Upper limb Closed-loop neurorehabilitation simulator (D5.12 – SGA3)

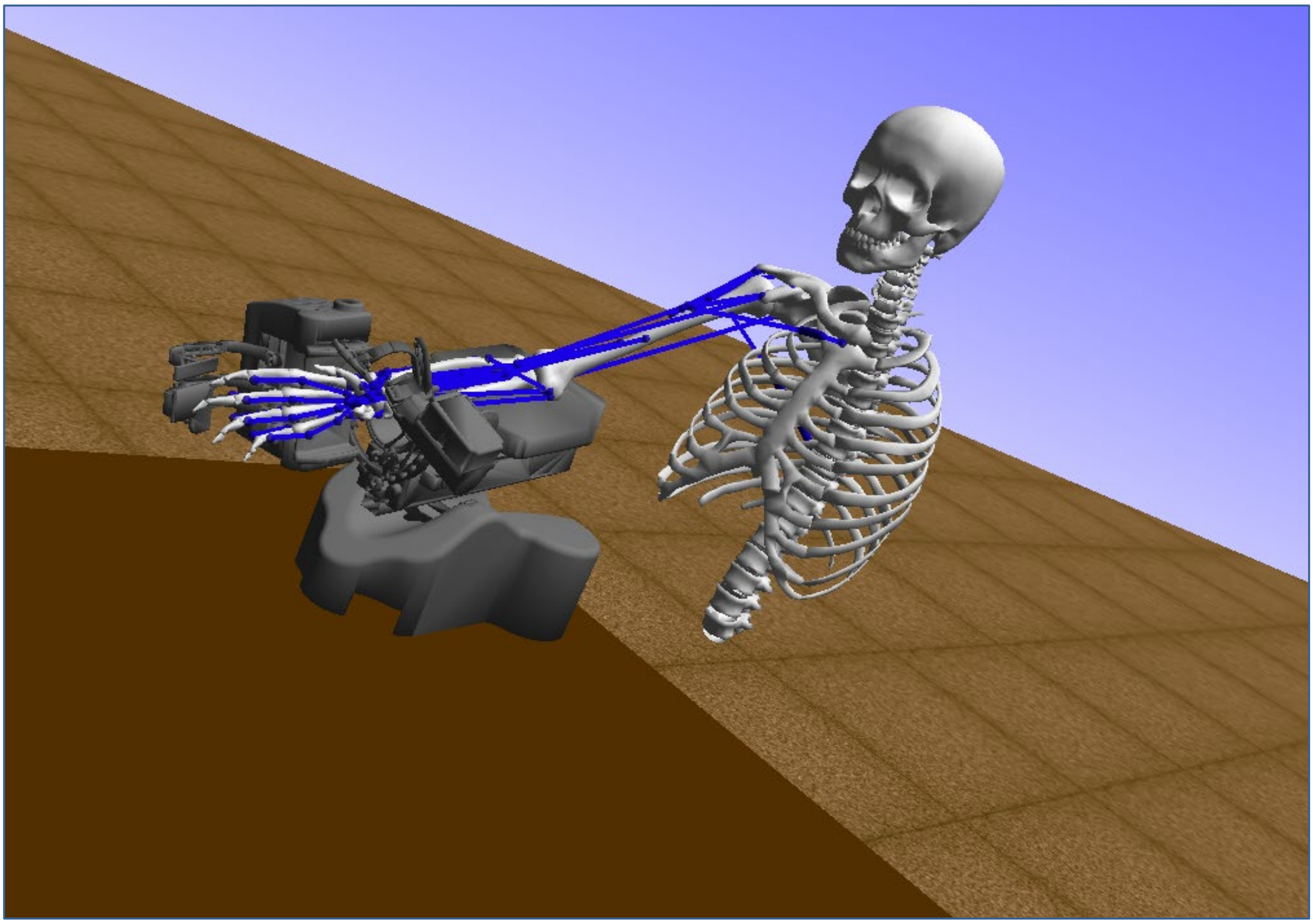

Figure 1: Integration of ISMORE, The Virtual Brain and upper limb biomechanical model

This figure represents the integration of the custom upper limb biomechanical model performing rehabilitation exercises with the Brain Computer Interface (BCI) exoskeleton ISMORE. This exoskeleton is connected to a custom Virtual Brain. More details of this integration can be found in Section 2.5.

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Description in GA:	Prototype of the functional simulator integrating the brain activity simulated by the TVB and the use of the ISMORE simulator with transfer to physical system.
Abstract:	This Deliverable describes the prototype of a digital twin simulator for upper limb closed-loop neurorehabilitation for stroke. The simulator has been implemented within the NRP Platform. It has two main modules. First, the right and left upper limb models have been developed in OpenSim. Moreover, the model of the ISMORE exoskeleton is created within this software. These models are coupled together through coupling constraints and contact geometry. We also developed two motion primitives for neurorehabilitation movements: 1) opening and closing the hand and 2) reaching with the arm. The second module is a brain activity simulator based on the TVB that uses data from a stroke patient to derive the connectivity matrix and to simulate brain activity. Both modules are connected using datapacks to send commands decoded from EEG activity to the exoskeleton or to send afferent information from the muscles back to the brain.
Keywords:	Neurorehabilitation, closed-loop, stroke, The Virtual Brain, neural afferent and efferent system, brain simulation.
Target Users/Readers:	Clinicians, computational neuroscience community, computer scientists, general public, HPC community, neuroinformaticians, neuroscientific community, neuroscientists, platform users, researchers, scientific community, students.

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History of Changes made to this Deliverable (post Submission)

Date	Change Requested / Change Made / Other Action
02/03/2023	Deliverable submitted to EC
02/12/2023	Resubmission with specified changes requested in Review Report. Main changes requested: • Change 1 (Discuss motivation and how data is integrated in the model) • Change 2 (The model choices, for example 2.51 in the deliverable seem to be arbitrary. There is no discussion of the choices presented.) • Change 3 (It should be clearly stated if the models are freely available as open source and where.) • Change 4 (Section 3 discusses the limitations of the work done but some points are missing.) • Change 5 (The outcomes are not convincing) • Change 6 (More details of work done to justify the resources)
11/12/2023	Revised draft sent by WP to PCO. We have thoroughly reviewed the deliverable and clarified all the comments raised by the reviewer to the best possible extent given the significant time constraints. In particular, we included two full annexes to describe the technical work (one for the processing of the stroke patient data and other in the implementation of the biomechanical models). This description was missing in the previous version, which may have provided the reviewers with a wrong impression as to the quantity of work produced in T5.21. We hope that the present version dispels this impression, which is fully unwarranted in our view. Please also note that this information was excluded from the original deliverable following the guidelines of the scientific reviewer of the PCO. We also made explicit which components were developed within T5.21, and which were used from EBRAINS to implement the closed-loop simulator prototype. Finally, we clarified the limitations of the simulator, identified and discussed their causes, and indicated how they impact the scope of our results from a technical point of view and also their validity from a clinical perspective. The establishment of a clinically relevant digital twin of a patient is a considerable undertaking and we believe that, although they are of a more limited scope than what we initially hoped for, our results provide much valuable information to the groups about to embark on this journey in EBRAINS 2.0. They certainly informed our own research directions as a company. To ease the reading of the updated version, the next list identifies the main changes made to the different sections for the main requests made from the reviewers (see row above): • Change 1 ○ Added motivation for a task based simulation in Section 1.1. ○ Added further information to the section 2.5 giving more detail about the integration of the modules inside the NRP. • Change 2 ○ Section 2.51 includes now some references and justifies the simplified model ○ Section 3.2 discusses the brain oscillatory model selection and limitations • Change 3 ○ Section 1 includes the link to the repository • Change 4 ○ Section 2,2,1 clarifies the protocol used to collect data ○ Section 3.2 clarifies the use of fMRI data ○ Section 4.2 discusses personalization limitations. ○ Section 4.1 identifies the main gaps to create a fully virtual twin using TVB and NRP. • Change 5 ○ Section 3.2 discusses the mismatch between input data and outcome ○ Section 4.1 and 4.2 discuss personalization • Change 6 ○ Added Annex with information about the developed models for the arm and the exo and about the controllers ○ Added Annex with the pipeline used to pre-process data for stroke patients
	○ Revised version resubmitted to EC by PCO via SyGMa

1. Introduction

This Deliverable includes the description of the prototype created in Task T5.12. The main goal that this project wants to achieve within the Human Brain Project (HBP) is to be part of a new line of projects within the institution involving the neurorehabilitation, this kind of rehabilitation is explained in Section 1.1.

The project contributes to the modelling part of the HBP, modelling a custom biomechanical and a brain model of a stroke patient with The Virtual Brain (TVB). Therefore, this project paves the way to the interaction between different tools from the HBP, the TVB and biomechanical models through use of the NeuroRobotics Platform.

All project-related data, processing pipelines, and essential information are centrally stored in a dedicated GitLab repository. The repository, available at https://gitlab.com/hbp-bitbrain/neurorobin, serves as a comprehensive hub for collaborative work and further improvement.

This project encompasses several topics such as prostheses, robotics, neuroplasticity, parameter optimisation, etc. The communities that may be interested in this project are:

- From a more clinical perspective: Clinicians and neuroscience community, which can be interested on the neurorehabilitation, neuroplasticity.
- From a more technical perspective: Computational neuroscientists and computer scientists, which can be interested on the biomechanical and brain modelling.

1.1 Neurorehabilitation

Nearly 13 million people all over the world suffer a stroke every year, around 8 million of them survive[1]. Around 85%[2] of them suffer some deficit in motor control due to the lesion. Neurorehabilitation aims to improve the recovery of severe paralysed patients using, for instance, Brain Machine Interfaces (BMI) controlling a neuroprosthesis[3] to associate volition and action and promote neuroplasticity[4]. ISMORE is an exoskeleton[5] that implements a closed-loop process whereby the EEG-based BMI predicts movement intention and the exoskeleton mobilises the paretic upper limb. Despite promising results, this type of rehabilitation still faces some challenges that include the variability in the brain activity of stroke survivors and the need to better study neuroplasticity mechanisms during therapy. Indeed, therapy is mostly pre-programed (not personalised) and only sometimes slightly adapted iteratively depending on the evolution and response to treatment. The research question is whether the therapy can be fully personalised and optimised to each patient, with the available clinical history and before therapy starts. Simulation is a potential tool to study this type of personalization and to gain a better understanding of the underlying brain mechanisms that are involved in the recovery of loss functions. It has already shown some promising results to determine individualized biomarkers of stroke recovery from the analysis of fMRI and DTI of resting

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[1] World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. http://ghdx.healthdata.org/gbd-results-tool

[2] López-Larraz E, Sarasola-Sanz A, Irastorza-Landa N, Birbaumer N, Ramos-Murguialday A. Brain-machine interfaces for rehabilitation in stroke: A review. *NeuroRehabilitation*. 2018;43(1):77-97. doi:10.3233/NRE-172394 https://pubmed.ncbi.nlm.nih.gov/30056435/

[3] Lo HS, Xie SQ. Exoskeleton robots for upper-limb rehabilitation: State of the art and future prospects. *Med Eng Phys*. 2012;34(3):261-268. doi:10.1016/J.MEDENGPHY.2011.10.004 https://pubmed.ncbi.nlm.nih.gov/22051085/

[4] Warraich Z, Kleim JA. Neural Plasticity: The Biological Substrate For Neurorehabilitation. *PM&R*. 2010;2(12):S208-S219. doi:10.1016/J.PMRJ.2010.10.016 https://pubmed.ncbi.nlm.nih.gov/21172683/

[5] Sarasola-Sanz A, Irastorza-Landa N, López-Larraz E, et al. A hybrid brain-machine interface based on EEG and EMG activity for the motor rehabilitation of stroke patients. *IEEE International Conference on Rehabilitation Robotics*. Published online August 11, 2017:895-900. doi:10.1109/ICORR.2017.8009362 https://pubmed.ncbi.nlm.nih.gov/28813934/

state[6]. Simulation tools can also provide information about the brain dynamics during the neurorehabilitation, not just in resting state, and they might be a valuable tool to guide the process based on the changes that occur during this process. This type of closed-loop simulation will require the interaction between the brain models and the models of the physical body, for instance the upper arm, and the physical tools, for instance a neuroprosthesis.

1.2 Objective and summary of undertakings

This Deliverable describes the prototype created in the Human Brain Project (HBP): A digital twin of an upper-limb neuro-rehabilitation session for a stroke patient. The objective of the digital twin is to provide tools to push forward research on neurorehabilitation improving the prognosis of the interventions and their outcome in terms of functional recovery. The ability to simulate closed-loop interventions is a very promising tool to tackle some of the open questions in neurorehabilitation, namely, the role of neuroplasticity in the reorganisation of the neural circuits after the stroke. Also, they provide a very effective tool to consider the variability and to personalise interventions to each patient.

More specifically, the objective of Task 5.21 is to develop an upper limb model including a neuroprothesis that combined with modules available off-the-shelf from EBRAINS (e.g., brain activity simulation and afferent/efferent communication with the peripheral nervous system) create a closed-loop simulator of a neurorehabilitation task. Such a simulator could in the long term become the core of a digital twin, used to extract markers and features to be utilized for prognostic purposes in assessing the rehabilitation progress of the patient. By leveraging the data generated within this closed-loop environment, the long-term aim is to eventually identify meaningful neurological indicators that can serve as valuable metrics for evaluating and predicting the effectiveness of the rehabilitation process. The work reported herein explores how the tools developed within the framework of the HBP can serve such purpose. Concretely, those tools are The Virtual Brain (TVB)[7] and the Neurorobotics Platform (NRP)[8].

The main idea is to develop a closed-loop simulator by:

- Using the TVB simulation tools to generate models of brain activity of stroke patients. This simulated brain activity would be generated on the basis of fMRI and EEG data collected while performing rehabilitation tasks with stroke patients.
- Developing a complete biomechanical model in OpenSim, these types of models are formed by muscles, bones, joints, each one of these has its own physical properties, anatomy and equations that represent the force and movement. In this case, for the upper-limb and a complete model of the ISMORE exoskeleton, a neural rehabilitation exoskeleton described in Section 2.4, as well as themotor primitives required for simulating neurorehabilitation intervention within the NRP.
- Integrating the previous simulation tools in a new use case in the NRP: ‘Closed-loop upper-limb neurorobotic simulator for stroke neurorehabilitation’.

The final aim is to help the progress of scientific research in stroke rehabilitation, stroke being a high prevalence disease with a huge impact both in economic and social terms, by providing tools that can be used by the neurorehabilitation community to develop and evaluate interventions. All the modelsdeveloped in the framework of this project are open source and available foruse in further experiments; in particular, the biomechanical model mentioned above that can be used to control a real version of the ISMORE exoskeleton and the brain models to simulate brain activity during motor tasks after a stroke can be found in a freely accessible repository[9]. We expect these tools to be of

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[6] MI Falcon, JD Biley, V. Jirsa, A. MMcInstosh, E. Chen, A. Solodkin, Functional mechanisms of recovery after Chronic Stroke: Modeling with the Virtual Brain, 10.1523/ENEURO.0158-15.2016

[7] The Virtual Brain: Delivering practical results. For novel clinical applications. https://www.thevirtualbrain.org/tvb/zwei

[8] NRP - Neurorobotics. https://neurorobotics.net/

[9] HBP Bitbrain / NeuroRobin · GitLab. https://gitlab.com/hbp-bitbrain/neurorobin

value mainly for research in neurorehabilitation, but they can also be used for basic research in motor control and for further development of a complete simulator of the nervous system.

1.3 Organisation of this document

The rest of this document is organised as follows. The next section describes the developed prototype of the digital twin including an overview of the system, the dataset required to build the TVB models, the brain and biomechanical models, and the experiments carried out so far to validate the system. Section 3 discusses the limitations of the work done as well as the opportunities for new research to make closed-loop digital twins.

2. Description of the prototype

2.1 Overview of the system

The main architecture of the simulator can be seen in Figure 2. It is a closed-loop system in which the biomechanical models are linked to the TVB in a bidirectional way. First, the TVB provides efferent information to the biomechanical system (i.e. the upper limb and/or the exoskeleton), while afferent information travels back to the TVB providing feedback based on the state of the muscles. Importantly, the virtual brain will eventually be optimised based on neural data (fMRI/EEG) and muscular activations of a stroke patient during a neurorehabilitation session.

