

CDP1 Annual Compound Deliverable Year 2
D1.3.2 - SGA2

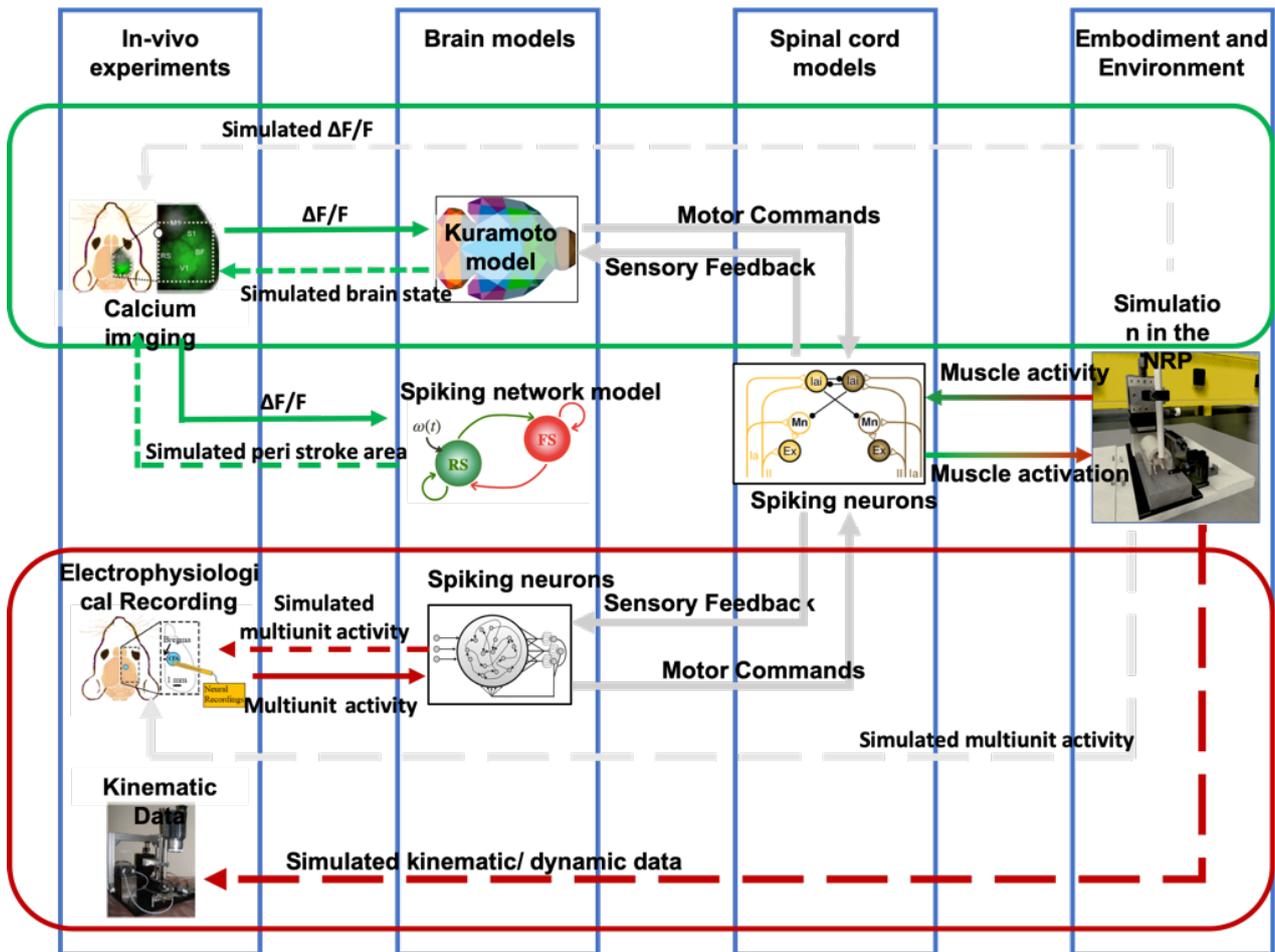


Figure 1: Closed loop experiments in CDP1

Closed-loop experiments in CDP1, guiding the development of the Mouse Brain Atlas, HBP Whole Brain simulations and virtual experiments. This figure is from the collective paper (Allegra Mascaro, Falotico, Petkosky *et al.* P2535, *in press*). Scheme of data and simulations. The upper path shows the Kuramoto pipeline, the lower shows the Spiking neurons pipeline. Connections between the components are presented as arrows: solid lines represent the output provided to other blocks; dashed lines indicate the output data of the models that are used for comparison with real data for validation. In gray, models and connections that are being refined.

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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:	This document shows outputs consolidated in the second year of SGA2 for Key Results obtained in CDP1 (KRc1.1, KRc1.2 and KRc1.3, respectively in Sections 3, 0 and 5). On the experimental side (KRc1.1), CDP1 exploits pioneering imaging techniques to produce mouse whole-brain functional and anatomical observations, enriching datasets available in the Mouse Brain Atlas of EBRAINS platform. Moreover, KRc1.1 developed the experiment for investigating the motor-evoked cortical plasticity in rehabilitated mice after stroke. This experiment has been used as a paradigm to drive the development of several models (KRc1.2) and tools to build a simulation framework (KRc1.3) with a closed-loop validation approach. This has been used as a paradigm experiment to dissect brain plasticity and connectivity. The post-stroke robotic rehabilitation experiment has been realised on the Neurorobotics Platform, thanks to a modelling effort that focused, on the neural side, on models of the motor cortices and their interactions with the spinal circuitry, and, on the physics side, on realistic musculoskeletal and robotic models.		
Keywords:	whole mouse brain connectome data, mouse spatio-temporal functional data, mouse multi-level models, rodent virtual behavioural experiments		
Target Users/Readers:	Neuroscientific community, Platform users, Clinicians		

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History of Changes made to this Deliverable (post Submission)

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18 May 2020	Deliverable submitted to EC
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1. Overview

The long term goal of this Co-Design Project 1 (CDP1) was to integrate contributions from multiple SPs aimed at developing a multi-level model of the whole mouse brain, and the corresponding mouse brain atlas. The workflow proposed by CDP1 was an iterative loop between experiments and simulation, which allows on one side to refine and validate models with experimental data and, on the other side, to redesign experiments based on simulations. This framework will allow neuroscientists to formulate and run their experiments on the HBP Infrastructure and to access and analyse results.

To make these goals tangible, CDP1 focused on real experiments on mice. These were used as representative paradigms of a larger class of experiments that users can perform using HBP Brain models and Platforms. This ensures that the mouse brain model and mouse brain atlas is useful to theoretical and experimental neuroscientists in many contexts.

CDP1 orchestrated the efforts from various HBP Subprojects to develop a workflow integrating complementary languages and standards - both on simulation and experimental side. This synergic action produced a new set of features and capabilities and advanced the quality of mouse atlas and mouse brain models together with experimental platforms and data. Experiments chosen to develop such an infrastructure were the motor task and the stroke model, but the final goal was the implementation of the cross-Subprojects workflow to be extended to a variety of others experiments.

The focal stroke model is a useful paradigm to dissect brain plasticity and connectivity. This is true both from an experimental and modelling side, since it uniquely allows investigating the features of brain activation and brain remapping when a crucial node is detached from the network.

In the collective paper (Allegra Mascarò, Falotico, Petkoski *et al.* P2535, *in press*) we explored the steps and methods that are needed to develop a simulation model (Embodied Brain) of a complete experiment on stroke and rehabilitation.

2. Introduction

The collaborative framework developed within CDP1 is innovative for two reasons: 1) it merges **cutting-edge activities at the experimental and simulation level**; 2) it allows building a new conception of **closed-loop neuroscience**, where experiments drive simulations and simulations guide experimental design. In this new conceptual framework, experiments are built and validated on theoretical models and virtual platforms, and *vice versa*. In addition, the **tight collaboration between experimental neuroscientists and model developers** is a unique opportunity for a cultural shift, where the experimental paradigm is better constructed based on theoretical predictions. This combined experimental and simulation approach is unique in the wide neuroscientific community and offers the possibility to investigate motor learning on a multitude of levels.

This document shows Outputs consolidated in the second year of SGA2 for the 3 Key Results (KRs) (Sections 3, 0 and 5) obtained in CDP1.

In detail, on the experimental side (KRc1.1), CDP1 exploits **pioneering imaging techniques** applied to the study of system neuroscience, i.e. light-sheet microscopy, simultaneous large field-of-view imaging in awake animals. Light-sheet microscopy is used to perform **high-resolution mapping** of different neuronal populations in the entire encephalon, providing robust basis to build **realistic models** of rodent brain. We are also **developing tools to understand basic mechanisms of neuronal computation**, e.g. through the investigation of the contribution of different cortical layers or different neuronal compartments to the global signal we record over the entire cortex by using wide-field imaging, or on the modulation of large-scale activity in the transition from deep anaesthesia to awake conditions.

