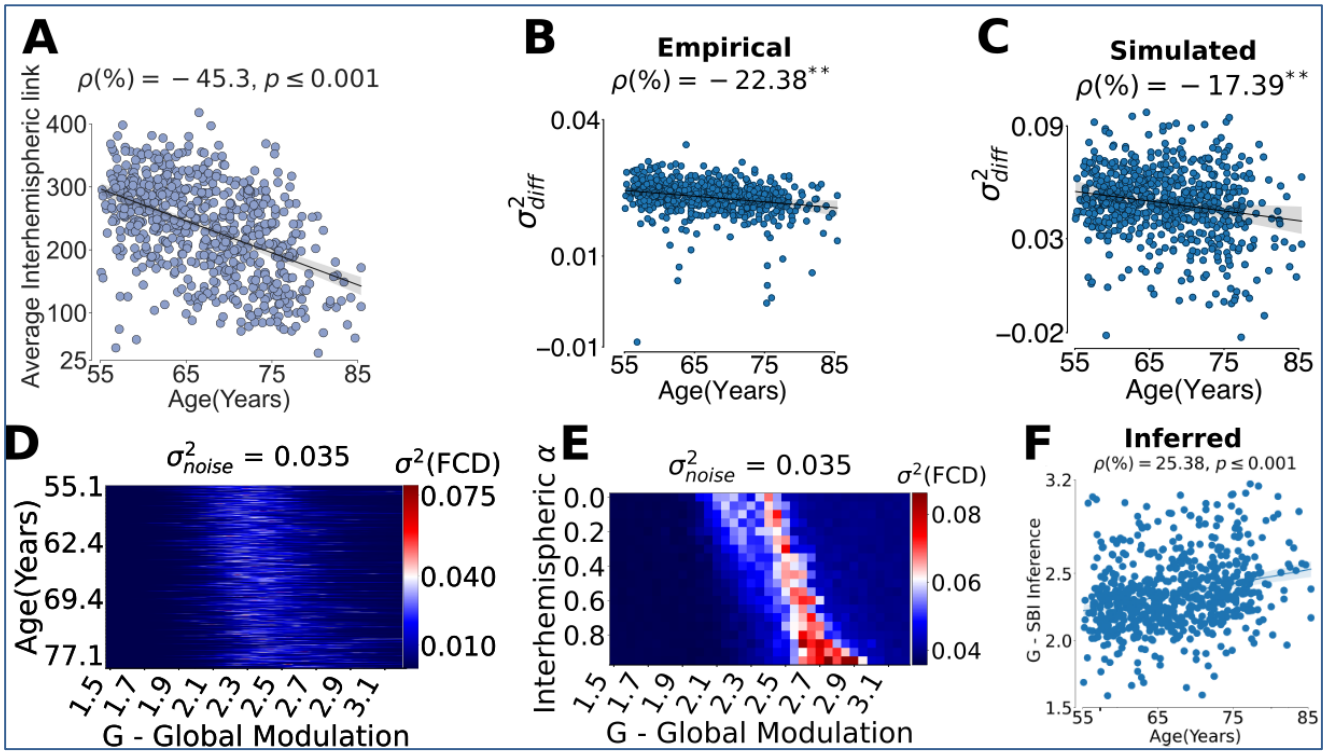

Figure 4: Inter-individual variability of structure and function in the empirical (1000BRAINS) and virtual ageing cohort

2.3 Progress from M9

The M9 Deliverable D1.1 (D7) was an early technical prototype in the development of Showcase 1, establishing the link between EBRAINS' multilevel human brain atlas and The Virtual Brain (TVB) simulator. It was the first use case for purely programmatic access to EBRAINS atlases, represented by the prototype release of a Python client for interacting with the multilevel human atlas, although with only partial functionality. There was no demonstrated scientific use of the M9 prototype.

The progress from M9 to M21 comprises

1) First demonstration of scientific use of the technical M9 prototype including data analyses and brain model building
2) Curated cohort data have been made available in EBRAINS
3) Extension of workflow to include model inversion (SBI, L2L)
4) Demonstration of proof of concept for identifiability of aging related mechanisms in cohort level data
5) Implementation of workflow to demonstrate increased predictive power of models with regional variability

6) Major rewrite of the brainscapes client into a better documented[7] library with more data features, broader functionality and higher technical readiness (siibra-python[8])
7) Implementation of interface for offloading computationally demanding parts of the workflow (parameter sweeps, parameter optimisation) from the interactive notebook to the HPC infrastructure through the pyunicore API[9]
8) Integration of direct access to the Knowledge Graph datasets both public[10] and protected by the Human Data Gateway[11]

2.4 How to access the Showcase

Showcase 1 is implemented as a series of interactive Jupyter notebooks covering the individual logical steps and can be accessed in a dedicated public EBRAINS Collab. The Collab can be found at:

https://wiki.ebrains.eu/bin/view/Collabs/sga3-d1-2-showcase-1

The EBRAINS Collab consists of interlinked *Drive*, *Bucket*, *Wiki*, and *Lab*. The Drive provides small file storage and contains the notebooks and all supporting code. The Bucket is a large file storage service and holds the pre-computed results of the extensive parameter sweeps and model optimisations to allow skipping the computationally demanding steps. The documentation of the Showcase implementation is collected in the Wiki. The Lab service is an instance of JupyterLab—an interactive computing environment where the notebooks can be run and worked with.

