CDP8 Results SGA2 (D5.10.1 - SGA2)

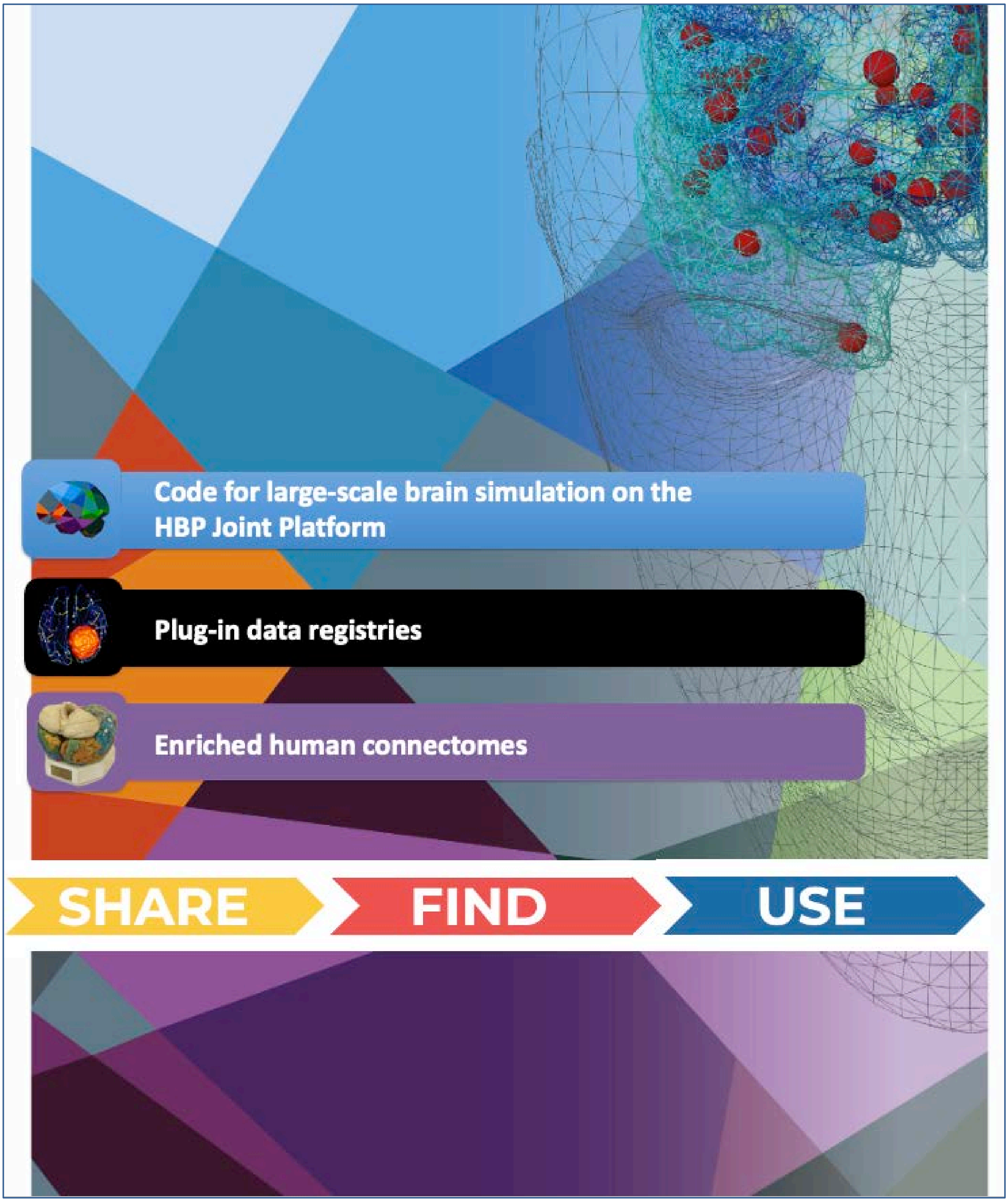

Figure 1: The Virtual Brain open source software has been made available on EBRAINS.

The Output of the CDP8 The Virtual Brain is software that bridges HBP's Brain Simulation Platform (SP6), Neuroinformatics Platform (SP5) and High-Performance Analytics and Computing Platform (SP7) https://ebrains.eu/services/simulation/virtual-brain.

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Description in GA:	For consistent presentation of HBP results, SGA2 M24 Deliverables describing the accomplishments of an entire SP, WP or CDP have been prepared according to a standard template, which focuses on Key Results and the outputs that contribute to them. Project management elements such as Milestones and Risks will be covered, as per normal practice, in the SGA2 Project Periodic Report.
Abstract:	Codesign Project 8 (CDP8) The Virtual Brain (TVB) reports three Key Results. With our first Key Result we provide a comprehensive software Suite for building and simulating personalised multi-scale models of the brain on EBRAINS. With our second Key Result we share simulation-ready data sets of patients and healthy human subjects on EBRAINS. These fully pre-processed multimodal (structural and functional) imaging data derivatives can be directly uploaded in The Virtual Brain to construct personalised brain models. Moreover, we provide didactic use cases comprising interactive jupyter notebooks, video tutorials, example data sets to facilitate the use of TVB and to assist in reproducing results of TVB-related publications. For the broader public, we have released a popular interactive brain atlas that is part of the HBP travelling exhibition, but can also be accessed as web application or downloaded as IOS App. With our third Key Result, we are presently finalising a digital anatomical atlas based on the von Economo and Koskinas Atlas. We are preparing the atlas as interactive web App and are linking it to TVB so that it can be used for heterogenous model parameterization.
Keywords:	The Virtual Brain, Multi-scale simulation, Enriched Connectome
Target Users/Readers:	Clinicians, scientists, general public, policymakers, students, industry

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1. Overview

For Codesign Project 8 (CDP8) The Virtual Brain (TVB), we report the development and deployment of a functional high-end software suite for personalised brain simulation.

With our first Key Result we provide a software suite for building and simulating personalised multi-scale models of the brain. The TVB suite is fully integrated in EBRAINS & HBP informatics environment. The Software can be operated via HBP's Collaboratory. It comprises pipelines for processing radiologic brain imaging data in BIDS format. Outputs contain meta data sets that are ready for Knowledge Graph ingestion along with the generated imaging data derivatives. Pipeline outputs can be uploaded to the TVB simulation framework. Thus, personalised models can be constructed on EBRAINS with processed data of the users' own uploaded patients or subjects' brain images.

With our second Key Result we share simulation-ready data sets of patients and healthy subjects on EBRAINS. These fully pre-processed multimodal (structural and functional) imaging data derivatives can be directly uploaded in TVB to construct personalised brain models. Data are discoverable via HBP's Knowledge Graph. Moreover, we provide didactic Use Cases comprising interactive jupyter notebooks, video tutorials, example data sets to facilitate the use of TVB and to assist in reproducing results of TVB-related publications. For the broader public we have released a popular interactive brain atlas. It is part of the HBP travelling exhibition, but can also be accessed as web application or downloaded as iOS App.

With our third Key Result, we are providing a digital anatomical atlas based on the von Economo and Koskinas Atlas. We are preparing the atlas as interactive web App using the same technology as for the popular TVB interactive brain atlas of the second Key Result. The atlas is interfaced with TVB so that it can be used for heterogenous and multi-scale model parameterisation.