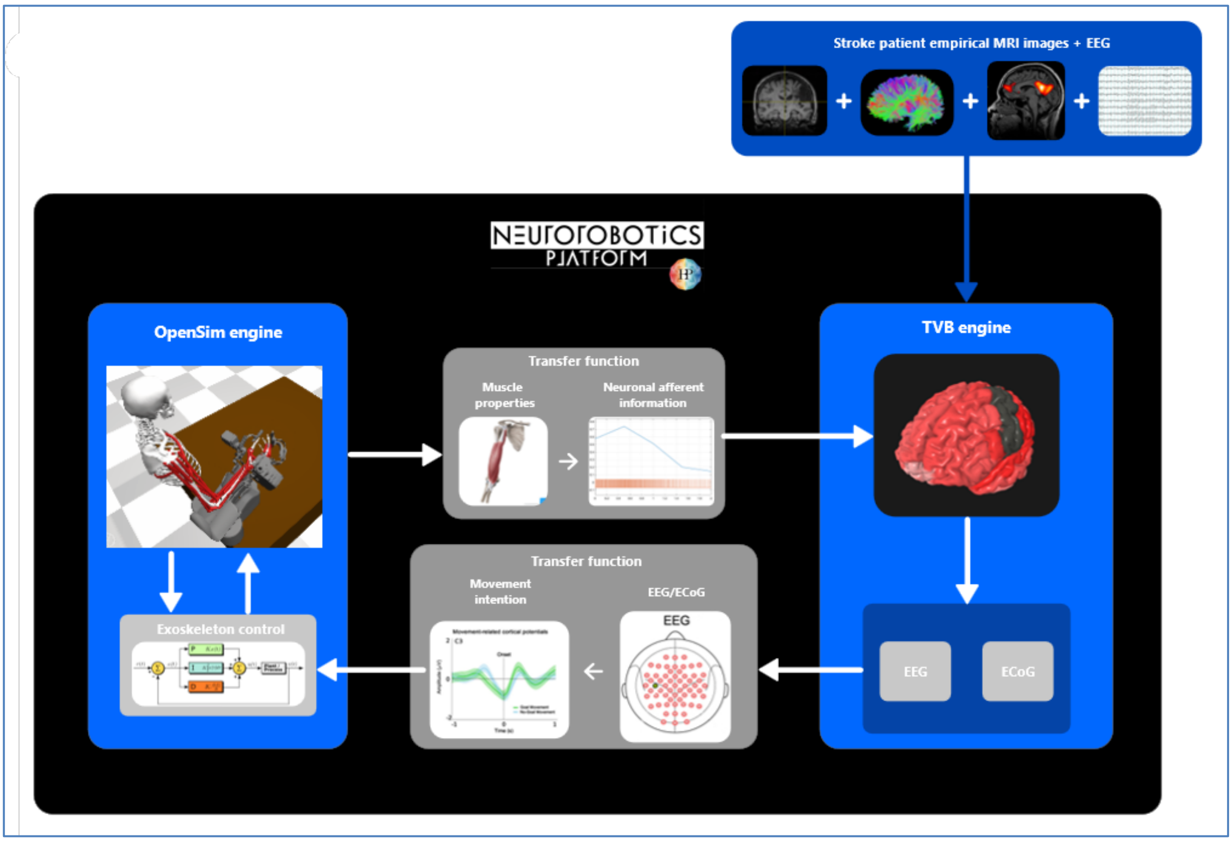

Figure 2: Overall scheme of the NeuroRobin project

In the development of our prototype, while leveraging tools from the EBRAINS ecosystem, we introduced several components to make possible its functionality:

- **Biomechanical Model of Upper Limb**: We incorporated an intricate biomechanical model representing the upper limb. This model encompasses the primary superficial muscles spanning the shoulder, arm, forearm, and fingers, enabling a vast range of movements. Each component's physical properties, including shape, weight, centre of mass, inertia, and force, were meticulously modelled.
- Integration of Real Rehabilitation Exoskeleton in OpenSim: The inclusion of a real rehabilitation exoskeleton within the OpenSim environment was a pivotal aspect of our work. This involved creating the necessary meshes in a CAD software, joints and defining physical properties in OpenSim. Additionally, the integration with the upper limb model was achieved using constraints to simulate rehabilitation exercises in line with real-world experiments.
- **Exoskeleton motor primitives**: we have implemented a control module to control the joints of the exoskeleton (and through the implemented coupling also the joints of the upper limb). Based on this joint controllers, we also implemented two motion primitives used in neurorehabilitation therapy: 1) shoulder and elbow flexion-extension (reaching) and 2) fingers flexion-extension (grasping). These controllers have also been integrated within the NRP and can be used directly sending commands using the API of OpenSim.
- **Afferent Modelling of Neural Signals**: Addressing the absence of tools for muscle-brain connection, such as a spinal cord, we developed a simple afferent model to simulate neural signals originating from the sensory organs of muscles and tendons. This novel block was constructed from scratch to transmit biomechanical information obtained from the upper limb model to the TVB module.
- Conversion of MRI Images to Virtual Brain: The conventional approach to converting MRI images to a virtual brain encountered challenges when dealing with patients exhibiting structural deformities within the brain. To overcome this, we devised an alternative approach, leveraging proposed pipelines that resolved issues stemming from the specific characteristic of the stroke patient’s data used in the evaluation.
- Parameter Optimization for the Virtual Brain: The Virtual Brain needs parameter optimization to closely emulate the patient's neural activity. We developed a novel approach based on a Bayesian optimization method, utilizing fMRI information from previous recordings to fine-tune simulation parameters.

All these software components and OpenSim models are available in the repository mentioned above. The next subsections provide more details of the different components.

2.2 Data to be used to model the closed-loop system

2.2.1 Input experiment

The originality of this project, compared to other projects about stroke related to The Virtual Brain[10], is that the brain activity was recorded during a motor task-related movement, which is a novel approach to The Virtual Brain.

In this particular case, the patient has suffered from a stroke affecting the left motor areas of the cortex. Since the focus of the work is on the technical development, we tested on a single subject The platform is generic and, once the limitations discussed later on this document are resolved, the modules can be used for a more thorough evaluation with a larger cohort of patients. Nevertheless, this person had several characteristics of interest to this preliminary technical study:

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[10] Falcon MI, Riley JD, Jirsa V, McIntosh AR, Chen EE, Solodkin A. Functional Mechanisms of Recovery after Chronic Stroke: Modeling with the Virtual Brain. *eNeuro*. 2016;3(2):202-208. doi:10.1523/ENEURO.0158-15.2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819288/

- The stroke outreach was only in the motor related areas, so the other brain areas have regular behaviour.
- The patient had a good rehabilitation prognosis, so some neuroplasticity can occur.

The objective is to promote neuroplasticity performing rehabilitation exercises with the ISMORE[11] exoskeleton, which is a motorized Brain Computer Interface system that reads EEG and predicts the patient movement intention and helps him with the execution of the movement.

The rehabilitation exercises consist in a loop containing 3 main parts (Figure 3):

- Instructions: The patient is prepared to execute the exercise by giving him some instructions about the following steps. This lasts 10 seconds.
- The next step can be:
  - A visual and auditory stimuli, which are instructions of the task that is going to be performed, reducing the uncertainty of the patient at the time to do the task.
  - The motor task involves the patient alternately opening and closing their hand. This specific protocol is designed to assess the impact on the motor cortex following a seizure, as the hand holds the largest area in the motor cortex relative to its size. The duration of this task is set at 12 seconds, allowing for a focused examination of motor responses and providing valuable insights into the post-seizure effects on the motor cortex.
- Finally, some rest that depends on each loop.

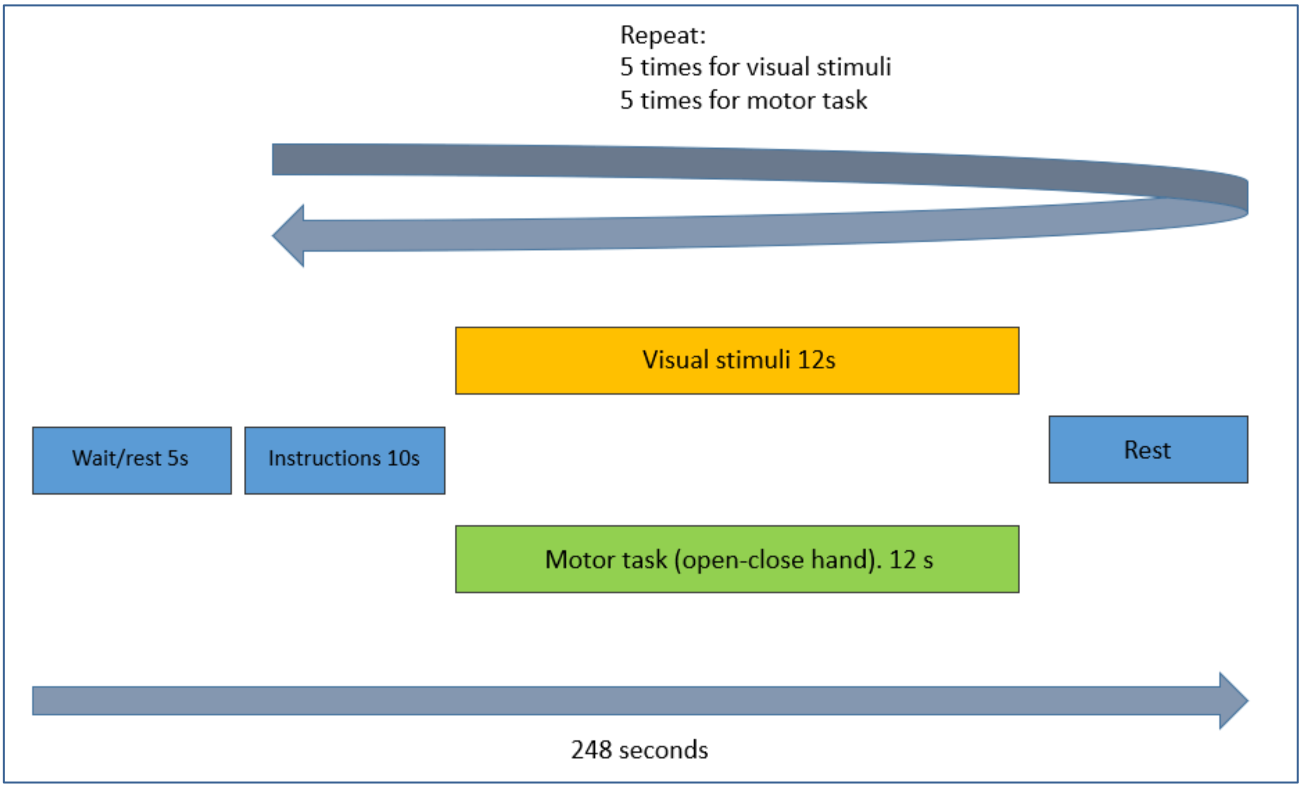

Figure 3: Simplified experiment event scheme

The exercises performed with the ISMORE exoskeleton are taken as the motor primitives that will be modelled for the closed-loop simulation. These ones are: 1) Coordinated reaching movement, and 2) Opening and closing the hand.

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[11] Sarasola-Sanz A, Irastorza-Landa N, López-Larraz E, et al. A hybrid brain-machine interface based on EEG and EMG activity for the motor rehabilitation of stroke patients. *IEEE International Conference on Rehabilitation Robotics*. Published online August 11, 2017:895-900. doi:10.1109/ICORR.2017.8009362 https://pubmed.ncbi.nlm.nih.gov/28813934/

2.2.2 MRI input data

The previous experiment was repeated twice with two different methods for data generation:

- fMRI and an EMG recording
- EEG and EMG recording

In addition to this experiment, MRI anatomical and diffusion images were recorded previously. These modalities enable mapping the anatomical structure and creating diffusion tensors of the axons, respectively. The MRI images obtained from the patient can be seen in Figure 4 (simple MRI), Figure 5 (diffusion MRI) and Figure 6 (functional MRI).

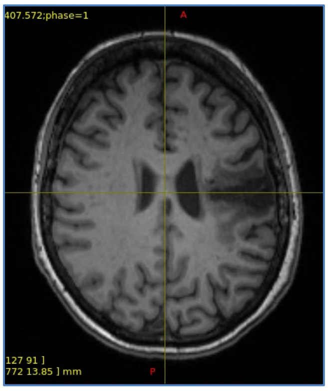

Figure 4: T1w MRI image

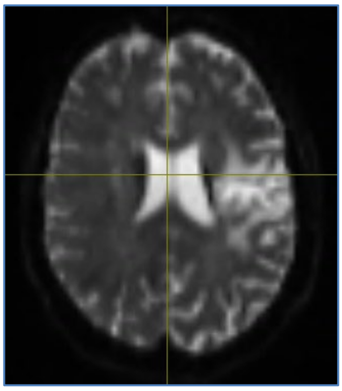

Figure 5: DWI MRI image

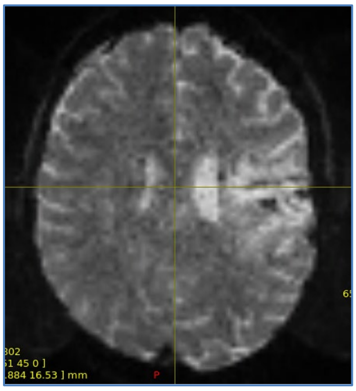

Figure 6: fMRI MRI image

2.2.3 Pre-processing pipelines

A virtual brain model, personalised with the anatomical structures of the patient, is created from patient data. Several already existing automated pre-processing pipelines were executed[12] . These pre-processing pipelines were recommended by the technical team of the TVB, where several neuroimaging algorithms process the MRI images:

- MRtrix_connectome pipeline creates a structural connectome out of the T1 and DWI images. This structure represents the connectivity between the different functional zones of the brain.
- fMRIprep, obtains the BOLD (see Section 2.3) activity recorded in the fMRI and performs several pre-processing techniques
- TVB converter: the outputs of the two previous pipelines are converted to files that can be read by the TVB platform using the TVB converter pipeline.

Nevertheless, the automated pipelines available in EBRAINS are adapted to healthy brains. Therefore, we had adapt them and add some extra steps for them to work in the case of the stroke patient used in the evaluation. In the particular case reported herein, we had to:

- Use the virtual brain transplant[13] for the registration of the brain images.
- Apply an alternative method for distortion correction because there were no reversed encoded images.
- Segmentate the stroke lesion to create an anatomically constrained tractography.

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[12] Schirner M, Rothmeier S, Jirsa VK, McIntosh AR, Ritter P. An automated pipeline for constructing personalized virtual brains from multimodal neuroimaging data. *Neuroimage*. 2015;117:343-357. doi:10.1016/J.NEUROIMAGE.2015.03.055 https://pubmed.ncbi.nlm.nih.gov/25837600/

[13] Solodkin A, Hasson U, Siugzdaite R, Schiel M, Chen EE, Kotter R, Small SL. Virtual brain transplantation (VBT): a method for accurate image registration and parcellation in large cortical stroke. Arch Ital Biol. 2010 Sep;148(3):219-41. PMID: 21175010.

- Correct skin and scalp surfaces due to some technical problems created by the anonymisation procedure applied on the image.
- A more detailed description of the developed pre-processing pipeline for data from stroke patients is presented in Annex 2.

2.3 Brain simulation using TVB

In the context of T5.21, the selected simulation approach was based on large scale simulations using the engines provided by the TVB. The virtual brain allows the structural connectome created with the pre-processing pipelines to reproduce raw brain activity according to the different interconnections within the patient brain. More in detail, an oscillation model optimized with the patient empirical activity is applied in the different nodes of the brain and it is propagated depending on the connections that are between the zones (connectome). The pre-processed fMRI data is employed to generate a Functional Connectome (FC). This FC reflects the correlation between activities in different brain regions reflecting the lesion of the patient. The TVB uses the empirical FC is used to optimize simulated signals. This optimization process enhances the fidelity of the simulated signals, aligning them more closely with the observed functional connectivity in the actual brain data. For these simulations, we used the tools from TVB, both the GUI simulator for simple simulations and the python library when optimizing the parameters of the model using Bayesian optimization.

This simulated raw activity of the brain can be used as the basis for the generation of synthetic data corresponding to different modalities of brain recordings. These are:

- BOLD: Represents the metabolic activity on the different regions of the brain
- EEG: Represents the brain electrical activity recorded on the scalp of the patient

The BOLD signal is used to compare the functional connectomes of the simulated data and the empirical signal recorded with the fMRI. The EEG signal is used to generate brain activity in the closed-loop system. This brain activity is used to give commands to control the exoskeleton in the rehabilitation exercises.

Closed-loop task based simulation is still an open challenge for the TVB. The currently supported models have been designed and evaluated for resting state. Among the available engines, we selected the oscillatory model Stefanescu-Jirsa 3D[14] due to its performance when simulating BOLD activity. Unfortunately, the time and budget constraints of the project did not allow for a full adaptation or the development of a full new model better suited for the type of motor tasks required by our simulation. We therefore decided to finalize a complete version of the closed loop-system using the selected model and studied how well the model could mimic activity when its parameter where optimized for our motor task. For this purpose, the standard parameter optimization techniques based on grid search and gradients were tested and we implemented a new approach based on Bayesian optimization, which is specially well suited when evaluating a set of parameters is costly, as it is the case for brain simulations with the TVB. In particular, we used BayesOpt[15] to explore the parameter landscape and try to find the best configuration. It is important to stress that the proposed closed-loop model also lacks a proper connection between the TVB and the afferent and efferent paths which limits strongly the validity of the obtained simulation results in a clinical context. This however does not compromise the value of the work carried out in terms of technical development and process design.

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[14] Simulation workflow in TVB. Graphic representation depicting the... | Download Scientific Diagram. https://www.researchgate.net/figure/Simulation-workflow-in-TVB-Graphic-representation-depicting-the-sequential-steps-of-TVB_fig1_299400048

[15] Martinez-Cantin R. BayesOpt: A Bayesian Optimization Library for Nonlinear Optimization, Experimental Design and Bandits. *Journal of Machine Learning Research*. 2014;15:3915-3919. https://bitbucket.org/rmcantin/bayesopt/

2.4 Biomechanical and exoskeleton model

The physical system of the digital twin is divided into two sections:

- The biomechanical model, which simulates the activation and forces produced on the muscles and bones (Figure 7 and Figure 8). The right limb has a paretic behaviour, and the left non-paretic. These models are customised to perform the necessary movements of the motor primitives in the neurorehabilitation exercises.