To simulate the paradigm experiment produced in KRc1.1 in its entirety, many building blocks were developed in KRc1.2 and KRc1.3. In detail, KRc1.2 developed several models to simulate brain activity in different brain states, taking into account the many scales of complexity of the brain. Brain network models were refined and validated on data before and in the acute and chronic phase during rehabilitation after stroke (Output 1). A calcium-to-spike transfer function was developed to explain and model the calcium activity (Output 2). Models of spiking activity and wave propagation were built and validated on the calcium data at multiple resolution in anaesthetised and awake conditions (Outputs 3-4). These models are key tools to describe the abnormal activity in the peri-infarct area of the stroke brain (Carmichael and Chesselet, 2002; Rijdsdijk *et al.*, 2008; Rabiller *et al.*, 2015, Nghiem *et al.*, 2018). A spiking model of cortical activity that can simulate the effect of a stroke in the motor cortex and the partial recovery of connectivity (Output 5) has been developed and used in KRc1.3.

KRc1.3 realised the simulation of the embodied mouse within the virtual environment: all the neural components developed were integrated together in a virtual mouse, implemented in the Neurorobotics Platform (NRP) (Output 1) and used to perform simulations of the post-stroke robotic rehabilitation experiment (Output 3), together with the physical simulated models.

3. Key Result KRc1.1 Exploration of spatio-temporal functional and anatomical data

3.1 Outputs

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to this KR

- Output 1: Storage, curation, and public dissemination of CDP1 datasets (C2242, C1765, C1742, C1745)
- Output 2: Functional connectivity of cortical neurons on GCaMP6f mice (C1765, C2304, C2391)
- Output 3: Whole-brain datasets at sub-cellular resolution (C1798, C1797, C1761)

3.1.1.2 How Outputs relate to each other and the Key Result

Output 1 is particularly referred to for the curation process of specific datasets used for the model validation (Output 2), it even has been applied under different conditions on all HBP datasets, including those of the whole-brain dataset (Output 3). Through the Output 1, integrating curated datasets in the Knowledge Graph, we reached the final goal of this KRc1.1: to enable the exploration and sharing of brain datasets (Output 2 and 3).

3.1.2 Output 1: Storage, curation and public dissemination of CDP1 datasets

The main activity from the curation team for CDP1 referred to calcium imaging datasets, since whole-brain datasets have been curated in the context of SP1.

The calcium imaging data (Output 2 of KRc1.1) were submitted to EBRAINS and shared in accordance with the F.A.I.R. Principles. Basic metadata were assigned using the EBRAINS curation services (see Figure 2).

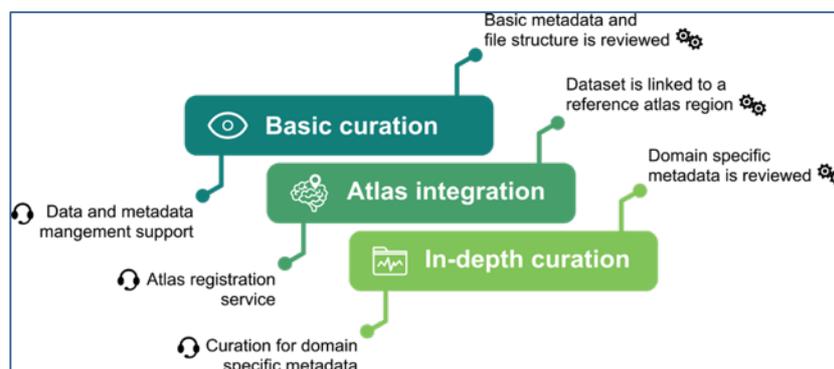


Figure 2: Curation services in EBRAINS

Diagram illustrating the three-tiered curation service offered for integration of multilevel and multimodal neuroscience data in the EBRAINS platform in agreement with the FAIR principles.

The anatomical position of the calcium imaging recordings were defined by stereotaxic landmarks that were transferred to the Allen Mouse Brain common coordinate framework, using the HBP tool

QuickNii ([RRID¹: SCR_016854²](https://scicrunch.org/resolver/RRID:SCR_016854)) to register landmarks, adjust for the 5 degree camera tilt, and project atlas delineations from cortical layer IV onto the camera field of view (see Figure 3).

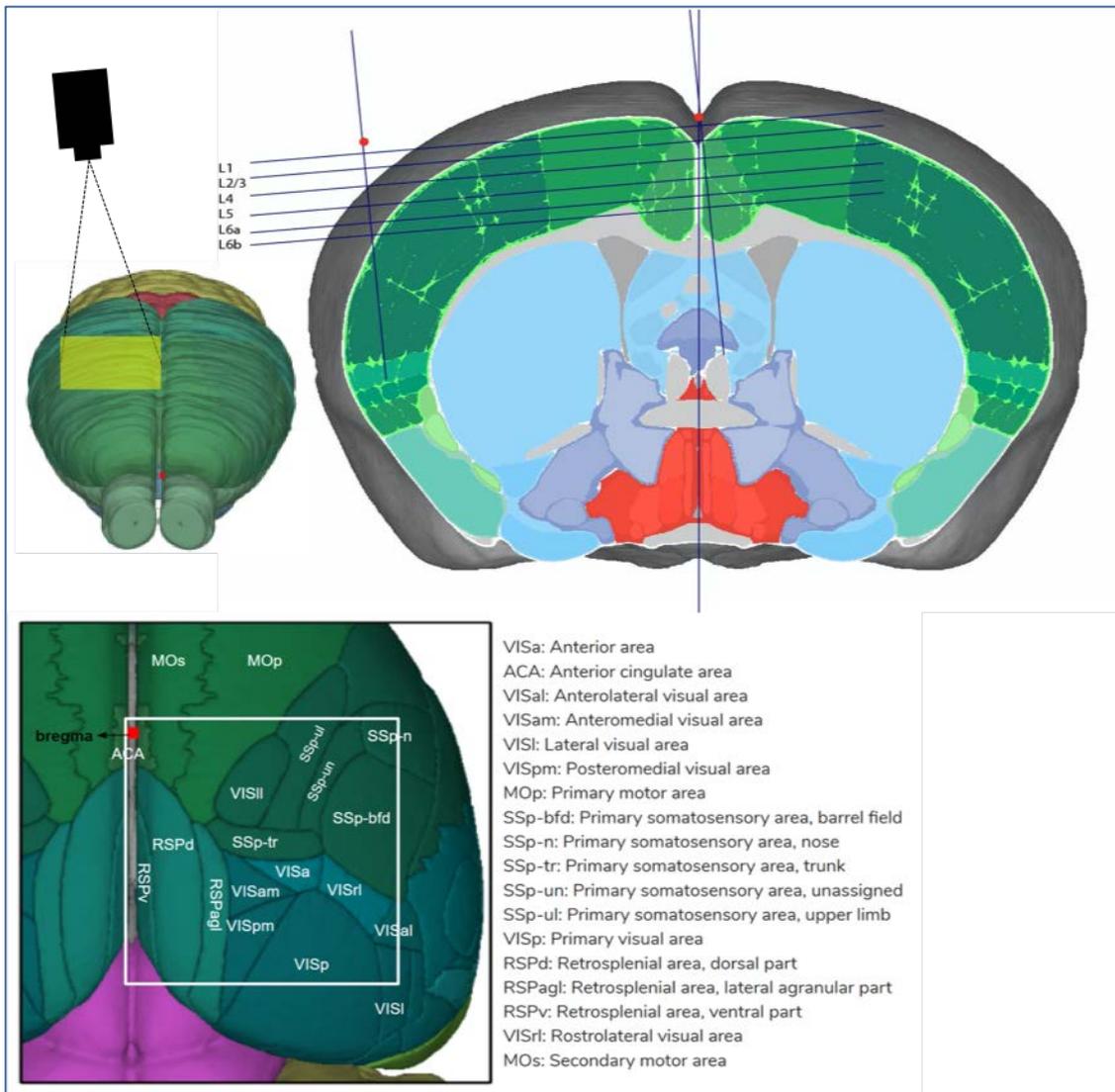


Figure 3: Registration of Calcium imaging

Illustration showing the spatial registration of the standard field of view used for calcium imaging to the Allen Mouse Brain reference atlas using stereotaxic coordinates and geometric correction for camera tilt. The resulting custom atlas map provides an overview of atlas subregions of relevance for the functional activity maps.

Table 1: Output 1 Links.

Component	Link to	URL
C2242	Software Repository	https://www.doi.org/10.25493/A0XN-XC1
	Technical Documentation	https://collab.humanbrainproject.eu/#/collab/5484/nav/42798
	User Documentation	https://collab.humanbrainproject.eu/#/collab/5484/nav/42798

¹ <https://scicrunch.org/resources>

² https://scicrunch.org/resolver/RRID:SCR_016854

3.1.3 Output 2: Functional connectivity of cortical neurons on GCaMP6f mice

This Output covers the following available datasets:

- *Slow-wave datasets*: mice imaged with Wide-Field (WF) and Two-Photon (2P) microscopy in resting state (awake and anaesthetised). This dataset refers to experiments described in detail in D1.6.2 on anaesthetised mice (*KR1.3 Output 2 Functional connectivity of cortical neurons on GCaMP6f mice*). Datasets collected in the framework of this KR have been exploited as testbench for the development of the SWAP (Slow Wave Analysis Pipeline) software tools, <https://github.com/INM-6/wavescalephant> (see Output 4 of KRc1.2).
- *Stroke and rehab datasets*: mice imaged with WF microscopy during a pulling task (see Figure 4). The specific dataset “*Longitudinal imaging of motor-evoked cortical activity before and after stroke*” has been shared to be used in the closed loop validation of the KRc1.2 *Output 1 Mouse network model before and after stroke*.