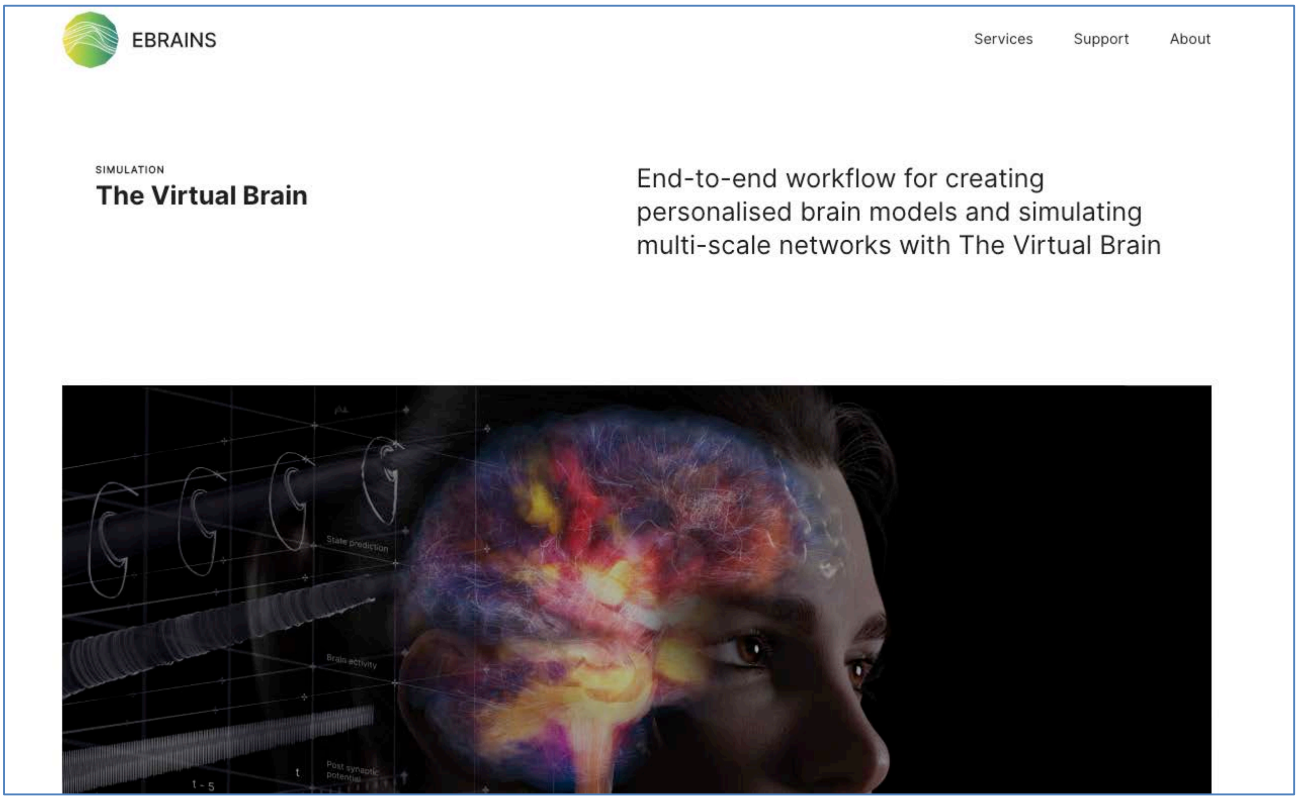

Figure 2: The Virtual Brain end-to-end workflow on EBRAINS.

The comprehensive Virtual Brain open source software tool suite delivers end-to-end workflows for creating personalised brain models. Simulations of multi-scale networks with The Virtual Brain is possible in the EBRAINS Cloud https://ebrains.eu/services/simulation/virtual-brain.

2. Introduction

In this report, we summarise the work performed by CDP8 during SGA2.

TVB uses neural masses and mean-field neural population models for efficient simulation of the entire brain. The main goal of the CDP was to develop and integrate the TVB software suite with existing infrastructure of HBP, i.e. HBP's Brain Simulation Platform, Neuroinformatics Platform and High-Performance Analytics and Computing Platform and with the back end of supercomputing resources. CDP8 produced three Key Results: KRc8.1: Code for large-scale brain simulation on the HBP Joint Platform; KRc8.2: Plug-in data registries; KRc8.3: Enriched human connectomes.

The HBP Collaboratory environment provides workspaces for HBP users where HBP software can be conveniently imported and executed. It also provides an interface for supercomputers based on the PyUnicore Api.

TVB has been added to the HBP's code-base to provide software for parallelised, high-performance, multi-scale brain simulation. The basis for brain simulation are structural models of large-scale brain networks. A major component of CDP8 is, therefore, to provide users with connectome extraction pipelines and pre-processed connectomes.

The TVB processing pipelines are being made available as BIDS Apps, that is workflows encapsulated in containers that read and output data in BIDS (Brain Imaging Data Structure) formats. The BIDS Apps are deployed on HBP's infrastructure. They generate structural connectomes, region-average fMRI time series and functional connectomes for simulation within TVB. The BIDS Apps generate meta data sets following HBP's MINDS standard that enable automated ingestion of newly generated data derivatives in HBP's data repositories and findability via HBP's Knowledge Graph.

In exhaustively documented Python notebooks we showcase users in a tutorial-style how data processing, personalised model construction and simulation can be realised step-by-step and provide further explanations on the usage of the involved software. Specifically, we make users acquainted with the usage of the HBP Collaboratory framework, e.g. how BIDS data sets can be uploaded to Collaboratory storage and from there imported into the jupyter client virtual filesystem; how datasets can be uploaded and downloaded from HBP supercomputers via PyUnicore and how PyUnicore can be used to create and execute batch job scripts on the supercomputer.

We provide users with preprocessed connectomes, along with educational aids to help users to get quickly acquainted with TVB tools. The TVB Brain Tumor data and code was the first complete and self-contained TVB study included in EBRAINS. The TVB software suite is presently being used in a clinical multi-centre trial in France to guide surgical planning in epilepsy.

Potential use of outputs comprises: biomarker development, surgical planning (e.g. tumour, epilepsy), therapy development, diagnosis, simulation of person-specific brain models to reveal inter-individual differences in brain dynamics, e.g. related to pathologies or behavioural features; personalised medicine — causal models that explain pathological brain dynamics on the basis of biophysical mechanisms in order to aid the creation of novel treatments for brain diseases; tractography results for surgical planning; simulation / unobservable parameter inference for personalised medicine.

The human brain atlas of von Economo and Koskinas (vEK), including its extensive quantitative descriptions of human cortical cytoarchitecture, has so far not been made available in an anatomically-verified, standard space. CDP8 defined a virtual 3D vEK model through 3D scanning two individual, well-preserved 3D plaster models of the vEK parcellation manufactured in the era of von Economo and scanning of the microphotographic plates from the atlas. The systematic quantitative macroscopic as well as microscopic anatomical descriptors, such as layer thickness, cell density and cell sizes found in the vEK are translated into the native vEK 3D brain space and subsequently interfaced to TVB, enabling users to explore a wide range of anatomically informed heterogeneous modelling parameters within the multi-scale co-simulation framework.

3. Key Result KRc8.1 Code for large-scale brain simulation of the HBP Joint Platform

3.1 Outputs

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to this KR

- Output 1: BSP-TVB Pipeline (C3046) - lead CHARITE (P122)
- Output 2: NIP-TVB Pipeline (C3047) - lead CHARITE (P122)
- Output 3: HPAC-TVB Pipeline (C3048) - lead CHARITE (P122)
- Output 4: Predictive Models based on Multi-scale biophysical TVB-derived parameters in NDD (C3061) - lead CHARITE (P122)
- Output 5: HPC-for-TVB software package (C3030) - lead JULICH (P20)

3.1.1.2 How Outputs relate to each other and the Key Result

Output 1 "BSP-TVB Pipeline" is a pipeline that links the Brain Simulation Platform (BSP) with TVB by providing a software to co-simulate TVB whole-brain models with BSP simulators handling spiking neurons and their connections to represent some of the brain regions at higher granularity. The basis for brain simulation with TVB are structural models of large-scale brain networks.

Output 2 "NIP-TVB Pipeline" links the Neuroinformatics platform (NIP) and TVB by providing users with connectome extraction pipelines that generate pre-processed connectomes from brain imaging data of patients or healthy subjects. The pipeline outputs are fully annotated obeying HBP's MINDS curation standards and hence can be automatically ingested by the Knowledge Graph.

With Output 3 "HPAC-TVB Pipeline" we provide a link between the High Performance Analytics and Computing platform (HPAC) and TVB by adding TVB's large-scale simulation facilities to the HBP's code-base in order to provide software for parallelised, high-performance, multi-scale brain simulation.

Output 4 "Predictive Models based on Multi-scale biophysical TVB-derived parameters in NDD" reflects the scientific outcome when using the Outputs 1, 2 and 3. It provides TVB enriched predictive models for neurodegenerative disease that resulted in publications and a clinical multi-centre trial.

3.1.2 Output 1: Brain Simulation Platform - TVB Pipeline (C3046)

This Output bridges TVB with existing more detailed simulators of HBP, specifically it provides a software solution for multi-scale brain simulation with TVB-NEST. In TVB-like whole-brain simulations a particular area in the brain is simulated at high-granularity, with a simulator handling spiking neurons and their connections (Figure 4). We have deployed and documented TVB software on HBP Collab. In addition, we have TVB-web app deployed in HBP OpenShift (Figure 3). We have a Keycloak client OIDC dedicated for TVB, which is used, thus Collaboratory.iam users can login into TVB web app. Currently, there is no HPC back end for TVB web app, all simulations are executed on that OpenShift deployment, but it can scale, in case the load is high, up to 10 pods now. We consider still that the scalability task can be improved, in case a high number of people will be using TVB there, but we will need a history of usage first, for doing this optimisation. From the technology itself, there are good chances to have an efficient and still simple deploy, without the HPC back end, but this is something yet to be benchmarked. We have in addition applied via ICEI for a TVB service account. With the service account in place, we will then have 2 TVB deployments at HBP.