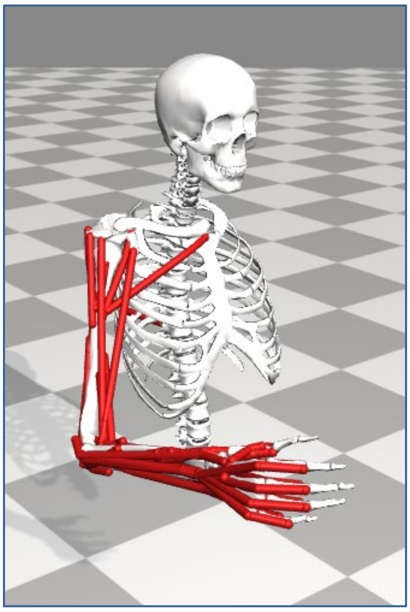

Figure 7: OpenSim model (right limb)

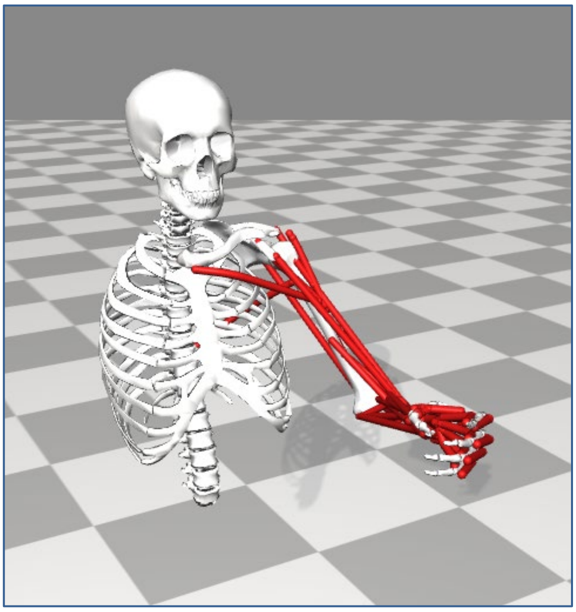

Figure 8: OpenSim model (left limb)

- The model of the ISMORE exoskeleton mentioned in Section 2.2. The exoskeleton was modelled using Computer Aided Design (CAD) files of the real exoskeleton sing SolidWorks and exported to stl files that can be read by the OpenSim engine. Moreover, it had to be coupled in simulation to the biomechanical model of the patient to move at the same time as the patient (Figure 9). Finally, some spatial restrictions were defined to delimit the exercise.

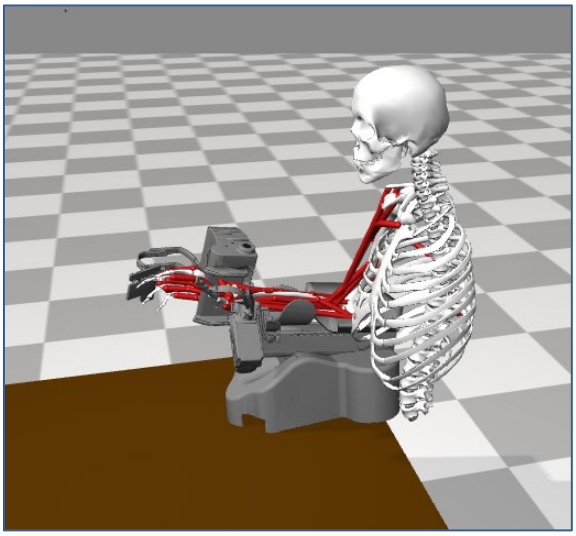

Figure 9: Exoskeleton coupled with the biomechanical model

For further details on the developed models and the controllers see Annex 1.

2.5 Integration within the NRP

The NeuroRobotics Platform16 is an integrative framework that allows different simulation engines to work concurrently and thus enables performing highly modular simulations with proper orchestration between the modules. In the case of the project, the two engines that have to communicate with each other are the OpenSim engine and the TVB engine.

They communicate with each other via so-called datapacks, which have a standardised generic data format in the NRP 4.0. For example, these datapacks can contain a joint position, a muscle activation, brain voltage, or any combination thereof.

In addition, NRP 4.0 implements so-called transceiver functions that are responsible for processing the information inside the datapacks, while at the same time ensuring that each engine receives data types that it can consume. An example would be transforming the muscle fibres' length and velocity to neural impulses. Transceiver functions thus serve both a technical purpose (conversion between data types) and a scientific one (implementation of signal processing and transforms). This latter purpose within the context of this project is described in the following sub-sections.

A general scheme of the NRP data flow for the experimental setup described in this Section is shown in Figure 10.

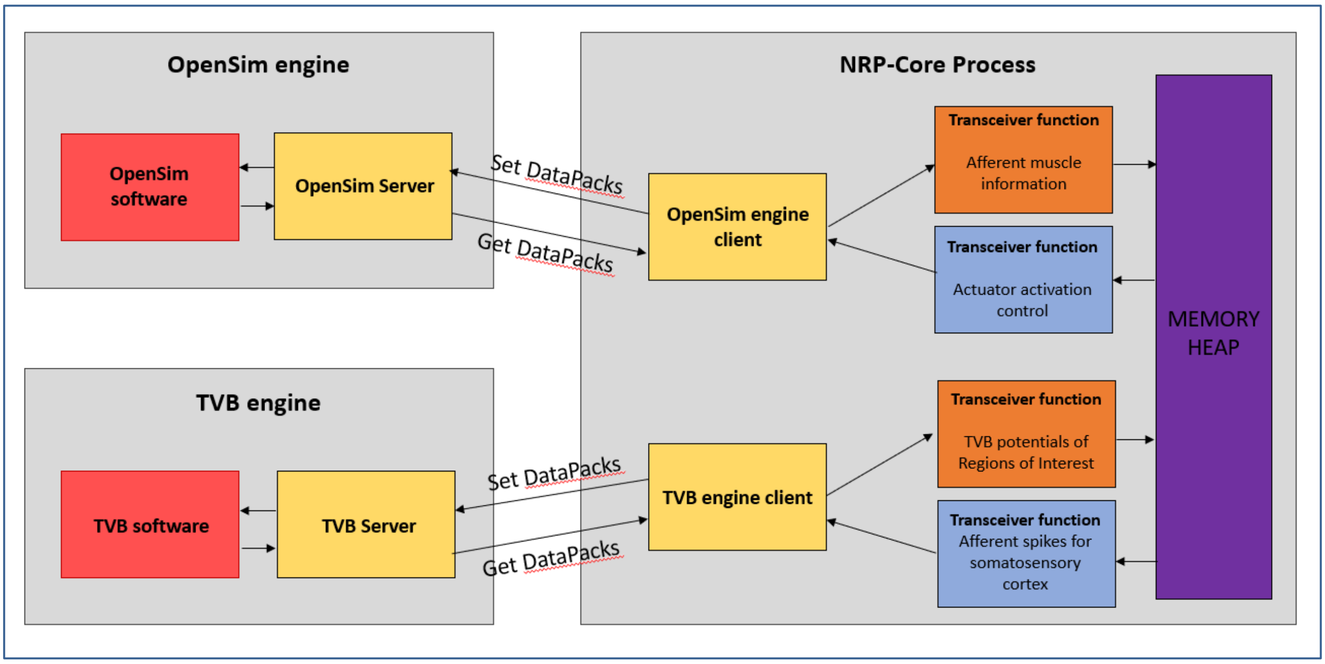

Figure 10: Data flow in NRP 4.0

The data management relies on a Docker container, providing a consolidated environment equipped with modules necessary for seamless experiment execution. Within this container, the pre-processed data is stored, comprising the OpenSim model featuring exoskeleton integration and the TVB connectome alongside meshes for simulating synthetic signals.

This data is then interpreted and executed by specialized engines. On one hand, the OpenSim engine, responsive to motor commands, orchestrates precise movements of the exoskeleton, thereby influencing patient dynamics. On the other hand, the TVB engine reads input files, implementing a virtual brain based on patient-specific data. Notably, parameters optimized through fMRI data are seamlessly integrated into the model.

Furthermore, transfer functions play a vital role in facilitating communication between the engines, representing the afferent system, translating muscle information into neural impulses, and the

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[16] Falotico E, Vannucci L, Ambrosano A, et al. Connecting artificial brains to robots in a comprehensive simulation framework: The neurorobotics platform. *Front Neurorobot*. 2017;11(JAN):2. doi:10.3389/FNBOT.2017.00002/BIBTEX https://www.frontiersin.org/articles/10.3389/fnbot.2017.00002/full

efferent system, issuing commands based on neural information. This cohesive structure highlights the containerized data management, engine functionality, integration of optimized parameters, and the significance of transfer functions in the overall project architecture.

2.5.1 Modelling of Afferent pathways

The afferent information goes from the peripheral parts of the body to the brain. In this particular case, the information comes from the muscles and tendons to give spatial information to the brain.

The biological organs responsible for this information translation are the Muscle Spindle and the Golgi Tendon Organ, they are sensitive to muscle length and velocity and tendon stretch force respectively. These physical properties are translated into neural impulses that travel through the spinal cord to the internal structures of the brain and finally to the somatosensory cortex. However, in the case of this simulation, the stimuli are directly plugged to the somatosensory cortex.

This information translation has been modelled with transfer functions.

- Muscle spindle: Type Ia fibres are sensitive to velocity and length and type II are specific to length.

$$f(type\ Ia) = \left[Neuron_{sensitivity_{Ia}} * \frac{dL}{dt}\right]_{v>0} + [Neuron_{sensitivity_{Ia}} * \%L]_{L>40\%} + \frac{0.4}{Neuron_{sensitivity}}$$

Eq. 2.1 firing frequency of type Ia fibres.

$$f(type\ II) = [Neuron_{sensitivity_{II}} * \%L]_{L>40\%} + \frac{0.4}{Neuron_{sensitivity_{II}}}$$

Eq. 2.2 firing frequency of type II fibres.

- Golgi tendon organ: Type Ib fibres are sensitive to tension within the tendon.

$$f(type\ Ib) = Neuron_{sensitivity_{Ib}} * Tension$$

Eq. 2.3 firing frequency of type Ib fibres.

It is important to clarify that the equations presented in this study are not intended to be precise representations, insofar as our aim was to establish the technical foundation for a digital twin capable of closed-loop simulation. More intricate and realistic models can be explored in the literature. Noteworthy examples include the work by Prochazka and Gorassini[17] on ensemble firing of muscle spindle afferents recorded during normal locomotion in cats, as well as the study by Mileusnic and Loeb[18] on mathematical models of proprioceptors, focusing on the structure and function of the Golgi tendon organ. It is acknowledged that the equations herein are adapted to the available information from the OpenSim model, which inherently has limitations in the breadth of information it can provide. Despite this constraint, the equations establish a direct correlation with empirical signals, aligned with existing literature.

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[17] Prochazka A, Gorassini M. Models of ensemble firing of muscle spindle afferents recorded during normal locomotion in cats. J Physiol. 1998 Feb 15;507(Pt 1):277-91. doi: 10.1111/j.1469-7793.1998.277bu.x. PMID: 9490851; PMCID: PMC2230775.

[18] Mileusnic MP, Loeb GE. Mathematical models of proprioceptors. II. Structure and function of the Golgi tendon organ. J Neurophysiol. 2006 Oct;96(4):1789-802. doi: 10.1152/jn.00869.2005. Epub 2006 May 3. PMID: 16672300.

2.5.2 *Efferent pathways*

The efferent pathways represent the information path that comes from the brain to the peripheral nerves and organs. In the context of this project, we have not used any models to send information for the motor control of the arm. This will require a model of the spine to convey brain signals during the closed-loop control. In the case of this project's patient, the motor cortex of the right arm is non-functional. However, the motor commands should be sent from other areas of the brain, such as the pre-motor cortex or the ipsilateral motor cortex.

Since this was beyond the scope of this project, we focused on the information required to trigger the motor control primitives of the exoskeleton for a neurorehabilitation intervention. This trigger signal is usually decoded from EEG activity, in particular, from power changes in the alpha and beta bands and from slow cortical potentials. Bitbrain had already developed models based on machine learning techniques to decode this type of information and had trained the models both in healthy subjects and stroke patients.

3. Simulations using the prototype

The project output is comprised by different blocks integrated within the NRP: the Virtual Brain, the OpenSim model, the afferent and efferent pathways, and the exoskeleton control.

In this section, the different experiments involving these different blocks in open and closed loop will be discussed.

3.1 Pre-processing pipelines outputs

We now present the results of the proposed pre-processing pipeline described in Section 2.2.3. This pipeline consists of three main steps:

MRtrix3 connectome: The cortex meshes are obtained from the MRI images, and the region labelling can be seen in Figure 11. The black mesh within the brain represents the necrosed tissue, which is non-functional. Moreover, the zones partially affected by the lesion are the postcentral and precentral regions which correspond to the motor and somatosensory cortex.

This representation can be utilized to observe more precisely the regions of the brain affected by the lesion and to discern the potential outcomes on brain activity based on those specific zones.

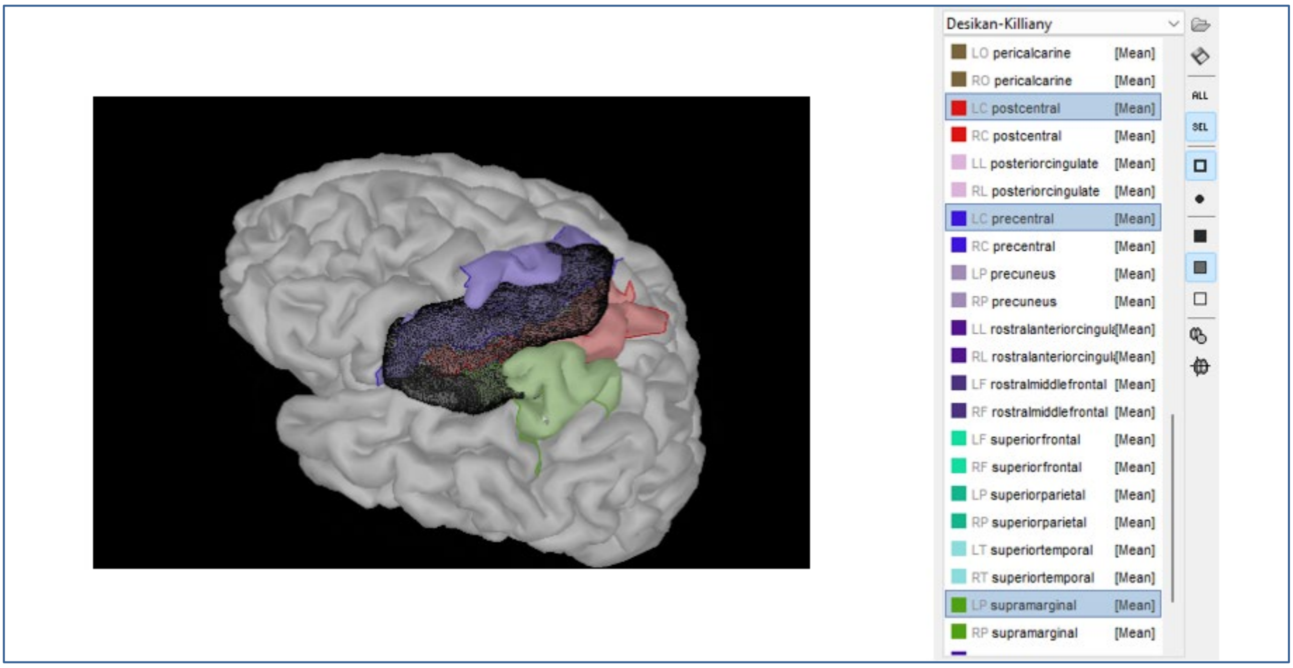

Figure 11: Brain regions affected by the lesion

From the diffusion-weighted images and the T1w images the structural connectome is obtained. As explained in previous sections, this represents the interconnections between functional zones within the brain (Figure 12).

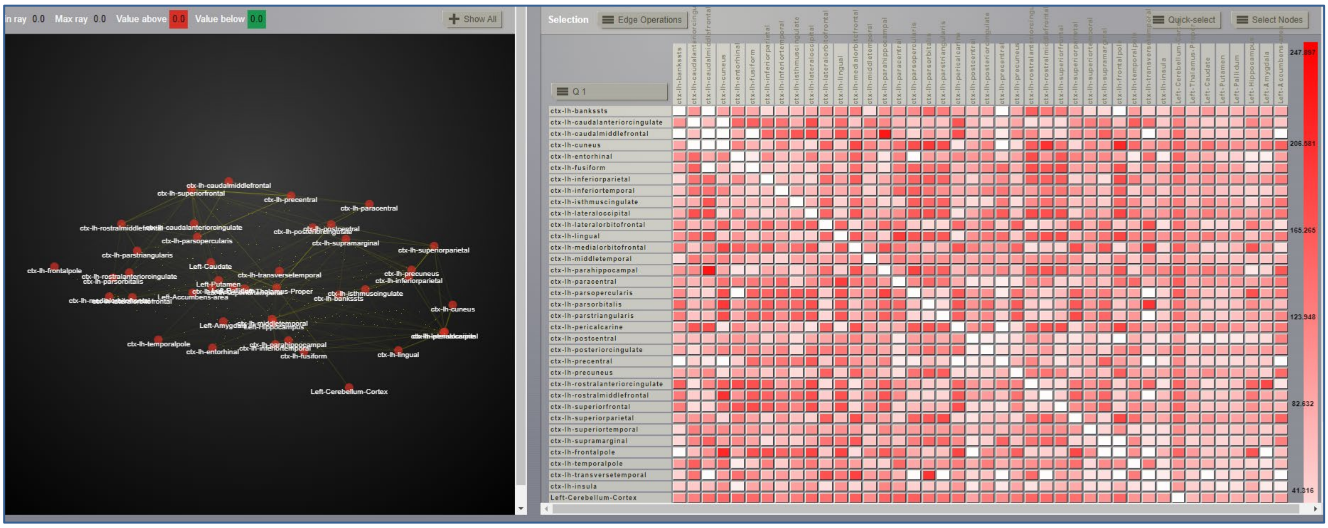

Figure 12: Connectome of the processed data

The provided data serves as a depiction of the interconnections among various regions within the patient's brain. The regions impacted by the lesion exhibit reduced interconnections with other brain regions compared with healthy patients, the regions affected by the lesion are visually indicated in Figure 11. This connectome effectively portrays the lesion's influence on the white matter tracks that communicate between different zones of the patient's brain. This connectome serves as a visual representation of the altered connectivity resulting from the lesion, offering valuable insights into the structural impact on inter-regional communication pathways.

fMRIprep pipeline: From the fMRI data, the BOLD signal of each pixel is calculated. This information is then projected on the most proximal functional zones of the cortex. This timeseries (Figure 13) represents the BOLD activity during the different loops of the rehabilitation exercises on each region of the cortex.