The notebooks in this Collab will load all required Python modules including siibra and The Virtual Brain, and the interfaces for launching the computationally demanding parts in the HPC infrastructure.

Running the notebooks requires an EBRAINS account with permissions to access the Lab and the Knowledge Graph API. In addition, to be able to interact with the HPC infrastructure, the user must have access to an active allocation on the corresponding FENIX site.

2.5 Looking Forward

In its current form, the advanced prototype in the M21 Deliverable of Showcase 1 already provides reusable and integrated EBRAINS components for the users in terms of data and atlassing services, whole-brain modelling and model inversion. In the following period, this integration will be further advanced with the focus on user experience. In addition, following activities are currently underway and will showcase their results in M42.

2.5.1 Data availability

With the cohort connectivity datasets being available, the development will focus on providing flexible access independent of the parcellation. For this, the 1000BRAINS dataset will serve as a point of entry, where the individual streamlines are already available in raw format in the Knowledge Graph. Access to these individual streamlines is already implemented in siibra-python, using the newly released EBRAINS Knowledge Graph (v3) and data proxy APIs. It will become available to users in January 2022, together with access to structural and functional connectivity matrices defined on EBRAINS parcellation maps for 200 individual subjects of the HCP cohort, thus providing a rich set of connectivity data that will be complemented by access to the high-resolution connectomes in 2022.

[7] https://siibra-python.readthedocs.io/en/latest/
[8] https://github.com/FZJ-INM1-BDA/siibra-python
[9] https://github.com/HumanBrainProject/pyunicore
[10] https://wiki.ebrains.eu/bin/view/Collabs/data-proxy/
[11] https://wiki.ebrains.eu/bin/view/Collabs/data-proxy/Human%20Data%20Gateway/

Furthermore, a new dataset of detailed layer-specific neuronal cell densities[12] in 12 cortical areas has been released as part of WP1. Exploiting a new functionality in siibra-python to sample layer-wise regional cortical image intensities from the BigBrain model, these precise measures can be used for a basic "calibration" of BigBrain's data values and thus allows to programmatically extract realistic brain-wide cell densities via siibra-python. During the first half of 2022, the results of WP1 will incrementally be made available providing high-resolution cross-modality data extracted from post-mortem brains. These include specific cell type maps (inhibitory interneurons), and connectivity obtained both from high field diffusion-weighted imaging and polarised light imaging (PLI). This dataset will be valuable in the detail provided in the individual modalities, but more importantly unique in the fact that these data are available for the same brain at once. The initial releases will be used to develop the workflows for incorporating this information in the construction of the models, with the ambition to make use of the final whole-brain coverage of the final release.

2.5.2 Model building

The next step in the evolution of the model is to include more high-resolution data, taking advantage of the richness of big data in EBRAINS, in addition to the currently employed receptor density maps. To demonstrate that the inclusion of multiscale data improves the predictive power (addressing the title question of Showcase 1 "When is Big Data big enough?"), the models will move from the parcellation-based brain network models to neural field models at high spatial resolution (translating the high-resolution technologies of WP1 Showcase 2 to applications outside of epilepsy), allowing for exploration of the added precision of both the various cortical gradients (e.g. cell-type specific densities), and high-resolution connectivity (PLI). Updated mean field models, suitable for principled incorporation of the cell-type specific regional variance (already integrated in TVB, see WP2 Showcase 3), will be integrated as part of WP1. Model performance will be benchmarked and assessed for simulated virtual cohort data and empirical cohort data (1000BRAINS, HCP).

2.5.3 Model inversion

Model inversion technology using dynamic causal modelling, Hamiltonian Monte Carlo (HMC), and Simulation Based Inference (SBI) will be integrated in the workflow of Showcase 1 and made available in EBRAINS. The algorithms will be applied to the use case data of ageing trajectories, adapted for regional variance and applied in cohort level validation. The model inversion technologies will be benchmarked on normative data sets (simulated, empirical 1000BRAINS, HCP).

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3. Showcase 2: Improving epilepsy surgery with the Virtual Big Brain, Demo 2

3.1 Introduction

Showcase 2 builds on a success story which started in the HBP's earlier SGA1 and SGA2 phases: the virtual brain epilepsy modelling and the associated clinical trial EPINOV (2019-2023), which aims at the confirmation of the modelling in 400 prospective epilepsy surgery patients.