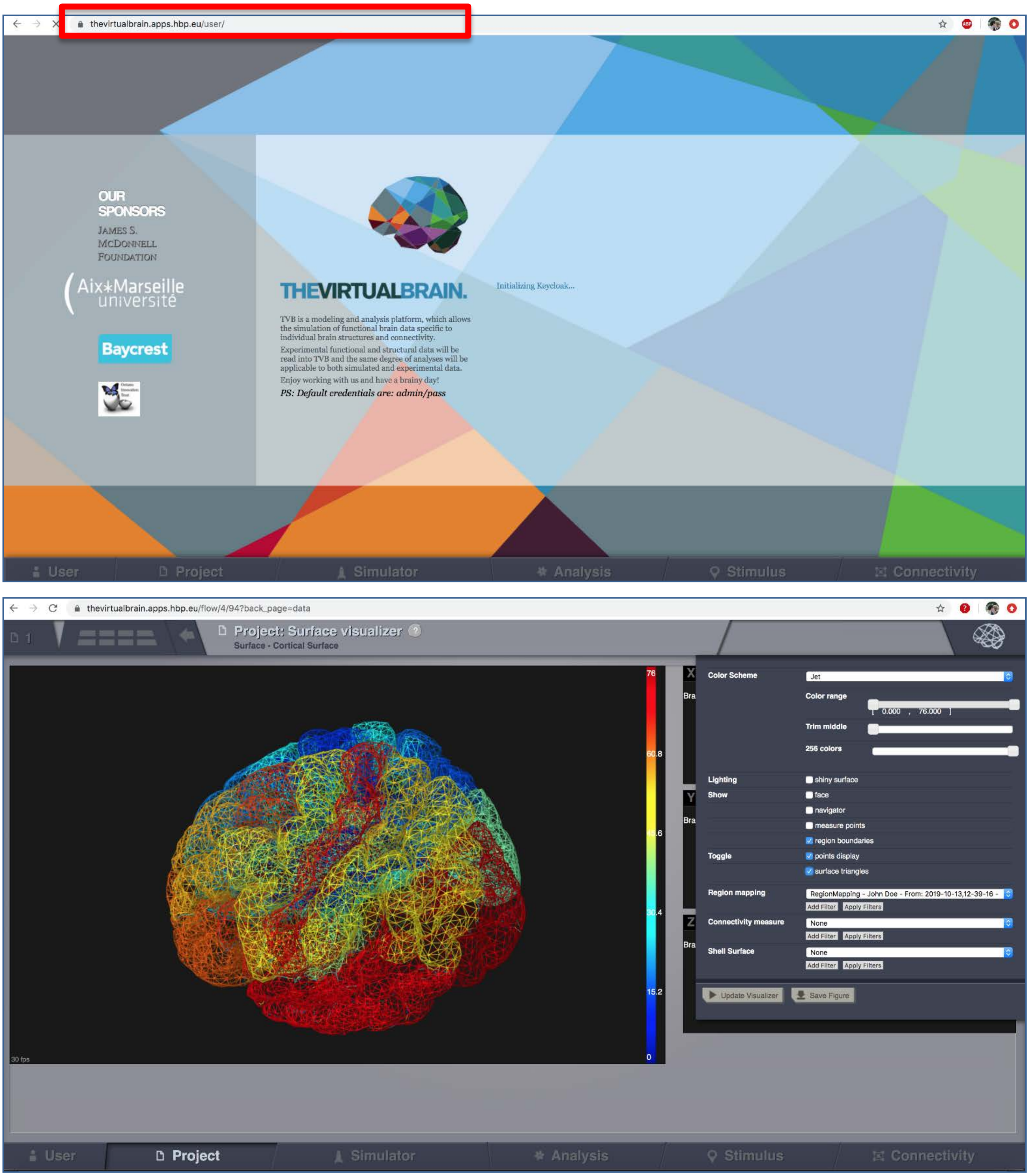

Figure 3: TVB GUI is accessible via HBP Collab and can be directly used in the Cloud.

Keycloak link ensures that Collaboratory.iam users can login. All simulations via TVB HBP web GUI are executed on the OpenShift pods. In case a high number of people will be using TVB GUI simultaneously, OpenShift will scale accordingly.

We link TVB with the Brain Simulation Platform (BSP) through multi-scale co-simulation with TVB-NEST.

C3046 has been released on 14 Jul 2019.

Since then we have provided few updates (API improvement, code review, optimisations, small bug fixes). It is the first functional public co-simulation software interfacing neuronal activity simulators of finer granularity with The Virtual Brain.

We have recently deployed TVB-NEST also on Docker Hub, and on a Jupyter Hub installation in HBP OpenShift env. These deployments allow us both to share easily the installation (Docker Hub), but also to demonstrate how it works immediately using the Jupyter ready to use and access deployment.

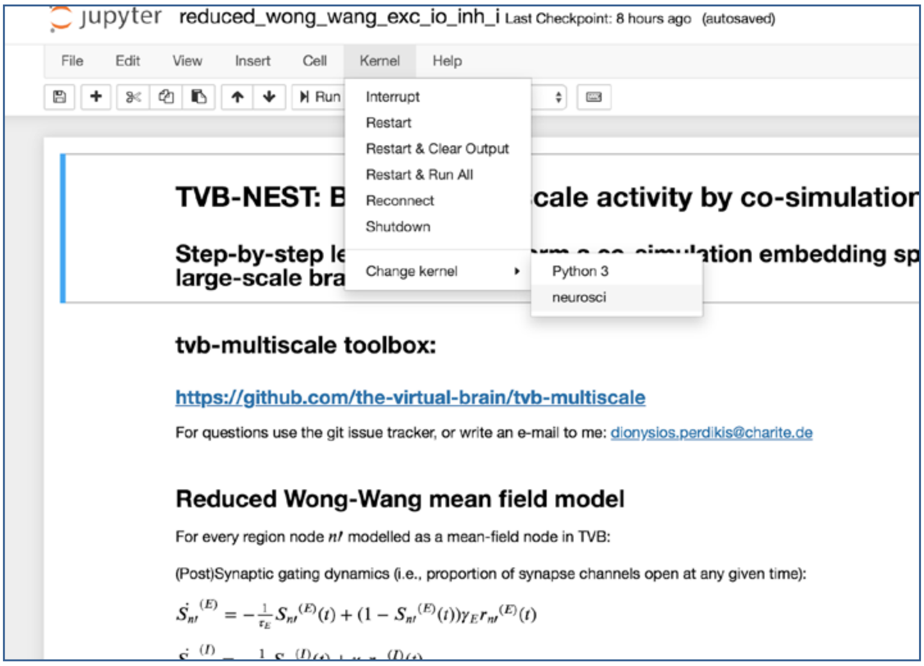

Figure 4: The Virtual Brain multi-scale co-simulation on EBRAINS

Keycloak client OIDC ensures that Collaboratory.iam users can login. Each user will get access to a public set of TVB-NEST examples, as well as access to a persisted user-personal folder, to store his own notebooks. You need to make sure the correct kernel (neurosci) is selected when you are to run TVB-NEST notebooks.

Table 1: Brain Simulation Platform - TVB Pipeline - Links

Component	Link to	URL
TVB C3046	Collab Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,The%20Virtual%20Brain
	Web-App	https://thevirtualbrain.apps.hbp.eu/
	Jupyter notebooks	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,The%20Virtual%20Brain
	Website	Thevirtualbrain.org
TVB-multi-scale C3046	Collab Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,TVB%20and%20NEST%202
	Docker	https://hub.docker.com/r/thevirtualbrain/tvb-nest)
	Jupyter notebook	https://collab.humanbrainproject.eu/#/collab/58136/nav/396819
	TVB-NEST App	https://tvb-nest.apps.hbp.eu/

3.1.3 Output 2: Neuroinformatics Platform - TVB Pipeline (C3047)

TVB brain model construction pipeline: A pipeline that takes structural, functional and diffusion-weighted MRI data and computes functional and structural connectomes (brain networks) that can be directly imported and used in The Virtual Brain Neuroinformatics Platform for brain simulation (Figure 5).