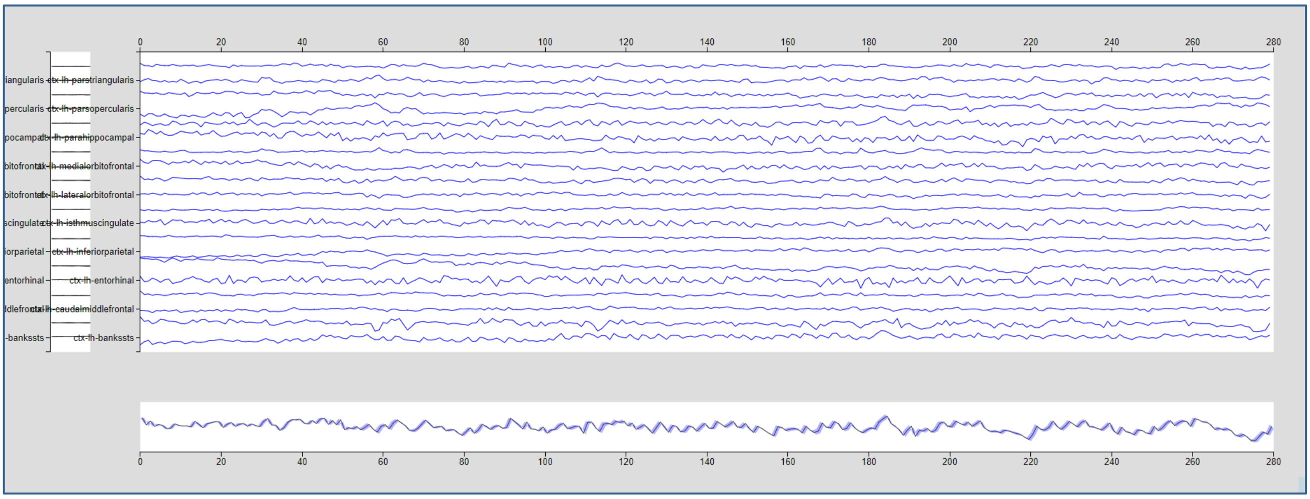

Figure 13: BOLD activity on each region during the entire experiment session

TVB converter: The final step is just a data formatting prior to importing the results in the TVB.

3.2 TVB simulations

Based on the outputs of the previous sections, we next present some results of simulated brain activity using the TVB. As discussed previously, the clinical validity of these simulations is limited due to the lack of proper models for task oriented brain activity. Therefore, we provide some examples of the technical validation of the approach in open loop to demonstrate the technical viability and correctness of the implementation.

- Simulated BOLD activity in open loop to optimise the functional connectomes from the fMRI scan and simulated data. A simple BOLD activity simulation with default parameters can be seen in Figure 14. Then, the functional connectomes both can be seen in Figure 15 and Figure 16. Moreover, this BOLD simulation will be repeated several times searching parameters with a Bayesian Optimization tool[19] until the simulation is optimised to the empirical signal.

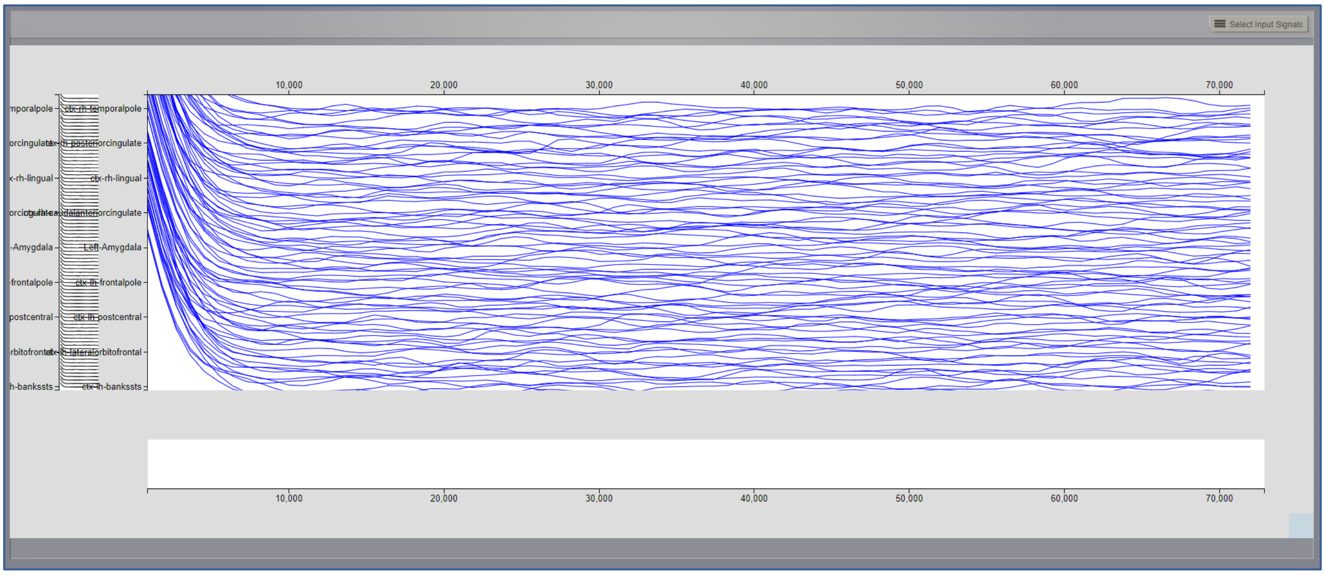

Figure 14: BOLD simulation

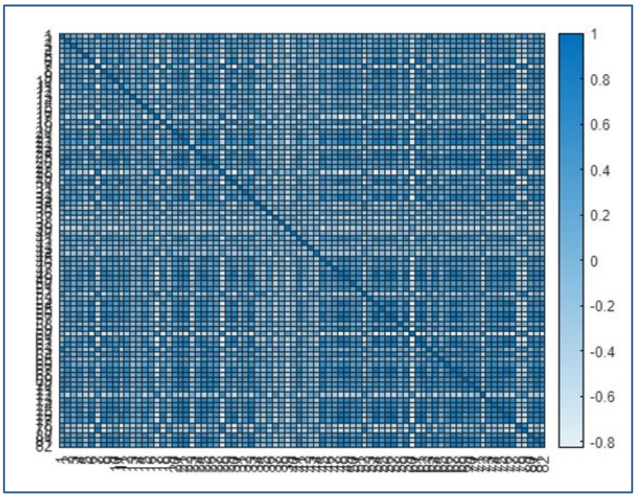

Figure 15: Functional connectome (FC)

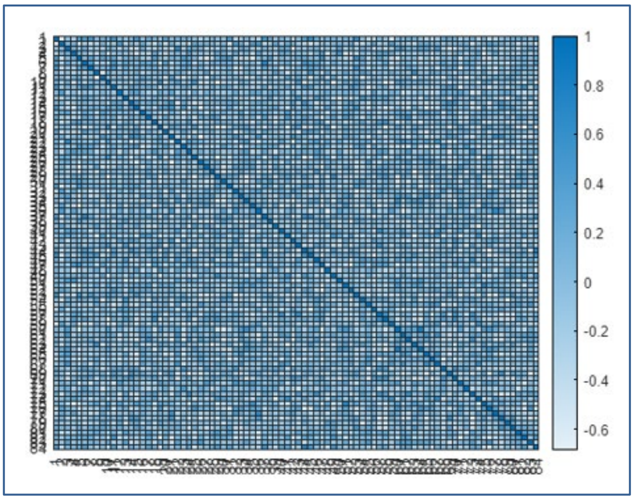

Figure 16: Simulated FC

The analysis of empirical data reveals a noticeable discrepancy when compared to the simulated BOLD signal. Despite optimization through Bayesian methods, the identified optimal combination did not yield the expected level of performance. One potential contributing factor is that many existing models are primarily designed for resting-state conditions, whereas in this project, fMRI activations stem from task-related events. This deviation from the norm introduces an additional layer of complexity to the optimization process.

Moreover, the unique context of the optimized brain, affected by stroke, adds further intricacies and challenges to the optimization framework. These factors collectively contribute to the observed

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[19] Martinez-Cantin R. BayesOpt: A Bayesian Optimization Library for Nonlinear Optimization, Experimental Design and Bandits. *Journal of Machine Learning Research*. 2014;15:3915-3919. https://bitbucket.org/rmcantin/bayesopt/

disparity between the simulated and empirical data, warranting a nuanced understanding of the intricacies involved in the optimization of the BOLD signal in this particular project.

- Simulated EEG activity in closed loop to create activity that can be interpreted by the exoskeleton in the NRP platform. This EEG simulation (Figure 17) will have the parameters optimised with the BOLD activity for task-related events plus the anatomical structures such as the cortex and scalp of the patient.

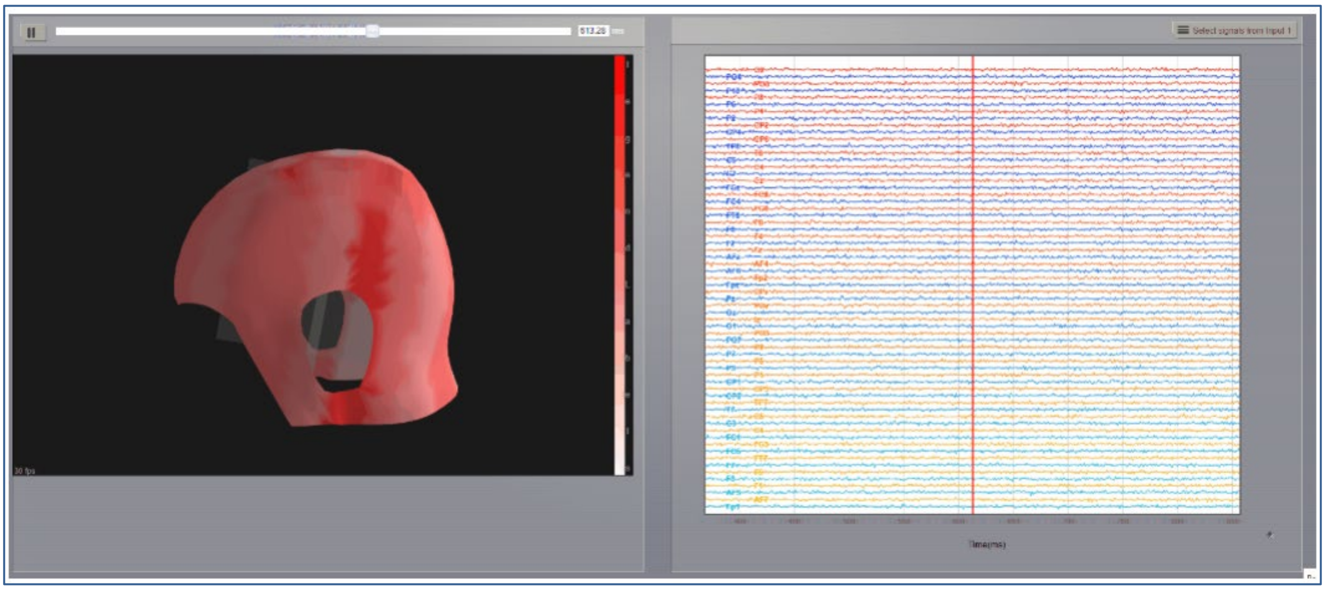


Figure 17: EEG simulation

Figure 17 depicts simulated EEG activity utilizing 3D spatial meshes, optimized parameters derived from fMRI data, and the stroke connectome. However, it is important to note, as detailed in other sections, that the TVB lacks the capability to simulate evoked potentials. This limitation leads to a simplified EEG output without the nuanced disturbances that could otherwise be interpreted to generate motor commands. As a result, the resulting EEG reflects a straightforward representation, lacking the complexity that might arise from evoked potentials and their potential implications for motor command interpretation.

It is important to stress that the ability to generate evoked activity is beyond the current capabilities of the TVB and beyond the scope of the activities described in this document.

3.3 Afferent system simulations

The next block to be discussed are the transfer functions that translate the physical properties of the muscles and tendons to neural spikes to be sent to the TVB. Firstly, the muscle spindle is the sensory organ inside the intrafusal fibres of the muscles. This organ is sensitive to:

- Stretch length (type Ia): An example of the flexor muscles closing and opening the hand can be seen in Figure 18: the higher the lengthening velocity, the higher the firing rate of the neurons.
- Lengthening velocity (type II): In the example of Figure 19, the flexor muscles when doing the reaching movement are lengthened in a lower rate and then in a higher rate resulting in a higher neuronal response.

The Golgi Tendon Organ measures the tension within the joint. In the case of Figure 20, the neuronal response is higher as the more tension is being applied in the joint.

It should be noted that the firing frequency is behaving as expected in the different fibres. As discussed before, this firing frequency is not as precise as other models that can be found in the literature but give a response that is directly proportional to the real response.

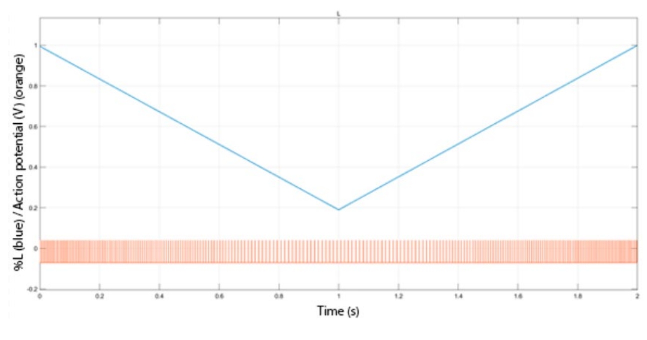


Figure 18: Type Ia fibres

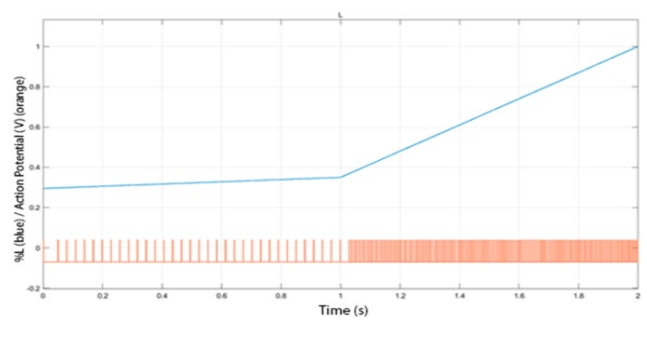


Figure 19: Type II fibres

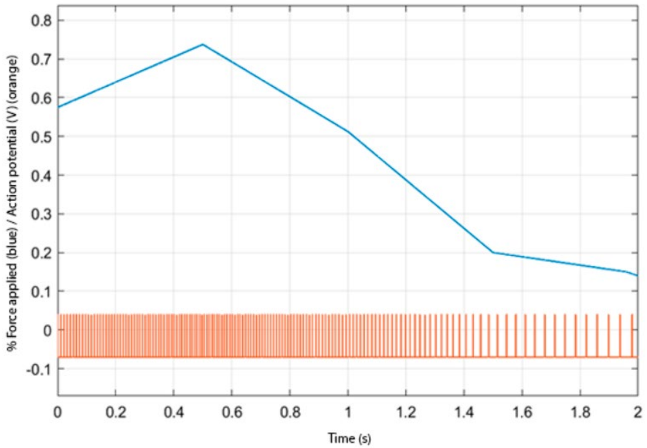


Figure 20: Type Ib fibres

3.4 Closed-loop simulation and control within the NRP

Finally, when the closed-loop system is integrated within the NRP, the resulting experiment shows as in Figure 21. The biomechanical model interacts with the exoskeleton and sends information to the virtual brain. The virtual brain then generates brain activity that in turn can be used to control the exoskeleton.