Worldwide, there are about 50 million people suffering from epilepsy, of which a third are medically refractory. In those patients, medication does not provide relief and the surgical removal of the epileptogenic zone (EZ) remains the principal alternative treatment option. The success of this intervention is based on correctly identifying the EZ within the brain network. Current surgery success rates are about 60-70% but reaching as low as 25% in extratemporal epilepsies. Previous modelling efforts during SGA1 and SGA2 have demonstrated an improved capacity identifying the EZ through personalised brain network modelling in a cohort of 50 retrospective patients. So far, the personalisation of epilepsy patients' brain models has been limited to the use of individual connectomes and SEEG data, maintaining an otherwise fully generic and regionally invariant network. The present Showcase has two aims: firstly, to demonstrate that the integration of high-resolution atlas data in personalised brain models results in significant improvement of the models' predictive power; and secondly, to expand the use of virtual brain technology in epilepsy to other interventions such as neurostimulation, which has technically not been usable with the current resolutions in The Virtual Brain (TVB), but will become accessible with high-resolution TVB. As only about 20% of all patients initially considered as candidates for epilepsy surgery finally undergo this procedure, neurostimulation is an important alternative. Showcase 2 illustrates the application of high-resolution TVB to epilepsy, crucially requiring the integration of a large number of EBRAINS services. Its successful application will lead to an improved epilepsy patient management and novel technologies in personalised medicine.

The current demonstrator for the Showcase 2 constitutes an uninterrupted workflow implemented in EBRAINS, starting with construction of the high-resolution neural field model, generation of synthetic high-resolution data and applying the state-of-the-art parameter inference techniques from the Bayesian Virtual Epileptic Patient framework. The neural field model is constructed in a parcellation-free manner with detailed vertex-to-vertex connectivity, which is constructed in two variants: using the connectivity derived from the high-field MRI dataset of a post-mortem brain of

the Chenonceau project, and connectivity derived from a clinical-grade 3T MRI. This parallel evaluation is aligned with the aim of the Showcase to fuse the high-resolution Big Brain with the patient-specific data. The model is then configured with a realistic epileptogenic zone profile and used to generate synthetic SEEG data. The synthetic data are then passed as input in the inference pipeline, which produces an estimate of the epileptic zone.

Showcase 2 now also integrates co-simulation technology developed during SGA3 and demonstrates co-simulation of the human hippocampus at cellular resolution and the rest of the brain network at mm-resolution scale. Here, the hippocampus is the region of interest and is equipped with spiking neuron models implemented in NEST while connected to the high-resolution neural field model implemented in TVB. Construction of such a model allows to address questions of ictogenesis, addressable only at the cellular scale, and draws upon the unique data available within EBRAINS such as the neural cell densities of the Big Brain or the high-resolution connectivity.

The current demonstrator Demo 2 of Showcase 2 is an important stepping stone towards development of the fusion of the high-resolution and patient-specific connectivity data in the inference loop with direct translational potential for the clinic.

3.2 Technical Specification

Demo 2 for Showcase 2 constitutes an uninterrupted workflow for the construction of an individual high-resolution virtual epileptic brain model. It comprises all steps for the construction of the high-resolution neural field model using fusion of in-vivo and ex-vivo data, simulation of synthetic SEEG data and model inversion for estimating the patient-specific epileptogenic zone. Figure 5 shows the detailed workflow diagram of Showcase 2.