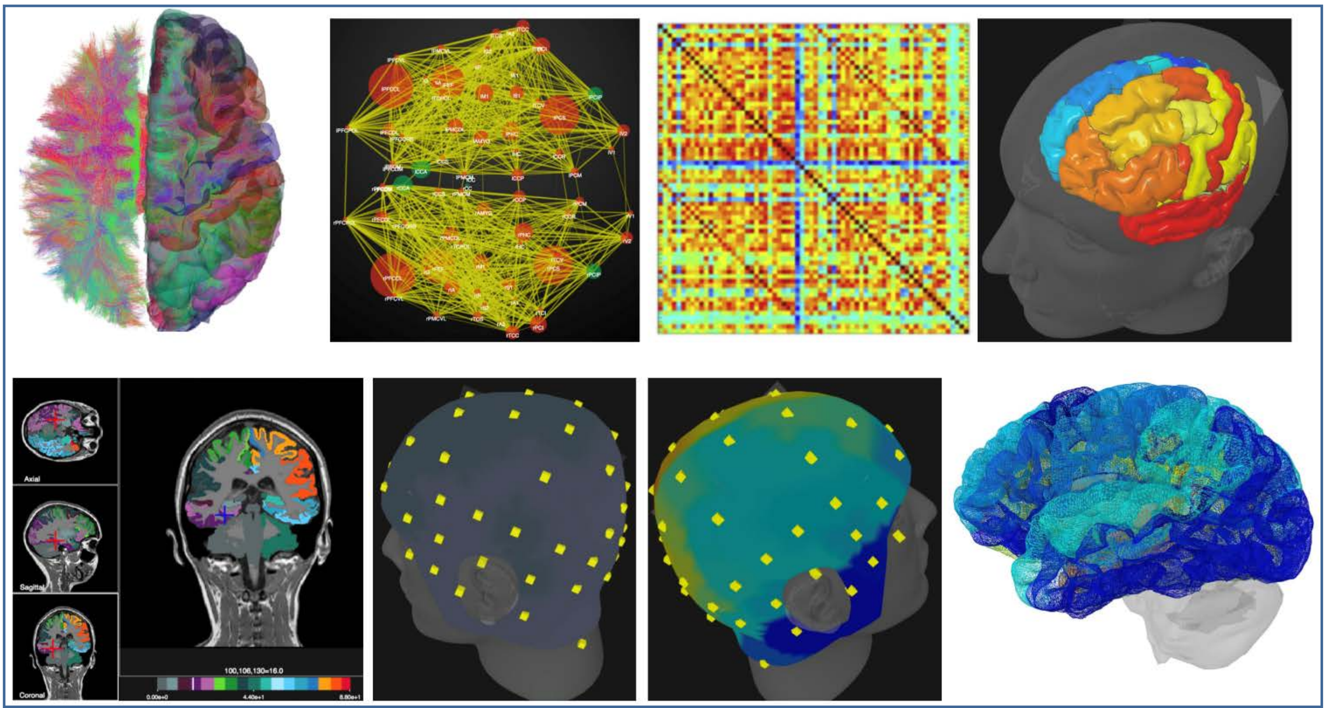

Figure 5: Some of the BIDS App outputs

Top row, from left to right: tractograms, structural connectomes, functional connectomes, region-average fMRI activity. Bottom row, from left to right: brain parcellations, M/EEG head and sensor models, source space / forward model, cortical surface triangulations.

The HBP Collab environment provides workspaces for HBP users where HBP software can be conveniently imported and executed. It also provides an interface for supercomputers based on the PyUnicore API. We used this framework to implement a pipeline that generates structural connectomes, region-average fMRI time series and functional connectomes for simulation within The Virtual Brain.

Furthermore, we extended the pipeline with a prototype script in which the pipeline users can enter MINDS format metadata that are relevant for integration with Knowledge Graph and stores them into a JSON data set (Figure 6). Following pipeline processing, users copy the MINDS metadata file together with pipeline output from Collab space into a designated secure area where the curation team can receive the data and metadata and automatic ingestion to Knowledge Graph may follow. The full pipeline is implemented as Docker container controlled by a Jupyter notebook from HBP Collabs.

Table 2: Neuroinformatics Platform -TVB Pipeline - Links

Component	Link to	URL
TVB Processing Pipeline	Collab Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,The%20Virtual%20Brain%20Neuroimaging%20Pipeline
	Docker	https://hub.docker.com/r/thevirtualbrain/tvb_converter

C3047	Jupyter notebooks	https://collab.humanbrainproject.eu/#/collab/57720/nav/456763

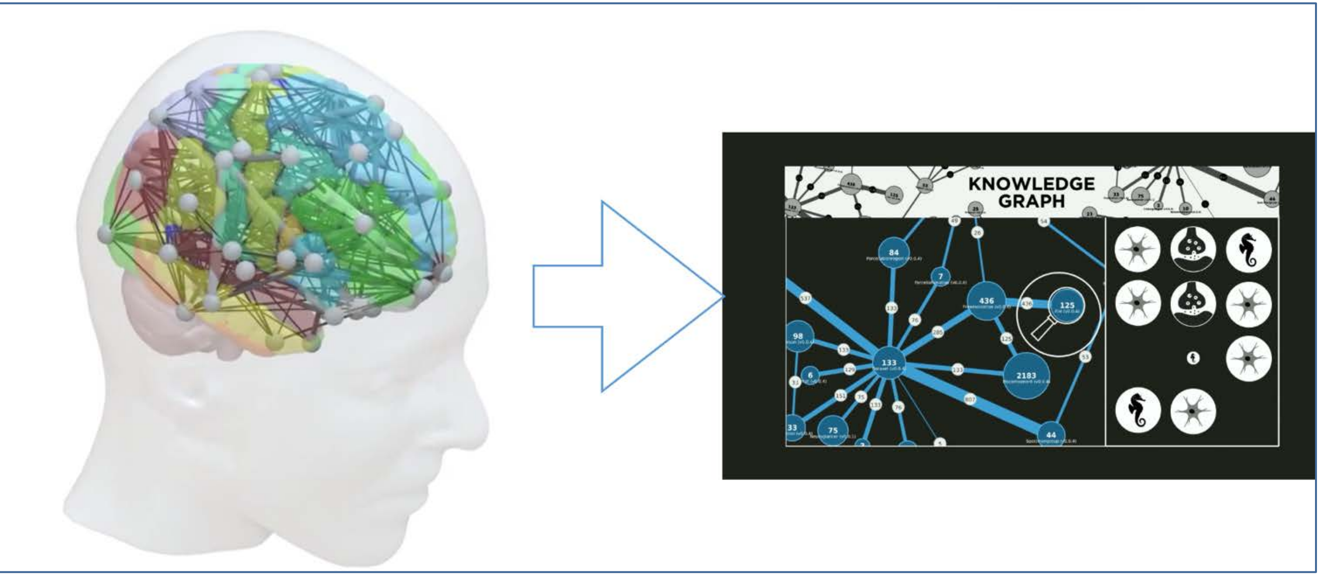

Figure 6: Pipeline outputs are fully annotated and can be directly ingested to Knowledge Graph

3.1.4 Output 3: High Performance Analytics and Computation Platform - TVB Pipeline (C3048)

The fast and parallel Virtual Brain: This version of the TVB simulator is written in C, making use of a variety of optimisation techniques that enable fast brain simulation. In addition to optimising sequential processing, we implemented thread-level parallelism, which exploits parallel chip architectures as we commonly find them on supercomputers and modern PCs.

Table 3: HPAC Platform - TVB Pipeline - Links

Component	Link to	URL
TVB Fast and Parallel C3048	Collab Documentation	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,fast_parallel_TVB
	Docker	https://hub.docker.com/r/thevirtualbrain/fast_tvb
	Jupyter notebooks	https://collab.humanbrainproject.eu/#/collab/57720/nav/456763
HPC-for-TVB C3048	Github	https://github.com/the-virtual-brain/tvb-hpc

3.1.5 Output 4: Predictive Models based on Multi-scale biophysical TVB-derived parameters in neurodegenerative disease / NDD (C3061)

Predictive Models based on Multi-scale biophysical TVB-derived parameters in NDD have been released and published (P1826).

In P1826 “Linking molecular pathways and large-scale computational modelling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer’s disease”, we demonstrate how TVB enables the simulation of systems effects caused by pathogenetic molecular candidate mechanisms in human virtual brains (Figure 7). Alteration of the molecular Amyloid-beta pathway in Alzheimer's disease (AD) causes hyperexcitation in the neural mass model. An altered pathway from soluble Amyloid-beta monomers to oligomers to insoluble plaques leads to potentially neurotoxic Amyloid-beta accumulation that can be quantified by positron emission tomography (PET). Region-specific Amyloid-beta burden from PET is linked to disinhibition in our neural mass model, thus building a bridge between molecular pathways and brain network modelling.

A didactic video tutorial, jupyter notebook and data set has been published on INCF training space.