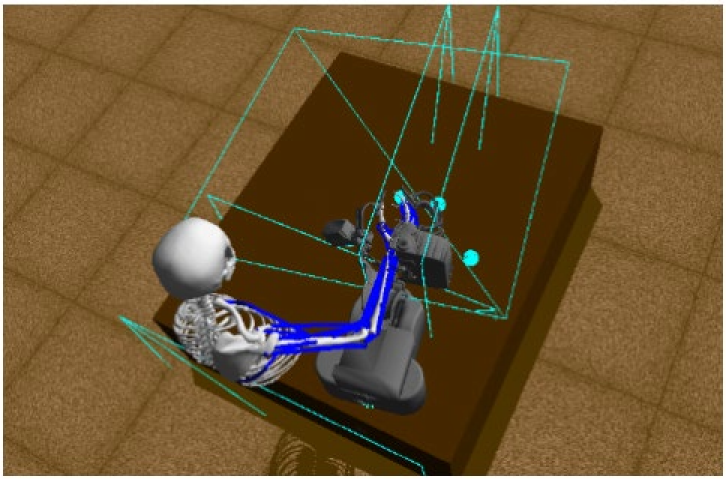
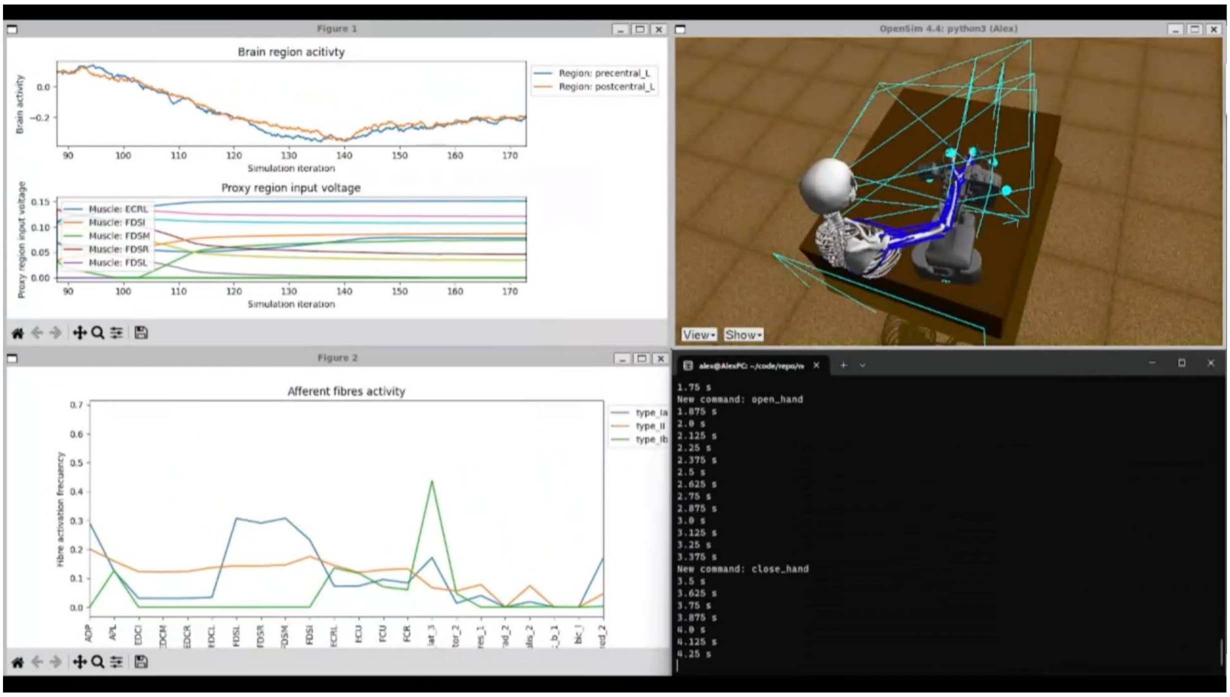


Figure 21: NRP (OpenSim + TVB) simulation



```
1.75 s
New command: open_hand
1.875 s
2.0 s
2.125 s
2.25 s
2.375 s
2.5 s
2.625 s
2.75 s
2.875 s
3.0 s
3.125 s
3.25 s
3.375 s
New command: close_hand
3.5 s
3.625 s
3.75 s
3.875 s
4.0 s
4.125 s
4.25 s
```

Figure 21: NRP (OpenSim + TVB) simulation

This exoskeleton is programmed to execute actuation in the different joints of the patient to help them perform the motor primitives mentioned in previous sections: 1) reaching movement, and 2) open-close hand.

4. Conclusions and perspectives

4.1 What we have achieved

We developed a novel biomechanical model or the upper limbs able to perform the main movements of rehabilitation and a model of the ISMORE exoskeleton. Both models are coupled in a way that allows simulation ofthe joint operation of the arm and the exoskeleton during standard rehabilitation exercises. To achieve this, we developed models for the upper limbs and the ISMORE exoskeleton. These models have been coupled in a way that can the exoskeleton can be controlled and move the arm while providing simplified afferent information to the TVB. The models are available in the repository and integrated within the NRP for further use.

Second, we used the TVB engine to simulate brain activity from a stroke patient based on data recorded during a neurorehabilitation session. This represents a first attempt to model this type of brain activity using the standard tools provided in the TVB. During this process, we have identified certain limitations in our approach that provide opportunities for further research. These opportunities range from some missing functionalities for a closed-loop simulation including the peripheral nervous system (e.g. proper afferent/efferent models), the possibility to improve the optimisation of the simulation hyperparameters or the need for different models to simulate closed-loop activity involving neural plasticity. Possible avenues of research are discussed in the next subsection.

Finally, to simulate the closed-loop system, we used the NRP, which enables connecting both engines and their communication with each other. Transceiver functions were created to make the communication as biologically plausible as possible, and an afferent and an efferent neural system were modelled and implemented for this purpose. Besides advantages in terms of usability and performance, the integration on the NRP is a first step towards the dissemination of the developed models, which are freely available.

The interconnection of these blocks results in the creation of a virtual patient engaged in a neuro-rehabilitation session. However, a notable aspect that remains unfulfilled is the implementation of this schematic design into an actual experiment. There are several open issues to achieve this. First, it is necessary to simulate task related brain activity. Based on this, it will be possible to optimize the brain models to match the activity of each patient and truly personalise the models to the patient's brain activity after the lesion. Second, the afferent and efferent pathways should be modelled in an integrated way through a spine model that simulates the connections and information flow between the brain and the peripheral nervous system. These gaps prevent the realization of a genuine digital twin that dynamically evolves with each iteration of real-time received data. The developments required for such a complete digital twin are beyond the scope of Task 5.21 which aimed at developing the coupled upper limb and prothesis models and at exploiting existing models to create a closed-loop simulator. In the next section, we discuss further research opportunities to overcome some of the limitation encountered in the development of the closed loop simulator.

4.2 Looking forward

Creating digital twins of patients is a promising approach in medicine, but it is also a massive technical challenge, for which practical implementation details remain to be demonstrated. The scope of this project was to evaluate tools produced in HBP to the create a digital twin of a stroke patient doing rehabilitation exercises with the long-term view to personalise therapy for this patient based on data obtained during a neuro-rehabilitation protocol. To this end, we leveraged some models and tools developed in the HBP (especially the NRP and TVB) as a starting point for a prototype. This in turn allowed us to identify technical limitations that will require further development and that were beyond the scope of our work.

First, our work on processing pipelines need to be applied to larger patient cohorts for verification. Indeed, given the constraint of working exclusively with data from a single patient, the model's generalizability remains unverified. A prospective avenue for future exploration thus involves extending the application of the developed pipeline to a broader cohort as more patients undergo similar procedures and contribute to the dataset. This pipeline is tailored for stroke patients and their personalized characteristics (muscle and brain activations), sets the stage for potential validation and broader applicability as a larger and more diverse patient population is incorporated into the study.

On the technical side, we identified several additional specifications that software tools need to take into account for the proper modelling of a closed-loop system. First, the TVB will need to be extended in several directions, including the ability to model motor activity instead of resting states, and the possibility of modelling plasticity in the brain after the lesion. Second, closing the loop requires modelling afferent information, allowing for its integration over time in the TVB, via a model of the spine and of the interconnection of the thalamus with the different regionsof the cortex. This is a fundamental research topic that requires collaboration of computationalneuroscientists with clinicians and biomedical engineers. We have started to work in this direction,and we believe that the first results could be obtained in the next three or four years. Given the scope and timeline of this project, some simplifications had to be made in the development of this first jointmodel of a biomechanical model of the upper limb and the virtual brain.

In particular, although theTVB model was created using state-of-the-art tools for pre-processing and simulation of resting state activity, there will bea need for specific developments to achieve a more realistic simulation of a motor task. In such context, TVB indeed lacks some utilities that wouldbe needed for its use in a digital twin. For example, the connectome is invariable so neuroplasticity cannot be modelled. Furthermore, the neural masses are optimised for resting state and our scope is to generate motor intention with it, so a new module of motor intention generation would have to be created to simulate spontaneous motor triggering within the brain.

In summary, we now have the elements of a roadmap towards a digital twin for simulation-based personalization of stroke neurorehabilitation. More generally, the results of this project have revealed important avenues for future research on digital twins that deal with the brain. They also include a first testbed to evaluate the potential benefits of brain simulation neurorehabilitation interventions, for instance, researching biomarkers related to stroke.

Annex 1: Biomechanical model of an upper limb rehabilitation

This annex describes the models of the arm and the exoskeleton used to simulate upper limb rehabilitation. The arm model has been developed from simpler models to provide the optimal functionalities required by upper limb movements in rehabilitation. Besides, a model of the ISMORE[20] exoskeleton has been implemented from scratch. Both models have been integrated and can be used together in with a compliant control to simulate join motion of the arm and the exoskeleton together.

These models have been developed keeping in mind the closed loop neuro-rehabilitation interventions of upper limb. All the models have been implemented in OpenSim. They are currently available in a private GIT repository[21] but will became public at a later stage within the NRP framework.

The rest of this section presents the rehabilitation exercises to be simulated, the arm and exoskeleton models, the motion primitives developed to control the exoskeleton and the modules developed to extract afferent information from the state of the arm.

ISMORE and rehabilitation exercises

The Figure 0.1 shows the degrees of freedom of the shoulder and elbow. This figure helps the understanding of the movements allowed with the exoskeleton.

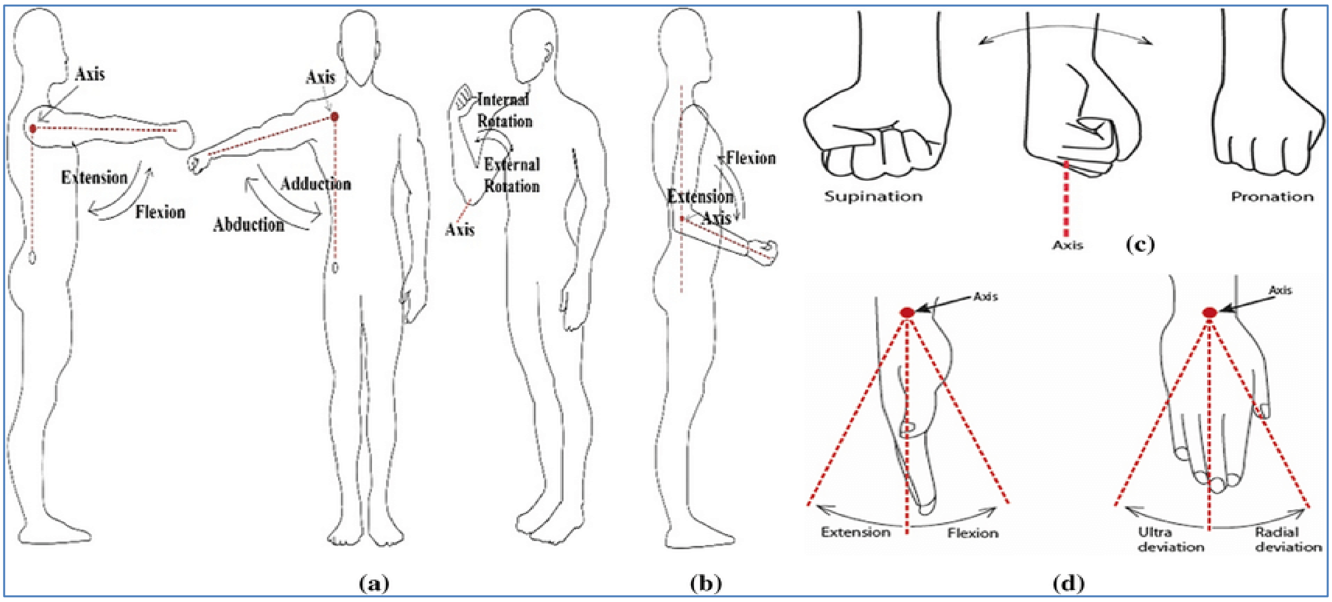


Figure 0.1: Scheme of the joint movements of the arm and shoulder[22]

The type of rehabilitation exercises depends on the type of exoskeleton to be used. In the case of the project, the digital twin is based on the ISMORE system which can move or being moved in up to 7 degrees of freedom (DOF).

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[20] ISMORE: https://www.tecnalia.com/activos/ismore-dispositivo-intracraneal-para-rehabilitacion-de-danos-neurologicos

[21] GIT repository: https://gitlab.com/hbp-bitbrain/neurorobin

[22] Schematic diagram of a shoulder flexion/extension, abduction/adduction,... | Download Scientific Diagram." https://www.researchgate.net/figure/Schematic-diagram-of-a-shoulder-flexion-extension-abduction-adduction-and_fig2_346509432 (accessed Sep. 26, 2022).

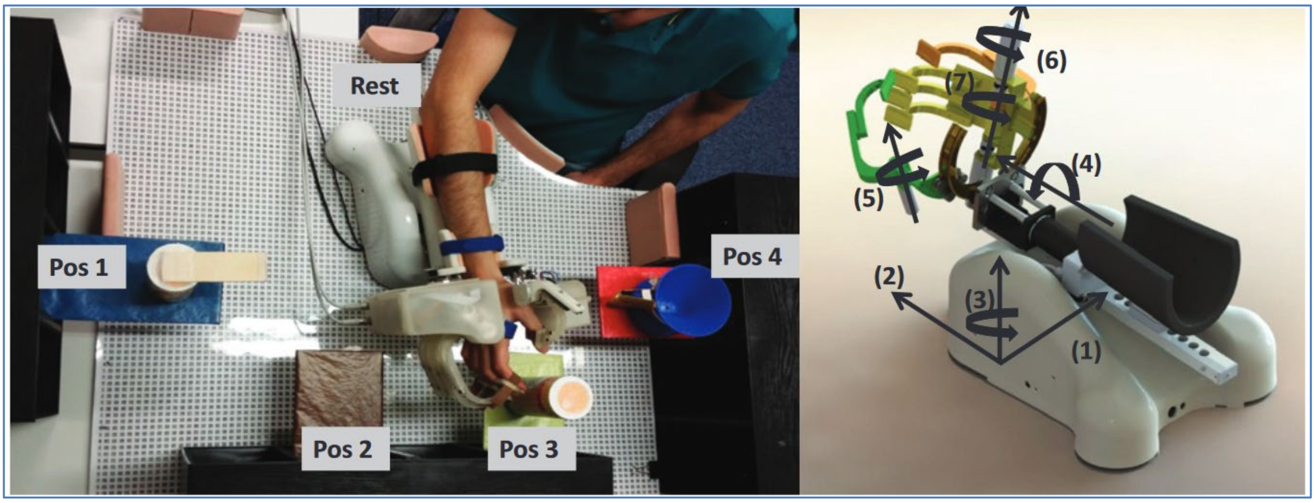

Figure 0.2: ISMORE exoskeleton

The main movements of the exoskeleton are going to be (see Figure 0.2):

- Flexo-extension of the shoulder and elbow (axis 2). When extending, the whole exoskeleton will move forward and incline the bar that holds the forearm downwards.
- Prono-supination of the arm (axis 4). The pieces holding the fingers and wrist will move synchronously with the hand when performing the rotation, the arm will rotate through the piece that holds the forearm. There is no motor in this axis, but the exoskeleton allows the movement.
- Flexo-extension of the fingers and thumb (axis 5 and axis 6+7). Each finger proximal phalanx will be extended and flexed at the same rate resulting a movement similar to a crab claw.

The movements that will not be included/modified are (see Figure 0.2):

- The translation in axis 1. This would result in an adduction-abduction of the shoulder.
- The rotation in axis 3. This would result in an internal rotation of the shoulder.
- The rotation of 6 and 7 is reduced to one to simplify the model.

The exclusion of the movements described above allows to reduce the effective number of degrees of freedom from seven to four. Hence, the OpenSim model to be developed and controlled will only have these four degrees of freedom: 2, 4, 5 and 6, 7 working together as one (see Figure 0.2).

Upper limb model

The initial step to create the upper limb model was to search for arm models that fitted our requirements of the degrees of freedom listed above. There are no current models in the OpenSim database that fitted them. However, we joined two models the arm26[23] (Figure 0.3) and wrist[24] (Figure 0.4) model. Additionally, we have added the dorsal, chest and deltoid muscles to perform extension, adduction, and abduction of the shoulder.

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[23] Arm26 model: https://github.com/opensim-org/opensim-models/blob/master/Models/Arm26/arm26.osim

[24] Wrist model: https://simtk.org/projects/wrist-model

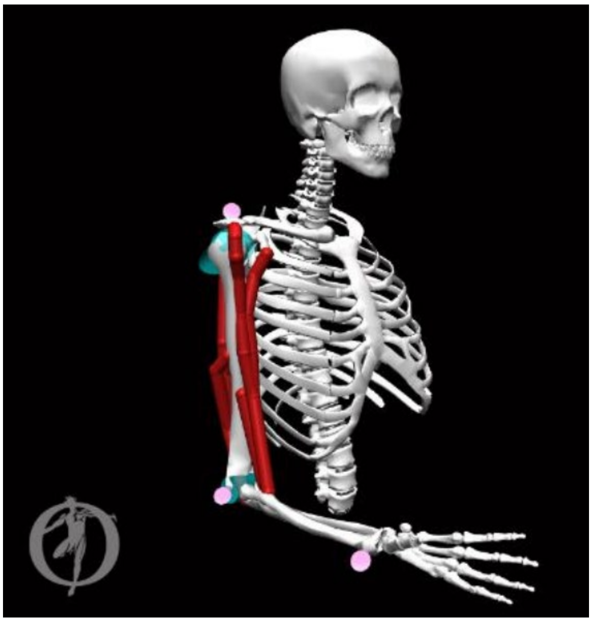

Figure 0.3: Arm26 model

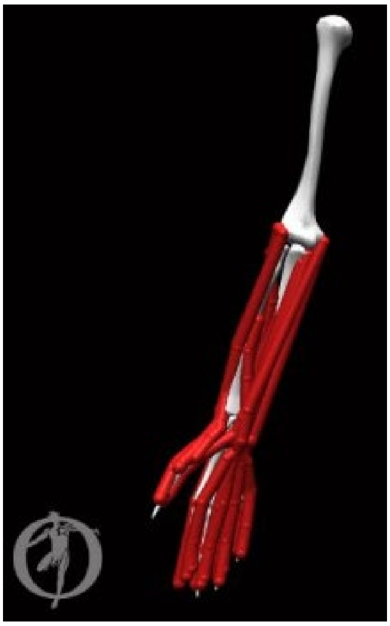

Figure 0.4: Wrist model

Figure 0.5 and Figure 0.6 show the resulting model that fits the necessities of the muscles and joints involved on the different rehabilitation movements. The biomechanical study can be read in the annexes. Nevertheless, to give general information about the model, there are 34 muscles conforming the biomechanical model:

- Pectoral, dorsal on the torso.
- Deltoid (the 3 heads), triceps (medial, long and lateral), biceps (long and short), brachial, brachioradial, pronator and supinator on the upper part of the arm.
- Flexor and extensor of the wrist and flexors and extensors of each finger on the forearm.