Based on this Output we proposed a methodological framework (named Embodied brain) to investigate a “brain in the loop” by a constructive refinement of experiments and simulation of an embodied mouse. Cortical recordings and behavioural data from experiments are used to build and validate brain models (KRc1.2) and the Output in the virtual environment (KRc1.3). In general, the framework could simulate new types of experiments that cannot be run in the real world (Allegra Mascaro, Falotico, Petkoski *et al.* P2535, *in press*).

Table 2: Output 2 Links

Component	Link to	URL
C1765, C2304, C2391	Data Repository, Technical Documentation and User Documentation	<ul style="list-style-type: none"> • Slow waves in resting state dataset (2P and WF): https://www.doi.org/10.25493/R7J6-S69 https://www.doi.org/10.25493/3E6Y-E8G • Stroke and rehab during pulling dataset (WF): https://www.doi.org/10.25493/Z9J0-ZZQ https://www.doi.org/10.25493/6864-QVG https://www.doi.org/10.25493/XJR8-QCA

A further dataset not yet delivered linked to this Output is the *2P stroke and rehab dataset*, which was not acquired yet due to several issues occurred in the ad-hoc platform development and then due to COVID19. Given the higher resolution of this dataset, it will give a close look on how the functionality of small networks is reshaped in specific cortical areas associated with recovery and expand the knowledge acquired with wide-field imaging. We aim anyway to acquire this dataset in the next future and integrate it in the EBRAINS Platform.

3.1.4 Output 3: Whole-brain datasets at sub-cellular resolution

Structural whole-brain datasets at sub-cellular resolution have been developed in the framework of SP1 and made available in the HBP Mouse Brain Atlas. In detail, these are the *C-Fos datasets* (<https://www.doi.org/10.25493/G20B-5QY>) and the *Cell distribution datasets* (<https://www.doi.org/10.25493/A0XN-XC1>). For details about this Output please refer to SGA2 Deliverable D1.6.2 (D7.2 D34) (Output 1 of KR1.3).

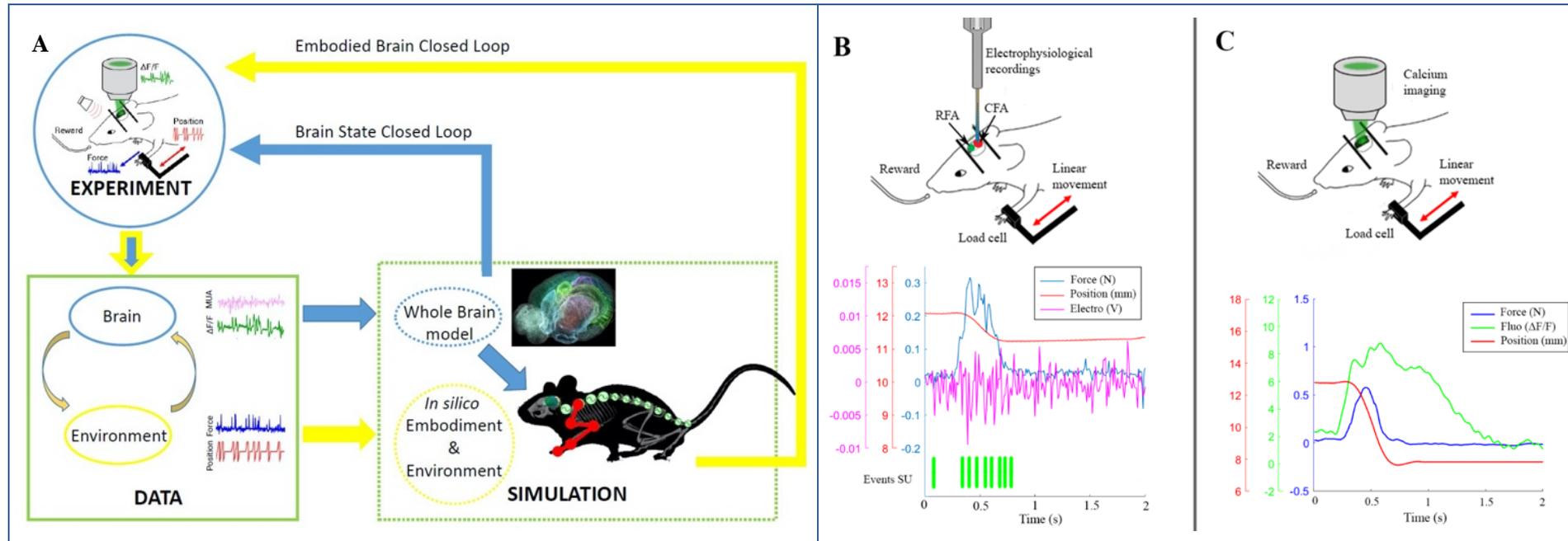


Figure 4: Closed-loop workflow linking real and simulated experiment.

Closed loop experiments and simulations. (A) The picture shows the closed-loop workflow linking real and simulated experiment. The different types of data obtained from the experiments, from brain activity to dynamic and kinematics of goal-directed movement, are used to feed the whole brain and spinal cord model, in addition to the virtual mouse and environment. The loop is closed by validation of *in silico* results on real data. Eventually, the simulated experiment raises novel hypotheses, to be validated by new real experiments. (B) Top, a schematic representation of the experiment during electrophysiological recording in Caudal Forelimb Area. Bottom, the synchronised data: force peak (blue), movement of the slide (red), high frequency electrophysiological signal of a single channel (magenta) and the timestamp of a selected single unit. (C) Top, a scheme of the experiment with the setup to record calcium activity. Bottom, the recorded data after synchronisation: force peak (blue), movement of the slide (red) and calcium response (green)

3.2 Validation and Impact

3.2.1 *Actual and Potential Use of Output(s)*

- Output 1: Storage and curation of CDP1 datasets

The CDP1 data sets have contributed to validation and optimisation of HBP workflows and tools for data curation and are shared via the new EBRAINS data sharing platform, thus contributing to KR5.4.

- Output 2: Functional connectivity of cortical neurons on GCaMP6f mice

All Functional datasets contribute to a deeper knowledge of brain functionality in mice by giving insights on the cortical activation of mice under different brain states, in physiological and pathological conditions. This study provides important information on how the cortex remaps his functionality in support of motor recovery induced by rehabilitation after stroke. This is contributing not only to KRc1.1 but more in general to the enrichment of knowledge on the mouse brain at the system level.

- Output 3: Whole-brain datasets at sub-cellular resolution

For details about this Output please refer to SGA2 Deliverable D1.6.2 (D7.2 D34) (Output 1 of KR1.3).

3.2.2 *Publications*

- Output 1: Storage and curation of CDP1 datasets

P2182 Puchades MA, Csucs G, Ledergerber D, Leergaard TB, Bjaalie JG (2019) Spatial registration of serial microscopic brain images to three-dimensional reference atlases with the QuickNII tool. PLoS ONE 14(5): e0216796. <https://doi.org/10.1371/journal.pone.0216796>.

Significance: User-friendly semi-automated tool for spatial registration of serial microscopic 2D images to 3D reference atlases, used for spatial integration of heterogeneous data to a common anatomical framework.

- Output 2: Functional connectivity of cortical neurons on GCaMP6f mice

P2108 A. L. Allegra Mascaro, E. Conti, S. Lai, A. P. Di Giovanna, C. Spalletti, C. Alia, A. Panarese, A. Scaglione, L. Sacconi, S. Micera, M. Caleo, F. S. Pavone, *Combined Rehabilitation Promotes the Recovery of Structural and Functional Features of Healthy Neuronal Networks after Stroke* (2019), Cell Reports, Vol. 28, No. 13, <http://dx.doi.org/10.1016/j.celrep.2019.08.062>.

Significance: Output 2 validated by a scientific peer-reviewed journal. The paper shows how a combined rehabilitation treatment with motor training and pharmacological silencing of the contralesional hemisphere, leading to a generalised recovery is associated with segregation of the motor representation and recovery of pre-stroke cortical activation transients.

4. Key Result KRc1.2 Mouse network model for the activity before and after stroke

4.1 Outputs

4.1.1 Overview of Outputs

4.1.1.1 List of Outputs contributing to this KR

- Output 1: Mouse network model before and after stroke (C1606)
- Output 2: Model of calcium imaging signals from spikes (C1234, C1235)
- Output 3: Spiking model of cortical activity under anaesthesia: Adex model (C1234, C1235)
- Output 4: Identification of the propagation wave-fronts tool and Toy Model of slow wave propagation (C2052, C2053)
- Output 5: Hybrid data driven and functional model of the motor cortex (C2612)

4.1.1.2 How Outputs relate to each other and the Key Result

To model the complexity of brain after stroke, several aspects have been modelled separately. In Output 1, a brain network model recapitulates the longitudinal modulation in global connectivity and coherence over one hemisphere in the weeks that follow a stroke. In parallel, a spiking model of motor-associated regions of the cortex model simulates the functional remapping on the spared motor regions, which is necessary for recovering motor functionality after a lesion (Output 5). Another important feature that is compromised after stroke and could be used as a biomarker of recovery is the spatiotemporal features of the propagation of neuronal activity across the cortex. Output 4 was designed to reproduce this feature *in silico*. Additionally, to recapitulate the abnormal oscillatory activity seen in peri-infarct region in the acute phase after stroke, an Adex model was tested (Output 3). Finally, to validate all the brain models based on spiking neuronal activity against our calcium imaging data, a transfer function was devised to model calcium imaging from spikes (Output 2).