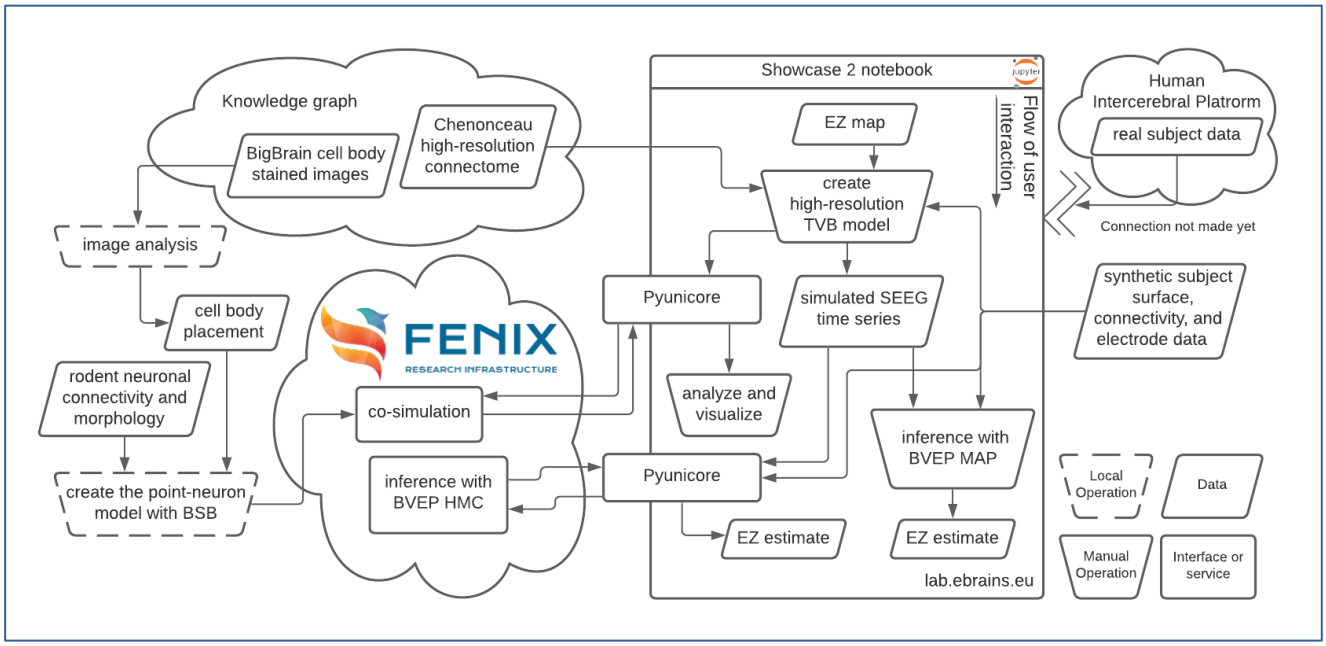

Figure 5: Showcase 2 workflow diagram

3.2.1 The Virtual Big Brain

Showcase 2 demonstrates the construction and simulation of the Virtual Big Brain, a high-resolution model for simulation of brain dynamics. The high level of resolution is achieved through (1) the use of neural fields instead of neural masses and (2) a high-resolution connectome connecting points of the neural fields instead of regions in a brain atlas. We make use of high-resolution post-mortem MRI data from the Chenonceau project, which estimates connections with greater accuracy.

Neural fields simulate neural activity across the continuous spatial extent of the cortical surface. To get the individual cortical surface of a subject, we process its T1-weighted MRI with the Freesurfer

software package (Dale et al., 1999). The cortical surface is resampled onto 3 levels of resolution, resulting in a triangular mesh with either 20,484, 81,924 or 327,684 vertices. On the template MNI152 brain, this results in an average vertex area of 10.6 mm2, 2.8 mm2 or 0.75 mm2, increasing the resolution by multiple orders of magnitude compared to a neural-mass-based simulation with about 100-200 network nodes, where a typical region is representing 16 cm2 of the cortex.

In this processing pipeline, the hippocampus is usually represented as a subcortical neural mass, when in reality it forms the extension of the neocortex and is connected to the parahippocampal and entorhinal cortex at the mesial temporal lobe (Duvernoy et al. 1988). Using the hippocampus subfield segmentation toolbox (Iglesias et al. 2015) of the Freesurfer package, we identify these structures in an individual T1-weighted MRI. The cortical surface is then modified to follow along the curvature of the subiculum and the cornu amonis. This allows the simulation of surface-based seizure propagation into and out of the hippocampus. As the subject-specific data cannot be made available at this time, we provide the cortical mesh of the MNI152 template brain.

A high-resolution connectome is constructed from diffusion-weighted imaging data. Instead of grouping connections between regions of the brain, we infer the connectivity on the level of vertex pairs. After preprocessing and streamline tractography, the Möller-Trumbore algorithm is used to search for intersections of reconstructed white matter fibres and the cortical mesh. Those two vertices, which are closest to each of the two intersections of the fibre, are assumed to be connected. This results in a sparse connectivity matrix with as many rows and columns as vertices of the mesh. The density of the connectivity matrix amounts to 0.98%, 0.13% and 0.01%, for each surface resolution level respectively. This high-resolution connectome is derived from seemingly low-resolution diffusion data with an isotropic voxel resolution of 2 mm. An average connectome of three example subjects is provided.

We make use of high-resolution diffusion data available from EBRAINS (currently under embargo[13]). The Chenonceau project scanned a post-mortem brain using high-field 11.7T MRI (Poupon et al., 2021). Multi-shell diffusion data were acquired at a resolution of 200 µm. We processed and co-registered the data to the MNI152 template. Streamline tractography was performed to obtain connectivity information between grey-matter voxels of the MNI152 template. Finally, the voxel level connectivity was mapped onto the vertices of the pial surface of the MNI152 brain, to be used for neural field simulations.

To simulate SEEG, we solve the electromagnetic forward problem using an analytical solution (Sarvas, 1987), where the electrical dipole location and orientation is given by the surface vertex normals and the SEEG sensor location is identified through co-registered CT scans. For the MNI brain and the Chenonceau data we use co-registered SEEG locations of a patient with hypothesised EZ location in the left temporal lobe and insula. This newly implemented forward solver for high-resolution brains will be used in the future application of brain stimulation.

For the simulation of seizure dynamics, we use the phenomenological epileptor (Jirsa et al., 2014), a model that has been developed and extended to model seizure propagation on neural fields (Proix et al., 2018) during SGA1 and SGA2. It is used in the virtual epileptic patient technology and the clinical trial EPINOV, describing seizure propagation in patient-specific neural mass network models. A dynamical system of five differential equations describes the evolution of the interictal period, ictal onset, propagation and offset, producing fast discharges, spike-wave patterns and travelling waves as observed in empirical electrophysiological recordings.

In Demo 2 we provide a Jupyter notebook for performing the simulations with the models constructed both from the synthetic subject and the Chenonceau brain, highlighting the differences in neural dynamics that are caused by increased spatial resolution, from neural masses to detailed neural fields, increased resolution of connectivity data and an improved SEEG signal due to a more realistic model of the hippocampus. The step from discrete neural masses to spatially continuous neural fields represents a qualitative step forward, as now novel pattern formation phenomena can be addressed, which was impossible before. As an example, slowly propagating ictal wave fronts may emerge with intense, continuous firing lasting a few seconds, which have been previously reported experimentally in recordings of brain slices and human multielectrode recordings (Smith et al., 2016). Figure 6

[13] https://search.kg.ebrains.eu/instances/1be7069f-fd40-4f15-b3b3-80904d95e360

illustrates the reconstruction and simulation. Shown are the surfaces and the patient-specific SEEG implantation scheme (A). For better visualisation the surface is inflated and projected onto a sphere (B). The neural field model is simulated with a highly excitable CA1 region, causing a seizure to develop with travelling wave propagation (C). The electromagnetic forward problem is solved, using the dipolar neural sources on the surface and the individual SEEG contact location, to project neural activity into SEEG time series (D).