On top of that, two different models were modelled. One of the right arm, the paretic one and one of the left arm, the non-paretic one. The muscle activations can be changed depending on the paretic characteristics of the affected limb.

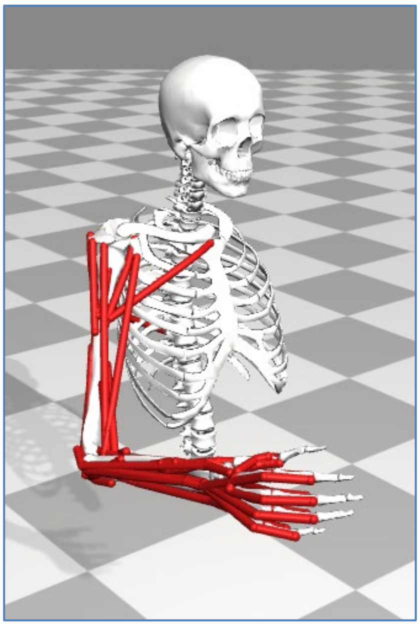

Figure 0.5: OpenSim model (right arm)

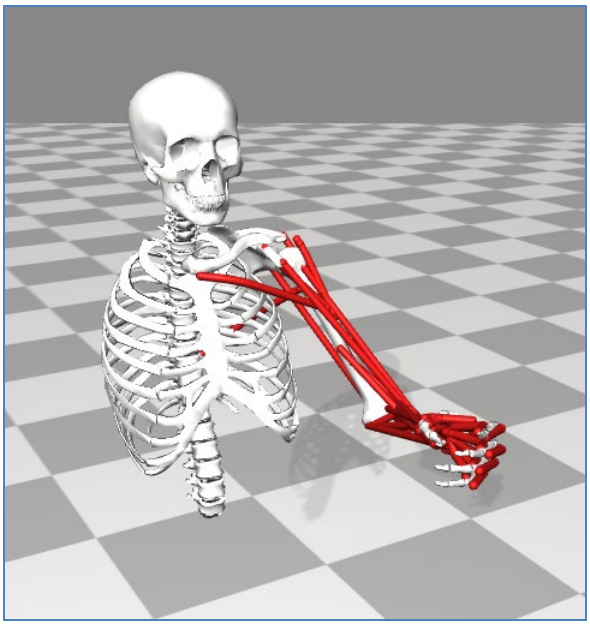

Figure 0.6: OpenSim model (left arm)

Exoskeleton model

ISMORE is an exoskeleton that is already in the market. However, it has to be modelled in OpenSim in order to interact with the biomechanical model. The modelling and control of the exoskeleton is going to be detailed in this section.

Model

To integrate the meshes of the exoskeleton to OpenSim the physical properties have to be defined. A mesh in OpenSim (Figure 0.7) is defined as a body that is connected to the rest of the bodies through a joint, additionally, it can be restricted by a constraint and moved by a force[25].

The first step was to create a body with the physical properties of each mesh. To define a body, these physical properties must be defined:

- Mass of the body.
- Centre of mass of the body.
- Moment of inertia.

These properties can be calculated with SolidWorks with the tool “calculate physical properties”. However, the mass was calculated with a weighting machine to be even more precise.

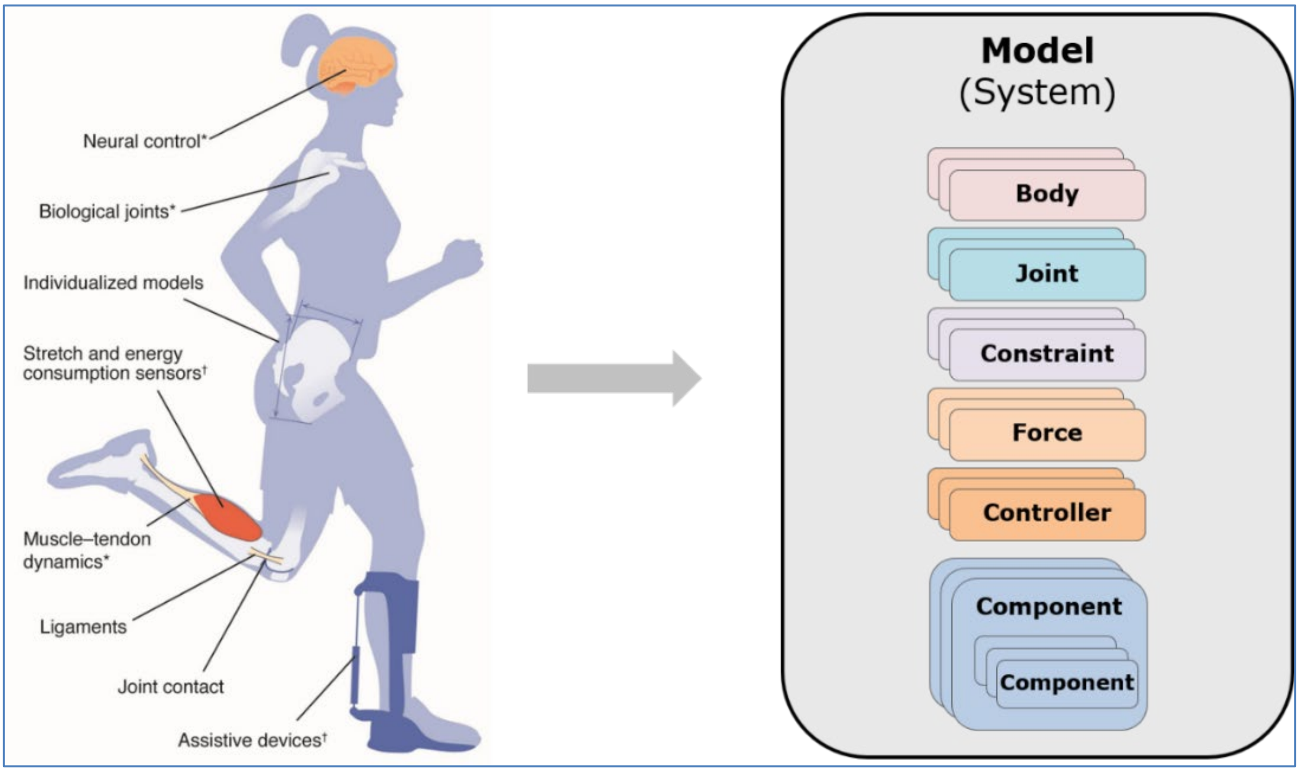

Figure 0.7: OpenSim object scheme[26].

Then, the joints let the bodies of the exoskeleton interact with each other in space. They are placed and move the same way as in real life. The resulting simulation built can be seen in Figure 0.8.

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[25] “OpenSim Models - OpenSim Documentation - Sitio global.” https://simtk-confluence.stanford.edu:8443/display/OpenSim/OpenSim+Models (accessed Oct. 06, 2022).

[26] “OpenSim Models - OpenSim Documentation - Sitio global.” https://simtk-confluence.stanford.edu:8443/display/OpenSim/OpenSim+Models (accessed Oct. 06, 2022).

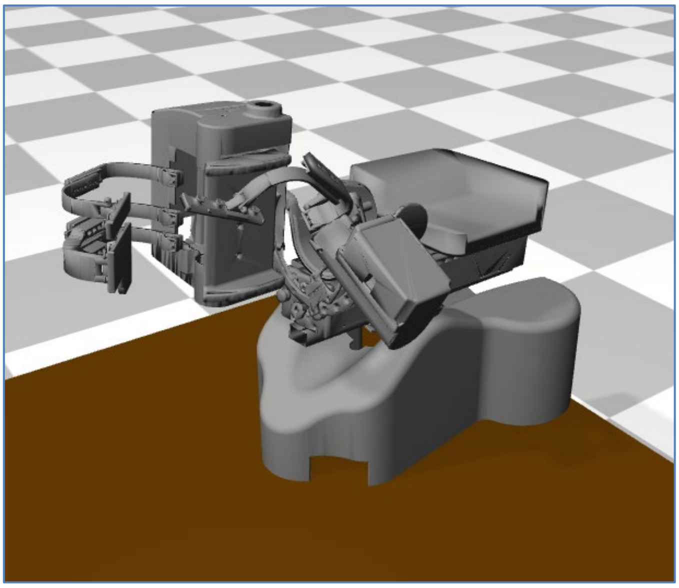

Figure 0.8: Table and exoskeleton pieces.

Exoskeleton control: Motor primitives

The exoskeleton is the responsible to guide the virtual patient to do the movements. There have been programmed different motor primitives: reach and close-open hand, which are the exercises of rehabilitation.

More precisely, the exercises developed to simulate the control between the biomechanical model and the exoskeleton consist of a command to move the robot forward (through activation of the shoulder flexors and elbow extensors) towards a marked position. Once the exoskeleton is in that position, the actuators of the fingers help the patient to close and open the hand.

The exoskeleton is controlled through a custom script implemented in the NRP platform. In this script, all the muscles of the musculoskeletal model are set with an activation of 10%, simulating a co-contraction model (characteristic of stroke patients).

Then, the motor primitives are going forward, opening the hand, and closing the hand. Depending on which state is found, one type of control or another will be applied.

While the system is in the forward state, the motor at the base of the exoskeleton is used as an actuator. Once the target position has been reached, the state changes to open hand/close hand, using the exoskeleton motors corresponding to the thumb and finger motors.

A PID algorithm is used for controlling the movements, this consists of three different parameters: proportional, integral, and derivative. The proportional value depends on the current error, the integral depends on past errors and the derivative is a prediction of future errors. The sum of these three actions is used to adjust the process by means of a control element. The speed of the coordinate is the variable used to control the PID.

Coupling the biomechanical model to the exoskeleton

OpenSim has the option to connect external pieces to the biomechanical model through constraints. The one used in this project is the Coordinate Coupler Constraint[27]. This allows to do a 1 to 1 interconnection of the exoskeleton and biomechanical model coordinates. The resulting movements can be seen in the Figure 0.9 and Figure 0.10.

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[27] "API: OpenSim::CoordinateCouplerConstraint Class Reference." https://simtk.org/api_docs/opensim/api_docs/classOpenSim_1_1CoordinateCouplerConstraint.html (accessed Oct. 06, 2022).

The drawback of this type of coupling is that does not simulate the mechanical looseness. However, it is negligible and simplifies the simulation.

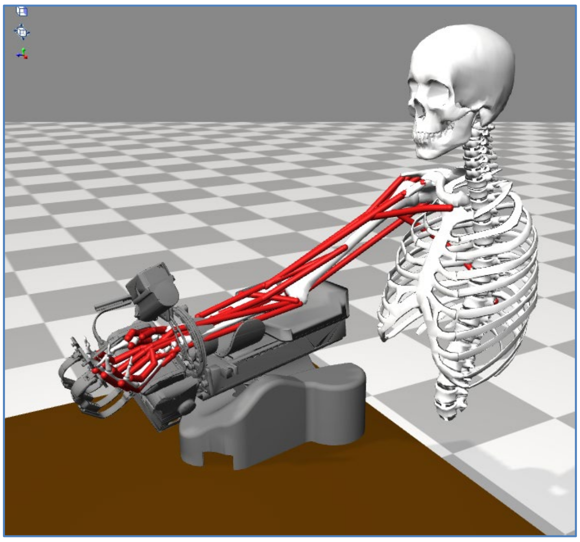

Figure 0.9: Shoulder-elbow extension, supination and finger flexion.

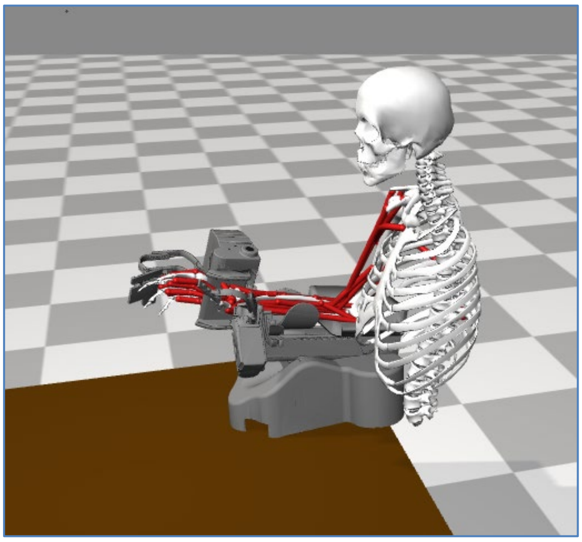

Figure 0.10: Shoulder-elbow flexion, pronation and finger extension.

Adding contact geometry

Even though there are no contact geometries in the real simulation apart from the table. Additional contact geometries have been added to constrain the movement of the model.

The different constraints can be seen in Figure 0.11, Figure 0.12 and Figure 0.13. They limit the flexo-extension of the shoulder and elbow, the flexo-extension of the fingers and the prono-supination respectively.

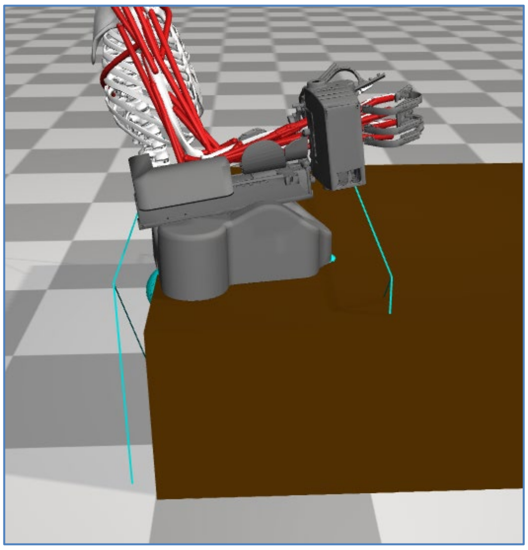

Figure 0.11: Forward-backward contact geometry.

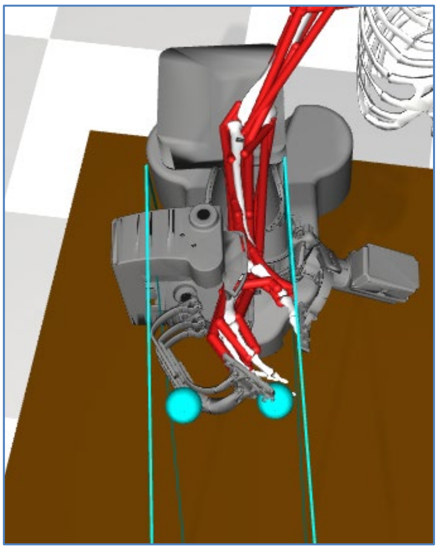

Figure 0.12: Flexo-extension contact geometry.

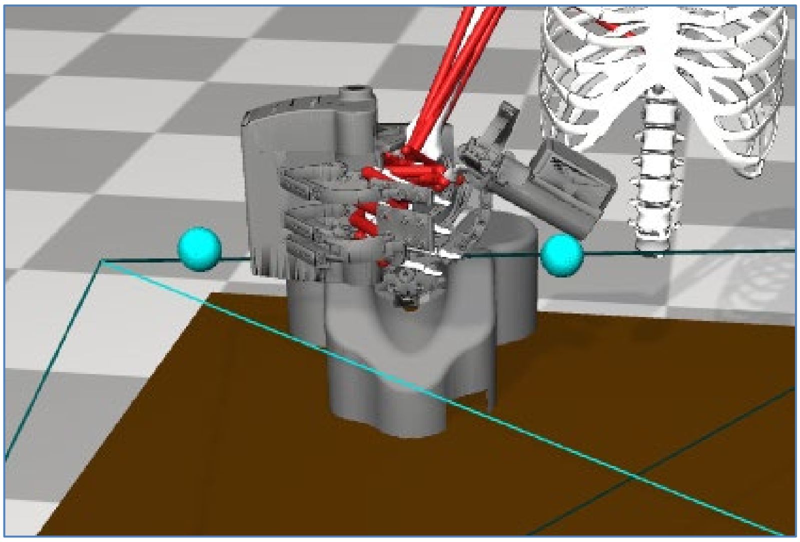

Figure 0.13: Prono-supination contact geometry.

Annex 2: Processing of stroke activity

This annex describes the data and models used to simulate brain activity for a stroke patient. The input data for our models is brain activity recorded during resting state and during motor tasks using fMRI scanners or electroencephalography systems. The data was recorded prior to the project and are provided by Tecnalia. They also contain muscular activity via electromyography recordings. This data has been pre-processed using tools provided by HBP and then imported in the TVB. In the next subsections we provide:

- A brief description of the input data used in the simulations and the protocols used to record them.
- The pre-processing pipeline used to convert the input data into the data formats required by the TVB. Here we describe mainly those aspects that required certain adaptation of the automatic pipeline. We also provide links to the results of the pre-processing and the scripts required to reproduce the results.

Input data

Tecnalia provided us with MRI images of a stroke patient to create a virtual brain. The different modalities needed are T1w image, diffusion weighted images and fMRI images. This data can be consulted in the repository of the project[28].

The T1w imaging (Figure 0.1) is the most popular MRI modality used in medicine, with this technique it is obtained a high-resolution image with a high time of acquisition. It is used to create an anatomical high-resolution base to differentiate between tissues like white and grey matter or cerebrospinal fluid. It is also used to create the cortical surface.

The DWI (Figure 0.2) is another modality of MRI which obtains an image of the water diffusion within the brain. It is used to create a tractography from the diffusion tensors of the water molecules through the neuron axons and subsequently a connectome of the different zones of the brain.