4.1.2 Output 1: Mouse network model before and after stroke

As reported in more detail in SGA2 Deliverable D4.5.1 (D25.1 D71), Task T4.5.2 *Mouse Brain Function from Structure* (AMU) has worked on a whole-brain mouse models of spontaneous resting state activity, which were validated against mouse recordings in 3 different modalities: fMRI, calcium imaging, and voltage-sensitive dye imaging VSDI. All work was built on the state-of-the-art open source mice tracer dataset of the Allen Institute (Oh *et al.*, 2014) that AMU has implemented in The Virtual Brain (TVB) (Sanz-Leon *et al.* 2015), thus allowing detailed Structural Connectivity (SC) to be obtained (Meloizzi *et al.* 2017). This is then used to build large-scale brain network models for the resting state Functional Connectivity (FC). For the network nodes we have used different neural masses depending on the activity that is modelled. The first Output of D4.5.1 is significant because, besides showing that the individual structural features constrain the mouse functional connectome, it validates the Allen Mouse Brain Connectivity Atlas (AMBCA). This then allows the other two Outputs to use this dataset for building mice brain network models for: 1) stroke and recovery, and 2) stimulation.

The large-scale Mouse Brain Model for simulating the stroke and rehabilitation (Output 2 in D4.5.1) allows modelling of the results of the experiment defined in CDP1: wide-field calcium recordings for 5 mice in the first and in the fourth week after stroke, compared with its healthy activity. The top-

down model systematically exploits the effects of the SC constraints upon network dynamics, and was compared with empirical cortical activation maps in healthy, stroke and rehabilitation. The systematic analysis of the structural impact of the stroke and of the recovery unveils the best fit for parameters, with the experimental functional results during the stroke and the recovery. Data analysis and modelling were finished for recordings of one hemisphere of one animal, and the modeling of the results of further recordings from both hemispheres from 5 more animals are ongoing.

In this work we have focused on fitting the structural changes due to stroke and recovery in order to validate the usage of AMBCA even in the cases when there are significant changes in SC as compared to the healthy state. Results from the model help to identify the route of the stroke and the recovery in the parameter space that can be related to neurophysiological quantities, such as the white matter tracts. We could thus identify which are the most important links that need to be restored, or prevented from occurring, for a successful recovery. The collective paper (Allegra Mascaro, Falotico, Petkoski *et al.* P2535, *in press*) validated the potential of a brain network model to predict the long-range stroke-induced connectivity changes measured in a real experiment.

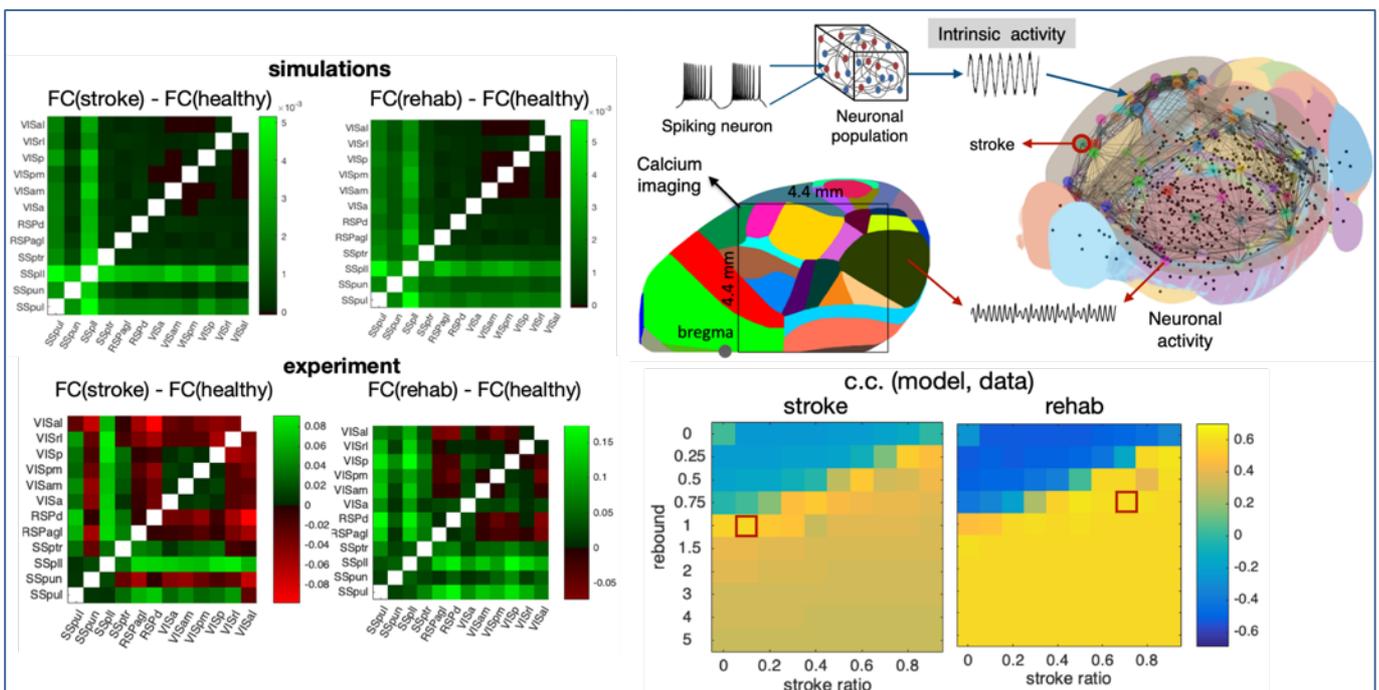


Figure 5: The macroscopic Brain Network Model (BNM)

(top right) The BNM is used to simulate macroscopic dynamics of different brain regions obtained by calcium imaging. (top left) The model simulates changes of the Functional Connectivity (FC) during stroke and recovery, compared with the healthy state (bottom left). Simulations are compared with the empirical FC (bottom left) and this allows identifying possible trajectories of recovery in the parameters space of the structural alterations (bottom right).

Table 3: Output 1 Links

Component	Link to	URL
C1606	Data Repository	Mouse stroke Brain network model, Petkoski S & Jirsa V: https://kg.ebrains.eu/search/instances/Model/2b9158547b4c0f15dc59d176081c1525
	Technical Documentation User Documentation	https://github.com/esaps/AllenMouse_strokeKuramoto

4.1.3 Output 2: Model of calcium imaging signals from spikes

It is known that the periphery of the stroke area undergoes a change in the spontaneous activity, displaying a pattern of slow oscillations that is also observed in unconscious brain states such as sleep or anaesthesia. With the global aim to detect stroke from brain activity, we developed a model that reproduces this pattern of slow oscillations and we fitted it with calcium imaging data from anaesthetised mice (see Figure 6). The model results are included in (Allegra Mascaro, Falotico, Petkoski *et al.* *Frontiers*, 2020 *in press*). This model could simulate the fluctuation in calcium concentration due to the spiking activity of homogeneous neuronal network, thus allowing the modelling of calcium imaging data.