In addition, the simulated data are then used in the Bayesian Virtual Epileptic Patient (BVEP; Hashemi et al., 2020) - a probabilistic framework designed to invert individualised neural mass whole-brain network models of epileptic seizures. We have benchmarked the performance of the current BVEP algorithm applied to the simulated SEEG data of the neural field model and estimated its reliability in identification of the epileptogenic zone. The performance turns out to be surprisingly good, given the error in the neuroelectric forward solution of the neural mass BVEP algorithm.

Currently both the neural field simulations and the inversion using BVEP can be executed in the EBRAINS Jupyterlab instances with increased memory (8GB), see Section 3.4 for more details.

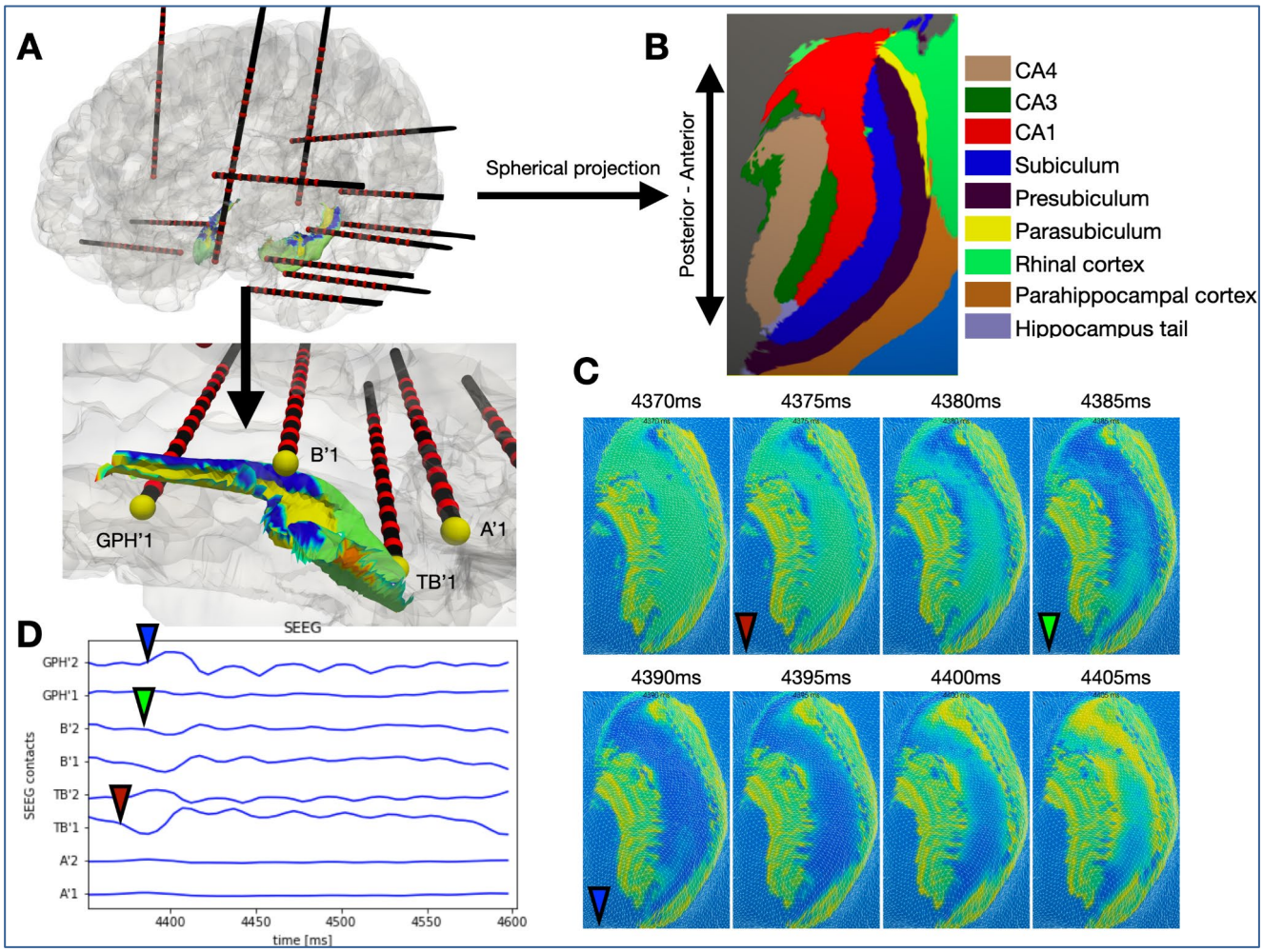

Figure 6: An epilepsy patient's virtual brain model with cortical and hippocampal high-resolution surfaces shows complex seizure propagation patterns in simulations

3.2.2 Co-simulation

For the simulation of cellular-level based regions of interest, Showcase 2 integrates co-simulation technology developed by WP1 and WP4 during SGA3. It links two EBRAINS simulators, TVB and NEST, and simulates the human CA1 hippocampus model at cellular resolution, while the remainder of the brain is represented by the high-resolution TVB model. This workflow exchanges data between TVB and NEST for each integration step using the Message Passing Interface (MPI) standard. Data exchange includes the instantaneous firing rate of the brain to each vertex of CA1 and the number

of spikes from each excitatory neuron of each vertex of CA1. The simulators are running in parallel because the exchange exists only between integration steps.