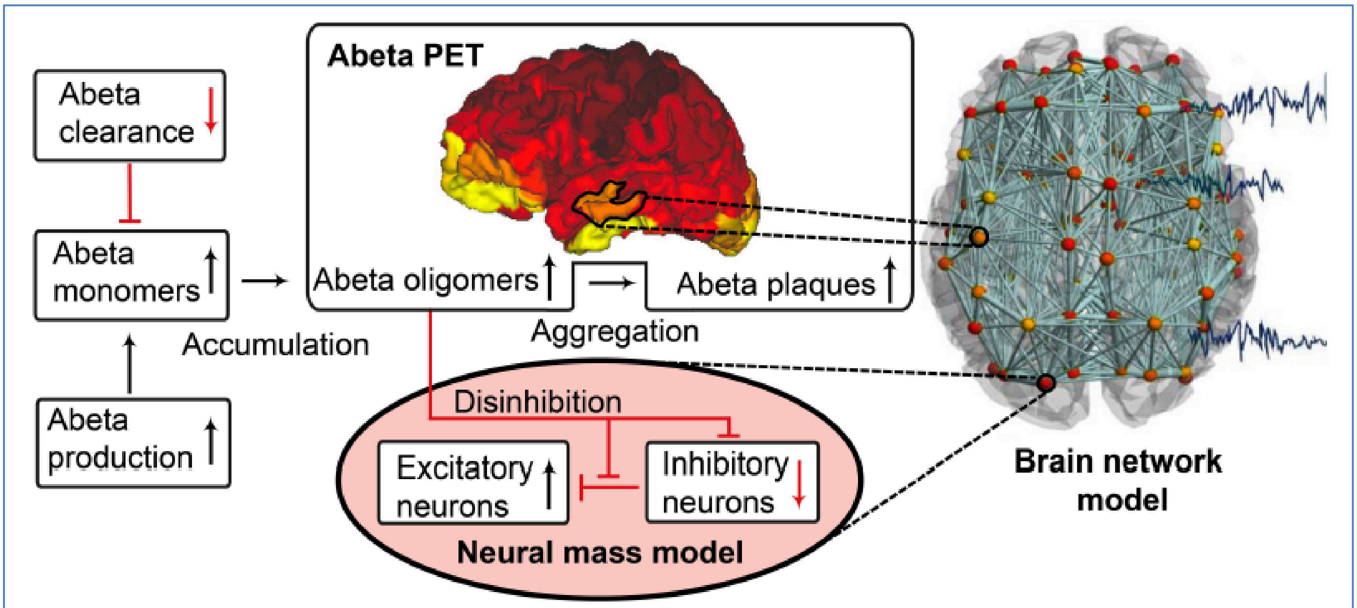

Figure 7: Biology inferred cause-and-effect model

Table 4: Predictive Models - Links

Component	Link to	URL
Predictive models C3061	Publication	https://www.frontiersin.org/articles/10.3389/fncom.2019.00054/full
	INCF Training Space Tutorial	https://training.incf.org/lesson/linking-molecular-pathways-and-large-scale-computational-modeling-assess-candidate-disease
	Jupyter notebooks	https://nbviewer.jupyter.org/github/BrainModes/TVB_EducaseAD_molecular_pathways_TVB/blob/master/Educase_AD_study-LS-Surrogate.ipynb
	Github code and data	https://github.com/BrainModes/TVB_EducaseAD_molecular_pathways_TVB

3.1.1 Output 5: HPC-for-TVB software package (C3030)

This software framework is implemented around a domain specific language (DSL) which can be used to describe TVB models and that can be processed to automatically generate Python code but also highly performant kernels optimised for available HPC back ends. The framework supports customisations to leverage simulation and parameter fitting pipelines in HPC environments.

The TVB DSL has been merged into the normal distribution of TVB to automatically produce python code compatible with the TVB simulation engine. The DSL is also available through the last release of the TVB-HPC code in the github repository of the project for the automatic generation of CUDA kernels to perform parameter fitting.

Table 5: HPC for TVB - Links

Component	Link to	URL
HPC for TVB C3030	Code	https://github.com/the-virtual-brain/tvb-hpc

3.2 Validation and Impact

3.2.1 Actual and Potential Use of Output(s)

As of April 2020, TVB was downloaded over 26,100 times. We suggest to continuously share access statistics for software and Collabs on EBRAINS with developers to receive useful feedback on usage. On 4 March we received the following analytics:

TVB Collab until 7.4.2020

- Page views: 1,180
- Unique page views: 722
- avg. time on page: 00:12:12
- Countries: Germany, Romania, Poland, France, Italy, Switzerland, UK, India, Greece, Canada, Norway, Ukraine

TVB-NEST Collab 1.7.2019-7.4.2020:

- Page views: 586
- Unique page views: 347
- avg. time on page: 00:17:11
- Countries: Germany, France, Switzerland, Romania, Greece, Italy

TVB-Pipeline Collab 7.4.2019-3.3.2020:

- Page views: 414
- Unique page views: 235
- avg. time on page: 00:36:12
- Countries: Germany, Switzerland, Romania, Greece, Italy, Brazil, Poland, Norway

TVB-fast_and_parallel Collab 1.9.2019-7.4.2020:

- Page views: 66
- Unique page views: 41
- avg. time on page: 00:30:05
- Countries: Germany, France, Switzerland

Dockerhub (https://hub.docker.com/u/thevirtualbrain) publishes the number of downloads of the containers. Download numbers by April 15, 2020:

- TVB-NEST: 1,000
- TVB-Pipeline: 225

- Fast_TVB: 25
- TVB-run: 1.9K

The pipeline is currently used to generate brain models from 10,000 subjects from the UK Biobank, which will be used to simulate person-specific activity in order to derive Biomarkers for neurological diseases.

Researchers who use TVB could in principle use standard brain models for simulation, but the more interesting applications lie in the simulation of person-specific brain models to reveal inter-individual differences in brain dynamics, e.g. related to pathologies or behavioural features. Personalised medicine has a high demand for causal models that explain pathological brain dynamics on the basis of biophysical mechanisms in order to aid the creation of novel treatments for brain diseases. However, brain model creation is a tedious process, typically involving several different software packages and the use of supercomputers. The core result of this Deliverable makes a neuroimaging pipeline accessible to researchers and general public that enables the construction of person-specific brain models on supercomputers in an accessible and reproducible way. Researchers working in biomarker development (e.g. Alzheimer's Disease), surgical planning (e.g. tumour, epilepsy), therapy development, diagnosis, etc. can benefit from high-quality brain models as those are only scarcely available today compared to the amount of existing neuroimaging data sets.

3.2.2 Publications

P1826 Linking molecular pathways and large-scale computational modelling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease (2019) Stefanovski, Triebkorn, Spiegler, Diaz-Cortes, Solodkin, Jirsa, McIntosh, Ritter & ADNI. Frontiers in Computational Neuroscience doi: 10.3389/fncom.2019.00054

This publication used software products developed by CDP8 during SGA2, that is multiscale simulation (Output 1) and TVB processing pipelines (Output 2).

4. Key Result KRc8.2 Plug-in data registries

Provide the community with fully processed structural and functional connectomes from public data repositories. Develop interactive tutorials for multiscale brain simulation tools. Ensure that HBP data models are discoverable and accessible.

4.1 Outputs

4.1.1 Overview of Outputs

4.1.1.1 List of Outputs contributing to this KR

- Output 1: EduPack C3049 (lead UGENT).
- Output 2: MIP-TVB pipeline: TVB interfaced with MIP repositories C3062 (lead CHARITE)

4.1.1.2 How Outputs relate to each other and the Key Result

CDP8 provides users not only with connectome extraction pipelines but also with preprocessed connectomes extracted from data repositories, along with educational aids to help users to get quickly acquainted with TVB tools and the data (Output 1). We provide the full toolset for personalised brain modelling of patient brains – entirely available via HBP Collab and fully operable on HBP computing resources. With Output 2 we demonstrate how the usage of this infrastructure leads to novel insights how alterations due to brain disease lead to changes in large-scale brain activity and cognitive function. In Output 2 we have demonstrated how (and what) features can extracted from TVB for sharing and further processing thus contributing to Task T8.3.5 'Data sharing between SP8 and other SPs'.

4.1.2 Output 1: EduPack

Educational software tutorials enable users to quickly learn and efficiently use the components developed within CDP8. Dedicated TheVirtualBrain INCF Training Space

Tutorials explain TVB software usage by providing didactic video tutorials, jupyter notebooks, data sets and TVB workshop recordings. They address both novices to TVB and advanced users. Some of the tutorials are dedicated to explaining how to use TVB tools on EBRAINS. Others demonstrate how the results of publications using TVB can be reproduced. EduCases include the usage of pipelines for extracting primate neuroimaging data for personalised brain model construction of typical and atypical brains (i.e. that contain structural abnormalities, such as brain tumours).

Fully processed brain tumour data set of N=36 individuals (11 glioma patients, 14 meningioma patients, and 11 healthy controls) in BIDS format and ready for constraining The Virtual Brain is available on EBRAINS to make data broadly accessible and discoverable via the HBP Knowledge Graph.