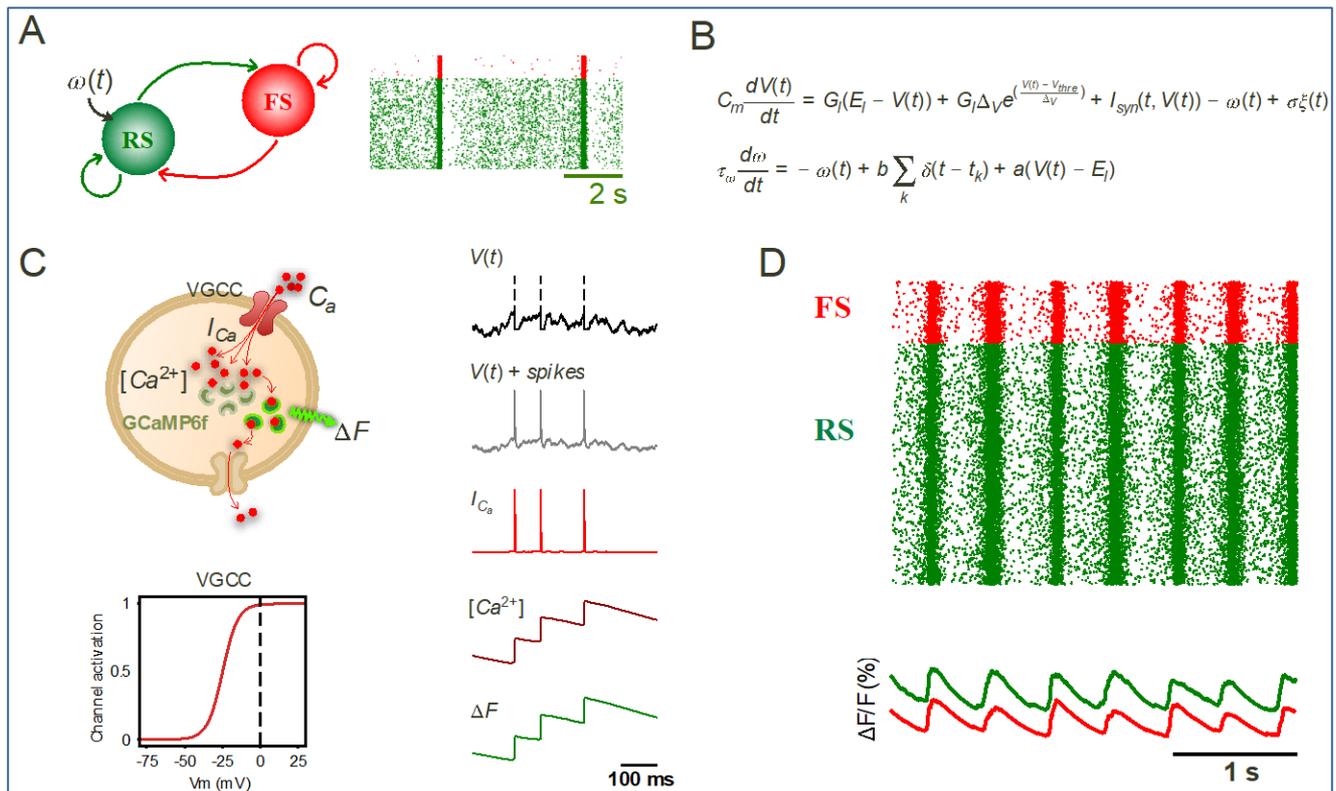


Figure 6: Model of calcium activity.

A. Spiking network of two populations (one of excitatory, regular spiking (RS), and one of inhibitory, fast spiking (FS) adaptive exponential integrate and fire (Adex) neurons) whose dynamics are governed by the equations in B. C. From the output of the simulations –spikes and membrane voltage– we calculated the calcium signal (fluorescence) taking into account the dynamics of the voltage gated calcium channels and the leak of calcium in the cell. D. Raster plot of the inhibitory (red) and excitatory (green) spikes and corresponding fluorescence traces during slow oscillations.

Table 4: Output 2 Links

Component	Link to	URL
C1234	Model Repository Technical Documentation User Documentation	https://collab.humanbrainproject.eu/#/collab/1571/nav/446790?state=model.1324953f-0457-41ce-9c0e-b1bf997352b7

4.1.4 Output 3: Spiking model of cortical activity under anaesthesia: Adex model

The decreased cerebral blood flow in the periphery of the region affected by a stroke produces a neuromodulatory change that leads to the emergence of slow oscillations, presumably due to an increase in the strength of adaptation of excitatory cells. We explore this hypothesis with a spiking network of Adex neurons that can display different patterns of activity depending on the adaptation strength. We use calcium imaging data of mice under different levels of anaesthesia to validate the

model (Figure 7) as documented in (Allegra Mascaro, Falotico, Petkoski *et al.* *Frontiers*, 2020 *in press*).

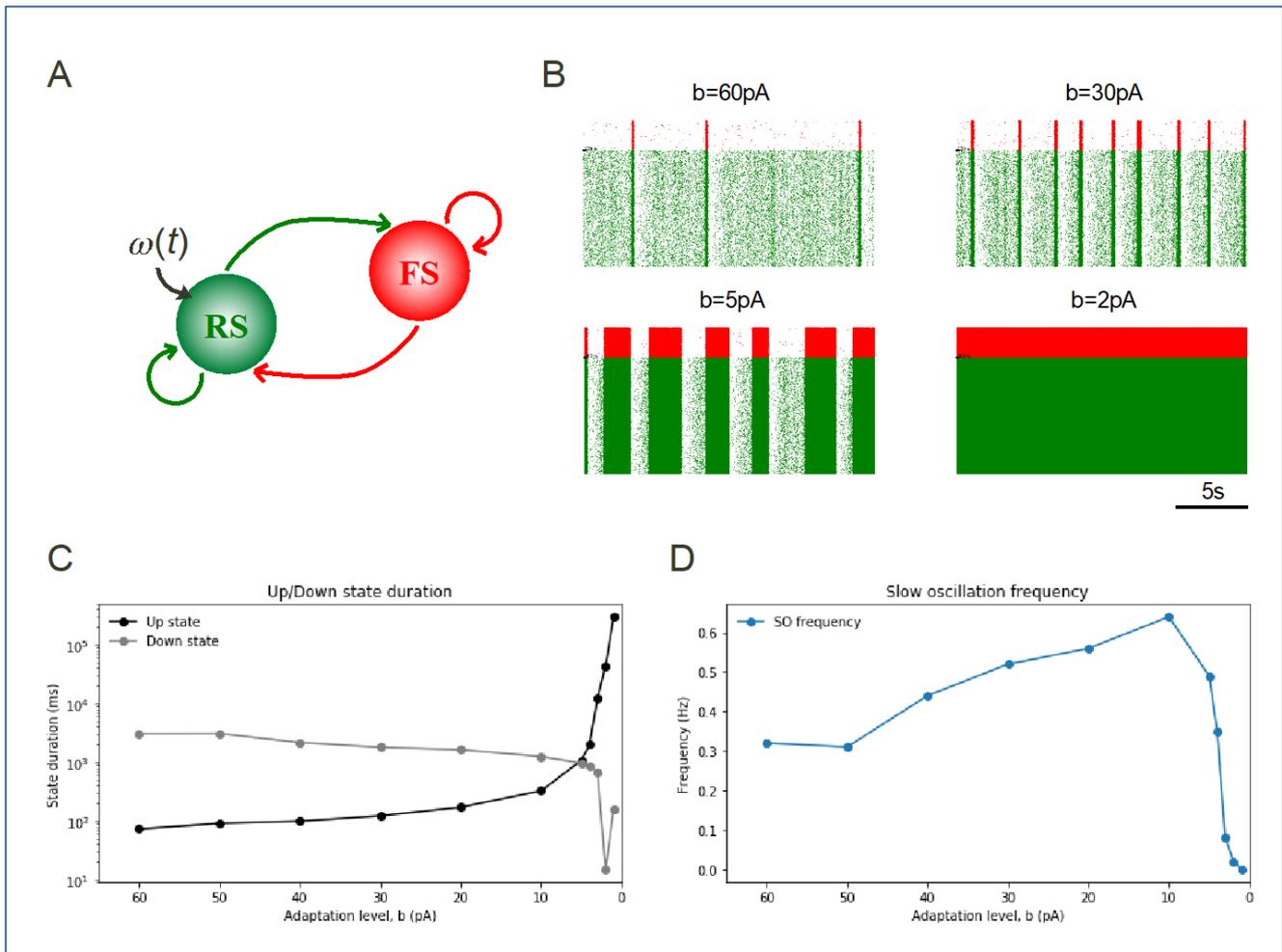


Figure 7: Spiking model of spontaneous cortical activity at different levels of anaesthesia.

A. Model of two populations of Adex neurons (as described in Figure 6). The excitatory population is affected by adaptation, $w(t)$, whose strength can be modulated by the parameter (b). B. Raster of the inhibitory (red) and excitatory (green) spikes at different strengths (b) of the adaptation, leading to different oscillatory patterns. C and D. Evolution of the Up and Down state durations (C) or the frequency of the slow oscillations (D) as a function of the strength of adaptation, (b).

Table 5: Output 3 Links

Component	Link to	URL
C1235	Model Repository Technical Documentation User Documentation	https://collab.humanbrainproject.eu/#/collab/1571/nav/446790?state=model.12a3a6e7-f2d7-407f-9d05-050da59f54bb

4.1.5 Output 4: Identification of the propagation wave-fronts tool and Toy Model of slow wave propagation

A simplified description of the activity observed in wide-field microscopy data is obtained with a Toy Model that approximates each pixel with a set of independent Poisson emitters oscillating between two states, Up (active) and Down (silent), see Figure 8; the two states differ for the expected value (mean) of the Poisson distribution. After convolving the pixel activity with a lognormal kernel that reproduces the GCamp6f light emission presented in (Chen *et al.*, *Nature* 2013), the Toy Model is

able to emulate the dynamics of the experimental data. The outcome of the Toy Model is used for the purpose of calibrating and validating the analysis procedure; both the Toy Model and the analysis procedure are detailed in Celotto *et al.*, *Methods and Protocols* 2020 (P2327).

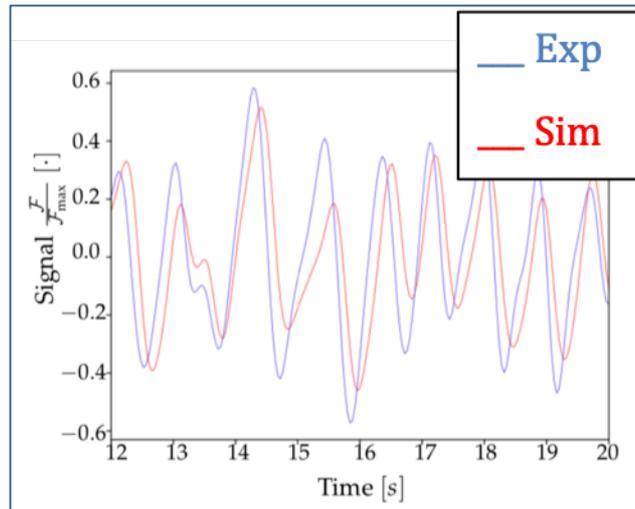


Figure 8: Pixel signal, simulated vs experimental

From: Celotto *et al.*, *Methods and Protocols* 2020 (P2327).