Finally, the fMRI (Figure 0.3) is a low-resolution data acquisition technique but faster than the T1w, then the changes in blood oxygenation levels can be acquired which is directly correlated to the activation of the brain regions. It is used to adapt the patrons of brain activation during the experiment to the virtual brain.

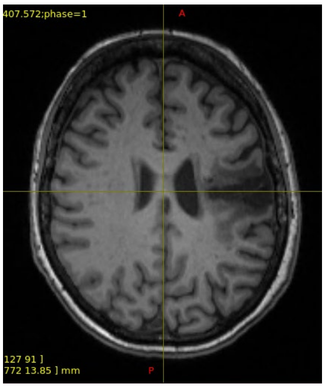

Figure 0.1: T1w stroke MRI image.

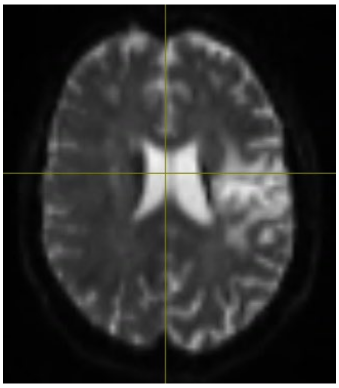

Figure 0.2: DWI stroke MRI image.

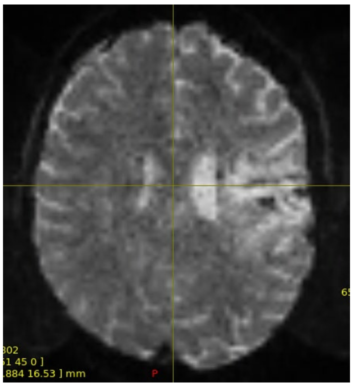

Figure 0.3: fMRI stroke MRI image.

In addition to the MRI images there was recorded EEG and EMG during the experiment.

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[28] https://gitlab.com/hbp-bitbrain/neurorobin

The EMG signals can be used to assure that the patient is moving the limb in the time instant marked in the experiment route or the level of co-activation of the paretic limb. It is recorded with bipolar Ag/AgCl electrodes adhered to the extensor and flexor digiti, biceps and triceps of both limbs. However, there can be seen in Figure 0.4 that the patient cannot move the paretic limb when he has to. In the Y axis represents the activation / type of exercise (blue) and the X axis represents time each 1 sample each 5ms.

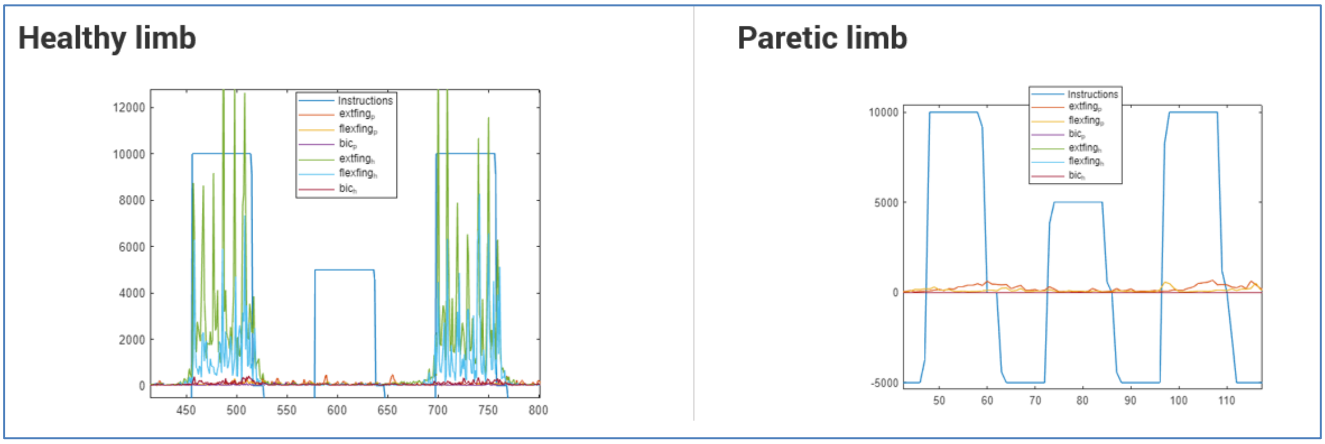

Figure 0.4: EMG recorded during the experiment with both limbs.

On the other hand, the EEG can be used for parameter optimization or extract features of movement of the patient. The EEG recorded with a 32 channels cap (Figure 0.5). And the target electrodes are the ones marked in red.

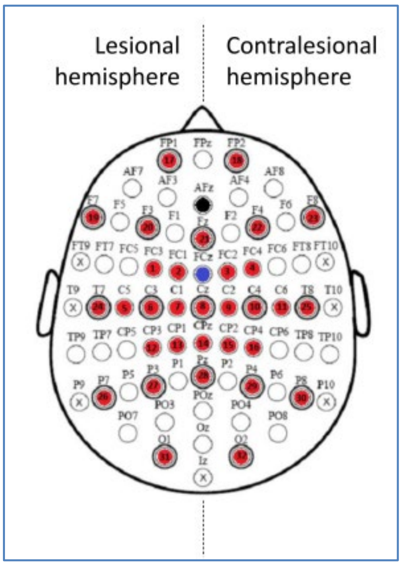

Figure 0.5: EEG configuration during the experiment.

Data acquisition

The data acquired was acquired in different sessions. These can be divided into 3:

- T1w and DWI imaging: The patient remains steady during the signal acquisition.
- fMRI and EMG: The patient performs rehabilitation exercises of the upper limb.
- EEG and EMG: The patient performs the same rehabilitation exercises in another session.

The rehabilitation exercises are recorded for both limbs, paretic and non-paretic. Moreover, the data acquisition is done before the rehabilitation sessions and after, when some neuroplasticity has occurred.

This experiment has different events and can be seen in Figure 0.6. This table describes one loop of the different cycles of the experiment. The whole experiment lasts 248 seconds.

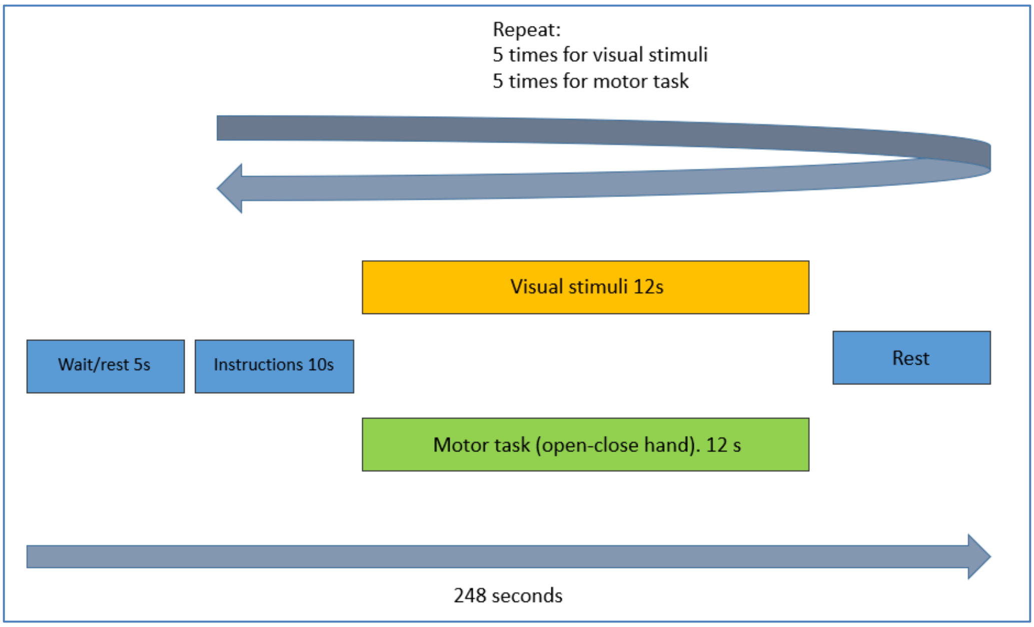

Figure 0.6: Simplified experiment event scheme.

- The patient receives instructions. E.g., the arm that has to be used, and the “ready, set, go”. This lasts 10 seconds.
- Then the patient sees some images or executes the motor task, depending on the instructions on the screen. This lasts 12 seconds.

This cycle is repeated 10 times, 5 for watching images and 5 for motor task.

BIDS format

The different layers of an MRI volume are stored in the DICOM format, which is a format used in medical applications.

To use them in the pipelines, the data must be translated into a NIFTI (volume) file and a json file containing the properties of the image acquisition. The function used is dcm2niix[29] that transforms a folder of DICOM images into a .nii volume and a json file[30].

The input folders are organized in the BIDS format which is a standard organization of the file system to pre-process files in neuroimaging[31]. This organization for our files can be consulted in the Gitlab repository[32].

The different modalities of MRI are stored in different folders:

- “anat”: The T1w Nifti volume is stored in, the file name is “sub-Tecnalia_T1w”.
- “dwi”: The DWI volumes of different magnetic field values stored in. An example of file is “sub-Tecnalia_acq-b1000_dwi”.

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[29] Dcm2niix: https://github.com/rordenlab/dcm2niix

[30] “GitHub - rordenlab/dcm2niix: dcm2nii DICOM to NIfTI converter: compiled versions available from NITRC.” https://github.com/rordenlab/dcm2niix (accessed Sep. 26, 2022).

[31] “Brain Imaging Data Structure.” https://bids.neuroimaging.io/ (accessed Jan. 13, 2023).

[32] GitLab Repository: https://gitlab.com/hbp-bitbrain/neurorobin

- “func”: Here it is stored the fMRI images concatenated in a unique volume, it is also stored the event file with the corresponding events happening through the experiment. An example of file is “sub-Tecnalia_task-closeopen_bold”.

Pre-processing

There are different automated pre-processing pipelines to transform the raw data obtained from MRI to the files needed for the virtual brain. Specifically, there are three and they are run in Linux in docker containers:

Mrtirx3_connectome: Uses the anatomical images and the diffusion weighted images to create a tractography and then a structural connectome (SC). This SC is a matrix that represents the structural connection between the functional zones of the brain.

fMRIprep: This uses anatomical and functional images to calculate the BOLD signal of each pixel. It registers the anatomical and functional images into the same space and identifies the activation of each functional zone into a time series region.

Tvb_converter: This pipeline is specific of the HBP and uses the output files of the two previous pipelines. Transforms some data into text files that can be ridden by the TVB software. Moreover, it creates data from these files like meshes of skull and scalp and projections for EEG, etc.

Mrtrix3_connectome

MRtrix3_connectome[33] enables generation and subsequent group analysis of structural connectomes generated from diffusion MRI data. The analysis pipeline relies primarily on the MRtrix3 software package and includes a number of state-of-the-art methods for image processing, tractography reconstruction, connectome generation and inter-subject connection density normalization. The version used is the 0.4.2 that is the one compatible with the latest version of the tvb_converter pipeline.

As it is an automated pipeline the individual steps of the pipeline will not be discussed. However, there were some issues during the execution, so this is going to be discussed in the following paragraphs.

There were not reverse encoded images to correct the distortion correction in the EPI images provided. However, we were provided with gradient echo images that can be used to correct it, but it is not implemented in the pipeline[34].

In order to correct it, all DWI/fMRI images were concatenated in order to have a 4D volume of all the images and apply pre-processing functions to all of them at the same time.

Some previous pre-processing steps functions were applied like dwidenoise and mrdegibbs to delete noise components.

The last step in the pipeline of the pre-processing is the distortion correction done with dwipreproc. An alternative tool that is used to do the distortion correction of EPI images that are distorted due to magnetic field inhomogeneities is FSL FUGUE[35].

- The first step is to extract the brain, this was done with “bet” with a high factor of tightness. One of the most important factors is to eliminate the skull completely from the image.
- Then, prepare the field map with the phase image, the EPI image, and the delta TE.
- Thirdly, prepare a gaussian mask to apply to the image.

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[33] MRtrix3_connectome: https://github.com/BIDS-Apps/MRtrix3_connectome

[34] “OSF | fMRI Wiki.” https://osf.io/k6rm5/wiki/1.1_Field_map_correction/ (accessed Oct. 07, 2022).

[35] FSL FUGUE: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FUGUE

- Finally, apply the distortion correction to the image.

The distortion of the field extracted is shown in Figure 0.7.

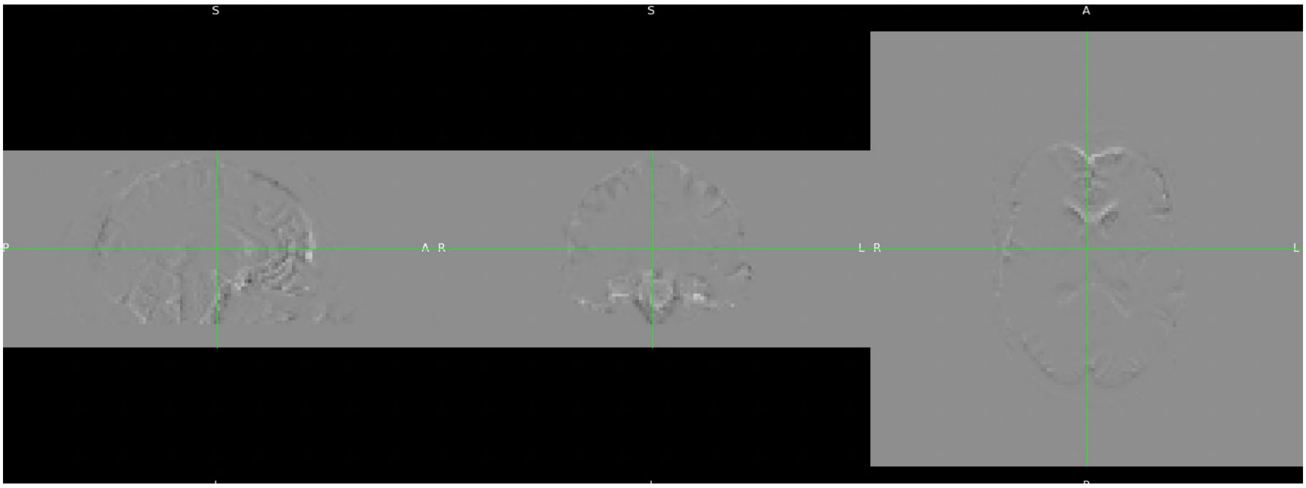

Figure 0.7: Difference between EPI images.

Moreover, to assure that there are no tracks calculated through the non-functional tissue, the lesion has been segmented and extracted from the images that are used to calculate the tracts. The result is shown in Figure 0.8.

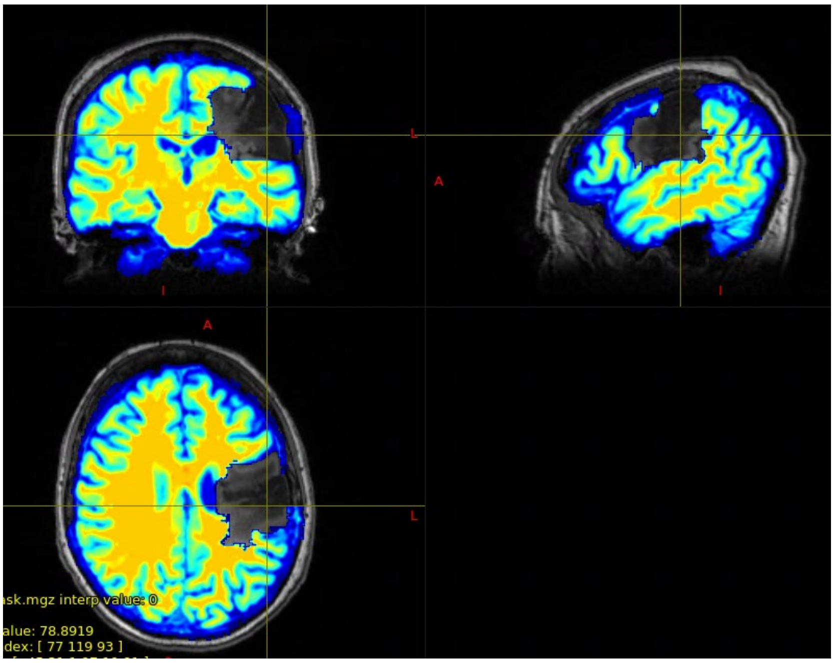

Figure 0.8: Brain mask excluding brain lesion.

On the other hand, there was applied the virtual brain transplant technique[36] which copies the same pixel information from the mirror healthy zone of the brain, and it is copied to the stroke zone (Figure 0.9 left). This had to be done due to the registration techniques of the pipelines which do not work well with there are necrosed tissue in the brain.

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[36] "Virtual brain transplantation (VBT): a method for accurate image registration and parcellation in large cortical stroke - PubMed." https://pubmed.ncbi.nlm.nih.gov/21175010/ (accessed Jan. 02, 2023).