The interface for external input in TVB is done by a proxy pattern, i.e. some nodes in TVB are replaced by fake nodes, which in turn have internal variables replaced by values received from NEST and send the incoming input of the node to NEST. In contrast, the interface of NEST uses dedicated devices for the interface, specific for the stimulation and recording of neurons. In this use case, stimulating devices are inhomogeneous Poisson generators for each brain region and their vertices connected to CA1, and their instantaneous rate is changing depending on the input from TVB. The recording device is a spiking recorder, which transmits the number of spikes, detected during the integration step, to TVB.

TVB doesn't use MPI for its internal communication, thus a wrapper is used for the management of the communication and the translation of the data between coarse and neuron scales. The data are transformed via a linear function, which maps the coupling variable to instantaneous rates and vice versa. It is the simplest function for coupling phenomenological neural mass models and spiking neural networks.

The co-simulation of the hybrid network comprising cellular resolution CA1 and TVB-based network was performed for the paradigm of a stimulation-induced seizure using 6 nodes in CSCS in 6 hours for 10s of biological time. The usage of MPI standards permits using the same code to run a down-sampled simulation on a personal computer before running the full model on multiple nodes which can provide the hundred gigabytes of memory required by the full model.

The co-simulation results are shown in Figure 7. The BigBrain histological data are used to create a NEST neuronal model. Neurons are mapped to the vertices of the neural field model in TVB (A). Specific pathological hypotheses on the scale of micro-circuits and their impact on macroscale dynamics are modelled with TVB-NEST co-simulations (B). The construction validity of the NEST model is demonstrated by replicating previous experimental results, in which stimulation of the single transversal slice in the proximity of the CA3 side showed a strong activation directionality towards Subiculum (C).

3.2.3 Reconstruction of human CA1 hippocampus

The high-resolution human post-mortem brain images of the Big Brain dataset (Amunts et al., 2013[14]), available in EBRAINS, were used for the reconstruction of the human CA1 hippocampal subregion. The 3D images, stained for cell bodies, were annotated for the identification of CA1 Oriens and Pyramidalis layers. An automatic cell-body-placement analysis based on grayscale image thresholding was adopted to obtain a realistic cell density distribution. The image analysis procedure returned 14 million putative cells (including glial cells and astrocytes) that we randomly subdivided into 4.8 million pyramidal cells and 480k interneurons (ratio of 10% between inhibitory and excitatory population). The CA1 human network connectivity was computed starting from the realistic morpho-anatomical connection strategy adopted for the point-neuron modelling of the mouse CA1 hippocampal subregion (see below). Missing data on human neuronal morphologies have been adapted from comparative studies on rodents and the CA1 human network connectivity yielded ~ 30 billions of connected pairs (cfr ~ 100M pairs in mouse distributed on a population of ~ 300k neurons). The simulation of the human CA1 microcircuit relies heavily on high-performance computing resources and necessitates the use of EBRAINS.