Table 6: Output 4 Links

Component	Link to	URL
C2052, C2053	Software Repository Technical Documentation User Documentation	https://github.com/INM-6/wavescalephant

4.1.6 Output 5: Spiking hybrid data driven and functional model of the motor cortex

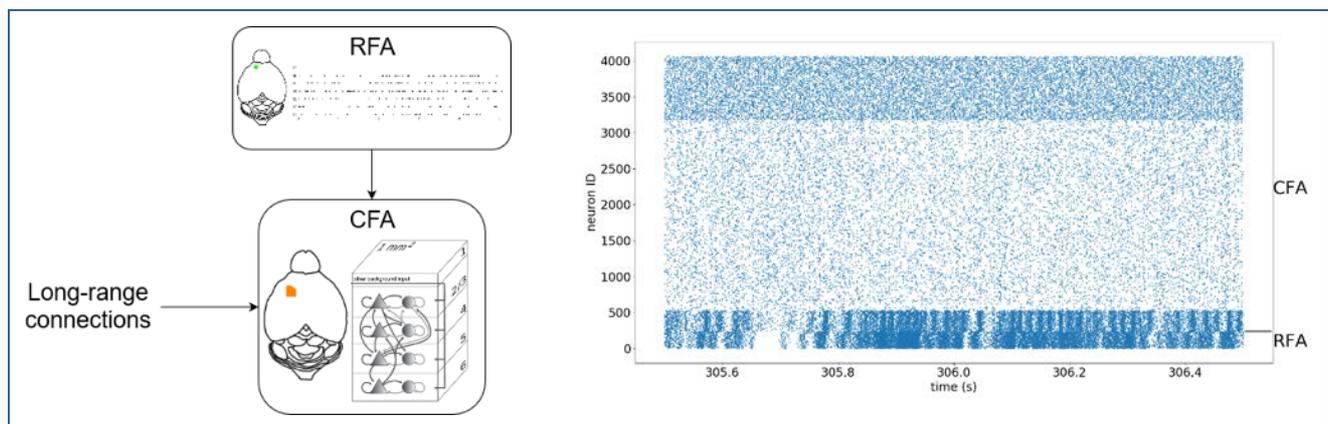


Figure: 9 spiking cortical model and simulated cortical activity

Left: spiking cortical model, including premotor (RFA) and motor areas (CFA). Right: simulated cortical activity.

The aim of this Output is to develop a spiking model of cortical activity that can simulate the effect of a stroke in the motor cortex and the partial recovery of connectivity thanks to structural plasticity. To this aim, a spiking functional model of relevant cortical areas was developed. The two main motor areas modelled are the rostral forelimb area (RFA) and the caudal forelimb area (CFA) which act as premotor and motor cortices, respectively (Figure: 9). RFA is directly modelled as a

population reproducing neurophysiological recordings from *in-vivo* experiments, which is connected to the CFA network. To limit the complexity of the simulation we only modelled layer 5 of the CFA, as this is the output layer of the area. CFA network is constituted of two population of neurons, pyramidal and fast-spiking interneurons. Values for the many parameters of the model were either taken from literature or tuned starting from neurophysiological recordings. In particular, the average weights of connections and the external drive to CFA were tuned using an evolutionary algorithm, in which the fitness functions rewarded individuals that more closely matched the firing rate computed from neurophysiological recordings of the CFA. More details on this model are available in SGA2 Deliverable D10.1.1 (D63.1 D94).

Table 7: Output 5 Links

Component	Link to	URL
C2612	Model Repository Technical Documentation User Documentation	https://bitbucket.org/lore_ucci/cortex-model/src/master/

4.2 Validation and Impact

4.2.1 *Actual and Potential Use of Output(s)*

Output 1: Mouse network model before and after stroke

The full-brain network decomposes the brain into a system composed of nodes and links, which is capable of spatiotemporal pattern formation. The Output of the stroke model is planned to be integrated with the Neurorobotic Platform together with the experiment, thus building a closed loop for validation of different hypothesis regarding the stroke. It could also be used for novel and improved strategies for rehabilitation after stroke. In future, combined with individualised connectome data during the recovery, a therapy could be proposed targeting specific parts of the brain, depending on the location and the size of the stroke.

Output 2: Model of calcium imaging signals from spikes

The simulated calcium signal reproduces the observed features of the two-photon signal recorded under anaesthesia.

Output 3: Spiking model of cortical activity under anaesthesia: Adex model

The model is able switch from awake-like activity to slow oscillations by tuning the adaptation strength, which will enable us to study mechanisms of emergence and recovery of slow oscillations in the periphery of a stroke area.

Output 4: Identification of the propagation wave-fronts tool and Toy Model of slow wave propagation

Output 4 and the related analysis procedure constitute a preliminary step towards the development of an advanced and structured analysis pipeline (C2053) and a modelling approach that aims at a non-stereotyped large-scale simulation of the activity and connectivity of the mouse cortex (C2052), as illustrated in SGA2 Deliverable D3.2.1 (D16.1 D37), Sections 5-6. This line of research carried out by Istituto Nazionale di Fisica Nucleare (INFN), leverage C1765 and links with KR3.2 Output 3 and 4.

Output 5: Spiking hybrid data driven and functional model of the motor cortex

The spiking cortical model developed as part of Output 5 is currently used as part of KRc1.3 for the simulation of a post-stroke robotic rehabilitation procedure. In the future, the model could be used to test different stroke-inducing protocols in simulations before performing in-vivo experimentation.

4.2.2 *Publications*

- Output 1: Mouse network model before and after stroke



P1893: Individual structural features constrain the mouse functional connectome. PNAS 15(2): e1006805. Melozzi *et al.* 2019.

Significance: This Output provides so far the strongest evidence in the literature for our capacity to individualise brain network models. On one hand, the approach has been validated against functional MRI data in the mouse, which establishes only a derived measure of cerebral activity, on the other hand a large range of structural connectomes (AMBCA connectome, individual DTI-based derived connectomes using different tractography methods, and various surrogates) has been applied, allowing detailed analysis of the structural constraints placed upon the dynamics.

- Output 4: Identification of the propagation wave-fronts tool and Toy Model of slow waves propagation

P2327: Marco Celotto, Chiara De Luca, Paolo Muratore Francesco Resta, Anna Letizia Allegra Mascaro, Francesco Saverio Pavone, Giulia De Bonis, Pier Stanislao Paolucci, *Analysis and Model of Cortical Slow Waves Acquired with Optical Techniques*, Methods and Protocols, Vol. 3, No. 1, 2020

Significance: This work constitutes a first step towards quantitative comparisons of different datasets and of experiments and simulations, aiming at going beyond visual inspection and at enlarging the offer of tools that support quantitative studies of neuronal dynamics from imaging data; in addition, we pursue an effort towards the adoption of free software, potentially enlarging the number of users.

5. Key Result KRc1.3 Implementation and simulation of the motor-task cases in the upgraded virtual behaviour lab app

5.1 Outputs

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

- Output 1: Models of neural circuits integrated in the Virtual Mouse (C2596, C2603)
- Output 2: Platform for rat rehabilitation (R-Platform) (C2616)
- Output 3: Simulation of the post-stroke robotic rehabilitation experiment (C2614)

5.1.1.2 How Outputs relate to each other and the Key Result

This KR was conceived to deliver a framework to simulate a motor task experiment. In particular, the focus was on the reproduction of a post-stroke robotic rehabilitation procedure performed on mice. To implement this experiment, we identified a set of components that had to be modelled/implemented:

- the robotic platform for motor training
- the animal musculoskeletal forelimb
- the spinal cord model for the forelimb muscles
- the cortical model (Output 5 of KRc1.2)



All the neural components were integrated together in a virtual mouse, implemented in the Neurorobotics Platform (Output 1) and used to perform simulations of the experiment (Output 3), together with the physical simulated models.

Output 2 (rat platform) extend previous experimental work on mouse to rat species.

An approach that allows continuous integration of new experimental data into a computational modeling framework that includes multiple components, working at different scales has been proposed in (Allegra Mascaro, Falotico, Petkosky et al. P2535, *in press*).

5.1.2 Output 1: Models of neural circuits integrated in the Virtual Mouse

The mouse skeletal model is obtained from a CT-scan. The skeletal model is fully rigged with the necessary degrees of freedom between any two links. The joint centres are anatomically relevant. In the current version all rotations are limited to simple revolute joints. If necessary, the user may define more complex joint rotations using the opensim-api exposed in NRP. For the current experiment, the mouse skeletal model is reduced in complexity by constraining all the degrees of freedom except the left forelimb. The forelimb consists of four segments and it is further constrained to only have flexion-extension movements, enough to reproduce the push-pull experiment. A muscles-tendon system is attached to the bones. In the current setup, a pair of antagonist hill-type muscles were added to each of the joints in the mouse forelimb. Muscle parameters used in the current experiment are hand-tuned to produce flexion-extension movements necessary for the experiment. Figure 10 shows the segments, the joints and the muscle attachments used in the current model.