Examples of TVB tutorials on INCF Training Space dedicated to HBP:

1) Human Brain Project (HBP) image processing pipeline for The Virtual Brain
2) Human Brain Project (HBP) TVB-NEST co-simulation
3) TVB-NEST co-simulation on local computer
4) Linking molecular pathways and large-scale computational modelling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease
5) An automated pipeline for constructing personalized virtual brains from multimodal neuroimaging data
6) Inferring multi-scale neural mechanisms with brain network modelling
7) Modeling Brain Dynamics in Stroke Patients Using the Virtual Brain
8) Modeling brain dynamics in brain tumor patients using The Virtual Brain

Uk Biobank: A proposal under lead of CHARITE with ten HBP partner institutions as co-applicants has been approved by Uk Biobank. All involved institutions have signed MTAs with Uk Biobank. Following the request by HBP DPO (Data Protection Officer), end to end encryption of personal data transferred to CSCS (via ICEI) has been enabled. Data have been downloaded to PizDaint at the CSCS. Thus, all preconditions are fulfilled to process Uk Biobank data within the HBP.

Brain atlas viewer: Interactive The-Virtual-Brain Atlas can be accessed as Web App. Users can flip, rotate, and click around this online 3D model to learn about the different regions of the brain and their functions. A MacOS App (beta version) is available for download as well.

Table 6: TVB EduPack & Interactive Atlas Viewer - Links

Component	Link to	URL
EduPack C3049	TVB ready data	https://kg.ebrains.eu/search/instances/Dataset/a696ccc7-e742-4301-8b43-d6814f3e5a44
	Training Space	https://training.incf.org/studytrack/virtual-brain-simulation-platform
	Tutorial Pipeline	https://training.incf.org/lesson/human-brain-project-hbp-image-processing-pipeline-virtual-brain

	Tutorial TVB-NEST HBP	https://training.incf.org/lesson/human-brain-project-hbp-tvb-nest-co-simulation
	Tutorial TVB-NEST local	https://training.incf.org/lesson/tvb-nest-co-simulation-local-computer
	Tutorial Molecular Pathways	https://training.incf.org/lesson/linking-molecular-pathways-and-large-scale-computational-modeling-assess-candidate-disease
	Tutorial Multiscale	https://training.incf.org/lesson/inferring-multi-scale-neural-mechanisms-brain-network-modelling
	Tutorial pipeline	https://training.incf.org/lesson/human-brain-project-hbp-image-processing-pipeline-virtual-brain
	Tutorial Stroke	https://github.com/kclauw/tvb-educase-stroke/blob/master/TVB_stroke.ipynb
	Tutorial Tumor	https://training.incf.org/lesson/modeling-brain-dynamics-brain-tumor-patients-using-virtual-brain
Interactive Atlas Viewer C3049	Collab	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=software,TVBBrainAtlasViewer
	Web App	https://www.brainsimulation.org/atlasweb/
	MacOS App (beta)	https://testflight.apple.com/join/Y4OTc6V3

4.1.3 Output 2: TVB interfaced with MIP repositories

Researchers who use TVB could in principle use standard brain models for simulation, but the more interesting applications lie in the simulation of person-specific brain models to reveal inter-individual differences in brain dynamics, e.g. related to pathologies or behavioural features.

Personalised medicine has a high demand for causal models that explain pathological brain dynamics on the basis of biophysical mechanisms in order to aid the creation of novel treatments for brain diseases. However, brain model creation is a tedious process, typically involving several different software packages and the use of high performance computers.

The core result of this output makes a TVB Tool & Data Suite accessible on EBRAINS to researchers and general public that enables the construction of person-specific brain models and their simulation on HBP's supercomputers in an accessible and reproducible way. Researchers working in biomarker development (e.g. Alzheimer's Disease), surgical planning (e.g. tumour, epilepsy), therapy development, diagnosis, etc. can benefit from high-quality brain models as those are only scarcely available today compared to the amount of existing neuroimaging data sets. Integration with the Medical Informatics Platform (MIP) has been achieved by augmenting the data available for researchers for modelling.

The TVB Suite (Figure 8) comprises imaging processing pipelines that use the BIDS (Brain Imaging Data Structure) standard – so called BIDS Apps – and that generate annotated data for easy ingestion to Knowledge Graph. In addition, TVB Suite offers already pre-processed connectomes of patients and healthy controls. TVB Suite ranges from multiscale simulation software deployed on HBPs supercomputing back end to a large library of didactic jupyter notebooks and video tutorials hosted by the INCF training space. The resulting software product is ready to be used for medical research. Deliberately we decided to link TVB's medical data sets, software and workflows to the integrating 'joint platform' environment of HBP, i.e. the Collaboratory, EBRAINS, the supercomputing back end and Knowledge Graph. We seamlessly integrated our tools in this elaborated infrastructure environment that provides easy access to a broad user community and allows us to provide the large repertoire of services that is a) required for personalised multi-scale brain simulation and b) to attract a large user community. The 'Medical Informatics Platform (MIP)' was during SGA2 not integrated in this large scale HBP informatics environment, yet integration of the centralised part of it had been planned. TVB Suite as an entirely integrated part of EBRAINS, will be interoperable with the MIP the moment it onboards EBRAINS. The possibility to run TVB simulations will enable enriching features generated by MIP processing pipelines with additional features (e.g. hidden neuronal processes) inferred through personalised simulations.

A multi-centre clinical trial (400 patients with epilepsy) putting TVB to test for planning of surgical interventions in epilepsy is ongoing.

Figure 8: Overview of The Virtual Brain Tool Suite on EBRAINS

A flyer detailing all TVB tools and services is available on The Virtual Brain website and on the Brain Simulation Section @ CHARITE website for download:

Table 7: TVB Suite for Medical Brain Modeling - Links

Component	Link to	URL
TVB Medical Suite C3062	Collab	https://collab.humanbrainproject.eu/#/collab/19/nav/2108?state=search,partner:CHARITE
	TVB website	https://www.thevirtualbrain.org/tvb/zwei/newswire-blog/single/280568
	Flyer for download	https://www.brainsimulation.org/bsw/zwei/news/single/4587-virtual-brain-tools-on-ebrains
	Clinical trial	https://www.humanbrainproject.eu/en/follow-hbp/news/improving-epilepsy-care-hbp-researchers-involved-in-major-clinical-trial/

4.2 Validation and Impact

4.2.1 Actual and Potential Use of Output(s)

INCF TVB TrainingSpace stats a total of 547 views from unique visits:

1) TVB made easy: 152 views
2) TVB Edupack: 134 views
3) Bernstein Lectures: 133 views
4) TVB node 6: 109 views
5) TVB tutorials: 19 views

The top 5 countries viewing TVB content on TS are: 1) US 2) Germany 3) Sweden 4) Brazil 5) Canada. Noteworthy: US has the most users for TVB Made Easy ad EduPack, while Sweden has the most users for Bernstein Lectures and Node 6. Germany is consistent with the 2nd highest number of users for all 4 courses.

The web atlas version has led to unprecedented attention and positive resonance in HBP social media (https://twitter.com/HumanBrainProj/status/1184068811009544193; https://twitter.com/HumanBrainProj/status/1232583193557073941; https://twitter.com/HumanBrainProj/status/1232221470564212736).

The web atlas is part of HBP's traveling exhibition (Figure 9). It is available in 5 languages: English, Arabic, Hebrew, German, Polish. More languages are being added.

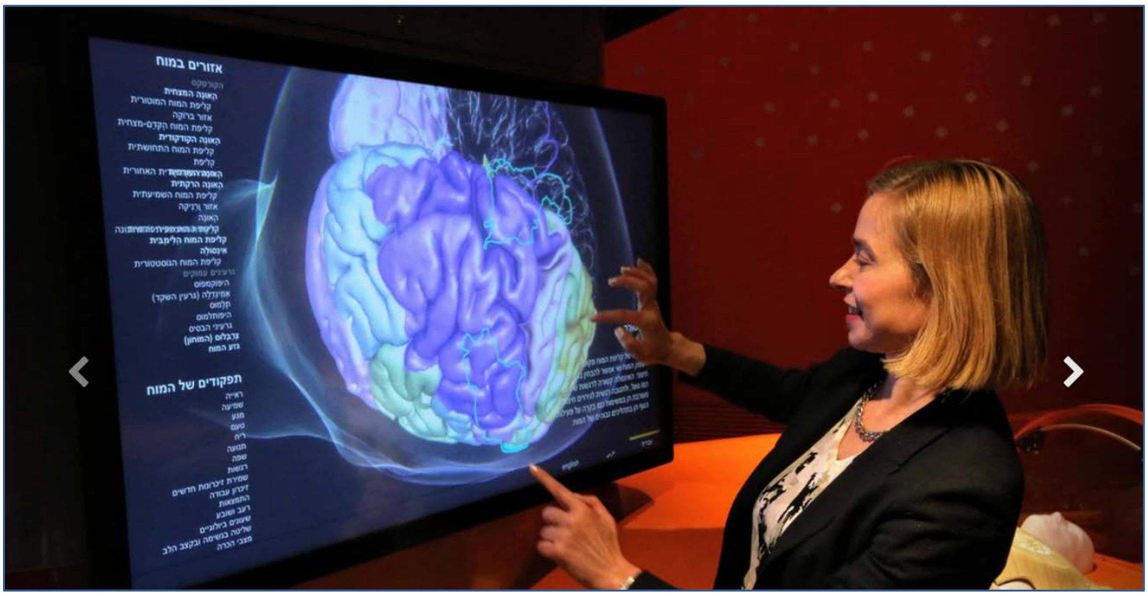

Figure 9: Educational Brain Atlas

Educational Brain Atlas, based on derivative data from the pipeline, is part of the HBP travelling exhibition in Jerusalem.