[14] https://search.kg.ebrains.eu/instances/d07f9305-1e75-4548-a348-b155fb323d31

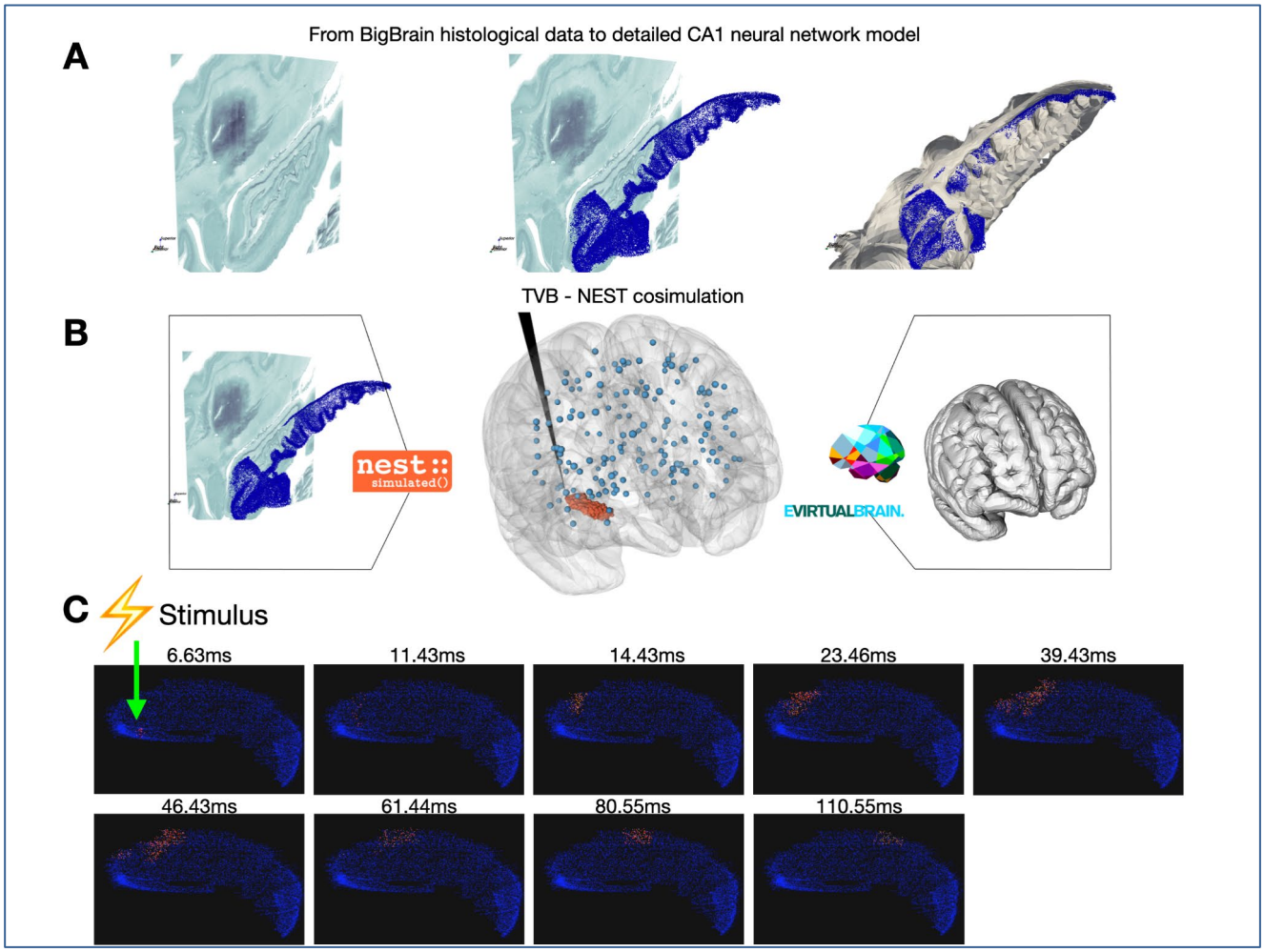

Figure 7: TVB-NEST co-simulation uses BigBrain histological data to create a NEST neuronal model embedded in a TVB-based full brain network

3.2.4 Morpho-anatomical connection strategy benchmarked for point neuron mouse CA1 hippocampus modelling

The mouse model workflow constitutes a fundamental benchmark preceding the human network simulation due to anatomical complexity (e.g. surface bending or sulci). The CA1 hippocampal subregion mouse model has been generated by employing the newly developed "Brain Scaffold Builder" tool (https://github.com/dbbs-lab/bsb), which is going to be integrated into EBRAINS. The model generation workflow was organised as follows:

Neuronal Placement: according to the Blue Brain Cell Atlas database (https://portal.bluebrain.epfl.ch/resources/models/cell-atlas/) neurons were positioned in the simulation volume respecting the 10% ratio between inhibitory and excitatory cells populations. Neurons were distributed among four layers (Oriens – SO; Pyramidalis – SP; Radiatum – SR; Lacunosum Moleculare – SLM) and were divided into 12 classes (1 excitatory and 11 inhibitory) according to their distribution among layers.

Neuronal morphologies: the geometrical probability volumes associated to pre-synaptic axons and post-synaptic dendrites were modelled as a combination of ellipsoids and cones respecting morpho-anatomical constraints obtained from the analysis of public databases and repositories (NeuroMorpho.Org http://neuromorpho.org/), Allen Brain Institute (https://portal.brain-map.org), Janelia Research Campus (http://mouselight.janelia.org/). In analogy with the formalism adopted by DTI tractography, the axonal probability volume was modelled as an ellipsoid, and it was parametrised as a covariance matrix where eigenvalues corresponded to the semiaxes lengths while eigenvectors corresponded to 3D orientations. Dendritic arborisations were parameterised as

ellipsoids or alternatively, as conical volumes. This parametric description allowed us to orient axonal and dendritic probability clouds along realistic anatomical landmarks.

Neuronal connectivity: the connectivity matrix has been derived by evaluating the intersection of presynaptic and postsynaptic volumes both for excitatory and inhibitory synapses. Putative connections were pruned to fit experimental data on pairwise connectivity (http://hippocampome.org/php/index.php). The cumulative indegree and outdegree distributions, namely the probability density of converging inputs or diverging outputs, were consistent with the expected experimental connectivity distribution shape.

NEST simulation: network activity was simulated in NEST through a variant of the "integrate and fire" neuron model developed by Hill and Tononi, accounting for both excitatory and inhibitory neurons coupled with "Tsodyks-Markram" synapses exploiting short-term dynamics which were specifically calibrated on pairs of connected cells (Ecker et al 2020).

Model validation: the construction validity of the model was assessed performing network activity simulation within single transversal slices following single pulse stimulation. According to the experimental results, the stimulation of the slice in the proximity of the CA3 side showed a strong activation directionality towards Subiculum. As it was also expected, the stimulation of the slice in the proximity of the Subiculum showed no backpropagation towards the CA3 region.