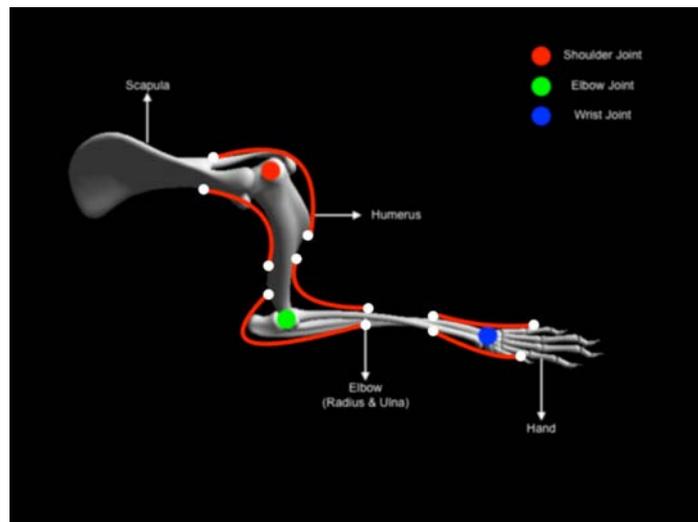


Figure 10: Antagonist pair of muscles for the mouse forelimb

A spinal cord model capable of actuating the simulated muscles has been previously developed and implemented as a spiking neural network in NEST. The spinal cord comprises a circuit for a single muscle, inhibitory connections between antagonistic pair of muscles and interneurons to modulate descending stimuli (Figure 11). An instance of the spinal circuitry was instantiated and adapted to the number of muscles of the mouse forelimb. Finally, the cortical model described in Output 5 of KRc1.5 was connected to the α -motoneurons of the spinal cord circuitry in order to drive the pulling motion of the forelimb. More details are present in SGA2 Deliverable D10.1.1 (D63.1 D94).

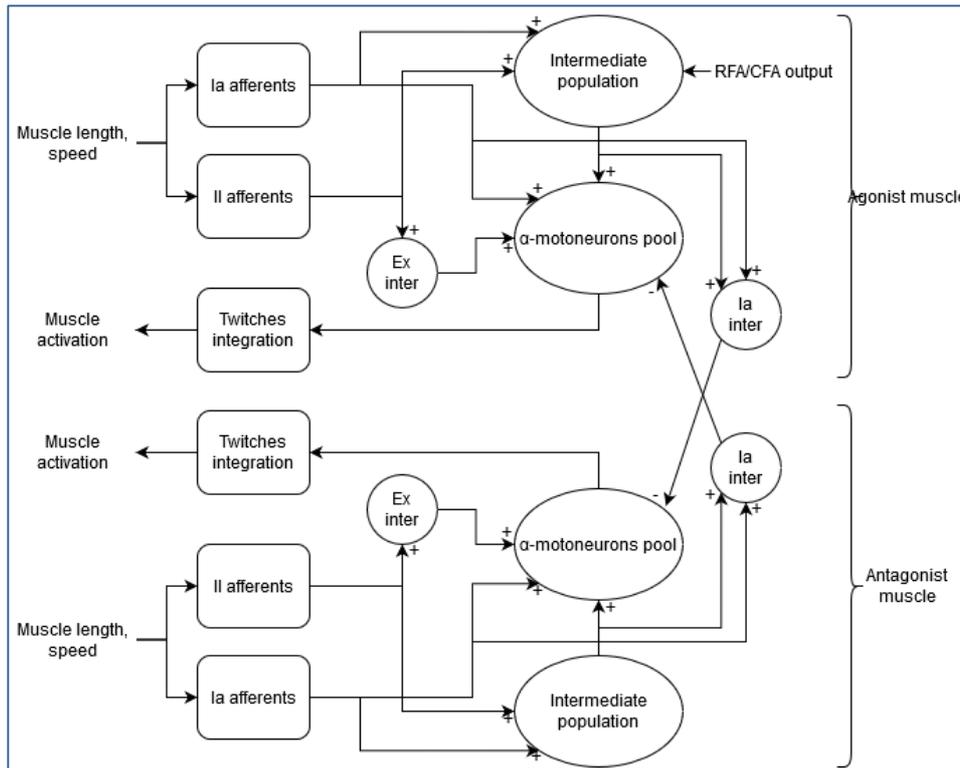


Figure 11: Spinal cord network model

Table 8: Output 1 links

Component	Link to	URL
C2596	Model Repository Technical Documentation User Documentation	https://gitlab.com/sssa-humanoid-robotics/NeuralModels
C2603	Software Repository Technical Documentation User Documentation	https://gitlab.com/hbp-nrp/mouse_model.git

5.1.3 Output 2: Platform for rat rehabilitation (R-Platform)

In order to perform assisted-reaching experiments, we developed a new platform for rats (see Figure 12 left). The device constrains the wrist of the rat and it has 4 degrees of freedom: three space dimensions and the prono-supination movement of the forelimb. In the plane x-y the movement is obtained with a parallel cinematic chain in a 40 x 20 mm² workspace; an EC-i 40 motor (Maxon) with a spindle drive gearbox allows the movement in the third direction of the space along a track defined by a linear slide (stroke 56 mm). The prono-supination movement is realised with a parallel shift gear mechanism.



Figure 12: (Left) 3D model of the R-platform. (Right) Performance of the task

This module was integrated with a custom-made restrainer, that allows to fix the rat both in a bipedal and in a four-leg position thanks to a jacket using Velcro. Two translation stages allow regulating the correct posture of the animal compared to the wrist restrainer part, further, two corner braces grant the rotation in three directions of the semi-cylinder component, where the animal is blocked.

This device has two different working modes, a passive modality, where the movement of the paw is completely driven by the robot and a pull active task, where the robot extends the forelimb of the animal that, after, has to pull back to home position the slide to receive a reward. The possibility to switch between these modalities allows to follow a rehabilitation process with a customised protocol.

The robot has been tested in collaboration with the laboratory of Grégoire COURTINE (Brain Mind Institute and Center for Neuroprosthetics, EPFL, Geneva, Switzerland). During the experiment (see Figure 12 right), movements were recorded with SIMI cameras and force signal was acquired by a 6-axis load cell (Nano 17, ATI). Moreover, the platform was embedded with VICON and Inscopix system, to record EMG signal and neural activity in the primary motor cortex (see Figure 13).

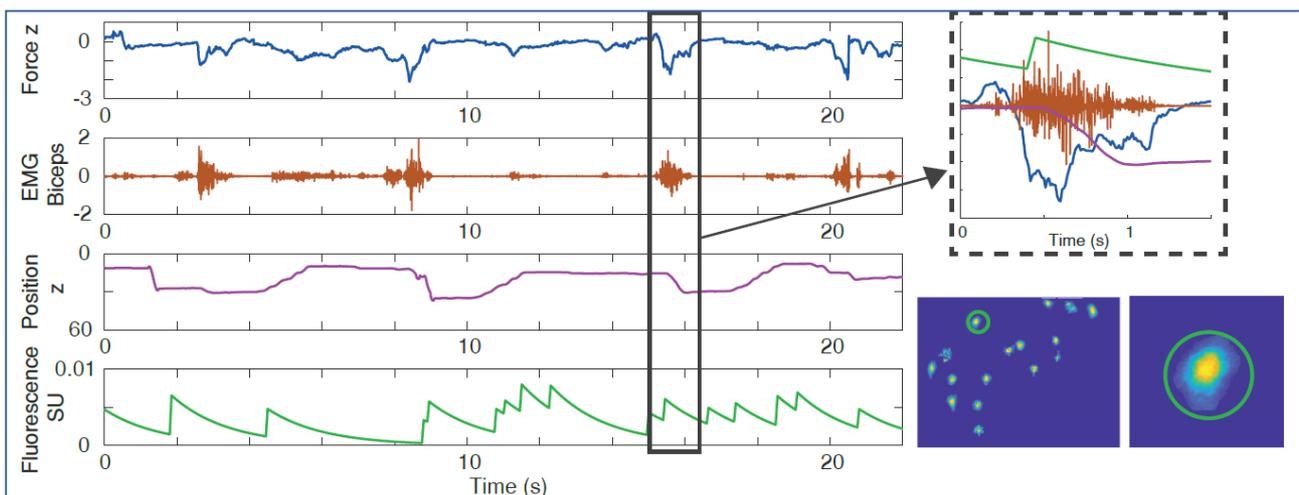


Figure 13: Recorded data of a healthy rat during a pull active task.