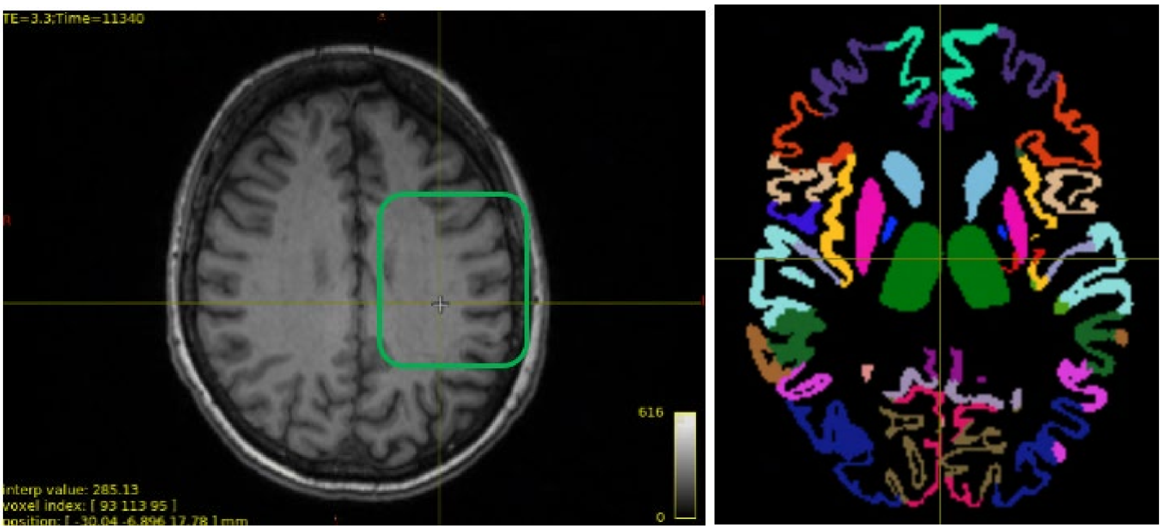

Figure 0.9: T1 image with virtual brain transplant (left) and Desikan cortex labelling (right).

When the pipeline finishes, there are some outputs files that can be checked. One of the main outputs files is the parcellation of the brain where the cortex is be labelled in different functional regions. In the case of this project, the one used is Desikan. The parcellation of the brain's project can be seen Figure 0.9 (right).

The track generation is anatomically constraint (ACT). This means that the track calculation is done in the zones that are possible to exist, other zones like CSF or the non-functional region are excluded.

The Figure 0.10, shows a reduced tractogram done with tckedit, reducing the number of tracts to 200k. Moreover, it can be observed there is no tracts in the stroke zone.

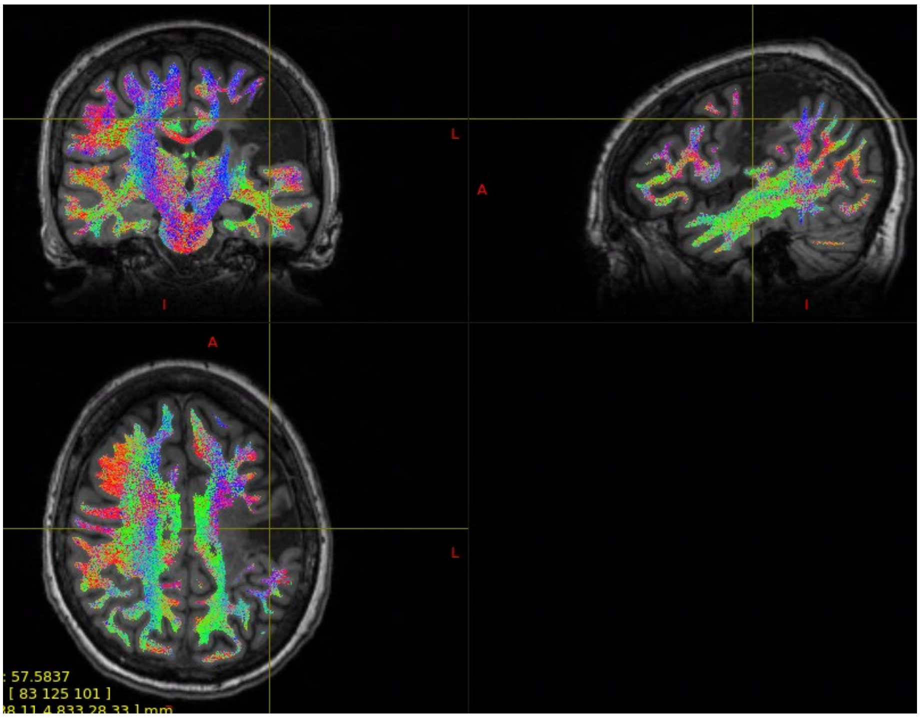

Figure 0.10: Reduced tractogram of stroke patient.

fMRIPrep

fMRIPrep is a robust and easy-to-use pipeline for pre-processing of diverse fMRI data. The transparent workflow dispenses of manual intervention, thereby ensuring the reproducibility of the results.

The version used for fMRIprep is the 20.1.1, the degrees of freedom for bold to t1w registration are 6 and the template image is MNI152NLin6Asym.

Before initializing the pipeline, the field map was corrected using the same tool and the same steps as the previous pipeline.

fMRIprep does different steps to pre-process and process all the fMRI information, T1w image and events. One of the main steps is the registration of the fMRI images to the T1 images and the BOLD signal calculation on each pixel. These can be seen in the images below (Figure 0.11, Figure 0.12 and Figure 0.13).

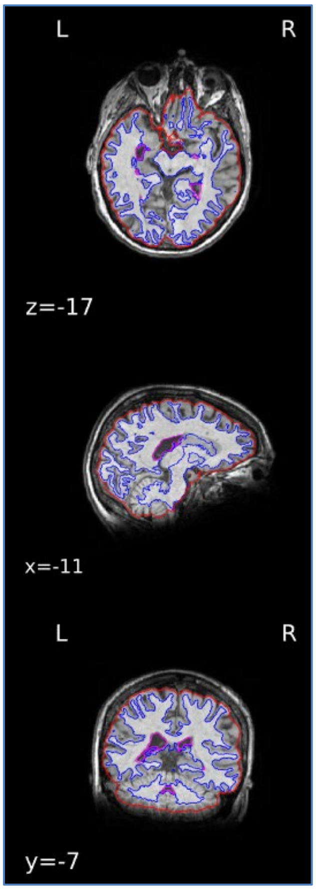

Figure 0.11: T1w image segmented.

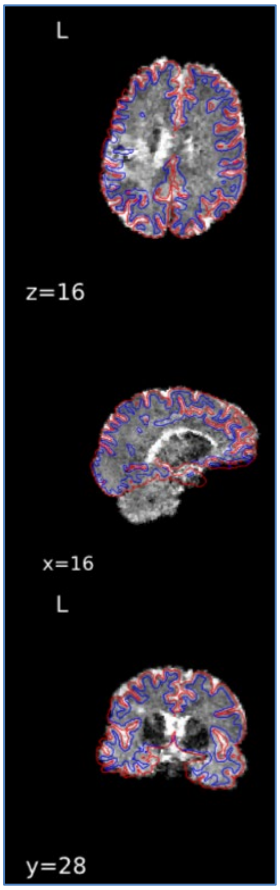

Figure 0.12: BOLD image registered and segmented.

This plot shows the intensity of values of each voxel during the experiment.

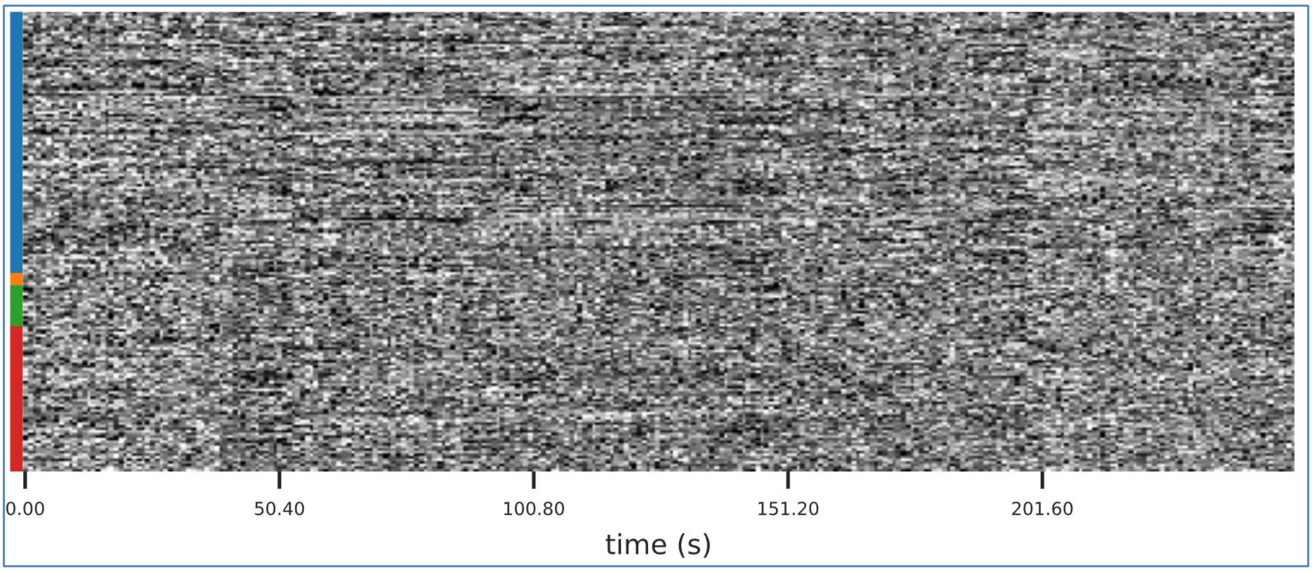

Figure 0.13: Carpet plot of the intensity values of each voxel.

TVB converter

It performs several post processing operations on the outputs of upstream structural/functional connectome BIDS Apps such as: non- aggressive cleaning of fMRI data using AROMA noise components, resampling of parcellation image from MRtrix docker pipeline to fMRI resolution, extraction of region-average fMRI time series, create region-mapping for volume-based parcellations, create cortical-surface and region- mapping. In addition, M/EEG source models are generated involving the computation of BEM head models and dipole forward model to compute lead field models importable to TVB.

One of the main issues that we had to overcome with this pipeline was to fix the BEM surfaces generated by the MNE mri_watershed function. An error occurs when checking if the skin and outer skull are outside the cortical and inner skull surfaces.

This error is caused when the subject is anonymized, this technique deletes the face. This does not affect the brain masking. However, the skin surface is not calculated correctly. This can be seen in Figure 0.14, where the brain mask surpasses the skull and skin surface at the inferior part of the volume.

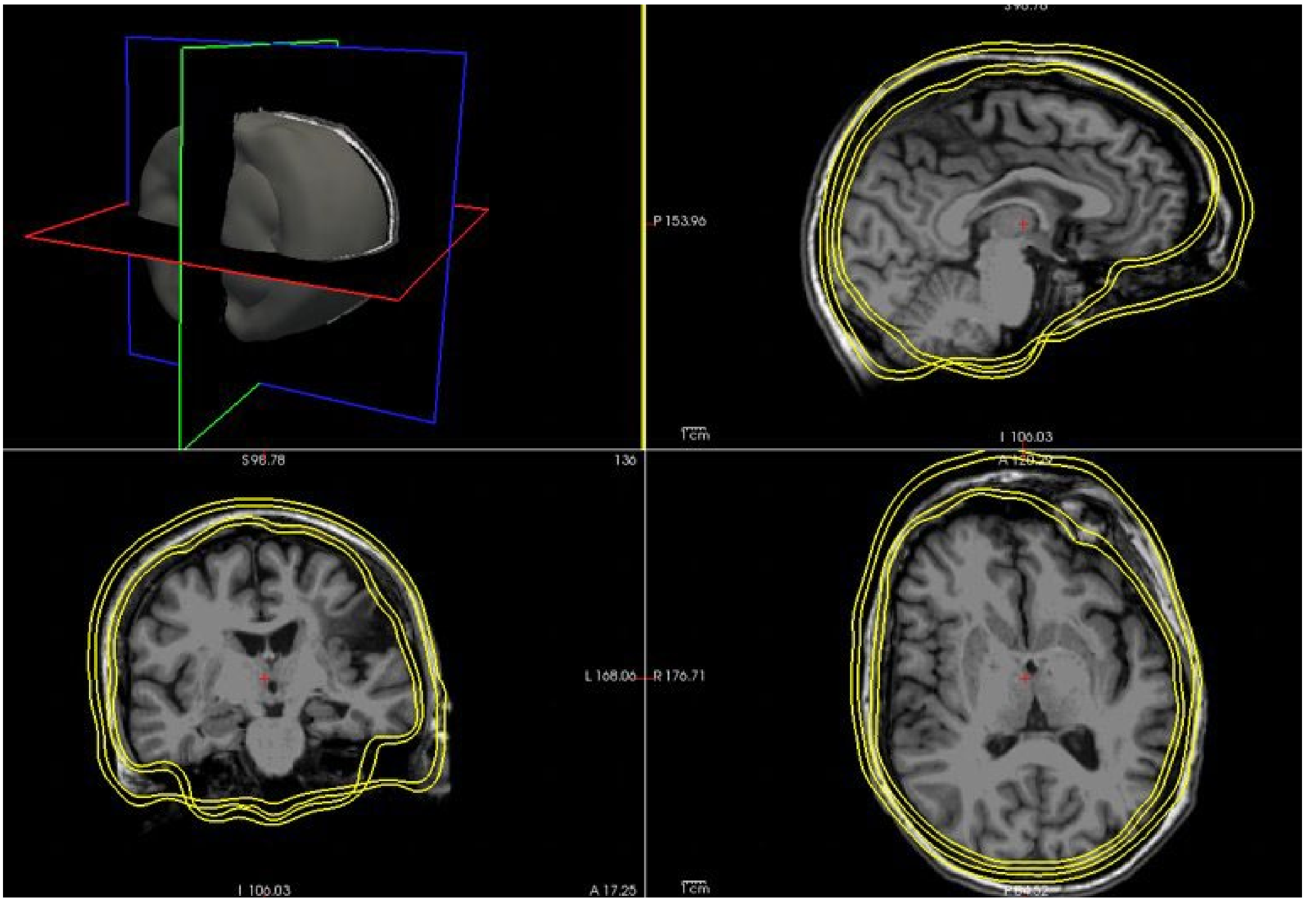

Figure 0.14: MRI_watershed surfaces.

The solution that was taken to this problem was to lower the five percent of the lowest vertices of the surface of the outer skin and outer skull by some millimetres to fit the surfaces.

The resulting surfaces can be seen in Figure 0.15 (left) where the brain and inner skull surfaces are completely inside of the other outer surfaces.

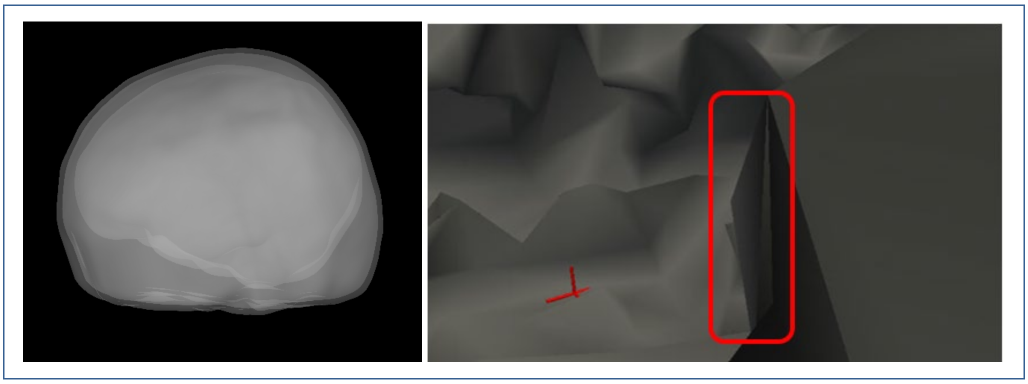

Figure 0.15: Fixed surfaces (left) and cortex internal triangles (right).

Whereas regarding the cortex surface was found to have internal triangles that had to be corrected like the ones in Figure 0.15 (right). The vertices were deleted, and the triangles were reordered. Therefore, the region mapping had to be modified too.

Another issue that had to be faced was that the thalamus triangles that are labelled as unknown triangles (black triangles in Figure 0.16). Those conform part of the cortex if deleted, a hole in the surface would be created.

Those were relabelled to right and left thalamus. And the unknown label, which corresponds to 0, is deleted.

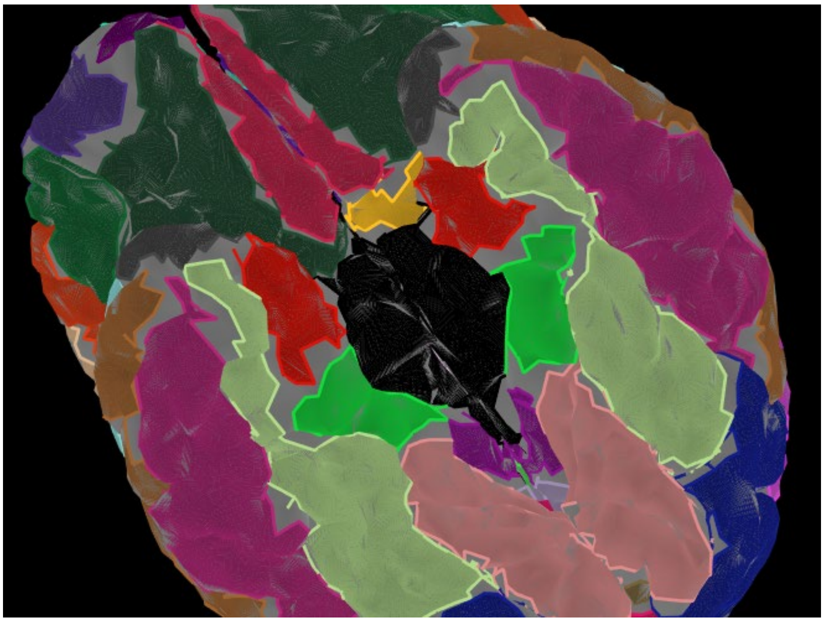

Figure 0.16: Surface labelling, black triangles correspond to both right and left thalamus.

The outputs files obtained from the pipeline are:

- A region map that maps source space (cortical surface) with parcellation regions.
- Cortical surface triangulation (source space).
- BEM inner skull, outer skull, outer skin surface triangulation.
- EEG sensor locations.
- Structural connectome: connection weights, distances, and region centres.
- Region orientations.
- Region areas.

These output data is converted into TVB-importable format.