3.3 The progress from M9 to M21 comprises

1) First implementation of VEP technology as uninterrupted workflow using notebooks in EBRAINS
2) Extension of workflow to include model inversion (BVEP, using Maximum A Posteriori (MAP), same technology as used in clinical trial EPINOV), including first benchmarking against simulated data generated by high-resolution TVB
3) Implementation and demonstration of co-simulation
4) Integration of high-resolution post-mortem dMRI (Chenonceau project)
5) Continuous hippocampal extension of the neocortex connected to the parahippocampal and entorhinal cortex at the mesial temporal lobe
6) Implementation of electromagnetic forward solution adapted to spatially continuous neural fields

3.4 How to access the Showcase

The Showcase is implemented as a series of interactive Jupyter notebooks covering the individual logical steps and can be accessed in a dedicated public EBRAINS Collab. The Collab can be found at:

https://wiki.ebrains.eu/bin/view/Collabs/sga3-d1-2-showcase-2

The EBRAINS Collab consists of interlinked *Drive*, *Bucket*, *Wiki*, and *Lab*. The Drive provides small file storage and contains the notebooks and all supporting code. The Bucket is a large file storage service and holds some of the input data and the pre-computed results to allow skipping the computationally demanding steps. The documentation of the showcase implementation is collected in the Wiki. The Lab service is an instance of JupyterLab—an interactive computing environment where the notebooks can be run and worked with.

The notebooks in this Collab will load all required Python modules including Siibra and The Virtual Brain, and the interfaces for launching the computationally demanding parts in the HPC infrastructure.

Running the notebooks requires an EBRAINS account with permissions to access the Lab and the Knowledge Graph API. The memory required to run the notebooks exceeds the 2GB available in the default image, users can request access to the high memory profile with 8GB by sending an email to support@ebrains.eu. In addition, to be able to interact with the HPC infrastructure, the user must have access to an active allocation on the corresponding FENIX site.

3.5 Looking Forward

3.5.1 Model inversion

The current model inversion technologies cannot be applied to spatially continuous surfaces. Technical challenges include the application of Monte Carlo sampling techniques to neural fields and achieving convergence in finite time. In the next period, we will scale up inversion technologies to the high-resolution virtual brain for Bayesian Inference (Maximum A Posteriori (MAP)) and Simulation Based Inference (SBI). This is part of the validation efforts in WP1 and we expect a fully functional prototype with multiple inversion and validation methods available in EBRAINS for M42.

3.5.2 Data availability

WP1 will provide high-resolution cross-modality data extracted from post-mortem brains emphasising the human hippocampus as one of the priority areas. The cell-type-specific density measurements and the detailed PLI connectivity will be used in the construction of the Virtual Big Brain model, including the co-simulation. The Human Intracerebral EEG Platform (HIP) is planned to host subject data by the third quarter of 2022 in a GDPR-compliant manner. Subsequently, the workflow of Showcase 2 will be extended to the Human intracerebral EEG Platform (HIP) (see Figure 5). An initial iEEG data set of pseudonymised recordings will become directly accessible via siibra in early 2022 and will be incorporated in Showcase 2 resulting in a data set demonstrating the seizure onset estimation available to all registered EBRAINS users. The high-resolution connectivity of the Chenonceau dataset is already in data curation, but still under embargo at the time of writing. Once the embargo is lifted, support for this high-resolution connectivity will be added to the siibra atlas interface.

3.5.3 Data fusion

Proof of concept for the enhanced predictive power of informative priors has been provided in Demo 2 of Showcase 2. This study will be extended to clinically realistic scenarios using cross modal data and systematically benchmarked. Post-mortem brain data in EBRAINS will establish a high-resolution template and will be integrated with data from individual patients (connectome, sodium imaging, PET).

3.5.4 Brain Stimulation

The availability of personalised high-resolution virtual brains is a necessary condition for the development of alternative therapeutic interventions such as brain stimulation. Proper mapping of the electromagnetic forward solution from source to sensor data was not possible at low resolutions. In the remainder of SGA3, brain stimulation will be implemented in high-resolution TVB. First proof of concept will be demonstrated for the application of diagnostic brain stimulation in personalised brain models for epilepsy.

3.5.5 Hippocampus modelling

The proof-of-concept implementation of the TVB-NEST model has been provided for the CA1 region of the human hippocampus. Subsets of data have been adapted from comparative studies on rodents and the human. For the next period we will complete the data sets for the human hippocampus and perform a full reconstruction. Ictogenesis and ictal organisation will be studied for common temporal lobe epilepsies involving the hippocampus.

3.5.6 EBRAINS integration

The TVB-NEST co-simulation now runs in the HPC infrastructure of CSCS and is available to all users. For the next iteration of the demonstrator, we will work on streamlining the execution of the co-simulator and lowering the barrier of usage for users with lower level of technical skills. To be able to work with real subject data, we will move the relevant parts of the demonstrator to the HIP, which will allow secured processing of such data in full compliance with applicable regulations such as GDPR. Many components required for the demonstrator are already part of the current development version of HIP, such as the JupyterLab environment with pre-installed TVB and Siibra.

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