The Educational Brain Atlas, based on derivative data from the pipeline is part of the **HBP travelling exhibition in Jerusalem** and is now available on the HBP Collab platform.

TVB interactive web atlas user sessions by month:

- September 2019: 23
- October 2019: 2735
- November 2019: 1519
- December 2019: 521
- January 2020: 470
- February 2020: 1945
- March 2020: 1666

4.2.2 Publications

P2145 Aerts, H., Schirner, M., Dhollander, T., Jeurissen, B., Achten, E., Van Roost, D., Ritter,P., Marinazzo, D. (2019). Modeling brain dynamics after tumor resection using The Virtual Brain. doi:10.1101/752931

This publication relates to Output 1 and contains the follow-up of the publication in which we described the feasibility and potential of virtualisation of individual brain tumour patients' brains. Here the patients (and matched controls) are virtualised six months after surgery, and we explore the stability and modulations of model parameters, as well as exploring the potential of the "virtual surgery" performed by intervening on the structural connectivity pre-surgery. The data set related to this study is published on EBRAINS.

P2143 The importance of standards for sharing of computational models and data (2019) Poldrack, Feingold, Frank, Gleeson, de Hollander, Huys, Love, Markiewisc, Moran, Ritter, Turner, Yarkoni, Zhan, Cohen. Computational Brain & Behavior 2, 229-232

This article addresses the need for standards for data and computational models to facilitate reproduction of published results. This article relates to Output 1 – the generation of didactic resources for reproducing and re-using published results of personalised multi-scale brain simulations with TVB.

5. Key Result KRc8.3 Enriched human connectomes

5.1 Outputs

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

- C3024 Online version of von Economo and Koskinas atlas (lead UKE)
- C3025 Linked connectivity to architectonic data (lead UKE)
- C3026 Human connectome predictions (lead UKE)

5.1.1.2 How Outputs relate to each other and the Key Result

Output 1 creates a digitalised version of the von Economo plaster brain. Output 2 links fundamental aspects of macroscopic and microscopic cortical organisation and connectivity and includes the vEK atlas into The Virtual Brain simulator infrastructure. This offers the prospect of reliably mapping human cytoarchitectonic information and inferred principles of connectivity (Output 3) into common cortical parcellation schemes, enabling and advancing the enrichment of the human connectome and thus refining multiscale models of the human brain.

EBRAINS project card to which all three resulting dataset cards of KRc8.3 are linked:

5.1.2 Output 1: Online version of von Economo and Koskinas atlas

The human vEK atlas with its extensive quantitative descriptions of human cortical cytoarchitecture, has so far not been available in an anatomically-verified, standard space, embedded in a collaborative infrastructure. To overcome the limitations of existing implementations, we explicitly defined a virtual 3D vEK model independent of existing reference geometries, which became possible through 3D scanning two individual, well-preserved 3D plaster models of the vEK parcellation manufactured in the era of von Economo. Significant efforts have gone into reconstructing the 3D model (Figure 10). In addition, the vEK microphotographic plates have been digitalized. The original & enhanced microphotographic plates containing cytoarchitectonics of the adult human cerebral cortex and region border delineations have been made available as a data set on EBRAINS.

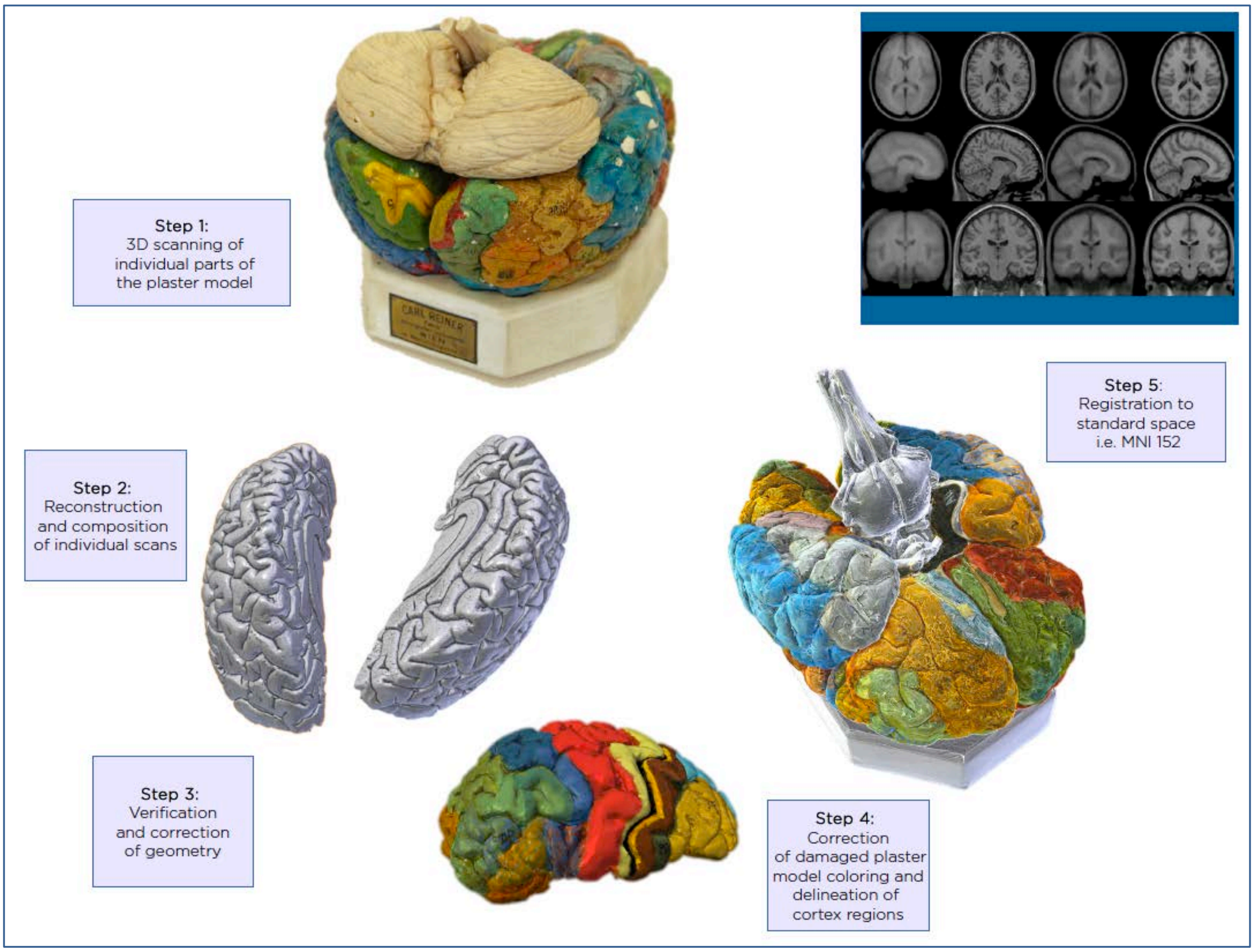

Figure 10: From plaster model to virtual 3D model

To circumvent previous limitations, we aim to explicitly define a virtual 3D von Economo and Koskinas model independent of existing reference geometries – this is made possible with the use of two individual, well-preserved copies of the 3D plaster model of the cortical parcellation manufactured in the 1920s for illustrative use in medical training.

Table 8: Online Version vEK Atlas - Links

Component	Link to	URL
Online vEK Atlas C3024	Documentation	https://kg.ebrains.eu/search/instances/Project/cf4b19be-725c-4047-a7ac-4f6f6bdb6b8f
	Data set	https://kg.ebrains.eu/search/instances/Dataset/1e1deaf9-52ef-4a26-a40f-c72138d51c3c

5.1.3 Output 2: Linked connectivity to architectonic data

For integration with TVB, we registered the vEK brain atlas to the brain standard coordinate system MNI (Montreal Neurological Institute). The Reconstructed & MNI registered reference geometry for cortical surface parcellation is stored in EBRAINS.