5.1.4 Output 3: Simulation of the post-stroke robotic rehabilitation experiment

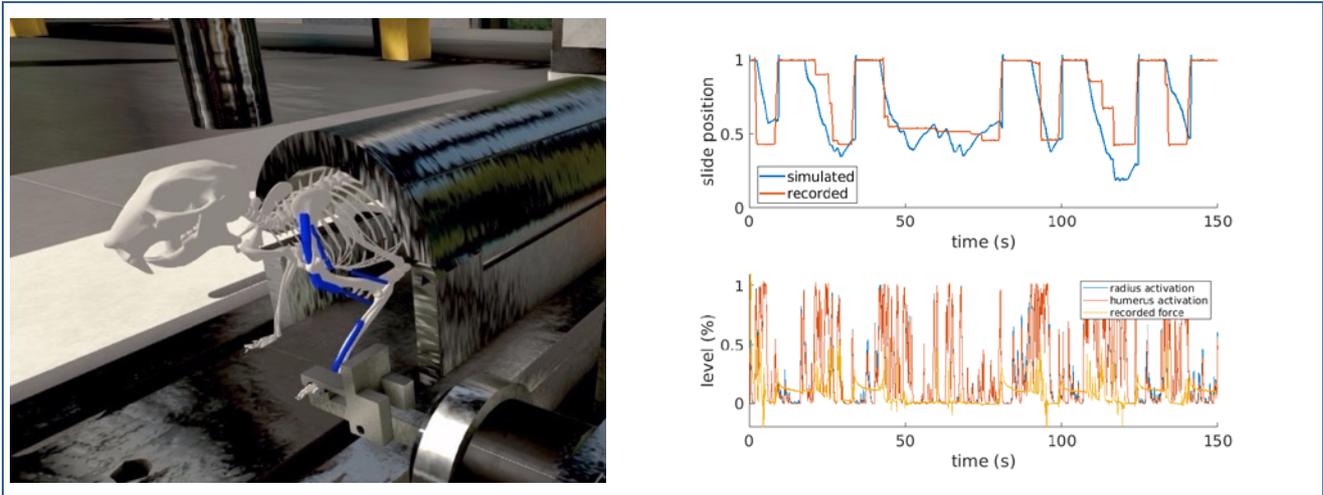


Figure 14: Simulated robotic experiment

Left: the simulated robotic M-platform and the musculoskeletal embodiment in the NRP. Right: results for the simplified cortical model.

Alongside the musculoskeletal embodiment and the neural circuitry described previously, we modelled the M-Platform. The slide mechanism was modelled as a prismatic joint, actuated by a PID controller. A state machine-based control mechanism for automatic reset of the sled position was developed, thanks to functionalities already present in the NRP. This mechanism actuates the sled at specific points in time and puts it in its initial position, simulating a reset of the experimental trial. In the *in vivo* experiment, a certain threshold of force is needed to move the slide due to friction. In the simulation we set a muscle activation threshold that, upon reaching, forced the slide control mechanism to deactivate the PID controller, effectively freeing the slide and allowing the mouse forelimb to carry out the pulling. The simulated environment can be seen in Figure 14. In a first set of tests only a simplified cortical model was employed. This model consisted in a set of static spike generators reproducing the events detected with the MU spike sorting in RFA. This was done to test whether it was possible to achieve results pre and post stroke by simulating a cortical area that is not directly affected by the stroke. Results, partially shown in Figure 14, demonstrated that it was possible to simulate activity of healthy mice, but not of post-stroke mice. This approach has been proposed in (Vannucci *et al.*, 2019, P2374, *in press*). Preliminary results with the more complete brain model held similar results for the healthy mice. More details are present in SGA2 Deliverable D10.1.1 (D63.1 D94).

Table 9: Output 3 links

Component	Link to	URL
C2614	Software/model Repository Technical Documentation User Documentation	https://gitlab.com/lore.ucci/closed-loop-mouse-stroke-simulation

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

These biologically realistic models (Output 1 and 3) will advance our knowledge of sensorimotor integration by testing neuroscientific theories through embodiment in closed-loop simulations. Experimenters will also benefit from the detailed model of the mouse and simulations by being able

to test different experimental conditions before performing a real experiment, thus saving time in the experimentation process.

5.2.2 Publications

- Output 1: Models of neural circuits integrated in the Virtual Mouse

P2379 S. Tata Ramalingasetty, S.M. Danner, A.J. Ijspeert, I.A. Rybak (2019) An integrated neurobiomechanical model of the mouse to study neural control of locomotion. In AMAM 2019, DOI: [10.5075/epfl-BIOROB-AMAM2019-52](https://doi.org/10.5075/epfl-BIOROB-AMAM2019-52)

Significance: Development of a detailed neurobiomechanical mouse model, from high resolution 3D scan of the mouse skeleton

6. Conclusion and Outlook

CDP1 continued in the closed-loop approach in helping developing and testing the HBP Platforms (NIP, BSP and NRP), making ad hoc real experiments to obtain datasets for validating models and simulations and to realise the virtual replications of a set of experiments with mice. We demonstrated CDP1's technological progress, with as objective investigating brain plasticity and improving the mouse brain atlas.

During the last year, we refocused CDP1 integrated efforts in order to achieve and finalise the virtual pulling experiment on the NRP Platform. Internal remodulation of some activities was necessary when the leader of scaffold whole brain model (Marc-Oliver GEWALTIG) had left the Project. Unfortunately, we had to abandon the activity developing a framework for a comparison of rehabilitation after stroke across species (KRc1.4) originally planned in the SGA2 Workplan, as it was conceived for a long-term activity continuing in SGA3, but CDP1 will end most of its activities at within SGA2.

As our results show, we managed to include in our experiments the multi-scale activity of several regions in the healthy hemisphere, thus allowing better modelling of the neuronal networks and large-scale dynamics, under physiological and pathological conditions. Indeed, high resolution two-photon calcium imaging data are now being used to complement large-scale functional measures, and this will be an essential tool to bridge large-scale (brain network, mean field) models with simulation of smaller neuronal networks with cellular resolution. Finally, first models of slow-wave activity, built and validated on our functional data, are providing the basis to understand many features of the abnormal functionality in peri-lesioned brain areas. These data and the related models are representative for the unconscious brain, planned to be investigated in SGA3. The calcium imaging model, e. g., will be formulated in mean-field, and will be linked to the other mean-field models in HBP. This will allow to constrain mean-field models from wide-field calcium imaging measurements (which will be done in SGA3 WP2, Task T2.5).

Workflows and protocols used for documenting and reporting anatomical locations in experimental studies of mice have been published: all users, HBP and externals, can adopt them for sharing and exploring datasets.

A novel longitudinal analysis from new datasets on rehabilitated mice are being validated on the Mouse network model. Development of the model for embedding of spiking model modules into the whole brain model is currently under development and will be released in the next few months. Indeed, the work on integrating the validated mean-field and population models developed in Task T4.1.3 and extending them towards pathological conditions including stroke and epilepsy is still ongoing. This work includes validating neuronal mass models against high-dimensional neuronal network models, enabling parameter space explorations to guide high performance computations (SP7). This has become much more crucial and far-reaching for bridging the scales of different levels of description, and as a such it will be of central importance in SGA3. Related to this is linking theoretical models at different levels of description to cross-bridge neuroscience and models implemented in various HBP Platforms, which will be integrated in EBRAINS. After SGA2, CDP1 results should also lead to a closed loop between real and virtual experiments within the Neurorobotic

Platform. Closing this loop also implies bridging different levels of description for the brain activity, hence converging towards the main goals of SGA3.

At simulation level, the post-stroke robotic rehabilitation experiment has been realised on the Neurobotics Platform, thanks to a modelling effort that focused, on the neural side, on models of the motor cortices and their interactions with the spinal circuitry, and, on the physics side, on realistic musculoskeletal and robotic models. This achievement has been possible thanks to NRP developments; experimental designs drove NRP development in terms of newly added features. It is important to stress that many of the models developed for this experiment are in fact more general and can be used separately for the development of other experiments. This is also strengthened by the fact that the code for most of the models, including documentation, has been made available to the public at large, via public repositories. Activities on the simulation of cortical circuits reorganisation after stroke and on the spiking model embedded into the whole brain model will be available in a Deliverable released within first months of SGA3 (Addendum of D10.1.1 (D63.1, D94), expected in June 2020).

In conclusion, CDP1 conceived and developed a methodological framework to investigate a “brain in the loop” by a constructive refinement of experiments and simulation of an embodied mouse (Allegra Mascaro, Falotico, Petkoski *et al.* P2535, *in press*). Our findings suggest that simulation of real experiments within the framework (Embodied Brain) will help better understand the complex mechanism that underlies the generation of behaviour. We believe that new features like the activation of different brain regions for performing the same task due to degeneracy (Price and Friston, 2002) and its impact on stroke and recovery will be disclosed by the simulation of the entire experiment as showcased in this manuscript.

The entire neuroscience community may take advantage of these “task dynamics” loops to simulate goal-directed behavioural tasks by reproducing the bidirectional motor-sensory interaction between brain and environment (Zrenner *et al.*, *Frontiers in cellular neuroscience* 2016). The framework developed within CDP1 will advance the field by offering *in silico* hints for formulating new hypotheses on the mechanism underlying goal-directed voluntary movements. These hypotheses could be additionally validated by *ad hoc* designed experiments, thus reinforcing the constructive loop between experiments and simulations. Once validated in the experiment on goal-directed movement, the framework developed here could represent a platform for testing new experiments that cannot be run in the real world. The enrichment of the framework with several brain and spinal cord models, in addition to multiple environments, could allow reproduction of many experimental paradigms. Last but not least, the virtual environment will be an essential tool to reduce the number of animals used in the experiments, thus making the “Reduction” rule on animal experimentation a feasible goal.