Table 9: MNI registered vEK Atlas - Links

Component	Link to	URL
MNI-registered vEK Atlas C3025	Data set	https://kg.ebrains.eu/search/instances/Dataset/08d9841d-1fcd-48a4-8599-454fc6306b24

5.1.4 Output 3: Human connectome predictions

Cytoarchitectonic descriptors are essential for linking fundamental aspects of macroscopic and microscopic cortical organisation and connectivity. The inclusion of the vEK atlas into the above open-source infrastructure offers the prospect of reliably mapping human cytoarchitectonic information into common cortical parcellation schemes, enabling and advancing the enrichment of the human connectome. Quantitative macroscopic as well as microscopic anatomical descriptors, such as layer thickness, cell density and cell sizes projected on the cortical parcellation have been made available as a data set on EBRANS. The implementation of the systematic quantitative macroscopic as well as microscopic anatomical descriptors, found in the vEK inside TVB, enable users to explore a wide range of modelling parameters within the multi-scale co-simulation framework. A dataset has been published on EBRAINS: Probabalistic von Economo and Koskinas Cytoarchitectonic Atlas of the human cortex.

The parcellations used in TVB are mainly Desikan, Destrieux and HCP (Glasser) parcellations. Currently supported reference spaces in HBP are MNI Colin 27 and MNI 152 ICBM 2009c. Parcellations from TVB pipelines (KRc8.1) are defined on the surface. These pipelines do not automatically generate segmentations in MNI volume space. To enable linking HBP atlases – including vEK - and TVB as well as data in EBRAINS in the supported reference spaces, we use parcellations that have been mapped to MNI space and converted to NifTi format, e.g. from the following sources:

- https://neurovault.org/images/23264/
- https://neurovault.org/images/23262/
- https://figshare.com/articles/HCP-MMP1_0_projected_on_MNI2009a_GM_volumetric_in_NIfTI_format/3501911.

Table 10: Probabalistic vEK Atlas - Links

Component	Link to	URL
Probabalistic vEK Atlas C3026	Data set	https://kg.ebrains.eu/search/instances/Dataset/1cb567c8-c7fa-4427-8094-04636935576f

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

This output directly contributes to TVB simulation software which has over 25,000 downloads. TVB is widely used by the Computational Neuroscience community, directly contributing toward numerous peer-reviewed publications. Within TVB, an interactive web-based atlas viewer was extended to feature the vEK parcellations of the cortex. Beyond the scope of simulations for clinical and scientific use-cases, the web-atlas feature in particular may be used for educational and show-case purposes - supporting the overall educational and outreach mission of EBRAINS.

5.2.2 Publications

P1958 An architectonic type principle integrates macroscopic cortico-cortical connections with intrinsic cortical circuits of the primate brain (2019) Hilgetag, Beul, van Albada, Goulas. Network Neuroscience https://doi.org/10.1162/netn_a_00100

The authors review an architectonic type principle that links cytoarchitectonic aspects of the cerebral cortex, such as neuron density or morphology across the cortical layers, to large-scale interregional cortical connection patterns. The reviewed findings highlight the existence of a natural axis of spatially ordered, concerted changes of multiple architectonic, connectional, and functional features stretching from less to more differentiated cortical areas. This framework comprises species-general, but also species-specific, principles of the organisation of the mammalian, and particularly the primate, cerebral cortex and highlights potential developmental underpinnings as well as functional ramifications of such principles (Output 3).

6. Conclusion and Outlook

In CDP8, we deployed a software suite of tools enabling personalised brain simulations on EBRAINS & HBP platforms. The suite includes, amongst several other tools, the processing pipelines that integrate with HBP's Knowledge Graph, a framework for multi-scale brain simulation that enables the co-simulation of spiking networks with NEST and large-scale networks with TVB and the interaction between the two. Another important aspect of this work is the HPAC-TVB pipeline where we implemented TVB's simulator engine as a high-performance, parallelised C code optimised for supercomputing architectures. Together, these three modules, i.e. 1) pipelines, 2) multi-scale simulator and 3) fast parallel TVB, comprise a powerful framework for brain simulation — from macroscopic to microscopic scales — based on person-specific large-scale brain architecture. This is complemented by an interfaced digital cytoarchitectonic atlas for a more biologically realistic and heterogenous parametrisation of the multi-scale brain models.

On top of this, we have made available high-quality plug-in data sets of patients and healthy controls that are fully processed and complying to BIDS standards - ready for brain simulation. These data are richly annotated and linked to comprehensive meta data. The combination of high-quality processed multimodal data and rich associated data makes the data sets potentially attractive for broad scientific exploitation.

In summary, during SGA2, CDP8 has developed and deployed on HBP infrastructure end-to-end workflows for personalised brain simulation. Thus, CDP8 has integrated the TVB software suite smoothly with the pre-existing infrastructure. While HBP computing infrastructure provides the necessary functionality for using the TVB suite – in turn TVB suite enriches HBP informatics infrastructure and provides compelling end-to end tool chains that demonstrate how EBRAINS can be utilised for multimodal data integration through multi-scale brain simulation. This new possibility serves to increase our understanding of how the brain works and it leverages the development of novel clinical tools.

Taken together, the Virtual Brain and its tools have been integrated with HBP's workbench Collaboratory, HBP's search engine Knowledge Graph, EBRAINS' data repositories and HBP's ICEI/FENIX supercomputing back end. Standardised data processing, annotation, integration through simulation and thus knowledge generation that can be translated to clinical application – all this has been achieved by CDP8 within the two years of SGA2. The further refinement of the multi-scale models through an 'enriched connectome' is ongoing.

In the next cycle of the HBP, in SGA3, the primary deliverables will be enabling infrastructure that can elevate scientific capacity for both HBP scientists and EU science in general.

HBP's goal is to enable and facilitate actual research, i.e. creating infrastructures users ask for. We suggest a measure that reflects what new knowledge was created – enabled through the new HBP infrastructure.

Therefore, a future project of CHARITE during SGA3 is a multiscale TVB brain model where we integrate several mechanisms: 1) A hippocampus that forms initial memories and consolidates these higher up the hierarchy using travelling waves; 2) a large-scale brain network that does predictive coding via ongoing synaptic plasticity and travelling waves; 3) a prefrontal-cortex (PFC) and lateral-intraparietal (LIP) circuit that is able to hold short term memory states and form decisions. For this model, we will then develop a task and give it data input. The goal is that the brain model internally generates a model of the world based on these inputs and on synaptic plasticity, consolidation, and travelling waves. Based on this world model, the brain model shall predict what the next input will be and adapt itself based on the errors it makes in these predictions (predictive coding). To achieve this, all the mentioned elements must work in concert. All skills the model acquires - i.e. its intelligence - shall only be the result of this process - an ongoing loop of learning, prediction and error-correction. This would be a device that learns by itself - a model of the world and the skills to manipulate this world. In other words, this would be a first brain model that implements a precursor for AGI (artificial general intelligence). If this could be realised within the EBRAINS framework, it would be a proof of principle how the newly created infrastructure is used to generate knowledge.

The return-on-investment (ROI) for HBP should be cast in terms of how well this elevation has happened. This can be assessed quantitatively and qualitatively and reported to the HBP Community and the lay public.

Attributed impact shall be assessed through surveys with a variety of stakeholders along with actual numbers. This can be achieved preferably by working with a company, like for example The Evidence Network (https://www.theevidencenetwork.com/) (as do other successful research entities like the Allen Institute, Ontario Brain Institute (OBI) or Centre for Aging and Brain Health Innovation (CABHI). The reports that are created shall be accessible by all. This can help to eliminate any negative impressions that 'HBP got all this money and did nothing'.

As a first step in this direction usage analytics of EBRAINS tools and services should be made transparent. The minimum required information would be the number of unique visits to different (sub)sites. In addition, uploads/downloads performed to storage or any other usage analytics/statistics that have been recorded. This would help us quantify impact/usage of the individual components of EBRAINS.

CDP8 tools on HBP platform/EBRAINS have several hundreds of active users in the research community resulting in a significant number of TVB-based publications – many with a clinical focus, such as epilepsy, stroke, brain tumors, dementia, pharmacodynamics. A multi-centre clinical trial based on the TVB software Suite is ongoing. It puts TVB to test for translation into the clinical routine of epilepsy neurosurgery. Several thousands of users of the broad public were attracted by the high-tech interactive brain software products developed by CDP8 during SGA2.